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Hypothesis

Hypothesis: Myalgic Encephalomyelitis (ME) as a Mast Cell Activation Disorder (MCAD)

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Abstract

Background: Myalgic encephalomyelitis (ME) is a severely debilitating neuroimmune disease with the characteristic feature of post-exertional malaise (PEM). Whilst multiple studies have found various abnormalities, there is significant heterogeneity in findings; as such there is no consensus regarding the underlying aetiology. Mast cells are immune cells most commonly recognised for their role in allergy. The scope of biological effects mast cells have is growing in recognition, with inappropriate mast cell degranulation increasingly recognised to cause a range of symptoms and downstream effects. **Hypothesis**: ME may be a mast cell activation disorder variant, with exertion being the primary trigger to inappropriate mast cell degranulation, possibly due to mast cell hypersensitivity to metabolically produced reactive oxygen species. Mast cell activation releases mitochondrial components which further act as an "autopathogen", whilst each degranulation cycle reduces mast cell metabolic flexibility. This cycle is perpetuated in those with genetic susceptibility towards Th2-dominance, which acts to both impede pathogen clearance and drive autoinflammation. The resultant chronic immune activation triggers immune and host metabolic changes resembling sickness metabolism. This causes a range of multisystemic symptoms, worsened by exertion, akin to a chronic sickness behaviour. Due to the close and bidirectional interactions between mast cells, the nervous system, and mitochondria, such a hypothesis can potentially explain various aspects of ME, such as: Why ME can be caused by a range of exposures; the core symptoms of ME; individual variances in clinical presentations; why pacing can prevent worsening; and time trends and symptoms of PEM. Several potential counterarguments are also discussed, along with methods to try and test the hypothesis. **Conclusion**: Several lines of evidence suggest it is at least plausible that (a subgroup of) ME could be a unique and distinct variant of a mast cell activation disorder. As the immune system and metabolism are intrinsically linked, it could be argued this is an immunometabolic mast cell disorder phenotype. However, this is one of many plausible hypotheses, requires testing and validation, and does not change the current recommendations for managing ME, nor should it be used as evidence that the aetiology of ME is established.

Keywords: allergy; cytokines; mast cell activation disorders; mast cell activation syndrome; ME/CFS; myalgic encephalomyelitis; oxidative stress; post-exertional malaise; post-exertional neuroimmune exhaustion; reactive oxygen species

1. Introduction

1.1. Myalgic Encephalomyelitis (ME)

Myalgic encephalomyelitis (ME) is a neuroimmune disorder characterised by cognitive impairment, fatigue, and problematic sleeping (e.g. hypersomnia, insomnia, unrefreshing sleep) (Carruthers et al., 2011; NICE, 2021). The cardinal feature differentiating ME from other fatiguing

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diseases is post-exertional malaise (PEM), also called post-exertional neuroimmune exhaustion (PENE). PEM is defined as "a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions" and is characterised by marked, rapid physical and/or cognitive fatiguability in response to exertion, post-exertional symptom exacerbation (PESE), post-exertional exhaustion, and prolonged recovery (Carruthers et al., 2011).

PEM should not be confused with isolated PESE, which many diseases exhibit (Harvey et al., 2026). PEM is multisystemic, affecting function beyond the site of exertion. For example, PEM related to cognitive exertion can lead to (worsened or new onset) insomnia, muscle weakness, pain, and photophobia (Carruthers et al., 2011). Because of this, repeated exertion becomes cumulatively more difficult, if it is even possible. Recovery from exertion typically takes > 24 h, but in the worst cases can result in a permanently lower baseline. Depending on various factors (e.g. ability to pace effectively, ME severity), exertion in this context can be minimal, including basic activities of living (e.g. eating) or simple mental tasks (Carruthers et al., 2011).

Further, PEM is objectively demonstrable, with the most consistent finding being metabolic abnormalities specifically on the second day of a 2-day cardiopulmonary exercise test (CPET) (Keller et al., 2024; Lim et al., 2020). Concordant findings have been demonstrated with other methods, such as repeat handgrip strength testing (e.g. Nacul et al., 2018), whilst post-exercise urinary metabolites suggest ME patients fail to adapt (Glass et al., 2023). Although these findings demonstrate that exertion is having pathological effects, they do not provide answers as to why. Several plausible hypotheses have been proposed to explain PEM (e.g. Germain et al., 2022; Jin et al., 2026; Kell & Pretorius, 2022; Shuka et al., 2015; Renz-Polster et al., 2022; Wirth & Scheibenbogen, 2020), and it is likely these and other factors interact.

Because exertion triggers such a pathological response with significant and prolonged functional decline, the primary management strategy for ME is pacing (Carruthers et al., 2011; NICE, 2021). Effective pacing can in the best cases prevent PEM (Sanal-Hayes et al., 2026), though this is not always feasible, especially for those more severely affected such as when digestion exceeds a patients' energy envelope.

Several pathophysiological abnormalities have been found in ME. However, findings are heterogeneous (e.g. Bested & Marshall, 2015; Huth et al., 2020; Maksoud et al., 2023; Taccori et al., 2023), and similar abnormalities are also found in many other diseases such as multiple sclerosis (MS) and type 2 diabetes (Table 1). That similar abnormalities can occur in other diseases without PEM suggests these may be consequences of underlying pathology, rather than direct causes, though they inevitably interact and help sustain illness. At present, there is no consensus regarding the underlying primary pathology driving ME.

Table 1. Examples of similarities in pathophysiological findings between myalgic encephalomyelitis, multiple sclerosis, and type 2 diabetes.

Abnormality	Myalgic encephalomyelitis	Multiple sclerosis	Type 2 diabetes
Autoantibodies	Bynke et al., 2020 von Mikecz et al., 1997	Zamecnik et al., 2024	Lomeli et al., 2025
Cerebral hypoperfusion, hypovolemia	Costa et al., 1995 van Campen et al., 2018	D'haeseleer et al., 2015	Cui et al., 2017 Laederach-Hofmann et al., 1999 Li et al., 2024a Rong et al., 2022
Coagulopathy	Berg et al., 1999	Plantone et al., 2019	Sobczak & Stewart, 2019

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	Kell & Pretorius, 2022 Nunes et al., 2022	Ziliotto et al., 2019	
Connective tissue & structural abnormalities	Bragee et al., 2020 Christoforou et al., 2025	Yamazaki et al., 2025	Rosenbloom & Silverstein, 1996
Dysbiosis	Fremont et al., 2013 Maes et al., 2007 Sheedy et al., 2009	Noto & Miyake, 2022	Yu et al., 2025
Dysmetabolism	Huth et al., 2020 Lane et al., 1998 van der Togt & Rossman, 2023	de Barcelos et al., 2019	Lowell & Schulman, 2005
Endocrine abnormalities	Addington, 2000 Demitrack et al., 1991 Miwa, 2017	Heesen et al., 2007	Bruehl et al., 2007 Wang et al., 2025
Immune dysfunction	Cliff et al., 2019 Maya, 2023	Khan et al., 2024	Berbudi et al., 2025
Intramuscular electrolyte abnormalities	Petter et al., 2022	Inglese et al., 2010	Kannenkeril et al., 2019
Neuroglial dysfunction & neuroinflammation	Renz-Polster et al., 2022 Tate et al., 2022	Lalmani & Deshmukh, 2026	Llorian-Salvador et al., 2024
Neuro-cardiovascular dysfunction	Joseph et al., 2023 Wirth & Scheibenbogen, 2020	Cashion et al., 2023 Zahoor et al., 2024	Grotle et al., 2021 Sawant & Bihl, 2026 Yu & Lee, 2021
Oxidative stress	Armstrong et al., 2015 Jammes & Retornaz, 2019 Shankar et al., 2025	Ohl et al., 2015	Caturano et al., 2023
Pathogen persistence	Kasimir et al., 2022 Schreiner et al., 2020	Tarlinton et al., 2020	Woelfle et al., 2022

1.2. Allergy & mast Cell Activation Disorders (MCADs)

Allergy can broadly be defined as an abnormal immune response against a non-infectious stimulus (allergen) (Galli et al., 2008). Several cells have a role in allergy, for example, basophils (Anvari et al., 2019; Galli et al., 2008; Galvan-Morales et al., 2025) and platelets (Pablo-Torres et al., 2023; Page & Pitchford, 2014; Yue et al., 2022), which release mediators such as histamine and serotonin (Borriello et al., 2017; Yue et al., 2022). Platelets also share common characteristics with neurons (Canobbio, 2019) and, like many immune cells, are implicated in neurological disease (Leiter & Walker, 2020). However, most literature on allergy is focused on mast cells and as such will be the focus of the hypothesis below.

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Allergy can be split into two branches: Immunoglobulin (Ig) E- and non-IgE-mediated (Galli et al., 2008). In IgE-mediated reactions, allergen-specific IgE antibodies bind to mast cells, triggering degranulation. Resultant symptoms are typically what most people recognise as "allergy" symptoms, such as anaphylaxis and hives, usually occurring within ~1 hour of exposure. Non-IgE-mediated reactions occur via other mechanisms, such as chemokines, cytokines, IgG, complement components, neuropeptides, and/or Toll-like receptor ligands, which can all activate mast cells (Galvan-Morales et al., 2025; Yu et al., 2016). These reactions tend to occur after some delay (hours to several days) and can be multisystemic (Calvani et al., 2020; Crook, 1975; Meyer et al., 2025; Ozdemir et al., 2024).

Mast cells are primarily located in and around tissue rather than in the blood (Krystel-Whittemore et al., 2016). As with basophils and platelets, mast cells store and release mediators which have a vast range of bioactivities. As many as 390 mediators have been identified, including cytokines, heparin, histamine, hormones, leukotrienes, neurotransmitters, prostaglandins (PGs), and proteases (Molderings & Afrin, 2023). Mediators can be stored in granules and released within seconds to minutes (e.g. histamine), or newly synthesised, taking minutes to hours (e.g. PGs) (Frossi et al., 2025; Solimando et al., 2022).

The phenotype and function of mast cells is diverse, and various factors can influence the extent to which they produce and release mediators, such as their development stage, environmental stimuli, and their location (Lichterman & Reddy, 2021; Tauber et al., 2023). The effect of mediators can differ depending on the site of activation, the surrounding microenvironment, and which receptor they bind to (Lichterman & Reddy, 2021). For example, histamine (H) 1 receptor agonism in the tuberomammillary nucleus in the brain is implicated in wakefulness (Thakkur, 2012), both H1 and H2 receptors can cause vasodilation (Sandilands et al., 2013), whilst stomach acid production is mediated by the H2 receptor (Lieberman et al., 2008). Mast cells and their mediators also help regulate wider innate and adaptive immune responses (Abraham & St John, 2010).

Several mast cell disorders are currently known. These include primary (i.e. intrinsic defect within mast cells or their progenitors), secondary (i.e. a known primary disease process such as IgE-mediated hypersensitivity), and idiopathic (i.e. mast cell activation that does not fit the primary or secondary definitions) (Khokhar & Akin, 2020; Figure 1). In many mast cell disorders, mast cells degranulate inappropriately, known as mast cell activation disorders (MCADs). Mast cell activation syndrome (MCAS) is a common MCAD. MCAS appears to more typically involve non-IgE-mediated reactions, though IgE-mediated reactions can occur (Galvan-Morales et al., 2025). Symptomatically, there tends to be a "baseline" state of mast cell-mediated symptoms, plus reactions to specific triggers (Afrin et al., 2026).

Diagnosis of MCAS is commonly based upon having a constellation of symptoms in two or more systems that can plausibly be attributed to the known bioactivities of mast cell mediators (with no better explanation), plus either evidence of elevated mast cell mediators and/or symptomatic response to mast cell targeted therapies, though there are other criteria that can be met (Afrin et al., 2026). Testing for mediators is limited for multiple reasons, including: Issues with sample degradation; that there are only a limited number of measurable mast cells mediators; and that there may be tissue-specific activation and mediator release that may not be detectable if systemic levels are normal.

Treatment of MCAS and allergies is centred on eliminating known triggers where possible. However, this alone is may not be sufficient and has its own challenges (e.g. risk of malnutrition or nutrient deficiencies). Common treatments include receptor antagonism of mast cell mediators (e.g. antihistamines, leukotriene receptor antagonists), or mast cell stabilisers. Other options, such as omalizumab (a monoclonal antibody that blocks IgE) are available, but are generally harder to access.

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The hypothesis herein will propose that ME is its own MCAD variant with unique characteristics (Figure 1). MCAS and other mast cell disorders will be used as a demonstrative comparator where applicable due to the mechanistic overlaps in the fundamental pathophysiology. Although the focus is on mast cells, it is appreciated that the immune system is a highly interactive and complex system which does not work in isolation. Mast cells are the focus due to their wide range of bioactive mediators, their prevalence across tissues, their roles in orchestrating wider immune responses, and importantly, their roles in allergy. Nonetheless, the focus on mast cells does not preclude involvement from other immune cells, nor other systems.

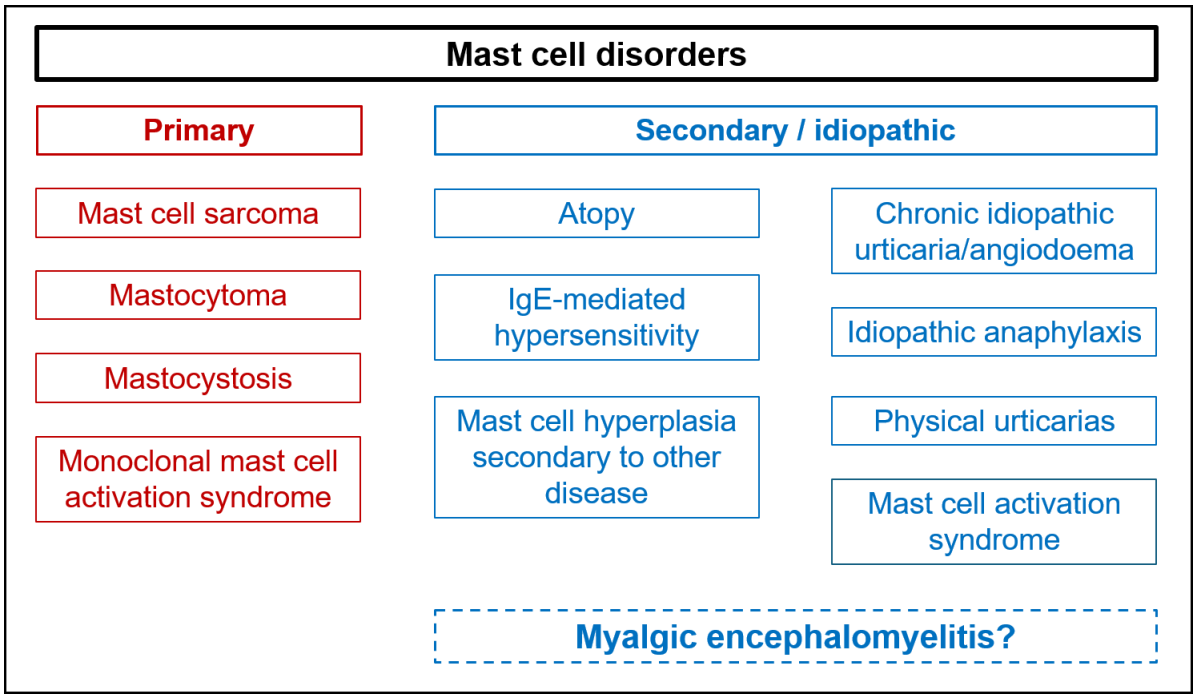


Figure 1. Example mast cell disorders. The hypothesis herein proposes that myalgic encephalomyelitis may be a mast cell activation disorder.

Abbreviations: IgE, immunoglobulin E. Adapted from Galvan-Morales et al. (2025), Khokhar & Akin (2020), and Jackson et al. (2021)

2. Immunometabolism & Mast Cells

Immunometabolism describes the close and bidirectional interaction between the immune system and metabolism (Hu et al., 2024). Mitochondria have an important role in regulating immune and inflammatory responses (Kumar et al., 2026; Lopez-Armada et al., 2013), including providing energy for immune cells to function. Acute systemic inflammation (e.g. from infection, traumatic injury) can induce a ~20 to > 100 % increase in basal metabolic rate (Kinney et al., 1970; Long et al., 1979; Plank et al., 1998; Xu et al., 2013), whilst chronic inflammation can increase basal energy expenditure by ~10 % (Piche et al., 2000; Utaka et al., 2005).

Depending on the immune cell, its state (e.g. resting versus activated), the (patho-)physiological milieu, and other factors, energy for immune function can come from various pathways, such as glycolysis, oxidative phosphorylation, and/or the tricarboxylic acid cycle (Krapic et al., 2021; Malla et al., 2025). When activated (e.g. from an inflammatory event), immune cells undergo metabolic reprogramming to facilitate their activity (Hu et al., 2024; Krapic et al., 2021).

In the context of infection, accompanying these inflammation-induced metabolic shifts, pathogens, such as bacteria, fungi, parasites, and viruses also reprogram host metabolism to promote their own survival (Krapic et al., 2021; Malla et al., 2025). For example, some viruses can shift host metabolism

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towards aerobic glycolysis, akin to the Warburg effect seen in many cancerous tumours (Sanzhez & Lagunoff, 2015); blocking these metabolic shifts is a promising antiviral treatment avenue (Pajak et al., 2022). Whilst these changes are most notable in the infected cells, metabolite levels in the surrounding tissues—and potentially systemically—can also be impacted (Krapic et al., 2021). In essence, during infection, there is a metabolic "battle" between the pathogen and host. In chronic inflammatory diseases, similar metabolic reprogramming to what is seen in acute infections have been observed, with some treatments aiming to exploit these metabolic pathways (Hu et al., 2024).

Mast cells primarily work in the innate immune system, acting as one of the first lines of defence against pathogens (Malla et al., 2025). Whilst they are significantly outnumbered compared to other immune cells, by mass they are estimated to make up the third largest proportion of immune cells in the body, totalling ~100 g (Sender et al., 2023). Mast cells are highly metabolically active immune cells, utilising different metabolic pathways to modulate immune responses (Phong et al., 2016). Adenosine trisphosphate (ATP) is required for mast cell degranulation (Erlich et al., 2014); an effect which is exploited by some experimental mast cell-inhibiting medications (Weatherly et al., 2015).

Mitochondrial fission is primarily mediated by dynamin-related protein 1 (Drp1); when activated Drp1 accumulates in the outer membrane of mitochondria resulting in fragmentation and reactive oxygen species (ROS) production (Chen et al., 2023). Inhibiting Drp1 and mitochondrial fission can mitigate allergic and inflammatory responses, implicating mitochondrial fragmentation and dynamics in allergies (Chen et al., 2023). Additionally, during degranulation, mast cell mitochondria translocate to the site of exocytosis; inhibiting this mitochondrial translocation also mitigates mast cell degranulation (Zhang et al., 2011).

Bioenergetic pathways within mast cells shift during activation, and vary between IgE- and non-IgE-mediated degranulation, though fatty acid oxidation appears to be dispensable (Frossi et al., 2025; Medoza et al., 2021a; Mendoza et al., 2021b; Phong et al., 2016). Resynthesis of granules after degranulation requires sufficient amino acid and lipid availability for protein and lipid synthesis. Although this process requires continuous metabolic reprogramming (Frossi et al., 2025; Iskarpatyoti et al., 2022), metabolic flexibility reduces after degranulation, with this effect being stronger after non-IgE-mediated activation (Mendoza et al., 2021). Speculatively, this degranulation-triggered mast cell dysmetabolism may be a factor in perpetuating MCADs.

Oxidative stress and high levels of glucose can induce mast cell degranulation, potentially reducing their threshold for degranulation, and altering mast cell mitochondrial function (Frossi et al., 2025; Kitahata et al., 2010). Mast cells express high levels of glucose transporter (GLUT) 1 and GLUT3. Inhibiting these transporters dampens both mast cell degranulation and the cytokine response to IgE receptor crosslinking—a response that is normally independent of glucose concentrations (Grujic et al., 2024). Pyruvate dehydrogenase (PDH), which increases in both active and passive muscles with exercise (Kiilerich et al., 2011; Putman et al., 1993; Putman et al., 1999), also has roles in mast cell activation; PDH inhibition decreases mast cell degranulation which correlates with reduced mitochondrial ATP production (Sharkia et al., 2017).

Whilst mitochondria help regulate immune responses, the immune system also impacts mitochondria and metabolism (discussed in more detail in Section 2.2). Chronic inflammation can lead to a metabolic switch from oxidative phosphorylation to aerobic glycolysis; this is both less energy efficient and causes unfavourable immunometabolic outcomes such increased ROS production and insulin resistance (Lacourt et al., 2018). Growing evidence suggests mitochondria-derived ROS have roles in T helper (Th) 2 polarisation and promotion of allergic responses (Chen et al., 2023).

Inflammation, including from mast cell activation, is implicated in cardiometabolic diseases such as diabetes and obesity, as well as with ageing (e.g. "inflammaging", cell senescence) and age-related diseases (e.g. Alzheimer's disease) (Kundu et al., 2020; Masini et al., 2021; Tian et al., 2025; Trim et al., 2018; Xu & Shi, 2012; Yao et al., 2025b; Zhang & Shi, 2012). Cell senescence can induce mast cell degranulation (Wicaksono et al., 2025), whilst senescent mast cells have been proposed to contribute to

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the inflammatory milieu accompanying dysmetabolic states (Cao et al., 2025a; Ibarra-Sanchez et al., 2025; Kleeblatt et al., 2024). To the authors knowledge, whether mast cell senescence is driving MCADs more widely has not been explored; such a hypothesis could explain why mast cells are inappropriately degranulating, as well as offering upstream treatments to reduce mast cell senescence.

Stimulation of mast cells can raise cellular ATP levels can by 40 % (Erlich et al., 2014). Upon activation, mast cells can also release mitochondrial components, including ATP and mitochondrial deoxyribonucleic acid (mtDNA), which can act as "autopathogens" (Zhang et al., 2012). This may create a self-perpetuating cycle of mast cell activation and mitochondrial dysfunction. Indeed, extracellular ATP has been implicated in allergic inflammation (Kouzaki et al., 2011).

2.1. Neuroimmune-Metabolism and Mast Cells

The nervous system, immune system, and metabolism interact to maintain homeostasis. Cytokines—several of which can be released by mast cells—have a bidirectional relationship with both metabolism and the nervous system (Szelenyi, 2001). Whilst cytokine production is partially under control of the nervous system, cytokines also influence neurological function (Szelenyi, 2001). The disequilibrium of this trifecta is implicated in many chronic diseases, with dysfunction in one system causing knock-on effects on the other systems (Deshpande et al., 2021). The brain alone accounts for ~20 % resting energy expenditure, despite being just ~2 % total body mass (Herculano-Houzel, 2011). For example, a single cortical neuron utilises ~4.7 billion ATP/second at rest (Zhu et al., 2012). Such a high energetic demand means any direct or indirect metabolic dysfunction has the potential to illicit a range of symptoms and downstream effects.

Neurological and psychological stimuli can alter energy expenditure and metabolism. For example, resting energy expenditure can increase by: ~60 % with acute non-traumatic pain (Holland-Fischer et al., 2009); ~20 % in those with episodic migraines (Martins et al., 2023); and ~10 % in those with high anxiety scores (Schmidt et al., 1996). Conversely, as the brain is constantly active, the energy cost of goal-directed cognition is only ~5 % greater than resting neural activity (Jamadar et al., 2025). Pain can also reduce insulin sensitivity (Greisen et al., 2001), whilst psychosocial stress can raise blood glucose concentrations (Hitze et al., 2010). Although current data are somewhat inconsistent (Melanson et al., 2018), light exposure also appears to be able to influence metabolism particularly in those with insulin resistance, such that (longer) dim (versus bright) light exposure results in improved metabolic parameters (e.g. lower postprandial glucose, increased insulin sensitivity) (Cheung et al., 2016; Harmsen et al., 2022; Versteeg et al., 2017) and lower sleep metabolic rate (Harmsen et al., 2022).

Glial cells are non-neuronal cells residing in the central nervous system. In some regions of the brain, glial cells significantly outnumber neurons (Herculano-Houzel, 2011). Glial cells have many functions in the nervous system; for example, astrocytes maintain extracellular potassium homeostasis, microglia have immune-related functions, and Schwann cells and oligodendrocytes insulate axons (Verderio & Matteoli, 2011). Bidirectional communication between glia and neurons can occur via ATP release (Verderio & Matteoli, 2011).

Microglia are the resident central nervous system immune cells and are increasingly implicated in neurological disorders, for example via increased oxidative stress (Bielanin & Sun, 2022; Hu et al., 2024). When exposed to inflammatory stimuli, microglia can undergo metabolic reprogramming including upregulating GLUT1; in turn this can impact mitochondrial morphology and function (Bielanin & Sun, 2022). Microglia have a bidirectional relationship with mast cells (Lakatos & Rosta, 2025), and stabilising brain mast cells can inhibit microglial activation (Tian et al., 2025).

Mast cells and nerves also have a bidirectional relationship, with dysfunction in one having potential to cause dysfunction in the other (Dines & Powell, 1997; Forsythe, 2014; Marshall & Waserman, 1995; Mittal et al., 2019; Theoharides et al., 2024; van der Kleij & Bienenstock, 2005). As described (Section 1.2), both neuropeptides and cytokines can cause non-IgE-mediated mast cell degranulation (Galvan-Morales et al., 2025; Yu et al., 2016). Evidence from models of cutaneous allergen

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exposure suggests that allergic responses are initially triggered by neurons (Perner et al., 2020), with sensitisation from repeat exposures being mediated by mitochondrial remodelling (Zhu et al., 2026). In diabetic neuropathy models, GLUT3-mediated glucose uptake results in neuronal mitochondrial impairment and oxidative stress, triggering mast cell degranulation and axonal damage, with mast cell deficiency preventing both demyelination and axon degeneration (Yao et al., 2025b). Additionally, inflammation (which can be caused or mediated by mast cells) can upregulate GLUT1 expression (Obaid et al., 2021), potentially exacerbating allergic responses, whilst GLUT3-dependent glucose uptake may promote the pathogenicity of Th17 cells, mediating inflammatory disease processes (Hochrein et al., 2022).

As GLUT1 and GLUT 3 are the predominant glucose transporters in both the central and peripheral nervous system (Jha & Morrison, 2018), both neurons and mast cells could be sensitive to the same stimuli. Further, microglia-induced GLUT1 upregulation may provide a stimulus for mast cell activation. This could create a cycle of mast cell-induced neuroinflammation mediated by microglia, contributing to mitochondrial and nervous system dysfunction.

Therefore, mast cell activation and the resultant inflammatory milieu has the potential to influence neurological function both directly (e.g. inflammatory damage) and indirectly (e.g. via impacting mitochondrial function). Furthermore, these interactions may create self-perpetuating cycles of dysfunction.

2.2. Sickness Metabolism & Behaviour

Under normal circumstances, despite constant internal and external changes (e.g. nutrient flux), the body maintains homeostasis via multiple coordinated mechanisms, such as the immune system, nervous system, and endocrine systems (Wensveen et al., 2024). Inflammatory events such as infections can disturb this homeostasis due to immune-directed inflammatory responses and changes to metabolism. This process is initially triggered by immune cell detection of pathogen- and danger-associated molecular patterns, but escalates to a systemic response if local responses are insufficient (Krapic et al., 2021; Wensveen et al., 2024). These compartment-specific responses mean immunometabolic changes can be localised where appropriate. This immune-mediated metabolic response provides a more optimal metabolic environment for immune system function (e.g. upregulation of GLUTs on immune cell surfaces) and pathogen elimination, and has been dubbed "sickness metabolism" (Krapic et al., 2021; Wensveen et al., 2024). However, if the immune response is excessive, it can cause harm (Krapic et al., 2021).

Resultantly, during acute illness, the central nervous and immune systems directly and indirectly (e.g. via metabolic shifts) cause humans and animals to exhibit sickness behaviour (Sullivan & Dulac, 2025), such as anorexia, fatigue, fever (or sometimes hypothermia), hypersomnia, and weakness (Krapic et al., 2021; Szelenyi & Szekely, 2004). These sickness behaviours are energetically costly (Ganeshan et al., 2019), and pose a survival risk from reduced nutrient intake, reduced activity and strength, and increased nutrient demands (e.g. from fever-induced protein degradation, nutrient efflux from white adipose tissue) (Krapic et al., 2021; Wensveen et al., 2024). Nevertheless, they are highly conserved, and interrupting these sickness behaviours (e.g. force feeding, sleep disturbance) can worsen outcomes, suggesting they yield an important evolutionary advantage worth the behavioural and energetic trade-off (Wensveen et al., 2024). Similar to sickness metabolism, sickness behaviour acts to optimise immune cell function and nutrient availability, whilst minimising resources for pathogen survival; such behaviours feedback and influence neuroimmune-metabolic function (Krapic et al., 2021) (Figure 2). The nature of infection determines the inflammatory response and in turn which sickness behaviours ensue (Krapic et al., 2021).

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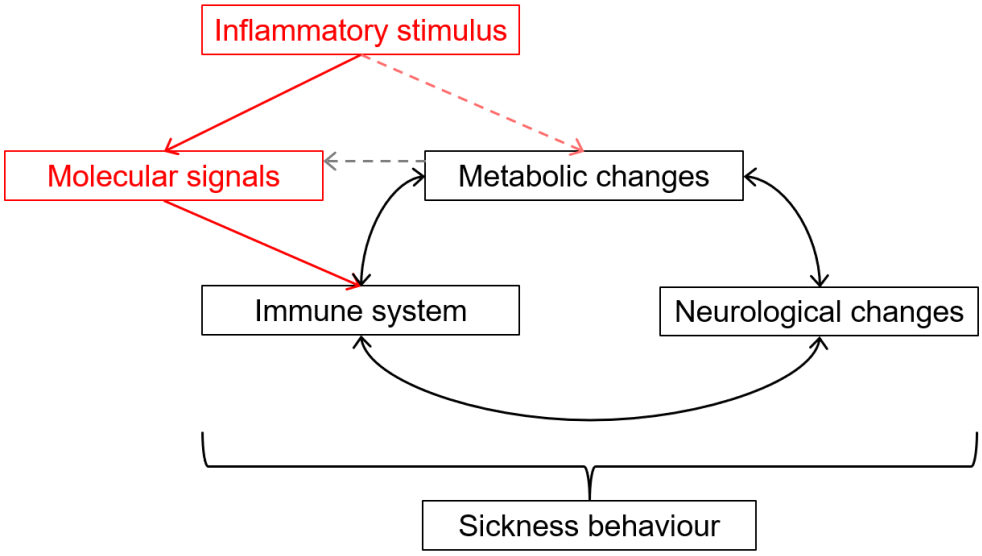


Figure 2. Pathway to sickness behaviour and resultant feedback loops. Black indicates the drivers of sickness behaviour. Lighter dashed arrows indicate the pathway is more dependent on the type of inflammatory stimulus.

With few exceptions, sickness behaviour is not typically caused by pathogens acting directly in the central nervous system; rather it is driven by innate immune cells, such as dendritic cells, macrophages, and mast cells which recognise both pathogens (via pathogen-associated molecular patterns) and tissue damage (via damage-associated molecular patterns) (Tizard, 2008). Consequently, cytokines are released which send signals to the brain, particularly the hypothalamus (which has a central role in homeostasis and sickness behaviour), directly (via the blood) or indirectly (via nerves) (Krapic et al., 2021; Tizard, 2008; Wensveen et al., 2024).

Inflammation activates peripheral neurons, with information being relayed centrally via the vagus nerve, resulting in homeostatic setpoint adjustments (Tizard, 2008); indeed, vagotomy can inhibit sickness behaviours (Rao et al., 2017). Interleukin- (IL) 1β, IL-6, high

mobility group box protein-1 (HMGB-1), and tumor necrosis factor-alpha (TNFα), among others, seem to be central intermediaries in this sickness response (Maier et al., 1998; Tizard, 2008). Several immune cells release these cytokines; notably, mast cells release IL-1β, IL-6, and TNFα (Aliyu et al., 2022; Solimando et al., 2022; Tizard, 2008). Inflammation can directly impact the hypothalamus due to its modified and more permeable blood-brain barrier (Haddad-Tovolli et al., 2017), notwithstanding that inflammation—including from mast cell activation and histamine—can further increase blood-brain barrier permeability (Dong et al., 2014; Kempuraj et al., 2020).

In addition, cytokines can be produced in the brain in response to infection and inflammation, primarily via microglia (Barrios-Gonzalez et al., 2024; Szelenyi, 2001; Tizard, 2008). Cytokines can bind to endothelial cells to promote cyclo-oxygenase (COX) 2 synthesis (Engstrom et al., 2012; Tizard, 2008). COX2 converts arachidonic acid to PGs. Both cytokines (Kelley et al., 2003) and PGs (Saper et al., 2012) are known to drive sickness behaviour, and both can be released and/or mediated by mast cells (as mast cells have a regulatory role in orchestrating wider immune responses, as well as their own direct immune effects; Abraham & St John, 2010).

Inflammation impacts metabolically active tissues, such as muscles, white adipose tissue, and the liver (Krapic et al., 2021). For example, transient systemic insulin resistance with hyperinsulinaemia is a common feature during acute infection and other inflammatory events (e.g. stress, surgery), typically yielding immunometabolic advantages (Krapic et al., 2021; Sestan et al., 2018; Wensveen et al., 2021). With milder infections, this insulin resistance does not tend to result in hyperglycaemia and may help supply the immune system with energy, but the hyperinsulinaemia can induce hypoglycaemia (which

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has antipathogenic effects) in more severe infections with higher cytokines (Wensveen et al., 2019; Wensveen et al., 2024).

Similarly, infections and inflammation can cause elevations in serum triglycerides (Khovidhunkit et al., 2004), trigger white adipose tissue browning (Ayari et al., 2020; Jing et al., 2022), and increase hepatic hepcidin production and amino acid uptake (Wensveen et al., 2024). Many of these metabolic changes have similarities to the metabolic syndrome (Wensveen et al., 2024), yet those with metabolic diseases have an impaired immune response to infection, including inhibited sickness behaviour (Krapic et al., 2021).

Inflammation can also impact hormone function, for example, via direct effects on the adrenal glands, hypothalamus, pancreas, and the pituitary, impacting hormones such as aldosterone, cortisol, epinephrine, insulin, and norepinephrine (Krapic et al., 2021; Opp et al., 1995; Quan et al., 1998; Tizard, 2008; Wensveen et al., 2024). Collectively, these can enhance dysglycaemia, for example, by inhibiting glycogen synthesis and promoting gluconeogenesis (Wensveen et al., 2024).

Overall, inflammation, the resultant dysmetabolism, and interactions with the nervous system, contribute to sickness behaviour.

2.3. Sickness Metabolism & Behaviour: Links to ME & Mast Cells

Several of the aforementioned interactions have links to ME (Table 2). ME is characterised as a neurological disease, and many patients with ME and/or mast cell disorders have dysautonomia or other nervous system disorders (e.g. small fibre neuropathy) (Ascue et al., 2023; Blitshteyn, 2023; Issa et al., 2025; Kohno et al., 2021; Novak et al., 2022; Ryabkova et al., 2024; Shibao et al., 2005; Stino et al., 2025; Yao et al., 2025a). The hypothalamus can get affected by inflammation. This has roles in autonomic processes, and therefore inflammation in ME may be contributing to dysautonomia. For example, TNFα is implicated in autonomic (e.g. gastric stasis) and cardiac (e.g. reduced cardiac output) dysfunction (Hermann & Rogers, 2007; Schumacher & Prasad, 2018), both prominent in ME. Therefore, neuroimmune-metabolism interactions could help explain the high prevalence of dysautonomia and neurological symptoms in ME.

As described above (Section 2.1), neurological, immune and metabolic function are tightly linked and could help explain multiple features of ME, including PEM. Firstly, the energy cost of chronic immune activation, including the resultant pain and any exposure to psychosocial stimuli such as light, is significant, and speculatively this may be even higher during PEM. The competing energy demands to sustain immune activation versus behavioural energy requirements may be implicated in ongoing fatigue in ME (Lacourt et al., 2018).

The features of sickness behaviour have similarities to ME, especially during PEM which many describe as "flu-like". Many ME patients have a long-term drop in their baseline from overexerting or "pushing through" PEM. Whilst this appears counter to sickness behaviour, acute—and speculatively, chronic—lower-grade inflammation can increase motivation for high reward tasks (Lacourt et al., 2018; Lasselin et al., 2017). In combination, this may cause patients to exceed their behavioural energy allocation when there is sufficient perceived reward (Lacourt et al., 2018). Further, in the context of infection, disrupting sickness behaviours results in worse outcomes. This may have overlaps with ME, such as sleep disruptions causing worsening. Most notably, however, is that if ME is a chronic sickness behaviour-like state, then exertion such as exercise may act to exacerbate this (Szelenyi & Szekely, 2004), offering a potential link to explain PEM.

Secondly, many ME patients appear to have some level of dysglycaemia and/or glycaemia-induced symptom worsening. Patients often report hypoglycaemia, or hypoglycaemia-like episodes whereby they have symptoms of hypoglycaemia with home monitoring equipment suggesting euglycaemia. As described above (Section 2.2), hyperinsulinaemia with euglycaemia is a common feature of inflammation, and a similar glucoregulatory profile has been seen in ME (Lidbury et al., 2017). Postural orthostatic tachycardia syndrome (POTS) is a common comorbidity in ME, in which the

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early signs of insulin resistance have also been found (Breier et al., 2022). The pattern of dysglycaemia in POTS is remarkably similar to that induced by inflammation, further supporting neuroimmune-metabolic interactions, particularly considering the role of cytokines in autonomic dysfunction (Hermann & Rogers, 2007; Schumacher & Prasad, 2018).

Moreover, ME patients commonly report sensitivity to sugar. Both glucose and GLUT3-mediated glucose uptake can cause mast cell degranulation, with the latter being implicated in mast cell-mediated neuronal mitochondrial impairment and nerve damage (Yao et al., 2025b). Chronic high exposure to insulin can induce a steatotic mast cell phenotype resulting in reduced histamine release but increased production of lipid mediators such as PGs (Aldan et al., 2019), which are implicated in sickness behaviour (Saper et al., 2012). Lipid mediators tend to be later-phase mediators due to de novo synthesis (Frossi et al., 2025), perhaps in line with the time trend of a postprandial hypoglycaemia-like phenomenon. In more severe inflammatory states, the hyperinsulinaemia can cause hypoglycaemia, which aligns with some experiences of ME patients regarding dysglycaemia. Therefore, sugar sensitivity in ME could be caused by a range of direct and/or indirect immune- (including mast cell-) mediated factors.

Thirdly, ME patients often have cardiometabolic abnormalities and overt or "borderline" nutrient deficiencies. ME patients exhibit a metabolic profile similar to the metabolic syndrome (Maloney et al., 2010); as above, this has a shared phenotype with inflammation-induced dysmetabolism. Inflammation is nutritionally costly, via multiple mechanisms. Immune cells undergo metabolic reprogramming upon activation, and glucose is often (though not always) the preferred substrate (Malla et al., 2025). This is likely part of the cause of the observed insulin resistance, which acts to reduce skeletal muscle glucose uptake, thereby prioritising glucose for immune function. Contrary to the above sugar sensitivity, some patients find sugar ingestion helpful; this may be providing fuel for their immune system and reducing metabolic demands. Speculatively, such patients may have better insulin sensitivity, which could offer insights into phenotypes.

Similarly, amino acid uptake increases with inflammation, potentially in line with the altered amino acid metabolism and preferential use of amino acids as an energy substrate found in some ME studies (Armstrong et al., 2012; Armstrong et al., 2015; Fluge et al., 2016; Hoel et al., 2021). This may account for some patients finding benefits from increased amino acid intake (Kraemer & Shoaib, 2021). Inflammation promotes proteolysis (Mitch & Goldberg, 1996; Reid & Li, 2001); there are several pathways for protein degradation, with the ubiquitin–proteasome system being energetically costly (Huang & Figueiredo-Pereira, 2010; Pang et al., 2023). The ubiquitin–proteasome system has roles in oxidative stress and inflammation (Huang & Figueiredo-Pereira, 2010), whilst inflammation can stimulate it (Melstrom et al., 2007; Mitch & Goldberg, 1996; Pang et al., 2023; Reid & Li, 2001; Tizard, 2008). This may lead to muscle atrophy some patients report, whilst adding an extra energy burden due to the proteolytic pathway being more heavily utilised.

Increased lipolysis from white adipose tissue releases free fatty acids and triglycerides into circulation, likely contributing to insulin resistance (Krapic et al., 2021). This might account for the altered fatty acid metabolism and preferential use of fatty acids as a substrate often found in ME studies (Hoel et al., 2021) The inflammation-induced white adipose tissue browning may contribute to the thermoregulatory difficulties patients report, such as fevers (as happens with infections) or low body temperatures if excess heat is lost—especially considering dysautonomia and small fibre neuropathy can result in hyperhidrosis and/or inappropriate/excessive vasodilation.

In ME and other chronic conditions, there is frequently a worsening of symptoms in around October, colloquially dubbed the "October slide". Interestingly, white adipose browning in response to seasonal cooling has been shown to be mediated by mast cell histamine release (Finlin et al., 2017). It may be that in chronic illnesses, mast cells are overresponsive to the lower temperatures (and likely other seasonal factors) in order to induce the small changes in adipose browning, resulting in symptom worsening. Similarly, a passive rise in body temperature of 0.7 °C can trigger mast cell degranulation

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in some people (Casale et al., 1986), highlighting the individuality of thresholds that may activate mast cells.

Further, some have likened ME to a dauer-, hibernation-, or torpor-like state (Naviaux et al., 2016). Torpor-like states have been used to describe children with non-IgE-mediated allergies (Crook, 1975; Speer, 1954). In some (albeit not all) animals, there appears to be an increase in mast cell count and activity during hibernation (Reiter & Davis, 1970) as well as in response to chronic cold exposure (LeBlanc & Rosenberg, 1957). Naviaux et al.'s (2016) hypothesis of a dauer-like state in ME predicts resistance to metabolic syndrome features, yet these features have been documented in ME (Lidbury et al., 2017; Maloney et al., 2010). Additionally, it has been proposed that the itaconate pathway remains active in ME, resulting in reduced ATP synthesis (Clarke et al., 2025), and what may be viewed as "hypometabolism".

Despite the seeming contradiction, these findings may be consilient with the hypothesis being presented. Sickness metabolism prioritises energy for immune function whilst altering wider host metabolism. Evidence of a hypermetabolic event with increased muscle protein degradation and altered metabolism has been found during PEM (McGregor et al., 2019), and metabolic changes indicative of immune activation have been found in ME (Maya et al., 2023); these findings are in line with sickness metabolism. Intestinal barrier deregulation was also shown during PEM (McGregor et al., 2019), which could plausibly—at least partially—be due to mast cell activity (Albert-Bayo et al., 2019). Itaconate is produced by myeloid cells during innate immune activation (e.g. inflammation), is involved in immune cell metabolic reprogramming, and has innate and adaptive immune-modulatory and antimicrobial properties (Aso et al., 2023; Lang & Siddique, 2024; Liu et al., 2025; O'Neill & Artyomov, 2019).

As such, whilst a dauer-like state and the itaconate shunt hypotheses may help demonstrate what is metabolically occurring, they do not offer an explanation as to why. The role of mast cells, elaborated on further below, can help explain this, as it is already established that some people have Th2-dominant immune systems, allergies, and mast cell activation. Chronic immune activation, primarily driven by mast cells, explains the hypermetabolic state with concomitant host hypometabolism potentially driven by increased itaconate.

In terms of micronutrients, the increased hepcidin production aids in iron sequestration and can result in the anaemia of inflammation (Weiss et al., 2018). During immune activation, one-carbon metabolism can be more heavily relied on (Ron-Harel et al., 2016). This may explain the increased B12, folate, and/or choline needs of some ME patients; indeed, one study found elevated cerebrospinal fluid homocysteine in ME, indicating potential central B12 deficiency (Regland et al., 1997). Itaconate exposure (e.g. from chronic innate immune activation) can also inactivate vitamin B12 (Shen et al., 2017), potentially predisposing to deficiency, including functional or compartmental (i.e. depending on where the immune activation is occurring) deficiency. Other micronutrients also get impacted by infection (Andrew, 2003), such as reduced vitamin C levels (Hemila, 2017) including in white blood cells (Hume & Weyers, 1973). Vitamin C may help improve/support metabolic syndrome markers (Ellulu et al., 2015), neurological function (Covarrubias-Pinto et al., 2015; Harrison & May, 2009; Kocot et al., 2017; May, 2012), and post-viral fatigue (Vollbracht & Kraft, 2021), alongside having broader mast cell stabilising and histamine degradation effects (Kakavas et al., 2021).

Notably, ("borderline") nutrient deficiencies have been described in the allergy and mast cell literature (Abadeh et al., 2023; Afrin et al., 2026; Kahn, 1927; Speer, 1954; Wu et al., 2015). There are a multitude of factors that may contribute to this, such as co-infections, comorbidities, extra nutrient requirements due to chronic inflammation, mast cell-related gastrointestinal problems (e.g. gastric stasis, malabsorption), restricted diets, stomach acid-inhibiting medication use, and/or the anaemia of inflammation (Abadeh et al., 2023; Roth-Walter et al., 2023). These factors may also apply to some ME patients.

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Along similar lines are the "borderline" or overt endocrine abnormalities often seen in ME (e.g. Miwa, 2017). As described (Section 2.2), inflammation directly and indirectly impacts hormone function. Endocrine abnormalities are also noted in the allergy and mast cell literature (Afrin et al., 2026; Kahn, 1927; Speer, 1954). Mast cells have a bidirectional relationship with many hormones, including synthesising some. As such mast cell dysfunction could at least partially explain endocrine abnormalities such as aldosterone (Lopez et al., 2020), corticotropin-releasing hormone (Bhuiyan et al., 2021), renin (Matsumoto et al., 2008; Silver et al., 2004), thyroid hormones (Landucci et al., 2019), and vasopressin (Matsumoto et al., 2008). For example, several chronic illnesses exhibit sick euthyroid syndrome, which is in part driven by cytokines such as IL-6 and TNFα (Mahashabde et al., 2024; McDermott, 2009; Warner & Becket, 2010) and may be associated with dysmetabolic conditions (Udenze et al., 2014).

Lastly, the vagus nerve is a key regulator of sickness behaviour. The model above therefore suggests ME may be a chronic state of parasympathetic overdrive; overcoming this requires significant sympathetic activity, resulting in hyperadrenergic symptoms. Vagus nerve stimulation is a common supportive therapy discussed in ME. In theory, such stimulation increases parasympathetic tone and reduces inflammation (Tracey, 2007), however, there is a paucity of research directly testing these effects. One pilot study in long COVID-related fatigue found no differences compared to sham stimulation (Gierthmuehlen et al., 2026), whilst another found improvement in some patients (Natelson et al., 2023). However, only 27 % of participants met ME criteria in one study (Natelson et al., 2023) and there was no indication how many patients met ME criteria in the other (Gierthmuehlen et al., 2026). Importantly, as pilot studies, the primary aim is to test feasibility rather than hypotheses. Indirect vagus nerve stimulation has shown promise in one small ME study (Rodriguez et al., 2023). Whilst little can be confidently concluded from these studies, the preliminary findings appear to match patient experience of mixed results (Eckey et al., 2025). These results and experiences may reflect patient-specific reactions to vagus nerve stimulation, i.e. triggering anti-inflammatory responses in some, whilst exacerbating neuroimmune-mediated sickness behaviours in others.

Table 2. Similarities between sickness metabolism and behavioural responses and ME.

Phenomenon	Links to myalgic encephalomyelitis
Adipose browning	"October slide" Thermodysregulation
Disrupted routine (e.g. sleep disturbance)	Can trigger PEM Precipitates worsening
Endocrine	Commonly ("borderline") abnormal
Energy & nutrient cost of immune activation	Common ("borderline") nutrient deficiencies Reduced energy & nutrient availability
Hypothalamic inflammation	Dysautonomic symptoms
Metabolic dysregulation	Dysglycaemia Dyslipidaemia Insulin resistance Sugar sensitivity or preference
Sickness behaviour	Often pronounced, especially during PEM
Vagus nerve-mediated sickness behaviour	Variability in response to vagus nerve stimulation

Abbreviations: PEM, post-exertional malaise

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If the above pathway is true—that ME is akin to a chronic sickness behaviour-like state—it begs the question of why the immune system is chronically activated in ME. Within this hypothesis, there are likely two main pathways to explain this, which are not necessarily mutually exclusive. Firstly, there may be an ongoing immune stimulus, such as a chronic infection or persistent pathogen remnants (e.g. Schreiner et al., 2020). This would perhaps suggest that patients have an inability to properly defend against and clear pathogens, which may be due an underlying genetic factor. Notably, Th2-dominated immune responses (which are implicated in allergy) can inhibit phagocytic cells (Romagnani, 2000), potentially providing a causal pathway between persistent pathogens (e.g. Aleebrahim-Dehkordi et al., 2021; Menezes et al., 2025) and allergy disorders like MCAS. Secondly, a genetic predisposition to (neuro-)immune overactivity (e.g. Genetics Delivery Team et al., 2025) may cause hypersensitivity to certain inflammatory stimuli. Both of these pathways have plausible links to allergy, mast cell activation, and speculatively, ME.

3. Hypothesis

3.1. Overview

In brief, the thesis below posits that ME is a specific MCAD variant, likened to an "allergy" to exertion causing chronic immune and mast cell activation. Resultantly, ME patients are in a chronic sickness metabolism- and behaviour-like state that is exacerbated with exertion. An "allergy" to exertion is not a new phenomenon, for example exercise-induced anaphylaxis (Barg et al., 2010), asthma (Ora et al., 2024), rhinitis (ten Hope & Yao, 2018), or urticaria (Sijapati et al., 2022); honeymoon rhinitis (Kocyigit et al., 2020; Massegur et al., 2025); and post-orgasmic illness syndrome (Pfaus & Yee, 2026). Notably, honeymoon rhinitis can occur in response to sexual ideation (i.e. cognitive exertion) without physical stimulation (Bhutta & Maxwell, 2008).

Along similar lines is takotsubo cardiomyopathy, sometimes referred to as "broken heart syndrome", or less commonly "happy heart syndrome" (Rhabneh et al., 2026). This form of cardiomyopathy is often precipitated by strong emotional events, though there are other triggers. The pathophysiology of takotsubo cardiomyopathy is not fully established, though a key mechanism is likely regarding catecholamines (Lyon et al., 2007). Increasingly it is being proposed that allergy, histamine, and mast cells may play a role in takotsubo cardiomyopathy (Taumann & Molderings, 2025; Wei et al., 2022; Zhou et al., 2011), including suggestions that it may be pathophysiologically linked to Kounis syndrome—a mast cell-mediated acute coronary event (Galanti et al., 2026; Koniari et al., 2017; Kounis & Filippatos, 2007; Kounis et al., 2016; Kounis et al., 2017; Munciullo et al., 2023; Yanagawa et al., 2009). If this link to mast cells is correct, takotsubo cardiomyopathy presents evidence that emotional exertion can trigger mast cell activation.

Just as anaphylaxis defines certain IgE-mediated food allergies, the characteristic symptom of PEM defines ME, with certain constitutional symptoms that are not entirely dissimilar to post-orgasmic illness syndrome. The examples above demonstrate that several forms of exertion that can be problematic in ME (cognitive, emotional, physical) are already known to trigger mast cell-mediated sequelae, providing proof-of-principle that this concept has validity even within the current limitations of medical knowledge.

3.2. Exposures Known to Trigger ME & Mast Cells

Multiple exposures are known to precipitate the onset of ME, including infections, injury/physical trauma, psychological/emotional stress/trauma, toxin exposure, and vaccines (Arron et al., 2024; Chu et al., 2019; Graves et al., 2024; Underhill, 2015). All these events, including psychological stress (Lagraauw et al., 2019; Theoharides, 2020), are inflammatory and can trigger mast cell activation.

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Childhood stress can also increase the risk of allergic diseases later in life (Oren & Martinez, 2020), whilst trauma can induce oxidative stress (Karanikas et al., 2021), perhaps priming mast cells for a triggering event in some people. Mast cells have also been implicated in neuropsychiatric diseases (Weinstock et al., 2023; Weinstock et al., 2025). This emphasises the organic nature and biological consequences of psychosocial factors that for some patients may precede and/or exacerbate their ME.

3.3. ME Trajectory & Mast Cells

Particularly in the milder stages of ME, symptoms can be highly fluctuant. This is one key argument against the deconditioning hypothesis which fails to explain why a (milder) patient is able to exert on one day, end up with PEM for several days after, and resume activity thereafter. This fluctuating pattern is in line with a mast cell disorder, explained by release of mast cell mediators (e.g. cytokine- and PG-induced sickness behaviour; Kelly et al., 2003; Saper et al., 2012) both at baseline and during/after exertion. As mast cells are reactive to change, various interacting stimuli (e.g. environmental, hormonal) can result in fluctuant or changing symptoms.

Depending on which mediators are released, where they are released, and how long they are released for, some damage may be longer lasting or permanent, for example if large fibre nerve damage occurs. This might contribute to longer-term baseline declines, regardless of PEM, and will be patient-specific, contributing to variances in disease trajectory.

Lastly, whilst rare, some ME patients report recovery, partial remission, or remission episodes. Operationalising recovery can be difficult as, for example, patients may have learnt to better adapt (Devendorf et al., 2020). If there is such a thing as "true" full recovery, this too would be in line with being a variant MCAD as allergies are also known to both appear and disappear (Anvari et al., 2019; De Martens et al., 2020); experientially, some MCAS patients report changes in their triggers over time too.

As such, mast cell activity can plausibly explain symptom chronicity, fluctuations, intensity, triggers, and remission or recovery.

3.4. General ME Symptoms & Mast Cells

As described (Section 2.3), ME has shared symptomatic features with sickness behaviour, which is primarily driven by the innate immune system, including mast cells. The link between allergy (including MCAS), fatigue, and ME has been discussed for decades (Borish et al., 1998; Carroll, 2026; Crook, 1975; Dechene, 1993; Kahn, 1927; Speer, 1954; Rohrhofer et al., 2025; Strauss et al., 1988; Theoharides et al., 2005), and similar cytokine profiles have been found in allergy and ME (Borish et al., 1998). Many of the more generalised symptoms of ME also overlap with the generalised symptoms of MCAS, such as cyclical worsening with the menstrual cycle, fevers, food/medication sensitivities, gastrointestinal complaints, migraines, nausea, paraesthesia, phonation difficulties, sensory sensitivities, swollen glands, and vestibular problems (Afrin et al., 2016a; Afrin et al., 2016b; Spantideas et al., 2019).

However, there are some more specific links to core ME symptoms and findings. A selection are reported below as well as in other areas of the manuscript to demonstrate potential links to mast cells; however, due to the expansive range of mast cell activities, it is not feasible to cover all possible symptoms.

3.4.1. Cerebral Hypoperfusion

Cerebral hypoperfusion has consistently been found in ME (Christopoulos et al., 2025). Similarly, it has been found in MCAS and hereditary alpha-tryptasaemia (HαT) (Novak et al., 2022), and a subset of mastocytosis patients (Boddaert et al., 2017; Ozdemir et al., 2010). The wider brain changes in mastocytosis are also suggestive of neuroinflammation and decreased serotonin (Boddaert et al., 2017).

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Neuroinflammation is a common finding in ME (Nakatomi et al., 2014), and low serotonin has been found in long COVID (Wong et al., 2023), though it is unclear how many of the participants met the diagnostic criteria for ME.

Amongst other relevant actions, mast cells and their mediators have a role in blood-brain barrier integrity (Dong et al., 2014; Kempuraj et al., 2020), neuroinflammation (Kempuraj et al., 2020), and vascular permeability (Inoue et al., 2025; Tizard, 2008). These and other factors could therefore contribute to impaired cerebrovascular regulation, with consequential cerebral hypoperfusion.

3.4.2. Cognitive Impairment

Cognitive impairment is well documented in the allergy and mast cell literature (Afrin et al., 2016b; Blasco-Fontecilla, 2023; Kahn, 1927; Marshall et al., 2000; Rosenberg et al., 2020), including mastocytosis (Boddaert et al., 2017; Moura et al., 2012; Sagues-Sese et al., 2023), and growing evidence suggests mast cells are implicated in neurocognitive diseases such as Alzheimer's disease (Huang et al., 2024; Lin et al., 2023). Inducing inflammation in healthy participants also impairs cognitive function and mood (Reichenberg et al., 2001).

As described (Section 3.4.2), the energy cost of goal-directed cognition is only ~5 % greater than resting neural activity (Jamadar et al., 2025). It could be argued that in a highly dysmetabolic state, even a small added energy expenditure could overwhelm energic demands. Alternatively (or even additionally), it could also be argued that an immune response better explains the profound and multisystemic effects cognitive exertion elicits in ME.

3.4.3. Neuromuscular Symptoms

Neuromuscular and related symptoms have been described in mastocytosis (Jendoubi et al., 2021) and MCAS (Afrin et al., 2016b). Inflammatory markers, including those that are released from mast cells, have been associated with weakness (Tuttle et al., 2020; Wensveen et al., 2024). Muscle pain is a common symptom in sickness behaviour, and several cytokines such as TNFα and HMGB-1 can induce allodynia (Das et al., 2016; Hermann et al., 2005).

Mast cells are prevalent in tissue, including muscle, where they are implicated in muscle healing (Duchesne et al., 2013); if in ME, mast cells are over-responsive, their involvement in post-exertional recovery may paradoxically cause more harm, perhaps contributing to PEM and the resultant failure to metabolically adapt (Glass et al., 2023). In animal models, mast cell degranulation is linked to neuromuscular disease (Trias et al., 2017), whilst in models of muscle injury, mast cells are implicated the necrosis phase (Helliwell et al., 1990). Higher levels of muscle necrosis have been found in ME (Booth et al., 2012), including after exertion (Appelman et al., 2024). Whilst not directly related to mast cells, HMGB-1 is passively released from necrotic cells, which can be induced by various stimuli, including inflammation and ROS (Chen et al., 2022). As described (Section 2.2), HMGB-1 is implicated in sickness behaviour suggesting ongoing immune-mediated necrosis—including triggered by exertion—could exacerbate symptoms.

3.4.4. Sleep Problems

Problems with sleep are documented in MCAS (Afrin et al., 2016b) and mastocytosis (Karakurt et al., 2026), as well as there being an association between Th2-dominance (implicated in allergies) and insomnia (Sakami et al., 2002). Mast cells and their mediators, including histamine and cytokines, are involved in circadian regulation, sleep, insomnia, and sickness-induced hypersomnia (Cui et al., 2026; Ertosun et al., 2019; Livieratos et al., 2025; Nishino et al., 2022; Opp et al., 1995; Thakkar, 2010; Tizard, 2008), and their effect on sleep and sleep architecture can be time- and cytokine level-dependent (Opp et al., 1991; Takahashi et al., 1995). IL-10 has a role in wakefulness, and Borish et al. (1998) found both

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allergy and ME patients had ~20 times lower peripheral blood mononuclear cell IL-10 levels than healthy controls, potentially contributing to the fatigue seen in both conditions.

Cytokine and mast cell activity have a circadian rhythm, with diurnal changes in symptom occurrence and severity common in allergies (Floyd & Krueger, 1997; Fonken et al., 2014; Nakao & Nakamura, 2022; Pan et al., 2002; Zielinski & Gibbons, 2022). Circadian dysregulation of peripheral blood mononuclear cells has been found in ME (Sweetman et al., 2019). Speculatively, if central and peripheral clocks are desynchronised (as has been proposed in ME; McCarthy, 2022), mast cell and related activity could have differential central and peripheral (or even compartmental) zeniths and nadirs. This may result in specific symptoms having their own rhythm, such as diurnally inappropriate somnolence or sleep (Tizard, 2008).

For example, ME patients experience unrefreshing sleep, with colloquial descriptions of a "concussion", "hangover", and/or "poisoned" feeling upon waking, which some report reduces during the day. This may be related to specific central circadian rhythms enhancing neuroinflammation earlier in the day. Such rhythms may help explain why patients often report certain times of the day to be better or worse symptomatically, including patterns for individual symptoms, with between-patient differences due to individual clock entrainment/desynchronisation. As mast cell activation is neuroinflammatory, and neuroinflammation is implicated in fatigue (Livieratos et al., 2025), it may be that histamine (a wakeful molecule) and other mediators are implicated in both fatigue as well as insomnia, resulting in the common description of "tired but wired".

3.4.5. Pathophysiological Findings

As described above (Table 1), several pathophysiological findings have been shown in ME. However, despite consistent evidence of various abnormalities, there is significant heterogeneity in findings (e.g. Bested & Marshall, 2015; Huth et al., 2020; Maksoud et al., 2023; Taccori et al., 2023). Such heterogeneity could be explained if an MCAD is driving the disease, as many of the abnormalities could plausibly be due to the known actions of mast cells and their mediators (see Table 3 for examples), notwithstanding knock-on endocrine, metabolic, neurological, and other effects.

Whilst the above links do not prove ME is an MCAD, they do provide evidence that core symptoms of ME are common in other mast cell disorders, and can be explained by the known actions of mast cells and their mediators. As such, it is biologically plausible that mast cells are implicated in these features of ME. It is also possible that the plethora of pathophysiological findings is explained by aberrant mast cell activity and subsequent downstream effects and interactions. Nonetheless, it is appreciated that such symptoms and pathophysiological findings could be caused by a multitude of other factors.

Table 3. Example findings in myalgic encephalomyelitis and their potential relation to the known bioactivities of mast cells and their mediators.

Finding	Relation to mast cells	References
Autoantibodies	Antigen presentation	Galli et al., 2005 Jensen et al., 2023 Lotfi-Emran et al., 2018 Rivellese et al., 2018
Cerebral hypoperfusion	Blood-brain-barrier integrity Cerebrospinal fluid dynamics Cerebrovascular regulation Vascular permeability	Inoue et al., 2025 Kempuraj et al., 2020 Lindsberg et al., 2010 Mamuladze et al., 2025

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Coagulopathy	Pro-inflammatory & clotting mediators	Choi et al., 1995 Guilarte et al., 2017 Wang et al., 2015
Connective tissue & structural abnormalities	Pro-inflammatory & protease mediators that could affect connective tissue integrity	Dai & Korthuid, 2011 Derakhshani et al., 2026
Dysbiosis	Interactions with the microbiome Regulation of gut permeability	Albert-Bayo et al., 2019 Bilgic et al., 2026 Krausfeldt et al., 2026 Mezour et al., 2018
Endocrine abnormalities	Interactions with endocrine systems	Bhuiyan et al., 2021 Bugakski et al., 1995 Landucci et al., 2019 Theoharides, 1996
(Neuro-)Inflammation	Pro-inflammatory mediators	Hendriksen et al., 2017 Kempuraj et al., 2020 Moon et al., 2014

3.5. Post-Exertional Malaise (PEM) & Mast Cells

Any proposal attempting to explain ME must be able to account for PEM as the hallmark feature of ME. PEM can be objectively observed with metabolic abnormalities on the second day of a 2-day CPET (Keller et al., 2024; Lim et al., 2020). As previously mentioned (Section 1.1), several plausible hypotheses have been proposed to explain PEM (e.g. Germain et al., 2022; Jin et al., 2026; Kell & Pretorius, 2022; Shuka et al., 2015; Renz-Polster et al., 2022; Wirth & Scheibenbogen, 2020), and it is likely these factors interact, including with mast cell activity.

However, to the authors best knowledge, whether PEM is primarily a mast cell-mediated reaction has not fully been explored. Considering the vast array of mast cell mediator bioactivities (Moon et al., 2014; Moulderings & Afrin, 2023), such a hypothesis links closely with other proposals regarding PEM, such as autoimmune, coagulopathic, (neuro-)inflammatory, neurological, and vascular abnormalities.

3.5.1. Exertion-Related Mast Cell Activity

Many forms of exertion are known to directly induce mast cell activation. Under non-pathological conditions, mediators such as histamine are released (albeit not necessarily entirely from mast cells) in response to various stimuli, such as chewing (Sakata et al., 1997; Sakata et al., 2003), exercise (Luttrell & Halliwill, 2017), memory formation (Nautiyal et al., 2012), and menstruation (Jensen et al., 2010; Jeziorska et al., 1995). Mast cells have several other roles, including in cognitive function (Blasco-Fontecilla, 2023; Lin et al., 2023), digestion (Bilgic et al., 2026), social behaviour (Mandal & Forsythe, 2026; Provensi et al., 2018), and vascular function (Kunder et al., 2011).

In mastocytosis, the mast cell response to exercise is exaggerated (Kulinski et al., 2018). It is possible that similar occurs in ME, even with minor exertion, such as chewing. Even without oral mast cell stimulation from food-derived allergens, if chewing-induced histamine release (Sakata et al., 1997; Sakata et al., 2003) is excessive in ME, it could (partially) explaining why eating can be a difficult or impossible task for some ME patients, notwithstanding other effects such as TNFα-mediated gastric stasis (Hermann & Rogers, 2007). As described (Section 3.4.3) mast cells are implicated in muscle repair (Duchesne et al., 2013) and injury-induced necrosis (Helliwell et al., 1990). Over-reactivity of mast cells to even microtears from minor activities may therefore be contributing to PEM.

Similarly, the role of mast cells in menstruation (Jensen et al., 2010; Jeziorska et al., 1995) and reproductive biology (Galvan-Morales et al., 2025) could explain why many ME patients have symptom

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fluctuations across the menstrual cycle, as well as the higher prevalence of ME in women (Thomas et al., 2026). Indeed, symptom worsening in relation to the menstruation cycle is found in other mast cell disorders (Graziottin & Serafini, 2016; Jensen-Jarolim & Untersmayr, 2008), including differences in skin prick allergy testing sensitivity (Kirmaz et al., 2004).

Exercise also induces inflammation and immune activation, such as the release of IL-6 (Docherty et al., 2022) and enhanced antigen presentation capacity (Song et al., 2026). Whilst improved immune surveillance may be beneficial under otherwise healthy circumstances, this may act as a further immune activator in ME, especially considering the role of mast cells in antigen presentation. Other metabolic processes, such as exercise-induced PDH activity, may also act to stimulate mast cells (Sharkia et al., 2017).

Beyond general requirements for maintaining homeostasis, there are specific metabolism-related requirements for certain functions. For example, extracellular ATP increases cochlear blood flow (Shi, 2011). If there is excessive extracellular ATP (e.g. from mast cell activation), this may cause heightened responses to noise or pulsatile tinnitus, particularly in combination with the unique energy burden of neurons (Misgelf & Schwarz, 2017), which would be required for sensory processing. Collectively this may exacerbate energy demands and promote further mast cell activation.

As previously described (Section 3.1), a mast cell response to cognitive (Bhutta & Maxwell, 2008), emotional (Taumann & Molderings, 2025; Wei et al., 2022; Zhou et al., 2011), and physical (Barg et al., 2010; Kocyigit et al., 2020; Massegur et al., 2025; Ora et al., 2024; Pfaus & Yee, 2026) triggers is not outwith the realm of known mast cell reactivities. Thus, it seems plausible that a range of stimuli (e.g. cognitive, emotional, environmental, physical, sensory, social) could be implicated in PEM if inappropriate mast cell activation is the primary cause.

3.5.2. PEM Symptoms

General ME symptoms, which can get exacerbated by PEM, could be (partially) mast cell-mediated, as described above (Section 2.3). Furthermore, PEM often involves constitutional ("flu-like") symptoms, resembling sickness behaviour, which is mediated by neuroimmune-metabolic interactions. Notably, cytokines (Kelley et al., 2003) and PGs (Saper et al., 2012) are heavily implicated in sickness behaviour, both of which can be released and/or mediated by mast cells.

Within the above, different patients will have varying thresholds for certain stimuli, both within- and between-patient. Mitochondria have context- and cell-dependent phenotypes, functions, and densities (Monzel et al., 2023), and there is a hierarchy of ATP-consuming reactions, where less essential cell functions can get deprioritised (Buttgereit & Brand, 1995), in keeping with sickness metabolism and behaviour. As such, it may be that ME patients have specific sensitivities to certain metabolic demands, in turn activating mast cells under certain conditions.

Accordingly, symptoms will depend on the location of mast cell activation, which mediator(s) is being released, and which receptors they attach to, as well as various other stimuli that might impact mast cell activity and energetic demands (e.g. barometric pressure, light exposure) and any downstream effects. Having different thresholds for allergens is common in allergic disorders (e.g. Morisset et al., 2003); individual differences in symptoms and PEM triggers in ME could therefore depend on the (dys-)function of, and interactions between, these various factors. Similarly, exertion-induced sickness behaviour could explain the multisystemic symptom profile of PEM, extending beyond the site of exertion.

3.5.3. PEM Time Trends

The time trend of PEM induction fits a mast cell-mediated reaction. There are broadly two trends with PEM, which are not necessarily mutually exclusive: Many patients initially experience worsening during or shortly after exertion, followed by a delayed (typically ~24-48 h) phase response. Both of these responses are known to occur in mast cell-mediated reactions.

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Most typically, IgE-mediated reactions occur rapidly (within minutes to ~1 hour), whilst non-IgE-mediated reactions tend to occur after some delay (typically within hours to several days (Calvani et al., 2020; Meyer et al., 2025). However, these are not guaranteed response times. For example, in alpha-gal syndrome (an IgE-mediated reaction to galactose-alpha-1,3-galactose) reactions can occur up to 8 hours post-exposure (Macdougall et al., 2022), whilst non-IgE reactions can occur within minutes, as in the case of non-IgE-mediated anaphylaxis (Cianferoni, 2021). Indeed, the mast cell response to exercise occurs within minutes (Kulinski et al., 2018). As such, it is plausible that a mast cell reaction to exertion accounts for the often bimodal time course PEM. Again, between-patient differences can plausibly be explained by individual factors pertaining to mitochondrial and mast cell sensitivities, such as which mediators are being released.

3.5.4. Proposed Pathway

Based on the above, the following pathway is proposed to explain the onset of ME, the chronicity of symptoms, and PEM (Figure 3). Initially, immunological and inflammatory exposures, such as a viral infection, trigger an immune response, including mast cell activation (Abraham & St John, 2010; Piliponsky et al., 2019; Rathore & St John, 2020). Depending on the exposure, mitochondrial function may be directly impacted (e.g. viral infection; Girdhar et al., 2021; Singh et al., 2020), or indirectly impacted via neuroimmune signals (e.g. injury).

The resultant mitochondrial changes trigger excessive ROS production, inducing oxidative stress. Whilst this can serve a helpful function, such as damaging pathogens in the case of infection (Kayesh et al., 2025), ROS also stimulates mast cell activation (Piotin et al., 2024). The resultant oxidative stress and inflammation causes ongoing mast cell activation and mitochondrial dysfunction, with mast cell release of mitochondrial components (Zhang et al., 2012) further contributing to the inflammatory milieu. Additionally, several cytokines, such as TNFα, stimulate cells to increase their own synthesis, or are stimulated by other cytokines, such as HMGB-1-stimulated IL-6 and TNFα (Lotze & Tracey, 2005; Tizard, 2008). Collectively, these cycles self-perpetuate, and are perhaps exaggerated, in those with a genetic predisposition to neuroimmune dysfunction (e.g. Genetics Delivery Team et al., 2025). As this model proposes Th2-dominance, there may be a failure of pathogen clearance via inhibition of phagocytosis causing or contributing to ongoing mast cell activation and dysmetabolism.

Oxidative stress has been found in long COVID and ME (Armstrong et al., 2015; Shankar et al., 2025), as well as mastocytosis (Gangemi et al., 2015), potentially acting as an ongoing mast cell trigger as well as perpetuating mitochondrial dysfunction (Guo et al., 2013). Additionally, circulating mtDNA has been found in ME, further increasing after exercise (Tsilioni et al., 2022), opening the possibility this was from mast cell activation. Speculatively, chronic mast cell activation may deplete certain protective mediators, such as antioxidants (Fukuishi et al., 2001), as seen with mast cell-derived dopamine (Ronnerg et al., 2012).

Following the initiation of disease, any form of exertion that exceeds a patients' neuroimmune-metabolic and mast cell tolerance will trigger mast cell activation, both directly (e.g. exercise-induced histamine release, ROS production) or indirectly (e.g. increased energy requirements, stimulation of the nervous system). These factors feed into the main cycle of baseline mast cell activation and sickness metabolism and behaviour, triggering PEM via additional ROS production and mast cell degranulation. The resultant inflammation perpetuates mitochondrial dysfunction, increases oxidative stress and mast cell release of mitochondrial components, and reduces the availability of energy in favour of mast cell degranulation and immune activation (Lacourt et al., 2018). Repeat exertion may be conceptually somewhat akin (though mechanistically distinct) to protein sensitisation in more classic allergy disorders, enhancing the immune response. This could account for the functional decline that is characteristic of PEM. Collectively, this results in the various symptoms of PEM, lasting until inhibition of mast cell degranulation and subsequent downstream effects occurs.

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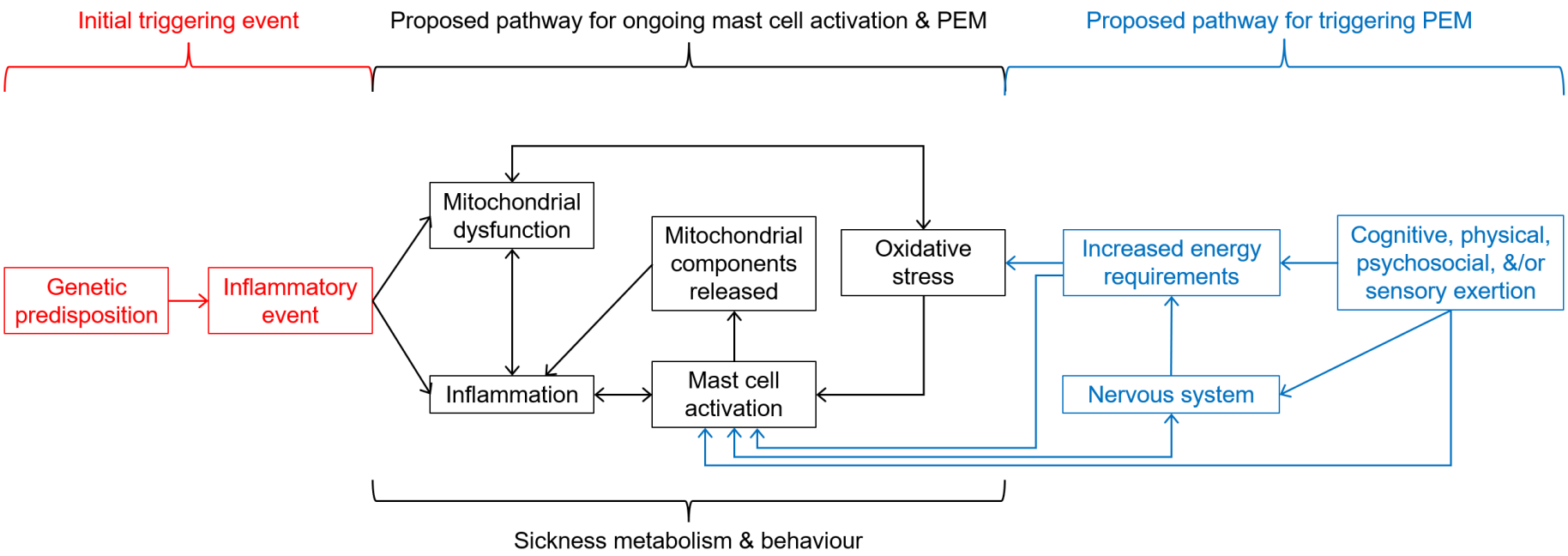


Figure 3. Simplified hypothesis linking mitochondrial function and mast cell activation. Abbreviations: PEM, post-exertional malaise.

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3.6. Treatments

The only known effective management strategy for ME is energy management or pacing (Carruthers et al., 2011; NICE, 2021). If PEM is a mast cell reaction to exertion, then pacing may be akin to trigger avoidance, which is the cornerstone treatment of allergies and MCADs (Molderings et al., 2016). As such, under the proposed paradigm, pacing in ME is equivalent to allergen/trigger avoidance in other allergies/MCADs.

Beyond pacing, there is insufficient evidence for generalisable effective treatments. As such, many patients try various treatments in the hope they bring improvement. Many ME patients and clinicians use mast cell targeted treatments such as antihistamines and mast cell stabilisers (Boneva et al., 2009; Christoforou et al., 2026; Grach et al., 2026; Habermann-Horstmeier, 2026; Rohrhofer et al., 2025; Rowe et al., 2017), as it is well-known that more obvious allergy/mast cell dysfunction is at least part of the clinical picture for a subgroup of patients.

As mentioned (Section 2), mast cell senescence has potential roles in both inflammation and dysmetabolism. Notably, both luteolin and quercetin are common MCAS treatments due to their mast cells stabilising properties, and both nutraceuticals have senolytic effects (Gokbilen et al., 2022; Lelarge et al., 2024; Zhu et al., 2021; Zumerle et al., 2024). In addition, H1 receptor antagonists are being researched in certain diseases due to their potential senolytic properties (Huang et al., 2025; Liu et al., 2024). Whether and how these senolytic effects impact mast cells and their function—particularly in the context of MCADs, and in this case, ME—is, nevertheless, unclear.

Other treatments that are commonly used in, or have promise for, ME may have direct or indirect effects on mast cells (see Table 4 for some examples) (Grach et al., 2026; Habermann-Horstmeier, 2026; Kraemer & Shoaib, 2021; Toogood et al., 2021). For example, many have antioxidant effects and, as above, ROS can trigger mast cell activation. Of course, the multi-faceted mechanisms and pleiotropic effects of many treatments preclude definitive claims that any improvements are (solely) due to mast cell-mediated effects.

Many ME patients find they need, or benefit from, high doses of certain vitamins or minerals; as discussed above (Section 2.3), this may in part be due to ongoing inflammation. Micronutrients may provide benefits for an MCAD via multiple mechanisms, such as anti-inflammatory effects, antioxidant effects, immune-modulation, metabolic support, rectifying deficiencies, and even direct mast cell targeted actions (Anogeianaki et al., 2010; Depeint et al., 2006; Gonzalez et al., 1979; Gonzalez et al., 2023; Kakavas et al., 2021; Kazama et al., 2022; Kabelitz, 2026; Trincianti et al., 2025).

In addition, micronutrients may have a role in reducing the impact of chronic mast cell activation. For example, vitamin B12 is fairly frequently used (sometimes in high doses) in ME patients (Grach et al., 2026). Certain mast cell mediators can cause nerve injury (Gupta & Harvima, 2018; Zuo et al., 2003), which may require more vitamin B12 to maintain proper function (Ramadhani et al., 2024). As described (Section 2.3), elevated cerebrospinal fluid homocysteine has been found in ME (Regland et al., 1997). Unfortunately, this has received little attention but recent work in other conditions suggests there may be autoantibodies targeting transcobalamin receptors causing central B12 deficiency (Pluvinage et al., 2024; Pluvinage et al., 2026).

As mast cells can act as antigen presenting cells and have close proximity to nerves, it is possible they have a role in such an autoimmune process if this occurs in ME.

Notably, homocysteine promotes oxidative stress and mast cell activation (Ermakova et al., 2024; Fujimi et al., 2009; Singh et al., 2008). In homocysteine-induced cardiac injury, mast cells may play a dual damaging and protective role (Joseph et al., 2005). Therefore, ME patients may be particularly sensitive to even minor fluctuations in homocysteine if elevations are triggering mast cell activation (even if such activation is counterregulatory and trying to mitigate damage), especially if levels are higher in the central nervous system.

Similarly, many dietary approaches have been discussed in ME and long COVID (though not all long COVID patients will have ME), such as alkaline diets, anti-inflammatory diets, fasting, and low sugar/carbohydrate or ketogenic diets (e.g. Bunker et al., 2025; Craig, 2015), but little research has

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been done on this topic. The underlying claims of many of these diets are frequently surrounding mitochondrial support. Nevertheless, anecdotally, patients have mixed effects. This would fit with an MCAD phenotype, whereby certain diets inadvertently eliminate triggering foods/ingredients, and such triggers vary between patients. Diets that do not contain a patients' own mast cell triggering foods may have direct effect on mast cells as well; for example, low sugar diets may be helpful to reduce chronic glucose exposure that can stimulate mast cells (Frossi et al., 2025; Yao et al., 2025b), whilst ketones can directly inhibit mast cell degranulation (Nakamura et al., 2014; Sato et al., 2023). However, as high fat diets can also stimulate mast cells (Frossi et al., 20205) and may promote mast cell steatosis, individual mast cell sensitivities (e.g. mast cell metabolic flexibility) will result in heterogeneous responses despite the overall anti-inflammatory effect of ketones.

Table 4. Examples of common or promising treatments for myalgic encephalomyelitis and some potential mechanisms relating to mast cells.

Treatment	Mechanism	References
Berberine / Metformin	Anti-inflammatory Antioxidant Antiplatelet Antiviral Mast cell stabilising Metabolic function	Chowdhury et al., 2025 Fineberg et al., 2025 Fu et al., 2019 Li et al., 2014 Malla et al., 2025 Xin et al., 2016
Coenzyme Q10	Anti-allergy Anti-inflammatory Antioxidant Antithrombotic Metabolic function	Chang et al., 2022 Du et al., 2021 Perez-Sanchez et al., 2017 Sakat et al., 2018
Creatine	ATP production Dendritic cell regulation Reduced post-exercise muscle damage/inflammation	Godlewska et al., 2024 Kang et al., 2026 Santos et al., 2004
Fibrinolytics	Anti-biofilm Anti-inflammatory Antioxidant Antiplatelet Antithrombotic	Granito et al., 2024 Grixti et al., 2024 Jadhav et al., 2020 Katsipis et al., 2025
Low dose naltrexone	Anti-inflammatory Immune modulation Metabolic function	Aalto et al., 2025 Leiber & Parker, 2025 Li et al., 2018 Younger et al., 2014
Melatonin	Anti-inflammatory Antioxidant Antithrombotic Antiviral Mast cell stabilising Metabolic function	Alomari et al., 2024 Cho et al., 2021 Leon et al., 2004 Reiter et al., 2016 Wirtz et al., 2008 Ye et al., 2024
Omega 3	Anti-inflammatory Antioxidant Mast cell stabilising Metabolic function	Arabi et al., 2024 Gutierrez et al., 2019 Hayden & Deane, 2026 Heshmati et al., 2019 Kraemer & Shoaib, 2021

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4. Contextualising ME as an MCAD

It is important to ensure the above framework has parity with other disease classifications in order to improve validity. Just as the allergic tension-fatigue syndrome had been likened to "cerebral" allergy (Speer, 1954), ME may be likened to "metabolic" or "exertional" allergy, i.e. the processes surrounding energy production are a mast cell trigger resulting in a dysmetabolic state. As energy production is constant, trigger avoidance is impossible, but the burden of energy production can be minimised (i.e. pacing). Just as more classic allergies have patient-specific thresholds (Morisset et al., 2003), so would exertional allergy.

Different clinical presentations can occur from the same fundamental pathophysiology. For example, dysautonomia can present as baroreflex failure. inappropriate sinus tachycardia, orthostatic hypotension, POTS, pure autonomic failure, or vasovagal syncope, among others. In other words, autonomic nervous system dysfunction can lead to a range of different classified symptom presentations.

Within the same disease, symptoms can vary considerably, for example, not all POTS patients experience syncope, and further subtyping can occur. For example, POTS can be further categorised according to the blood pressure response to standing: hyperadrenergic (elevated orthostatic blood pressure) or POTS with hypotension (decline in orthostatic blood pressure precipitated by elevated heart rate) (Lau et al., 2026). Patients can also have multiple forms of the same disease; in the case of dysautonomia, patients may have comorbid inappropriate sinus tachycardia and POTS (Lau et al., 2026).

Similarly, MCADs have subtypes, such as anaphylaxis, MCAS, or physical urticarias, among others (Akin, 2014). Within these, further subtyping can occur, such as IgE-mediated versus non-IgE-mediated anaphylaxis. Within MCAS, symptom presentations vary considerably (e.g. predominant gastrointestinal symptoms versus pain), and there are arguably sub-classifications based on common symptoms clusters, such as psychiatric presentations (Weinstock et al., 2023; Weinstock et al., 2025) or the allergic tension-fatigue syndrome (Carroll, 2026; Crook, 1975; Speer, 1954). These differences can impact treatment decisions (e.g. eliminating foods and stabilising gut mast cells versus centrally acting antihistamines/mast cell stabilisers).

Why mast cells activate in such a way to create different clinical presentations is unknown, as is true for many other diseases (e.g. different forms of dysautonomia; Lau et al., 2026). The known differences in mitochondrial (Monzel et al., 2023) and mast cell (Lichterman & Reddy, 2021; Tauber et al., 2023) characteristics in various tissues could explain why symptoms fit a certain general phenotype (fatigue, cognitive impairment, PEM, sleep issues), whilst also having unique baseline symptoms, thresholds, triggers, etc from tissue- and mediator-specific mast cell degranulation that is sensitive to certain energy demands, perhaps due to a specific "ME" mast cell phenotype.

Genetic predispositions may help explain individual susceptibilities. For example, > 90 % of the global population are estimated to be positive for Epstein-Barr virus (EBV) (Smatti et al., 2018), which is a leading cause of MS (Bjornevik et al., 2023). Yet most people who are exposed to EBV do not get MS. Similarly with allergies, it is not known why some people are allergic to (e.g.) peanuts rather than shellfish or have no allergies, with early life exposure only explaining some of this variance (Logan et al., 2022). Similarly, certain (epi-)genetic mast cell characteristics (and likely other interacting factors, such as environmental exposures and sex) may predispose someone to getting ME versus another MCAD.

There may be unique mast cell mutations that define different MCAD subtypes. Little research has been done on this area (Afrin et al., 2026), opening the possibility that certain variants in mast cell-regulating genes could predispose to an ME phenotype. Understanding this might also proffer information regarding personalised treatments (Afrin et al., 2026). Indeed, one preliminary study found different mast cell phenotypes, with greater mast cell activation, in moderate and severe ME patients compared to healthy controls (Nguyen et al., 2017). Whether this is genetically driven, or unique to ME, is currently unclear.

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A similar concept has been proposed to explain the role of dysfunctional mast cells in Alzheimer's disease versus type 2 diabetes; whilst both diseases involve insulin resistance and mast cells, they present very differently perhaps in part due to different mast cell phenotype and polarisation states (Caslin et al., 2025). Abnormal lipid metabolism in microglia has also been shown in Alzheimer's, resulting in lipid accumulation and impaired microglial function and neuron communication (Hu et al., 2024). As described (Section 2.1), mast cells and microglia interact, and lipid accumulation in mast cells can alter their mediator pool (Aldan et al., 2019). Collectively, this suggests unique mast cell phenotypes, perhaps mediated by mast cell metabolism, could result in specific clinical patterns.

Lastly, there is the possibility that the defining feature of ME—PEM—could be caused by more than one upstream cause. In such a scenario, an MCAD could be one cause of PEM, whilst other causes could apply to other subgroups of ME patients. This is akin to other diseases—for example, POTS can be caused by dysautonomia (Goldstein, 2024), MCAS (Gonzalez-Alvarezet al., 2024; Shibao et al., 2005; Yao et al., 2025a), pelvic venous disorders (Davis et al., 2026; Spencer et al., 2026), severe deconditioning such as microgravity exposure (Jordan et al., 2022), or vitamin B12 deficiency (Mittal et al., 2021)—as well as symptoms—for example, fatigue can be caused by anaemia, demyelination, hyperglycaemia, neuroinflammation, etc.

As such, characterising ME as an MCAD seems concordant with other disease classifications.

5. Evidence Against the Hypothesis

The hypothesis presented posits that ME is an MCAD variant, with PEM essentially being an "allergic response" to exertional stress, perhaps akin to Hoobler's (1916) concept of "suppressed anaphylaxis". Whilst mast cells have been the focus, other immune cells such as basophils and platelets likely have nontrivial roles within this pathomechanism, alongside wider neuroimmune-metabolic interactions, and downstream effects. Although inevitably the above proposal cannot fully explain every aspect of ME, such an evidentiary standard does not apply to other diseases (i.e. we do not understand the biomechanisms underpinning all possible symptoms and individual variations of all known diseases). However, it does offer a perspective that could explain the core features of ME as well as the heterogeneity in biomedical research findings.

Nevertheless, it is important to consider counterarguments and contradictory evidence, as well as methods to falsify the hypothesis. Within this, it should be recognised that the full scope of allergy and mast cell pathology, and how that interacts with metabolism and the nervous system, is not known. As such, some current anomalies and unknowns may be due to absence of evidence rather than evidence of absence.

5.1. Symptoms

Many ME patients do not fit the current diagnostic criteria of an MCAD, such as MCAS, whilst those with both ME and MCAS discuss the diseases as separate (albeit interacting) diseases, with awareness of what is an ME versus an MCAS trigger or reaction. This would seem to suggest the two diseases can be distinguished and are therefore separate entities.

If the hypothesis above is correct, it could be argued that the symptoms of ME are MCAD symptoms. Under this paradigm, in those with comorbid MCAS, symptoms could be distinguishable between ME and MCAS because these are separate diseases under the same umbrella; whilst the underlying pathophysiology (i.e. inappropriate mast cell activation) is the same, the symptomatic consequences of that dysfunction are separate, per the aforementioned dysautonomia example (see Section 4).

As such, it is not implausible to consider that an MCAD could present differently even within the same person, perhaps related to specific mast cell and/or mitochondrial phenotypes. In support of this is that the core features of ME (fatigue, cognitive dysfunction, sleep problems, and flu-like symptoms) can be attributable to inappropriate mast cell activation.

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5.2. Pathophysiology

The proposed pathophysiology (summarised in Figure 3) is currently unproven, and as with any hypothesis requires testing. If it does hold merit, it is likely a simplified model. Metabolism is extremely complex and it may be that other metabolic processes and/or byproducts are causing or contributing to ongoing mast cell activity. Equally, some aspects of metabolism appear counter to the proposed hypothesis. For example, uric acid has both antioxidant and pro-inflammatory roles (Ghaemi-Oskouie & Shi, 2011) making it difficult to reconcile with the above model.

Similarly, 4-octyl itaconate (a synthetic itaconate derivative used to investigate the effects of endogenous itaconate) can inhibit mast cell degranulation (Hu et al., 2020; Liu et al., 2025). This may be evidence against the proposed hypothesis, especially considering animal and epidemiological evidence suggests that low itaconate is implicated in allergies (Albers et al., 2025; Li et al., 2024b). Alternatively, as itaconate is responsive to inflammation, elevated itaconate may provide supporting evidence that chronic mast cell activation is perpetuating dysmetabolism. This is supported by elevated levels of itaconate after allergen exposure in a model of allergic airway inflammation (Xie et al., 2023). This is arguably a more valid model (though still limited to acute allergic responses, rather than chronic inflammation). However, this is not supported in humans, where lower levels of itaconate are seen after allergen exposure (Albers et al., 2025), likely contributing to the inflammatory response. Itaconate (derivatives) are also a promising target for treatment of allergies (Gu et al., 2026). Again, these findings are difficult to reconcile with the proposal. It should be acknowledged that to the authors knowledge the itaconate shunt hypothesis has not been proven in ME, though elevated levels do seem plausible under the sickness metabolism paradigm.

Additionally, elevated lactate is a common finding in ME (Ghali et al., 2019), yet lactate has mast cell inhibiting effects (Abebayehu et al., 2019; Caslin et al., 2019; Frossi et al., 2025; Zhang et al., 2026). This would seem counter to proposed hypothesis, but could equally be viewed as a counterregulatory response to mitigate further inflammatory damage as lactate is often high in inflamed tissues (Zhang et al., 2026). Elevated lactate may even be directly released from mast cells, co-secreted with histamine (Yoshizaki et al., 1993), or a downstream effect of mast cell activation.

For example, PGD2 is released from mast cells and gets converted to PGF2α (Arima & Fukuda, 2011; Wendelborn et al., 1988). PGF2α can induce vasoconstriction (Fara et al., 1979; Katsuyama & Morgan, 1993) at levels similar to norepinephrine (Heaslip & Sickels, 1989). The resultant decreased perfusion and relative ischaemia could result in elevated lactate, potentially followed by reperfusion with ROS production; a pathway that is well recognised in dysmenorrhea (Bendetto, 1989; Dawood, 2006; Guimaraes & Povoa, 2020; Jin et al., 2025; Pelevin et al., 2026) and has similarities to other hypotheses attempting to explain PEM (Kell & Pretorius, 2022).

Increased mast cell counts and activity are commonly found in angiogenic, dysmetabolic, inflammatory tissues with high lactate, such as in endometriosis (Makoui et al., 2025; Mo et al., 2026) and cancer tumours (Frossi et al., 2025; Lichterman & Reddy, 2021). Notably, endometriosis is overrepresented in ME (Compton et al., 2025), possibly due to shared vascular mediators and mechanisms (Wirth & Lohn, 2023). Mast cells are able to survive hypoxic environments where they release ROS, and pro-angiogenic and pro-inflammatory mediators (Frossi et al., 2025). As described (Section 2), sickness metabolism has some similarities to the Warburg effect, in fitting with some of the metabolic findings in ME including elevated lactate.

Indeed, mast cells may have a primary role in hypoxia-induced inflammation. In rats, Steiner et al. (2003) found that: Mast cell degranulation in normoxic conditions produced similar microvascular effects to hypoxia; hypoxia could induce mast cell degranulation; mast cell stabilisation inhibited hypoxia-induced ROS, vascular permeability, and leukocyte adhesion/migration; and lipoic acid and nitric oxide could inhibit hypoxia-induced mast cell degranulation. Hypoxia-inducible factor 1-alpha (HIF-1α) may play a role in ME (Morris et al., 2019) and is also implicated in the metabolic changes in immune cells seen in sickness metabolism (Hu et al., 2024).

Several other mast cell mediators also have vasoactive effects (the direction of which—constriction versus dilation—can sometimes depend on factors such as receptor activation, or

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concentration), for example, leukotrienes (Ford-Hutchinson & Letts, 1986), renin (Reid et al., 2007), and serotonin (Bjoro & Stray-Pedersen, 1986), as well as interactions between mast cells and other vasoactive compounds (Shepherd et al., 1996). Further, many mediators are implicated in thrombosis and endothelial inflammation (Cao et al., 2025b; Kashiwagi et al., 2019; Ponomaryov et al., 2017; Seidel et al., 2021; Taumann & Molderings, 2025), which may act to exacerbate ischaemia and promote lactate accumulation.

These mechanisms may help explain why antithrombotic agents without obvious mast cell-related mechanisms can be helpful in ME (e.g. Carroll et al., 2026; Wright et al., 2025), i.e. by targeting downstream impacts of mast cell activity, resultantly improving perfusion and metabolism which were perpetuating mast cell activation. Such diverse bioactivities of mast cell mediators can also explain some disparities in research findings, such as those finding (e.g. Berg et al., 1999) or failing to find (e.g. Kennedy et al., 2006) hypercoagulable states in ME. This may also explain seemingly contradictory symptoms, such as "sticky blood" causing difficulties with phlebotomy (seeming hypercoagulability) whilst experiencing easy bruising (e.g. potentially from excessive mast cell heparin release, perhaps as an attempted counterregulatory response to hypercoagulation).

Equally, the model above (summarised in Figure 3) may be incorrect regarding the role of metabolism, ROS, and/or the proposed pathways to ongoing mast cell activation, but the general idea that an MCAD underlies ME (or a subgroup of ME patients) may still be correct for reasons we are yet to elucidate. Outcome studies (discussed in Section 5.5) may provide evidence of this, even if the full causal pathway remains unclear.

Lastly, whilst inappropriate mast cell activation can plausibly explain many features of ME, such as inflammatory, vascular, and potentially metabolic findings, such a hypothesis does not preclude further downstream effects. In other words, an MCAD might explain the primary trigger, but especially with ongoing disease progression, direct and indirect/downstream effects of mast cell activity will likely cause further interacting systems of dysfunction, as found in other diseases (e.g. MS; Table 1).

Nonetheless, the complexity of immunometabolic interactions does complicate, and potentially contradict, the some of the core ideas underlying the proposal.

5.3. Treatments & Treatment Response

A subgroup of ME patients do not report partial, let alone significant, improvement with mast cell targeted medications, such as antihistamines or mast cell stabilisers, and some find these cause worsening (Eckey et al., 2025). This could suggest that an MCAD is not implicated in ME (notwithstanding comorbid MCAS), or that (as above; Section 4) there are subgroups whereby only some patients' ME is an MCAD. If the hypothesis above is correct and generalisable, there are other possibilities that could explain this non-response.

Medication sensitivity is a well-known phenomenon in both ME and MCAS, and it is possible that the unique mast cell characteristics of ME enhances these sensitivities. Whilst a significant number of MCAS patients do find at least some relief with basic medications like antihistamines, ketotifen, and oral sodium cromolyn, MCAS in itself is a difficult disease to manage and not all patients yield (significant) improvements. This is, in part, due to the reactogenic nature of MCAS, whereby certain active ingredients, excipients, or interactions between medications/supplements/other factors can cause a reaction. Beyond the somewhat unique challenges with MCAS, non-response to medication is not a unique phenomenon—there are, for example, heterogeneous responses to several medications such as antihypertensives (Gueyffier et al., 2015), biologics (Mobayed et al., 2025), chemotherapy (Hagerty et al., 2024), and GLP-1 receptor agonists (Su et al., 2026).

In addition, current treatments predominate around histamine receptor antagonism, leukotriene receptor antagonism, and broad mast cell stabilisation. Notwithstanding their pleiotropic effects, specific receptor antagonism is limited in scope considering the vast range of mast cell mediators and receptor subtypes (Molderings & Afrin, 2023), whilst broad mast cell stabilisation may have

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deleterious effects by blocking the release of unproblematic or helpful (e.g. antioxidant) mediators. In addition, systemic administration may not provide sufficient pharmacological effects to specific local areas with high mast cell activation (Masini et al., 1985). Other treatments, such as omalizumab, have much more limited availability.

Therefore, one reason some ME patients do not find any improvement with current mast cell targeted therapies may be due to the limited access to certain medications, or the generally limited pool of mechanisms current medications target. If ME is its own MCAD variant, then treatments may require specific tailoring. For example, in a case series of n = 5 ME patients with MCAS, continuous high dose oral sodium cromolyn was found to be beneficial (Christoforou et al., 2026). Whilst definitive conclusions cannot be made from this case series, it perhaps highlights that ME patients may require different timing and higher doses to more typical MCAS-only patients.

Further, if ME is specifically a dysmetabolic state of immune cells, then targeting immunometabolic pathways may be more fruitful, as is increasingly recognised in other (neuro-)immunometabolic conditions (Hu et al., 2024). For example, inhibiting mast cell mitochondrial translocation (Zhang et al., 2011), fission (Chen et al., 2023), or uncoupling (Weatherly et al., 2015), or more directly targeting mast cell senescence may be novel routes to inhibit mast cell degranulation via altering their metabolism. Better mast cell characterisation, including how this differs between MCADs, could help target treatments.

An alternative angle regarding critique of this hypothesis is that some promising ME medications may activate mast cells. As discussed above (Sections 2 and 3.5.1), PDH inhibition decreases mast cell activation (Sharkia et al., 2017). Preliminary research using sodium dichloroacetate plus a nutraceutical has yielded favourable results (Comhaire, 2018b), albeit with seeming responders and non-responders (Comhaire, 2018b). However, sodium dichloroacetate is a PDH kinase inhibitor resulting in sustained PDH activity (Matsuhashi et al., 2015). It is possible that non-responders had a greater mast cell phenotype in line with the proposed hypothesis, or that such results are evidence against the above hypothesis. Further adding to this critique is that upregulated PDH kinase activity and subsequent impaired PDH activity has been seen in ME (Fluge et al., 2016).

Another example is pyridostigmine which has been found to improve handgrip strength (Schlomer et al., 2025) and metabolic parameters on a 2-day CPET (Joseph et al., 2022). Pyridostigmine is an acetylcholinesterase inhibitor and can modulate sympathetic tone (Lamotte et al., 2023). Cholinergic histamine release and mast cell degranulation has long been recognised (Forsythe, 2014; Masini et al., 1985), and there are cautions for acetylcholinesterase inhibitor use in those with asthma (Hansen & Schlunssen, 2020). Furthermore, research in mice suggests pyridostigmine may increase muscle oxidative injury in response to exercise (Jagannathan et al., 2001). Both honeymoon rhinitis and post-orgasmic illness have at least partly been attributed to parasympathetic activity (Bhutta & Maxwell, 2008; Kocyigit et al., 2020), including acetylcholine-induced mast cell degranulation (Kocyigit et al., 2020). As with the aforementioned vagus nerve stimulation (Section 2.3), pyridostigmine may enhance sickness responses and improvements from it may therefore be evidence against the above hypothesis.

Conversely, improved parasympathetic activity from pyridostigmine may act as an anti-inflammatory (Forsythe, 2014; Tracey, 2007). Indeed, in a rat model of methotrexate-induced liver injury, pyridostigmine had protective effects against oxidative stress (Ulusan et al., 2025), whilst anti-inflammatory effects were found in a mouse model of lipopolysaccharide-induced acute respiratory distress syndrome (Choque et al., 2021). These seemingly contradictory findings are likely due to several interacting factors, such as expression of acetylcholine receptor subtypes and synergistic neurotransmitter interactions (Forsythe, 2014). Therefore, in the case of pyridostigmine, the mast cell effects of acetylcholine could be patient-dependent, and may explain heterogeneity in responses to the medication.

Lastly, some patients improve with factors seemingly unrelated to mast cells, such as thoracic outlet syndrome surgery (Christoforou et al., 2025). This may support there being multiple aetiologies underpinning ME, or there may be neuroimmune-metabolic links that are not fully understood yet,

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i.e. treating these pathologies directly or indirectly removes a trigger to ongoing mast cell activity. In the case of a structural compression, haemostasis, inflammation, and nerve irritation can occur, which may activate mast cells.

5.4. Reverse Causality

The hypothesis above broadly proposes that inflammation-induced alterations to mitochondrial function triggers ongoing mast cell activation (Figure 3), i.e. the metabolic dysfunction is primarily a byproduct of mast cell (and wider immune) activation. However, it could equally be argued that the mast cell activation is a byproduct of dysmetabolism (Figure 4). As outlined above (Section 2), mitochondria have a key role in regulating immune and inflammatory responses (Kumar et al., 2026; Lopez-Armada et al., 2013), including providing ATP for mast cell activation (Erlich et al., 2014). Many ME symptoms are similar to known metabolic diseases, such as the cardiac issues, exercise intolerance, hypoglycaemia, and weakness found in glycogen storage diseases (Koh, 2025; Massese et al., 2022).

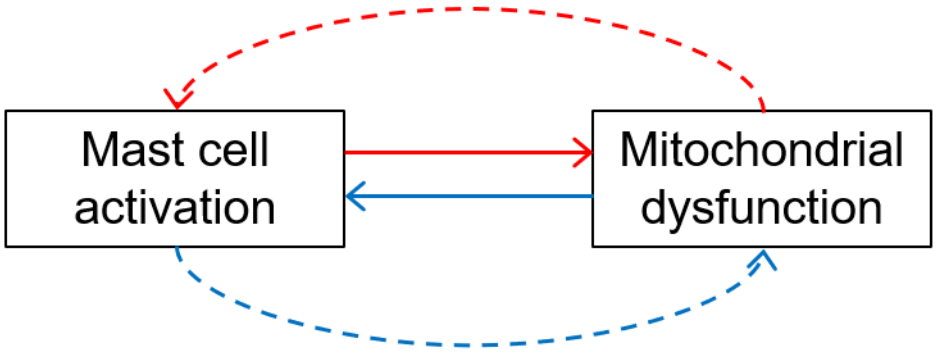


Figure 4. The proposed model places mast cell activation as the core pathological feature driving dysmetabolism (red lines); however, it may be that dysmetabolism is driving (comorbid) mast cell activation (blue lines). Dashed lines represent feedback loops.

Metabolic diseases can be acquired or inherited (Garus-Pakowska, 2023). Acquired metabolic diseases are relatively common (e.g. type 2 diabetes) and are likely a result of genetic and environmental interactions. Inherited metabolic diseases are usually present at the time of birth (though there are cases of somatic mutations) (Ferreira et al., 2021); whilst they typically present in early life, they can sometimes present in adulthood (Massese et al., 2022). For inherited metabolic diseases, specific diets (where applicable) are reliably helpful, which has thus far not been seen in ME. Failure to treat inherited metabolic diseases can quickly become fatal.

Whilst it cannot be ruled out that ME is a unique acquired metabolic disease yet to be properly characterised, the symptomatology of ME does not appear to fit currently known metabolic diseases (notwithstanding secondary metabolic syndrome features), but several features are in line with mast cell pathology. As described (Section 2.2), those with the metabolic syndrome tend to have an impaired (rather than exaggerated) sickness response (Krapic et al., 2021), whereas ME appears to be akin to a chronic (often fluctuant) sickness behaviour. Additionally, the metabolic abnormalities found in ME thus far have been heterogeneous (Huth et al., 2020; Maksoud et al., 2023; Taccori et al., 2023), suggesting there may be an upstream cause resulting in a variety of abnormalities. This could plausibly be explained by individual differences in mast cell reactivities and mediator release.

Another argument against the above hypothesis is that mast cell activation is also implicated in many other diseases that are not primarily classed as MCADs, such as Alzheimer's disease (Lin et al., 2023), cancer (Lichterman & Reddy, 2021), endometriosis (Makoui et al., 2025), MS (Conti & Kempuraj, 2016), obesity (Tian et al., 2025), Parkinson's disease (Hong et al., 2018), type 2 diabetes

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(Conti et al., 2018), and a subgroup of psychiatric disease patients (Weinstock et al., 2023; Weinstock et al., 2025). This may suggest that mast cell dysfunction is a contributory or downstream effect of other pathology, rather than a primary causal factor. Interestingly, these diseases all have a metabolic link, suggesting metabolic and mast cell dysfunction are closely related.

In the context of ME however, there appears to be several other lines of evidence that support it being an MCAD (Table 5), including: That symptoms are common in other mast cell disorders and can plausibly be explained by the known bioactivities of mast cell mediators; the various exposures known to trigger ME; the high comorbidity between allergies/MCAS and ME; the time trend of responses; the known hyperreactivity/hypersensitivity of ME patients to a range of stimuli; individual differences in PEM triggers and symptoms severity; and the primary management tool being trigger avoidance (pacing). Nevertheless, these observations certainly do not prove ME is an MCAD but rather provide a framework in which an MCAD could plausibly explain the disease.

Lastly, there is the possibility that it is specifically mitochondrial dysfunction within mast cells that is causing ME, considering the energetic demand and metabolic flexibility mast cells require for proper function (Mendoza et al., 2021b). Whether this would be classed as a primary mast cell versus metabolic dysfunction is a matter of perspective.

Table 5. Qualitative assessment regarding the strength of supporting evidence for the plausibility of mast cell involvement for various phenomenon in myalgic encephalomyelitis.

Phenomenon	Plausibility of mast cell involvement
Key:	**Low**
Causal exposures	Known to activate MCs
Coinfections	Th2-dominance prevents proper pathogen clearance
Core symptoms	Common in MCADs Fits known MC bioactivities
Exertion-based triggers	Other known exertion-based MC triggers
Individual variances	Common in MCADs
Metabolic involvement	Bidirectional relationship with immune system
Neurological involvement	Bidirectional relationship with MCs
Pacing	Exposure avoidance is the first-line treatment for MCADs
Parity with other disease classifications	Similar to other disease classifications
Pathophysiological findings	Heterogeneity may be due to underlying MC activity Mast cell abnormalities have been found Similar cytokine profiles to allergy
Post-exertional malaise time trend	Fits with other MC-mediated reactions
Recovery and remission episodes	Fits with other MCADs
Symptom trajectory	Fits with other MCADs
Post-exertional malaise	Currently plausible but theoretical
Potential treatments	Several MOA preclude direct MC-targeted claims

Abbreviations: MCADs, mast cell activation disorders; MCs, mast cells; MOA, mechanisms of action; Th2, T helper 2

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5.5. Testing the Hypothesis

Accurate diagnosis of MCADs can be difficult, especially if ME is a unique phenotype. However, there are some ways to provide at least preliminary evidence to support or refute the above hypothesis.

As PEM is the characteristic feature of ME, any treatment must be able to improve this response. The most reliable test for PEM currently is a 2-day CPET (Lim et al., 2020). As some ME patients are responders to currently available MCAS medications, 2-day CPETs with versus without MCAD medications could be done. If there are improvements in the second day response with MCAD-targeting medications, such testing would provide proof-of-principle evidence that mast cell dysfunction can cause or contribute to PEM, and at least a subgroup of ME is (fully or partially) driven by an MCAD.

Such a protocol is not without ethical challenges; not only are there (potentially long-term) risks with a 2-day CPET designed to trigger PEM, but also risks with asking patients to withdraw from helpful medications. Beyond acute symptom provocation, medication withdrawal may cause lasting deterioration if mast cell mediators cause irreparable damage or mast cells become harder to control after medication abstention. These risks would need to be fully explained to patients, and expert-led medical care should be provided throughout the testing protocol and for as long as needed afterwards. Such care should include living support (e.g. home adaptions, financial support if income is reduced), especially if there is a long-term or permanent decline in function.

Another approach could be to survey ME patients with known severe allergies (anaphylaxis) to see if they have (by chance) had to use their epinephrine autoinjectors during PEM, and if so, what effect it had. The rationale for this is that epinephrine is a first-line treatment for severe allergies; if PEM is a sort of allergic response to exertion, then epinephrine may be helpful. Directly testing this approach would carry substantial risks and is not advised without much stronger preliminary work indicating suspected benefit. As this would trigger a sympathetic response, there is a risk that PEM symptoms would worsen, alongside general risks of administering epinephrine off-label, which may be particularly detrimental in ME patients with hyperadrenergic phenotypes (such as comorbid hyperadrenergic POTS). If epinephrine did yield improvements in severe allergy sufferers with ME, it may be more difficult to specifically attribute any benefit to mast cells due to the wide-ranging effects epinephrine has. As such, this approach seems less targeted but may offer preliminary insights into PEM physiology.

Other approaches such as intravenous antihistamines or steroids could also be tried, though experientially it is not uncommon for ME patients to respond negatively to steroids and there may be added risks such as enhanced endogenous cortisol suppression (Jerjes et al., 2007). Steroids are also less targeted so causal inference regarding the role of mast cells would be difficult.

A broader test of whether altered immunometabolism could result in PEM is to induce an inflammatory response in healthy people (e.g. with a vaccine) and conduct 2-day CPETs before, during, and after the inflammatory response (i.e. during recovery). Whilst this would not prove mast cells specifically are the primary modulator of PEM, it would provide proof-of-concept that inflammation-induced metabolic shifts (i.e. sickness metabolism) underlie PEM.

More mechanistically, as discussed above (Section 4), characterising mast cell phenotypes, such as metabolic differences in ME compared to other MCADs and diseases with known mast cell activity, could offer insights regarding the spectra of clinical presentations and possibly novel treatment routes. Similarly, measuring markers of mast cell activation across various tissue types in baseline and PEM states may offer clues as to whether mast cell activation could be implicated in symptoms. Such tests would likely have some challenges, for example, there may be mast cell phenotypic or activation differences in specific tissues, some of which (e.g. the brain) would be infeasible to study.

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6. Conclusion

The hypothesis described above proposes that (a subgroup of) ME may be a unique and distinct MCAD variant, with various forms of exertion triggering mast cell degranulation. Ongoing inflammation disrupts metabolism, increases oxidative stress, and perpetuates further inflammatory signalling, akin to sickness metabolism. Resultantly, patients experience a chronic sickness behaviour response, which worsens with exertion, causes harm, and prevents stress adaptation.

This could be driven by an underlying genetic predisposition towards Th2-dominance which can impair pathogen clearance. Unique mast cell phenotypes may underpin ME, such as steatosis or reduced metabolic flexibility. If this is the case, current treatments may not effectively target the pathological mast cell metabolism driving ongoing activation.

Such an idea has the potential to explain several features of ME, including PEM, wider symptoms, individual variances, and why pacing is important. Even if the crux of the idea is correct, the details are likely incomplete and require refining. Whilst several lines of evidence suggest the plausibility of this proposal, there are several gaps in the idea; as such, it is premature to apply the idea to ME patients until it has been validated.

Abbreviations

ATP, adenosine trisphosphate; CPET, cardiopulmonary exercise test; COX, cyclo-oxygenase; Drp1, dynamin-related protein 1; EBV, Epstein Barr Virus; GLUT, glucose transporter; H, histamine; HαT, hereditary alpha-tryptasaemia; HIF-1α, hypoxia-inducible factor 1-alpha; HMGB-1, high mobility group box protein-1; Ig, immunoglobulin; IL, interleukin; MCAD, mast cell activation disorder; MCAS, mast cell activation syndrome; ME, myalgic encephalomyelitis; MS, multiple sclerosis; mtDNA, mitochondrial deoxyribonucleic acid; PDH, pyruvate dehydrogenase; PEM, post-exertional malaise; PENE, post-exertional neuroimmune exhaustion; PESE, post-exertional symptom exacerbation; PG, prostaglandin; POTS, postural orthostatic tachycardia syndrome; ROS, reactive oxygen species; Th, T helper; TNFα, tumor necrosis factor-alpha

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Use of artificial intelligence: None.

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