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Review

# Mast cells in the autonomic nervous system and potential role in disorders with dysautonomia and neuroinflammation

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**Key Messages**

- Mast cells are located close to the blood vessels and neurons.
- Mast cells secrete many vasoactive and neurosensitizing mediators without histamine or tryptase.
- Mast cells can affect and be affected by the autonomic nervous system.
- Mast cells could contribute to dysautonomias and neuroinflammation.
- There is a need for development of effective inhibitors of mast cell activation.

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ABSTRACT

Mast cells (MC) are ubiquitous in the body, and they are critical for not only in allergic diseases but also in immunity and inflammation, including having potential involvement in the pathophysiology of dysautonomias and neuroinflammatory disorders. MC are located perivascularly close to nerve endings and sites such as the carotid bodies, heart, hypothalamus, the pineal gland, and the adrenal gland that would allow them not only to regulate but also to be affected by the autonomic nervous system (ANS). MC are stimulated not only by allergens but also many other triggers including some from the ANS that can affect MC release of neurosensitizing, proinflammatory, and vasoactive mediators. Hence, MC may be able to regulate homeostatic functions that seem to be dysfunctional in many conditions, such as postural orthostatic tachycardia syndrome, autism spectrum disorder, myalgic encephalomyelitis/chronic fatigue syndrome, and Long-COVID syndrome. The evidence indicates that there is a possible association between these conditions and diseases associated with MC activation. There is no effective treatment for any form of these conditions other than minimizing symptoms. Given the many ways MC could be activated and the numerous mediators released, it would be important to develop ways to inhibit stimulation of MC and the release of ANS-relevant mediators.



## Introduction

Mast cells (MC) are ubiquitous in the body,[1] and they are critical for allergic diseases.[2] MC disorders are divided in primary, including cutaneous and systemic mastocytosis, secondary, including atopic (IgE dependent such as asthma and atopic dermatitis) and other allergic diseases, and idiopathic, including MC activation disorders (MCADs).[3] The latter were recently renamed "MCA-related disorders" (still MCADs) and were subcategorized with "atopic diathesis and hypersensitivity disorders" listed under MCADs as "conditions predisposing to MCA/MCAD."[4] However, it is apparent that MCA can occur in many MC disorders in response to known or unknown triggers.[5] To avoid any confusion, the term "diseases associated with mast cell activation" is used in this review presenting evidence linking MC and MCA with the autonomic nervous system (ANS) and discusses their possible involvement in the pathophysiology of certain conditions characterized by dysregulation of the ANS.

The role of MC in health and disease has been discussed extensively not only in allergies[2,6-15] but also in immunity and

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inflammation.[2,16-19] MC can secrete histamine and multiple proinflammatory cytokines and chemokines,[15,20] including interleukin-1 beta (IL-1β),[21] IL-6,[22] IL-31,[23] and tumor necrosis factor (TNF).[24] Most reviews have focused on mastocytosis,[3,25-29] but MC activation has been gaining interest because of its potential involvement in the pathophysiology of neuroinflammatory[5] and neuropsychiatric disorders,[30,31] especially because patients with mastocytosis present with cognitive impairment[32-34] that may be related to brain abnormalities.[35]

MC respond not only to allergens but also to many other stimuli that can act alone or increase MC reactivity.[3] When stimulated by IgE through aggregation of its high-affinity IgE surface receptor (FceRI), MC can release several neurosensitizing, proinflammatory, and vasoactive mediators.[36,37] Some of these mediators are prestored in secretory granules (eg, histamine, tryptase, and TNF)[38,39] and are released immediately after stimulation. MC can also secrete mitochondrial DNA (mtDNA) extracellularly,[40] which serves as an alarmin and can stimulate proinflammatory mediator secretion from immune cells.[41,42] Other mediators are newly synthesized such as chemokines (eg, C-C motif chemokine ligand 2 [CCL2], C-X-C motif chemokine ligand 8 [CXL8/IL-8],[43] and cytokines [IL-6,[22] IL-1β,[21] and TNF][24]). Even though IL-6 is not specific for MC, it can be released selectively,[22,44] was elevated in systemic mastocytosis, and correlated with disease severity.[45-47] In fact, IL-6 promotes an increase in MC numbers.[48] MC can be activated by viruses.[49,50] MC can also secrete anti-inflammatory molecules such as IL-10, transforming growth factor beta, and chondroitin sulfate.[51-53]

In addition to allergic triggers, MC can be stimulated by nonallergic agents,[2,54,55] especially neuropeptides,[56] such as substance P (SP)[21,57] and the SP-related hemokinin-1 (HK-1),[58] which have proinflammatory properties.[59-63] Moreover, SP induced the ST2 receptor for IL-33[24] further exacerbating MC activation. Under such conditions, especially when primed by the alarmin IL-3,[55,64] MC can release mediators without histamine or tryptase,[65] a process by which MC can participate in inflammatory diseases.[2,17]

The regulation of MC by neurotransmitters and neuropeptides has been reviewed,[56,66,67] with emphasis on corticotropin-releasing hormone (CRH),[37] HK-1,[58] nerve growth factor,[68] neurotensin (NT),[69] SP,[57] and somatostatin[70,71] acting by activation of high-affinity receptors. MC can also be stimulated by cationic molecules and drugs through activation of the low-affinity surface receptor Mas-related G-protein coupled receptor member X2 (MRGPRX2).[72-74] Secretion of mediators can occur using different signaling[14,75-77] and secretory[75,77] pathways.

In addition to the connective tissue and mucosal location, MC are also located in many endocrine glands, including the hypothalamus, pineal, and pituitary glands (Table 1)[56]; hence, they may be able to regulate homeostatic functions that seem to be dysregulated in many conditions, all of which worsen with psychological stress[78] and some of which are discussed subsequently.

However, the available evidence of the involvement of MC in the ANS is not uniform; it is often circumstantial, with many contradicting reports depending on the species and trigger. Moreover, human studies were based on a few subjects who are often not well defined. In particular, the definitions of MCAD and more so of MC activation syndrome (MCAS) are often not precise and are used interchangeably casting doubt on the validity of some associations reported, especially with dysautonomias.

**Table 1**
Anatomic Sites of Mast Cells Relevant to ANS

- Adrenal glands
- Blood-brain barrier
- Cardiac pacemakers
- Carotid bodies
- Coronary arteries
- Hypothalamus
- Pineal gland
- Vagus nerves
- Vasculature

Abbreviation: ANS, autonomic nervous system.

## Mast Cells in the Autonomic Nervous System

MC are located in close proximity to the blood vessels and peripheral nerves, which allow them to be strategically positioned to modulate sympathetic activity and vascular tone (Table 1). In fact, MC can communicate with neurons[79] by either direct contact,[80] through the nanotubes,[81] or through release of relevant mediators. MC can also take up from the extracellular space and store and release additional mediators such as dopamine, epinephrine, norepinephrine, and serotonin (Table 2). MC could be affected by the ANS, especially at sites such as the carotid body,[82] the coronary arteries,[83] and the heart (Table 1, Fig 1).[84,85] MC could also affect the ANS in many different ways (Table 3) through activation of MC receptors by molecules released from the ANS (Fig 2) and through the release of ANS-acting MC mediators such as acetylcholine (Ach), angiopoietins, calcitonin gene-related peptide, CRH, endorphins, HK-1, histamine, nerve growth factor, prostaglandin D2 ($PGD_2$), TNF-α, tryptase, and vascular endothelial growth factor (VEGF) (Table 2), to be discussed subsequently (Fig 2).

There is a long history of contradictory results concerning the effects of Ach, which could affect MC by both the muscarinic and nicotinic receptors,[86] but the published evidence is mostly based on rodent MC and on super pharmacologic concentrations of Ach or its agonists. In addition to the vagus nerve,[87] there are many non-neuronal sources of Ach such as epithelial, endothelial, and immune cells, including MC, themselves.[88] In humans, Ch was increased as much as 14-fold in the epidermis of skin biopsies from patients with atopic dermatitis (AD), implying it must be somehow involved.[89] One article reported that Ach stimulated the skin only in the cholinergic urticaria type with anhidrosis or hyperhidrosis through activation of M3 cholinergic receptors.[90]

It was originally reported that Ach could stimulate histamine release from abdominal and thoracic MC of Wistar albino rats at concentrations as low as $10^{-10}$ $M^{-}$.[91] However, subsequent publications using different types of rodents did not confirm those original findings. For instance, the Ach agonist pilocarpine stimulated histamine release from rat peritoneal MC, but only at a concentration of $10^{-2}$ M,[92] whereas another article reported that Ach could not stimulate histamine release from rat MC even at $10^{-2}$ M.[93] The Ach analogue carbachol ($10^{-4}$ M) did not stimulate rat peritoneal MC histamine release but augmented the effect of SP.[94] Instead, other scientists reported that carbachol neither stimulated nor augmented histamine release from rat peritoneal MC.[95]

**Table 2**
ANS-Relevant Mast Cell Mediators[a]

- Ach
- Angiopoietins
- CGRP
- CRH
- Endorphins
- HK-1
- Histamine
- NGF
- $PGD_2$
- TNF-α
- Tryptase
- VEGF

Abbreviations: ANS, autonomic nervous system; Ach, acetylcholine; CGRP, calcitonin gene-related peptide; CRH, corticotropin-releasing hormone; NGF, nerve growth factor; PGD2, prostaglandin D2; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.
[a]Mast cells can also internalize from the extracellular space and store and release additional mediators such as dopamine, epinephrine, norepinephrine, and serotonin.

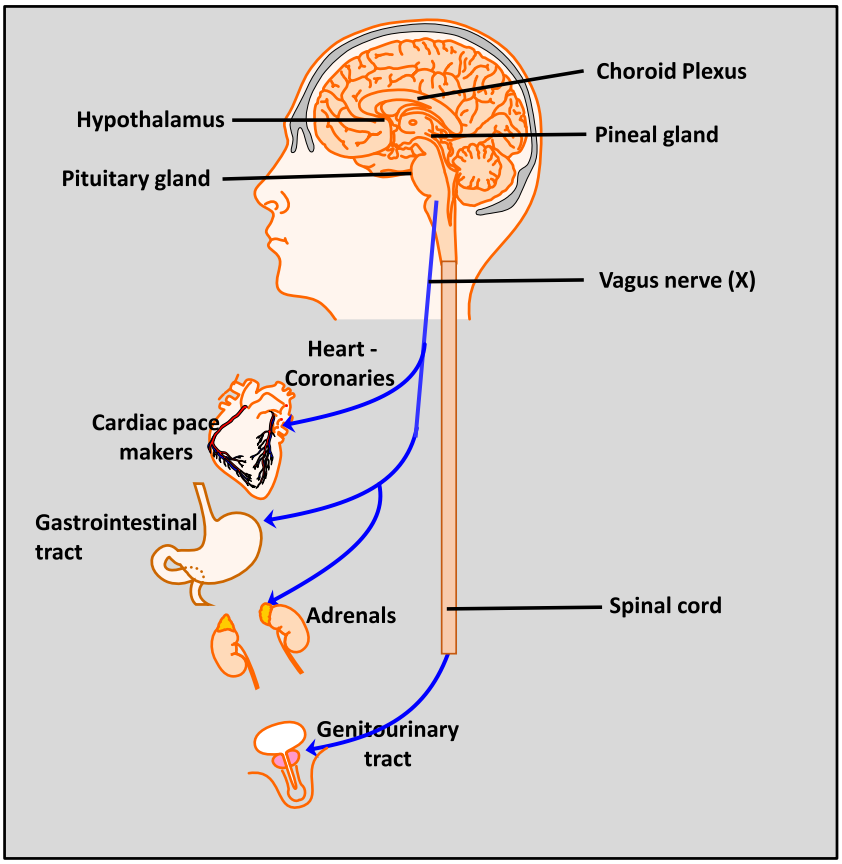


**Figure 1.** Diagrammatic representation of anatomic sites where mast cells may interact with the ANS. ANS, autonomic nervous system.

In contrast to the Ach effect through activation of the muscarinic receptors, activation of the nicotinic receptors may have the opposite effect. For instance, Ach inhibited histamine release from isolated human bronchi.[96] Mucosal MC activation was also found to be negatively regulated through the a7 nicotinic receptor subunit.[97] The a7 nicotinic receptor subunit, which has anti-inflammatory effects, was significantly elevated in a mouse model of stress.[98] Activation of nicotinic receptors inhibited vagus-stimulated histamine release in a murine food allergy model,[99] including the allergy-induced release of leukotrienes and cytokines, but not release of histamine or degranulation.[100] The same was true in mucosal-like MC.[97] Adrenergic agents could also inhibit Ach-stimulated histamine release from isolated rat MC through activation of the beta-adrenoreceptor.[101] However, the clinical effects of adrenergic drugs are more complex mostly due to their actions on other organs/tissues. Adrenergic agonists such as terbutaline dilate the bronchi, and intramuscular epinephrine is used to counter bronchoconstriction and hypertension associated with anaphylaxis. In contrast, the beta-blocker propranolol is useful for anxiety, palpitations, and migraines often experienced by patients with MCADs. Hence, the effect of the parasympathetic system may depend on the relative MC expression of muscarinic and nicotinic receptors, including adrenoreceptors, which may vary depending on species, anatomic location, and disease activity.

There is additional evidence that MC may participate in autonomic function and dysfunction. MC are located close to and communicate with the pineal gland[102] and may both regulate and be affected by the circadian clock.[103-105] Moreover, extrapineal melatonin was identified in platelets and endothelial and immune cells, including MC.[106] A thermoregulatory neuron circuit axis was reported through MC-derived chymase leading to hypothermia during anaphylaxis.[107] Post-exercise hypotension and collapse were linked to MC.[108] Decreased cerebral blood flow and small fiber

**Table 3**
ANS-Associated Mast Cell Actions

- Activation of microglia and astrocytes
- BBB disruption
- Cardiac pacemaking
- Circadian clock
- Coronary artery constriction
- HPA axis regulation
- Neuroinflammation
- Neurosensitization
- Vascular tone control

Abbreviations: ANS, autonomic nervous system; BBB, blood-brain barrier; HPA, hypothalamus-pituitary-adrenal.

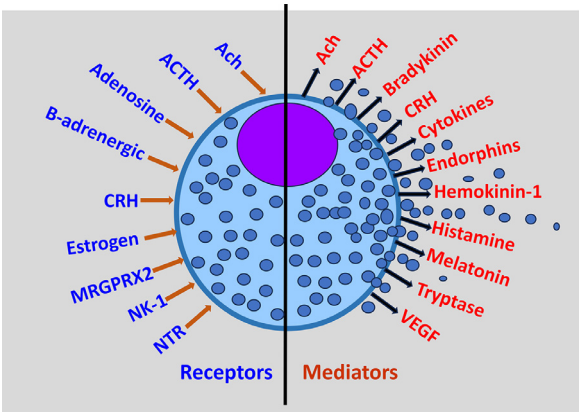


**Figure 2.** Diagrammatic representation of receptors and mediators relevant to the ANS. Ach, acetylcholine; ACTH, adrenocorticotropic hormone; ANS, autonomic nervous system; CRH, corticotropin-releasing hormone; VEGF, vascular endothelial growth factor.

neuropathy were found to be present in patients with systemic mastocytosis.[109]

## Mast Cells in the Central Nervous System

MC are present in the CNS perivascularly,[110,111] especially in the meninges,[80,112] and the median eminence[113] of the hypothalamus,[80,114,115] The presence of an increased number of MC-containing histamine has been reported in the human brain,[116] especially in brain lesions of patients with multiple sclerosis (MS).[117-120] We had called brain MC the "immune gate to the brain."[110] We reported increased levels of MC tryptase in the cerebrospinal fluid of patients with MS.[121] Interestingly, a letter to the editor reported that the tryptase level in the cerebrospinal fluid of 4 patients with mastocytosis was not elevated,[122] but none of these patients apparently had neurologic symptoms and the serum tryptase level of one of the 4 patients was not even elevated (3.2 ng/mL).

Stimulation of the brain and nasal MC resulted in stimulation of the hypothalamus-pituitary-adrenal (HPA) axis,[37,123-126] possibly through MC release of histamine,[127] IL-6,[127,128] and CRH,[129] implying that either these mediators from the nasal MC reached the hypothalamus or the antigen reached the hypothalamic MC. In addition, perivascular brain MC could be stimulated by various triggers including environmental and food allergens leading to disruption of the blood-brain barrier (BBB) and subsequent entry of additional triggers in the brain. In fact, MC-derived histamine,[130-133] tryptase,[134] and cytokines[135,136] increased BBB permeability,[114,133,137] thus permitting MC mediators and other molecules to enter the brain parenchyma.[138,139] In particular, prostaglandin E2 was reported to cross the BBB.[140]

Functional interactions have been reported between MC and neurons[80,141,142] that are often positive for CRH[80,143] secreted under stress.[80] The effect of stress on MC has also been reviewed.[78,144] Restraint stress in rodents increased BBB permeability[114,137,145] through CRH-stimulating MC.[137,146,147] Restraint stress also led to increased mammary adenocarcinoma brain metastases in mice.[146] This process could worsen with stress acting through CRH stimulation of MC,[137,146] leading to increased dura vascular permeability. We found that stress stimulates MC[78,144] through CRH[78] leading to increased dura vascular permeability, an effect that was absent in MC-deficient mice.[148] Interestingly, meningeal MC affected the integrity of the BBB and promoted T-cell brain infiltration.[149] MC were found to be an early activator of lipopolysaccharide (LPS)-induced neuroinflammation and BBB dysfunction in the hippocampus.[150] Stress has also been linked to the possible priming of immune cells, thus contributing to neuroinflammation in Alzheimer's disease.[151,152]

Moreover, NT[153] and SP,[154] neuropeptides implicated in inflammation, induced CRHR-1, thus creating an autocrine loop. Furthermore, SP induced the ST2 receptor for IL-33[24] further exacerbating MC activation by the combined action of neuropeptides and IL-33.

Restraint stress in rodents increased BBB permeability[114,137,145] through CRH-stimulating MC.[137,146,147] MC-derived mediators, such as cytokines,[135,136] increased BBB permeability not only to small molecules[114,137] but also to mammary adenocarcinoma brain metastases in mice.[146] This process could worsen with stress acting through CRH activation of MC,[137,146] leading to increased dura vascular permeability. Interestingly, meningeal MC affected the integrity of the BBB and promoted T-cell brain infiltration.[149] MC were found to be an early activator of LPS-induced neuroinflammation and BBB dysfunction in the hippocampus.[150] MC responsiveness may be regulated by the neuroimmune stimuli and effects of the different receptors involved. For instance, MC expresses high-affinity neurokinin-1 receptors for SP.[24,154,155] Moreover, SP[154] and NT[153] induced the expression of CRHR-1 in human MC. MC are the richest source of histamine in the amygdala, hippocampus, hypothalamus, and thalamus.[156] Neuronal histamine is involved in neurodevelopment[157] and acts as an alert signal in the brain.[158] In fact, brain histamine is critical for arousal,[159] memory consolidation and retrieval,[160] and motivation.[156,159–167] However, extensive release of histamine from brain MC or peripheral histamine crossing a disrupted BBB could have opposite results. Activated brain MC were found to contribute to postoperative cognitive dysfunction by activating microglia[168] through the release of mediators.[169] Activation of MC[151,170] and microglia[171] in the hypothalamus[172] could lead to dysfunctional homeostasis and cognitive dysfunction,[168] most often also found in patients with MCADs,[34,173] and may be related to brain abnormalities.

## Mast Cells Communicate With Microglia in Neuroinflammation

Microglia have been considered key players in brain injury[174] and the development of complex[175,176] neuroinflammatory[175,176] and neurodegenerative[177-184] disorders. Microglia express toll-like receptors[185] activated by damage-associated molecular patterns and pathogen-associated molecular patterns. Microglia are typically characterized as proinflammatory (M1) and anti-inflammatory (M2).[186] On stimulation, activated microglia adopt an ameboid shape (M1) that renders them capable of phagocytosis and antigen presentation, including the release of proinflammatory cytokines, free radicals, and fatty acid metabolites.[187] Microglia also communicate with astrocytes.[188] As a result, microglia have been found to play a key role in neuroinflammation and neurodegenerative diseases.[115,189] An important consequence of microglial priming is that the cytokines and chemokines released can induce astrogliosis, amyloid deposition, and subsequently, further worsening neuroinflammation.[190-192] Microglia express receptors for NT,[193] and we reported that NT can activate human microglia to secrete proinflammatory molecules.[194] Microglia also express receptors for CRH, secreted under stress.[195] Psychological stress can increase microglial reactivity to other challenges[196] and lead to cognitive decline.[197]

MC communicate with microglia[198,199] leading to their activation[169,198,200,201] and contributing to neuroinflammation[199-202] and neurodegenerative diseases.[199,203,204] This effect is absent in MC-deficient mice.[203,205,206] Microglia can be activated by molecules released from MC, such as histamine[207] and tryptase.[208] In fact, MC proteases can activate astrocytes and glia/neurons to release IL-33.[209] Stabilization of MC was found to inhibit LPS-induced neuroinflammation by inhibiting activation of the microglia.[210] Food allergy that depends on MC activation has also been found to increase both the total and the activated microglia, including levels of TNF, in the hippocampus associated with behavioral and learning impairments.[167]

## Mast Cells in Ehlers-Danlos Syndrome/Postural Orthostatic Tachycardia Syndrome

MC activation-associated disorders have also been reported in conditions characterized by dysfunction of the ANS, such as cholinergic urticaria and possibly postural orthostatic tachycardia syndrome (POTS),[211,212] patients who experience flushing in addition to tachycardia, and Ehlers-Danlos syndrome (EDS).[213,214] In such cases, MC activation may be compensated by hyperadrenergic stimulation.[215] Sporadic reports suggested that some of these patients may even present with the "triad" of MCAS, POTS, and EDS.[216] One retrospective study reviewed records of patients with EDS and POTS (n = 195) and reported that 31% of these patients had MCAS as compared with 2% for the healthy control (Table 4)[212]; however, the criteria for defining MCAS were not clear.

One retrospective case series (n = 98) reported that 24% of patients with EDS had MCA.[217] Other papers reported on the comorbidity of other MC activation-associated diseases. One retrospective case series of patients with either hypermobility syndrome (n = 126) or EDS (n = 162) as compared with healthy controls (n = 221) revealed that there was a significant increase in the frequency of respiratory symptoms in subjects with both hypermobility syndrome

**Table 4**
Characteristics of Studies Reviewed

| Type of study | Comorbidity[a] | Diagnosis | Evaluation | No patients | Findings | Conclusions |
|---|---|---|---|---|---|---|
| EDS, POTS | | | | | | |
| Prospective | MCA | Hyperadrenergic POTS | Clinical examination | 177 | | MCA was common[211] |
| Prospective | Asthma | Joint hypermobility | Clinical examination | Asthma (n = 100)<br>Healthy controls (n = 100) | Hypermobility was present in 70.1% of patients with asthma as compared with 29.9% in controls | Hypermobility was common in patients with asthma[216] |
| Prospective | Asthma, atopic conditions | HMS, EDS | Questionnaires | 509 subjects (126 HMS, 162 EDS, and 221 healthy controls) | HMS(asthma OR, 2.4; 95% CI, 1.4-4.1, $P = .002$ and atopy OR, 2.7; 95% CI, 1.6-4.5, $P < .001$) and EDS (asthma OR, 3.1; 95% CI, 1.8-5.2, $P < .001$ and atopy OR, 2.6; 95% CI, 1.6-4.4, $P < .001$) compared with controls | Asthma and atopic conditions were more frequent in patients with HMS and EDS[215] |
| Retrospective | MCAS | POTS + EGID | EMRs | 7 | Autonomic dysfunction was 5- to 10-fold higher in EGID than expected in the general population | 2 Subjects (29%) had comorbid EDS and MCAS[217] |
| Retrospective | MCAS | EDS + POTS | Record review—diagnostic codes | 195 | 31% vs 2% controls | MCAS was more common[208] |
| Retrospective | MCA | MCA + POTS | Record review—diagnostic codes | 69 | 42% of patients with POTS had elevated biochemical markers suggesting MCA disorder. | MCA disorder is common in POTS[218] |
| Prospective | MC | Connective tissue disorders | Skin biopsies | 12 Patients and 16 controls | 1.7-fold greater number of chymase-positive skin MC | MC may be related to arterial hypertension in the patients[219] |
| ASD | | | | | | |
| Retrospective | Allergies,mastocytosis, UP | ASD | Questionnaire | 41 | 10 × higher | MCAD increased the risk for ASD[220] |
| Retrospective | Asthma | ASD | 2007 National Survey of Children's Health Data Base | 77,951 | OR, 1.19; 95% CI, 1.03-1.36 | Asthma was 35% more common in ASD[221] |
| Retrospective | Food allergies | ASD | CHARGE study | ASD (n = 560), control (n = 391) | OR, 2.23; 95% CI, 1.28-3.89 | Food allergies are more common in ASD[222] |
| Systematic review | AD | ASD | 18 Studies up to 2015 | | HR, 3.4; OR, 1.24 ($P < .001$) | AD increased the risk for ASD[223] |
| Retrospective | AD | ASD | Taiwan's National Health Insurance Program (2000-2010) | 387,262 with AD | HR: 1.75 | AD before 2 y old increased the risk of AD[224] |
| Retrospective | Food allergy | ASD | Population-based, cross-sectional study using data from the National Health Interview Survey (1997-2016) | 199,520 | OR, 2.29; 95% CI, 1.87-2.81 | Food allergy increased the risk for ASD[225] |
| Retrospective | Food allergies | ASD | National Health Interview Survey (2011-2015) | 53,365 of whom 905 with ASD and 2977 with food allergies | 2.5 higher ASD in the presence of food allergies | Food allergies increased the risk for ASD[226] |
| Retrospective | Food hypersensitivities | ASD | 8 Data bases before 2020 | 434,809 | OR, 2.79; OR, 2083.75 ($P < 0.1$) | Food sensitivities increased the risk for ASD[227] |
| Prospective | AD | ASD | Record review | 446 | OR, 4.26; 95% CI, 1.36-13.36 | AD increased the risk for ASD[228] |
| Prospective | Asthma, allergies, eczema, and hay fever | ASD | Clinical assessment | 45 with ASD vs 93 controls | 2.4 times higher | Atopy increases the risk for ASD[229] |
| Retrospective | AD | ASD | UK health records data | 409,431 with AD vs 1,809,029 without AD | HR, 1.02; 95% CI, 0.98-1.06 | AD increases the risk for ASD[230] |
| Retrospective | Food allergy | ASD | Meta-analysis included 12 published articles with 434,809 subjects. | 434,809 | OR, 2.79; 95% CI, 2.01-3.75 | Food allergy increases the risk for ASD[227] |
| Retrospective | Allergic disorders | ASD | Pediatric database of Clalit Health Services (2000-2018) | 117,022 with allergies vs 116,968 without allergies | OR, 1.17; 95% CI, 1.08-1.27 | Allergic disorders increase the risk for ASD[231] |
| Retrospective | Asthma | ASD | Familial co-aggregation of asthma and ASD in individuals born in Sweden (1992-2007) | 1,569,944 including their full- and half-siblings (1,704,388 and 356,544 pairs) | OR, 1.33; 95% CI, 1.28-1.37 and OR, 1.44; 95% CI, 1.38-1.50, for full siblings | Asthma increased the risk for ASD[232] |

(*continued*)

**Table 4** (*Continued*)

| Type of study | Comorbidity[a] | Diagnosis | Evaluation | No patients | Findings | Conclusions |
|---|---|---|---|---|---|---|
| Prospective | Asthma and other atopic conditions | ASD | Enrolled at birth and followed clinically | 2580 Children enrolled at birth were followed prospectively, of which 119 have ASD vs 1273 controls | OR, 1.38; 95% CI, 1.15-1.66 for asthma and OR, 1.52; 95% CI, 1.28-1.81 for combined atopic conditions | Asthma increased the risk for ASD that increased further in the presence of multiple atopic conditions[233] |
| ME/CFS | | | | | | |
| Prospective | Allergies | CFS | Clinical assessment and blood cytokines | CFS (n = 18)<br>Allergic (n = 14)<br>Control (n = 11) | 15/18 Patients with CFS have allergy | Allergies were more common in patients with CFS[234] |
| Retrospective | MCA | ME/CFS | Patients with CFS/ME were defined in accordance with the International Consensus Criteria; blood samples collected | 31 | There was a significant increase in CD40 ligand and MHC-II receptors on differentiated MC populations in severe CFS/ME compared with healthy controls and moderate CFS/ME. | Significant increase of naive MC in patients with moderate and severe CFS/ME compared with healthy controls[235] |
| Retrospective | | EDS | Rehabilitation clinic | 98 | 24% of patients with EDS had MCAS | MCAS was more common in patients with EDS[214] |
| COVID-19 | | | | | | |
| Retrospective | MC | COVID-19 | Lung autopsies | COVID = 6 and HC = 10 | Increased perivascular and septal CD117 + MC | Increased perivascular and septal MC in the lungs[236] |
| Retrospective | MC-associated proteases | COVID-19 | Lung autopsies and serum | COVID = 19 and HC = 20 | Proteases were significantly increased in the serum and their gene expression in the lungs | Increased MC-associated proteases in the serum and lungs of patients with COVID-19[237] |
| Retrospective | Chymase | COVID-19 | Plasma | Intubated = 7<br>Inpatient = 18<br>Community = 12<br>HC = 13 | Chymase levels were increased in hospitalized patients compared with mild community patients | Increased serum chymase correlated with disease severity[238] |
| Retrospective | MC | COVID-19 | Lung autopsies with or without DAD | COVID = 19<br>Controls = 4 | Organizing DAD in COVID-19 lungs revealed a 3-fold increase in MC between low- and high-density areas | Chymase and tryptase-positive MC were increased only in lung areas with DAD[239] |
| Retrospective | MC were identified by KIT (CD117), tryptase, and chymase immunohistochemistry | COVID-19 | Lung autopsies | 30 | Increased numbers of chymase-positive MC at early stage and further augmentation of MC during late stage of alveolar damage compared with controls | Increased number of MC in the lungs of patients with COVID-19[240] |
| Retrospective | MC-associated chymase, tryptase and carboxypeptidase A3 | COVID-19 | Lung autopsies and serum | COVID = 60andHC = 17 | All 3 proteases were increased in the serum and the density of degranulated MC was increased compared with control lungs. | SARS-CoV-2 was strongly associated with activation of MC[241] |
| Long-COVID | | | | | | |
| Retrospective | MCA | Long-COVID | Online assessment,MCMRS score | Long-COVID = 136<br>MCA = 80<br>HC = 136 | Long-COVID = 136<br>MCAS = 80<br>MCMRS score in patients with Long-COVID resembled that of patients with MCAS before treatment | MCA symptoms were increased in Long-COVID and mimicked the symptoms and severity reported by patients who had MCAS[242] |
| Retrospective | Cytokines and proteases | PASC | Serum | PASC = 13<br>PAAC = 13<br>HC = 20 | Chymase, tryptase, and carboxypeptidase A3 levels were elevated in active COVID-19, but only tryptase level remained elevated in PASC | MC-associated proteases are differentially expressed in active COVID-19 as compared withPASC[243] |

Abbreviations: AD, atopic dermatitis; ASD, autism spectrum disorder; CHARGE, Childhood Autism Risks from Genetics and Environment; CI, confidence interval; DAD, diffuse alveolar damage; EDS, Ehlers-Danlos syndrome; EGID, eosinophilic gastrointestinal disease; EMR, electronic medical record; HC, healthy control; HMS, hypermobility syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MC, mast cell; MCA, mast cell activation; MCAS, mast cell activation syndrome; MCMRS, mast cell mediator release syndrome score; MC mediator release syndrome; OR, odds ratio; PAAC, post-acute asymptomatic COVID; PASC, post-acute symptomatic COVID; POTS, postural orthostatic tachycardia syndrome.

[a]The comorbidities are listed as indicated by the authors of the respective publications.

(asthma odds ratio [OR], 2.4; 95% CI, 1.4-4.1; $P = .002$ and atopy OR, 2.7; 95% CI, 1.6-4.5; $P < .001$) and EDS (asthma OR, 3.1; 95% CI, 1.8-5.2; $P < .001$ and atopy OR, 2.6; 95% CI, 1.6-4.4; $P < .001$) compared with controls (Table 4).[218] In another study, joint hypermobility was present in 70.1% of patients with asthma (n = 100) as compared with 29.9% in healthy controls (n = 100).[244] In a small retrospective study of 7 patients with POTS and eosinophilic gastrointestinal disease, which is associated with activated MC, autonomic dysfunction was 5- to 10-fold higher in eosinophilic gastrointestinal disease than expected in the general population; moreover, 2 subjects (29%) had comorbid EDS and MCAS.[219] Another retrospective study of 69 patients with POTS found that 42% had elevated levels of biochemical markers suggesting the presence of MCA.[245]

One review[246] summarized several of these papers and included 2 abstracts, one by Szalewski[247] (2019) reporting an increased prevalence of idiopathic urticaria in patients with EDS and another by Cheung and Vadas[216] (2015) reporting that in patients with EDS (n = 198) from a rehabilitation center, 24% had a diagnosis of MCAS, but the criteria for this diagnosis were not clear.

Unfortunately, the definitions of MCAD and especially of MCAS were often not precise and used interchangeably, and some studies made inferences from the symptoms described in medical records casting doubt on the validity of some associations reported.[248]

## Mast Cells in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is characterized by difficulties in communication and apparently purposeless repetitive movements, cognitive impairment,[249] but also extreme sensory sensitivities.[250] The prevalence of ASD is estimated to be approximately 5% in the United States.[251] However, ASD pathogenesis is still unknown. In addition, most children with ASD have a number of comorbidities such as hyperactivity, gastrointestinal problems, allergies, and seizures,[252] making objective diagnosis and the development of effective treatments difficult.

We advanced the premise that focal inflammation in the amygdala due to MC and microglia activation can reset the fear threshold and throw the body into a perpetual fight-or-flight mode, thus "neglecting" higher functions.[206,220,253,254] Using a questionnaire, we had reported that children born to mothers with systemic mastocytosis or with cutaneous mastocytosis themselves (n = 40) had an almost 10-fold higher risk of developing ASD[255] (Table 4). Parental history of AD was also strongly associated with children developing AD.[256] It had been reported that maternal immune activation[257] and autoimmune diseases,[258] especially psoriasis, but also allergies and asthma, were associated with a higher risk of ASD.[259] In another study, almost 50% of children with ASD reported having relatives with rheumatoid diseases as compared with 26% in the control group.[260] In a large study, mothers who experienced asthma, allergy, atopy, or eczema during pregnancy was associated with a higher risk of neuropsychiatric problems in the offspring.[261] A meta-analysis of 119 studies revealed that patients with parental history of atopic diseases had an increased risk for ASD (OR, 1.81; 95% CI, 1.65-1.99, $P < .001$).[256]

A recent publication revealed that the mother's circulating immune IgE resulted in vertical transmission of AD in the newborn through stimulation of fetal MC[262]; both passive and active prenatal sensitization conferred allergen sensitivity.[262] This important study indicated that fetal MC were functional and could be stimulated by specific IgE and allergens present in the mother during gestation.[262] Fetal MC could potentially respond to other stimuli such as neuropeptides and toxins, including the alarmin IL-33,[55,263] with detrimental effects on brain development especially in premature babies.[264] Inflammation during gestation could adversely affect the developing brain,[265,266] including cortical dendritic arborization.[267] In fact, prenatal allergen exposure was even found to program lifelong changes in the social and sexual behaviors of adult rats, including effects on microglia activation and neonatal dendritic spine density.[268]

Subsequently, several large epidemiologic studies reported a strong association between AD and behavioral problems in general[269] and ASD in particular[224,270–275] (Table 4). A strong association was reported between risk for developing ASD and allergies,[220–223,274] especially asthma[223,228] and AD,[230] which could lead to brain inflammation and cognitive impairment.[167] One retrospective study reviewed 77,951 patients from the National Survey of Children's Health Data Set and found that asthma was 35% more common in ASD (OR, 1.19; 95% CI, 1.03-1.36).[228] Another retrospective study investigated the effect of maternally reported asthma and allergies from the Childhood Autism Risks Genetics and Environment (CHARGE) study of 560 patients as compared with 391 healthy controls and found that food allergies were more common in ASD (OR, 2.23; 95% CI, 1.28-3.89) and correlated with the severity of symptoms.[223] Another retrospective study using Taiwan's National Health Insurance Program (2000-2010) reviewed 387,262 children with AD and found that there was an increased risk for ASD (hazard ratio [HR], 1.75).[274] A systematic review of 18 studies also found that AD increased the risk for ASD (HR, 3.4; OR, 1.24; $P < .001$).[230]

Additional studies confirmed the increased risk of ASD by the presence of atopic conditions (Table 4). One study reviewed records from 444 subjects and concluded that AD increased the risk of ASD (OR, 4.26; 95% CI, 1.36-13.36, $P < .001$)[229] Another study investigated 409,431 patients with AD as compared with 1,809,029 subjects without AD and found that the presence of AD increased the risk of ASD (HR, 1.02; 95% CI, 0.98-1.06, $P < .001$)[231] (Table 4). One more retroactive study using the pediatric database of Clalit Health Services (2000-2018) evaluated 117,022 children with allergies as compared with 116,968 without allergies and concluded that allergic disorders increased the risk for ASD (OR, 1.17; 95% CI, 1.08-1.27, $P < .001$)[232] (Table 4). Another retrospective study investigated familial co-aggregation of asthma and ASD in individuals born in Sweden (1992-2007); the results from 1,569,944 children including their full- and half-siblings (1,704,388 and 356,544 pairs) were that asthma increased the risk for ASD which increased further in the presence of multiple atopic conditions (OR, 1.38; 95% CI, 1.15-1.66, for asthma, and OR, 1.52; 95% CI, 1.28-1.81 for combined atopic conditions, $P < .001$)[233] (Table 4). A prospective study of asthma and other atopic conditions that investigated 2580 children enrolled at birth and followed clinically, of which 119 had ASD compared with 1273 healthy controls, concluded that asthma increased the risk for ASD which increased further in the presence of multiple atopic conditions (OR, 1.38; 95% CI, 1.15-1.66, for asthma, and OR, 1.52; 95% CI, 1.28-1.81 for combined atopic conditions)[276] (Table 4). One more prospective study of 45 patients with ASD and 93 healthy controls concluded that the presence of asthma, allergies, eczema, or hay fever increased 2.4 times the risk of ASD[277] (Table 4).

Food allergies and food intolerance also apparently increased the risk of ASD[225–227,278–280] (Table 4). A population-based, cross-sectional study using data from the National Health Interview Survey (1997-2016) evaluated 199,520 subjects and concluded that food allergies increased the risk of ASD (OR, 2.29; 95% CI, 1.87-2.81; $P < .001$)[278] (Table 4). In a retrospective study of parent-reported food allergies using the National Health Interview Survey (2011-2015) of 53,315 children, there were 905 patients with ASD and 2977 patients with food allergies resulting in 25 times more common food allergies in ASD (Table 4).[279] One meta-analysis of 12 studies with a total of 434,809 subjects concluded that the presence of food hypersensitivities increased the risk of ASD (OR, 2.79; 95% CI, 2.08-3.75; $P < .001$)[226] (Table 4). In fact, the presence of allergies was associated with elevated serum levels of autoantibodies against brain antigens in children with ASD.[281] It should be noted that parent-reported food allergies and sensitivities may also include food intolerances such as for histamine and phenols that are associated with dysfunctional

catabolic enzymes, such as diamine oxidase and catecholamine-ortho-methyl transferase, respectively.

Clearly, these results do not provide evidence of causation but certainly suggest some involvement of MCA at least in atopic diseases and ASD.

## Mast Cells in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex chronic, debilitating disorder[282,283] with 4:1 female-to-male ratio,[235] characterized by unrelenting fatigue, and autonomic, cognitive, and sleep dysfunction,[172,284–286] especially physical and mental fatigue.[287] The prevalence of ME/CFS is approximately 1% in the United States.[235,288–291] Approximately half of the patients with ME/CFS develop symptoms after a sudden, influenza-like illness,[292] implying the possible involvement of pathogen-associated molecular patterns, including mycotoxins, such as ochratoxin A (OTA).[293] As a result, ME/CFS may have an autoimmune component to its pathophysiology,[294,295] involving neuroinflammation.[296–298] Even though serum levels of proinflammatory cytokines, especially IL-1β and IL-6,[299–304] have been reported to be increased in patients with ME/CFS,[304,305] other studies have not supported such findings,[289,306] except maybe for elevated IL-6 level.[304,307] In addition, there was no difference in cytokine content of extracellular vesicles from patient with ME/CFS as compared with healthy controls even though the number of vesicles was increased.[308]

Although the exact cause of ME/CFS remains unclear,[309] evidence points to the involvement of some pathogenetic mechanism(s),[303,310–312] such as neurovascular inflammation,[112,200,313] endothelial dysfunction, BBB disruption, and reduced blood flow to the brain.[314–318] Anti-receptor antibodies[319] and autoimmune gene expression[320] have also been reported because MC-derived inflammatory, vasoactive, and neurotoxic mediators can disrupt the BBB,[110,134] alter blood flow to the brain,[109] and can activate microglia,[199,200] leading to neurovascular inflammation.[151] MC have also been linked to fatigue in patients with mastocytosis[321] and neuropsychiatric symptoms.[33,322] One study reported increased MC precursors in the blood of patients with ME/CFS,[284] and another study revealed that the higher presence of atopic symptoms increases the risk of ME/CFS.[323–326] A small prospective study investigated patients with MC/CFS and found that allergies were present in 15 of 18 patients (Table 4), which is higher than the general population (less than 30%).[234] In this study, allergy was defined as “the presence of a wheal of 3 mm or greater in diameter on skin prick testing to one or more antigens in the standard Colorado inhalant panel and the presence of an atopic disease (allergic rhinitis, asthma, or atopic dermatitis).”[234]

We further revealed that cell-free mtDNA was increased in extracellular vesicles obtained from the blood of patients with ME/CFS[327] and can amplify neuroinflammation.[328] We reported that cultured human microglia can be stimulated by NT to release IL-1β and CXCL8/IL-8.[194] This action was mediated through the regulatory complex mammalian target of rapamycin (mTOR),[194,329] which has been implicated in brain development,[330] aging,[331] dementia,[332] neuropsychiatric disorders,[333–339] brain injury,[340] neuroinflammation,[341] and central fatigue.[342]

## Mast Cells in COVID-19 and Long-COVID Syndrome

Infection with SARS-CoV-2 leads to COVID-19, the severity of which derives from the host’s immune response,[343] especially the release of a storm of proinflammatory cytokines,[344–351] such as IL-6,[352–356] known as cytokine storms.[357] Moreover, circulating mtDNA which is secreted from activated MC[40] was reported to be an indicator of severe illness and mortality in patients with COVID-19, as was extracellular mtDNA.[358]

A number of human and animal studies discussed MCA associated with SARS-CoV-2 infection or in COVID-19.[236–238,241–243,359–368] In particular, one study of a few patients with COVID-19 (n = 6) reported increased MC density of CD117+ MC in the lungs of autopsies from patients with COVID-19 as compared with deceased controls (n = 10)[243] (Table 4). Another article reported an increased number of chymase-positive MC in lung biopsy samples of patients with COVID-19 (n = 30)[369] (Table 4).

Two papers reported increased serum levels of chymase in patients with COVID-19.[237,241,368] In the second study, serum levels of chymase correlated with disease severity[237] (Table 4). A third article reported that levels of chymase, tryptase, and carboxypeptidase A3 were all elevated in the serum of patients with COVID-19 (n = 60) as compared with healthy controls (n = 17); the number of degranulated MC in lung autopsies was also elevated[242] (Table 4). A fourth study reported that lung autopsies from COVID-19 lungs had a 3-fold increase in MC between low- and high-density areas with diffuse alveolar damage (DAD)[370] (Table 4). Interestingly, one study reported that MC promotes viral entry of SARS-CoV-2 through the formation of chymase-spike complexes.[362]

Infection with SARS-CoV-2 may contribute to neurologic[239,240,371–375] and psychiatric[376-382] disorders. Approximately one-half of COVID-19 survivors experience fatigue and other neuropsychiatric symptoms, especially the presence of mental fatigue or brain fog, referred to as Long-COVID.[383-385] This persistent fatigue is independent of the severity of the initial symptoms.[386] Perivascular damage and inflammation[387-389] has also been reported in the brains of patients with COVID-19,[390] but also dysregulation of innate and adaptive immune rersponses[391,392] and autoimmunity.[375] Symptoms experienced by patients with Long-COVID, especially cognitive impairment,[287,393] are similar[394,395] to those present in patients with ME/CFS.[172,289] Such symptoms are also present in those with MCAS[396,397] or systemic mastocytosis.[3]

MC activation was in fact found to be associated with Long-COVID. One study investigated post-acute symptomatic (PASC = 49), post-acute asymptomatic (PAAC = 48) patients and healthy controls (n = 20) and patients with COVID-19 from a previous cohort; levels of chymase, tryptase, and carboxypeptidase A3 were found to be elevated in those with active COVID-19, but only tryptase level remained elevated in PASC but significantly lower than in COVID-19 (Table 4).[346] We recently reported that recombinant SARS-CoV-2 spike protein could stimulate cultured human MC to release chymase and tryptase and proinflammatory cytokines, an effect augmented by the cytokine IL-33.[398,399] We further found that SARS-CoV-2 spike protein could stimulate cultured human microglia to release IL-1β, IL6, TNFα, and S100B through activation of different receptors.[400] Obviously one would wonder how MC and microglia may continue to be stimulated past the initial infection. A recent review discussed evidence that the SARS-CoV-2 in its spike protein may persist in certain “reservoirs.”[401] In particular, SARS-CoV-2 spike protein could be detected in patients with Long-COVID for 6 to 12 months.[402] Other authors reported that the spike protein persisted in CD16+ monocytes for up to 15 months post-infection[403] and was associated with sustained CD4+ reponses to the spike protein.[404] Another paper reported that the spike protein may acumulate in the brain.[405]

We recently reported a few common genes involved in the regulation of immune responses in both ME/CFS and COVID-19,[406] including human leukocyte antigens.[407,408] We further hypothesized that the spike protein could contribute to not only COVID-19[360] but also Long-COVID syndrome,[359,360,395,409] especially neuro-COVID.[31]

## Conclusion

The available evidence indicates that MC can affect the ANS through a variety of actions, such as activation of microglia and

astrocytes, BBB disruption, cardiac pacemaking, circadian clock, coronary artery constriction, HPA axis regulation, neuroinflammation, neurosensitization, and vascular tone control (Table 3), thus potentially contributing to a number of dysautonomias and neuroinflammatory conditions with dysfunctional homeostasis.

However, the presented available evidence of the possible involvement of MC in the ANS is not uniform, often circumstantial, and with many contradicting reports depending on the species and trigger. Moreover, human studies in some of the conditions discussed were based on a few subjects who were not always well defined. Nevertheless, given the many ways MC could be activated and their numerous mediators released, it would make sense to inhibit the activation of MC. Better clinical studies are necessary as is the development of an in vitro disease surrogate system. We are presently working on developing neuroimmune organoids[410–412] using human-induced pluripotent stem cell–derived MC,[413] co-cultured with endothelial cells, microglial cells, and neurons using a multichannel microfluidic model where neuroimmune interactions can be studied under defined conditions that also allow testing of effective inhibitors.

## Disclosures

Dr Theoharides is the Scientific Director and shareholder of Algonot, LLC, a company that develops and sells dietary supplements. Dr Theoharides has been awarded the following patents: US 5,855.884; US 6,020,305; US 8,268,365; and EPO 0618796 licensed to Algonot, LLC.

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