Transdermal Histamine in Multiple Sclerosis, Part Two: A Proposed Theoretical Basis for Its Use.

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Abstract

This paper is the companion to an earlier publication, which discussed preliminary results of transdermal histamine use for ameliorating symptoms of both relapsing-remitting and progressive multiple sclerosis (MS). Here we include preliminary findings on the impairments of digestion and assimilation in MS patients seen in a private clinic. Although only a small number of patients was surveyed, an association was found between impaired gastric acid production, impaired protein hydrolysis, and subnormal plasma histidine levels in patients with MS. Impaired digestion might, therefore, impair the ability of MS patients to synthesize histamine. This paper discusses how impairment of histamine synthesis might lead to symptoms of MS, and conversely how exogenously administered histamine might alleviate symptoms. Various mechanisms of action are suggested, including: enhanced gastric acid and pancreatic enzyme secretion, augmentation of subnormal cerebral tissue levels of histamine, improved electrical function of demyelinated fibers, increased cerebral blood flow, suppression of aberrant autoimmune responses, and stimulation of remyelination. We also discuss the observed failure of digestive function in MS and point out that pathological changes which parallel CNS findings have been found in the enteric nervous system (ENS) of patients with Parkinson's disease. Similar parallels might exist between the CNS and ENS in multiple sclerosis.

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Introduction

A previous paper[1] discussed preliminary results of usage of a transdermal histamine/caffeine preparation for ameliorating symptoms of multiple sclerosis (MS). Improvement was seen in 37 of 55 patients (67%) followed for at least six weeks. This work has continued, and at the time of writing 167 patients had been followed for at least six weeks, with 26 percent of patients experiencing significant improvement as defined previously,[1] 29 percent experiencing some improvement, and 45 percent seeing no benefit. Improvements at three months have, in most cases, continued at six months.

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Areas of improvement have been observed in extremity strength, balance, bladder control, fatigue, heat tolerance, cognitive function, peripheral edema, and activities of daily living. Improvement is often seen within a few hours or days of starting therapy, and there have been minimal side-effects. This is in keeping with the findings of others who have administered similar amounts of subcutaneous histamine for such clinical problems as vertigo, headache,[2] and cancer.[3]

Five possible mechanisms of action of histamine on the symptoms and clinical manifestations of MS were introduced in Part One of this article.[1] These include augmentation of subnormal cerebral tissue levels of histamine, improved electrical function of demyelinated fibers, increased cerebral blood flow, modulation of autoimmune responses, and stimulation of remyelination.

Although the respective bodies of literature on histamine and MS are vast, there are no recent studies exploring histamine's role in the treatment of MS, and only a few studies even tangentially examine the role of histamine in the pathophysiology of MS. A recent Medline search under the terms "histamine and multiple sclerosis" returned 16 citations, with only some of these papers relevant to the issues discussed here. Consequently, we emphasize that the ideas discussed here are mostly speculative and unsupported by direct experimentation. Should histamine therapy continue to show promise, we hope other researchers will use this paper as a starting point for testing these hypotheses.

Histamine Neurophysiology and Neuroanatomy

There is considerable evidence in the literature that histamine is an ancient and pervasive regulator of physiologic processes. Histaminergic neural paths extend throughout the bodies of lower organisms, including insects[4] and marine animals.[5] Histaminergic fibers are found in the sympathetic chains of mice[6] and higher mammals.

Histaminergic neural paths extend from the brain to synapses in the higher cervical spinal cord.[7] In humans, histaminergic fibers project from a dense population of cell bodies in the hypothalamus to almost all areas of the brain, including the cerebellum.[8-10] The goat pineal gland contains a large amount of histamine.[11] This suggests a link between histamine and melatonin production, although similar data on humans has not been obtained. Histamine is synthesized within these neurons by decarboxylation of the amino acid histidine.

The hypothalamic histaminergic system modulates diverse and crucial aspects of physiology, including thirst, hunger, sex drive, circadian rhythm, arousal level,[12] urine output,[13,14] thermoregulation,[15] nociception,[12] and vestibular function.[16,17] Histamine also participates in other aspects of neuroendocrine function, including stress-induced secretion of such mediators as adrenocorticotropin (ACTH), beta endorphin, melatonin, prolactin, and peripheral catecholamines.[18,19]

Three different receptor subtypes, denoted H1, H2, and H3, mediate these responses. Discussion of these receptors can be found in reference 20. Briefly, all the histamine receptors are thought to be G-protein coupled receptors. Stimulation of the H1 receptor is, in general, associated with an increase in intracellular Ca^{2+} and formation of inositol triphosphate and diacylglycerol. Stimulation of the H2 receptor results in an elevation of intracellular cyclic adenosine monophosphate (cAMP). The intracellular coupling of the H3 receptor is not well understood; possible mechanisms include coupling to calcium channels. On neurons, the H3 receptor is a presynaptic receptor that is inhibitory both for release of histamine (autoreceptor) and other neurotransmitters (heteroreceptor).

The interpretation of experimental findings pertaining to histamine is sometimes

difficult due to the number of histamine receptors and their diverse actions. For a given phenomenon, the action of histamine at H1 receptors often opposes that seen at H2 receptors.[21] Sometimes the effects of stimulation at both receptors are the same.[18] Furthermore, H3 receptor stimulation inhibits the release of histamine from mast cells, including brain mast cells.[22] The effect of histamine in any given situation may, therefore, be sensitive to the relative populations of the three receptor subtypes at a given location, as well as the concentration of histamine in the vicinity of the receptors.

The following examples illustrate the diversity of action of histamine in the brain. In rats, H1 stimulation decreases feeding,[13] increases alertness, and increases nociception,[12] whereas H3 receptor stimulation provokes drinking.[13] Both H1 and H2 stimulation (via intracerebroventricular histamine receptor agonist injection) elicited hypothermia in mice, whereas H3 stimulation prevented development of hypothermia.[15] Intracerebroventricular injection of histamine also stimulates diuresis in rats[13] via H2 receptors. Histamine also stimulates release of melanocyte stimulating hormone from the pituitary via both H1 and H2 receptor stimulation.[18]

Approximately one-half of the histamine in the mouse brain resides in mast cells, as shown by Maeyama, who studied mutant mice devoid of mast cells.[23] Outside the brain, considerable histamine is stored in the enterochromaffin-like (ECL) cells of the gastric mucosa, where histamine plays a critical role in acid secretion. Histamine is also found in circulating basophils, eosinophils and platelets, as well as mast cells in many tissues, including the skin, heart, lungs, liver, kidneys, spleen, bladder, ovaries, and testicles.[24-27] Further discussion of the role of histamine in these tissues is beyond the scope of this article.

Pathophysiology of MS

The majority of current research supports the view that MS is an autoimmune disorder in which immune cells (T lymphocytes and macrophages) in the blood are "primed" (sensitized), possibly by viral-related antigens, to attack myelinated neurons and glial cells of the central nervous system.[28,29] Candidate viruses include measles,[30] herpes,[31] vaccinia,[32] and multiple sclerosis retrovirus.[33,34]

The concept of Th1/Th2 balance is central to any discussion of the immunologic aspects of MS. Briefly, many diseases recognized as autoimmune can be classified according to the activity of two T cell subpopulations: Th1 and Th2.[35] Differentiation of naive CD4+ T cells to a Th1 phenotype is induced by interleukin-12 (IL-12).[36] Th1-polarized cells up-regulate various aspects of cell-mediated immunity by the secretion of cytokine mediators, including IL-1, αIL-1, βIL-2, IL-8, IL-12, tumor necrosis factor alpha (TNFα), and interferon gamma (IFNγ). Th1-dominant conditions include infection by intracellular pathogens, rheumatoid arthritis (RA), Crohn's disease, autoimmune thyroiditis, and delayed hypersensitivity reactions.

Differentiation of naive T cells to a Th2 phenotype is primarily promoted by IL-4.[36] Th2-polarized cells secrete mediators including IL-4, IL-5, IL-10, and IL-13, which up-regulate humoral immune responses commonly regarded as "allergic," including IgE production and eosinophil function.[36] Th2-dominated conditions include parasitic infections, atopic dermatitis, asthma, systemic lupus erythematosus, and progressive systemic sclerosis. Pregnancy is also considered to be a Th2 dominated state.[35] Th2 cells may also control the development and activity of Th1 cells.[37]

Immunochemical factors, including IL-1, granulocyte-macrophage colony stimulating factor (GM-CSF), TNFα and others act to bias naive CD4+ cells toward a Th1 state by stimulating production of IL-12 from antigen-presenting cells, including monocytes and

dendritic cells. Other factors, including IL-10, histamine, corticosteroids, vitamin D3, and beta agonists inhibit production of IL-12 from these same cells. Nagelkerken has suggested that hypothalamic-pituitary-adrenal (HPA) axis dysfunction, with deficient corticosteroid production, may lead to Th1 dominant states.[37]

MS is regarded as a Th1 dominant state, and Beck[38] reported increased Th1 cytokine (IL-1, TNFα) secretion prior to relapse. Van Boxel-Dezaire[39] demonstrated increased IL-12 mRNA and decreased IL-10 mRNA in MS patients compared to controls, and IL-12 mRNA levels correlated with disease activity. Administration of Copolymer 1 (Copaxone) has been shown to rebalance the immune response in MS by encouraging Th2 responses.[40,41] In contrast, administration of interferon beta (IFNβ) actually promotes IFNα production (Th1 response), yet IFNα is beneficial for some MS patients.[42] Also, evidence of increased activity of Th2 cells in MS is seen in the form of elevated levels of autoantibodies.[43] This illustrates that although the Th1/Th2 paradigm is very useful, it is not a complete description of immune dysregulation in MS.

Accepting that "priming" of the immune system occurs, permeability of the blood-brain barrier is an important factor to consider, since no nerve damage occurs unless the primed cells gain access to the central nervous system. Spatial and temporal correlations between breaches in the blood-brain barrier and subsequent development of MS lesions support the central role of changes in permeability of the blood-brain barrier.[44,45] Kwon demonstrated that longstanding plaques exhibit evidence of permanent damage to the blood-brain barrier.[46]

Various factors known to alter the permeability of the blood-brain barrier have been directly or epidemiologically linked to the initiation of MS, or are associated with relapse. Examples include thiamine deficiency,[47] heavy metal toxicity,[48] and heat stress.[49] A good summary of some of the evidence supporting the importance of blood-brain barrier permeability in MS is given by Wallace[50] along with a discussion of the evidence supporting the use of various supplemental nutrients to improve the integrity of the blood-brain barrier.

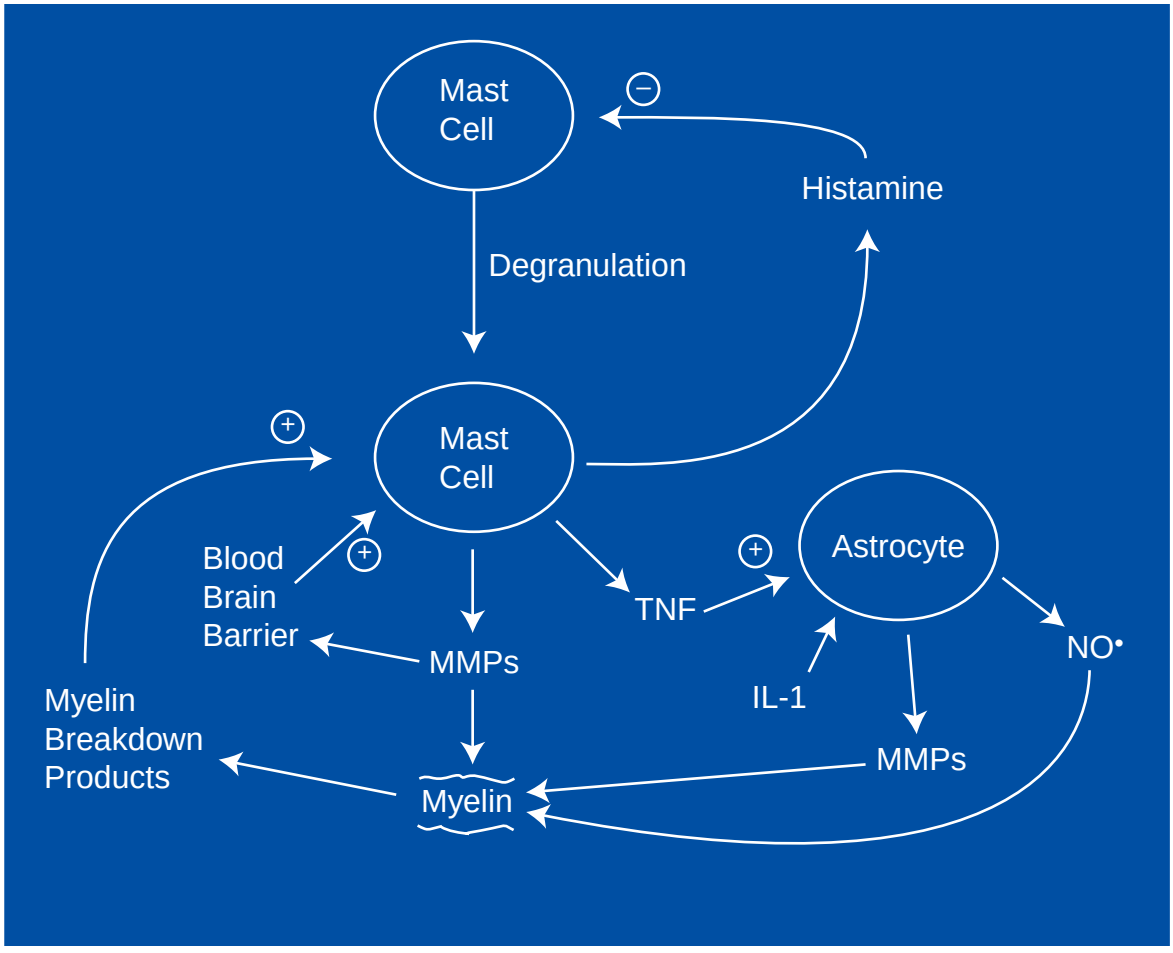
The microscopic appearance of MS plaques changes with time, but in both acute and chronic MS there is an inflammatory reaction dominated by T lymphocytes and macrophages. Myelinated fibers are engulfed by macrophages[51] while other cells, such as peripheral lymphocytes and plasma cells, are also seen in close contact with myelin.[52] In fresh lesions, demyelination is accompanied by destruction of other tissue elements, including oligodendrocytes, astrocytes, and axons. This destruction ends within a few weeks in many cases, and remyelination may follow, once the lesion has been repopulated with oligodendrocytes.[53]

Blakemore[54] and Franklin[55] conclude that remyelination depends on migration of oligodendrocyte progenitors, such as those observed by Prineas,[56] from nearby undamaged tissue into the area of inflammation. Franklin also suggests extensive, recurrent, or longstanding inflammation will deplete surrounding healthy tissue of oligodendrocyte progenitors, ultimately limiting the repopulation of plaques and the remyelination of damaged axons.

Stimuli to remyelination include growth factors, such as platelet-derived growth factor,[57] triiodothyronine (T3),[58,59] and vitamin B12.[60,61] Elevation of intracellular cAMP has also been shown to play a role in induction of oligodendrocyte progenitor differentiation and myelin synthesis in the rat brain[62] and in peripheral Schwann cells.[63,64]

Thiamine also plays a role in myelination. Demyelination is a hallmark of thiamine deficiency,[65] although deficiencies of other nutrients such as copper[66] also cause demyelination. Thiamine, in the form of thiamine pyrophosphate, helps stabilize nerve cell membranes.[67] Myelin-synthesizing oligodendrocyte

Figure 1. Role of Mast Cell Mediators in CNS Inflammation.



cell bodies contain thiamine pyrophosphatase (TPPase),[68] the enzyme which generates thiamine pyrophosphate. TPPase has been localized to the Golgi complexes of various neuronal cells,[69] and Trapp found protein zero (P0), the main component of myelin basic protein, in Golgi complex membranes in rat Schwann cells.[70]

The inflammatory cascade leading to demyelination is complex, and current understanding of it is by no means complete. There has been increased awareness lately of the important role of mast cells in central nervous system (CNS) inflammatory processes, including MS.[71,72] Substances released from mast cells can attack myelin, and myelin breakdown products can stimulate further mast cell degranulation.[73] Skaper has suggested that down-regulation of mast cell activation could be a therapeutic strategy in neuroinflammatory conditions,[74] and proxicromil, a mast cell stabilizer, has been employed successfully in experimental autoimmune encephalomyelitis (EAE), the mouse model of MS.[75]

Mast cells are known to release leukotrienes,[76] inflammatory mediators that affect vascular permeability and exhibit chemoattractant properties. Elevated levels of leukotriene C4 and leukotriene B4 are found in the cerebrospinal fluid (CSF) of MS patients.[77] Inhibition of 5-lipoxygenase, an enzyme involved in the synthesis of leukotrienes, prevented the development of symptoms in guinea pig EAE and significantly reduced histologic inflammation scores.[78]

Matrix metalloproteinases (MMPs), a family of zinc-containing enzymes which can digest connective tissue and myelin,[72,79] are

another important class of inflammatory mediators. They are also known to be disruptive to the blood-brain barrier.[80] Mast cells contain and release MMPs,[72,79,81] and MMPs are found to be elevated both in the CSF of MS patients[82] and in EAE mice.[83] Blockage of MMPs inhibits or reduces the severity of EAE.[83,84]

Earlier, reference was made to "priming" of peripheral immune cells. An example of this is the observation that peripheral monocytes and macrophages contain elevated levels of MMPs.[80,82,83] The release of MMPs by mast cells may feed the inflammatory spiral in several ways. First, by generating myelin fragments such as myelin basic protein, which elicit further mast cell degranulation,[74,79,85] and second, by liberating cytokines such as TNFα from the cell membranes of monocytes[86] or myelin autoreactive CD4+ T cells.[84] TNFα levels in the CSF of MS patients have been correlated to disease severity.[87,88] Blockade of TNF by anti-TNF antibodies prevented the development of EAE in one mouse study.[89]

Mast cells also release TNFα directly[71,74] and mast cell-derived TNF affects the release of neurotoxic NO radicals (from astrocytes in mast cell/hippocampal co-cultures)[90] and MMPs.[91] Thus, as mentioned, mast cell degranulation, with release of mediators such as MMPs and TNF, might set up a potential positive feedback loop (Figure 1) promoting more mast cell degranulation.

Histamine is the most widely recognized mediator released by mast cells. Release of histamine by brain mast cells may initially accelerate inflammation by increasing the permeability of the blood-brain barrier, an H2 receptor-mediated phenomenon.[92] Increased blood-brain barrier permeability would then presumably increase the influx of sensitized peripheral immune cells. This process is thought to be central to the pathophysiology of MS. Ongoing mast cell degranulation with histamine release might also create an increased demand for histidine (the direct precursor of histamine), and potentially compromise the supply of histidine at other histamine-synthesizing sites in the brain, such as histaminergic neurons.

Interestingly, the number, location, and histamine content of mast cells in mouse brain have been shown to be inherited traits.[93,94] If this is also true in humans, some individuals might exhibit increased susceptibility to MS and other inflammatory conditions because of this genetic programming.

Gut Function in MS

Constipation is a common complaint of MS sufferers. For example, 68 percent of 280 patients surveyed by Weber[95] reported constipation or fecal incontinence. These symptoms may reflect CNS damage as well as enteric nervous system (ENS) dysfunction.[96] (Reference 96 is an overview of the ENS.)

Other aspects of gut function impairment in MS are less well recognized. These include impaired digestion and assimilation of nutrients. Gupta[97] reported evidence of fat malabsorption and protein maldigestion in 40 percent of 52 MS patients. Xylose malabsorption was seen in 27 percent, and B12 malabsorption in 12 percent. Absorption of fat-soluble vitamins A and beta carotene was also impaired to a certain extent. Iarosh noted endoscopic atrophic changes, gastritis, and ulcerations consistent with achlorhydria in 32 MS patients.[98] The total number of MS patients in that study was 89, but selection criteria for endoscopy were not given.

Over the past 25 years, one of the authors (JW) has observed abnormal gastric acid secretion, as assayed by Heidelberg capsule,[99] in approximately 70 percent of patients with MS, although these findings have never been published. Recently Gillson found severe hypochlorhydria or achlorhydria in 9 of 14 (64%) patients with MS, also using the Heidelberg capsule. Fasting plasma essential amino acid levels were also measured in 12 unselected patients with MS, prior to their starting histamine treatment. Ten of 12 had at least five ab-

Table 1. Gastric Acid Secretory Status and Amino Acid Status in MS Patients.

Patient Initials	Impaired gastric acidity	Abnormal levels of more than 5 essential amino acids	Low or borderline plasma Histidine level
BG	√	√	√
JR		√	√
JW	√	√	√
GW	√	√	Low normal
LM	√	√	√
JM	Not tested	√	√

normal values (out of 10 measured).

A small number of MS patients at our (JW/GG) clinic recently had both a Heidelberg assay as well as measurement of fasting plasma essential amino acids, including histidine. Six of six patients had low values on six or more of the 10 essential amino acids measured. Five of the six had histidine levels very close to the low end of the normal range, and five of six patients were achlorhydric or severely hypochlorhydric. Five of these six patients have had a favorable response to exogenous histamine therapy. These results are summarized in Table 1.

Little has been written about plasma amino acid levels in MS. Oriente[100] noted significantly decreased histidine, methionine, and valine levels in nine patients with progressive systemic sclerosis (equivalent to MS in the Russian literature) compared to 15 controls. A study by Ivanokov[101] on 45 MS patients reported "marked deaminoacidemia tending to hypoaminoacidemia." The abstract did not elaborate regarding which amino acids were measured. Quereshi[102] noted decreased levels of methionine, valine, phenylalanine, and lysine in 12 patients with MS versus 12 controls. A total of 24 amino acids were measured in the study, and the levels of other amino acids were "more or less the same in the two groups" according to the abstract, although histidine was not mentioned specifically.

Overall, the present work supports published abnormalities of amino acid levels in general in MS patients. Our work and one previous study also show decreased histidine levels in MS; findings from two previous studies are equivocal. Nyhan reported five cases of hypohistidinemia in males without MS. Interestingly, all had CNS abnormalities.[103]

Evidence of malabsorption of other nutrients, such as zinc[104] and copper[104,105] has also been reported in MS. Both zinc and copper deficiency have been tied to histidine depletion in dogs,[106] and copper deficiency has been linked to demyelination, as mentioned earlier. Copper is also a mast cell stabilizer.[107,108] A possible connection between CNS histidine deficiency, copper deficiency, mast cell degranulation, and demyelination might, therefore, be worth investigating.

Proposed Connections between Histamine, Histidine, and the Pathophysiology of MS

With the foregoing background information in mind, the framework outlined in Figure 2 is proposed.

A central feature is the establishment of a systemic depletion of histidine on the basis of impaired gut function, as well as possible additional histidine depletion due to ongoing or intermittent episodes of CNS mast cell

degranulation. Mast cell mediators are presumed to be involved in promulgation of demyelination, as discussed earlier. Demyelination is assumed to underlie some of the motor symptoms seen in MS, in accord with accepted thinking.

Histidine is needed for histamine synthesis (both systemically and in the CNS) for mast cells, and histaminergic neurons. Histidine deficiency may, therefore, lead to impairment of histaminergic pathways in the CNS via diminished release of histamine in synaptic clefts of histaminergic synapses. We postulate that some of the symptoms of MS, such as fatigue, impaired balance, and poor heat tolerance might be due to this impairment.

The Possible Role of Carnosine

Carnosine is a histidine-alanine dipeptide found primarily in skeletal muscle, cardiac tissue, and the brain.[109] A murine study showed carnosine can be absorbed intact from the gut.[110] If the same is true in humans, carnosine might be subject to the same factors putatively impairing histidine assimilation in MS. A carnosine deficiency might then contribute to an existing histidine deficit, since carnosine might provide a rapidly mobilizable source of histidine in times of high histamine turnover.[111] Both Fitzpatrick[112] and Flancbaum[113] demonstrated increased conversion of carnosine to histamine in various tissues of animals under stress. Carnosine may also act as a histidine reservoir for normal metabolic demands. Prolonged or episodic inflammatory episodes in MS might, therefore, eventually deplete carnosine muscle stores, which would not be replenished by uptake from the gut. Deficiency of carnosine might also make the CNS more susceptible to damage from inflammation, in light of its status as a lipophilic antioxidant.[114-116]

Conversion of carnosine to histidine is carried out by the enzyme carnosinase, and decreased carnosinase activity has been demonstrated in MS.[117] This may be due to subtle thyroid impairment, since decreased serum carnosinase activity is also seen in hypothyroidism.[118] Kiessling[119] observed elevated T4 levels with reduced T3 levels in MS patients, suggesting possible impaired conversion of T4 to T3.

The Possible Role of Thiamine

Histidine residues are known to be critical sites in thiamine-binding proteins, such as thiamine pyrophosphokinase, the enzyme that generates thiamine pyrophosphate from thiamine and ATP.[120] Histidine residues are also critical residues in other proteins known to bind TPP or thiamine itself.[121,122] Histidine deficiency might therefore result in decreased TPP synthesis or decreased transport of TPP or thiamine to relevant sites such as the brain.

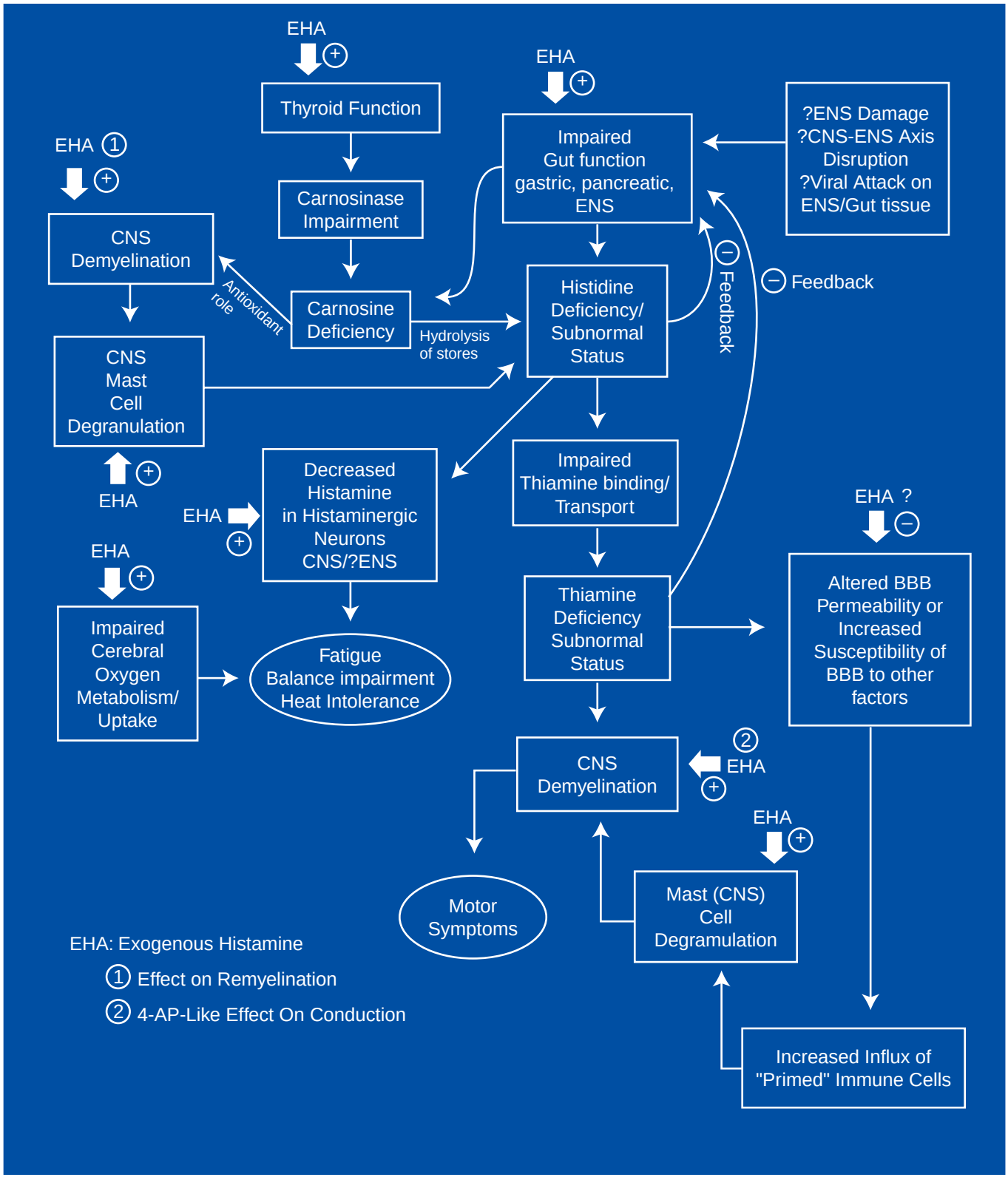
As mentioned, thiamine is involved in maintaining the stability of the blood-brain barrier and also in myelin formation — two central aspects of MS pathophysiology. Thiamine deficiency can also feed back to impair gut function in rats, as shown by Khramtsov[123] who demonstrated impaired gastric secretory function in response to histamine in thiamine-deficient animals.

Given the dependence of thiamine binding proteins on histidine residues, abnormal thiamine status might develop in MS as a consequence of histidine deficiency, and once established, may reinforce the histidine deficiency. A thiamine deficiency would then promote demyelination as discussed above; alternatively, subclinical thiamine deficiency might be a factor which tips a predisposed individual closer to acute MS or relapse.

A Possible Viral Connection

The notion that a histamine deficit exists in the histaminergic neurons of some patients with MS due to a slow viral attack has been proposed by DeLack.[124] If such a viral attack occurs, it might be centered on the

Figure 2. Framework of Proposed Mechanisms of Action of Exogenous Histamine.



hypothalamus, since this is where histaminergic neurons originate. Since these histaminergic neurons regulate basic physiologic functions, one might expect the course of MS to be more aggressive, with more pronounced disruption of "life support" functions. There is at least one report in the literature[125] of wasting and a rapidly fatal course in MS, with lateral hypothalamic lesions, but such presentations are rare. Immunologic assays directed toward detection of such a viral attack on histaminergic neurons might help to determine the extent and selectivity of a possible viral attack on histaminergic neurons.

Detailed Discussion of Potential Mechanisms of Action of Exogenous Histamine in the Proposed Framework

Symptom alleviation in patients who have benefited from exogenous histamine has at times been rapid — hours to several days.[1] One inference, which might be drawn from this observation, is that the effects are due to the direct action of histamine once a threshold concentration has been achieved in the target tissue. If the primary mechanism involved is an indirect action such as modulation of the immune response, stimulation of repair of damaged tissues, or improved nutritional status, one might expect a longer timescale of action (similar, for example, to the response of rheumatoid arthritis to disease-modifying agents). Some users of exogenous histamine report they continue to improve over a time span of weeks to months. This suggests that mechanisms with longer timescales of action might also be operative in some cases.

Effect of Exogenous Histamine on Gut Dysfunction

Local release of histamine from the ECL cells of the gastric mucosa stimulates release of acid by an H2 receptor-mediated mechanism. Histamine also stimulates the release of pancreatic secretions via H1 receptor stimulation.[126-128] If there is a local deficiency of histamine synthesis in the ECL cells, exogenous histamine may stimulate gastric and pancreatic function, improve protein hydrolysis, and eventually replenish histidine and carnosine levels. Improved gastric acid secretory function might improve B12 and thiamine absorption, with possible beneficial effects on myelination. Absorption of various other nutrients important for maintaining myelin (such as copper) should also improve due to improved gastric acidity.

Histaminergic fibers have been noted in the submucous ganglion cell layer of the ileum of the rat and the guinea pig.[129] If such fibers are also present in the human ENS, they may be involved in the regulation of peristalsis, as well as the regulation of secretory functions through the action of histamine either on histamine receptors or serotonin receptors (cross-talk between histamine and serotonin receptors is discussed in reference 20). Diminished histamine synthesis in these postulated enteric histaminergic pathways might therefore impair secretory and peristaltic functions. Conversely, exogenous histamine might improve the function of enteric histaminergic pathways by directly increasing the concentration of histamine in relevant synapses, or indirectly, by stimulating gastric acid production and absorption of histidine, and eventually improving endogenous histamine production.

At this juncture, it is not clear whether gut dysfunction is a primary or secondary feature of MS. Primary failure mechanisms might include a cell-mediated attack on the ENS which parallels that experienced by the CNS, or a viral attack on intestinal mucosa, pancreatic tissue, and/or neuronal tissue. Secondary mechanisms might include a disruption of CNS vagal efferents (due to the effects of MS in the brain), which are involved

in the control of gut function. One of the authors (GG) has measured achlorhydria in two patients within months of first onset of neurologic symptoms, supporting the notion that gut dysfunction might precede development of neurologic symptoms.

The concept that pathological processes affecting the CNS might be mirrored in the ENS is discussed by Gershon[96] and is supported by research on patients with Parkinson's disease. Singaram[130] observed depletion of colonic dopaminergic neuron populations in 9 of 11 Parkinson's patients, and decreased levels of dopamine in muscularis externa specimens in four of four patients versus zero of four controls. Wakabayashi[131] also reported the presence of Lewy bodies — markers of neuronal degeneration characteristic of Parkinson's disease — in the ENS (myenteric and submucosal plexuses from the upper esophagus to the rectum) of 28 of 30 patients with Parkinson's disease.

Measles viral antigens have been noted in jejunal biopsies of MS patients,[32] supporting the notion that direct viral attack on the gut might be a factor in some patients.

Central vagal outflow is important for gastric acid secretion,[132] and various investigators have studied the central effect of histamine on vagal tone. Both inhibitory and stimulatory effects, depending on histamine concentration, have been observed.[133,134] Vagal tone is also influenced by other factors, including thyrotropin releasing hormone[135] and inflammatory mediators such as IL-1β.[136] Failure of central vagal outflow to the stomach might explain reduced gastric acid secretion in MS, but it is unclear how this might arise, or whether an alteration in central histaminergic activity is even involved.

A reasonable body of evidence supports the existence of impaired digestion and uptake of nutrients in MS, but the mechanisms are not well understood at this time. This is an important area that needs additional study, since similar gut dysfunction may be associated with other chronic diseases. For example, Gerber[137] reported on 26 patients with active rheumatoid arthritis who had significantly lower serum histidine levels compared to controls. Also, histidine has been shown to be an important residue for binding and uptake of other nutrients, including biotin[138] and folate.[139] Histidine-deficient dogs also had lower whole blood concentrations of zinc and copper,[106] as mentioned earlier.

Histidine levels and gastric acid secretory capacity data are needed from a larger number of MS patients. Data on thiamine and carnosine status would also help to confirm or refute some of our hypotheses. It remains to be seen whether the MS patients studied via Heidelberg capsule will recover gastric acid secretory capability with long-term transdermal histamine supplementation. Immunohistochemical studies of pathology specimens obtained from MS patients who undergo intestinal surgery could be fruitful to delineate the role of histaminergic fibers in the human ENS, and whether the ENS in general exhibits demyelination or other degeneration in MS.

Effect of Exogenous Histamine on the Proposed Histaminergic Neuronal Histamine Deficit

Exogenous histamine supplementation might directly increase the concentration of histamine in CNS synaptic clefts, as well as indirectly through increased synthesis of histamine (due to increased availability of histidine through effects on the gut). Either way, increased synaptic cleft histamine might account for improvements in symptoms such as fatigue, balance impairment, and heat intolerance. This is envisioned to be rapid-acting if direct, slower if indirect.

It might reasonably be asked if any decrease in the CSF histamine level is seen in MS patients (assuming CSF is representative of the environment within the synaptic clefts). CSF histamine concentrations have been

measured by various researchers, with inconsistent findings. Suojaranta-Ylinen[140] measured CSF histamine levels in normal patients and found them to be on the order of 60 ± 40 pg/ml. Kiviranta[141] found histamine levels in the CSF of 21 normal children to be 40 ± 8 pg/ml. Rozniecki[142] found histamine concentrations in the CSF of 55 patients with MS to be 40 ± 40-80 pg/ml and saw no difference, compared to 39 controls with other neurologic disease.

In the same study, Rozniecki also saw no difference in CSF tele-methylhistamine (the CNS metabolite of histamine) levels between controls and MS patients. The level of tryptase, a mast cell mediator, was however, found to be significantly higher in MS patients, compared to controls ($p<0.002$). Rozniecki's data, therefore, reflect evidence of mast cell degranulation, but not histamine elevation.

The findings of both Tuomisto[143] and Molnar[144] are markedly in contrast, and show a significant elevation of CSF histamine levels in patients with MS compared to controls. Elevated levels were seen both in patients with relapsing-remitting and progressive MS. Control levels of histamine were roughly 10-fold higher in Tuomisto's study (440 pg/ml) and 50-fold higher in Molnar's study (2200 pg/ml) compared to the other three studies (40 pg/ml). The data from the three most recent papers (<10 years old)[140-142] are all in agreement. The two earlier papers are older, and it is difficult to say how much of the disparity between the two groups of results is due to differences in analytical methods. It is also possible that CSF histamine levels are simply not representative of histamine status in brain tissue, as was proposed by Rozniecki.[142] For these reasons, no firm conclusions may be drawn from the CSF histamine data.

The only other data with even a tangential connection to synaptic cleft histamine levels was reported by Iarosh[98] who measured whole blood histamine levels in controls and MS patients as a function of disease duration. He reported an elevation of histamine levels compared to controls in patients who had MS less than five years, with the greatest elevation seen less than two years after disease onset. Patients who had MS greater than five years were found to have lower blood histamine levels than controls. Patients with gastric ulcerations (shown by concurrent endoscopic studies) had the lowest histamine levels.

Once again, it is difficult to interpret this data. Whole blood histamine levels vary with both sex and age, with females having higher histamine levels at any given age, and levels in both sexes declining with age.[145] Unless control patients were age and sex matched, there is potential for significant bias in the Iarosh study. Unfortunately, the age and sex stratifications of the study and control groups were not provided in the article.

Histamine is intimately involved in various aspects of reproductive physiology, including uterine contractility (guinea pig),[146] estrogen and progesterone secretion by human ovarian granulosa cells,[147] and ovulation (hamster).[148] Thus, an increased need for histidine and histamine for orchestration of reproductive function in women seems reasonable. It is possible that the whole blood histamine level reflects the body's histidine pool, since basophils, eosinophils, and platelets all either synthesize or store histamine. This might explain why young women have the highest whole blood histamine levels, and why these levels peak in the childbearing years.[145] The blood level may merely reflect the need for higher circulating histidine levels (to support histamine's role in reproduction).

From the foregoing, any process which impairs CNS availability of histidine might tend to affect women of reproductive age more than men, since the body might tend to divert available histidine toward reproductive endeavors, and short-change the CNS. Because the incidence of MS is highest in women of

reproductive age, another tentative link between MS and histidine/histamine might be proposed; i.e., those with a greater systemic need for histidine/histamine might be more susceptible to MS.

It appears the available evidence from CSF and blood does not conclusively support or refute the concept of a deficit of histamine in histaminergic neurons or synapses. Also, it remains to be explained how a histamine deficit could even arise in the face of mast cell degranulation, with release of presumably copious amounts of non-synaptic histamine. Non-synaptically released histamine should still be able to diffuse into the synaptic clefts and "make up" for any intrinsic neuronal synthetic deficit. This seems logical, but in the face of ongoing or recurrent inflammatory episodes, we postulate a depletion of mast cell histamine (due to a lack of histidine precursor) but not other inflammatory mediators. Degranulation would still occur, but non-synaptic histamine would no longer be available to drift into the histamine synapses. In the light of this idea, perhaps Rozniecki's data can be interpreted in a different way; i.e., no histamine was seen in the CSF because mast cells were no longer releasing it (although they were still degranulating as evidenced by the tryptase data).

Accepting that a histaminergic synaptic histamine deficit may exist at some point after the onset of MS, how might such a deficit cause symptoms, such as difficulty maintaining balance when walking, fatigue, and heat intolerance? How are histaminergic neurons involved in these aspects of function?

Hypothalamic histaminergic neurons project to the human cerebellum as shown by Panula,[10] and also to the vestibular nuclei in the cat brainstem.[16] Both areas are important for maintaining balance; the cerebellum for coordination of motor impulses, and the vestibular nuclei for processing sensory afferents from the vestibular apparatus in the inner ear. A left-right imbalance in electrical or caloric stimulation of the middle ear (effectively stimulating the inner ear) resulted in increased firing of hypothalamic histaminergic neurons in rats.[17] Decreased release of histamine by relevant histaminergic neurons in MS might, therefore, result in problems with balance. None of these studies determined the relevant receptor type, although H1 receptor blockade is a common pharmacological intervention for vertigo arising from vestibular disorders.

Fatigue is a common, though difficult to define, symptom in MS.[149] Many MS patients describe their fatigue as a lack of motivation or lack of interest, as well as actual sleepiness or difficulty staying awake. Although the cause of "fatigue" is undoubtedly multifactorial, many users of exogenous histamine report a substantial improvement in this symptom in the personal experience of the principal author. This may be partly attributable to the action of exogenous histamine at H1 receptors, since H1 receptor stimulation appears to have an animating effect on behavior. H1-receptor-deficient rats displayed significantly less interest in their environment and less activity on an exercise wheel,[12] and H1 receptor blocking agents are also common ingredients in non-prescription sleep aids.

Heat intolerance is a common symptom in MS.[150] The accepted explanation for worsening of MS symptoms upon heat exposure is conduction block of demyelinated nerve fibers, although at least one author has proposed the etiology of heat intolerance is multifactorial, since conduction block does not explain various anomalous or paradoxical responses.[151] Therefore, it is worthwhile to examine the potential role histamine may play in the response to warming.

Intracerebroventricular injection of histamine lowered rectal temperature in rats; this was shown to be mediated by both H1 and H2 receptors.[15] We postulate that histamine release by hypothalamic histaminergic neurons might be part of the response to warming in humans also. Mounting the proper response

to warming (such as increased skin vasodilation) likely takes precedence over other CNS uses of histamine, since brain temperature is a vital physiologic parameter. In MS patients, warming might therefore consume available histidine to stabilize brain temperature at the expense of other histamine-requiring neurologic processes, including those responsible for maintaining alertness, and may thus result in the "wilting" or fatigue experienced with warming. Once again, exogenous histamine may mitigate this effect by directly increasing the amount of histamine available; this should manifest over a short time period.

Histamine is also well recognized as a peripheral vasodilator.[152] Increased blood flow to the skin with exogenous histamine supplementation should improve heat tolerance by improving the ability to release excess heat through the skin.

The Effect of Exogenous Histamine on the Electrical Properties of Demyelinated Nerve Fibers

The foregoing has focused on suboptimal functioning of otherwise undamaged histamine-dependent neural pathways, which might be improved by exogenous replacement of histamine. The majority of neurologic deficits in MS however, are thought to be due to faulty conduction by demyelinated fibers, although there is some evidence that reversible secondary factors are important.[153] Rapid-onset beneficial effects of histamine supplementation might be expected if histamine can enhance the conduction of demyelinated fibers; moreover, this should be a reversible phenomenon, with effects being observed only when sufficient histamine is present in the tissue around the demyelinated axons.

A "booster" effect of this type has been observed with 4-aminopyridine (4AP), which is known to modify conduction in demyelinated nerves by blocking potassium channels.[154] In two animal studies 4AP also restored conduction in blocked, demyelinated nerves.[155,156] Two controlled trials [157,158] have demonstrated the ability of 4AP to reversibly improve symptoms of MS. One researcher commented that effects usually manifested within 60 minutes of oral administration, and reversed gradually over four to seven hours.[157] The clinical utility of 4AP is somewhat compromised by side-effects, including dizziness, paresthesias, and seizure in higher doses.[158]

Histamine has been shown to facilitate nerve conduction in the same fashion as 4AP; i.e., by blocking a slow polarizing potassium current. This effect has been observed in human cortical neurons,[159] rat cholinergic neurons,[160] rat supraoptic nucleus neurons,[161] and ferret vagal afferent neurons.[162] Histamine was also shown to depolarize neurons by inhibition of a slow post-spike hyper-polarizing potassium aftercurrent.[162,163] Both effects were mediated through H1 receptor activation.

There have been reports of synergistic effects of histamine and 4AP. Histamine-induced vasoconstriction was augmented in rabbit ear arteries by 4AP-stimulated release of glutamate from hippocampal neurons.[164,165] Co-administration of histamine and 4AP might, therefore, prove beneficial for enhancing nerve conduction in demyelinated fibers.

If this mechanism is operative to any significant extent, then treatment with H1 blockers might be expected to abolish its effect. A study of the effects of H1 blockers on the response of MS patients to exogenous histamine should clarify the relative importance of this mechanism.

Effect of Exogenous Histamine on Immune Function

Histamine can suppress its own release by inhibiting mast cell degranulation. Its possible role as a modulator of the severity of inflammation was proposed by Bourne.[166] Exogenous histamine might, therefore, serve to

slow or halt the inflammatory spiral provoked by the release of other CNS mast cell inflammatory mediators, taking over the role of endogenous CNS mast cell histamine if its synthesis and release is impaired by decreased availability of histidine. This effect could operate over both short and long timescales.

It is generally recognized that histamine can exert bivalent effects on the immune system, with stimulatory effects generally mediated by H1 receptors and suppressive effects generally mediated by H2 receptor stimulation.[21] For example, mouse H1 receptor-deficient T cells demonstrated impaired proliferative response to antigens in one study,[167] and subcutaneous histamine administration (4 mg/day) plus an oral H2 blocker (thereby stimulating H1 receptors) resulted in prolongation of survival in patients with metastatic melanoma.[3] This is the same dose range currently being used in MS (3-6 mg/day), suggesting small amounts of histamine seem to exert pronounced effects on immune function. Inhibition of IL-2 production in mitogen-stimulated human monocytes was shown to be mediated by H2 receptors.[168]

Sometimes the inhibitory effects of H2 receptor stimulation can enhance the overall immune response. In one report, the tumor cell-killing ability of natural killer (NK) cells was enhanced by the addition of histamine.[169] The effect was shown to be H2 receptor-mediated and involved suppression of the release of NK cell-toxic reactive oxygen intermediates from intratumoral monocytes.

Exogenous histamine may also be acting to suppress the overactive Th1 cell-mediated immune response seen in MS and boost the underactive Th2 response. Two researchers[170,171] have demonstrated that histamine (H2 receptor-mediated) can suppress the production of IL-12. Elenkov also showed histamine stimulates the production of IL-10, once again by H2 receptor stimulation.[170] As discussed earlier, down-regulation of IL-12 and up-regulation of IL-10 is thought to be beneficial in MS. Exogenous histamine might exert an overall favorable effect on the immune system in MS by this mechanism, although this has not been studied. Note also that histamine may exert the same effect on Th1/Th2 balance as copolymer 1;[40] this suggests the two might be used simultaneously for a synergistic effect.

The concept that histamine release may provide negative feedback on inflammation mediated by mast cells was mentioned above. The dose-dependent inhibition of antigen-induced release of histamine from human leukocytes by exogenous histamine reported by Bourne was shown to be H2 receptor mediated.[172] Histamine has been shown to exert the same effect on CNS mast cells via H3 receptor stimulation.[22] Therefore, there is reasonable support for the view that exogenous histamine might exert a braking effect on CNS inflammation in MS, possibly by balancing Th1/Th2 activity and by stabilizing mast cells.

Caffeine is included in the transdermal histamine patch utilized in the Part One study previously published in this journal[1] and may synergize with histamine in several ways. Mast cell degranulation involves several processes: an influx of Ca^{2+} ions to the cell, a transient decrease in the intracellular concentration of cAMP,[173] and a transient increase in the activation of protein kinase C (PKC).[174] Phosphodiesterase inhibitors, such as theophylline[173] and caffeine[175] are able to stabilize mast cells against degranulation by preventing a drop in intracellular cAMP levels and preventing activation of PKC. Therefore, caffeine would synergize with histamine in this regard.

Most H2 receptors have cAMP as a second messenger; i.e., stimulation of an H2 receptor by histamine results in the transient increase in intracellular cAMP. Co-administration of a phosphodiesterase inhibitor with histamine would then serve to amplify the "message" delivered by histamine, by prolonging the elevation of cAMP. Thus, cAMP-specific phosphodiesterase inhibition would seem to be a therapeutic strategy worth

investigating. In fact, phosphodiesterase Type IV inhibitors have been proposed as a treatment for MS[176] and have been successfully employed in the treatment of EAE.[177]

Recent work has shown phosphodiesterase inhibitors exhibit Th1-suppressing and Th2-enhancing effects on human leukocytes[178] and in MS patients;[179] as mentioned, histamine also exerts these effects. If caffeine acts similarly to other phosphodiesterase inhibitors, this is yet another point in favor of the concurrent use of histamine and caffeine. Caffeine may reinforce the actions of histamine and in parallel, may produce some of the same immune-modulating effects as histamine.

Since the CNS damage in MS is presumed to be due to the influx of autoreactive T cells, permeability of the blood-brain barrier (BBB) is an important factor to consider when discussing aspects of the immune response in MS. Both Sharma[49] and Gulati[92] have shown histamine increases BBB permeability through H2 receptor stimulation, which suggests exogenous histamine should worsen MS symptoms by increasing BBB permeability. It may well be that exogenous histamine does increase BBB permeability (which could easily be proven with an MRI tracer study), but potential negative sequelae of this permeability increase are over-ridden by other beneficial effects.

The Effect of Exogenous Histamine on Myelination

Exogenous histamine may exert a positive influence on remyelination by direct and indirect means. Exogenous histamine might directly stimulate remyelination by enhancing migration of oligodendrocyte progenitor cells into areas of inflammation, by inducing and/or facilitating the development of mature oligodendrocytes, and by stimulating myelin formation by oligodendrocytes. Although stimulation of H2 receptors elevates intracellular cAMP, and elevation of intracellular cAMP has been linked to induction of oligodendrocyte differentiation and myelin synthesis, no studies directly connect histamine to myelin formation through elaboration of cAMP.

Exogenous histamine may indirectly spur remyelination by its effect on other factors tied to myelination, including T3 and vitamin B12. For example, histamine is known to trigger the release of thyrotrophin releasing hormone,[180] and mouse thyroid has been shown to bear H2 receptors, which stimulate thyroid hormone secretion.[181] Histamine may exert a similar stimulating effect on the human thyroid gland, so exogenous histamine may assist remyelination through stimulation of thyroid function. Exogenous histamine might enhance uptake of B12 in particular, and other nutrients in general, and this may impact myelination over a longer time period. Note also that improved thyroid function might increase carnosinase activity.

The Effect of Exogenous Histamine on Oxygenation of Cerebral Tissues

Decreased cerebral blood flow (CBF) and decreased oxygen metabolism are well recognized in MS, as demonstrated by early studies employing radio-labeled xenon gas[182] and later studies employing MR[183] and PET[184] imaging. Both white and grey matter exhibit decreased cerebral blood flow. Lycke found decreased CBF correlated to neurologic disability, cognitive function, and visual performance.[185] Sun demonstrated cerebral hypometabolism (a measure of oxygen consumption) was correlated with the number of relapses.[184] Lycke also demonstrated that patients with progressive MS had a greater decrease in grey matter CBF than relapsing-remitting patients.[185]

Recent data concerning the effect of histamine on CBF generally agree. Various researchers have reported that histamine stimulates vasodilation by an H2 receptor-mediated mechanism, and vasoconstriction by an H1

receptor-mediated effect. The observed effect (vasodilation or vasoconstriction) is concentration dependent,[186-188] and also depends on the anatomic location of the vessel.[188] No recent studies measuring the net effect of low-dose systemic histamine administration on CBF were found, but older studies may shed some light on the question.

In the January 1951 issue of *Postgraduate Medicine*, Horton stated, "The results of a recent study indicate that histamine causes a greater increase in blood flow to the CNS than any other drug known. Photographic records of the pulsations of the human brain indicated that the subcutaneous administration of 0.25 mg of histamine base produced a 725 percent increase in the amplitude of the pulsations of the brain."[189] Later in the same article, Horton also reported that during an exploratory craniotomy, he observed the following effect of the intravenous administration of histamine: "The cortex became fiery red and vessels which usually were hardly visible became prominent."

These data support the notion that exogenous histamine increases CBF and oxygenation. Increased oxygen delivery could lessen fatigue, increase alertness, and increase cognitive performance. Over the long term, continued augmentation of CBF could also exert beneficial effects through stimulation of repair by enhanced delivery of oxygen and nutrients.

Conclusion

A framework has been proposed in which histamine supplementation might alleviate some of the symptoms of MS. Central to this framework is the notion of a systemic histidine deficiency, which limits the ability of the body to synthesize requisite amounts of histamine at sites such as the CNS and the gastric mucosa. We have reported preliminary findings which support the existence of a histidine deficiency in some patients with MS, and correlate it with impaired or absent gastric acid production as measured by the Heidelberg capsule. The proposed histidine deficiency might be brought about by a failure of gastric and pancreatic exocrine function, but it is unclear whether impairment of gut function might be a primary or secondary feature of MS, and what might initiate the impairment. CNS mast cell degranulation may also contribute to a shortage of histidine.

Histamine supplementation may impact this state of affairs by directly augmenting the concentration of histamine in relevant synaptic clefts, by suppressing CNS mast cell degranulation, or by improving protein digestion and histidine status. Exogenous histamine might also augment cerebral blood flow, improve the conductivity of demyelinated nerve fibers, or help balance Th1 and Th2 immune functions. The timescales over which these mechanisms might act are roughly consistent with observed timescales of improvement.

As pointed out in the introduction, many of the ideas discussed in this paper are speculative. A host of unanswered questions remain, and we have proposed various ways some of these questions might be addressed. Whole brain n-acetylaspartate (NAA) assay via MRI has recently been proposed as a marker of disease progression.[190] This technique might prove to be particularly useful for studying mast cell degranulation and the role of histamine in MS, if brain mast cells contain NAA as do peritoneal mast cells.[191] We hope histamine will continue to show promise for MS patients, and that the curiosity of other MS and histamine researchers will be stimulated by some of the ideas presented in this paper.

Secondary deficits of nutrients such as histidine, thiamine, carnosine, and copper may feed back and amplify the damage done by the primary disease process in MS. We believe broad-spectrum nutritional support along with efforts to improve gastric acidity and protein digestion are strongly indicated, in conjunction with whatever other treatment modalities are used for this disease. We also believe significant effort should be put into untangling

the interlocking ways in which secondary nutritional deficits sustain and intensify MS and other chronic disease processes.

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