VIEWPOINT

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Te Whare Tohu Rata o Aotearoa

A neuro-inflammatory model can explain the onset, symptoms and flare-ups of myalgic encephalomyelitis/chronic fatigue syndrome

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ABSTRACT

A neuro-inflammatory model is proposed to explain the onset, symptoms and perpetuation of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) via characteristic flare-ups (relapses). In this article, I explore the proposition that a range of triggers (intense physiological stressors such as severe viral infections, chemical toxin exposure or emotional trauma) in ME/CFS-predisposed people causes disruption in the neural circuitry of the hypothalamus (paraventricular nucleus), which induces a neuro-inflammatory reaction in the brain and central nervous system of ME/CFS patients, via over-active innate immune (glial) cells. Resulting dysfunction of the limbic system, the hypothalamus and consequently of the autonomic nervous system can then account for the diverse range of ME/CFS symptoms. Ongoing stressors feed into a compromised (inflamed) hypothalamus and if a certain (but variable) threshold is exceeded, a flare-up will ensue, inducing further ongoing neuro-inflammation in the central nervous system, thus perpetuating the disease indefinitely.

Introduction

Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) is a poorly understood debilitating disease that has a dramatic impact on the lives of affected people, as well as their economic output. It does not discriminate between race and socioeconomic class, affecting an estimated 20,000 people in New Zealand (20 million people worldwide), but there appears to be a genetic susceptibility and a predisposition towards the female gender (approximately 4:1 ratio). Diagnosis is challenging, requiring in-depth interviews of patients regarding the history and symptoms of the disease and is made by excluding other fatigue-causing diseases or conditions.[1]

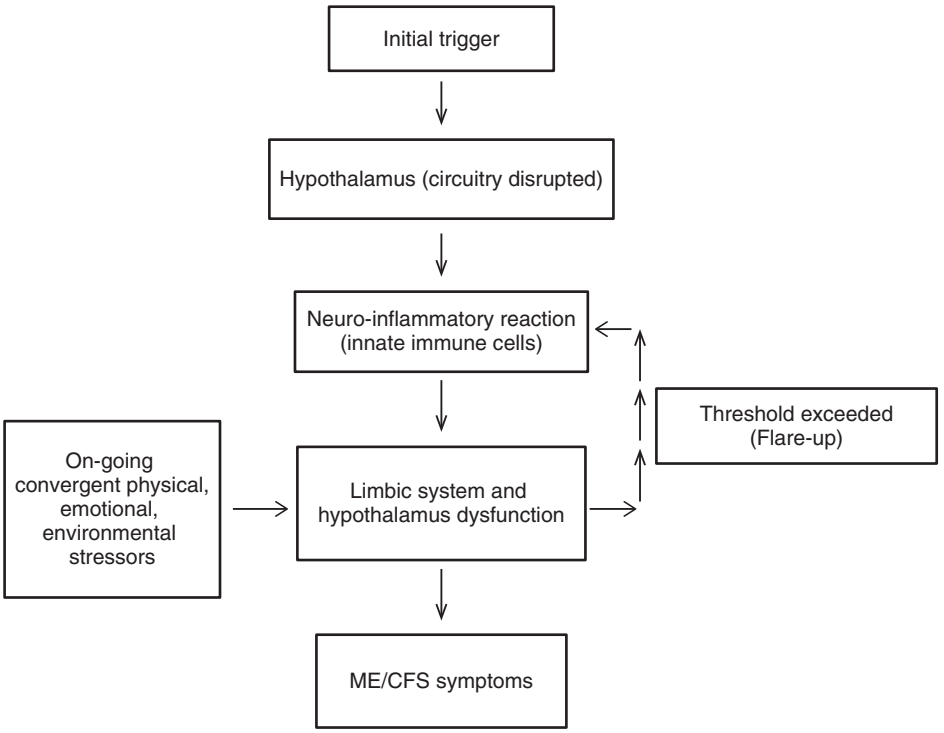
Due to its complex nature and ongoing, but unwarranted and damaging scepticism of its physiological nature,[2] there has been inadequate funding for ME/CFS scientific research globally. According to a United States of America (USA)-centred report published in 2014, only US$5 per patient per annum was spent on research into ME/CFS (affecting ~1 million people in the USA) in comparison to US$255 per patient per annum for multiple sclerosis (affecting ~400,000 people in the USA).[3]

This personal narrative, written from the perspective of being both a long-term sufferer and a researcher of ME/CFS, provides an account of how I developed my ideas to explain this debilitating disease: its onset, symptoms and perpetuation via characteristic flare-ups (relapses). Ultimately, I propose a neuro-inflammatory model for ME/CFS (Figure 1).[4]

Personal background

I first succumbed to ME/CFS in 1995 after becoming ill with infectious mononucleosis (glandular fever), a common trigger for ME/CFS.[1] Like many

Figure 1. A neuro-inflammatory model to explain the onset, symptoms and perpetuation of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This figure is a modified version of Figure 1 in the study by Mackay and Tate (2018).[4]



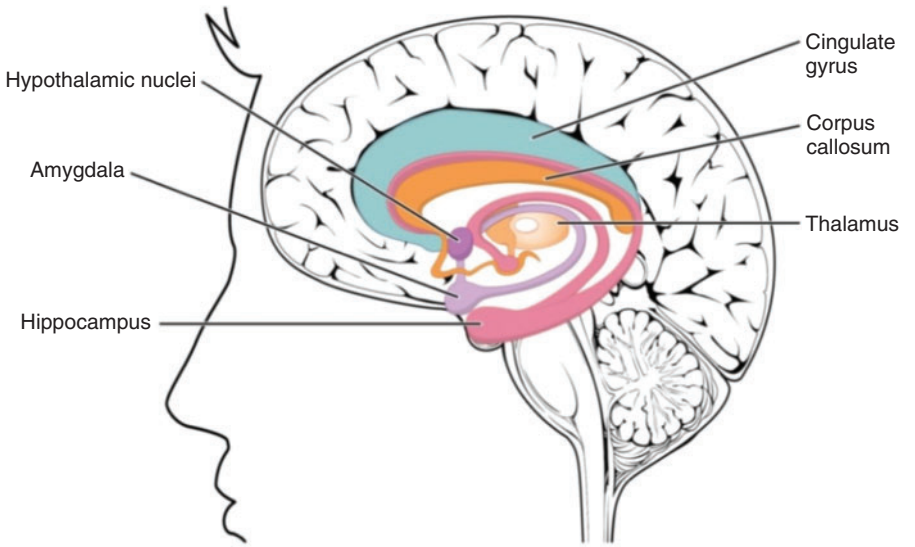
others who have ME/CFS, I previously led a full and active life (ex-British army officer, biology teacher, rugby coach and outdoor expedition leader). Ever since, and typically for most ME/CFS sufferers, my life physically, socially and career-wise has been severely compromised. However, like many millions of other sufferers around the world deemed "missing" (as portrayed in the inspirational award-winning film of 2017: UNREST, by Jennifer Brea), I have tried to adapt and do the best I can within the limitations of my health.[2]

I arrived in Dunedin in 2011, via Auckland, to start a PhD in Professor Warren Tate's laboratory (Biochemistry Department, University of Otago) investigating patients' blood samples for possible protein-biomarkers indicative of a chronic viral presence in ME/CFS patients. I was patient ME001. The studies proved to be quite challenging because I had not been in a university laboratory since graduating with BSc (Hons) from Dundee University, Scotland, in 1982. I struggled with the long hours required to complete my lab work, which led me increasingly to divert my attention to the online literature available, while exploring alternative theories to the chronic viral hypothesis we were following at that time.

Making sense of my condition

What alternative hypothesis could there be? Living with ME/CFS as a constant, if unwelcome companion over many years of never-ending flare-up, recovery cycles probably gave me a different perception from healthcare professionals and other researchers of what might be going on. This helped to shape my ideas, along with the online scientific literature I could still readily access from home. For example, flare-ups, although undesirable due to their severity and their associated malaise and anguish, were particularly informative in my quest to identify the root cause of my condition because I could note the symptoms in detail. Aching eyes, temples and spine (from nape of neck down to below my shoulder blades), accompanied by "brain fog" (concentration, decision-making and memory problems), lack of coordination (bumping into things), anxiety, depression and withdrawal, debilitating fatigue by day, yet insomnia

Figure 2. The limbic system. For more information, see https://en.wikipedia.org/wiki/Limbic_system.



at night, feeling overly cold, not hungry, accompanied by nausea and my gastro-intestinal tract seizing up, all suggested to me that ME/CFS was a **neurological disease** with **neuro-inflammation** at its core. Encephalomyelitis means "inflammation of the brain and spine". I also noticed, as is common among ME/CFS patients and for every flare-up that I experienced, as the intensity of the (perceived) inflammation in my brain (particularly within the temple region) and spine dissipated over the days and weeks following symptom onset, so my other symptoms would abate accordingly, and with much relief.[1]

There was plenty of literature available, especially more recently, which added growing support for a neuro-inflammatory concept to explain ME/CFS.[5,6] Most of the evidence involved either brain scanning techniques[7–11] or cerebrospinal fluid studies of ME/CFS patients,[12–15] but it was evident that the brain scanning technology being used was simply not sophisticated enough to detect chronic and fluctuating inflammation in the brains of ME/CFS patients that mirrored the chronic and fluctuating symptoms described above.

A breakthrough study

In 2014, a Japanese group published a paper that showed, for the first time, clear evidence of inflammation in the brains of ME/CFS patients, using a special form of magnetic resonance imaging (MRI), termed positron emission tomography (PET/MRI).[16] Glial cells (the innate immune cells of the brain) were highlighted in this small study as overactive in ME/CFS patients (a type of autoimmune response). Their activity (inflammatory response) appeared to be in proportion to the severity of symptoms recorded. When the areas of the brain affected (hippocampus, amygdala, cingulate gyrus, thalamus and brainstem) were cross-referenced, they nearly all pertained to a region of the brain called the limbic system. Central to the limbic system is the acorn-sized hypothalamus (hypothalamic nuclei) known as the master gland (Figure 2).

Recent complementary studies

Younger (University of Alabama, USA) has been using alternative less-invasive forms of brain-scanning technology, which are able to detect molecules like lactate (indicative of anaerobic respiration and mitochondrial stress) and small temperature changes (indicative of chronic inflammation) in the brains of ME/CFS patients.[17] Lactate had previously only been detected in samples of cerebrospinal fluid of ME/CFS patients.[12,13] In a very recent study involving 15 ME/CFS patients and 15 healthy controls, consistently raised levels of lactate were detected in regions of the brain of ME/CFS patients, especially in the cingulate gyrus

of the limbic system.[17] The raised lactate levels were found to be not as high as they have been measured in the more permanently damaging neurodegenerative diseases. Widespread increased temperature changes were detected throughout the brains of ME/CFS sufferers. Indicative of a reliable methodology, not a single healthy control showed increased levels of either lactate or temperature in their brains.

Also, recently, a comprehensive PET/MRI study detected inflammation in the brains of fibromyalgia patients (part of the limbic system was specifically identified as being affected).[18] Fibromyalgia is a very closely related disease to ME/CFS, where patients experience similar symptoms including cognitive dysfunction and sleep problems, but with more emphasis on the pain (myalgia) in fibromyalgia.

Symptoms explained

The limbic system is the mood-centre of the brain and also controls memory and influences cognition. The hypothalamus contains sleep, appetite and temperature control-centres. It also controls the autonomic nervous system (ANS), which is the extensive nervous system that branches off the spinal cord, working subconsciously to control things like bowel motions (peristalsis), heart rates and blood pressure, all of which are affected in ME/CFS patients. If the limbic system and its hypothalamus were inflamed and thereby dysfunctional – causing the ANS to be disrupted as well – then this might help to explain the diverse range of symptoms experienced by ME/CFS sufferers affecting, for example, mood, vitality, concentration, memory, sleep, thermoregulation, appetite, bowel motions and blood pressure.[1,4]

The five senses of light, sound, touch, smell and taste, which are all significantly affected and sensitized in ME/CFS patients as well, feed neurological signals into the limbic system. The lower blood pressure that results in ME/CFS sufferers might also help to explain another common symptom for ME/CFS sufferers: dizziness when standing up (orthostatic intolerance).[1,4]

Flare-ups explained

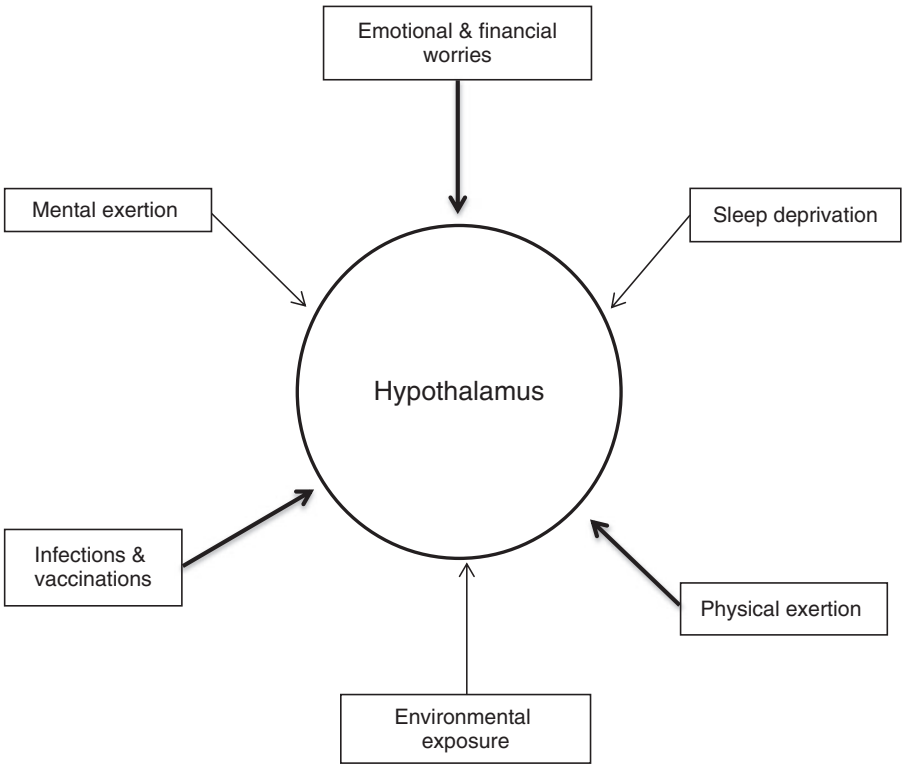
I also noted (in common with other ME/CFS sufferers) that the causes of my flare-ups varied, as a range of potential stressors were involved.[1,4] Sometimes, flare-ups could be attributed to a specific stressor like physical over-exertion. At other times, it was less clear and could have been related to a combination of stressors including physical or mental over-exertion, emotional or financial stress, infections or vaccinations. Environmental stressors such as chemical toxins and sleep deprivation due to late nights or insomnia might also contribute towards a flare-up. As ME/CFS sufferers know, avoiding flare-ups through pacing oneself and minimising potential stressors is the key to any hope of sustained recovery.[1] However, how could these quite different types of stressors all cause the same kind of flare-ups?

In my ongoing research of the online databases of scientific journals, I came across an article that provided my eureka moment.[19] In particular, there was a diagram that clearly indicated that signals from a range of stressors, via different physiological routes, *all* target the hypothalamus. For example, emotional stress signals are sent directly and neurologically from the mood-centre in the limbic system to its closely connected hypothalamus; however, stressors such as an infection (or vaccination) or physical overexertion cause longer range signals to be sent by a combination of blood (messenger) and then neurological routes that each target the hypothalamus. So, along with its many other functions, the hypothalamus appears to act as a "stress response centre" (Figure 3).[4]

Other literature helped to confirm this particular role, whereby incoming stress signals from a range of different stressors were directed at the hypothalamus, which processed them before responding in a variety of ways, either hormonally or via the autonomic nervous system.[20]

Might a dysfunctional (inflamed) hypothalamus therefore help to explain why ME/CFS patients have such a low tolerance to stressors of any kind,[1,4] be they physical, mental, emotional or environmental? And when a certain threshold for incoming stress signals is exceeded, might that trigger a flare-up originating in the hypothalamus but spreading out like a tidal wave to specific targets within the brain and central nervous system?[4]

*Figure 3. Diverse range of stressors known to affect myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) patients, which may ALL target the hypothalamus. The **arrows** in **bold** represent known physiological routes, the others are hypothetical, but plausible. This figure is a modified version of Figure 2 in the study by Mackay and Tate (2018).*[4]



Post-exertional malaise, a classical and defining symptom experienced by ME/CFS sufferers, from minimal physical or mental exertion[1] (which crucially differentiates it from depressive disorders) could also be explained by this concept – as a mini flare-up.[4] For women with ME/CFS, their vulnerability to flare-ups might be exacerbated by an additional ongoing physiological stressor targeting their hypothalamus, which they experience up to and including menopause – that of oscillating levels of their sex hormones.

Onset explained

It occurred to me that the multiple triggers of ME/CFS,[1] including particular viruses (like Epstein–Barr virus causing infectious mononucleosis), chemical toxin exposure and severe trauma were not dissimilar to the kind of stressors that perpetuated the disease (Figure 3) other than in their intensity. When each trigger is regarded as a different form of an intense physiological stressor, might they too target the hypothalamus by similar physiological routes as used by ongoing stressors? Might the hypothalamus, therefore, be a key vulnerable site in individuals predisposed to ME/CFS? And if so, might this be the location of a genetic malfunction often sought in ME/CFS research, which is fundamental to the disease becoming manifest?

The area of the hypothalamus targeted by incoming stress signals is known as the paraventricular nucleus, which is made up of complex neurological circuitry.[19,20] The literature also indicated that a dysfunctional hypothalamic paraventricular nucleus was not only integral to some other physiological diseases, but was also likely caused by localised neuro-inflammation from overactive glial cells.[20–22] Might this circuitry be jolted into dysfunction by the triggers of the disease, thereby initiating a neuro-inflammatory response within the brains of ME/CFS patients? Then, neuro-inflammation (and ME/CFS itself) could then be

self-perpetuated indefinitely according to the rationale for flare-ups presented above (and as illustrated in Figure 1).

Neuro-inflammation: mechanistic detail

The mechanistic detail required to support the idea of a possible inflammatory response in the brains of ME/CFS sufferers proved more challenging to provide. Although the literature postulated that conditions such as migraines,[23] epilepsy[24] and even psychiatric disorders[25] might result from localised neuro-inflammation involving glial cells, mechanistic detail was lacking. I turned my attention to the well-established neurodegenerative diseases. I found one particular review article thought-provoking. It outlined how neurodegenerative diseases like Alzheimer's Disease, Parkinson's Disease and Multiple Sclerosis all appeared to be ignited by a common neuro-inflammatory response, which also involved activated glial cells in the central nervous system (CNS) of sufferers, before each diverged according to their own disease-specific pathways and characteristic outcomes.[26] Might ME/CFS (and other potential neuro-inflammatory conditions mentioned above) share this common (initial) neuro-inflammatory reaction too?[4]

Each neurodegenerative disease is associated with a particular disease-related alien factor, which develops in location-specific areas within CNS tissues of affected people and appears to drive each disease-specific neuro-inflammatory response into an out-of-control state (tangled protein-aggregates in the case of Alzheimer's Disease, for example).[26] What alien factor, neurologically linked to an overloaded and compromised hypothalamus, might be the driver of glial-cell over-activity (and neuro-inflammation) in the brains and CNS of people with ME/CFS? Any such factor was clearly going to be much more subtle (possibly molecular) and dynamically changing to account for fluctuating symptoms in ME/CFS than the alien factors permanently set *in situ* for progressively deteriorating neurodegenerative diseases. A couple of candidates from many potential neurologically stress-sensitive CNS-based candidates, which we term the 'missing link', are discussed in our recent paper.[4]

A neuro-inflammatory model for ME/CFS

A modified form of the neuro-inflammatory model[4] to explain the onset, symptoms and perpetuation of ME/CFS is shown in Figure 1. Although the model is largely theoretical with limited scientific evidence to support it, at this stage, its coherent nature may be used by scientific researchers as a framework to test, critique and develop.

The future

According to this model, one would expect the main gains in understanding and developing drugs to treat ME/CFS to come from increasingly sophisticated and sensitive brain- and cerebrospinal fluid-directed research. A more coordinated (global) approach towards such research into ME/CFS and fibromyalgia, which affects four-fold as many people as ME/CFS, should be mutually beneficial to the understanding of both diseases. Importantly, the Japanese group are repeating their study with a larger cohort and more refined PET/MRI techniques, but results are not yet available nor ratified.[16]

As PET/MRI is being intensively used across a wide range of neuro-inflammatory and neurodegenerative disease studies, rapid technological advances are being made, especially in the range of tracers (ligands) becoming available and possible receptors they can target within the brain, which will likely benefit PET/MRI studies of ME/CFS (and fibromyalgia) patients in the future.[27] I hope that as the technology becomes increasingly sensitive, a specific MRI 'brain signature' for ME/CFS, which can distinguish it from other potential neuro-inflammatory conditions, might one day be attainable and used as a diagnostic aid or to monitor progress resulting from possible drug interventions.[28]

Blood biomarker studies may also continue to be instructive. Following a series of comprehensive and recently completed metabolomics studies that indicated a hypo-metabolic state in ME/CFS patients and possible mitochondrial dysfunction,[29–31] one of its investigators has developed a possible blood test for ME/CFS utilising nanotechnology.[32]

It is possible that a drug designed to dampen down glial cells might also become available. Younger (2017) has been investigating drugs already approved for other ailments, such as low-dose naltrexone, which has had some success with fibromyalgia patients.[33] USA drug development company, Cortene (Cortene Inc., http://corteneinc.com/contact), has successfully carried out a preliminary trial of a drug (CT38) that targets a stress-related receptor present in the limbic system and intends to move onto the next phase of their research into this drug shortly.[34]

If ME/CFS is shown to be a neuro-inflammatory disease, which is plausible within the next 5–10 years, then, unlike neurodegenerative diseases, it is potentially reversible and therefore curable once the right antidote is found. This gives something vital for all ME/CFS (and fibromyalgia) sufferers to cling onto — hope!

Competing interests

The author declares no competing interests.

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