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Uncovering the Pathophysiological Role of Mast Cell Overactivation and Histamine Metabolism Dysregulation in ASD, ADHD and PTSD Symptoms. A Hypothesis on Shared Mechanisms and Potential Therapeutic Implications.

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Abstract

Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD) and Post-Traumatic Stress Disorder (PTSD) are complex neuropsychiatric conditions whose pathophysiology until now remains unclear. In this article, we expand on the author's earlier hypothesis that Mast Cell Activation Syndrome (MCAS) and impaired histamine metabolism, called Histamine Intolerance (HIT), may play a key role in the development of the commonly observed symptoms of this disease. By integrating current scientific evidence on the role of mast cells, histamine, neurotransmitters, and biological, chemical, physical, nutritional, and environmental factors, this study aims to elucidate potential mechanisms underlying the etiopathogenesis of these disorders. Systematic review and meta-analyses presenting a significant correlation between MCAS, histamine accumulation, GABA reduction, glutamate hyperactivity, and neuroinflammation, leading to excitotoxicity, neuronal damage and clinical manifestations. The author suggests that symptoms such as sensory hypersensitivity, gastrointestinal dysfunction, sleep disturbances, and emotional instability, commonly observed in patients with ASD, ADHD, PTSD, MCAS, and HIT, may result from histamine hyperactivity. Excess histamine leads also to activation of H1–H4 receptors, affecting multiple physiological systems, including the respiratory, gastrointestinal, circulatory, immune, and nervous systems. It can also cross the blood-brain barrier, promote blood clot formation, stimulate H3 receptors in the brain, and trigger neuroinflammation. As a working hypothesis of therapeutic interventions, it is proposed that a combination of sensory-soothing environments, internal rhythm–synchronizing technologies (such as Vinci Power Nap®), low-histamine diets, and targeted supplementation (vitamins D, A, B6, B9, B12, C, zinc, copper, H1–H4 receptor blockers, and DAO enzyme, etc.) may alleviate symptoms by modulating mast cell activity and excitotoxicity, improving sleep quality, and promoting balanced immune and nervous system responses, which was noticed in pilot experiments. These findings may inspire further research for randomized clinical trials (RCTs) to validate these strategies as well as for further research to explore the role of mast cells and histamine in neuroimmune disorders including also stroke, Alzheimer and Parkinson disease.

Keywords: ASD; ADHD; PTSD; Mast cells; Histamine; Enzyme DAO; H1; H2; H3 receptors; GABA; Glutamate; Excitotoxicity; Neuroinflammation; Neuroarchitecture.

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Introduction

Autism Spectrum Disorder (ASD), Attention-Deficit/ Hyperactivity Disorder (ADHD), and Post-Traumatic Stress Disorder (PTSD) are complex neuropsychiatric conditions that significantly affect the quality of life of patients and their families. According to the most recent estimates from the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, approximately 1 in 31 (3.2%) children aged 8 years were diagnosed with ASD in 2022 [1], [2], compared with approximately 1 in 59 children in 2020 [3]. A meta-analysis of multiple studies demonstrated that the global prevalence of ADHD among children and adolescents is approximately 8.0%, with rates of 10% in boys and 5% in girls in the analyzed epidemiological samples [4]. Between 2009 and 2017, based on parent-reported data, approximately 1 in 6 (17%) children aged 3–17 years in the United States were diagnosed with at least one developmental disability. These included, among others, ASD, ADHD, blindness, and cerebral palsy [6]. Post-traumatic stress disorder (PTSD) is a mental health condition that may develop following exposure to, or witnessing of, a traumatic event. Such events include, but are not limited to, armed conflict, natural disasters, terrorist attacks, motor vehicle accidents, as well as prolonged abuse or neglect during childhood [7]. Experts indicate that PTSD arises from stress-induced neurobiological changes in the brain. In many individuals, symptoms emerge shortly after the traumatic event, whereas in others they may develop after a prolonged latency period, sometimes years later [8]. PTSD affects approximately 6–8% of the general population across all racial, ethnic, and socioeconomic groups [5].

The aforementioned disorders are characterized by a complex etiology involving genetic, environmental, and immunological factors, and despite extensive research, their pathophysiological mechanisms remain incompletely understood, which continues to hinder the development of effective therapeutic strategies. Symptoms such as, among others, sensory hypersensitivity, gastrointestinal disturbances, allergic manifestations, cognitive difficulties, emotional instability, and sleep disorders suggest the presence of shared neurobiological mechanisms [9], [10]. Notably, these symptoms show a strong overlap with those described in the recently identified and published "histamine storm" mechanism implicated in the development of systemic inflammatory response syndrome (SIRS) and sepsis [11]. Recognition of these correlations led the author to further observations pointing to a potential role of excessive Mast Cell Activation Syndrome (MCAS) and Histamine Intolerance (HIT) as contributing factors to neuroinflammation and dysregulation of neurotransmission in ASD, ADHD, and PTSD [12]. Mast cells, localized predominantly in barrier tissues such as the skin, mucosal surfaces, gastrointestinal tract, lungs, heart, and also within the vascular endothelium, are highly sensitive to a wide range of environmental biological, chemical, and physical stimuli. These include, among others, extreme cold or heat, cold and dry air to breathe [13], mechanical pressure, vibration, ionizing radiation, sensory stressors, allergens, pharmaceuticals, toxins, and heavy metals. Upon activation, mast cells undergo degranulation and release a broad spectrum of pro-inflammatory mediators, most notably histamine. Histamine exerts its effects through activation of H1–H4 receptors, thereby amplifying local and systemic inflammatory responses and modulating neurotransmission, ultimately influencing central and peripheral nervous system function [14], [15], [16]. It is important to emphasize that MCAS represents a distinct clinical entity from mastocytosis, differing in pathophysiology, diagnostic criteria, and clinical course. In addition, the exogenous histamine load derived from dietary sources plays a significant role in overall histamine homeostasis. Impaired histamine metabolism, known as histamine intolerance (HIT)— most commonly associated with reduced activity or deficiency of diamine oxidase (DAO)—may further exacerbate spectrum of symptoms as well as neurological dysfunction. Excessive levels of this endogenous and exogenous biogenic amine, which also functions as a neurotransmitter, have been shown to critically contribute to the dysregulation of cognitive, emotional, and autonomic processes [17].

A growing number of studies indicate that mast cell activation syndrome (MCAS) and histamine intolerance (HIT) may be linked to alterations in neurotransmitter homeostasis, particularly affecting the balance between glutamate and gamma-aminobutyric acid (GABA). Glutamate, the principal excitatory neurotransmitter, and GABA, the primary inhibitory neurotransmitter, play critical roles in the regulation of neuronal activity and synaptic homeostasis [18]. Dysregulation of this excitatory–inhibitory balance may lead to neuronal hyperexcitability, altered sensory processing, hypersensitivity, and impairments in emotional regulation. Histamine released within the central nervous system (CNS) modulates neurotransmission through multiple receptor subtypes, including the H3 receptor, which functions predominantly as a presynaptic autoreceptor and heteroreceptor. Activation of H3 receptors inhibits the release of several neurotransmitters, notably GABA, thereby indirectly promoting increased glutamatergic signaling [19]. This shift toward excitatory dominance may contribute to heightened neuronal excitability, excitotoxicity, and the initiation or amplification of neuroinflammatory processes [20], [21], [22]. Building upon published evidence and observational data, the present review investigates these mechanisms, their possible involvement in the pathophysiology and symptom expression of ASD, ADHD, and PTSD, and the potential role of therapeutic approaches aimed at modulating mast cell function and histamine metabolism regulation. Such interventions include low-histamine dietary approaches, optimization of the external environment to minimize stressors, mast cell stabilization strategies (e.g., vitamin

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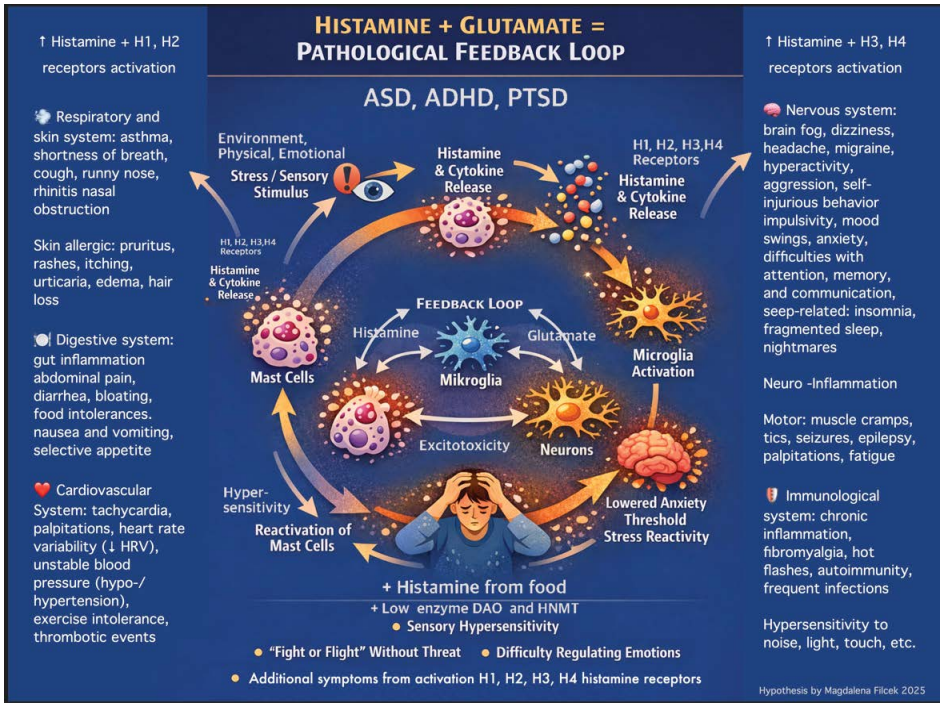
supplementation and antihistamine use), and reduction of histamine levels through enzymatic degradation via diamine oxidase (DAO) supplementation [23], [24], [11], [25], [26].

Hypothesis: overlapping factors that elevate histamine levels may act synergistically, thereby amplifying one another and contributing to a broad range of symptoms observed in ASD, ADHD, and PTSD:

Environmental factors → Mast cell activation ↑ → histamine ↑ → H1, H2, H3, H4 receptors ↑ H3 → GABA ↓ → Excessive glutamatergic activity ↑ → neuronal excitability ↑ → Excitotoxicity and neuroinflammation ↑ → Oxidative stress ↑ → Symptom severity ↑

High-histamine foods ↑ + low diamine oxidase (DAO) activity ↓ → Elevated histamine levels ↑↑ → H1, H2, H3, H4 receptors ↑ H3 → GABA ↓ → Excessive glutamatergic activity ↑ → neuronal excitability ↑ → Excitotoxicity and neuroinflammation ↑ → Oxidative stress ↑ → Symptom severity ↑

Amplification (1+2): Environmental factors + High-histamine foods ↑ + low diamine oxidase (DAO) activity ↓ → histamine levels ↑↑↑ → H1, H2, H3, H4 receptors ↑↑ → GABA ↓↓ → Excessive glutamatergic activity ↑↑ → Increased neuronal excitability ↑↑ → Excitotoxicity and neuroinflammation ↑↑ → Oxidative stress ↑↑ → Mast cell activation ↑ → histamine levels ↑↑↑ → Exacerbated symptoms of ASD, ADHD, and PTSD ↑↑ (Picture 1)



Picture 1: Hypothesis: overlapping factors that elevate histamine and glutamate levels, also activating H1-H4 receptors may act synergistically, thereby amplifying one another and contributing to a broad range of symptoms observed in ASD, ADHD, and PTSD. Illustration was generated using AI (ChatGPT 4.0.) and reviewed and completed by the author.

The Relationship Between MCAS, HIT, Histamine Accumulation, and ASD, ADHD, PTSD

Conclusions from meta-analyses: MCAS + HIT → Excess histamine → Activation of H3 receptors → Reduced GABA release → Excessive glutamatergic activity → Excitotoxicity and neuroinflammation → Disrupted homeostasis and neuronal damage → Potentially explains shared symptoms of ASD, ADHD, and PTSD.

An increasing body of evidence from meta-analyses demonstrates a significant association between immune-mediated mast cell activation (MCAS), including the degranulation of histamine, and dysregulated histamine metabolism (histamine intolerance, (HIT)), and neuroinflammation and the neuropsychiatric symptoms observed in ASD, ADHD, [27], [28], [29], [30], as well as in PTSD [31]. Some of the most comprehensive and detailed meta-analyses describing an overlooked mechanism helpful in understanding this connection is explained in the article titled: "Discovery of the Mechanism of COVID-19, SIRS and SEPSIS, Defense and Treatment. Mast Cells and Histamine Storm: An Overlooked Aspect in COVID-19 and in Ventilated Patients – Potential Role of Antihistamines" [11], also as one of the chapter in the book „Oddech" entitled: "Breathe with Vinci Power Nap® – Harmonize Your Body and

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Mind in the Sleep Cafe®: A Neuroarchitectural System for Synchronizing Sleep, Breathing, Heartbeat, and Brainwaves that Reduces Stress, Mast Cell Activation Stimuli, and Histamine" [27]. The author's hypothesis identifies this overlooked mechanism as a potential pathophysiological factor underlying certain features of ASD, ADHD and PTSD [10], [27] because MCAS is associated with chronic histamine release, which exacerbates neuroinflammatory and behavioral symptoms also characteristic of HIT [32]. The analyzed studies indicates that patients with mastocytosis frequently experience neuropsychiatric symptoms, including depression (68–75%), anxiety, elevated stress levels or irritability (27–54%), cognitive impairment—particularly memory deficits (27–39%), headaches (55–69%), attention deficits and learning difficulties in 13% of children, dental [33] and neurodevelopmental disorders in (8–12%) of cases [34]. Several clinical features of MCAS and mastocytosis [35], including excessive histamine release, activation of histamine receptors (H1, H2, H3, H4), and reduced enzyme diamine oxidase (DAO) activity resulting in histamine intolerance (HIT), overlap with symptoms commonly observed in ASD, ADHD, and PTSD [24], [36], like:

- Gastrointestinal: abdominal pain, diarrhea, bloating, food intolerances, selective appetite.
- Skin allergic: pruritus, rashes, itching, urticaria, edema.
- Sensory hypersensitivity: light, sound, smell, and touch sensitivity.
- Neurological: headaches, migraines, "brain fog," mood and emotional fluctuations.
- Respiratory: asthma, shortness of breath, cough,
- Cardiovascular: tachycardia, palpitations, heart rate variability (↓ HRV), unstable blood pressure (hypo- / hypertension), exercise intolerance, dizziness, thrombotic events, hypotension.
- Behavioral: hyperactivity, impulsivity, anxiety, self-injurious behavior, aggression, reduced social engagement.
- Motor: muscle cramps, tics, seizures, palpitations, fatigue.
- Cognitive: difficulties with attention, memory, and communication.
- Immunological: chronic inflammation, fibromyalgia, hot flashes.
- Neuronal: glutamatergic excitotoxicity, neuroinflammation, neuronal damage.
- Sleep-related: insomnia, fragmented sleep, nightmares.

These findings suggest a potential coexistence of MCAS and HIT, mediated through impaired histamine metabolism due to reduced activity of enzymes: DAO or histamine N-methyltransferase (HNMT). Such impairments have also been observed in patients with ADHD [37], ASD [38], as well as in individuals carrying polymorphisms in the AOC1 and HNMT genes [39]. These alterations can lead to histamine accumulation and potentially exacerbate the aforementioned symptoms, including neurological and behavioral manifestations. For the diagnosis of HIT, consumption of histamine-rich foods must coincide with DAO deficiency; otherwise, the condition may be more accurately classified as histamine intoxication [29]. The role of mast cells in brain inflammation and autism spectrum disorder has also been highlighted in expert discussions and presentations [40]. The author notes that very similar symptoms are also observed in PTSD (Mental Health America. *What are the symptoms of PTSD?)* [8], suggesting that experienced trauma and intense stress may have activated and sensitized mast cells [41], potentially leading to MCAS, HIT, and/or reduced DAO enzyme production. This hypothesis is promising but warrants further investigation in larger studies.

Localization and Biology of Mast Cells: Their Role in the Regulation of Inflammation and Neurotransmission

Mast cells (MCs), discovered 140 years ago by Paul Ehrlich, are tissue-resident cells found in various organs [42]. Mast cells originate in the bone marrow and circulate in the blood as immature precursors. They complete their differentiation only after homing to target tissues, typically localizing in perivascular regions on the abluminal side of the vascular endothelium [43]. This strategic positioning allows them to interact with other cell types, the extracellular matrix, and the vasculature. Mast cells are also capable of migrating from the blood into the brain under both physiological and pathological conditions [44].

Mast cells play a key role in host defense, acting as one of the first responders of the immune system and initiating immune responses—particularly at sites of contact with the external environment, such as the skin, mucous membranes (e.g., nasal mucosa), respiratory tract (e.g., lungs), and gastrointestinal tract (e.g., intestines). They are located in close proximity to peripheral nerve endings in various tissues, as well as in the heart and brain. Within the brain, mast cells are found in multiple regions, including: near the blood–brain barrier (in areas of increased permeability, suggesting a potential role as sentinels in pathogen responses) [45], the choroid plexus and the protective membranes of the brain and spinal cord, the layers that surround and protect the central nervous system (the meninges) [23], [24]. They are also present in the hypothalamus, where they may influence emotional regulation, appetite, and stress responses, suggesting a potential modulatory role on the HPA axis (hypothalamus–pituitary–adrenal) [46]. Stress, infection, autoimmune diseases, or neuroinflammatory conditions,

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may promote mast cell activation and recruitment within the central nervous system [25], showing the relationship and involvement of mast cells in the brain, including multiple sclerosis [47].

Mechanisms of Mast Cell Activation

Mast cells are key first responders to most harmful or extreme stimuli (stressors), i.e., those that could potentially compromise the biological integrity of the organism, providing immediate defense, stress response, repair, and survival mechanisms. Their role as the "first link in the immune response chain" is underscored by their strategic localization in tissues near blood vessels, nerve endings, and mucosal surfaces. Mast cells express receptors (e.g., FcεRI for IgE) that allow for rapid recognition of pathogens or allergens. Immune activation can occur through IgE-dependent mechanisms or independently of IgE, as mast cells are also sensitive to external stressors, including biological, chemical, and physical factors, as well as internal stimuli such as stress, emotions, and hormones [48].

IgE-mediated triggers: seemingly harmless antigens, including many present in foods (e.g., proteins, eggs, nuts, wheat), medications (e.g., penicillin), inhalants (e.g., grass and tree pollens, house dust mites, animal dander), and contact allergens (e.g., latex, detergents, cosmetics, preservatives) can elicit IgE-mediated MCs activation [49].

Biological triggers:

Infections (viral, bacterial, parasitic), including COVID-19, Epstein-Barr virus (EBV, mononucleosis), and Lyme disease, can disrupt immune homeostasis and dysregulate mast cells [42], [50].

Dental caries, pulpitis, periapical periodontitis, periodontal disease, peri-implantitis, and other chronic oral infections [33].

Fungal exposure and mold infections can also act as biological triggers [51].

Chemical triggers:

Toxins (e.g., fire ant venom, hymenoptera toxins, mycotoxins), poisons, opioids, alcohol, and certain odors can directly or indirectly activate mast cells [52].

Drug-induced triggers: Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen) [53], opioids [54], certain antibiotics (e.g., vancomycin) [55], anesthetics [56], [57], [58] and contrast agents can induce mast cell degranulation [59], [60]. Personalized approach is recommended to address drugs inducing MCs activation [61].

Food allergens and intolerances: Gluten, dairy, histamine, biogenic amines, and sulfites can also stimulate mast cells via non-IgE mechanisms [62].

Environmental and toxic exposures: Heavy metals (e.g., aluminum, mercury) [48], [63], some dental materials (acrylic, metal alloys (e.g., nickel-containing fillings), cements [33], orthopedic and dental implants constructed from metal alloys or IV- or V-generation titanium are subject to corrosion and a biological reaction known as tribobiocorrosion [63], [64], microplastic [65], [66], mold, and pesticides often provoke chronic inflammation and can "prime" the immune system for increased mast cells reactivity [67], [68].

In same cases, vaccination can trigger immune reactions ranging from mild local inflammation to allergic responses. Certain vaccine components, such as adjuvants containing aluminum salts, may transiently interact with the immune system to enhance antigen presentation. In individuals with pre-existing hypersensitivity conditions, immune responses may be more pronounced, [68], [69], [70]. There is a distinction between oral ingestion of heavy metals and direct intravenous exposure [71] in relation to ASD, discussed in media commentary by Robert F. Kennedy Jr., Secretary of the U.S. Department of Health and Human Services, among others [72], [73], [74], [75].

Physical triggers:

Temperature changes excessive heat (including sunlight) or cold, dry and cold air to breathe, intense light, noise (including constant background noise from AC units, devices, or servers), pressure or constriction (e.g., shoes, elastic bands in socks or underwear), physical exertion (intense exercise, physical urticaria) can all activate MCs [76].

Mechanical factors in the oral cavity can also play a significant role. For example, chronic pressure or irritation caused by poorly fitting dentures, dental crowns, orthodontic appliances, occlusal overload, or persistent soft tissue trauma can trigger sterile inflammation and neurogenic signaling (including the release of neuropeptides, particularly substance P and calcitonin gene-related peptide (CGRP) [33].

Electromagnetic fields, radiation, ionizing radiation [77], and vibrations [78], [79], [80].

Stress and internal factors:

- Physical or psychological stress, anxiety, trauma, and fatigue can activate mast cells [81], [67]. Acute short-term stress may transiently suppress mast cell degranulation via epinephrine and glucocorticoid cortisol, but chronic stress destabilizes this system, increasing mast cell numbers and reactivity [82]. Animal models demonstrate increased mast cell density and activity in the skin and gut under chronic stress, while in humans, chronic stress exacerbates allergic and gastrointestinal conditions (e.g., urticaria, IBS) in which histamine plays a key role [83].
- Oxidative stress and neurohormonal triggers: Certain neurotransmitters and neuropeptides—including Substance P, Compound 48/80 [46], [84], adrenomedullin,

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bradykinin, Calcitonin Gene-Related Peptide (CGRP), Corticotropin-Releasing Hormone / Factor (CRH/CRF), enkephalins/endorphins, 17β-estradiol, HK-1, Mastoparan, Nerve Growth Factor (NGF), Neurotensin (NT), Parathyroid Hormone (PTH), Stem Cell Factor (SCF), Vasoactive Intestinal Peptide (VIP), urocortin, IL-1, and IL-33—can stimulate mast cells [81], [84].

- Hormonal triggers: Hormonal fluctuations, including the menstrual cycle, pregnancy, and menopause, can influence mast cell activity. Estradiol, for example, can stimulate mast cell degranulation [85].
- Gastrointestinal triggers: The gut contains a high density of mast cells, making it a major site for activation. Conditions such as SIBO, dysbiosis, or leaky gut can excessively activate mast cells [86], [87].
- Impaired histamine metabolism (e.g., DAO deficiency) and elevated biogenic amines (tyramine, putrescine) may enhance mast cell activation by reducing histamine degradation, increasing gut permeability, and amplifying inflammatory signals or pseudoallergic reactions [88], [89].
- Dietary triggers: Additives, preservatives, and colorants in processed foods can provoke pseudoallergic mast cell reactions. Elimination diets that exclude gluten, lactose, casein, or caffeine are commonly used in individuals with ASD [90]. Increasing attention is also given to low-histamine diets (avoiding aged cheeses, fish, tomatoes, fermented foods) in children with impaired DAO/HNMT activity.

Mediator release by mast cells occurs very rapidly, whereas prolonged activation leads to de novo synthesis of mediators [91]. In many situations, degranulation does not result in mast cell death; these are resilient and multifunctional cells capable of surviving activation and responding repeatedly to subsequent stimuli [92]. Mast cell degranulation releases, among other mediators, histamine, cytokines (e.g., TNF-α, IL-6), and additional pro-inflammatory mediators, thereby affecting the immune, gastrointestinal, respiratory, and nervous systems, as well as neurological functions such as memory and stress responses [93]. Consequently, mast cells play a crucial role in regulating inflammation and neurotransmission, i.e., neuroimmune communication. They act as sentinels of immunity, but when overactive, they can be harmful [49].

Often, it is not a single factor but a combination of the elements described above that leads to the development of Mast Cell Activation Syndrome (MCAS). For instance, in individuals with a genetic predisposition, a viral infection combined with stress and food intolerance may together "overload the system," potentially triggering even anaphylactic shock [49]. The first-line treatment for anaphylaxis is epinephrine (adrenaline), which stabilizes mast cell membranes and rapidly inhibits further mediator release [94]. Cortisol, which rises during stress, exerts immunosuppressive effects by reducing mast cell activity, inhibiting pro-inflammatory cytokine production, and limiting enzyme release. Synthetic glucocorticoids, analogs of cortisol, are used to treat allergic diseases precisely because they block mast cell activation [95]. However, chronic stress (prolonged elevation of cortisol and adrenaline) can gradually dysregulate the immune system. In some individuals under chronic stress, mast cells become hyperreactive or increase in number, which may exacerbate allergic reactions [96].

- Acute stress → epinephrine and cortisol → inhibition of mast cells (reduced histamine release).
- Chronic stress → potential dysregulation of the system and secondary mast cell hyperreactivity → increased histamine release.

Chronic Stress and KIT Mutation, Low-grade Inflammation

Errors in DNA repair or prolonged exposure to oxidative stress can lead to a KIT D816V mutation in exon 17 of the KIT gene in mast cells [97A]. This mutation results in constitutive, SCF (Stem Cell Factor)-independent activation of the receptor, leading to excessive proliferation and activation of mast cells [98]. The KIT D816V mutation is characteristic of systemic mastocytosis (SM), which involves increased mast cell numbers in multiple tissues and can induce symptoms arising from excessive mediator release (e.g., histamine), similar to those observed in MCAS (mast cell hyperreactivity). The benefits of localized mast cell activation during infection contrast sharply with the detrimental effects of systemic activation, which reduces survival in sepsis induced by cecal ligation and puncture (CLP) [99]. Studies show that systemic mast cell degranulation significantly worsens survival during sepsis [100].

Chronic stress → KIT mutation → continuous mast cell proliferation + lowered activation threshold → easier mediator release → clinical manifestations of MCAS/mastocytosis → some overlapping symptoms of ASD [25], [30].

This explains why mast cells can become more sensitive and active with age, while mechanisms controlling inflammation weaken. Studies show an age-dependent increase in mast cell numbers in the gut and brain [101], accompanied by chronic low-grade inflammation, also referred to as "inflammaging." The so-called "low-grade inflammation of histamine" is a chronic [102], mild inflammatory state in which histamine is continuously released by mast cells, most often in adipose tissue or the lungs, for example in obesity, chronic metabolic diseases, or allergies [103]. It does not produce dramatic symptoms of acute inflammation but contributes to long-term health problems.

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Mast Cells, Meta-Inflammation and Obesity in ASD

Obesity is now widely viewed as a long-term inflammatory and immunometabolic condition linked to greater mast cell activity and a higher density of these cells in adipose tissue [102], along with increased histamine release [104], oxidative stress and endothelial dysfunction [105], as well as adipose tissue–driven "meta-inflammation" mediated by pro-inflammatory cytokines and adipokines such as leptin [106], [107]. These processes may contribute to asthma exacerbation, insulin resistance, hypertension, atherosclerotic changes, gastrointestinal inflammation [87], increased stroke risk [108], [101], and broader metabolic, cardiovascular, and immunological complications [109]. Histamine signaling further influences appetite regulation and fat metabolism through central H1/H3 (in brain) receptor pathways affecting decrease satiety at the same time increase appetite and have influence on energy expenditure [110], as well as peripheral H2 (in stomach and adipose tissue) receptor pathways involved in lipolysis (fat breakdown) and metabolic regulation like: gastric juice production and insulin secretion [111]. The relationship between obesity and histamine is well known and studied [112], [113]. Experimental studies indicate that pharmacological stabilization or inhibition of mast cells can reduce inflammation of adipose tissue and improve metabolism of glucose [114], supporting the concept that mast cell-targeted interventions may represent a promising therapeutic strategy in obesity-associated inflammatory and metabolic disorders [115].

Increased rates of overweight and obesity have been observed in children with ASD, potentially reflecting complex interactions between neuroinflammation, altered stress responses, sensory-related eating behaviors, gastrointestinal dysfunction, and metabolic dysregulation. Emerging evidence suggests that chronic mast cell activation and histamine-mediated inflammatory pathways may also contribute to these metabolic abnormalities [116], [117], [118], [119]. Mast cells are anatomically and functionally coupled to sensory nerves, autonomic nerves, enteric nerves, meningeal structures, vagus-nerve signaling, and brain-associated neuroimmune niches. They respond to neuropeptides, neurotransmitters, glutamatergic signals, stress mediators, and neural injury signals, while neurons and glial cells respond to mast cell-derived histamine, tryptase, cytokines, prostaglandins, leukotrienes, and extracellular vesicle cargo. Mast cells have therefore been conceptualized as signal converters between tissues and neurons [120]. Peripheral inflammation can also activate brain mast cells through vagus-nerve-dependent mechanisms involving glutamate and NR2B receptorsignaling [121], [122].

On the other hand peripheral inflammation can occur in the course of abdominal and visceral obesity. Of particular interest is the metainflammation that develops in the course of insulin resistance. As a result of the accumulation and subsequent hypertrophy of adipose tissue, inflammation develops. Cytokines (TNF-alpha, IL-6, MCP-1) are released, which leads to the activation of M1 macrophages. Cytokines block insulin signaling. This leads to increased release of free fatty acids and the development of hyperinsulinemia. This, in turn, causes lipogenesis and adipocyte hypertrophy. As a result, inhibition of lipolysis is impaired, leading to the development of systemic and organic insulin resistance. This results in the development of oxidative stress, leading to the development of numerous complications, including fatty degeneration of the bone marrow, which leads to decreased osteogenesis and increased lipogenesis (yellow bone). Mechanistically, the bone marrow functions as both a developmental origin and a target compartment for the organization of mast cells. Mast cells originate from hematopoietic stem and progenitor cells, with initial differentiation occurring within the bone marrow prior to progenitors entering the circulatory system and achieving full maturation in peripheral tissues. According to [123] adult mouse bone marrow contains mast cell progenitors capable of differentiating into mature mast cells, thus establishing a well-defined hematopoietic foundation for the replenishment and distribution of mast cells within tissues. The marrow niche is not merely a production site. It encompasses vascular sinusoids, endothelial cells, mesenchymal stromal cells, osteoblast-lineage cells, osteoclast-lineage cells, macrophages, adipocytes, extracellular matrix, cytokine gradients, and hematopoietic stem and progenitor cells, any of which may influence mast cell progenitor survival, migration, and maturation [124]. In cases of mast cell proliferative disease, marrow infiltration further exemplifies that mast cells can become integrated within the niche, thereby affecting bone, stromal, and hematopoietic processes [125].

In a physiological context, this axis links mast cell biology to the supply of progenitors, the competence of the marrow niche, tissue repopulation, clonalexpansion, skeletal turnover, and the remodeling of marrow adipose tissue. From a modeling perspective, bone-marrow coupling requires variables for progenitor abundance, progenitor egress, stromal support within the marrow, sinusoidal trafficking, marrow adiposity, clonal mast cell burden, and feedback mechanisms from peripheral tissue demand to marrow output. Tissue injury activates mast cells and neurons in parallel; neural mediators further stimulate mast cells; mast cell mediators sensitize sensory endings, autonomic circuits, enteric nerves, meningeal structures, and brain-associated neuroimmune compartments; the resulting pain, itch, nausea, vascular reflex, thermoregulatory response, cognitive change, or autonomic output feeds back onto tissue physiology and inflammatory behavior. This is a bidirectional tissue-neural-brain amplification loop rather than a local sensory annotation from the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Congress of Neurological Surgeons

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(CNS), European Society of Neuroradiology (ESNR), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Stroke Organization (ESO), Canadian Interventional Radiology Association (CIRA), Society of NeuroInterventional Surgery (SNIS), Society of Interventional Radiology (SIR), Society for Cardiovascular Angiography and Interventions (SCAI), and World Stroke Organization (WSO); [126].

Mast Cells in the Brain and Neuroinflammation

Mast cells in the brain are a growing focus of interest in neuroimmunology [127]. Their presence is particularly studied in the context of neurodegenerative diseases such as Alzheimer's disease [128] and autism spectrum disorder (ASD) [30], where they may contribute to the development of neuroinflammation, in line with immunological hypotheses of these conditions. Their significant role has also been observed in multiple sclerosis and migraine [45], and understanding the pathophysiology of this phenomenon suggests that mast cell-stabilizing agents could be a promising therapeutic strategy for migraine [84]. A large body of research indicates that inflammatory processes in the brain play a key role in the development of neuropsychiatric disorders. During stress, the hypothalamus releases corticotropin-releasing factor (CRF), which, together with neurotensin (NT), can activate mast cells present in the brain. In response, these cells release inflammatory (e.g., histamine) and neurotoxic mediators, leading to blood-brain barrier (BBB) disruption, microglial activation, and the formation of inflammatory foci [129]. Consequently, mast cells may contribute to symptoms such as "brain fog," headaches, or ASD-related behavioral and cognitive disturbances, which can be exacerbated by stress [23], [24].

Children with ASD often display difficulty regulating anxiety and exhibit exaggerated responses to subtle triggers. Environmental stressors can activate mast cells, which then influence microglia, resulting in abnormal synaptic pruning and disrupted neuronal communication [25], [48], [67]. Notably, children with ASD have been found to have significantly higher serum levels of CRF and NT compared to controls, further supporting their involvement in autism pathogenesis [12], [26]. Research indicates that carbon dioxide [130] and vitamin D3 can inhibit mast cell degranulation and histamine release, offering promising prospects for individuals with MCAS [131], [132]. Findings from Professor Afaf El-Ansary's research, which show the beneficial effects of vitamin D3 supplementation in individuals with ASD, further support the hypothesis that overactive mast cells and the histamine they release may play a significant role in the development of autism symptoms, influencing neuroinflammatory processes in the brain [133], [10].

Mast Cells, Glial Cells, and Neuroinflammation: Shared Mechanisms

Mast cells belong to the effector cells of the innate immune system, and it is they—not microglia—that act as the "first responders" to injury or activating stimuli [134]. Mast cells can serve a protective role, responding immediately and limiting cellular disturbances and brain damage by releasing both cytotoxic substances and factors that support regeneration. However, their chronic activation carries the risk of severe, destructive consequences [135]. Allergens, neuropeptides, stress, or toxins can activate mast cells to degranulate, releasing mediators such as histamine, which leads to blood–brain barrier (BBB) disruption and microglial activation, ultimately promoting neuroinflammation [29]. Glial cells, including microglia, produce pro-inflammatory substances that strongly influence central nervous system function. They modulate neuropathic pain, seizure activity, and neuronal damage. Glial cells communicate with other non-neuronal cells, primarily mast cells, and respond to their pro-inflammatory signals, which can exacerbate symptoms of neurodegenerative diseases, accelerate disease progression, and increase pain perception.

Astrocytes involved in chronic inflammatory disorders, including multiple sclerosis and ASD, are often found near mast cells, sharing the perivascular space [136], [137]. Both mast cells and glial cells can initiate endogenous regulatory mechanisms in response to chronic inflammation [138]. Consequently, CNS neurons may be "attacked" by a network of microglia–astrocytes–mast cells, particularly when regulation of these non-neuronal cells (e.g., mast cells) is insufficient due to excessive or chronic exogenous and/or endogenous stimuli and limited capacity to suppress their activity [138]. In neuroinflammatory disorders, the immune response can destructively affect nervous system cells and tissues following Karolinska Institute [139]. Increasing evidence points to interactions between mast cells and glial cells, offering new opportunities for therapies targeting neuroinflammation. Such strategies could involve selective modulation of mast cell activity, which plays a role in regulating neuronal hypersensitivity in both the peripheral and central nervous systems [140].

Histamine as a Hormone/Neurotransmitter – a Mediator of Coagulation, Interacting with H1–H4 Receptors in the Immune, Respiratory, Digestive, and Nervous Systems

Histamine is an organic compound belonging to the biogenic amine group and plays a key role in human physiology. It was first chemically characterized in 1910 by George Barger and Henry H. Dale during their studies of ergot alkaloids, where its pharmacological properties were first described [141]. Dale's subsequent research

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in the 1920s demonstrated the profound physiological effects of histamine, particularly its role in smooth muscle contraction, vasodilation, regulation of blood pressure, and stimulation of gastric acid secretion, leading to the concept of histamine as a biologically active mediator in the body [142], [143]. Later work by Ash and Schild contributed to further understanding of the pharmacology of histamine receptors, including the distinction of H1 receptor-mediated effects and the development of the antihistamine theory [144]. Histamine has proven to be crucial in allergies, anaphylactic reactions, stomach ulcers, and chronic inflammation. "The histaminergic system modulates various processes, including wakefulness, feeding, learning, and memory consolidation." [145]. It is a biologically active substance, often classified as a tissue hormone or neurohormone, because it regulates multiple physiological processes and systems. Chemically, histamine is 2-(1H-imidazol-4-yl) ethylamine [146], produced from the amino acid histidine through the action of the enzyme histidine decarboxylase (HDC) [147]. Structurally, histamine consists of an imidazole ring attached to an ethylamine chain, with the molecular formula $C_5H_9N_3$. Histamine functions as a signaling molecule in intercellular communication and is recognized as one of the main mediators of allergic reactions and inflammatory processes [148].

Sources of Histamine in the Body

Endogenous production :

Histamine is produced endogenously, mainly by immune system cells such as mast cells and basophils, and it is also synthesized by macrophages. It is stored in an inactive form within the granules of mast cells and basophils until various stimuli trigger its release, such as allergens, strong sensory or environmental stimuli, injuries, or infections [149].

In the central nervous system, histamine is produced by histaminergic neurons as well as perivascular mast cells, while the brain endothelium also serves as a physiological reservoir for histamine [150].

Certain gut bacteria, including strains from the genera Lactobacillus (e.g., L. reuteri), Enterococcus, Morganella morganii, and Klebsiella, can also produce histamine in the intestines, especially in the presence of a high-histidine diet. This microbial histamine production can irritate the intestinal mucosa, causing diarrhea and abdominal pain [151], [147].

Histamine is produced when the amino acid histidine undergoes decarboxylation, a reaction driven by the bacterial enzyme named histidine decarboxylase (HDC). In the intestinal microbiota, this process may lead to excessive histamine formation, which in some cases is associated with symptoms of histamine intolerance (HIT) [147]. This pathway can activate immune responses, including inflammation and allergy-like effects, as well as affect the gastrointestinal system. After entering the bloodstream, elevated histamine levels may trigger reactions similar to HIT—such as headaches, skin flushing, and pruritus—often referred to as pseudoallergic responses [152], [153].

Factors that increase endogenous histamine production:

- Some medications can strongly inhibit the activity of the DAO enzyme, which may lead to the development of HIT. Such medications include aspirin (acetylsalicylic acid), nonsteroidal anti-inflammatory drugs (NSAIDs), morphine, clavulanic acid, acetylcysteine, cimetidine, and isoniazid [154].
- Since many of these medications are administered to children for various illnesses [155], [156], it is also important to consider the possibility of DAO inhibition in young children, especially when medications are used long-term or for chronic conditions. However, there is currently no conclusive evidence confirming this effect. Nevertheless, some of these medications are excluded in low-histamine diets for children [157].
- A diet rich in histidine
- Imbalances in gut microbiota (dysbiosis)
- Certain gastrointestinal disorders (e.g., SIBO–small intestinal bacterial overgrowth) [152].

Exogenous sources:

- Histamine is also supplied through food, especially fermented, pickled, and moldy products, or those that undergo bacterial fermentation (e.g., improperly stored fish). Excess dietary histamine can lead to food poisoning [152], [158]. Foods and beverages high in histamine include:
- Yeast and yeast extracts
- Aged cheeses such as camembert, parmesan, and blue cheeses
- Fermented dairy products
- Alcohol, especially red wine and beer, and soy sauce
- Canned fish, such as mackerel and tuna, and other canned products
- Sauerkraut, pickles, and other fermented vegetables
- Smoked products, such as sausage, ham, bacon, and salami
- Seafood and shellfish, edible insects
- Chocolate and nuts
- Carrageenan, monosodium glutamate (MSG)
- Certain fruits: strawberries, citrus, pineapple, ripe bananas, raspberries, kiwi
- Certain vegetables: tomatoes, avocado, eggplant, spinach

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- Vinegar and vinegar-containing products: ketchup [159], mayonnaise, mustard, pickles [160], [161], [162], [163].
- Foods containing other biogenic amines, such as tyramine or putrescine, which often occur alongside histamine, can competitively inhibit the activity of the DAO enzyme. As a result, even normally tolerated amounts of histamine may trigger symptoms of HIT [154], [164]. Examples of such foods include fish, fermented sausages, and sauerkraut [165], [166].

Histamine released from mast cells, as well as that obtained from food, accumulates in the body, which can lead to exceeding its optimal levels and intensifying its effects, especially when the DAO enzyme, responsible for its breakdown, is at low levels. This situation results in so-called "histamine excess" in the body, which can have clinical relevance in certain inflammatory conditions or in HIT. To diagnose HIT, the consumption of histamine-rich foods must be accompanied by a DAO deficiency [164]. Otherwise, the condition should be diagnosed as histamine poisoning [153].

Functions of Histamine – Positive and Negative Effects

Histamine, in appropriate amounts, is essential for proper bodily function and affects multiple systems [154]:

- **Immune and inflammatory system:** Acts as a mediator of immune responses and allergic reactions, releasing other pro-inflammatory substances via its receptors [148], supports the body's "first-line defense" against bacteria, viruses, parasites and other enemies [167].
- **Nervous system:** Functions as a neurotransmitter; through H1 and H2 receptors, it regulates the sleep-wake cycle (e.g., promoting wakefulness) [9], [168] and stress [169]. By modulating microglial function, histamine indirectly affects neuronal survival and functions such as memory [170] and cognitive processes [171]. In the brain, it acts on H3 receptors, modulating release of other neurotransmitters and inflammatory states [172], [20], [21].
- **Digestive system:** Stimulates gastric acid production, aiding digestion [173].
- **Respiratory system:** Involved in the pathogenesis of bronchial asthma [174], [175].
- **Circulatory system:** Regulates cardiovascular function and promotes blood coagulation [176], [177], [178], [179]. Histamine has a direct and significant effect on the heart, as H1 and H2 receptors are physiologically present in the myocardium, conduction system, and coronary vessels, affecting heart rate, blood pressure, and coronary contraction [180], [181].
- **Other roles:** Influences fetal development, smooth muscle contraction (intestine, uterus, bronchi), endometrium [182], menstrual pain [183], thermoregulation, appetite control, and mediates anaphylactic reactions [168], [184], [185], [186], [187], [188].
- **Wound healing and tissue repair**: Histamine increases vascular permeability to allow immune cells and nutrients to reach damaged tissue. Can promote angiogenesis and tissue remodeling [189], [190], [191], [192].

However, in excessive amounts histamine is harmful and can lead to frequent, sometimes health-threatening multisystem symptoms. Elevated histamine levels may contribute indirectly to the activation of the coagulation cascade, which can increase the risk of thrombus formation and disseminated intravascular coagulation (DIC). As a consequence, this may be associated with higher blood pressure and serious cardiovascular complications such as stroke, myocardial infarction, and tachycardia. At the same time, histamine excess can increase vascular permeability, which may result in hypotension, edema, and urticaria, as well as greater sensitivity to pain. It is also linked with a range of allergic-type manifestations, including pruritus, skin rashes, sneezing, watery rhinorrhea, and asthma. In the gastrointestinal tract, high histamine levels may lead to hyperacidity of the stomach, gastroesophageal reflux, nausea, vomiting, and diarrhea. Other possible systemic effects include insomnia, chronic fatigue, muscle cramps, and hair loss, as well as a tendency toward chronic neuroinflammatory states. In addition, associations have been reported with obesity, rheumatoid arthritis, and various chronic inflammatory conditions.

This suggests that excess histamine in the body may exacerbate symptoms of ASD, ADHD, and PTSD. At the same time, exhaustion of coagulation factors and platelets increases the risk of bleeding, which may occur in sepsis, severe infections, malignancies, pregnancy complications, and similar conditions [12], [25], [26]. Similar symptoms were observed in a VAERS-based study from 2005 following administration of a combined tetanus-containing vaccine with hepatitis B vaccination [69], [70]. These findings suggest the possibility that certain components, for example, may chronically stimulate mast cells to release histamine.

After activation (degranulation), mast cells release inflammatory mediators such as tryptase, heparin, cytokines, and histamine. Histamine not only performs the functions described above, but also "calls for reinforcements" through histamine receptors H1, H2, H3, and H4, which may lead to the release of cytokines (e.g., TNF-α, IL-1, IL-4, IL-6, IL-8, IL-10), thereby initiating and shaping the entire immune response in both allergic reactions, infections, and tissue repair processes. If this process becomes amplified, inflammatory reactions within tissues may activate additional mast cells, leading to the release of further amounts of histamine. This can

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contribute to a vicious cycle known as a "histamine storm," occurring in organs such as the lungs, intestines, heart, and brain, and may result in increased thrombus formation and multi-organ inflammation—a mechanism that can lead to systemic inflammatory response syndrome (SIRS) and, in the most severe cases, to sepsis [11], [193], [194].

Histamine Receptors H1, H2, H3, and H4 on Mast Cells and on Histaminergic Neurons

Histamine functions both as a hormone and a neurotransmitter. It influences the permeability of the blood–brain barrier (BBB) and exerts its effects through four types of receptors (H1–H4) located in various tissues, including the brain [195]. This widespread distribution explains the pleiotropic effects of histamine, ranging from allergic and neurological responses to regulatory functions [154].

The H1 receptor is expressed, among others, in vascular endothelium, the lungs and cardiac muscle, smooth muscle (including bronchi, gastrointestinal tract, and uterus), the brain, neutrophils, and macrophages. Upon activation by histamine, H1 receptors contribute to responses such as smooth muscle contraction (e.g., bronchoconstriction leading to asthma symptoms and uterine contractions during menstruation), as well as relaxation of vascular smooth muscle, resulting in vasodilation and increased vascular permeability (edema, erythema). H1 receptors play a key role in allergic reactions and are also involved in myocardial inflammation. In the central nervous system, H1 receptors are predominantly postsynaptic and mediate the excitatory effects of histamine, including wakefulness and stress responses [196], [180].

The H2 receptor is expressed in the stomach and cardiac muscle, as well as in T lymphocytes and basophils. Upon activation by histamine, it stimulates gastric acid secretion, contributes to the regulation of cardiac rhythm, and participates in myocardial inflammation [181]. In the central nervous system, H2 receptors are predominantly postsynaptic and modulate neurotransmission and synaptic plasticity. Excessive activation of H2 receptors by histamine may disrupt these processes, leading to exaggerated long-term potentiation (LTP), impaired regulation of learning and memory, and potentially contributing to difficulties with attention, hyperexcitability, sleep disturbances, and anxiety [197].

The H3 receptor is virtually absent on mast cells and does not play a significant role in mast cell degranulation. In contrast, it is highly expressed in the central and peripheral nervous systems. In the brain, H3 receptors function primarily as presynaptic autoreceptors, inhibiting the release of multiple neurotransmitters, including acetylcholine, dopamine, serotonin, noradrenaline, and histamine itself. H3 receptor activation also reduces GABAergic tone, thereby promoting glutamatergic hyperactivity and excitotoxicity, which may further disrupt neurochemical balance. Through these mechanisms, H3 receptors influence cognitive processes, attention, behavior, and the regulation of the sleep–wake cycle. Pharmacological blockade of H3 receptors increases synaptic availability of histamine and other neurotransmitters [198], [9].

The H4 receptor is expressed in eosinophils, basophils, mast cells, T and B lymphocytes, neutrophils, and dendritic cells, and is also present in peripheral tissues, bone marrow, and the spleen. Upon activation, H4 receptors regulate leukocyte migration (chemotaxis) and activation of inflammatory cells, playing an important role in allergic, inflammatory, and autoimmune diseases [199].

Histamine stimulates **H1 or H2 receptors on neurons** → neurons may alter signaling to microglia → microglia release cytokines (IL-1β, TNF-α, IL-6), which leads to a local inflammatory state.

Chronic excess of histamine → excessive stimulation of **H1 and H2 receptors** → neuronal hyperexcitability and disturbances of synaptic plasticity, neuroinflammation, and impaired brain regeneration → possible symptoms of excessive brain activity, so-called "burnout," "brain fog," sleep disturbances, cognitive fatigue, impaired concentration, anxiety, hyperexcitability, and sensory hypersensitivity [200].

Histamine stimulates **H3 receptors on neurons** → inhibits the release of neurotransmitters: dopamine, serotonin, acetylcholine, and histamine from the neuron → decrease in GABA ↓ → increase in glutamate and excitotoxicity ↑ → neuroinflammation → potentially contributes to the development of depression, anxiety, autism, Alzheimer's disease, Parkinson's disease, and others ↑

[201], [202].

In the central nervous system, the histaminergic system consists of the cell bodies of histaminergic neurons located in the posterior hypothalamus, from where they project to the brainstem, telencephalon, and spinal cord [203], [204]. Therefore, it is likely that histamine plays a key role in regulating the activity of all regions of the brain [205]. When mast cells are excessively activated and repeatedly stimulated (e.g., in mast cell activation syndrome—MCAS), they release excessive amounts of histamine, producing symptoms similar to those observed in HIT. In both conditions, elevated histamine levels, through excessive autocrine and paracrine stimulation of histamine receptors H1–H4, may negatively affect the functioning of the immune, gastrointestinal, cardiovascular, respiratory, reproductive, and nervous systems [198], [154].

First Antihistamine Drugs (anti-H1, H2, H3) and Mast Cell-Modulating Substances

The Nobel Prize for the discovery of the first

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antihistamine drug was awarded to Daniel Bovet in 1957. This Swiss–Italian pharmacologist discovered, in 1937, a substance capable of blocking the action of histamine, which constituted a major breakthrough in the treatment of allergic reactions (Nobel Prize, 1957) [206]. Another Nobel Prize in this field was awarded to Sir James W. Black in 1988. The British pharmacologist recognized the immense therapeutic potential of receptor-blocking drugs and, in 1964, developed the first clinically useful β-adrenergic receptor antagonist, propranolol. This class of drugs is now widely used in the treatment of coronary artery disease (including angina pectoris and myocardial infarction) as well as arterial hypertension. In 1972, Black identified and characterized a new class of histamine receptors—the H2 receptors—and subsequently developed the first clinically effective H2 receptor antagonist, cimetidine, which revolutionized the treatment of peptic ulcer disease and gastroesophageal reflux disease (GERD) (Nobel Prize, 1988) [207]. First H1 antihistamines (allergic / "classic" antihistamines), early discovery (1930s–1940s).

The first clinically useful H1 antihistamines emerged in the 1940s. First widely used modern H1 antihistamines became the "first generation", next „second generation" and now is „ third generation". First clinically successful H2 blocker was introduced ~1976. H3 receptors are mainly presynaptic autoreceptors in the CNS regulating histamine release were discovered: late 1980s, but first H3 drug was delivered in 2016. Mast cell stabilizers (Cromolyn, Ketotifen, biologics like Omalizumab) are know from 1960s and developing until present [208], [209]. In the past, the classical therapeutic strategy for treating various histamine-mediated diseases involved the combination of H1 and H2 receptor antagonists, which demonstrated higher efficacy compared with the use of either antihistamine alone. Recent studies further suggest a fundamental role of histamine and H1R and H2R receptors in the development of anxiety disorders, osteoarthritis, and post-exercise hypotension [210], [211], [212], [213]. Today, a wide range of antihistamine agents is available. A medically accurate list of antihistamine drugs, categorized according to generation and receptor selectivity (H1, H2), as well as dietary supplements of clinical and scientific relevance, is presented below:

In clinical practice, it may be beneficial to consider therapeutic strategies beyond receptor blockade, particularly

Table 1: A medically accurate list of antihistamine drugs, categorized according to generation and receptor selectivity (H1, H2), as well as dietary supplements of clinical and scientific relevance.

H1 antihistamines – first generation (cross the blood–brain barrier, exert sedative effects) **Effects:** strong central nervous system activity, sedation/drowsiness, anticholinergic effects, used: allergy, nausea, motion sickness	**Diphenhydramine** (for example: Benadryl) **Clemastine** (Tavegyl) available in oral and intravenous formulations **Dimetindene** (Fenistil) **Hydroxyzine** (Atarax) **Promethazine** **Chlorpheniramine** **Cyproheptadine** (also a serotonin antagonist)
H1 antihistamines – second generation (less penetration into the CNS, less sedative) **Effects:** selective blockade of peripheral H1 receptors	**Loratadine** (Claritine) **Cetirizine** (Zyrtec) **Levocetirizine** (Xyzal) **Desloratadine** (Aerius) **Fexofenadine** (Telfast) **Rupatadine** (Repeller) also acts on PAF (plateletactivating factor)
H1 antihistamines – third generation (active metabolites, highly selective) **Effects:** optimal safety profile, minimal sedative effects	**Bilastine** **Levocetirizine** **Desloratadine**
H2 antihistamines (primarily used in gastric diseases, but also of immunological relevance) **Effects:** block **H2 receptors** on, among others, T lymphocytes, mast cells, and in the stomach, gastric acid suppression	**Famotidine** - available in oral and intravenous formulations **Cimetidine** **Ranitidine** (withdrawn in many countries) **Nizatidine**
H3 antihistamines Currently, the only H3 drug approved for clinical use is **Pitolisant**. **Effects:** primarily modulate the nervous system by increasing or inhibiting histamine release in the brain, thereby affecting sleep-wakefulness, attention, and cognitive functions, using: narcolepsy, sleep disorders	**Pitolisant (Wakix®)** – primarily used in the treatment of **narcolepsy with cataplexy and excessive daytime sleepiness**. **Ciproxifan** – investigated experimentally for the therapy of **cognitive and neurodegenerative disorders** (e.g., Alzheimer's disease). **Thioperamide** – mainly used in **preclinical research**, rarely in clinical practice. **GSK189254** – under investigation in the context of **sleep disorders and cognitive functions**. **BF2.649** – an experimental **agonist/antagonist** studied in **neurological research**.

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Drugs and supplements indirectly affecting histamine (clinically relevant) **Mechanism of action:** mast cell stabilization and enzymatic degradation of histamine	**Mast cell stabilizers:** **Quercetin** (regulatory effects on activation mast cells) **Cromolyn sodium** (cromoglicate) (inhibits mast cell degranulation, for symptomatic relief) **Ketotifen (**H1 antagonist + mast cell stabilization**)** **Lodoxamide** (eye drops) **Omalizumab** **Olopatadine** (often in eye/nose drops) **Azelastine (**mainly nasal spray, partially stabilizes MCs) **Luteolin (**strongly inhibits mast cell degranulation, reduces neuroinflammation**)** **Apigenin** (inhibits mast cell activation in-vivo) for example Chamomile (Matricaria chamomilla) **Baicalin** (inhibits mast cell activation in -vivo) **Boswellic acids** (frankincense) exhibits mast cell-modulatory properties in experimental studies) **Moringa oleiferan** (inhibits mast cell activation in -vivo) **Vitamin D3** (regulatory effects on activation mast cells) **Nicotinamide (vitamin B3)** **Vitamin C (**accelerates histamine breakdown, inhibits mast cell degranulation, supportive in neuroimmunological disorders**)** **Enzymatic histamine degradation:** **Diamine oxidase (DAO)** – supplements supporting histamine metabolism
Clinically important note (especially in MCAS / POTS / HIT) **POTS** – Postural Orthostatic Tachycardia Syndrome	In clinical practice, a combination is often used: **H1 antihistamine** (e.g., cetirizine, loratadine) + **H2 antihistamine** (e.g., famotidine) + **Mast cell stabilizer** (e.g., cromolyn sodium)

in conditions characterized by persistent (chronic) or impaired histamine release. Ketotifen is a pharmacological agent with a dual mechanism of action, combining antihistamine activity at H1 receptors with mast cell stabilization [214]. This means that it not only blocks histamine receptors but also inhibits the release of histamine and other inflammatory mediators from mast cells. Olopatadine, used in topical preparations, also has a comparable pharmacological profile [215]. Mast cell stabilizers, such as sodium cromoglycate [216], also exert preventive effects by limiting mediator release without directly antagonizing histamine receptors [217]. The distinction between these mechanisms is clinically important because it reflects different therapeutic strategies: symptomatic blockade of histamine receptors is slightly different compared to the initial modulation of immune cell activity. Experimental evidence suggests that mast cell activity may not be regulated solely by receptor-mediated signaling and external factors but is also determined by the metabolic and bioenergetic state of the cell. Studies [218] involving redox-active compounds such as methylene blue and toluidine blue [219] have shown that modulation of cellular energetics can alter mast cell response in vitro. Furthermore, these studies revealed that these effects are reversible by glucose supplementation, suggesting a potential role for energy-dependent mechanisms in mast cell regulation. In this context, the mast cell hyper-responsiveness observed in mast cell activation syndrome (MCAS) may involve not only impaired immune signaling but also impaired metabolic control of the cells. These observations highlight a potentially under-explored aspect of mast cell biology and support the need for further systematic studies on the relationship between immune activation and cellular energetics in mast cell-related disorders, inflammation, neuroinflammation, ASD, ADHD, PTSD, obesity, etc.

Another substances which could be taken into consideration for future research for mast cells and histamine stabilization:

1. Extracts of Commiphora Myrrha may exert indirect inhibitory effects on MCs activation through modulation of inflammatory signaling pathways, as they demonstrated anti-inflammatory, antimicrobial, and antioxidant properties, mediated in part through the inhibition of pro-inflammatory cytokines and related signaling cascades [220], [221], [222].
2. Moringa oleiferan - Extracts from moringa leaves, seeds, and pods have been shown to: inhibit mast cell degranulation, reduce histamine release, inhibit the release of β-hexosaminidase (a marker of mast cell activation), reduce the secretion of IL-4 and TNF-α cytokines, mediators of late-phase allergic reactions. An inhibitory effect of ethanol extract from Moringa oleifera Lam. seeds on systemic and local anaphylaxis has also been observed. [223].
3. Saffron (Crocus Sativus) exhibits anti-inflammatory and antioxidant properties that may indirectly modulate mast cell–related inflammatory pathways [224].

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4. Boswellia Serrata exhibits mast cell–modulating properties primarily through inhibition of inflammatory lipid mediators (e.g., leukotrienes) and NF-κB signaling, rather than direct mast cell stabilization [225].
5. Limonene, as a component of citrus peel essential oils, has been suggested as part of a mixture of bioactive compounds that may modulate mast cell activation and histamine release, as observed in studies on lemon juice and peel extracts [226].
6. Creatine supplementation may reduce endogenous creatine synthesis, sparing methyl groups (SAM) and potentially increasing substrate availability for histamine degradation via HNMT [227], [228]. Creatine could be one of the metabolic modulators of histamine-driven inflammatory cascades in early sepsis [229], reducing also neuroinflamations [230].

creatine supplementation ↑ → SAMe ↑ → HNMT ↑ → histamine ↓ → neuroinflammation ↓

Children with congenital defects in creatine synthesis or transport have severe neurological symptoms and profound brain creatine depletion. It is clear that creatine plays a critical, yet under-appreciated, role in brain function. Creatine supplements are also taken by patients suffering from cerebral atrophy, muscular dystrophy, and neurodegenerative diseases [231], [232].

Crossing the BBB: H3 Activation, Microglial Activation, Stimulation of Neuroinflammation, Reduction of GABA, Acetylcholine, Glutamatergic Hyperactivity, Excitotoxicity, Sleep Disturbances

Barrier structures such as the BBB (Blood–Brain Barrier), BCSFB (Blood–Cerebrospinal Fluid Barrier), BRB (Blood–Retina Barrier), BLB (Blood–Labyrinth Barrier), and BNB (Blood–Nerve Barrier) play a crucial role in maintaining proper homeostasis in organs and tissues. Although they can effectively protect against acute inflammatory processes, chronic inflammation and oxidative stress may damage these barriers, leading to a generalized inflammatory response affecting the nervous system, blood vessels, nerve endings, the retina, and cartilage [135]. BBB – it can be described as a kind of defense system that generally allows the passage of many molecules, especially those that are essential for the basic functions of the central nervous system, while protecting against harmful ones (e.g., bacteria) [233], [234], [235]. The ability of a molecule to cross the blood–brain barrier depends not only on its physicochemical properties, but also on how it interacts with metabolism, the availability of appropriate transport mechanisms—both influx and efflux—as well as the presence of relevant receptors and metabolic processes for drugs [150], [236], [237].

The BBB (blood–brain barrier) is less tight in newborns and the elderly. Factors influencing pathological BBB permeability include trauma, stroke, infections, and inflammatory mediators such as histamine [238], [239]. Environmental stressors, including toxins and heavy metals, can also impair BBB integrity [240], as well as oxidative stress [240]. Neuroinflammation, for example in ASD and PTSD, also increases BBB permeability [23], [24]. Mast cells are also present in the central nervous system, on the brain side of the blood–brain barrier (BBB), where their distribution allows them to modulate the function of this barrier. Factors such as allergens, neuropeptides, stress, and toxins [29], and according to recent studies, also ionizing radiation [241], [77], GSM mobile phones [242], [243], [244], Wi-Fi [245], can induce changes in the BBB [246], even in the developing fetus [88].

These factors stimulate mast cells to degranulate inflammatory mediators, including histamine and proteases such as tryptase and chymase, which degrade proteins, damage cells, and can contribute to neurological disorders, including ASD. Tryptase promotes the generation of complement components C3a and C5a, sensitizes smooth muscle to histamine, stimulates eosinophil chemotaxis, and activates fibroblasts, contributing to fibrosis. Chymase increases mucus secretion, damages the basement membrane, and inactivates bradykinin [247], [248], also generates angiotensin (ACE), which may have vascular, inflammatory, neurological, or developmental consequences. ACE increases stress, inflammation, and vasoconstriction, while angiotensin-converting enzyme 2 (ACE2) down regulates these effects and protects tissues, including the fetus [249], which is further supported by studies showing elevated ACE2 during the COVID-19 pandemic [250].

Although histamine is a small, hydrophilic molecule and does not cross the blood–brain barrier (BBB) directly, it should be noted that this vasoactive amine is synthesized and metabolized within the brain endothelium, where it influences specific properties of the barrier [238], [239] and can increase BBB permeability [246], allowing the passage of various other inflammatory cells and molecules into the brain parenchyma [140]. Glutamate and GABA do not freely cross the blood–brain barrier under normal physiological conditions; however, they may penetrate in pathological conditions, such as during inflammation [251]. Histamine and glutamate exhibit complex, bidirectional interactions. Glutamate can enhance histamine release via N-methyl-D-aspartate (NMDA) receptors, and can activate histaminergic neurons, promoting wakefulness while simultaneously exacerbating sleep disturbances [252]. Conversely, histamine can induce glutamate release through H1 receptors [253].

Histamine, H3 Receptor Activation, Microglial Stimulation and Neuroinflammation

Theoharides' work (2016) [12], [26] indicates that

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histamine from mast cells, as well as systemic histamine excess (e.g., due to MCAS, HIT (dietary), DAO/HNMT enzyme deficiency, or genetic factors), can accumulate systemically, enter the bloodstream [254A], and potentially cross the blood–brain barrier (BBB), enhancing signaling [12], [25]. This process activates microglia and astrocytes [145] and can trigger coagulation factors leading to disseminated intravascular coagulation (DIC), resulting in neuroinflammatory responses, thrombus formation, and neural tissue damage [255]. ATP, glutamate, and histamine can modulate microglia activity in the vicinity of synapses or blood vessels [256]. Histamine, by activating H3 receptors, can disrupt the GABA/glutamate balance in the brain, inhibiting GABA release [20], [21], promoting glutamatergic hyperactivity and excitotoxicity [198], [257], ultimately disrupting neuronal function and contributing to neuroinflammation observed in ASD [258]. Glutamate and histamine exhibit complex, bidirectional interactions.

Mast cells → mediators (histamine) → microglia/astrocytes → neuroinflammatory effects

To confirm the above, studies have shown in the brains of individuals with autism an increased mast cell activity, including elevated histamine levels [258], [259] and glutamate [260], deficiencies in the DAO enzyme [39], GABA deficiencies (with an interesting relationship between DAO and GABA [261], [262], as well as increased production of pro-inflammatory proteins such as IL-1β, IL-6, TNF-α, and TGF-β [263], [264], [265], [266]. This confirms the significant role of histamine in the central nervous system, including in various environmental contexts [267], especially since it can cross the blood–brain barrier and activate H1, H2, H3, and H4 receptors, which are constitutively expressed on microglia [258]. Clinical studies indicate that H1R and H2R antagonists may have beneficial effects in children and adolescents with ASD, particularly in cases with co-occurring sleep and behavioral problems [268], [269].

The H3 receptor inhibits not only GABA but also the release of other neurotransmitters such as dopamine, serotonin, and acetylcholine, whereas H3 receptor blockade (e.g., with an antagonist) results in increased release of these substances [270], enhancement of fast cortical rhythms, and improvement in cognitive and memory functions [271], [272], with clinical studies also showing mitigation of symptoms and disease progression in Alzheimer's disease [203], [204]. It is noteworthy that approximately 25–30% of individuals with ASD exhibit elevated platelet serotonin (so-called hyperserotonemia), one of the most common biochemical deviations in ASD [273]. However, hyperserotonemia in ASD primarily concerns peripheral blood (platelets), not the synaptic space in the brain. The histamine H3 receptor is a presynaptic autoreceptor and heteroreceptor; upon activation, it inhibits the release of certain neurotransmitters, including serotonin in the brain, but does not affect systemic blood levels. H3 does not "block" serotonin systemically; it suppresses its release from nerve terminals in specific CNS regions, meaning an individual with ASD may have high blood serotonin (hyperserotonemia) [274] while simultaneously exhibiting disrupted brain signaling, e.g., reduced release or altered receptor function. Serotonin in the brain regulates neuronal proliferation, migration, differentiation, and synaptic plasticity. Disruption of serotonin levels during prenatal and early postnatal periods may affect neuronal connectivity and social behaviors [275]. It has been found that "H3 heteroreceptor-mediated inhibitory regulation of synaptic transmission may play a role in modulating sensory information processing, such as taste and visceral sensations, in the ventral nucleus" [276].

Sleep Problems in Children with ASD

Histamine, as both a hormone and a neurotransmitter, was identified over half a century ago, but only recently have scientists understood how it, acting also through H1, H2, and H3 receptors, modulates fundamental physiological and behavioral processes, including sleep and wakefulness [9], [277]. Strong evidence indicates that histamine, through H1 and H3 receptors, participates in and plays a key role in regulating sleep and wakefulness [278]. Data presented in these studies clearly highlight the therapeutic potential of the neuroregulatory role of histamine, thereby opening possibilities for the treatment of circadian rhythm disorders [279], [9]. Sleep disturbances are among the most commonly reported co-occurring health issues in children and adolescents with ASD [280], [281], which negatively affects both the child's development and the dynamics of their entire family [282], [283].

Research from other groups suggests that mast cell stabilization (controlling activation or degranulation) and reducing histamine levels (both endogenous and exogenous) [284]—and thereby preventing activation of H1, H2, and H3 receptors—can attenuate neuroinflammation and memory impairment [203], [204], representing a potential therapeutic strategy aimed at protecting the blood–brain barrier and treating neurodegenerative diseases associated with neuroinflammation (limiting neuroinflammatory damage) [31]. Mast cell stabilization with vitamin D3 may support the restoration of higher-quality sleep in children with ASD [285]. Research by Dr. Nedergaard sheds light on the relationship between sleep and brain physiology and their relevance in neurodegenerative diseases. According to her studies, the glymphatic system plays a key role in clearing β-amyloid from the brain during sleep. This system functions exclusively during sleep, which provides an explanation for why sleep is necessary for clearing metabolic waste that accumulates during wakefulness. This concept links sleep disturbances with histamine, neuroinflammation, and later-onset diseases such as Alzheimer's, Parkinson's, Huntington's, and frontotemporal dementia (HFSP Nakasone Award, 2024)

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[286], [287], [288], [289], [290], [291]. Studies suggest that H3 receptor antagonists may have therapeutic potential in treating a range of central nervous system disorders [292], including Alzheimer's disease, epilepsy, attention-deficit hyperactivity disorder (ADHD), and narcolepsy [293], [145], schizophrenia (SCH), and more recently Tourette's syndrome [294], as well as ASD [295], [296], [297]. These findings support the author's previous hypothesis regarding the influence of histamine and its receptors on ASD [10].

Influence of Mental and Physical Stress on Sleep

Mental and physical stress profoundly disrupt normal sleep through activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, leading to increased cortisol and catecholamine release, which promote hyperarousal, delay sleep onset, reduce slow-wave and REM sleep, and cause fragmented, non-restorative sleep [278]. Acute stress may produce transient insomnia, while chronic stress can create a self-perpetuating cycle in which poor sleep further impairs emotional regulation, cognitive performance, immune function, metabolic health, cardiovascular function, pain perception, and mental health, increasing the risk of anxiety, depression, obesity, diabetes, hypertension, and reduced quality of life [279].

Excessive physical stress from overtraining, illness, chronic pain, or strenuous exercise close to bedtime similarly elevates stress hormones and delays recovery, whereas regular moderate exercise generally improves sleep quality [287]. Early recognition of stress-related sleep disturbances and a comprehensive approach—including stress management, good sleep hygiene, cognitive behavioral therapy for insomnia (CBT-I), appropriate exercise timing, relaxation techniques, and treatment of underlying medical or psychiatric disorders—are essential to restore healthy sleep and prevent long-term health consequences [9], [288].

Individuals with ASD and PTSD and High Sensory Sensitivity

Our perception of the world is based on the senses and their receptors. Up to 90% of children with ASD exhibit sensory hypersensitivity, making them more sensitive (hyper-responsive) to environmental stimuli such as light and sounds [298], tastes, and touch (including tight shoes and irritating clothing). This also applies to smell and "internal" senses, such as body awareness (proprioception), posture, balance, and movement (vestibular system) [299]. Some children, on the other hand, exhibit reduced responsiveness (hypo-responsiveness) and seek stronger sensory input [300]. Some children are so sensitive to smells (imperceptible to others) that being in a restaurant can be very uncomfortable, or they may be selective about certain foods, while others show little reaction to smells, which can result in indifference to food. Hypo-responsiveness to touch can lead to a desire for stronger stimuli—these children may enjoy jumping, bumping into objects, firm pressure, or weighted blankets—while hypersensitivity manifests as resistance to hugging, avoidance of touch, which may be perceived as painful [301]. Typical symptoms following trauma leading to PTSD include heightened sensory sensitivity due to the constant search for danger in order to avoid or defend oneself, resulting in sensory overload. Common PTSD symptoms include hypervigilance, nightmares, flashbacks, insomnia, and anxiety [302].

Noise hypersensitivity is one of the symptoms of post-traumatic stress disorder (PTSD) and can be particularly challenging and stressful because it is difficult to control environmental noise [303]. For individuals with PTSD and complex PTSD (CPTSD), sounds such as children screaming, a bouncing ball in the park, or a lawnmower can trigger physical pain, anxiety, and the urge to escape [304]. This is described as misophonia—a condition in which a person with PTSD reacts to triggering sounds, which can also cause heightened vigilance toward other people. Consequently, such individuals often avoid spending time with family, friends, or partners, especially if they are associated with trauma. Persistent fear and a sense of threat in individuals with CPTSD can lead to auditory hypersensitivity (a hearing disorder related to neural auditory pathways), causing everyday sounds to seem extremely loud, irritating, or even painful. This may result in social withdrawal to avoid such experiences. This hypersensitivity can also be a consequence of mechanical head injuries [305], Bell's palsy, or Lyme disease. People with CPTSD may experience strong, unpleasant auditory emotions—for example, in a crowded restaurant where people are talking, dishes and cutlery are clattering, and music is playing. The situation can be further worsened by hypersensitivity to other environmental factors, such as smells, light, or histamine-containing foods (Complex PTSD and Noise Sensitivity) [306], [307]. These individuals may experience anxiety in public spaces, hyperarousal, and disrupted sleep, which is consistent with findings from translational neuroscience [308], [309].

Environmental factors (sensory stress, toxins, infections, trauma) + a histamine-rich diet + DAO/HNMT deficiency → Histamine ↑ (accumulation of endogenous and exogenous) → Activation of H3 receptors in the brain (inhibition of GABA release) → GABA ↓ (inhibitory neurotransmitter) → Increased glutamatergic activity (excitatory) → Excitotoxicity and neuroinflammation (neuronal damage, oxidative stress) → Clinical manifestations of ASD and PTSD: sensory hypersensitivity, gastrointestinal disturbances, emotional instability, sleep disorders, cognitive difficulties.

The author's hypothesis is based on scientific evidence and extensive clinical experience working with individuals who have experienced trauma in various environments. This framework suggests that the Vinci Power Nap® may serve as a tool to support the initiation of recovery processes. Additionally, it could be considered for exploration in

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mitigating or potentially limiting damage induced by radiation exposure, such as some side effects of radiotherapy. However, controlled experimental studies are necessary to rigorously evaluate its efficacy and mechanisms of action [310].

GABA and Glutamate – Excitotoxicity

GABA (gamma-aminobutyric acid) is the primary inhibitory neurotransmitter in the central nervous system, acting through GABA-A receptors (ion channels) and GABA-B receptors (metabotropic receptors), reducing neuronal excitability. It is crucial for neuronal balance, mitigating excessive excitation, for example, that induced by glutamate [311], [312]. GABA is also present in the gut, pancreas, immune cells, muscles, and skin (Neuroexpert, GABA) [290], [313], [314]. The enzyme Glutamic Acid Decarboxylase (GAD) converts glutamic acid into the inhibitory neurotransmitter GABA through decarboxylation, a reaction that requires vitamin B6 in the form of pyridoxal phosphate (PLP) as a cofactor [315], [316]. Glutamate, also known as glutamic acid, is an organic compound belonging to the amino acid group [317]. Glutamate is a neurotransmitter in the nervous system, playing a key role in signal transmission between neurons. It is the main excitatory neurotransmitter in the brain and is involved in processes related to memory, learning, and synaptic plasticity [318].

Glutamate occurs naturally in foods but is also added as a flavor enhancer in the form of monosodium glutamate (MSG, E621), which imparts the umami taste. MSG is commonly used in Asian cuisine, processed foods, instant soups, and snacks. In healthy individuals, dietary glutamate barely crosses the blood-brain barrier (BBB); however, under pathological conditions, when the BBB is compromised, partial penetration may occur, which can have neurotoxic effects [319], [320], which has been observed in individuals with ASD [260]. Glutamate is particularly common in Asian cuisines: Chinese (MSG is widely used in sauces, soups, stir-fried dishes, and spice mixes), Japanese (natural umami sources such as kombu, soy sauce, and dashi are rich in glutamate; MSG is also added to prepared seasonings), Korean, Thai (in soups, curry pastes, fish sauces, and marinades), as well as in processed Western foods (chips, instant soups, powdered sauces, ready meals, fast food—MSG is used to enhance the flavor of meats, sauces, and snacks). Glutamate occurs naturally in tomatoes, mushrooms, aged cheeses (e.g., Parmesan), seaweed, meat, and fish [321]. Glutamate is released at synapses in response to stimuli, but under pathological conditions (e.g., stress, injury, neuroinflammation), its concentration in the synaptic cleft may become excessively elevated [202].

The balance between excitation and inhibition in the cerebral cortex depends on the number and activity of glutamatergic and GABAergic neurons. An increased excitation/inhibition ratio may result from the combined effects of genetic and environmental factors that modulate the functioning of specific neuronal circuits [251]. Imbalances in glutamate and GABA are well documented in ASD [18], [322]. Neuroimaging studies [323], [324], [325], indicate reduced GABA levels in the brains of children with ASD, which correlates with the severity of behavioral symptoms and may be partly modulated by histamine activity. Studies [169], [20], [21] show that histamine, via H3 receptors, can reduce the activity of GABAergic neurons in the hippocampus, disrupt neuronal inhibition, and induce excessive glutamatergic signaling, which may enhance glutamate activity, leading to excitotoxicity [257] and increased oxidative stress [18], [326].

Excess histamine (e.g., in HIT or MCAS) and pro-inflammatory cytokine release may increase blood-brain barrier (BBB) permeability, thereby amplifying glutamatergic signaling and excitotoxicity. Excitotoxicity is a pathological process in which excessive or prolonged activation of excitatory neurotransmitter receptors, mainly glutamate receptors (e.g., NMDA, AMPA), leads to neuronal damage or death [311]. Neuron loss in key brain regions, such as the hippocampus, prefrontal cortex, and amygdala, results in cognitive, emotional, and behavioral impairments [251]. Excitotoxicity contributes to multiple neurological and neurodegenerative disorders and can cause behavioral symptoms: in autism (ASD – increased sensory sensitivity, cognitive fog, communication difficulties, irritability), in post-traumatic stress disorder (PTSD – heightened anxiety responses, flashbacks, amygdala hyperactivity, aggressive behaviors), and in stroke (loss of neurological functions, e.g., paralysis, speech impairment). Chronic excitotoxicity and oxidative stress contribute to neuronal death in conditions such as ASD, PTSD, Alzheimer's disease [128], amyotrophic lateral sclerosis (ALS), and epilepsy [327]. (Picture 2).

Neuroinflammation often co-occurs with excitotoxicity (e.g., related to excessive glutamate activity) and oxidative stress, forming a vicious cycle [328]. Neuroinflammation (driven by mast cell mediators and histamine) impairs the ability of glial cells to regulate glutamate, leading to further excitotoxicity. In turn, excitotoxic neuronal damage releases pro-inflammatory molecules, perpetuating the inflammatory state. These inflammatory processes can additionally damage blood vessels, activate mast cells to release histamine, and promote inflammations and local thrombosis, particularly in the brain microcirculation [329], [330]. Chronic neuroinflammation may lead to changes in cerebral blood flow (e.g., due to vessel constriction or microthrombosis) [331]. This cycle may underlie and exacerbate symptoms of ASD and PTSD [19], [332], [251], [30].

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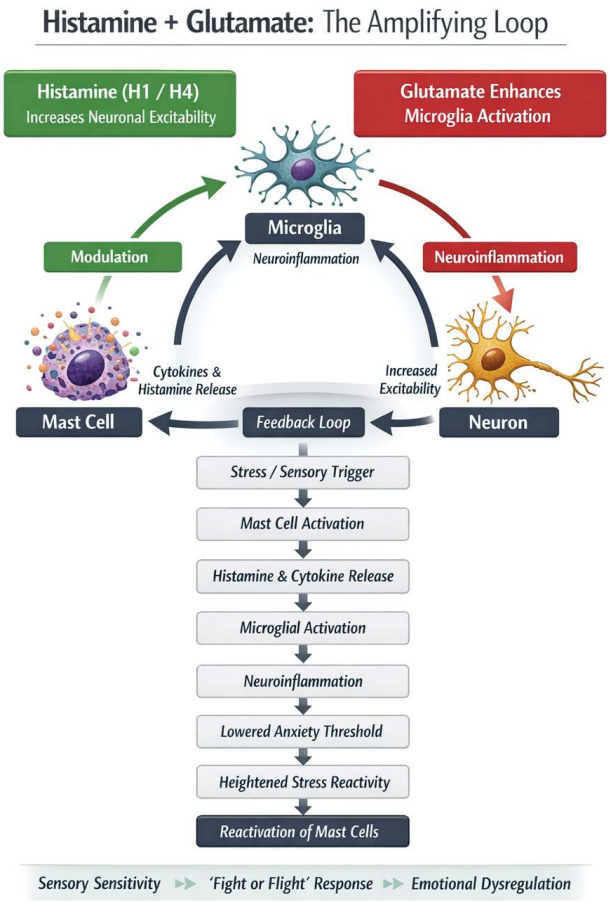

Picture 2: Hypothesis: overlapping factors that elevate histamine levels may act synergistically, thereby amplifying one another and contributing to a broad range of symptoms observed in ASD, ADHD, and PTSD. Illustration was generated using AI (ChatGPT 4.0.) and reviewed, corrected and completed by the author.

Glutamate–GABA Imbalance in ASD Pathophysiology

GABAergic and glutamatergic neurotransmission disruptions, which are symptomatic of glutamate–glutamine–GABA cycle failure, are regularly seen in biochemical investigations of ASD [333], [334]. GABA and glutamate activity and release are crucially modulated by redox signaling, which involves ROS and RNS. Post-mortem cortex tissue exhibits elevated glutamate, decreased GABA, and decreased kidney-type glutaminase activity [335]. Notably, ROS increase glutamate/GABA release and alter NMDA receptors, whereas redox pathways control GABAergic micro inhibitory postsynaptic current frequency, GABAA receptors, and GABA release [336]. According to [335], histological investigations reveal astrocytic structural abnormalities in ASD, suggesting reactive gliosis and poor neuroglial communication that worsen neurotransmitter dysregulation. In animal models of early-life mercury exposure, these neurochemical abnormalities, which are symptomatic of glutamate–glutamine–GABA cycle failure, are reliably reproduced. In these models, rats show increased extracellular glutamate, decreased GABAergic signaling, and down regulated glutamine synthetases. Importantly, by upsetting the delicate excitatory/inhibitory balance—a hallmark of ASD pathophysiology—Hg-induced astrocytic dysfunction, which is characterized by changes in astrocyte morphology and impaired neuroglial communication, critically underlies these observed ASD-like behavioural phenotypes [333], [337], [338], [339].

Histamine H3 Receptor and Acetylcholine

Acetylcholine (ACh) is released by neurons through an enzymatic reaction occurring at axon terminals and exerts broad neurotransmitter functions in the central, peripheral, and autonomic (sympathetic and parasympathetic) nervous systems, as well as at the neuromuscular junction, where it induces muscle contraction and thereby regulates the functional efficiency of many organs, such as the heart, lungs, intestines, urinary bladder, and endocrine and exocrine glands [340], [341]. Activation of histamine H3 receptors in the brain, for example in the hippocampus, may inhibit the release of the neurotransmitter acetylcholine (ACh) from cholinergic neurons, which are involved in cognitive processes and modulate attention, wakefulness, memory, and reward processing [342]. As a result, this may lead to impaired cognitive functions and memory in individuals with ASD. Low levels of acetylcholine have been investigated as a potential contributing factor to autism symptoms, as individuals with ASD exhibit certain abnormalities in the brain cholinergic system, including acetylcholine neurotransmission [343]. Enhancement of acetylcholine signaling in certain brain regions may improve cognitive functions, attention, and social interactions; however, excessive ACh activity in other areas may exacerbate sensory hypersensitivity and anxiety, worsen impulse control, executive functions, and emotional regulation [344]. There is also a feedback mechanism: acetylcholine, through its action on muscarinic or nicotinic receptors, can regulate mast cell function, leading to reduced histamine release under certain conditions (resulting in an anti-inflammatory effect of the cholinergic system) [345].

Many preclinical studies have demonstrated that histamine H3 receptor antagonists improve social functioning and reduce repetitive behaviors [203], [209], [270], [295], [297], [346], [347], [348], [349]. The antioxidant properties of H3 receptor antagonists clearly indicate that these compounds may represent a promising therapeutic option for the treatment of autism spectrum disorder (ASD) [350], [351], as well as other brain disorders in which microglia-driven neuroinflammation plays a central role, such as Alzheimer's disease (AD), schizophrenia (SCH), and behavioral and psychological symptoms of dementia (BPSD)[200], ADHD, PTSD [352], [353].

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Endothelium, Histamine and Thrombosis in Systemic Inflammation

The vascular endothelium plays a critical role in regulating histamine metabolism, coagulation, inflammation, and blood–brain barrier integrity through the balanced activity of histamine-synthesizing and histamine-degrading enzymes such as HDC, DAO, and HNMT [354]. When histamine degradation becomes impaired, excessive histamine signaling may promote endothelial dysfunction, platelet activation, coagulation cascade activation, vascular hyperpermeability, and immunothrombosis, potentially contributing to tissue hypoxia, neurological complications, stroke, myocardial infarction, and multisystem inflammatory responses [255], [355], [356], [357], [358], [359] also contributing to neuroinflammatory mechanisms through microglial activation, oxidative stress, and neurotransmitter dysregulation mediated by H1, H2, H3 and H4 receptors [129], [180], [181], [255]. Chronic inflammatory conditions such as obesity, diabetes, sepsis, and COVID-19 further amplify oxidative stress and endothelial injury, thereby increasing the risk of thrombotic [360] and neurovascular complications [361], [362], [11], [363], [364]. Moreover, ionizing radiation and oxidative stress may impair endothelial histamine-metabolizing capacity by reducing DAO and HNMT activity, leading to histamine accumulation, enhanced mast cell activation, blood–brain barrier disruption, cerebral edema, and intensified inflammatory and thrombotic responses [365], [366] often starting with DIC [367], which is associated with the sticking together of platelets and damage to erythrocytes that transport oxygen. Severe and prolonged hypoxia associated with impaired oxygen delivery in the context of thrombotic and inflammatory processes is associated with multi-organ dysfunction, including potential neurological impairments ranging from cognitive deficits to loss of consciousness, cardiac complications such as arrhythmias, heart failure, or myocardial ischemia [368], and renal and hepatic damage. In advanced or chronic cases, peripheral ischemic changes may occur, including cyanosis and tissue necrosis, which, under extreme conditions, can develop into gangrenous changes. In critically ill patients, such pathophysiological cascades can contribute to life-threatening conditions, especially when oxygen delivery remains inadequate due to persistent thrombosis [329] or systemic hypo-perfusion [369].

Importance of Methylation and Vitamins B6, B9, B12

Research shows that in both neurodevelopmental and neuropsychiatric disorders, including ASD, ADHD, PTSD, and related disorders, elevated histamine levels and impaired histamine degradation are associated with increased neural excitability, cognitive and emotional dysregulation, sleep disturbances, and multisystem symptoms [370], [371]. HIT and genetic variation in DAO and HNMT potentially exacerbate neuroinflammatory and behavioral symptoms [372], [373]. Histamine metabolism is mediated by DAO and HNMT. HNMT function plays a crucial role in neurodevelopment, as many mutations in the HNMT gene have been found in individuals with profound intellectual disabilities [374]. Methylation is a key biochemical process that involves the transfer of methyl groups ($–CH_3$) to molecules such as DNA (DMNT), neurotransmitters, and histamine, thereby regulating gene expression, detoxification, and neurotransmitter metabolism through SAM-dependent enzymes such as histamine N-methyltransferase (HNMT) [375], [164]. Therefore, proper methylation is essential for maintaining normal cellular and nervous system function. This system depends on one-carbon metabolism and adequate levels of vitamins B6, B12, and folate (B9) [810] to maintain SAM production [376], [377], [378], [379]. Importantly, a form of vitamin B6 called pyridoxal phosphate (PLP) plays a cofactor role for the enzyme glutamate decarboxylase (GAD), which consequently converts glutamate to GABA [380], [381]. PLP deficiency further reduces GAD activity, lowering GABA synthesis and potentially increasing glutamate, while simultaneously impairing HNMT function, which may lead to elevated histamine levels and neuroinflammation [380], [382]. Disturbances in this system may impair histamine and neurotransmitter degradation, increase homocysteine levels, and increase oxidative stress [383A], thereby contributing to neuroinflammatory [384], [385], cardiovascular, and neurodevelopmental disorders observed in conditions such as ASD, ADHD, and other neuropsychiatric or neurodegenerative disorders [12], [26], [386], [387].

The Role of Neurotensin, CRH and Substance P in Inflammation

Neurotensin (NT) [388] and corticotropin-releasing hormone (CRH) are stress-related mediators that can activate mast cells [389] promoting histamine release and contributing to neuroinflammation and dysregulation of the gut-brain axis [390]. They link the nervous and immune systems, acting both centrally (HPA axis) and locally in tissues [391]. Both of these hormones have also been found to be elevated in conditions such as ASD [12], [26], [392], [81]. Similarly, substance P is a neuropeptide (a member of the tachykinin family) that activates mast cells, induces neurogenic inflammation, and promotes histamine degranulation, thereby linking stress, pain signaling, and inflammatory processes in the gastrointestinal and respiratory systems [393], [394], [81], [395]. Substance P has also been linked to several chronic diseases, such as obstructive pulmonary disease (COPD), asthma, anxiety, depression, nausea, and inflammatory bowel disease [396].

The Body's Response to Antigens - Oral and Intravenous

To better understand these mechanisms, it is valuable

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to examine the pioneering lectures and discoveries of Nobel Prize–winning scientists who laid the foundations of modern immunology, neurophysiology, and histamine research, including Ivan Pavlov (neural digestive reflexes, 1904), Charles Richet (anaphylaxis, 1913), Sir Henry Dale (histamine and chemical neurotransmission, 1936), Daniel Bovet (antihistamines, 1957), and Sir James W. Black (histamine receptor pharmacology, 1988) (Nobel Prize lectures) [397].

Oral Intake and Mast Cell–Histamine Responses

The gastrointestinal tract represents the first stage of the body's contact with nutrients delivered from the outside. It is a continuous tube running through the entire body, remaining in open communication with the external environment, which makes it, in a way, an "internally hidden" part of the body surface. Digestion occurs with the involvement of substances that retain their properties both in the digestive tract and outside the body under laboratory conditions, allowing them to be analyzed using chemical methods and described by the laws of chemistry. These substances are called enzymes, formerly known as ferments (Pavlov Lecture Nobel Prize) [398]. The process of digestion involving enzymes consists of the breakdown of food by enzymes secreted by the host organism in the gastrointestinal tract, enabling the absorption of nutrients. Fermentation, on the other hand, is the transformation of organic compounds (e.g., sugars) that occurs with the involvement of enzymes secreted by microorganisms (mainly bacteria and yeast), which break down organic substances (usually anaerobically), producing by-products such as organic acids or gases. Fermentation is used in many culinary processes, including sauerkraut production, yogurt and kefir preparation, and bread dough leavening, which promotes the formation of histamine (Fermentation) [399].

Histamine is one of the so-called biogenic amines—compounds formed from amino acids through the action of bacterial enzymes. Therefore, fermentation and histamine are closely related. During fermentation (e.g., pickling, cheese aging, wine fermentation), fermentative bacteria break down various compounds, including amino acids such as histidine, which can be converted into histamine through histidine decarboxylation by the bacterial enzyme histidine decarboxylase. Consequently, fermented products (aged cheeses, wine, beer, pickled vegetables, fish products) often contain elevated levels of histamine and other biogenic amines (tyramine, putrescine, cadaverine). In sensitive individuals (e.g., those with a deficiency of the DAO enzyme, which breaks down histamine), such products may trigger pseudoallergic symptoms (headache, urticaria, redness). A similar process occurs during putrefaction, where protein breakdown by bacteria leads to the release of biogenic amines. During spoilage of meat, fish, or cheese, bacteria produce histamine and other amines (putrescine, cadaverine), and consumption of histamine-rich food can cause histamine poisoning (e.g., scombroid poisoning from fish) or HIT.

Mast cells are present in human and animal salivary glands (parotid, submandibular, sublingual) as well as in the tonsils [400]. Their numbers increase, for example, during salivary gland inflammation, autoimmune diseases, or allergies. Upon contact with an allergen or food (e.g., milk, wheat, eggs, nuts, fish, strawberries, tomatoes, chocolate, seafood, aged cheeses, wine, fermented vegetables), mast cells undergo degranulation and release histamine and other mediators. The released histamine can modulate saliva secretion (acting on H1 and H2 receptors in the epithelium and blood vessels), participate in hypersensitivity reactions, and increase vascular permeability within the salivary glands, causing edema and inflammatory infiltration. Histamine plays a key role in the stomach, where enterochromaffin-like cells (ECL) secrete histamine, which binds to H2 receptors on the parietal cells of the gastric mucosa, stimulating the secretion of hydrochloric acid (HCl), the main component of gastric juice [401]; (Pavlov Lecture Nobel Prize) [398]. It has long been known that some people are sensitive to cheese, strawberries, fish, shellfish, eggs, raw meat, and even milk (lactose, casein A1). The symptoms observed in these individuals after consuming such foods are analogous to a histamine storm: acute abdominal pain, vomiting, diarrhea, colic, erythema, urticaria, severe itching, and sometimes heart problems, fever, and leukocytosis—these are anaphylactic phenomena. Anaphylaxis has become a common pathological phenomenon. "Anaphylaxis is the cause of adverse reactions that occur in a small number of people in response to certain proteins found in food." (Nobel Prize Speed read: A shock response) [402]. Victor Hutinel, a Parisian pediatrician at the beginning of the 20th century, developed the term "food anaphylaxis," which described analogous reactions and symptoms after ingestion of, for example, milk [403], [404], [405]. Wheat allergy associated with the risk of anaphylaxis represents a serious global food safety issue. Gliadins, glutenins, albumins, and globulins of wheat, as well as pesticides from spraying, can act as allergens and trigger severe allergic reactions in which histamine is released [406], [407], (Pavlov Lecture Nobel Prize) [398].

Potential Reason of Food Selectivity

These findings regarding food anaphylaxis may have significant clinical implications. Many cases of mild digestive discomfort, so-called indigestion, may result from mild anaphylactic reactions. It has long been believed that maintaining a regular, consistent diet is more beneficial than experimenting with diverse dietary patterns. Repeated consumption of the same protein may lead the body to gradually become accustomed to it, developing tolerance to this common antigen. This may explain why children with ASD often display so-called food selectivity, sometimes consuming only one or a very limited set of foods—

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possibly as a subconscious way to avoid triggering further histamine release. Analysis of numerous substances capable of inducing anaphylactic reactions, as well as those that can induce immunological tolerance, indicates that chemical and humoral diversity between individuals is practically limitless, highlighting the complexity and individuality of immune responses. It was previously assumed that organisms of the same age, race, and sex have identical body fluids. However, each organism possesses unique characteristics that make it distinct. Therefore, studying the physiology of the species alone is insufficient—understanding the physiology of the individual is necessary (Richet Lecture Nobel Prize) [399].

Intestinal Injection and Mast Cell–Histamine Responses

The human body is generally structured so that intact proteins are not expected to enter the bloodstream unless they are first broken down into smaller components by digestive enzymes (Nobel Prize, 1913) [408]. When foreign proteins do reach the circulation, the immune system reacts, triggering a defensive response that can lead to increased sensitivity upon subsequent exposure. It occurs when the immune system, after prior sensitization to an antigen such as food and food additives (e.g., monosodium glutamate, colorants) [406], venom [409], drugs (or various medications (e.g., depolarizing muscle relaxants, contrast agents, antibiotics, or latex) [410], or other substances, responds on re-exposure (repeated parenteral administration) [99], with IgE-mediated or idiopathic activation of mast cells and massive histamine release, it makes immune system more fragile and susceptible [411].

In 1906, Rosenau and Anderson demonstrated that anaphylaxis could be triggered not only by toxins but by many different proteins, even in extremely small amounts (0.00001 ml) given parenterally, through subcutaneous or intravenous injection in experimental animals, including milk, eggs, serum, plant or muscle extracts, dead microbial bodies, bacterial protein toxins, yeast cells (Richet Nobel Prize Lecture) [412]. The key observation was that introducing foreign proteins directly into tissues or the bloodstream could sensitize the organism and, upon re-exposure, trigger systemic hypersensitivity reactions (anaphylaxis) [413], (Richet Biography) [414]. Anaphylaxis may be triggered not only by classical allergens, but also by physical factors such as extreme temperatures (sometimes in combination with recently consumed food) [415], strenuous exercise, mechanical stimulation like vibration [80], [94], [416], and some vaccine adjuvants [417], [418], [419]. Symptoms range from mild itching and urticaria to severe systemic reactions such as hypotension, bronchospasm, edema, neurological impairment, and in severe cases to potentially life-threatening reaction, such as anaphylactic shock [420], also death [99]. Histamine is the key mediator of these processes, and treatment relies primarily on epinephrine, which counteracts its effects, with antihistamines used as supportive therapy [421].

There is a hypothesis that some components of intravenous vaccines entering and circulating in the bloodstream may activate mast cells in the endothelium and surrounding blood vessels, leading to excessive histamine release and additional activation of H1–H4 receptors, potentially contributing to chronic inflammation in multiple organs in the body. Some studies have suggested that, in susceptible individuals, immune activation following vaccination or exposure to certain antigens may contribute to excessive mast cell activation, histamine release, and chronic inflammatory or autoimmune-like symptoms. In a healthy individual, exposure to an antigen usually induces a balanced immune response, resulting in antibody formation and long-term immunological memory. In people in people with MCAS or with deficiency of HNMT or DAO enzymes [69], [70], [422], [423], exposure to vaccines components or other antigens may more easily trigger an exaggerated response, with strong mast cell activation and histamine buildup. This can result in allergic reactions, shock, or pseudo-anaphylaxis, where histamine plays a key driving role rather than a secondary one [69], [422], [424]. These significant differences in physiological responses are particularly important in the context of vaccination individuals.

These mechanisms are conceptually linked to classical research on anaphylaxis and hypersensitivity by Charles Richet and others, emphasizing that repeated exposure to specific antigens can, in predisposed individuals, trigger exaggerated immune responses mediated by mast cells and histamine rather than protective tolerance alone (Richet Nobel Prize Lecture) [412], [425], [426]. The concept of heightened reactivity to repeated exposure was described by Clemens von Pirquet in 1906, who introduced the term “allergy” to describe an altered immune response [427], [428]. Early research by Charles Richet and Paul Portier also helped establish the concept of anaphylaxis as a systemic hypersensitivity reaction to foreign proteins. Overall, these observations contributed to the understanding that the immune system can respond differently to repeated or systemic exposure to antigens, sometimes with severe reactions. Studies indicate that perivascular mast cells can capture IgE directly from the bloodstream through the vascular wall [429]. Bose et al. further demonstrated that cutaneous mast cells form cytoplasmic extensions reaching into the lumen of blood vessels [430], which may enable rapid mast-cell activation and intravascular degranulation after intravenous antigen or IgE exposure [431], [432]. The immune system may respond to a foreign protein or drug by producing antibodies that bind to the substance and form immune complexes. These complexes can accumulate in tissues, particularly within blood vessels, triggering inflammation, tissue injury, and the development of clinical

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symptoms. The reactions discussed above involve parenteral administration, where substances are delivered intravenously, subcutaneously, intrathecally, or intraperitoneally, bypassing the digestive tract. However, anaphylaxis may also develop after oral exposure, as food allergens absorbed through the gastrointestinal tract can trigger systemic immune and mast-cell activation (Richet Nobel Prize Lecture) [412]. In addition, histamine it participates in the development of SIRS and sepsis [11], which—like anaphylaxis—are systemic rather than local reactions [433]. In medical practice, vaccines are usually given in a monitored and controlled setting. In certain situations, preventive administration of antihistamines or other safety measures may be used to lower the likelihood of allergic responses or anaphylactic reactions.

Anaphylaxis

The phenomenon of anaphylaxis was first systematically described by Charles Richet and Paul Portier in 1902 titled *On the Anaphylactic Action of Certain Toxins,* and later classified as a form of immediate (Type I) hypersensitivity within broader immunological frameworks (Richet Nobel Prize lecture: Anaphylaxis, 1913) [412], [425], [426], [403]. Charles Richet received the Nobel Prize for his work on this phenomenon, inspiring further studies [434].

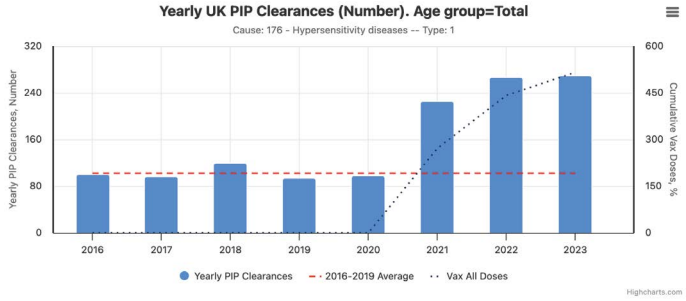
In most cases it involves prior sensitization with IgE antibodies against a specific antigen, although this is not obligatory, since reactions can also occur to individual components of a formulation. Clinically, it is classified into IgE-mediated anaphylaxis (occurring upon re-exposure), non–IgE-mediated pseudoanaphylactic reactions often triggered by excipients such as adjuvants, stabilizers or preservatives, and idiopathic anaphylaxis where no identifiable cause is found in a substantial proportion of patients [435].

This difference helps explain why the body responds differently to substances depending on whether they are ingested or introduced directly into the bloodstream, such as aluminum (Aluminium in blood) [436] or mercury. The same substance can have completely different effects depending on the route of administration: the intestines limit exposure, blood and tissues provide complete and rapid distribution, and the immune system responds more vigorously to systemic exposure.

Aluminium salts are commonly included in some vaccines as adjuvants, meaning substances that enhance and prolong the immune response to the antigen [437]. Aluminium is present in food, water, and some vaccines and is normally eliminated in small amounts via the kidneys, so it does not usually accumulate [438]. With higher or prolonged exposure, it may deposit in tissues and has been studied for potential neurotoxic effects and associations with neurological disorders, also such as Alzheimer's and Parkinson's disease [439], [128], [440], [441]; particularly in vulnerable populations [442], [443]. Some studies suggest a potential link between mercury exposure (as hapten bind with skin or plasma proteins [444], [445] and the presence of brain-reactive autoantibodies in individuals with ASD. It has also been reported that levels of these autoantibodies may correlate with both autism symptom severity and measured mercury concentrations in the blood [446], [447]. Reactions to aluminium and mercury [448] are generally non–IgE-mediated [449] and are more consistent with delayed inflammatory mechanisms rather than immediate allergic responses [450], [451], [452], often contributing to immune dysregulation and mercury-induced astrocytic dysfunction accompanied by autism-like behavioral characteristics [337], [339], [453]. Claims and statements of concern regarding vaccine components, including thimerosal, have been discussed publicly by various figures, including Robert F. Kennedy Jr. Jr., Secretary of the U.S. Department of Health and Human Services (HHS) [75], in recent speeches ((Mr. Kennedy speeches, 2025) [454], (Others speeches, 2025) [455]. Following extensive research and analysis, HHS adopted a recommendation to remove thimerosal from all U.S. influenza vaccines (HHS, July 23, 2025) [456]. Some examples from UK PIP Analysis data: E.R. Dalby, Carlos Alegria, "Analysis of UK New Claims for Personal Independence Pension (PIP) by Underlying Causes," data from UK DWP, ONS, and NHS vaccination statistics (UK PIP Results link) [815]. (Figure 1, 2,3,4,).

Intestines, DAO, Histamine, and ASD

A review article, "Histamine: A Mediator of Intestinal



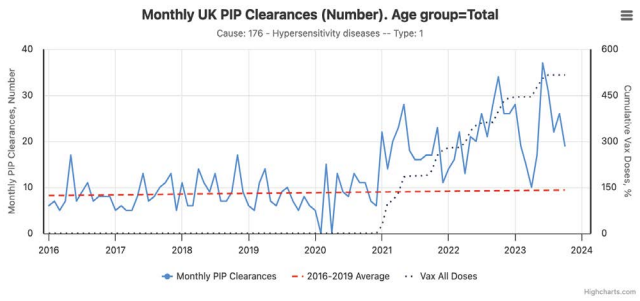


Figure 1: Hypersensitivity diseases. Yearly UK PIP Clarences. Cause nr: 176. Age group = Total.
Figure 2: Hypersensitivity diseases. Monthly UK PIP Clarences. Cause nr: 176. Age group = Total.

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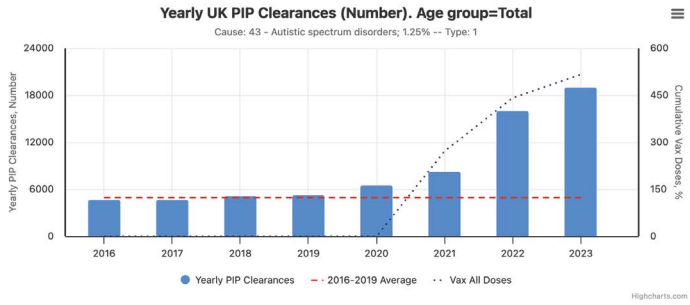

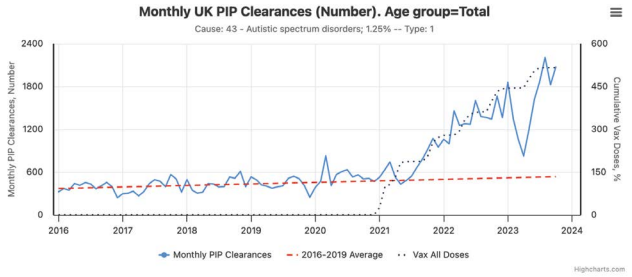

Figure 3: Autistic Spectrum Disorder 1,25%. Yearly UK PIP Clarences. Cause nr: 43. Age group = Total.
Figure 4: Autistic Spectrum Disorder 1,25%. Monthly UK PIP Clarences. Cause nr: 43. Age group = Total.

Disorders," describes the role of histamine in gastrointestinal function, including its production, action through various receptors, and involvement in intestinal disorders, noting that in inflammatory states its levels are often elevated and may contribute to maintaining chronic low-grade inflammation [87]. In intestinal inflammation (e.g., food intolerances, Crohn's disease, celiac disease, SIBO, intestinal infections) [457], the intestinal epithelium and enterocytes—the cells that produce the enzyme DAO (diamine oxidase)—are damaged [458]. In a healthy body, DAO neutralizes excess histamine in the intestine before it enters the bloodstream [459]. The level of diamine oxidase (DAO) measured in serum is an indicator of the integrity and condition of the small intestinal mucosa and may serve as a marker in diagnosing inflammatory bowel diseases, detecting allergic disorders, and liver cirrhosis (whose pathology is represented by changes in bacterial composition (gut dysbiosis) and SIBO (small intestinal bacterial overgrowth) [460], the risk of miscarriage, assessment of drug toxicity, and HIT [461]. Unfortunately, the cost of testing is high, and additionally, menstrual cycle, diet, medications, and sex may affect the reliability of the enzyme in diagnostics. DAO supplementation and a low-histamine diet can significantly help reduce symptoms of HIT and intestinal disorders [458], [462], [463].

Increased intestinal permeability and low-grade inflammation can secondarily reduce DAO levels [464]. The involvement of mast cells in regulating intestinal permeability and gut microbiota balance indicates their role in gastrointestinal disorders co-occurring with ASD [30]. These disorders also occur in older adults and in certain chronic diseases, which according to studies posed higher risk in COVID-19 infections [465] and higher mortality risk from COVID-19 in these three groups „ After the Elderly, Those with Intellectual Disabilities are at Greatest Risk of Death from COVID-19" [466], [467]. These studies support the author's hypothesis that intestinal condition affects DAO levels, which in turn influence histamine levels, playing a significant role in the pathology of COVID-19, as well as in ASD, ADHD, and PTSD [10], [11], [468].

Changes in the gut microbiome and metabolites, such as propionic acid, can additionally disrupt the GABA–glutamate balance in the brain [469], exacerbating autistic behaviors [470]. Probiotic interventions show potential in modulating neurotransmitter balance and reducing excitation/inhibition imbalance in the nervous systems [471]. Studies suggest that disturbances in gut microbiota balance may play a role in the emergence of HIT symptoms. Further analyses are still needed to determine whether microbiota changes are a direct cause or rather a consequence of this intolerance [472] in [473]. In studies of individuals with ASD, the dominant symptoms of HIT were diffuse abdominal and head pain, recurrent diarrhea and vomiting, as well as skin rashes [474]. After starting a low-histamine diet (low in histamine-containing foods), symptoms resolved, and the use of H1 and H2 antihistamines was necessary only in two clinical situations [157]. Notably, in the human gastrointestinal tract, H1, H2, and minimally H4 receptors are present, whereas the H3 receptor is absent. It has also been observed that in patients with gastrointestinal diseases, the expression of these receptors changes [475], and under acute stress in rat gastrointestinal tracts, histamine content increases in colonic mast cells. This is associated with the release in the brain of interleukin-1 followed by corticotropin-releasing factor (CRF), because immune signaling between the gut and the central nervous system occurs via cytokines, and their levels depend on gut condition and microbiome composition [83]. Studies indicate that disrupted neuronal pathways in ASD may be modulated by mast cell mediators, such as histamine, serotonin, and cytokines, which influence both neuronal function and immune system responses, contributing to the development of characteristic symptoms of this disorder [476], [30]. In individuals with ASD and their mothers, autoimmunization is often observed, and mast cells can initiate and amplify these reactions by regulating lymphocyte numbers or releasing autoantigens [372].

Embryonic Development

New research directions also include analyses of prenatal environmental factors related to ASD occurrence, such as maternal use of antibiotics, analgesics, selective serotonin reuptake inhibitors, exposure to environmental toxins, immune, allergic, or metabolic disturbances, changes in gut microbiota, and IL-17 levels [477], [478], elevated levels

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of hormones, biogenic amines (including histamine), and oxidative stress – all influencing the development of the child's brain and the later emergence of ASD. These potential biological mechanisms may serve as preventive strategies [479].

Mother Inflammation During Pregnancy

During pregnancy, inflammatory processes in the mother disrupt the normal function of the placenta, increasing the likelihood of neurodevelopmental disorders in the child [480]. In mice, induced maternal inflammation leads to increased conversion of tryptophan to serotonin in the placenta, which disrupts the development of serotonergic neurons in the fetal brain; as a result, the fetal forebrain is exposed to elevated levels of this biogenic amine, leading to characteristic changes in key neurogenic processes regulated by serotonin (5-HT) [481], indicating a mechanism by which maternal inflammation can affect brain development in the child [482]. Furthermore, in a decade-long cohort study involving 555 mother–child pairs, the presence of specific proinflammatory proteins during pregnancy correlated with an increased risk of neurodevelopmental disorders in offspring [483]. Other studies confirmed that mothers with asthma, diabetes, or extreme obesity during pregnancy had a very high likelihood of giving birth to a child later diagnosed with ASD [484]. Another study of 1,241 mother–child pairs showed that elevated levels of selected inflammatory cytokines in the placenta and umbilical cord blood were associated with developmental delays, and that the negative impact of a proinflammatory intrauterine environment on children's neurological development was exacerbated by low maternal vitamin D levels [485]. Another studies shows that supplementation of vitamin D has effects on interleukin -6, serum serotonin and on reduction of core symptoms in children with ASD [486], [487], better results were dependent of the earliest age of this treatment [488].

Histamine and Embryonic Brain Development

Histamine appears very early in the developing brain and influences neural stem/progenitor cells depending on the type of receptor activated. Scientific studies provide a broad overview of the role of histamine in brain embryogenesis [489]. These studies present the dynamics of histamine levels during the prenatal period, its effects on developing brain cells, and potential links to developmental disorders [200], [490]. A classic study describing HNMT activity in the pineal gland, thalamus, and peripheral nerves during chick development shows the appearance of enzyme activity already in the embryo and its increase with maturation. It covers the development of enzymatic activity that methylates and degrades histamine [491]. Research shows that measurements of DNA methylation during pregnancy, as an important epigenetic feature, may correlate with the later development of ASD in children [492].

A better understanding of epigenetic mechanisms also allows comprehension of how the developing epigenome is susceptible to genetic and environmental influences (for example, factors that raise histamine levels) [493], [494], including already in the placenta [495]. For example, altered GAD1 methylation patterns in ASD may affect its expression and reflect heterogeneity in epigenetic regulation at the cellular level [496], while higher methylation of the oxytocin receptor OXTR in intron 1 observed in adults with ASD compared to neurotypical individuals has generated great interest in social neuroscience and psychiatry regarding oxytocin's role in social cognition, and OXTR hypermethylation as a biomarker for adults with ASD [497].

For DNA/histone methylation, the main methyl group donor in the body, SAM (S-adenosylmethionine), is required – which also supports histamine breakdown via HNMT. Proper levels of, among others, folic acid, vitamin B6, and B12 support the synthesis of S-adenosylmethionine (SAM) – a key methyl group donor in the CNS – thereby exerting a neuroprotective effect by limiting oxidative stress, histamine levels, excessive microglial activation, and neuroinflammation. In the case of their deficiency, SAM levels decrease while SAH (S-adenosylhomocysteine, which acts as an inhibitor of methyltransferases) increases, leading to impaired DNA and protein methylation, slower histamine degradation (particularly via HNMT), and consequently elevated histamine levels in tissues and body fluids. This may result in symptoms of HIT, allergic hyperreactivity, migraines, and may also contribute to the pathogenesis of certain neuropsychiatric disorders (ASD, depression) [498]. High histamine levels may signal a burden on the DNA methylation cycle, thereby influencing the epigenetic regulation of genes in the embryo. Additionally, signs of oxidative stress and disturbances in DNA methylation processes are frequently observed in individuals with ASD [498]. Supplementary therapy studies indicate that supplementation with components such as vitamins B6, B9, B12, C, E, D, omega-3 fatty acids, glutathione, and choline can effectively influence methylation regulation and nutrition, support metabolic functions, and significantly alleviate ASD symptoms [499].

Histamine Metabolism – the Enzymes HNMT and DAO

The enzymes DAO and HNMT are crucial for histamine degradation. DAO functions extracellularly, breaking down histamine derived from the diet. HNMT works intracellularly and is the main enzyme responsible for histamine breakdown in the central nervous system. HNMT methylates histamine (N-methylation), whereas DAO oxidatively deaminates it, producing different metabolites. Reduced activity of these enzymes can result in excess histamine and symptoms that exacerbate autistic behaviors in ASD [168], [164].

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HNMT

HNMT (histamine N-methyltransferase) is an enzyme responsible for the intracellular degradation of histamine. The highest HNMT activity is observed in the central nervous system —particularly in the brain—as well as in the liver, kidneys, and lungs. HNMT is a monomer with a molecular weight of approximately 33 kDa and is dependent on the presence of magnesium ions (Mg^{2+}) and SAM (S-adenosylmethionine) as a methyl group donor. HNMT catalyzes the methylation of histamine, leading to the formation of N-methylhistamine. This is the main pathway of histamine degradation in the CNS, where DAO is not present. HNMT regulates histamine levels in the brain and thus influences processes related to sleep, memory, learning, and emotional responses [373], [93]. Polymorphisms (genetic variants) in the HNMT gene may lead to altered enzyme activity and are being investigated in the context of neurological and psychiatric disorders such as ADHD, Parkinson's disease, and schizophrenia [500], as well as autism [39]. Research results indicate that HNMT plays an important role in human neurological development, and its deficiency may increase sensitivity to histamine (HIT), particularly in brain tissues. Reports of mutations in the HNMT gene in humans and their associations with intellectual developmental disorders provide evidence that the HNMT gene has functional significance in the development of the nervous system [501].

DAO

DAO is an enzyme belonging to the oxidase group; it is an enzymatic protein composed of an amino acid chain—therefore, it is a globular protein. DAO is produced mainly by the epithelial cells of the small intestine (enterocytes), but it is also present in the kidneys, liver, placenta, and to a lesser extent in other tissues, where it breaks down and neutralizes histamine. DAO is a dimer, and its activity depends on proper expression of the AOC1 gene and the availability of cofactors. Its structure contains an active site with a copper-containing coenzyme, which participates in the oxidation reaction [452], [453]. The DAO enzyme plays a key role in catalyzing the breakdown of histamine and other biogenic amines (e.g., putrescine, cadaverine) [454], converting them into the corresponding aldehydes, ammonia, and hydrogen peroxide [455]. DAO catalyzes the oxidative deamination of histamine, leading to the formation of imidazole acetaldehyde, which is then further metabolized [452]. Its main function is the degradation of histamine derived from the diet (exogenous histamine, e.g., from fish, cheeses, wine, and fermented foods), thereby protecting the body against excess histamine supplied with food [455].

The DAO enzyme may also be released by heparin [456]. The body's response to heparin in the form of increased DAO levels is poorly predictable and strongly depends on individual characteristics [457]. DAO deficiency or low DAO activity may lead to the accumulation of histamine and symptoms of HIT, such as headaches, diarrhea, urticaria, skin flushing, and even allergy-like reactions, so-called pseudoallergies [11], [458]. DAO activity may decrease in inflammatory bowel diseases (e.g., celiac disease, Crohn's disease, SIBO), with damage to the intestinal mucosa, under oxidative stress, due to certain medications or toxins that inhibit DAO, when DAO is continuously utilized in the presence of excess histamine, or when cofactors (copper, vitamin B6, zinc) are deficient. In practice, this means that chronically high histamine levels may "overload" DAO, causing its efficiency to decrease and histamine to accumulate in the body [372].

Serum DAO activity differs significantly by sex, with women showing higher serum DAO levels than men, what is shown in article "Sex is the main factor determining DAO activity in healthy individuals" [509]. Some studies have shown that individuals with ASD may have lower activity of the DAO enzyme, which can result in excess histamine and symptoms that exacerbate autistic behaviors (e.g., anxiety, aggression, sleep disturbances) [168]. Low blood DAO levels may indicate a reduced capacity of the body to degrade histamine—for example, in HIT or in cases of damage to the intestine, liver, or kidneys. High blood DAO levels are sometimes observed during pregnancy (the placenta produces DAO) or as a result of enzyme release from tissues in certain disease states.

Histamine induces estrogen production in the ovaries, while estrogen induces the release of histamine from mast cells in the uterus [85]. For example, women with endometriosis have high histamine levels and a tendency toward allergies, which suggests reduced DAO levels [184]. When there is an excess of histamine in a woman's body, it may increase estrogen levels and disrupt hormonal balance. Histamine additionally intensifies uterine contractions and activates pain receptors [510], [511], thereby increasing sensitivity to menstrual pain, cyclic headaches, and digestive problems [183]. However, not all women who experience these symptoms suffer from HIT. Before menstruation, the body demands an increased amount of histamine in order to intensify uterine contractions, which during menstruation are a natural mechanism for clearing the uterus of unnecessary tissue and enabling the start of a new menstrual cycle (PMDD and PMS) [512], [513], [514], (IAPMD) [515]. Therefore, before their period, women experience cravings for histamine-rich foods such as chocolate, cheeses, ketchup, and herring, and the physiologically required high level of histamine at that time causes irritability, nervousness, mood swings, headaches, sleep problems, bloating, and abdominal pain—so-called PMS (Premenstrual Syndrome) [516], [517], [518]. Serum DAO levels vary depending on the menstrual cycle; studies indicate that plasma DAO concentrations are significantly lower in the follicular phase than in the luteal phase [519]. In addition, DAO produced in the placenta plays an important role in female reproductive functions, including the maintenance of pregnancy [184].

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During Pregnancy, the Placenta Produces 500 Times More DAO

A review of the role of histamine in embryo–uterus interactions, proliferation, and differentiation during pregnancy indicates that both excessively low and excessively high histamine levels may affect the course and development of pregnancy. Prenatal exposure to stressors (such as infections or toxins) may simultaneously influence the development of the embryonic immune and nervous systems [490], including stimulation and sensitization of mast cells and the development of MCAS (i.e., frequent or continuous histamine release) [459]. In addition, estrogens affect mast cell function (via estrogen receptors) and may increase their tendency to degranulate, thereby increasing local histamine concentrations. This explains observations of "estrogen → increased histamine" in the context of allergies, PMS, or pregnancy [514].

Scientific studies report that during pregnancy the placenta produces large amounts of the enzyme DAO (diamine oxidase); it is estimated that the placenta may produce up to 500 times more DAO than other tissues, such as the intestines or kidneys, depending on the stage of pregnancy and individual differences [184], [520]. Within the first 20 weeks of pregnancy, DAO levels measured in maternal plasma increase exponentially—up to 1000-fold compared with pre-pregnancy levels [521]. This high production is crucial for histamine metabolism in both the mother and the fetus, protecting against excessive histamine levels that could harm the developing organism, specially with Rh or ABO blood group incompatibility [185]. DAO in the placenta degrades histamine derived from the maternal diet or released during immune reactions, preventing its transfer into the fetal circulation. This is particularly important because the fetus has an immature histamine-metabolizing system. It has also been observed that while DAO activity in the mother's body shows a steady upward trend, only minor fluctuations in its concentration occur in amniotic fluid and fetal blood [522]. Histamine concentrations in maternal blood during normal pregnancy fall below levels observed in healthy non-pregnant women [185]. In contrast, in complicated pregnancies, a halt in the increase of maternal plasma DAO levels and an elevation of circulating histamine levels are observed, significantly increasing the risk of preeclampsia, threatened miscarriage, and spontaneous miscarriage [523], [524].

High expression of the AOC1 gene in the placenta ensures increased DAO enzyme activity, which represents an adaptation to physiological changes in pregnancy such as increased vascular permeability and inflammatory responses. Certain genetic mutations, such as polymorphisms in the AOC1 gene (encoding DAO) or the HNMT gene, may lead to deficiencies of these enzymes and elevated histamine levels [39]. These genetic variants have also been observed in some children with autism spectrum disorder (ASD) [154]. DAO deficiency in a pregnant woman combined with exposure to environmental stressors—external stimuli, trauma, or histamine-rich or histamine-releasing foods—may increase the risk of pregnancy complications and potentially affect child development [525]. Maintaining a balance between histamine and DAO plays a key role in the normal course of pregnancy and the health of the child [184]. When most histamine in the mother's body has been degraded by DAO, pregnant women may intuitively reach for so-called "cravings," i.e., histamine-rich foods such as herring, chocolate, or pickled cucumbers, in order to improve digestion.

Immediately after childbirth, when the placenta is removed, DAO levels drop sharply and return to pre-pregnancy values. This means that the body loses the additional "buffer" protecting against excess histamine. As a result, histamine may act more strongly for some time, which in some women manifests as increased sensitivity to histamine-rich foods or histamine-releasing stressors. Symptoms attributed to histamine sensitivity after childbirth may include headaches, migraines, fatigue, skin problems (itching, urticaria), hair loss, and mood disturbances (postpartum depression may be partially modulated by neurotransmitters and histamine, although this is a complex mechanism) [526], [527], [184].

DAO, Cooper and A2 Casein in Breast Milk

The enzyme DAO (diamine oxidase) is present in human breast milk, although its concentration is relatively low compared to other tissues, such as the placenta, which produces it in much larger amounts. The presence of DAO in breast milk is important for histamine metabolism in infants, particularly during the first months of life, when their own enzymatic system is not yet fully developed (Centers for Disease Control and Prevention) [528] and may have a protective effect [529]. DAO activity is highest in colostrum, and significant DAO activity is also observed in mature human milk (up to 30 days of lactation), which may be related to the need for histamine degradation during early lactation [530], [531]. The highest concentrations are generally observed around the peripartum period [529]. Research indicates that DAO in breast milk also originates from the secretions of mammary glands [529] and may support the breakdown of histamine provided by the mother's diet or produced endogenously by the infant [157]. In newborns and infants, the digestive system—including DAO production—is immature, making the presence of this enzyme in breast milk crucial for protection against excess histamine, which could trigger allergic reactions or inflammation [532], [533]. However, in cases of mastitis, higher concentrations of histamine, spermine, and putrescine are found in breast milk [534], which may lead to HIT symptoms in children [165], [535]. DAO levels in milk are variable and depend on the stage of lactation, the mother's diet, and her individual expression of the AOC1 gene (which encodes DAO). DAO concentrations in milk are insufficient to fully compensate for

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enzyme deficiency in children carrying AOC1 gene variants (e.g., children with HIT). In such cases, the mother's diet (avoiding histamine-rich foods) may be crucial [527]. It should be noted that "in lactating rats, all newly absorbed copper is preferentially directed to the mammary gland, where it is delivered at higher concentrations to the milk" [530]. Copper-transporting ATPases are expressed on mammary epithelial cells, but according to the researchers, "their role in delivering copper to the milk has not been clarified" [536]. According to the author's hypothesis, if we know that copper is a cofactor for the enzyme DAO, and the baby is no longer protected by this enzyme from the placenta after birth, then perhaps it must be supplied in large quantities so that the baby's body can neutralize histamine, which supports the statement that "in mammals, adequate copper supply during early development is critical, because inadequate copper during pregnancy and early infancy can be fatal" [536].

After weaning, the child's DAO levels begin to depend on their own production, which gradually develops over the first years of life [165]. A 2006 study found that children who were not breastfed were at significantly increased risk of developing autistic disorders. The same applied to children fed formula without simultaneous supplementation with docosahexaenoic acid (DHA) and arachidonic acid (AA). The results were compared to children who were breastfed for more than six months, suggesting that longer breastfeeding or supplementation with DHA/AA is associated with a reduced likelihood of ASD [537]. These findings align with information that human milk (breast milk) contains exclusively A2-type casein, as do goat, sheep, buffalo, and camel milk—proteins that are more natural for humans and better tolerated by the digestive system [538].

Lactose, A1 and A2 Casein in Milk

Lactose is the so-called milk sugar—a natural disaccharide found in milk and dairy products. In order for lactose to be absorbed, the body requires the enzyme lactase (β-galactosidase), which is produced in the small intestine. Lactase hydrolyzes lactose into its constituent monosaccharides, glucose and galactose, allowing their subsequent absorption through the intestinal wall into the bloodstream. When lactase is absent or insufficient, lactose is not digested and passes into the large intestine, where it undergoes bacterial fermentation, which can increase intestinal permeability, indirectly activate mast cells, and exacerbate histamine-related symptoms. Accompanying symptoms include bloating, abdominal pain, cramps, diarrhea, nausea, and a feeling of "sloshing" in the stomach. This is not an allergy, but an enzymatic lactose intolerance [539]. Casein is a group of milk proteins to which the human body can respond differently (inflammatory or allergic reactions). In humans, casein constitutes about 20–40% of milk proteins, with the remainder being whey proteins. In cow's milk, casein makes up about 80% of the protein content [540]. Casein is highly valuable because it contains phosphorus, calcium, and proteins, forming a casein clot in the stomach that is digested slowly over many hours, providing a steady stream of amino acids, which are used, among other things, in hemoglobin synthesis (the oxygen-carrying protein) [541]. It has been observed that some people who are allergic or sensitive to various cow milk casein proteins tolerate goat milk well. One explanation may be the A1/A2 hypothesis, referring to variants of beta-casein that differ by only a single, but significant, amino acid at position 67 [540].

A2 casein (with proline at position 67) occurs naturally in almost all mammals. However, in European dairy cattle, a genetic mutation occurred (A1/A1 or A1/A2), which changed the protein structure to A1 casein (with histidine at position 67) [542]. The A1/A1 or A1/A2 mutation, due to higher milk yield, was propagated through selective breeding, and only a few cows carry the A2/A2 genotype, producing milk containing only A2 casein. Cows with the A2/A2 genotype are most commonly found in developing countries, mainly in Asia and Africa. Keith Woodford, in his book "Devil in the Milk", compiled over 100 scientific publications linking A1 casein with increased risks of various health issues, including skin problems, joint pain and inflammation, diabetes, heart disease, autoimmune disorders, mental health issues, autism spectrum changes, and schizophrenia [543]. For this reason, consumption of milk containing A2 casein is recommended (also demonstrated in mouse studies) [544], [545]. This small difference in the amino acid of the A1 and A2 β-casein molecule is highly significant [546], because A1 and A2 β-casein interact differently with digestive enzymes in our stomach and intestines [547].

During digestion of A1 casein (with histidine), the stomach produces the peptide beta-casomorphin-7 (BCM7), which has pro-inflammatory and opioid-like effects (similar to morphine or heroin), meaning it acts as a drug and toxin [548]. This peptide can negatively affect the digestive, nervous (brain function), hormonal, and immune systems, potentially exacerbating autism symptoms [549]. These facts and observations support the author's hypothesis regarding the important role of histamine in ASD pathophysiology. They suggest that not only the BCM7 peptide (as a biologically active toxin) can induce histamine and cytokine release, leading to gut inflammation, which promotes further histamine degranulation from mast cells and impairs histamine breakdown by DAO (diamine oxidase), but also that histidine in A1 casein can, through decarboxylation in the gastrointestinal tract by bacterial or tissue enzymes, be converted into histamine. Excess histamine may slow intestinal motility, increase intestinal barrier permeability, and exacerbate symptoms observed in various medical conditions [550]. A1 casein milk can indirectly increase histamine levels in the body. As a result, sensitive individuals

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(e.g., with HIT, gut disorders, or reduced DAO activity) may experience symptoms similar to histamine excess or HIT after consuming it [547]. (Table 2).

Summary of the possible mechanism:

A1 milk (β-casein with histidine) → Digestion in the gut → Formation of BCM-7 → Increased intestinal permeability ↑ + inflammation ↑ → Mast cell activation ↑ → Histamine release ↑ → DAO inhibition ↓ → Histamine is not broken down → Rise in body histamine levels (intolerance symptoms) ↑ → Possible histamine excess symptoms from A1 milk → headaches, migraines, runny nose, shortness of breath, nasal congestion, rapid heartbeat, skin itching, hives, bloating, diarrhea, reflux, anxiety, insomnia ↑ → Inflammation ↑ → Impaired development ↓

Table 2: Secondary reactions in the intestine and tissues – elevated histamine levels and intensified histamine response.

Phenomenon	Mechanism	Final effect
Inflammation	BCM-7 activates opioid receptors and NF-κB	Cytokine and histamine release
Mast cell activation	Mast cells respond to inflammatory stress	Histamine released locally and systemically
Intestinal barrier damage	Increased intestinal permeability	Endotoxins and allergens penetrate into the bloodstream, intensifying the histamine response
Decrease in DAO activity	DAO (diamine oxidase) breaks down histamine, but BCM-7 and intestinal stress inhibit it	Histamine is not broken down – its level rises
Histidine in A1 casein	Histidine decarboxylase, the gut microbiota is disrupted, and the intestinal environment promotes fermentation and decarboxylation	Converted into additional histamine

Studies have shown that children fed milk containing A1 casein also develop more slowly than those fed milk with A2 casein [551], and A1 casein has also been linked to SIDS (sudden infant death syndrome) and other health issues in infants [552]. Therefore, A2 human milk is considered safe for infants, including those sensitive to A1-type cow milk proteins [553], [554].

Neonatal Sepsis and Hyperbilirubinemia (Jaundice) in Newborns

Researchers suggest that neonatal sepsis is primarily related to immunological immaturity, particularly in premature infants and boys [555], supporting the hypothesis proposed by Filcek [11]. Although sepsis is suspected in 7–13% of newborns, only 3–8% of cases demonstrate confirmed bacterial infection [556], suggesting that many newborns may experience sepsis-like inflammatory responses associated with excessive histamine signaling, DAO reduction (placenta removal) and antibiotic-induced [556] (damaging the intestines where DAO is produced), and excessive mast cell activation caused by invasive hospital procedures commonly used in premature infants [556], [557]. The author hypothesizes that loss of placental DAO after cord clamping combined with labor (prolonged compression activates mast cells in the skin), a change in ambient temperature from 37 °C (inside belly) to 18°C (outside), cold air in the lungs, and hospital environmental factors may induce mast cell degranulation, resulting in increased histamine release, with time leading to histamine storm, activating also histamine receptors H1-H4. This cascade can contribute to microthrombus formation, erythrocyte hemolysis, hyperbilirubinemia, jaundice, impaired circulatory function, and, in some cases, neurological complications, multi-organ inflammations, symptoms that resemble sepsis [11], [558], [559], [560], [561], [562].

Clinicians should consider important factors that could increasing the risk of neonatal sepsis [563] and implement appropriate preventive measures [564]. Prolonged recovery from sepsis may be associated with the risk of neurodevelopmental disorders [564], as well as with elevated bilirubin levels [565], the excess of which in severe neonatal jaundice [563] can lead to brain dysfunction [566]. It has also been shown that elevated unconjugated bilirubin levels has neurotoxic effects and may contribute negatively to brain tissue also cause the neurological damage [567], [568]. The author hypothesizes that erythrocyte aggregation [569] may be associated with microthrombosis and disseminated intravascular coagulation (DIC), potentially induced by excessive histamine levels and secondary hematological abnormalities, including thrombocytosis. These mechanisms may lead to increased erythrocyte breakdown and increased bilirubin levels, manifesting as jaundice of the skin and sclera, similar to those observed in sepsis [11], [570], [571]. This mechanism may be further enhanced by body's estrogens, estrogens from environmental, and other toxic factors that activate mast cells to release histamine [559], [181], [560], [561], [514]. The hypothesis is that loss of placental DAO after birth, in combination with environmental factors and potential blood group incompatibility, may lead to mast cell degranulation, increased histamine levels, congenital metabolic disorders, microthrombi formation, erythrocyte disintegration, hyperbilirubinemia, jaundice (which appear after 2-3 days of life), exacerbate the inflammatory response through histamine release and activation of H1–H4 receptors [555] and potentially SIRS, sepsis or brain damage [569].

Biological, chemical, physical, environmental factors → mast cell degranulation → histamine release → microthrombus formation → erythrocyte hemolysis → hyperbilirubinemia → jaundice → impaired circulatory function, neurological

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complications, multiorgan inflammations → symptoms that resemble SIRS and sepsis.

Histamine Pathway Genes and Environmental Factors Play a Role in ASD

The histaminergic nervous system (HS) is responsible, among other things, for regulating cognitive functions and behavior, and it is associated with various neurological disorders such as Tourette syndrome (TS), which is frequently observed in individuals with ASD [572]. This suggests a significant role for histamine in the development of ASD symptoms [259]. The hypothesis presented suggests that identifying and understanding the physiological role of disturbances in the histaminergic system (HS) could indicate potential directions and key insights for the development of prevention strategies and new therapeutic approaches in ASD, which may also involve both genetic and environmental factors [150]. Interactions between genetic and environmental factors influence the immune system, leading to cytokine imbalance, which, as research shows, occurs in ASD and, together with MCAS and histamine, may underlie ASD [573]. This is particularly relevant because inappropriate or excessive immune activity, including cytokines activated by histamine receptors, can significantly affect the nervous system and have neurological consequences [265].

Key genes that influence histamine regulation in the body include: HDC, which affects endogenous histamine production; genes involved in histamine and metabolite breakdown, including AOC1 (encoding DAO), HNMT (encoding HNMT), MTHFR (C677T and A1298C mutations), which helps regulate methylation necessary for reducing intracellular histamine via HNMT; PEMT, which indirectly supports mast cell stabilization; as well as CYP2C19 (implicated in histamine metabolism Diamine oxidase (histaminase)), COMT (Important for catecholamine and phenol metabolism [574], MAOB, CYP3A4 (important for the metabolism of most drugs), PST (Phenol sulfur transferase - important for metabolism polyphenols) and ALDH7A1 [575], [576]. Gene Ontology classification lists over 200 genes participating in the histamine pathway, encoding other enzymes and proteins [577]. Polymorphisms in genes encoding histamine-degrading enzymes influence individual differences in histamine metabolism and may predispose to various diseases [578], [579]. For example, genetic variants in AOC1 and HNMT affect autism spectrum disorders [39], as well as Parkinson's disease and schizophrenia [500]. These genetic variations, together with environmental factors that activate the immune system, support the histaminergic hypothesis in the development of neurodevelopmental disorders [580], [581] as well as in systemic diseases [582].

AOC1 Gene of the DAO Enzyme

The AOC1 gene is located on chromosome 7q36.1 in humans. It encodes the DAO protein, which is a copper-containing enzyme belonging to the amine oxidase family. DAO catalyzes the oxidation of biogenic amines such as histamine, putrescine, and cadaverine, converting them into less active metabolites, for example imidazole-4-acetic acid from histamine. AOC1 expression can be modulated by dietary factors, inflammatory states, or genetic polymorphisms. Mutations or variants in AOC1, for example rs10156191 and rs1049742, are associated with reduced DAO activity, which may lead to HIT [154]. Studies suggest a link between AOC1 polymorphisms and ASD or autoimmune diseases, where DAO deficiency may exacerbate inflammation and allergies [583], [578]. DAO deficiency causes histamine accumulation, which manifests as migraines [584], urticaria, sleep and digestive problems [88].

HNMT Gene of the HNMT Enzyme

The HNMT enzyme (histamine N-methyltransferase) is encoded by the HNMT gene, located on chromosome 2q22.1 in humans. It is the main enzyme responsible for the intracellular metabolism of histamine in the central nervous system and the brain [581]. HNMT catalyzes the methylation of histamine, converting it into the inactive metabolite N-methylhistamine with the help of the cofactor S-adenosylmethionine (SAM) [167]. HNMT expression is regulated at the transcriptional level and can be modulated by factors such as inflammatory states, drugs (e.g., methylation inhibitors), or genetic polymorphisms. Genetic variants, such as rs11558538 (Thr105Ile), are associated with reduced HNMT enzyme activity [585], [586]. Polymorphisms in HNMT are being studied in the context of allergies, asthma, migraines, autism spectrum disorder (ASD), and schizophrenia, where impaired histamine methylation may exacerbate inflammation or neurotransmission [587], [501], [588]. Genetic deficiencies such as polymorphisms in the AOC1 and HNMT genes [587] as well as NOS2, or functional deficiencies acquired, for example through intestinal inflammation, lead to histamine accumulation, exacerbating neuropsychiatric symptoms [154].

NOS2 – Gene for iNOS

Studies suggest that insufficient expression of AOC1 and NOS2 determines susceptibility to disease, increasing the risk of infections, and also participates in the development of COVID-19 [589]. Additionally, it is important to note the NOS2 gene, which encodes inducible nitric oxide synthase (iNOS), located on chromosome 17q11.2-q12 [590]. The iNOS enzyme is responsible for producing large amounts of nitric oxide (NO) in response to infection, stress, inflammatory, and immunological factors. It plays a key role in defense mechanisms, inflammatory processes, and sepsis, but excessive NO production can also lead to tissue damage. NOS2 polymorphisms (e.g., rs2297518) may affect NO regulation, which is associated with the risk of asthma, ulcerative colitis, and major common diseases in intensive care units, including

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the development of SIRS and sepsis [591], acute lung injury, and multiple organ failure [592]. NO is also being studied in relation to susceptibility to cardiovascular disease, diabetes, cancer, and neuroinflammatory diseases [593]. High iNOS expression is often associated with excessive NO production, leading to nitrosative stress and subsequent mitochondrial and neuronal damage [594]. Hyperactive NOS2 stimulates iNOS to continuously produce large amounts of NO, independently of calcium concentration [592]. Under oxidative stress, this NO reacts with free radicals, especially superoxide anion ($O_2^{\bullet-}$), forming peroxynitrite ($ONOO^-$), a highly reactive and toxic oxidant capable of damaging lipids, modifying proteins, and inducing DNA damage [595]. This mechanism is highly relevant in sepsis, neurodegenerative diseases such as Parkinson's and Alzheimer's [596], autoimmune diseases, and chronic inflammatory conditions [593]. Research on peroxynitrite decomposition offers hope for restoring cardiovascular function in sepsis [591].

Common Biological Pathways: Histamine and NO, and NMDA Receptors

Histamine, through H1 and H2 receptors, activates endothelial nitric oxide (NO) production [597], [598]. As a result, NO acts as a vasodilator, which explains why histamine causes decreased blood pressure, skin flushing, and increased blood flow during inflammation and allergic reactions [599]. When histamine is not properly degraded, for example due to HNMT or DAO polymorphisms, it enhances inflammatory responses, which can sustain NOS2 expression. Both histamine (in cases of HNMT deficiency) and NO (in cases of NOS2 overexpression) contribute to neuroinflammation, neurotoxicity, and impairments in memory, concentration, and psychiatric symptoms such as ASD, PTSD, and depression [596], [93]. A shared mechanism is glutamate excitotoxicity: histamine and NO modulate the activity of NMDA receptors (N-Methyl-D-Aspartate receptors), which are one of the main receptor types for glutamate, the primary excitatory neurotransmitter in the brain [600]. Excessive NMDA activation leads to overproduction of NO, causing nitrosative stress and neurotoxicity. Additionally, NO acts retrogradely on presynaptic terminals, increasing glutamate release and further amplifying excitotoxicity. NMDA modulation is observed in Alzheimer's disease [601] and schizophrenia [602]. NMDA antagonists or agonists are used therapeutically [593].

Inflammatory states and mast cell activators → released histamine → stimulates endothelium and immune cells → increased NOS2 expression → iNOS induction in response to inflammation, infection, or immune stress → more NO → excessive NMDA activation → overproduction of NO + glutamate release → excitotoxicity → neuroinflammation in the brain → neurodevelopmental and neurodegenerative diseases.

Genetic Associations and Clinical Significance

The genes AOC1, HNMT, and NOS2 are functionally connected through a shared pathway: mast cells → histamine → NO.

- Polymorphisms in AOC1 (e.g., rs10156191, rs1049742) are associated with reduced DAO activity → higher histamine levels in the body and brain → histamine intolerance HIT.
- Polymorphisms in HNMT (e.g., rs11558538 – Thr105Ile) → lower enzyme activity → higher histamine levels in the brain.
- Polymorphisms in NOS2 (e.g., rs2297518) → iNOS overexpression → increased NO → higher glutamate levels in the brain [811].

When disruptions occur simultaneously in these genes → a synergistic effect arises: chronic inflammation, oxidative stress, neuronal damage, and neurotoxicity [68], which has clinical relevance in:

ASD, ADHD, and PTSD: Studies indicate that both excessive histaminergic activity (HNMT ↓, DAO ↓) and NO overproduction (NOS2 ↑) contribute to deficits in attention, memory, and emotional regulation [37]; [603], [373]. These mechanisms are neurotoxic, contributing to neurodegenerative diseases such as Alzheimer's and Parkinson's [267], [604], [605] and may also contribute to the development of SIRS and sepsis [11A], [606]. Research supports the author's hypothesis that systemic mast cell degranulation increases mortality during sepsis [99], [100], [607].

Sepsis / SIRS: Mast cells → histamine storm → coagulation + activation of H1–H4 receptors → cytokine storm → NOS2 induction → massive NO production → vasodilation, hypotension, septic shock → potential death.

ASD is Over 3 Times More Common Among Boys Than Among Girls

In a study conducted on 25 women and 25 men, higher mean DAO activity was observed in women than in men, and the findings clearly indicate that sex-related differences influence DAO enzyme activity [509]. A population study revealed significant associations between DAO gene polymorphisms rs3918346 and rs3825251 and boys with ASD [38], where ASD occurs more frequently in boys (approximately a 4:1 ratio compared to girls) [608]. DAO deficiency or dysfunction, together with environmental factors (e.g., exposure to oxidative stress), can affect inflammation and disrupt neurotransmitter balance (e.g., histamine, glutamate, and GABA), influence neurological development, and increase the risk of ASD [609], [251], [610]. These findings shed light on why ASD is more frequently observed in males and simultaneously support the previous and proposed hypothesis regarding the role of

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histamine in ASD development. Additionally, a case report described a male patient with an HNMT mutation who presented with speech delay, sleep disturbances, ASD traits, and gastrointestinal problems. This confirms that HNMT mutations can lead to phenotypes including autistic features. Researchers noted that significant overall improvement was observed with administration of hydroxyzine (a histamine H1 receptor antagonist) combined with a low-histamine diet [374].

Gene expression studies of the histaminergic system in the brains of individuals with ASD, including HNMT and DAO, suggest that modulation of histamine receptors may represent a promising therapeutic strategy [259]. These findings highlight the importance of histamine regulation in the pathophysiology of autism spectrum disorders and simultaneously indicate that polymorphisms in AOC1 and HNMT affect therapeutic efficacy. Furthermore, they suggest that dietary modification may be an effective tool to support cognitive and behavioral development in children with ASD [39] and for tailoring therapy intensity according to sex [611], [612], [613]. A better understanding of the physiological significance of the histaminergic system (HS) and how its dysfunction affects the body may enable the development of new therapies for individuals with ASD [150]. At the same time, because ASD is multifactorial [614], and DAO is only one of many risk genes, sex-specific mechanisms require further study, including consideration of gene–environment interactions, with efforts to carefully separate cause from effect—continuously asking whether mutations found in ASD genes increase sensitivity to environmental factors or are induced by them [611]. Unraveling the causes of autism is like solving a complex puzzle, and interdisciplinary knowledge that interprets hormonal, genetic, epigenetic, social, and environmental factors can be highly valuable [36].

The Role of Climate, Environment, Noise, Chronic Stress, and Neuroarchitecture in ASD

„One of the great mysteries facing humanity is the question of how we sense our environment. The mechanisms underlying our senses have triggered our curiosity for thousands of years, for example, how light is detected by the eyes, how sound waves affect our inner ears, and how different chemical compounds interact with receptors in our nose and mouth generating smell and taste. We also have other ways to perceive the world around us. Imagine walking barefoot across a lawn on a hot summer's day. You can feel the heat of the sun, the caress of the wind, and the individual blades of grass underneath your feet. These impressions of temperature, touch and movement are essential for our adaptation to the constantly changing surrounding." (Nobel Prize 2021Medicine) [615]. The 2021 Nobel Prize in Physiology or Medicine [616] recognized the discovery of heat-sensitive and pressure-sensitive receptors that respond to touch and mechanical stimuli. This groundbreaking research revealed the fundamental mechanisms by which the nervous system detects temperature, pain, and pressure — transforming our understanding of the intricate interplay between sensory perception and the environment [615], [617].

Environmental factors triggering mast cell activation syndrome (MCAS) include, among others, sensory stressors such as light (including blue light from screens), sound, smell, touch, extreme temperatures, as well as bacteria, fungi, allergens, toxins, pollutants, and heavy metals (e.g., mercury, aluminum) [68], vibrations [416], [618], [78], [80], ionizing radiation, variable electromagnetic fields [77], [619], [620], [621], [622], emotional and oxidative stress, and foods rich in histamine. These factors can enhance mast cell degranulation and lead to histamine accumulation in the body, thereby exacerbating the development and symptoms of autism spectrum disorder (ASD) [12], [25], [26], [623], [573]. Although specific studies are still lacking, there is evidence suggesting that climate may under certain conditions influence DAO and histamine levels, which is why people living in different climates have developed traditions that allow them to cope with chronic stress [81], [624].

In extremely hot climates with blazing sun and limited water or greenery, the level of chronic stress—which increases mast cell reactivity, raising histamine levels and worsening MCAS/HIT symptoms—will be higher than in temperate climates. In extreme climatic conditions, continuous stimulation of mast cells and elevated histamine levels can lead to microthrombi, making the blood thicker, simultaneously reducing oxygen transport to organs, increasing intolerance to certain histamine-containing foods and drinks, and accelerating anxiety, anger, and aggression [464]. Similarly, very low temperatures in winter or in air-conditioned rooms can activate mast cells, which in some individuals may lead to symptoms resembling a common cold [625], [626].

Environmental sources that can activate mast cells and raise histamine levels—if these factors occur simultaneously—can result in histamine accumulation and more severe symptoms [627].

- It has been confirmed that extreme high or low temperatures [628], [629] or sudden temperature changes are common triggers of mast cell mediators (The Mast Cell Disease Society) [630], as well as humidity promoting mold and fungal growth [631], environmental pollution [64], and heavy metals [632], including lead and its toxicity [633], can increase histamine levels, and thus ASD symptoms [634], as observed in children in Jordan [468].
- Mast cells in the lungs are sensitive to cold; [635], [636] when ventilated without active warming and humidification, this can cause a histamine storm and

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exacerbate pulmonary inflammatory responses, as observed in sepsis and COVID-19 [11], [242].

- Dietary factors, including traditional foods that vary by climate, may contain more or less histamine [637], which can influence the gut microbiome and indirectly affect intestinal enzymes, including those involved in histamine metabolism [154]. High temperature and time allows naturally present bacteria to convert free histidine into toxic histamine in fish [638]. This may explain why in hot climates the consumption of alcohol, which is high in histamine, is restricted.
- Brief sun exposure can influence vitamin D production, which in turn may modulate the immune system by stabilizing mast cells [639] however, prolonged sun and UV exposure can trigger mast cell degranulation [640], [641], increasing histamine levels.
- Dependence on chronic stress and noise exposure arises because these triggers activate mast cells through neuroimmunological mechanisms, mainly involving CRH, nerve growth factor (NGF), substance P, neuropeptides, and the HPA axis, leading to mast cell degranulation and exacerbation of the inflammatory response. Particularly sensitive groups include individuals with MCAS/HIT, PTSD, ASD, ADHD, critically ill patients (ICU), mechanically ventilated patients, children, and neurodivergent individuals [642].
- Ionizing radiation induces mast cell degranulation and releases histamine [77], heparin, tryptase [242], and cytokines, intensifying local and systemic inflammatory responses [254], [643]. This effect is particularly pronounced at high altitudes (e.g., in airplanes, in space), in polar regions, and may influence mast cell activation, as indicated by research (UMCS) [644A]. Exposure to radiation also occurs in medical diagnostics: e.g., computed tomography (CT), X-rays (RTG), nuclear medicine (e.g., PET, scintigraphy), medical equipment sterilization devices, and radiotherapy for cancer treatment, where high doses of radiation (e.g., gamma, X-rays) are used to destroy cancer cells but can also activate mast cells. In cases of large-scale radiation exposure (nuclear accidents), it can trigger inflammatory reactions and a histamine storm—radiation sickness (ARS) [645]. Scientific studies, including high-energy physics experiments (e.g., at CERN) [646], generate low levels of ionizing radiation, which can be useful for studying biological effects on the human body [647], [648].

Mast cells activated by these factors release histamine, serotonin, and proinflammatory cytokines, modulating neuroinflammatory pathways that are dysregulated in autism spectrum disorder. This amplifies overactivation of presynaptic H3 histamine receptors, increases neuronal excitability, exacerbates synaptic dysfunction, and intensifies the cognitive and other symptoms characteristic for ASD [30].

Environmental Noise Versus Silence; the Impact of Air-Conditioning Systems on Individuals with Autism and Sensory Hypersensitivity

Environmental noise is increasingly recognized as a significant stressor for individuals with sensory processing differences, including those on the autism spectrum. Common sources of low- and high-frequency noise, such as air-conditioning units, ventilation systems, and HVAC equipment, can induce physiological and psychological stress, particularly in sensitive populations. Individuals with ASD often exhibit heightened sensitivity to auditory stimuli. Even moderate or constant background noise, such as the hum or vibrations from air-conditioning, can trigger: increased anxiety and irritability, difficulties with concentration or verbal information processing, sleep disturbances including delayed sleep onset or frequent awakenings, and exacerbation of repetitive or stereotyped behaviors. Similar effects are observed in individuals with ADHD, PTSD, or sensory processing disorder (SPD), where exposure to continuous or unpredictable noise can impair cognitive function, mood regulation, and overall comfort. Chronic exposure to environmental noise impacts the nervous and autonomic systems, potentially through mechanisms such as activation of the hypothalamic-pituitary-adrenal (HPA) axis, increasing stress hormone levels, heightened activation of sensory cortices leading to cognitive overload, and amplification of neuroinflammatory responses, which may interact with mast cell activation and histamine signaling in sensitive individuals [626], [649].

In people with ASD, who may already exhibit neuroinflammation and excitation/inhibition imbalance (glutamate–GABA), environmental noise can further increase neuronal hyperexcitability and behavioral dysregulation [18]. Unfortunately, home and school environments are filled with pervasive noise [650], including noise and cold from air-conditioning systems (especially in countries with hot climates) [625], which affects the glutamate–GABA balance as well as neuroimmunological and behavioral responses in children with ASD [333].

The combination of multiple environmental stressors increases the risk of toxic damage to the body and exacerbates the development and duration of diseases, depending on genetic predisposition [626], [651]. Therefore, it is important to understand how the physical, chemical, biological, and architectural environment affects children with ASD and their hormonal, neuronal, and emotional (psychological) functioning [652], [573], and how sensory-friendly environmental design—such as choosing quieter HVAC units with low vibration and low low-frequency noise levels,

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using sound-absorbing materials around ventilation systems, and providing sound-dampening devices or earmuffs for sensitive individuals, especially in schools, clinics, and workplaces as part of therapy—can improve emotional regulation and reduce oxidative stress [653], [654]. This, in turn, may contribute to the reversal of epigenetic processes [655] within the gene–environment relationship [656], [36]. Silence, in contrast, is not merely the absence of noise—it can be a powerful stimulus for brain development. In 2013, a research team led by neurobiologist Imke Kirste published a study titled "Is silence golden? Effects of auditory stimuli and their absence on adult hippocampal neurogenesis." Silence turned out to be the stimulus that most strongly promoted the formation and survival of new neurons in the hippocampus, a brain region crucial for memory, learning, and emotional regulation. Unlike other sounds, silence not only stimulated brain activity but also appeared to help new neurons mature and integrate more effectively. In a world saturated with noise, giving the brain moments of quiet may be more important than we realize [657], [658].

Greenery in Schools

Living in an urban environment and the modern city lifestyle expose individuals to environmental toxins and infections, which contribute to the complexity of ASD treatment [659]. Children aged three to six spend most of their time in preschool buildings, with limited access to nature, even though contact with nature provides many benefits for child development [660]. Scientific studies emphasize the positive impact of green areas on academic performance and students' skills; likewise, lower residential building density and greater availability of green spaces have a positive effect on the play behavior of children with ASD [661]. These findings form a foundation for implementing and monitoring improvements in human–nature relationships, introducing innovative, more nature-oriented solutions in cities lacking greenery [662], and for a conscious approach to architectural design and built environments for people with autism spectrum disorders [663], [664], [665], [666], [667], [668]. A continuous global increase in the number of children with autism spectrum disorder (ASD) has been reported worldwide (CDC Autism) [669], with particularly high prevalence rates observed both in the United States and in countries such as the United Arab Emirates [670]. For this reason, the Zayed Higher Organization (ZHO) [671] for People of Determination in the UAE established an Autism Center in Al Ain for children with ASD, and researchers have begun efforts to identify the causes of ASD, develop prevention strategies, reduce symptoms, and support the well-being of children with ASD and their families [672]. Researchers are also investigating the impact of various aspects of the home environment on children with ASD [673], as well as how built environments affect mental health—for example, how crowding or noise in places such as airports can intensify psychological stress [674]. Today, people spend far more time in enclosed spaces without contact with the natural environment than their ancestors did; this may of course vary depending on geographic or cultural context, but nevertheless this shift in lifestyle affects health and well-being [675], [658].

Meta-analyses suggest that greenery and potted plants in rooms can be highly beneficial in reducing stress and enhancing well-being in children, including those with ASD [676], [677]. At the same time, it has been noted that a major challenge is the high cost of plants and their maintenance in buildings in countries with warm climates. Researchers therefore hypothesized that artificial green elements might have the same positive effect on the mental and emotional health of children with ASD as real greenery [678]. The findings showed that children preferred spaces with greenery and even demonstrated a better response to artificial greenery (likely because children may fear insects and react negatively to molds and fungi that can be present in natural greenery) [679]. The above-mentioned benefits as well as phobias were also identified in another study [680], which showed that planners and designers should consider contact with safe greenery as an intervention strategy and as therapeutic spaces that better respond to the needs of children with ASD, support their motor-sensory, emotional, and social interactions, and improve health and well-being in the built environment [681].

Neuroarchitecture of Vinci Power Nap®

Neuroarchitecture is an interdisciplinary field that studies and applies the influence of the built environment on the functioning of the brain and nervous system, integrating knowledge from architecture, neuroscience, and psychology to design spaces that support physiological health, psychological well-being, and human cognitive processes [682]. Vinci Power Nap® is an innovative, pioneering neuroarchitecture system based on the principles of relaxation of all senses, created to enable rapid stress reduction, mental and physical regeneration, and improved well-being (Vinci Power Nap®) [683]. Developed by Polish designer Magdalena Filcek, it combines the latest advances in neuroscience and architecture to create a safe, soothing environment—particularly important for highly sensitive individuals and children with ASD. The central element of the system is the "cocoon" experience within an enclosed, pollution-free green, forest-like space that limits sensory overload and modern environmental stressors, such as noise (including the absence of ditioning hum), restoring silence, clean air, gentle warm light, birdsong, pleasant touch, taste, and non-personalized deep pressure. Combined with gentle pendular movement and controlled sensory stimulation (Sensory Integration) [684], this environment fosters a sense of safety and calm [685], [686]. It is an oasis in which, within 15–20 minutes, deep relaxation, tension reduction, and restoration of emotional balance are possible [653], [687], [688].

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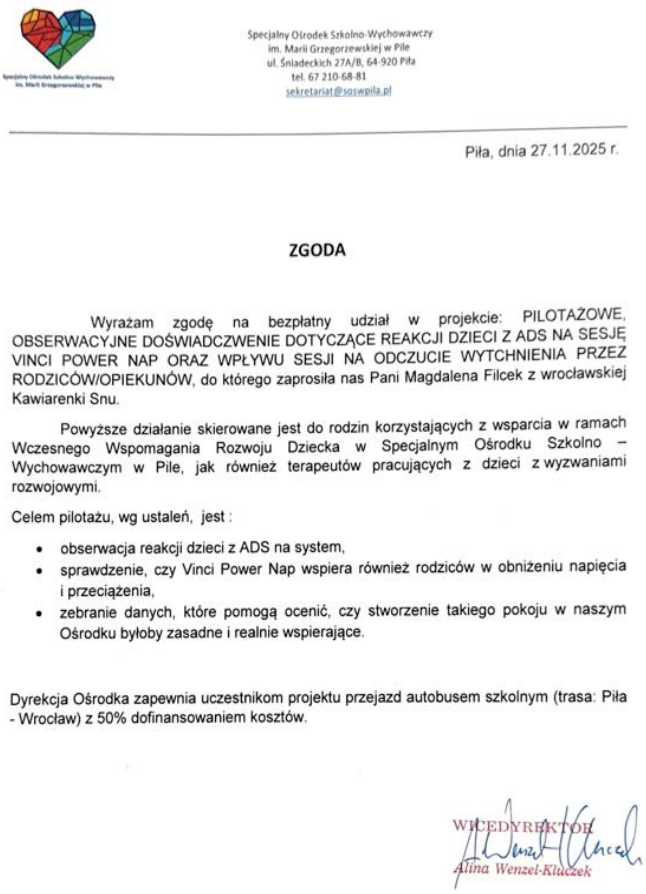
The system was created to accommodate a wide range of users, including individuals working in highly demanding conditions—such as executives, pilots, astronauts, and military personnel experiencing PTSD—as well as children, who are especially vulnerable to sensory overload. By synchronizing the body's natural rhythms (breathing, heart rate, brain waves), Vinci Power Nap® helps reduce cortisol levels while simultaneously supporting the release of oxytocin and serotonin—neurotransmitters associated with calm, bonding, and positive mood—as supported by research [688], [689]. Such an approach—through the integration of greenery, science, architecture, and care for sensory



Specjalny Ośrodek Szkolno-Wychowawczy
im. Marii Grzegorzewskiej w Pile
ul. Śniadeckich 27A/B, 64-920 Piła
tel. 67 210-68-81
sekretariat@soswpila.pl

Piła, dnia 27.11.2025 r.

ZGODA

Wyrażam zgodę na bezpłatny udział w projekcie: PILOTAŻOWE, OBSERWACYJNE DOŚWIADCZWENIE DOTYCZĄCE REAKCJI DZIECI Z ADS NA SESJĘ VINCI POWER NAP ORAZ WPŁYWU SESJI NA ODCZUCIE WYTCHNIENIA PRZEZ RODZICÓW/OPIEKUNÓW, do którego zaprosiła nas Pani Magdalena Filcek z wrocławskiej Kawiarenki Snu.

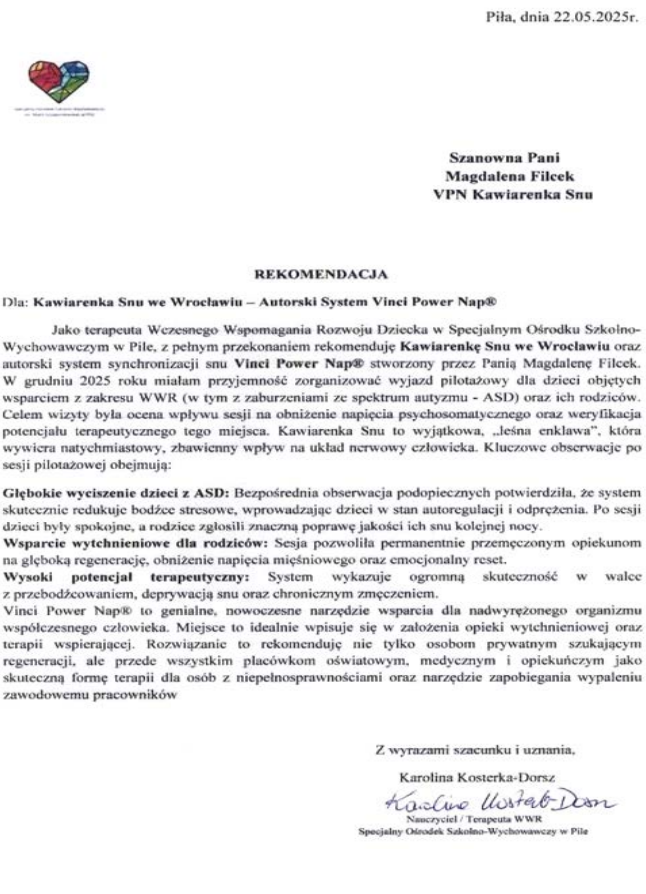
Powyższe działanie skierowane jest do rodzin korzystających z wsparcia w ramach Wczesnego Wspomagania Rozwoju Dziecka w Specjalnym Ośrodku Szkolno – Wychowawczym w Pile, jak również terapeutów pracujących z dzieci z wyzwaniami rozwojowymi.

Celem pilotażu, wg ustaleń, jest :

- obserwacja reakcji dzieci z ADS na system,
- sprawdzenie, czy Vinci Power Nap wspiera również rodziców w obniżeniu napięcia i przeciążenia,
- zebranie danych, które pomogą ocenić, czy stworzenie takiego pokoju w naszym Ośrodku byłoby zasadne i realnie wspierające.

Dyrekcja Ośrodka zapewnia uczestnikom projektu przejazd autobusem szkolnym (trasa: Piła - Wrocław) z 50% dofinansowaniem kosztów.

WICEDYREKTOR
Alina Wenzel-Kluczek



Piła, dnia 22.05.2025r.

Szanowna Pani
Magdalena Filcek
VPN Kawiarenka Snu

REKOMENDACJA

Dla: **Kawiarenka Snu we Wrocławiu – Autorski System Vinci Power Nap®**

Jako terapeuta Wczesnego Wspomagania Rozwoju Dziecka w Specjalnym Ośrodku Szkolno-Wychowawczym w Pile, z pełnym przekonaniem rekomenduję **Kawiarenkę Snu we Wrocławiu** oraz autorski system synchronizacji snu **Vinci Power Nap®** stworzony przez Panią Magdalenę Filcek. W grudniu 2025 roku miałam przyjemność zorganizować wyjazd pilotażowy dla dzieci objętych wsparciem z zakresu WWR (w tym z zaburzeniami ze spektrum autyzmu - ASD) oraz ich rodziców. Celem wizyty była ocena wpływu sesji na obniżenie napięcia psychosomatycznego oraz weryfikacja potencjału terapeutycznego tego miejsca. Kawiarenka Snu to wyjątkowa, „leśna enklawa", która wywiera natychmiastowy, zbawienny wpływ na układ nerwowy człowieka. Kluczowe obserwacje po sesji pilotażowej obejmują:

- **Głębokie wyciszenie dzieci z ASD:** Bezpośrednia obserwacja podopiecznych potwierdziła, że system skutecznie redukuje bodźce stresowe, wprowadzając dzieci w stan autoregulacji i odprężenia. Po sesji dzieci były spokojne, a rodzice zgłosili znaczną poprawę jakości ich snu kolejnej nocy.
- **Wsparcie wytchnieniowe dla rodziców:** Sesja pozwoliła permanentnie przemęczonym opiekunom na głęboką regenerację, obniżenie napięcia mięśniowego oraz emocjonalny reset.
- **Wysoki potencjał terapeutyczny:** System wykazuje ogromną skuteczność w walce z przebodźcowaniem, deprywacją snu oraz chronicznym zmęczeniem.

Vinci Power Nap® to genialne, nowoczesne narzędzie wsparcia dla nadwyrężonego organizmu współczesnego człowieka. Miejsce to idealnie wpisuje się w założenia opieki wytchnieniowej oraz terapii wspierającej. Rozwiązanie to rekomenduję nie tylko osobom prywatnym szukającym regeneracji, ale przede wszystkim placówkom oświatowym, medycznym i opiekuńczym jako skuteczną formę terapii dla osób z niepełnosprawnościami oraz narzędzie zapobiegania wypaleniu zawodowemu pracowników

Z wyrazami szacunku i uznania,
Karolina Kosterka-Dorsz
Nauczyciel / Terapeuta WWR
Specjalny Ośrodek Szkolno-Wychowawczy w Pile

Picture 3: Letter of approval for a pilot study evaluating whether the implementation of the Vinci Power Nap® room would be beneficial for autistic children, their families, and their therapists.

Picture 4: Letter of recommendations following a pilot study evaluating whether the implementation of the Vinci Power Nap® room would be beneficial for autistic children, their families, and their therapists.

comfort—can be particularly valuable in working with autistic children, for whom excessive environmental stimulation is often a source of stress and functional difficulties. Creating a friendly, predictable, and regulating space allows them not only to regenerate, but also to cope more easily with everyday challenges. This is consistent with research showing how greenery and architecture support physiological restoration [690], particularly in children with ASD [691], [692], [693], [694].

The system Vinci Power Nap® has been presented at international forums, including the COP24 conference in 2018, where it received very positive feedback from 465 participants representing diverse backgrounds, UN/ WHO United Nations/World Health Organization Regional Conference on Space Technologies for Advancing Global Health 2024 [695], WHO officially on the the (WHO Implementome) [696] recommends it for implementation. NASA JPL has expressed interest in its potential application for supporting astronauts' health, particularly in stress reduction, improving sleep quality, mitigating the effects of space missions, and reducing jet lag in aviation [9], [27], [665], [685], [686], [687], [688], [695]. More detailed information, including analyses and expert opinions, can be found in sources such as Fortune Journals and ResearchGate – Magdalena Filcek and (Human- Space Institute) [697].

On December 4th, 2025, a official pilot study was

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conducted at Vinci Power Nap® involving 3 boys (7-8 years) diagnosed with ASD from Specjalny Ośrodek Szkolno-Wychowawczy in Pila, along with 4 mothers and 3 therapists. During the 20-minute VPN session, the children gradually became calmer and showed less physically restless compared to the beginning of the session. Afterward, the children went for a walk with their therapists, while the mothers had the opportunity to experience the VPN session themselves, they fell asleep immediately. Afterward, they shared, with tears in their eyes, that it had been one of the most peaceful and restorative moments of their lives—comparable to the best holidays. What was particularly surprising was that the boys, after their walk in the city center, immediately asked for the next VPN session. The participants reported that the constant demands of caring for a child with ASD, combined with overall family responsibilities, often lead to overstimulation, extreme fatigue, and lack of restorative sleep, regeneration for body and mind. They highly recommended the VPN respite sessions for all caregivers, family members, and therapists supporting individuals with ASD, ADHD, and PTSD (Picture 3), (Picture 4). This pilot study was presented on IV International Autism Conference in Abu Dhabi, and describe in more detail in conference publications.

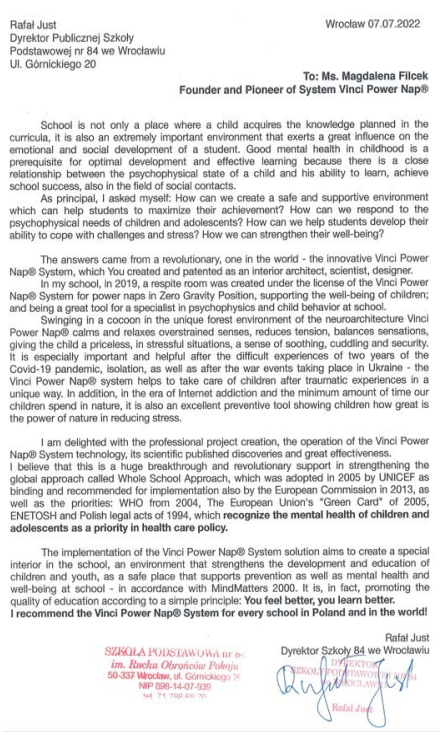
The First Vinci Power Nap® Respite Room in a School

Knowledge about the impact of the environment on the human body—especially the role of green elements—is highly important for parents and teaching staff in preschools and primary schools in order to provide children, including autistic children, with appropriate support in overcoming developmental and educational challenges [676]. In Poland, in Wrocław, there is Public Primary School No. 84, whose principal is highly aware of these issues and has purchased, under a Vinci Power Nap® license, a specially designed green and quiet room that soothes overstimulated senses. In this space, noise, strong light, pollution, and odors have been reduced. Both children and teachers can take a moment of respite and regeneration of body and mind in a supportive neuroarchitectural environment [665], [666], (Picture 6).

Recommendations from the principal of Public Primary School No. 84 in Wrocław and the certificated psychologist responsible for supporting children within the Vinci Power Nap® system, highlight the importance of integrating such sensory-friendly environments into everyday school practice. They emphasize that regular use of the green and quiet room can significantly improve children's emotional regulation, concentration, and overall well-being, so important particularly among those with sensory processing difficulties. (Picture 4), (Picture 5).

Clinical and Therapeutic Implications

The clinical and therapeutic implications of this scientific discovery relate to its practical significance in diagnosis,



Rafał Just
Dyrektor Publicznej Szkoły
Podstawowej nr 84 we Wrocławiu
Ul. Górnickiego 20

Wrocław 07.07.2022

To: Ms. Magdalena Filcek
Founder and Pioneer of System Vinci Power Nap®

School is not only a place where a child acquires the knowledge planned in the curricula, it is also an extremely important environment that exerts a great influence on the emotional and social development of a student. Good mental health in childhood is a prerequisite for optimal development and effective learning because there is a close relationship between the psychophysical state of a child and his ability to learn, achieve school success, also in the field of social contacts.

As principal, I asked myself: How can we create a safe and supportive environment which can help students to maximize their achievement? How can we respond to the psychophysical needs of children and adolescents? How can we help students develop their ability to cope with challenges and stress? How we can strengthen their well-being?

The answers came from a revolutionary, one in the world - the innovative Vinci Power Nap® System, which You created and patented as an interior architect, scientist, designer.

In my school, in 2019, a respite room was created under the license of the Vinci Power Nap® System for power naps in Zero Gravity Position, supporting the well-being of children; and being a great tool for a specialist in psychophysics and child behavior at school.

Swinging in a cocoon in the unique forest environment of the neuroarchitecture Vinci Power Nap® calms and relaxes overstrained senses, reduces tension, balances sensations, giving the child a priceless, in stressful situations, a sense of soothing, cuddling and security. It is especially important and helpful after the difficult experiences of two years of the Covid-19 pandemic, isolation, as well as after the war events taking place in Ukraine - the Vinci Power Nap® system helps to take care of children after traumatic experiences in a unique way. In addition, in the era of Internet addiction and the minimum amount of time our children spend in nature, it is also an excellent preventive tool showing children how great is the power of nature in reducing stress.

I am delighted with the professional project creation, the operation of the Vinci Power Nap® System technology, its scientific published discoveries and great effectiveness.
I believe that this is a huge breakthrough and revolutionary support in strengthening the global approach called Whole School Approach, which was adopted in 2005 by UNICEF as binding and recommended for implementation also by the European Commission in 2013, as well as the priorities: WHO from 2004, The European Union's "Green Card" of 2005, ENETOSH and Polish legal acts of 1994, which **recognize the mental health of children and adolescents as a priority in health care policy.**

The implementation of the Vinci Power Nap® System solution aims to create a special interior in the school, an environment that strengthens the development and education of children and youth, as a safe place that supports prevention as well as mental health and well-being at school - in accordance with MindMatters 2000. It is, in fact, promoting the quality of education according to a simple principle: **You feel better, you learn better.**
I recommend the Vinci Power Nap® System for every school in Poland and in the world!

Rafał Just
Dyrektor Szkoły 84 we Wrocławiu

SZKOŁA PODSTAWOWA nr 84
im. Ruchu Obrońców Pokoju
50-337 Wrocław, ul. Górnickiego 20
NIP 896-14-07-939

Wrocław 20 February 2020

mgr Agnieszka Bogusz - psychologist, works with trauma, educator, supervision trainer in institutions:

Szkoła Podstawowa nr 84	Zespół Szkół nr 8	Fundacja Promyk Słońca
ul. Górnickiego 20	ul. Mikołaja Reja 3	ul. Swobodna 8a
50-377 Wrocław	50-354 Wrocław	50-088 Wrocław

RECOMMENDATIONS

for the VINCI POWER NAP® system - DREAM'S CAFE®
in terms of the legitimacy of the existence of the "Peace of respite"

The Dream's Cafe® based on the relaxing, proprietary Vinci Power Nap® neuroarchitecture system perfectly supports the psychological work with the client in the area of reducing stress and tension in the body, reducing the level of general tenseness, supports the process of self-regulation of emotions and intrusive thoughts.

It is a very helpful tool when working with people exposed to permanent stress (e.g.: caring for a loved one, stressful work, sudden, crisis situation, coping with loss, mourning, working through traumatic or traumatic experiences, alleviating post-traumatic stress disorder PTSD , supporting people fighting addiction in line with compassion and commitment therapy).

The Vinci Power Nap® system allows the free integration of the senses and sensations from the body - while stimulating, alleviating and synchronizing them, it is a tool perfectly supporting psychological work in many psychotherapeutic trends (cognitive - behavioral, systemic) where stress reduction by means of work with the body plays the key meaning and is a necessary stage to move to the next stages of working with the patient.

The Vinci Power Nap® method wonderfully and modernly supports therapeutic trends based on mindfulness, compassion, commitment and acceptance, which are the foundation of most directions of cognitive-behavioral therapies. Transferring session participants to "out-of-threshold" places, helping to broaden perspective, and the process of psychological and diffusion helps alleviate the affect associated with crisis and traumatic experiences.

In the most important discovery of the Vinci Power Nap® system in the Zero Gravity position during rocking : "dreaming - flying" occurs, detached from the ground, and at the same time stable and giving support. Unexpected body sensations reminiscent of returning to the mother's womb non-invasively trigger a lot of good emotions and processes in sensual memory, giving relief and enabling you to re-experience and work through what is difficult and painful, leaving a person with a sense of "putting together" and filling with security, love and acceptance.

The legitimacy of the need to work in this area with the majority of beneficiaries / clients at the "Promyk Słońca" Foundation is unquestioned.
Covering many of them with this type of support would speed up many processes and increase the efficiency of work for the needy.

MSc Agnieszka Bogusz - psycholog

Picture 4: Recommendations for VPN from the principal of Public Primary School 84 in Wrocław.

Picture 5: Recommendations for VPN from the psychologist of Public Primary School 84 in Wrocław.

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treatment, and care. This section discusses how research findings can potentially be translated into real-world clinical practice and how they may influence future therapeutic strategies.

The Role of Vitamin D and A

Research indicates that deficiencies in vitamin A and vitamin D exacerbate symptoms in children with autism spectrum disorders (ASD) [698]. Biologically active vitamin D (calcitriol) functions as a steroid hormone and has been associated with a reduced risk of depression and neurodevelopmental disorders, including ASD [133], [699]. Vitamin D obtained from dietary sources or synthesized in the skin under sunlight (cholecalciferol, D3) requires activation in the liver and kidneys, resulting in the biologically active form 1,25-dihydroxyvitamin D3 (calcitriol). Calcitriol binds to the nuclear vitamin D receptor (VDR), which functions similarly to other steroid hormone receptors (e.g., estrogen, cortisol) and is expressed in various tissue types. Through this mechanism, calcitriol regulates the expression of multiple genes involved in calcium-phosphate homeostasis, while supporting the immune, endocrine, reproductive, cardiovascular, nervous, gastrointestinal, skeletal, and muscular systems. It helps prevent osteomalacia and rickets, reduces the risk of osteoporosis and fractures, enhances muscle strength, and protects against oxidative stress and inflammation [700]. Evidence suggests that vitamin D also contributes to stabilizing mast cell membranes, thereby modulating their responsiveness to external stimuli. This is particularly relevant in conditions characterized by excessive mast cell activation, such as MCAS and HIT. Vitamin D deficiency is frequently observed in patients with allergic and autoimmune conditions, including MCAS and ASD [701]. Supplementation with vitamin D has been shown in some studies to improve symptoms related to mast cell hyperactivity, including allergic and inflammatory responses, indirectly preventing excessive release of histamine, tryptase, cytokines, and H1-H4 receptor-mediated inflammatory cascades [702]. Given the higher density of mast cells in the brains of children with ASD, vitamin D may help stabilize these cells, suppress histamine release, support immunological balance in histamine-related disorders, and consequently alleviate ASD symptoms [703], [133], [699].

Mechanistic summary: High mast cell density in the brains of children with ASD → Vitamin D → mast cells stabilization → inhibition of histamine release → reduction of autism-related symptoms.

Maintaining adequate vitamin D levels may stabilize mast cells, mitigate MCAS symptoms, and strengthen overall immune function. Its effectiveness may vary depending on the individual patient, symptom severity, and comorbid conditions. Vitamin D supplementation is not a universal treatment for MCAS or HIT but should be considered as part of a comprehensive therapeutic strategy alongside other clinically validated interventions [133], [699].

Furthermore, researchers have highlighted that retinoic acid (vitamin A) deficiency during pregnancy or early fetal development can affect brain development, potentially leading to long-term or even permanent impairments in learning, memory, and cognitive function [704], [93]. Vitamin A also plays a critical role in gastrointestinal function in children with ASD [705]. „A study observed vitamin A deficiency in 77.9% of children with autism. Serum retinol levels were significantly lower, while 5-hydroxytryptamine (5-HT) levels were significantly higher compared with controls, correlating with symptom severity. Notably, supplementation with vitamin A led to substantial improvements in symptoms" [706]. This suggests that vitamin A supplementation, including precursors such as beta-carotene (found in carrots), may be a justified adjunctive therapy to mitigate ASD symptoms in children.

Oxytocin and Its Relationship with Vitamin A and Vinci Power Nap®

Vitamin A, through its active form – all-trans retinoic acid (ATRA) – indirectly regulates oxytocin release in the central nervous system, including the brain, by inducing the expression of the enzyme CD38 and enhancing calcium-dependent neuronal signaling in the hypothalamus [707]. In mice lacking the CD38 gene, and therefore exhibiting impaired oxytocin release, deficits in social behaviors were observed [704]. Analogous deficits in social behavior are observed in humans with autism spectrum disorder (ASD), and certain variants of the CD38 gene are considered temporal factors that increase susceptibility to this neurodevelopmental disorder [708], [709], [710], [711]. Research indicates that sessions conducted within the Vinci Power Nap® system may promote increased oxytocin release in the body. This effect is likely related to the pulsating, rhythmic pressure applied to the body by the wrap during rocking, which stimulates cutaneous mechanoreceptors, including receptors sensitive to deep touch. Such somatosensory stimuli can trigger oxytocin release in the central nervous system. Consequently, enhanced activity of the oxytocin system may support stress reduction, modulation of the autonomic nervous system, serotonin production, and regenerative processes [686].

Vagus Nerve

In children with autism, symptoms of vagus nerve dysregulation are frequently observed. [712]. The vagus nerve is the longest nerve in the body and a key component of the parasympathetic nervous system, serving as the primary communication pathway between the brain and the visceral organs. This nerve is involved in the regulation of many essential physiological functions, including: regulation of intestinal activity and digestive functions (the "brain–gut axis"); modulation of the immune system

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and inflammatory responses; control of the cardiovascular and respiratory systems; integration of sensory signals and hormonal homeostasis via the parasympathetic nervous system; and influence on stress responses and overall bodily balance, including emotional regulation and the ability to maintain calm [713]. To reduce fear, fight-or-flight, or freeze responses, it is necessary to optimize the autonomic nervous system through vagus nerve stimulation, as demonstrated by research. "Vagus nerve stimulation may be a potential adjunct to behavioral therapy in autism and other neurodevelopmental disorders." [714]. Vagus nerve stimulation supports multiple physiological systems and neurochemical processes in the body, including helping to increase oxytocin levels—enhancing trust and social bonding—reducing anxiety, and facilitating sleep onset, which is particularly important for children with autism [715]. It takes time but the vagus nerve can be reprogrammed to restore balance. This process takes time, but with patience and consistency it is possible.

Vagus nerve stimulation can be achieved in several ways—ranging from clinical to very simple, natural techniques that genuinely influence the parasympathetic ("rest & digest") nervous system. Clinical (medical) methods include, for example: VNS—implantable vagus nerve stimulation, which has been approved by the FDA as a safe and effective therapy [716]. This method is highly effective but invasive. Another approach is transcutaneous, non-invasive vagus nerve stimulation (tVNS), using electrodes placed on the auricle of the ear (the auricular branch of the vagus nerve). Natural and behavioral methods include: diaphragmatic breathing / slow breathing at a rate of 5–6 breaths per minute; prolonged exhalation, which activates the vagus nerve and constitutes the strongest natural stimulus for it. Singing, humming, chanting, speaking in a low voice, cold stimulation, cold water on the face, physical contact and deep pressure—such as hugging, weighted blankets, and deep proprioceptive pressure (very effective in children with ASD and sensory hypersensitivity)—as well as meditation, mindfulness, silence as a powerful regulator of neuroplasticity, circadian rhythm and sleep, naps, contact with nature and silence, greenery, noise reduction, natural light, and body movement (The Vagus Nerve and Autism) [717]. Using Vinci Power Nap® technology as a form of autonomic synchronization of the body with rhythmic rocking, activation of diaphragmatic breathing during relaxing nap sessions —supported by research findings [688] and recommended by the World Health Organization (WHO) for implementations [696].

Proposed Diagnostic Framework for Individuals with Neurodevelopmental Disorders.

Neurodevelopmental disorders should be approached from a systems perspective, as a child's functioning reflects the interaction of multiple interconnected biological axes, including the central nervous system, the gastrointestinal system, the immune system, the circulatory system, metabolic processes, and the gut microbiota. High-quality diagnostics begin with a thorough clinical and family history, covering pregnancy, birth, development, existing disorders, sleep, diet, environment, noise exposure, sensory hypersensitivity, emotional regulation, and cognitive, executive, and social functioning. This should be followed by basic diagnostic tests, with subsequent targeted, step-by-step investigations as needed, such as immunology, gut health, allergies, and infections.

A. Basic possible laboratory diagnostics:

1. A complete blood count, enabling assessment of anemia, inflammation, immune status, and indirect indicators of malabsorption disorders and infections; biochemical tests (AST, ALT, ALP, GGT, CRP, ESR, creatinine, glucose) allowing evaluation of liver and kidney function, inflammatory status, and carbohydrate metabolism; as well as assessment of micronutrient and vitamin status (iron, ferritin, vitamin D, vitamin B6, vitamin B12, folate/vitamin B9, zinc, magnesium, copper, selenium), deficiencies of which may significantly affect cognitive development, nervous system function, immune function, and gastrointestinal health. Interpretation of results should always be made in reference to the patient's clinical presentation and analysis of parameter trends over time [718], [719].
2. Classic IgE-mediated allergies include assessment of total IgE levels, measurement of specific IgE antibodies (sIgE) against food and inhalant allergens in serum, as well as skin prick tests commonly used in allergy practice. In some children with autism spectrum disorders, an increased prevalence of allergic conditions and features of immune dysregulation is observed; however, this phenomenon is not universal and requires individualized clinical evaluation [720].
3. Histamine intolerance (HIT), described as a "pseudoallergic" reaction, is diagnosed based on the clinical presentation, which may include chronic gastrointestinal symptoms, skin manifestations, and pain complaints. Diagnosis can also be supported by histamine provocation tests and measurement of diamine oxidase (DAO) activity in serum or plasma, as reduced activity of this enzyme is observed in some patients suspected of HIT and can aid in diagnosis within the appropriate clinical context [265], [721], [722].
4. Stool analysis includes both bacteriological and mycological cultures, performed in microbiology laboratories (including microbiome panels and NGS sequencing), as well as the assessment of potentially pathogenic bacteria such as Klebsiella, Citrobacter, Pseudomonas, or Proteus, which allows for targeted antibiotic therapy, dietary modifications, or probiotic supplementation. For parasite diagnostics, the classical "Ova & Parasites" examination is used to detect eggs,

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cysts, and trophozoites. Due to irregular excretion of parasites, it is recommended to collect 2–3 samples. In selected laboratories, antigen tests or PCR assays are also available for Giardia, Entamoeba, Cryptosporidium, and other intestinal pathogens [723], [724], [725].

5. Inflammatory and intestinal permeability markers include, among others, calprotectin and lactoferrin, zonulin, α-1-antitrypsin, and NGAL – proteins present in stool whose levels increase during inflammation of the intestinal mucosa and which serve as sensitive, non-invasive indicators of inflammatory activity [726].

B. Extended diagnostics – metabolism, microbiota, infections

1. These are biomarkers of a more scientific than routine nature. They can provide a valuable addition to an extended assessment of immune response and inflammatory processes; however, they do not replace standard laboratory tests, and their interpretation requires experience and caution: Organic acid panels (for example: OAT, Metabolomix, Organix Gastro/Neuro, etc.) allow for the identification of metabolic and gut-related conditions that may contribute to increased histamine load, even though there is no direct histamine marker [727], [728].
2. Gut microbiota panels (CSA, Valida Test, Microflora Scan, various 16S/NGS) [729], [730], [731].

C. Diagnostic panels for chronic infections, including:

1. Neuro 14 PCR, CNS panel, Meningitis 14 PCR, Encephalitis PCR Panel, as well as tests for HSV-1, HSV-2, HHV-6, VZV, CMV, EBV, parvovirus B19, enteroviruses, adenoviruses, Chlamydia pneumoniae, Mycoplasma pneumoniae, etc, allow reliable detection of active, systemic infections with potential neurotoxic effects [732].
2. Lyme disease evaluation involves medical history and clinical symptoms (such as erythema migrans, tick exposure, neurological manifestations, etc.) and consideration of co-infections. Two-tiered serology is standard: ELISA (or CLIA) for antibodies against Borrelia, followed by confirmatory Western blot if the ELISA is positive. In suspected neuroborreliosis, cerebrospinal fluid (CSF) analysis is performed, assessing pleocytosis, intrathecal production of specific antibodies, and, in some cases, CXCL13 levels [733], [734], [735], [736].
3. Immunological and inflammatory markers from blood and urine (Immunoglobulins and their subclasses: total IgG, IgA, IgM (sometimes IgE), IgG subclasses (IgG1, IgG2, IgG3, IgG4)) [737], [738], [739].
4. Immunological panels: Th1/Th2/Th17, Treg, lymphocyte subpopulations, as well as blood-based flow cytometry analysis: CD3, CD4, CD8, NK cells, B-cells, etc. [720], [740].
5. Nerve damage marker: NSE (Neuron-Specific Enolase), an enzyme primarily present in neurons and neuroendocrine cells. Studies have shown that this enzyme was elevated in 97.5% of children with ASD, suggesting it may reflect neuronal stress and neuroinflammation in the brain [741].
6. Immune system activation marker: NEOP (Neopterin), measured in urine and/or serum, is a metabolite of GTP (Guanosine Triphosphate) produced by monocytes/macrophages under the influence of IFN-γ. It serves as a marker of cellular immune activation and inflammation. Elevated NEOP with low CRP indicates cellular (Th1) inflammation. GTP is also a precursor for BH4 (tetrahydrobiopterin), which is essential for the production of dopamine, serotonin, norepinephrine, and nitric oxide (NO). Impaired GTP utilization is associated with neurological and vascular problems. Histamine can reprogram GTP metabolism toward inflammation, supporting the author's hypothesis [742], [743], [744], [745], [746], [747].
7. D-dimer: a biomarker of chronic urticaria resistant to antihistamines [748], [749]. Studies show that patients diagnosed with various autoimmune diseases have elevated D-dimer levels [812], resulting from simultaneous activation of coagulation and fibrinolysis (also mediated by histamine, observed in children with MCAS, as well as in allergic reactions where DIC—disseminated intravascular coagulation—occurs). Furthermore, D-dimers are also responsible for triggering histamine release from mast cells [750]. "The serum D-dimer concentration may help identify children for whom neuroimaging could be beneficial in assessing potential brain injury. Further studies will be necessary to better determine the accuracy and utility of this and other markers." [751].
8. Bilirubin testing: can have significant diagnostic and prognostic value, as bilirubin is not only a marker of liver function but also an indicator of systemic inflammation, hemolysis, high histamine and DIC levels, oxidative stress, and endothelial dysfunction. Elevated bilirubin levels are observed in conditions such as sepsis, liver disease, hematological disorders, hypoxia, and conditions associated with chronic inflammation and blood-brain barrier damage. Importantly, unconjugated bilirubin can cross the blood-brain barrier and exert neurotoxic effects, particularly in vulnerable structures such as the brainstem, hippocampus, and basal ganglia. Therefore, monitoring bilirubin levels can support early identification of neurological complications, assess disease severity, and assess treatment efficacy [752], [565], [567].

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9. Thyroid hormones TSH (FT3/FT4): when levels are adequate, they maintain high expression of DAO enzymes and methylation activity (SAMe → HNMT), and T3 stabilizes mast cells. High TSH with low FT3 and FT4 indicates hypothyroidism, which not only slows metabolism but also biologically predisposes to excess histamine and hyperactive mast cells. In this state, DAO and HNMT enzymes function less efficiently, histamine accumulates even with a "normal" diet, mast cells degranulate more easily, the threshold for allergic reactions decreases, resulting in increased histamine, tryptase, prostaglandins, and chronic inflammation, leading to "pseudoallergic" symptoms without IgE-mediated allergy. Peristalsis slows down (SIBO / dysbiosis of histamine-producing bacteria), more histamine is released from the gut, further burdening DAO (already weak), and thyroid function worsens. Hypothyroidism can elevate fibrinogen and promote increased D-dimers. Clinical manifestations of this combination, often seen together, include: "allergies without allergy, urticaria, flushing, anxiety, palpitations, brain fog, heat/cold intolerance, food reactions, bloating + constipation, autoimmune thyroiditis (Hashimoto)," commonly observed in individuals with ASD, ADHD, and PTSD [753], [754]. Research has demonstrated that maternal hypothyroidism is associated with an increased likelihood of autism spectrum disorder (ASD) and developmental delay (DD) in offspring compared with children born to mothers without thyroid dysfunction. It has been shown that prolonged maternal thyroid hormone disturbances during pregnancy are associated with an increased risk of ASD in offspring [755], due to the crucial role of thyroid hormones in proper brain development. During the early and middle stages of pregnancy, the developing fetus remains fully dependent on thyroid hormones supplied by the mother's body [756], while later fetal brain development requires proper thyroid hormone production by the fetus itself [757]. In fetuses and young children, the thyroid is particularly sensitive, and even minor maternal T4 disturbances affect brain development [758]. Similar conclusions are reported in a more recent study from 2025 [759]. The causes of hypothyroidism may be autoimmune, iatrogenic, congenital [753], or result from deficiencies or environmental factors. One potential cause is also iodine deficiency (less common in countries with salt supplementation) or selenium deficiency, which is necessary for the action of deiodinases (enzymes that convert T4 into active T3). Importantly, fluoride competes with iodine, reducing thyroid hormone synthesis (T4, T3), especially in iodine deficient individuals, while also increasing thyroid oxidative stress, which may contribute to autoimmune responses and, in combination with low iodine intake, a potential risk of neurodevelopmental disorders.
10. EEG (particularly in cases of sleep disturbances, developmental regression, suspected epilepsy) [760].
11. HRV (heart rate variability as a marker of vagus nerve tone) [761].

Therapeutic Strategy Hypotheses for ASD, ADHD and PTSD

Preliminary studies indicate that some children with autism show improvement in symptoms after treatment with antihistamines, suggesting the involvement of mast cells and histamine in certain manifestations of ASD. This is further supported by observations of increased numbers of active mast cells in the brain and meninges of individuals with ASD, which contribute to the development of neuroinflammation [762]. Research in ASD has shown that children with autism often exhibit histamine metabolism issues, which may be related to decreased DAO activity. For example, polymorphisms in the AOC1 gene (encoding DAO) can lead to reduced enzyme activity, increasing histamine levels and exacerbating inflammatory states [763]. To alleviate allergic symptoms and hypersensitivity, some patients with ASD are treated with DAO enzyme supplementation and medications used in MCAS therapy [764]. From a therapeutic perspective, interesting findings include clinical efficacy of warfarin in treating patients with chronic spontaneous urticaria [765], and other studies have noted that heparin inhibited the formation of a positive skin reaction in the ASST procedure [766]. The following strategies may have potential in mitigating excitotoxicity, neuroinflammation, and excessive glutamatergic signaling, thereby alleviating symptoms of ASD [655], ADHD, PTSD, and MCAS [35], and according to research, may also potentially reverse epigenetic mechanisms [767].

It is important to emphasize, however, that any therapeutic approach should be preceded by proper diagnostics and always individually consulted with a specialist physician.

Lowering Histamine Levels:

- **Natural Reduction of Mast Cell Activators:** Minimize emotional stress and sensory stressors, temperature extremes, and intense stimuli (light, noise), mold, and toxins [768]. Limit exposure to vibrations, electromagnetic, and ionizing radiation in daily and medical environments: implement monitoring and preventive measures in high-exposure areas, especially for children with ASD [619], [620], [621], [769].
- **Low-Histamine Diet and the Microbiome:** Avoid foods high in histamine (aged cheeses, cured meats, fermented products such as sauerkraut and soy sauce), alcohol (especially red wine and beer), fish (particularly stored for long periods), seafood, sardines, tuna, tomatoes, ketchup, avocado, eggplant, spinach, cheese, chocolate, spices and

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nuts. Reducing a diet rich in gluten, casein, and caffeine, as well as supplementing with probiotics and prebiotics, may alleviate symptoms, although effects are individual. Include foods rich in beta-carotene (carrots), eggs, and onion (quercetin) in the diet [609]. A ketogenic diet can be implemented, but with the elimination of foods that contain or trigger histamine [770], [468], [576].

- **Pharmacological:** Receptor modulators H3, GABA-A/B, glutamate antagonists – supplementation after diagnostic assessment [771]. **Vitamins and supplements:** Vitamins A, B6, B9 (folic acid), B12, C, zinc, copper, selenium, DAO enzyme (to reduce histamine), as well as vitamin D, quercetin, apigenin, luteolin, frankincense may stabilize mast cells (see more in: Chapter 4.4. (Table 1)), which could indirectly reduce histamine levels and ASD-related symptoms, especially given that vitamin D deficiency is common in children with autism [772], [576]. Worth to consider Acemannan from Aloe vera as it exhibits strong immunomodulatory, antiviral, anti-inflammatory, and tissue-healing properties [773]. **Receptor blockers:** H1, H2, and H3 (including black seed oil) are used to reduce the effects of histamine, potentially alleviating symptoms in ASD, ADHD or PTSD by counteracting histamine effects and theoretically neuroinflammation, which may mitigate symptoms such as sensory hypersensitivity or irritability [774]. **Historical use:** Black seed oil (Nigella sativa), known as the "Gold of the Pharaohs," was already used in ancient Egypt as a general health-supporting agent and to alleviate various ailments [775]. Studies have shown that black seed oil also has gastroprotective effects on gastric mucosal damage [776], [777].
- **Regulation of neurotransmitter balance, reduction of excitotoxicity:** Antioxidants such as glutathione, vitamin C, vitamin E, N-acetylcysteine (NAC), and coenzyme Q10 may further neutralize reactive oxygen species (ROS) and protect cells. Balancing iodine levels in cases of confirmed deficiency and hypothyroidism is also important. Supplementation should be conducted under medical supervision, especially in children, due to the lack of safety and efficacy data in ASD.
- **Calm environment and sensory support:** A soothing environment promotes self-regulation, and appropriate adaptation of home and school spaces supports the child's functioning (Sensory Integration) [684], [666], [778]. Relaxation techniques (e.g., breathing exercises, yoga, meditation) combined with deep pressure [653] —such as sessions in Vinci Power Nap® [665], [686], weighted blankets, or sessions in a compression suit [779]—can further reduce mast cell activation, modulate neurotransmitter activity, and decrease oxidative stress and excitotoxicity [780]. (Picture 6).

Autism is a disorder with a complex etiology, encompassing genetics, neuroinflammation, gut dysfunction, and other factors. It is worthwhile to implement a combined therapeutic approach, which may lead to significant improvement across all symptoms. Response to DAO supplementation or other interventions can vary between patients, for example depending on genetic variants of the AOC1 gene or coexisting gut or environmental issues.

Design frameworks such as Autism ASPECTSS™ [782] establish environmental guidelines to support sensory processing [778], while sensory research [9], [27], [665], [685], [686], [687], [695] underscores the impact of ambient stimuli like noise and others triggers on neurological function. These foundations suggest that targeted neuroarchitectural interventions, exemplified by the Vince Power Nap® pendulum's harmonic with modulation of frequencies, could actively support autonomic regulation and sensory homeostasis in neurodiverse populations [688]. Furthermore, such evidence-based design approaches highlight the need

Picture 6. Vinci Power Nap® room with Zero Gravity Position and with indoor environmental elements influencing sensory processing and human well-being. Zero Gravity Position and its recreation on Earth in VPN. Picture of VPN green room at school: foto Pawel Pajot, source: own by author. Astronaut image used in illustration, source: (NASA Courses Neuro-Ophtalmology, Vestibular Physiology), child image: [781]. Illustration on right was generated using AI (ChatGPT 4.0.) and reviewed, corrected by the author.

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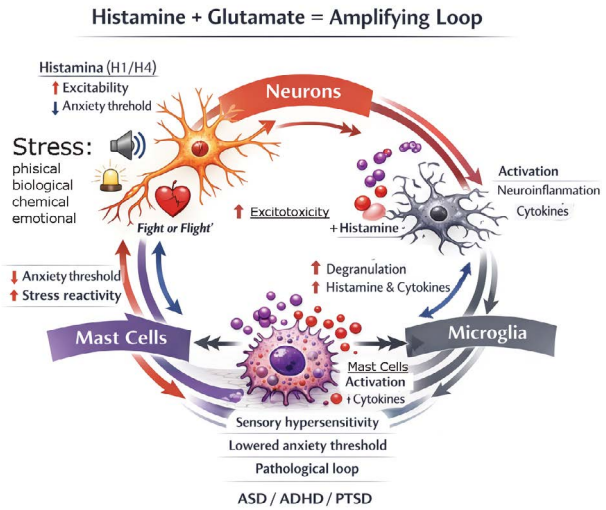

Picture 7: Showing that: Histamine + glutamate = amplifying loop: Mast cell activation: histamine (H1/H4) increases neuronal excitability, glutamate enhances microglial activation and mast cell degranulation, together they lower the anxiety threshold and increase stress reactivity. Illustration was generated using AI (ChatGPT 4.0.) and reviewed, corrected and completed by the author.

for interdisciplinary collaboration between architects, educators, and healthcare professionals to optimize learning environments for children with diverse sensory needs.

The Need for RCT (Randomized Controlled Trial)

Randomized clinical trials are lacking, but preliminary data indicate promising directions in exploring mast cell overactivity, histamine metabolism, and anti-histamine diets in neuroimmunological, neuropsychiatric, and neurodevelopmental disorders including ASD, ADHD, PTSD, Alzheimer's, and Parkinson's, as well as the role of vitamin D, A, B6, B12, zinc, copper, selenium, H1/H2 blockers, DAO supplementation, and calming sensory environments in reducing excitotoxicity and excessive glutamatergic signaling [10], [12], [26]. Although there is a theoretical basis that increasing DAO activity may help alleviate ASD symptoms by reducing histamine, there is insufficient clinical evidence to confirm this. Additionally, the activity of the histamine-degrading enzyme diamine oxidase (DAO), necessary for adequate histamine breakdown, is significantly higher than the theoretical values provided in commercially available dietary supplements. Considering this, it is clear that improved supplements need to be developed to assist individuals with HIT, and thereby individuals with ASD and PTSD [455]. Further research is also needed to determine thresholds at which HVAC noise affects individuals with ASD and other sensory sensitivities. Studies should consider:

1. The interaction between chronic low-level noise and neuroimmunological dysregulation.
2. The cumulative impact of environmental factors, including noise, light, and temperature fluctuations. [306], [625], [649], [650].
3. Vinci Power Nap® helpful service to reduce stress, improve sleep and wellbeing for people wth ASD, ADHD, PTSD and their families [686].
4. Interventions combining environmental modifications with dietary, pharmacological, and behavioral strategies. Since noise generated by HVAC systems is a modifiable environmental stressor that can significantly affect individuals with autism and other sensory sensitivities, incorporating building design, careful selection of HVAC systems, and individualized accommodations may improve quality of life and reduce behavioral and cognitive disturbances in these populations and how environmental stressors can amplifying histamine and glutamate loop (Picture 7).

Feedback loop: mast cells ↔ microglia ↔ neurons. In ASD, ADHD, and PTSD, a pathological loop develops: stress/sensory stimulus → mast cell activation → release of histamine and cytokines → microglial activation → neuroinflammation → lowered anxiety threshold → increased reactivity to stimuli → reactivation of mast cells → release of histamine and cytokines

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This mechanism can explains sensory hypersensitivity, "fight or flight" responses without real danger, and difficulties with emotional regulation.

Discussion

This article does not mean that a cure for autism in humans has been found. Rather, it represents a step in research, pointing to potential regions that may be responsible for certain symptoms and suggesting mechanisms that could be targeted in future preventive and therapeutic interventions. Currently, there are no clinically effective therapies for ASD, ADHD, or PTSD. Nevertheless, positive pilot clinical studies using natural compounds with antioxidant and anti-inflammatory properties, which stabilize mast cells and thereby reduce histamine levels, offer hope [12], [26]. MCAS and HIT may contribute to symptoms frequently observed in ASD, ADHD, and PTSD [10]. Diagnosis is based on clinical symptom assessment, measurement of DAO enzyme levels, and observation of the patient's response to a diet eliminating histamine-containing foods (or foods that trigger histamine release); implementing such a diet very often leads to rapid improvement in the patient's condition [157]. Building on the author's previous findings [10], [783], the present hypothesis expands this concept to a broader scale by proposing that chronic mast cell overactivation, together with impaired histamine metabolism, contributes to inflammatory processes, reduced GABA signaling, and excessive glutamatergic activity. These interconnected mechanisms are suggested to play a central role in the pathophysiology and symptom development of ASD, ADHD, and PTSD. This is often the result of complex interactions among neurotransmitters, genes, gut microbiome, immune system, and environmental factors. Preclinical data suggest that elements of interior architecture [666], exposure to stressors, Wi-Fi, ionizing radiation (X-rays, radiotherapy) (National Cancer Institute) [310], [643], as well as simultaneously consumed dietary components—for example, large amounts of ketchup (high histamine content), caffeine [90], casein, gluten, or wheat-containing products [784] —interact with these mechanisms, explaining the overlapping and amplifying nature of the symptoms [609]. Recognizing these relationships and eliminating them to prevent excessive activation of mast cells and microglia, as well as better understanding the mechanisms of HIT, may help limit neuroinflammatory processes [140] and open new therapeutic avenues [783]. Maintaining optimal levels of vitamin A (beta-carotene) and vitamin D (EDS CLINIC) [785] stabilizes mast cells, which, according to research, may also enhance antiviral immune responses, suppress retroviral infection [42], reduce histamine levels, and thus represent one of the key strategies in alleviating symptoms of MCAS, ASD, ADHD, and PTSD [284], [208], [209], [31].

Although ASD, PTSD, and ADHD differ in terms of developmental timing and clinical presentation, it looks that they share a common neuroimmunological pathway involving mast cell activation induced by chronic stress, neuroinflammation, dysregulation of histaminergic and glutamatergic signaling, and altered neuron–glia communication. Disorder-specific patterns reflect the timing and context of autonomic (immune–nervous) system programming: ASD has a prenatal origin (the system is "set" early), ADHD arises from a combination of developmental and environmental factors, and PTSD develops secondarily (the system is "reprogrammed" by trauma). A comprehensive review of ASD epidemiology in Arab countries by Newschaffer [786], categorized potential risk factors as: "1) maternal genetic predispositions, 2) environmental factors affecting the mother, 3) child genetic predispositions, and 4) environmental factors affecting the child, including absent or short breastfeeding, advanced maternal and paternal age, cesarean delivery, prenatal complications, vitamin D deficiency, exposure to pollutants, and heavy metals" [627]. According to [25] prenatal stress and inflammations [610] are associated with a higher risk of ASD in offspring [787], [610]. Mast cells in children with ASD have been observed to react disproportionately even to mild environmental triggers, where histamine can stimulate microglia, leading to dysfunction in neuronal connectivity and a low "fear threshold," resulting in an exaggerated "fight-or-flight" response, which may be a key factor contributing to the pathogenesis of ASD and PTSD [788]. Future research on this hypothesis should focus on mast cell stabilization, DAO/HNMT genetics, histamine catabolism, dietary and environmental influences, and neuroimmunological interventions. Effective therapeutic strategies should consider individual differences in response to triggers, pharmacological, sensory, dietary, climatic, and environmental interventions in an integrated manner, forming a promising foundation for personalized therapies that provide relief to patients [789]. For example, clinical studies have shown that treatment with hydroxyzine (an H1 antihistamine) combined with a low-histamine diet led to significant overall improvement in individuals with intellectual disability [374], as well as treatment with H2 antihistamine could be a future therapeutic target of ADHD [790]. The simultaneous use of H1 and H2 receptor antagonists has shown positive effects not only in cardiac disease management [210], but also in the prevention and treatment of anaphylaxis [421], as well as in improving sleep architecture and behavior in children and adolescents with ASD [268], [270], [269], [258], and the antioxidant properties of H3 receptor antagonists have shown that these compounds may represent a promising therapeutic option in treating autism spectrum disorders (ASD) [258], [297]. These findings extend to other brain disorders in which microglia trigger inflammation, such as Alzheimer's disease [203], [209], schizophrenia [791], and BPSD [258], suggesting new strategies for treating neuroinflammation-related disorders [284]. Due to their ability to limit

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chemotaxis, H4 receptor antagonists are being studied in conditions such as atopic dermatitis, asthma, and chronic intestinal inflammation as potential anti-inflammatory and anti-allergic drugs [792], [793].

Considering histamine and the blood–brain barrier, drugs that suppress mast cell degranulation (e.g., luteolin [794], apigenin [795] and quercetin represent promising support in ASD therapy [796], [797]. Additionally, histamine receptor antagonists are presented as candidates for treating and preventing brain inflammation or edema [798], [214], as well as in improving post-stroke prognosis [101], [799], and in multiple sclerosis [137], which indicates that glial cells should be studied alongside mast cells as an interconnected network [138]. The importance of mast cells and the development of studies on their role in ASD is highlighted by [10] and can also be found in the later review article [30]. Variability in histamine metabolism among different individuals (e.g., levels of DAO, HNMT) depending on genetic, environmental, and dietary factors emphasizes the need for a personalized approach to the diagnosis and treatment of conditions that may be histamine-dependent, including symptoms of ASD, PTSD, ADHD, etc. [37]. Inflammatory states and immune dysregulation are key features characteristic of both neurodevelopmental and allergic disorders, suggesting overlapping pathophysiology. A 2025 study indicates that food, skin, and respiratory allergies are strongly associated with ADHD [800], [801]. Research from 2020 indicates that individuals with allergies have a 30–50% higher risk of ADHD and ASD [802]. Another study showed that children with ADHD exhibited rhinitis, eczema, significantly lower hemoglobin levels, higher IgE, and elevated eosinophil counts compared to controls, as well as microbiome dysbiosis and sleep disturbances [801]. A clinically important issue is the preparation of individuals with MCAS and HIT for surgical procedures, as invasive procedures and anesthesia are considered additional risk factors for anaphylaxis or adverse reactions "triggered by direct mast cell degranulation induced by mechanical irritation and tissue trauma, stress and pain, catheters, and anesthetic drugs during surgical procedures" [802]. Researchers propose the use of prophylactic antimediator therapy (PAT), including H1 and H2 histamine receptor antagonists [210], glucocorticoids, and benzodiazepines 1 hour prior to surgery, as this approach is not associated with adverse effects and reduces the likelihood of mast-cell mediator-dependent symptoms. Based on current evidence on the role of histamine in inflammatory, stress-related, and anaphylactoid reactions, it can be hypothesized that preoperative supplementation with diamine oxidase (DAO) and antihistamines may offer potential benefit in selected patients with HIT, MCAS [803], mastocytosis [804], or HIV infection [805], conditions that are associated with immune dysregulation and an increased prevalence of autoimmune comorbidities [806]. This proposed mechanism may involve a reduction in exogenous histamine load as well as a decrease in the overall histamine pool available to trigger systemic symptoms. However, this hypothesis remains speculative and requires confirmation through well-designed, controlled clinical trials and evidence-based clinical guidelines [774].

This review provides an understanding of these shared factors as potential mechanisms and their integration (interactions between mast cells, histamine, GABA/glutamate, and neuroinflammation) underlying the pathogenesis of ASD, ADHD [806], and PTSD [31], which may help explain comorbidities, overlapping symptoms, and suggest new therapies. The author emphasizes that this all suggests the existence of a shared etiology—in this case, the relationship between histamine levels and multiple symptoms—and calls for interdisciplinary research (including RCTs, genetics [811], environmental mast cell triggers [812], DAO, neonatal jaundice [813], D-dimers [814] and histamine levels) to test this hypothesis, taking into account individual variability. Conducting such studies will also allow for understanding the relationships between environmental elements and the human body, as well as applying safety engineering in the design of calming, human-centered spaces [807], particularly preventive spaces, with guidelines [782] for project elements—such as apartment layouts, selection of materials, colors, lighting, acoustics, shared spaces, and the outdoor environment [808] —which influence well-being and may reduce symptoms of ASD [809], ADHD, and PTSD, as exemplified by the pioneering neuroarchitecture system Vinci Power Nap® [665], [667], [668]. Recently, reports from the USA Department of Health and Human Services, working to find the cause of ASD, in September 2025 they announced indicated a correlation between prenatal acetaminophen use and later autism spectrum diagnoses in children (U.S. Department of Health and Human Services, 2025) [75]. However, the question arises whether the observed correlations are truly dependent on the medication itself, or rather on infections or inflammatory conditions during pregnancy (i.e., histamine release), the symptoms of which the mother attempted to alleviate with acetaminophen as an antipyretic and analgesic. The author's previous discoveries and hypothesis [11], [13] were sent in emails dated 15.02.205 to the offices of Mr. Robert F. Kennedy Jr., Secretary General of the U.S. Department of Health, and emails dated 25.06.2025 with letter dated on 12 June 2025 to the offices of Mr. Robert F. Kennedy Jr. in MAHA and TeamKennedy, along with a link to the abstract of above hypothesis published on 19.05.2025 [10] to bring the attention of the Department while it was investigating the causes of autism spectrum disorder, with the intention of contributing to its ongoing efforts.

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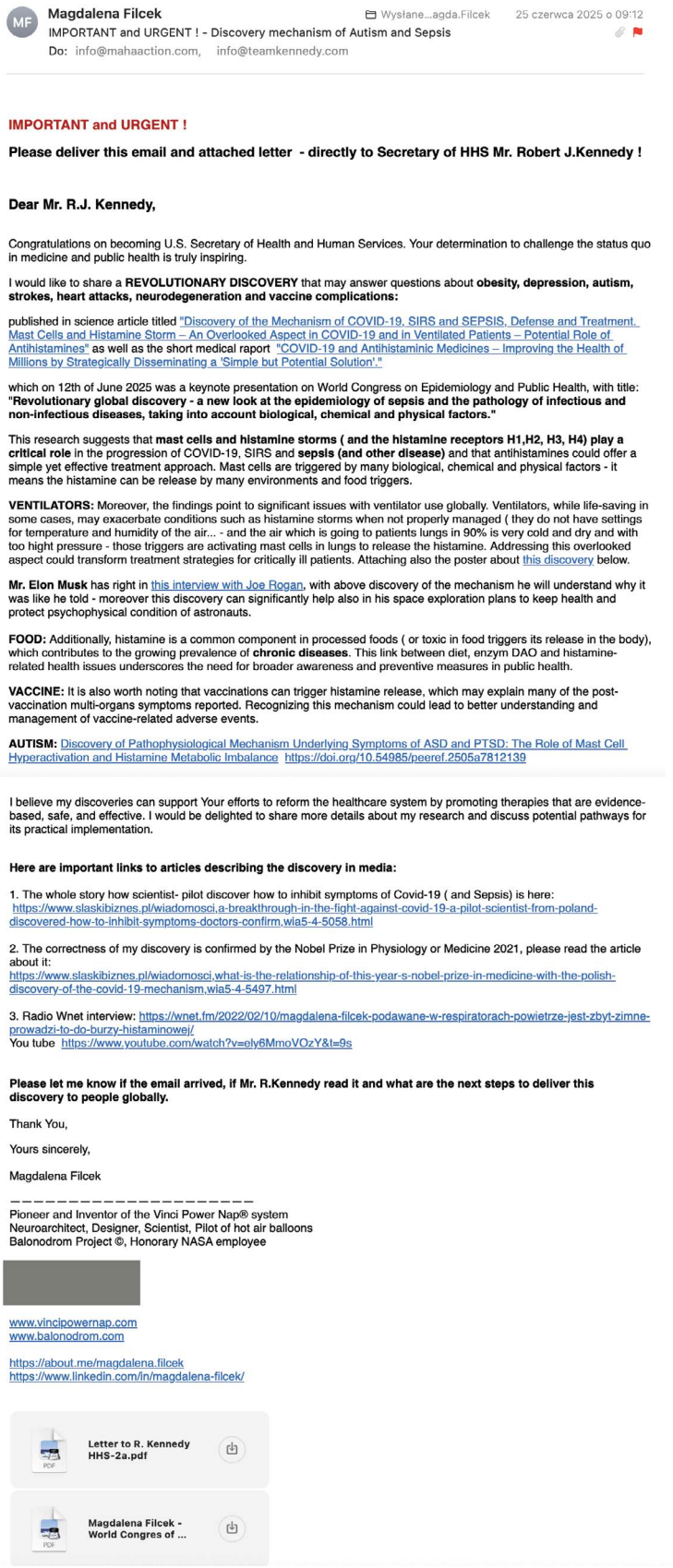

Magdalena Filcek — Wysłane...agda.Filcek — 25 czerwca 2025 o 09:12
IMPORTANT and URGENT ! - Discovery mechanism of Autism and Sepsis
Do: info@mahaaction.com, info@teamkennedy.com

IMPORTANT and URGENT !

Please deliver this email and attached letter - directly to Secretary of HHS Mr. Robert J.Kennedy !

Dear Mr. R.J. Kennedy,

Congratulations on becoming U.S. Secretary of Health and Human Services. Your determination to challenge the status quo in medicine and public health is truly inspiring.

I would like to share a **REVOLUTIONARY DISCOVERY** that may answer questions about **obesity, depression, autism, strokes, heart attacks, neurodegeneration and vaccine complications:**

published in science article titled "Discovery of the Mechanism of COVID-19, SIRS and SEPSIS, Defense and Treatment. Mast Cells and Histamine Storm – An Overlooked Aspect in COVID-19 and in Ventilated Patients – Potential Role of Antihistamines" as well as the short medical raport "COVID-19 and Antihistaminic Medicines – Improving the Health of Millions by Strategically Disseminating a 'Simple but Potential Solution'."

which on 12th of June 2025 was a keynote presentation on World Congress on Epidemiology and Public Health, with title: **"Revolutionary global discovery - a new look at the epidemiology of sepsis and the pathology of infectious and non-infectious diseases, taking into account biological, chemical and physical factors."**

This research suggests that **mast cells and histamine storms (and the histamine receptors H1,H2, H3, H4) play a critical role** in the progression of COVID-19, SIRS and **sepsis (and other disease)** and that antihistamines could offer a simple yet effective treatment approach. Mast cells are triggered by many biological, chemical and physical factors - it means the histamine can be release by many environments and food triggers.

VENTILATORS: Moreover, the findings point to significant issues with ventilator use globally. Ventilators, while life-saving in some cases, may exacerbate conditions such as histamine storms when not properly managed (they do not have settings for temperature and humidity of the air... - and the air which is going to patients lungs in 90% is very cold and dry and with too hight pressure - those triggers are activating mast cells in lungs to release the histamine. Addressing this overlooked aspect could transform treatment strategies for critically ill patients. Attaching also the poster about this discovery below.

Mr. Elon Musk has right in this interview with Joe Rogan, with above discovery of the mechanism he will understand why it was like he told - moreover this discovery can significantly help also in his space exploration plans to keep health and protect psychophysical condition of astronauts.

FOOD: Additionally, histamine is a common component in processed foods (or toxic in food triggers its release in the body), which contributes to the growing prevalence of **chronic diseases**. This link between diet, enzym DAO and histamine-related health issues underscores the need for broader awareness and preventive measures in public health.

VACCINE: It is also worth noting that vaccinations can trigger histamine release, which may explain many of the post-vaccination multi-organs symptoms reported. Recognizing this mechanism could lead to better understanding and management of vaccine-related adverse events.

AUTISM: Discovery of Pathophysiological Mechanism Underlying Symptoms of ASD and PTSD: The Role of Mast Cell Hyperactivation and Histamine Metabolic Imbalance https://doi.org/10.54985/peeref.2505a7812139

I believe my discoveries can support Your efforts to reform the healthcare system by promoting therapies that are evidence-based, safe, and effective. I would be delighted to share more details about my research and discuss potential pathways for its practical implementation.

Here are important links to articles describing the discovery in media:

1. The whole story how scientist- pilot discover how to inhibit symptoms of Covid-19 (and Sepsis) is here: https://www.slaskibiznes.pl/wiadomosci,a-breakthrough-in-the-fight-against-covid-19-a-pilot-scientist-from-poland-discovered-how-to-inhibit-symptoms-doctors-confirm,wia5-4-5058.html

2. The correctness of my discovery is confirmed by the Nobel Prize in Physiology or Medicine 2021, please read the article about it:
https://www.slaskibiznes.pl/wiadomosci,what-is-the-relationship-of-this-year-s-nobel-prize-in-medicine-with-the-polish-discovery-of-the-covid-19-mechanism,wia5-4-5497.html

3. Radio Wnet interview: https://wnet.fm/2022/02/10/magdalena-filcek-podawane-w-respiratorach-powietrze-jest-zbyt-zimne-prowadzi-to-do-burzy-histaminowej/
You tube https://www.youtube.com/watch?v=ely6MmoVOzY&t=9s

Please let me know if the email arrived, if Mr. R.Kennedy read it and what are the next steps to deliver this discovery to people globally.

Thank You,

Yours sincerely,

Magdalena Filcek

Pioneer and Inventor of the Vinci Power Nap® system
Neuroarchitect, Designer, Scientist, Pilot of hot air balloons
Balonodrom Project ©, Honorary NASA employee

www.vincipowernap.com
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https://www.linkedin.com/in/magdalena-filcek/

Letter to R. Kennedy HHS-2a.pdf

Magdalena Filcek - World Congres of ...

Picture 8: Letter to Mr. Robert F. Kennedy Jr., Secretary General of the U.S. Department of Health

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Conclusion

The findings suggest the existence of a pathophysiological continuity between earlier exposures or biological events and later clinical manifestations. The collected data indicate that ASD and related neuropsychiatric conditions, such as ADHD and PTSD, result from a complex interaction between the nervous system, the immune system, and the environment. Analysis of the available data and literature suggests that disorders associated with chronic mast cell hyperactivation—and consequently with histamine metabolism, the related dysregulation of the glutamate–GABA balance, and chronic neuroinflammation—may play a key role in the pathophysiology of ASD, ADHD, PTSD, as well as other neuroimmunological disorders in which this pathological loop develops. Accordingly, stabilization of mast cell activation, reduction of histamine levels, and modulation of neuroinflammatory pathways represent promising preventive and therapeutic strategies that may support cognitive functions, emotional regulation, and improve the overall quality of life of individuals affected by neurodegenerative disorders and gastrointestinal symptoms. In individuals with ASD, impairments in the enzymatic degradation of histamine (DAO, HNMT) are frequently observed, which may lead to excessive histamine accumulation in the body and secondary mast cell activation. A low-histamine diet, supplementation with the DAO enzyme, vitamins D3, A, B6, B9, and B12, as well as minerals such as zinc, selenium, and copper, acemannan, together with appropriate sensory interventions, show potential in supporting the management of symptoms related to neuronal hyper-excitability, heightened sensitivity, and maladaptive stress responses.

Within a personalized medicine framework that accounts for individual genetic variability in histamine metabolism pathways, selected natural bioactive compounds—such as quercetin, apigenin, and luteolin—black seed oil, as well as certain antihistamine medications (H1, H2, and H3 receptor antagonists), may exert mast cell–stabilizing effects, limit neuroinflammatory processes, and support blood–brain barrier integrity, potentially providing therapeutic benefits for selected patients with ASD, ADHD, and PTSD; however, this requires further validation in controlled studies. The environment also plays a significant role in modulating the aforementioned processes. Adverse environmental factors, stress, pollution, intrusive technologies and sensory overstimulation may exert epigenetic effects on mast cell hyperreactivity, thereby increasing the risk of ASD development (Marzi et l. 2025). Biological, physical, and chemical factors—such as molds, fungi, bacteria; toxins, poisons, and medications; cold and noise (including low-frequency noise emitted by air-conditioning systems), vibrations, mechanical pressure (e.g., elastic bands in clothing), air pollution, heavy metals, microplastics, ambient temperature, excessive light exposure, and electromagnetic radiation—may exacerbate sensory stress (similarly to prenatal stress, emotional stress, and trauma) and induce IgE-independent mast cell degranulation. This can leads to increased levels of histamine and pro-inflammatory cytokines, and consequently to infection-like symptoms, neonatal jaundice, blood–brain barrier permeability, microglial activation, elevated glutamate levels, neuroinflammation, lowering of the anxiety threshold, heightened stimulus reactivity, and further mast cell activation.

In the context of sensory hypersensitivity, "fight-or-flight" responses in the absence of real threat, as well as sleep disturbances and difficulties with emotional regulation, suggest that appropriately designed, supportive surroundings characterized by low noise levels, comfortable temperatures, access to green spaces, biophilic design features, and a strong sense of safety may promote recovery and well-being. Such environments can facilitate neuroregenerative processes, enhance emotional regulation, and provide restorative benefits for both affected individuals and their families. Although ASD, ADHD, and PTSD differ in their timing of onset and clinical presentation, at the cellular level they activate similar neuroimmunological pathways associated with chronic stress, neuroinflammation, and excessive neuronal excitability. Prolonged activation of mast cells and histamine release may influence inflammatory processes that could potentially shorten lifespan, suggesting a link between mast cell regulation and longevity. Regulation of mast cells and histamine may represent a key mechanism affecting aging processes and lifespan. Despite the growing number of descriptive studies and case reports, randomized interdisciplinary clinical trials (RCTs) are needed to confirm the proposed hypothesis and the effectiveness of the suggested interventions. Understanding the converging mechanisms of mast cell activation, histamine signaling, neurotransmitter imbalance (GABA/glutamate), and neuroinflammation will enable more accurate assessment of overlapping symptoms and the identification of novel therapeutic targets. Future research should focus on mast cell activity, genetic determinants of DAO/HNMT enzymes, the impact of the sensory environment, and integrated neuroimmunological therapy models encompassing pharmacological, dietary, behavioral, and architectural components, in order to evaluate their effects on the prevention or progression of many diseases.

A holistic approach integrating knowledge from cellular biology, neurochemistry, neuroarchitecture, and safety engineering opens new perspectives for the personalized medicine of the future—aimed not only at symptom reduction but also at improving the quality of life of individuals with ASD, PTSD, ADHD, MCAS, HIT, and other disorders, including Alzheimer's and Parkinson's diseases. Increasing evidence suggests that, in many cases, the underlying basis

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of symptoms may be neurochemical rather than exclusively psychological. This work constitutes a biological bridge between immunology, neurobiology, neuroarchitecture, developmental psychiatry, sleep, longevity and personalized medicine.

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Conflict of interest statement

Author is also the creator and researcher of Vinci Power Nap® neuroarchitecture pioneering system.

GenAI Disclosure Statement

ChatGPT 4.0 has strictly been used for grammar review, writing clarity in some sections of this paper and help with infographic. No part of the substantive content, arguments, or conclusions were generated by AI, they are solely the work of the author. Chosen illustrations was generated using AI ChatGPT 4.0., reviewed, corrected and completed by the author.

List of Abbreviations

AA – Arachidonic Acid

ACLF – Acute-on-Chronic Liver Failure

ACLD – Advanced Chronic Liver Disease

ADHD – Attention-Deficit/Hyperactivity Disorder

ADDM – Autism and Developmental Disabilities Monitoring

ALDH7A1 – Aldehyde Dehydrogenase 7 Family Member A1

AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (ionotropic glutamate receptor)

ASD – Autism Spectrum Disorder

BBB – Blood–Brain Barrier

BCM7 – Peptide beta-casomorphin-7

BCSFB – Blood–Cerebrospinal Fluid Barrier

BLB – Blood–Labyrinth Barrier

BNB – Blood–Nerve Barrier

CDC – Centers for Disease Control and Prevention

CGRP – Calcitonin Gene-Related Peptide

CLP – Cecal Ligation and Puncture

COMT – Catechol-O-Methyltransferase

COPD – Chronic Obstructive Pulmonary Disease

CRF – Corticotropin-Releasing Factor

CRH/CRF – Corticotropin-Releasing Hormone / Factor

CRP – C-Reactive Protein

CNS – Central Nervous System

DAO – Diamine Oxidase

DHA – Docosahexaenoic Acid

DIC – Disseminated Intravascular Coagulation

DNMT – DNA Methyltransferases

ECL – Enterochromaffin-like Cells

EBV – Epstein-Barr Virus

ESR – Erythrocyte Sedimentation Rate

GABA – Gamma-Aminobutyric Acid

GERD – Gastroesophageal Reflux Disease

GGT – Gamma-Glutamyl Transferase

HNMT – Histamine N-Methyltransferase

HDC – Enzyme Histidine Decarboxylase

HCl – Hydrochloric Acid

HPA axis – Hypothalamic-Pituitary-Adrenal Axis

HIT – Histamine Intolerance

IL-1β – Interleukin-1 Beta (silnie prozapalna cytokina)

IL-6 – Interleukin-6 (cytokina o działaniu dwoistym: ostra faza vs przewlekłe zapalenie)

LTP – Long-Term Potentiation

MAOB – Monoamine Oxidase B

MCs – Mast Cells

MCAS – Mast Cell Activation Syndrome / Mastocytosis

MSG – Monosodium Glutamate

NMDA – N-Methyl-D-Aspartate Receptor (jonotropowy receptor glutaminianu)

NT – Neurotensin

NSAIDs – Nonsteroidal Anti-Inflammatory Drugs

OXTR – Oxytocin Receptor

POTS – Postural Orthostatic Tachycardia Syndrome

PTH – Parathyroid Hormone

PMDD – Premenstrual Dysphoric Disorder

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PMS – Premenstrual Syndrome

RCT – Randomized Clinical Trials

SAH – S-adenosylhomocysteine

SAM – S-adenosylmethionine

SCF – Stem Cell Factor

SCH – Schizophrenia

SIBO – Small Intestinal Bacterial Overgrowth

SM – Systemic Mastocytosis

SIDS – Sudden Infant Death Syndrome

SIRS – Systemic Inflammatory Response Syndrome

TGF-β – Transforming Growth Factor Beta (cytokina regulacyjna / immunosupresyjna)

TNF-α – Tumor Necrosis Factor Alpha

VPN - Vinci Power Nap®

WHO – World Health Organization

5-HT – Serotonin

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