


A compromised paraventricular nucleus within a dysfunctional hypothalamus: A novel neuroinflammatory paradigm for ME/CFS

International Journal of
Immunopathology and Pharmacology
Volume 32: 1–8
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2058738418812342
journals.sagepub.com/home/iji


Angus Mackay and Warren P Tate

Abstract

A neuroinflammatory paradigm is presented to help explain the pathophysiology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The hypothalamic paraventricular nucleus (PVN) is responsible for absorbing and processing multiple, incoming and convergent 'stress' signals, and if this cluster of neurons were affected (by neuroinflammation), the ongoing hypersensitivity of ME/CFS patients to a wide range of 'stressors' could be explained. Neuroinflammation that was chronic and fluctuating, as 'inflammatory-marker' studies support, could reflect a dynamic change in the hypothalamic PVN's threshold for managing incoming 'stress' signals. This may not only be a mechanism underpinning the characteristic feature of ME/CFS, post-exertional malaise, and its associated debilitating relapses, but could also be responsible for mediating the long-term perpetuation of the disease. Triggers (sustained physiological 'stressors') of ME/CFS, such as a particular viral infection, toxin exposure, or a traumatic event, could also target the hypothalamic PVN, a potentially vulnerable site in the brains of ME/CFS susceptible people, and disruption of its complex neural circuitry could account for the onset of ME/CFS. In common with the different 'endogenous factors' identified in the early 'neuroinflammatory' stages of the 'neurodegenerative' diseases, an as yet, unidentified factor within the brains and central nervous system (CNS) of ME/CFS patients might induce both an initial and then sustained 'neuroinflammatory' response by its 'innate immune system'. Positron emission tomography/magnetic resonance imaging has reinforced evidence of glial cell activation centred on the brain's limbic system of ME/CFS patients. Neuroinflammation causing dysfunction of the limbic system and its hypothalamus together with a consequently disrupted autonomic nervous system could account for the diverse range of symptoms in ME/CFS relating, in particular to fatigue, mood, cognitive function, sleep, thermostatic control, gastrointestinal disturbance, and hypotension.

Keywords

dysfunctional paraventricular nucleus, hypothalamus, limbic system, myalgic encephalomyelitis/chronic fatigue syndrome, neuroinflammation, stress

Date received: 22 July 2018; accepted: 16 October 2018

Introduction

Komaroff,¹ in an informative opinion piece, surmised the current myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) conundrum:

“On the one hand, it is clear the underlying pathology involves the nervous system, energy metabolism, and

Department of Biochemistry, University of Otago, Dunedin, New Zealand

Corresponding author:

Angus Mackay, Department of Biochemistry, University of Otago, 710 Cumberland Street, Dunedin 9016, New Zealand.
Email: anguslmackay@hotmail.com



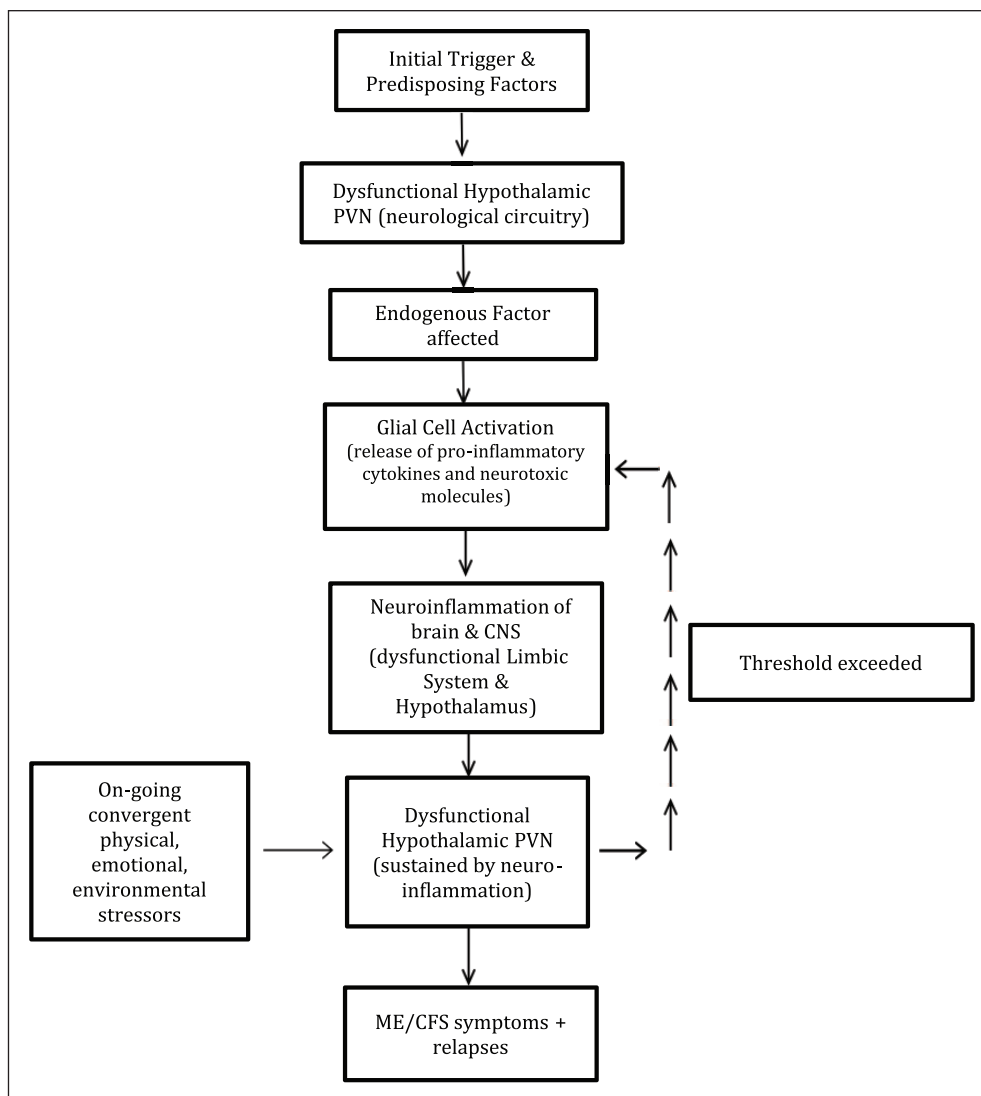


Figure 1. A 'neuroinflammatory' paradigm for ME/CFS. A range of triggers (sustained 'physiological stressors'), for example, particular viral infections, chemical toxin exposure and emotional trauma, in ME/CFS susceptible people induce dysfunction in the 'neural circuitry' of the hypothalamic paraventricular nucleus (PVN). This leads to an unidentified 'endogenous factor' within the CNS to be affected, which provokes an 'innate immune response' leading to neuroinflammation of specific areas of the brain and CNS of ME/CFS patients. This results in dysfunction specifically of the limbic system and hypothalamus and consequential disruption of the autonomic nervous system (ANS), all of which can account for the majority of symptoms for ME/CFS. Further dysfunction of the PVN (possibly by neuroinflammation) could also help to explain characteristic relapses and the ongoing perpetuation of ME/CFS.

the immune system. On the other hand, it is not clear what ties together the pathology seen in these different systems, nor which of the abnormalities came first, nor what triggered that first abnormality".¹

The purpose of this article is to present a 'neuroinflammatory' paradigm for ME/CFS pathophysiology to help explain its ongoing perpetuation via characteristic relapses, its onset and its diverse range of symptoms in a simple, unifying and coherent way (Figure 1).

The possible role of a dysfunctional hypothalamic paraventricular nucleus in ME/CFS pathophysiology

Disturbances in the hypothalamic–pituitary–adrenal (HPA-axis) axis as a key mediator in the body's response to physical, emotional or environmental stressors have been well documented, and the HPA-axis of ME/CFS has also been reported as dysfunctional.² Within the hypothalamus, a key regulator of the HPA-axis and autonomic nervous system (ANS),

is the paraventricular nucleus (PVN) consisting of a number of distinct nuclei, made up of extensive neural circuitry that can communicate with a variety of receptors throughout the brain and central nervous system (CNS). A dysfunctional PVN has been linked to congestive heart failure and hypertension. Neuroinflammation of the hypothalamic PVN resulting from heightened and sustained microglial activity has been implicated and may also be relevant to ME/CFS pathophysiology.^{3,4}

Perpetuation of ME/CFS

The literature provides a compelling account of how a range of physiological and emotional ‘stressors’ can stimulate the hypothalamic PVN through separate but convergent pathways. Sensory information (‘stress’ signals) is received by the PVN from physiological changes in the body, including respiratory and cardiovascular changes, pain and elevated levels of circulating inflammatory mediators via both neural (involving the ascending vagus nerve) and humoral pathways. Emotional ‘stress’ signals, however, are received by the PVN directly from the limbic system, such as the amygdala and hippocampus. The PVN integrates and processes these incoming ‘stress’ signals before activating the ANS and HPA-axis, to mount a homeostatic response.^{3,4}

A dysfunctional hypothalamic PVN, in ME/CFS, might help to explain the significantly lowered tolerance level to stressful events that is well recognised in ME/CFS patients. Ongoing ‘stressors’ to which ME/CFS patients are particularly vulnerable, and perpetuate the disease, include physical or mental overexertion, experiencing of emotional or financial stress, sleep deprivation and exposure to environmental stressors, including chemical toxins, infections and vaccinations.⁵ The concept that such a diverse range of ‘stressors’ can all affect ME/CFS patients, independently or in a combined manner, by converging on an already dysfunctional hypothalamic PVN is represented by Figure 2.

Some of these ‘signal pathways’ to the hypothalamic PVN have been documented, others are more conjectural but highly plausible. The following sequence of events is suggested to occur in ME/CFS patients. When a certain stress ‘tolerance level’ or ‘threshold’ is exceeded, then an already compromised PVN (from neuroinflammation) becomes overloaded, causing a debilitating ‘relapse’, or perhaps more aptly

termed (in the light of neuroinflammation) a ‘flare-up’ (Figure 1). This could signify a dramatic increase in glial cell (microglia and astrocytes) activity, and its associated neuroinflammation, throughout the CNS, but particularly centred within the limbic system of ME/CFS patients and with a correspondingly dramatic increase in the severity of their symptoms.⁶

‘Inflammatory marker’ studies, including magnetic resonance imaging (MRI) pre- and post-exercise studies, support the concept that symptom severities likely ‘wax and wane’ in tandem with fluctuating levels of chronic neuroinflammation in the brains and CNS of ME/CFS patients, and this is an important feature of this paradigm.^{1,6-9} Following a relapse, chronically activated glial cells, as mediators of inflammation, would gradually return to their quiescent states and allow the hypothalamic PVN to attain, once more, a higher threshold of ‘stress’ tolerance, decreasing the likelihood of relapses. Chronic but fluctuating neuroinflammation of the hypothalamic PVN, in ME/CFS, might certainly help to explain why the ‘stress’ tolerance levels appear to be constantly changing in ME/CFS patients: the more severe the neuroinflammation of the PVN, the lower the level of ‘stress’ required to trigger a relapse. The defining symptom of ME/CFS, post-exertional malaise (PEM),⁶ can also be explained by this paradigm (Figure 1); in this case, through physical (or mental) overexertion-induced ‘stress’ signals targeting a compromised hypothalamic PVN in ME/CFS patients. Interestingly, a recent MRI study indicated that PEM could be correlated to a reduction in cognitive function of ME/CFS patients, and with increased brain activity, which was detected within the inferior and superior parietal and cingulate cortices – a region of the limbic system.⁸

Onset of ME/CFS

This paradigm (Figure 1) supports the concept that an initial triggering event, in conjunction with predisposing factors, such as being of ‘female gender’ and a likely ‘genetic susceptibility’, leads to a sustained and chronic ‘innate immune response’ within the brains and CNS of ME/CFS patients. Common ‘triggers’ include several different viruses, especially from the Herpes virus family, Lyme Disease, chemical toxins, multiple vaccinations and emotional trauma.⁵ These independently acting physiological ‘stressors’, of a sustained and particularly

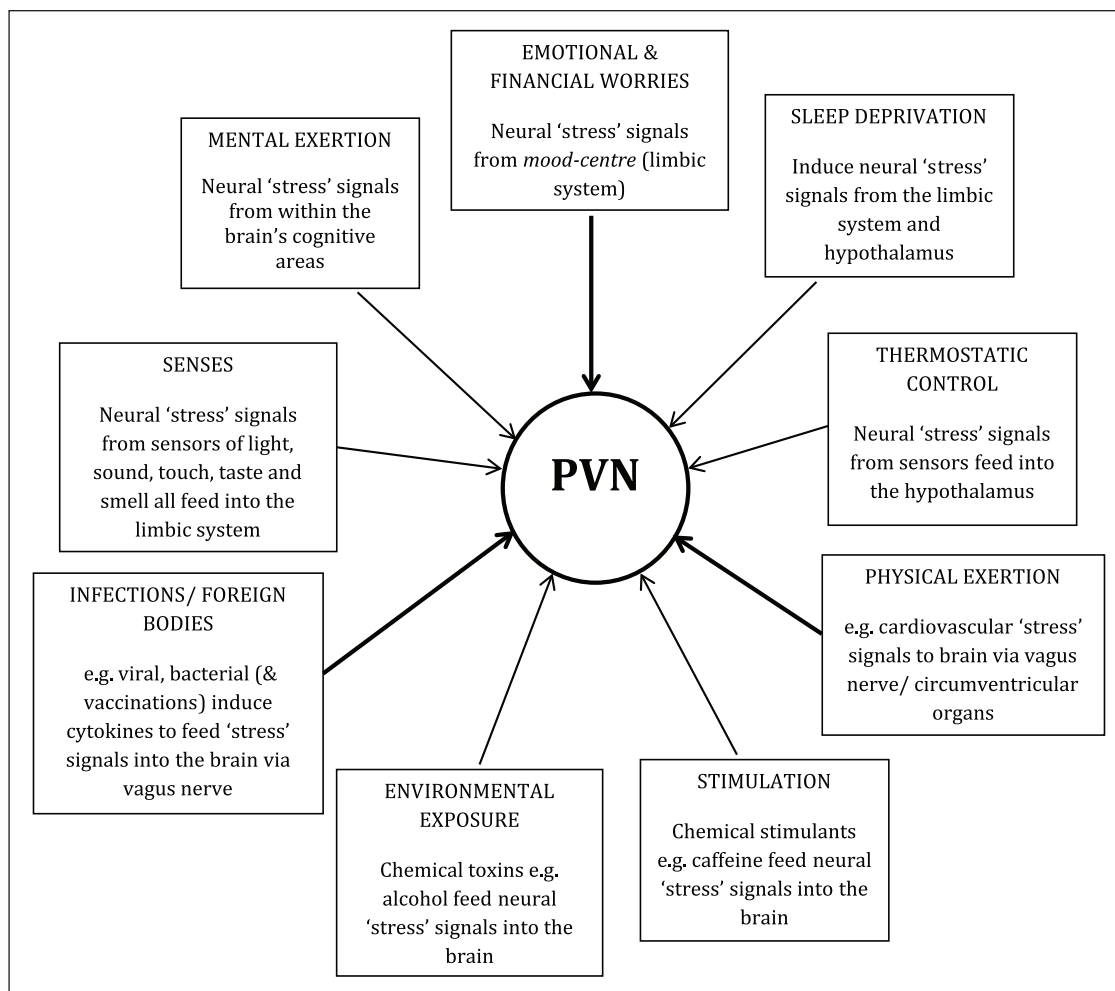


Figure 2. A diverse range of 'stressors' are known to affect ME/CFS patients, who are also known to be hypersensitive to 'stress' of any kind. Hypothetically, these multiple, but divergent 'stress' signals appear to converge by *known* or by *plausible*, but unconfirmed routes, into the hypothalamic paraventricular nucleus (PVN).

known = \longrightarrow ; plausible = \rightarrow .

severe nature, could target the hypothalamic PVN by the same physiological routes that perpetuate the disease (and as illustrated in Figure 2). Emotional trauma, for example, would emanate within the limbic system and, therefore, could send a persistent and intensive neurological 'stress' signal directly at the PVN. Viral infections that trigger ME/CFS such as glandular fever (Epstein-Barr Herpes virus) are severe enough, in their own right, to send a sustained and intensive 'stress' signal at the hypothalamic PVN, but by a different route, using a combination of humoral and neural pathways.^{3,4} The mechanism of how the PVN could be affected, in ME/CFS susceptible people, is of course highly conjectural, but perhaps it might cause a form of ongoing disturbance within its complex neurological circuitry. As a consequence of this 'assault', the PVN might send

out distorted neural ('stress response') signals, which in turn stimulate localised neuroinflammatory responses throughout the brain and CNS of ME/CFS patients.

ME/CFS – a neuroinflammatory disease of the CNS

The World Health Organization classified ME/CFS as a neurological disorder from as early as 1969, and it has increasingly been suspected to have a neuroinflammatory component.^{10,11} Recent advances in MRI, such as 'diffusion-tensor imaging', have allowed detection of abnormalities in a white matter tract of the brains of ME/CFS termed the 'arcuate fasciculus', with a strong correlation between the degree of abnormality and the severity of their

symptoms. Neuroimaging studies have also highlighted metabolic differences, such as increased concentration of lactate in the ventricular space and cerebrospinal fluid (CSF) in ME/CFS patients, indicating an anaerobic state, and possible mitochondrial dysfunction. Baraniuk and Shivapurkar⁹ reported altered levels of microRNAs (miRNAs) in the CSF of ME/CFS patients pre- and post-exercise and in comparison to both healthy controls and patients suffering from a closely related disorder to ME/CFS, called Gulf-War-Illness (GWI). In particular, miR-let-7i, downregulated in ME/CFS patients post exercise, appears to be linked to the expression of specific proinflammatory cytokines (interleukin (IL)-6, IL-8 and HMGB1), and miR-126-5p also downregulated in ME/CFS patients might allow monocytes and lymphocytes to cross the ‘blood–brain barrier’ (BBB) more freely – both of these changes in miRNAs might lead to neuroinflammation and help explain ‘post-exertional malaise’.⁹ Other CFS studies have found elevated numbers of leucocytes, proteins and variations in cytokines, indicative of an activated innate immune system within the CNS of ME/CFS patients, compared to healthy controls and compared to patients with depressive disorders.

A possible ‘neuroinflammatory’ response mechanism in ME/CFS

An initial ‘neuroinflammatory’ response, due to persistently activated microglia and astrocytes, is reported to occur across ‘early-stage’ neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Intriguingly, what appears to differentiate their pathological outcomes are the presence of disease and (CNS) location-specific ‘endogenous factors’ that help stimulate and sustain each of these uncontrolled ‘inflammatory’ responses: ‘amyloid-beta’ for AD, ‘ α -synuclein’ for PD, ‘mutant SOD1’ for ALS and ‘myelin-peptide-mimetic’ for MS.¹²

Different triggers and predisposing factors, in combination with a disease-specific ‘endogenous factor’, for ME/CFS, inducing a similar type of initial ‘neuroinflammatory’ response, but at different locations within the CNS and with different pathological outcomes, seems plausible. A resultant chronic, but lower level activation of microglia and astrocytes in the CNS of ME/CFS patients, as

suggested here, might also be the defining factor in the development of a variety of other ‘neuroinflammatory’ diseases and, as has been implicated, in mental disorders, migraines and epilepsy, for example. This paradigm (Figure 1) proposes that the ‘neuroinflammatory’ response, which likely occurs in ME/CFS, follows a similar process to that which occurs in ‘early-stage’ neurodegenerative diseases and is outlined below.

Microglia can sense the presence of these alien forms (‘endogenous factors’) in their local environment, and the cells transform from sedentary, neuroprotective states into more active, neuroinflammatory responsive cells. In particular, ‘pattern recognition receptors’ expressed on microglia play a significant role in the initial detection and inflammatory response. This is amplified by downstream signal transduction pathways present in microglia and astrocytes, resulting in the production of proinflammatory cytokines, such as tumour necrosis factor (TNF)- α , IL-1 β , and IL-6, as well as neurotoxic reactive oxygen species (ROS) and nitric oxide (NO). These may cause further amplification of the immune response, as well as neuroinflammation and neuronal damage, and become progressively more damaging if the process continues unabated. Adenosine triphosphate (ATP) released by necrotic neurones, during apoptosis, might also contribute to this process by further activation of microglia through positive feedback loops. Both microglia and astrocytes possess purinergic receptors that can bind ATP present in the interstitial fluid.¹²

Microglia when activated can also release the neurotransmitter glutamate in a sustained form which is thought to have a deleterious effect on neuronal mitochondria (mitochondrial respiratory chain complex IV becomes inhibited). Mitochondrial dysfunction then could be a key component in the neuroinflammatory process and accounts for the reports of lactate, produced by anaerobic respiration, as mentioned earlier, being found in the CSF of ME/CFS patients.

Possible ‘endogenous factors’ for ME/CFS

Such a hypothetical factor specific to ME/CFS pathophysiology would likely be different in nature and operate more dynamically than those more ‘permanent forms’ associated with the neurodegenerative diseases. The ‘endogenous factor’ itself could then increase or decrease in proportion to any

ongoing neural ('stress response') signals from a dysfunctional hypothalamic PVN and account for fluctuating levels of neuroinflammation and severity of symptoms in ME/CFS. One possibility for such an 'endogenous factor' is suggested from the observation that reactivation of viruses like Herpes Simplex from latent neuronal infection occurs in response to psychological stress, which is a known 'stressor' to impact on ME/CFS patients. Then, viral 'pathogen-associated molecular patterns', present within the CNS, could be the (dynamically changing) 'endogenous factor' that stimulates localised microglial activation and neuroinflammation. A number of studies have shown that psychological chronic stress can also affect mitochondrial function and morphology in the brains of animals. In ME/CFS such dysfunction could lead to the release of 'alarmins' in the form of (alien) mitochondrial DNA (potentially another form of 'dynamically' changing 'endogenous factor') stimulating localised microglial activity and a neuroinflammatory response. Nevertheless, there could be many other potential candidates as 'endogenous factors' involved in ME/CFS pathophysiology, and as described in the literature involving other neuroinflammatory pathways.

Neuroinflammation can explain the diverse symptoms of ME/CFS

A key positron emission tomography (PET)/MRI study by Nakatomi et al.⁶ implied that the physiological change that sustains ME/CFS could indeed be chronic neuroinflammation associated with the activation of the brain's innate immune system. ME/CFS patients showed significant evidence of enhanced activation of glial cells within a number of specific regions of the brain. The severity of symptoms self-reported, such as fatigue, cognitive impairment, pain and depression, correlated with the intensity of their brain glial cell activation.⁶

A dysfunctional limbic system

Almost all of the specific areas of the brain highlighted as affected in this PET/MRI study, such as the amygdala, hippocampus, thalamus and cingulate cortex,⁶ are found to be within a region of the brain termed the limbic system. Sensitive emotions, mood swings, cognitive dysfunction, memory loss and increased anxiety all commonly experienced by ME/CFS sufferers⁵ might therefore be explained by

inflammation (and dysfunction) of the limbic system. The 'feeling' of profound fatigue⁵ could also be partially accounted for by inflammation of the limbic system, not dissimilar to that proposed for major depressive disorder (MDD). Classic symptoms of ME/CFS—heightened and distorted senses of sound, light, touch, smell and taste⁵—could all emanate from a dysfunctional limbic system. While the five sensory centres are located outside of the limbic system, they all feed signals into it.

A dysfunctional hypothalamus

The hypothalamus, located centrally within its limbic system, was not highlighted specifically in the imaging study,⁶ but a more recent MRI study which correlated autonomic dysfunction, measured by heart rates and blood pressure readings, for ME/CFS patients and healthy controls found abnormalities in the brain stem and hypothalamus itself. It seems highly plausible that the hypothalamus might be directly or indirectly compromised by the proximal inflammation of its other closely connected limbic system components, and if so could account for many of the diverse symptoms experienced in ME/CFS.

The hypothalamus contains the sleep, appetite and thermostatic control centres and regulates the HPA-axis and the ANS, thereby indirectly controlling clarity of vision, heart rate, blood pressure and gastrointestinal motions, for example. Lack of refreshing sleep, insomnia, fluctuations in appetite control often leading to dramatic weight changes, abnormal thermostatic control and hypersensitivity to extremes of temperature, blurred vision, heart arrhythmias and hypotension—itsself plausibly linked to orthostatic intolerance—as well as sluggish peristalsis and bloating are all common symptoms experienced by ME/CFS patients.⁵

Hypothalamic-ANS dysfunction might even provide an explanation for the subtle 'downstream' immune system changes in the blood reported in numerous ME/CFS studies⁵ (and summarised in Figure 3). 'Psycho-neuro-immunological' studies provide support to the concept of glial cell activation in the brains of psychosocial stress-affected subjects, leading to further immune system changes 'downstream', which may also be of some relevance in the elucidation of ME/CFS pathophysiology.

A dysfunctional hypothalamus, causing HPA-axis disruption, might account for aberrant

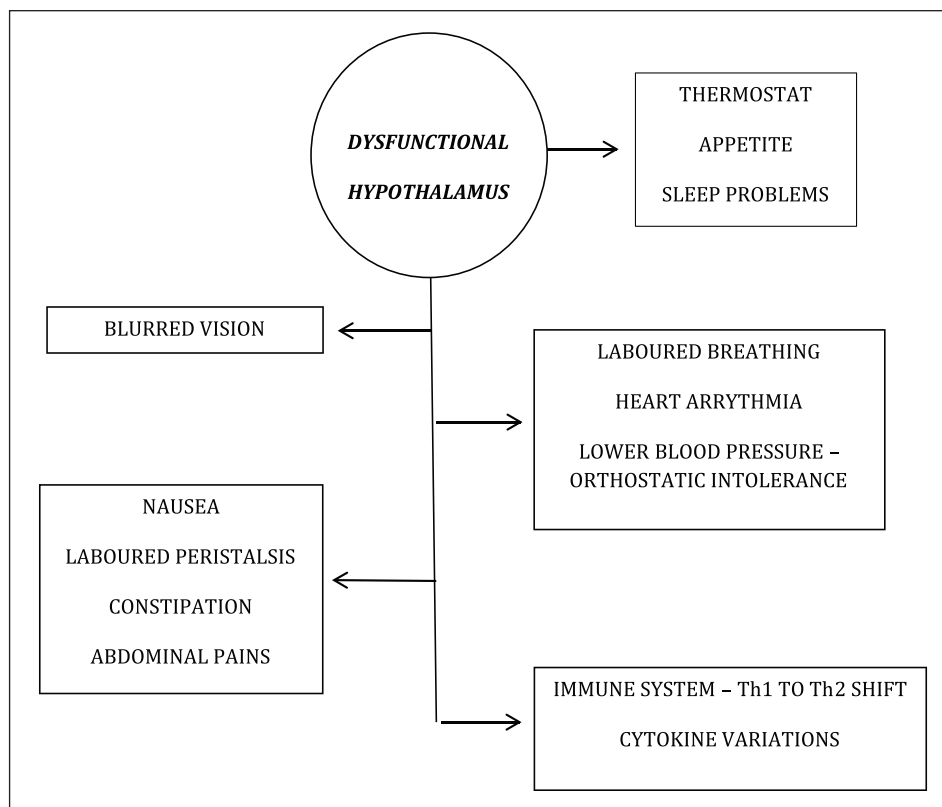


Figure 3. Consequences of a dysfunctional hypothalamus on the autonomic nervous system (ANS) and possible outcomes (symptoms) as reported in ME/CFS patients. Th1 = T-Helper Cell type 1 (humoral immune response) and Th2 = T-Helper Cell type 2 (cell-mediated immune response).

neuroendocrine messages to the pituitary gland and adrenal glands and help to explain the increased frequency of urination experienced by ME/CFS patients and ‘hypocortisolism’ often reported in ME/CFS.^{2,5}

It is hoped that the paradigm presented here (and Figure 1) will provide a useful ‘framework’ for scientific debate to facilitate better understanding of the neurological pathophysiology in ME/CFS. Critical investigative research to test out the hypotheses put forward here and to fill the gaps in the mechanistic detail required is desired. If activated glial cells are detected in the hypothalamus, and in particular, the hypothalamic PVN of ME/CFS patients, then this would strengthen the evidence for PVN involvement. Then, mechanistic detail of how multiple ‘triggers’ for onset and multiple ‘stressors’ for perpetuation of ME/CFS translate into amplification of glial cell activity in the CNS in ME/CFS via plausible ‘endogenous factors’ would need to be resolved. Within the recent studies on ME/CFS, there has been insufficient focus on the involvement of the CNS in its pathophysiology. However, it is encouraging to learn

that neuroimaging technology is advancing rapidly and is being used increasingly to investigate the whole range of neurological brain disorders and diseases. In particular, rapid advances are being made in the range, sensitivity and effectiveness of ligands and potential cellular receptors for PET/MRI, which should significantly enhance ME/CFS neuroimaging as well. Indeed, it is to be hoped that a diagnostic ‘brain-signature’ for neuroinflammatory diseases (like ME/CFS) using advanced, more sensitive MRI technology may not be too far away.

Acknowledgements

The authors have drawn on their own experiences and those of close family members with ME/CFS and acknowledge their contributions. The authors thank Alex Noble, Department of Biochemistry; Dr Margaret Ryan, Department of Anatomy and Professor Cliff Abraham, Co-Director Brain Research NZ and Department of Psychology, University of Otago, Dunedin, NZ, for their critique and acknowledge helpful discussions with Dr Ros Vallings, General Practitioner, Howick Medical Centre, Auckland, NZ; Dr Karl Iremonger, Department of Physiology, University of

Otago, Dunedin, NZ; Dr Fiona Pickering, General Practitioner, Student Health Services, University of Otago, Dunedin, NZ and Dr Grace Bateman, Assistant Research Fellow, Biochemistry Department, University of Otago, NZ.

Declaration of conflicting interests

The authors have no conflict of interest or financial benefit from the ideas expressed, but direct (AM) and indirect (WT) in-depth experience of ME/CFS has inspired this contribution.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The authors gratefully acknowledge funding from Lottery Health (New Zealand), ANZMES, University of Otago and Private Bequests.

References

1. Komaroff AL (2017) Inflammation correlates with symptoms in chronic fatigue syndrome. *Proceedings of the National Academy of Sciences of the United States of America* 114(34): 8914–8916.
2. Tomas C, Newton J and Watson S (2013) A review of hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. *ISRN Neuroscience* 2013: 784520.
3. Ferguson AV, Latchford KJ and Samson WK (2008) The paraventricular nucleus of the hypothalamus – A potential target for integrative treatment of autonomic dysfunction. *Expert Opinion on Therapeutic Targets* 12(6): 717–727.
4. Olson KL, Marc MS, Grude LA, et al. (2012) The hypothalamic-pituitary-adrenal axis: The actions of the Central Nervous System and Potential Biomarkers. *Anti-Aging Therapeutics* 13: 91–100.
5. Members of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) and Primer Writing Committee (2014) *ME/CFS: A Primer for Clinical Practitioners*. Chicago, IL: IACFS/ME and Primer Writing Committee.
6. Nakatomi Y, Mizuno K, Ishii A, et al. (2014) Neuroinflammation in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ¹¹C-(R)-PK11195 PET study. *Journal of Nuclear Medicine* 55: 945–950.
7. Shan ZY, Kwiatek R, Burnet R, et al. (2016) Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study. *Journal of Magnetic Resonance Imaging* 44(5): 1301–1311.
8. Cook DB, Light AR, Light KC, et al. (2017) Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Brain, Behavior, and Immunity* 62: 87–99.
9. Baraniuk JN and Shivapurkar N (2017) Exercise-induced changes in cerebrospinal fluid miRNAs in Gulf War Illness, Chronic Fatigue Syndrome and sedentary control subjects. *Scientific Reports* 7(1): 15338.
10. Glassford JAG (2017) The neuroinflammatory etio-pathology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Frontiers in Physiology* 8: 88.
11. Monro JA and Puri BK (2018) A molecular neurobiological approach to understanding the aetiology of Chronic Fatigue Syndrome (Myalgic Encephalomyelitis or Systemic Exertion Intolerance Disease) with treatment implications. *Molecular Neurobiology* 55(9): 7377–7388.
12. Glass CK, Saijo K, Winner B, et al. (2010) Mechanisms underlying inflammation in neurodegeneration. *Cell* 140(6): 918–934.