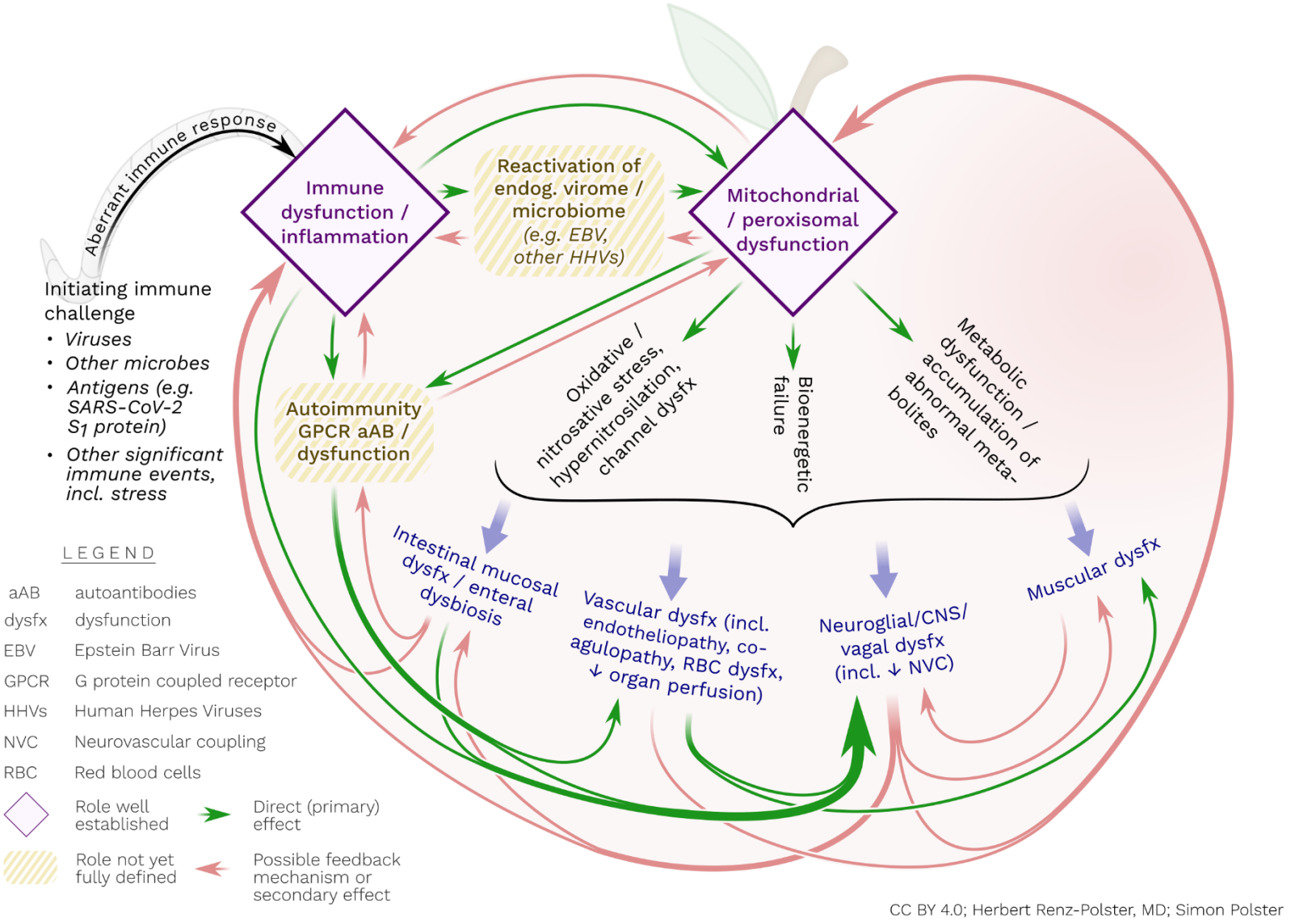
Herbert Renz-Polster, MD

Harmed by friendly fire?

ME/CFS is Sustained by a Deficient Stress Response in the Central Nervous System

ME/CFS – a bewildering disease



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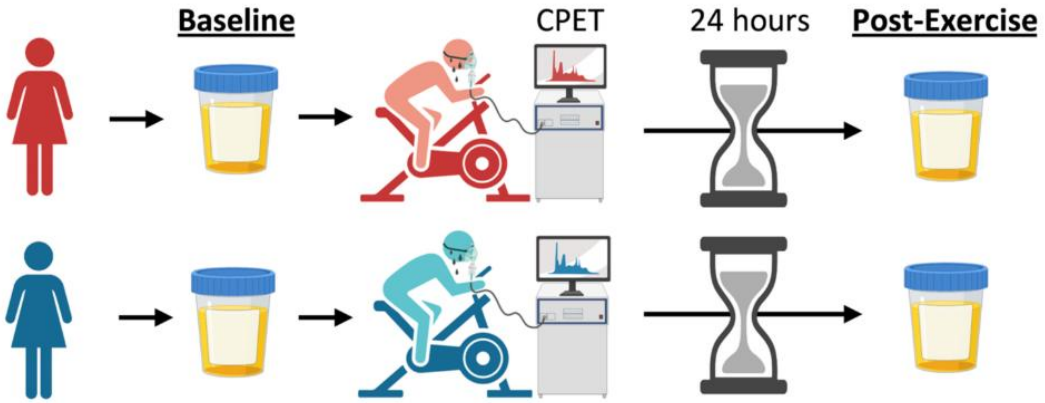
Renz-Polster H, Tremblay M-E, Bienzle D and Fischer JE (2022) The Pathobiology of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: The Case for Neuroglial Failure. Front. Cell. Neurosci. 16:888232. doi: 10.3389/fncel.2022.888232

- Unfortunately we don´t know how the arrows run …

Disentangling the threads…



… through exercise testing.

The findings in a nutshell

In the healthy controls, exercise induces a flurry of adaptive changes – on many levels: cardiovascular, respiratory, metabolic, transcriptomic, in T-cells, in NK-cells, in monocytes, in extracellular vehicles, in muscle cells…

And, what happens in ME/CFS?

NOTHING

Compared to healthy controls, ME/CFS patients show… (1):

- lack of metabolic adaptation in response to exercise (Glass 2023)
- lack of transcriptomic adaptation in response to exercise (Van Booven 2023)
- lack of changes in circular RNA expression after exercise (Cheng 2023)
- lack of adaptation of T-cells and NK cells in response to exertion (Van Booven 2023)
- lack of the normal rise of the concentration of extracellular vesicles (EVs) after exercise (Giloteaux 2024)

Compared to healthy controls, ME/CFS patients show… (2) :

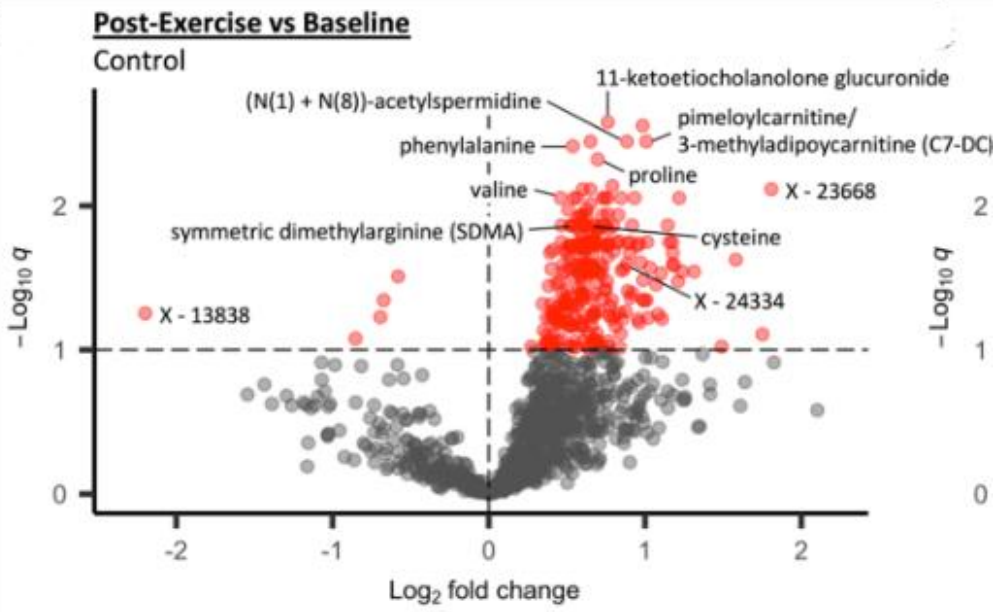
- Lack of adequate T and B cell signaling, downregulation of IL-17 and cell-cell communication pathways (Germain 2025)
- lack of changes in microRNA levels in peripheral blood mononuclear cells after exercise (Cheema 2020)
- lack of an adaptive response of classical monocytes after exercise (Ahmed 2022)
- lack of the acute phase response to luminal gut antigens translocated into the bloodstream during exercise (Uhde 2023)
- lack of adequate rise of cell-free DNA in the blood after exercise (Simon, 2024)
- Lack of metabolic adaptation in response to microbial stimulation before and after exercise (Che/Lipkin 2025)

Compared to healthy controls, ME/CFS patients show… (3):

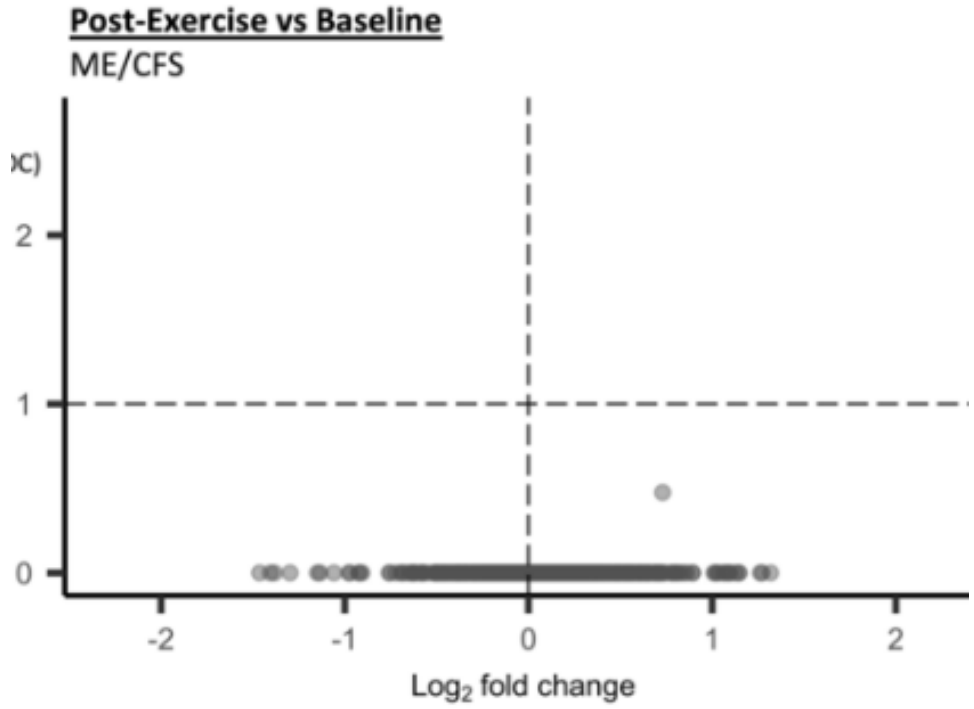
- lack of cardiovascular and respiratory adjustment in response to exercise (Cook 2022, Joseph 2023)
- lack of adjustment of brain metabolites (measured in spinal fluid samples) in ME/CFS after exercise. In controls, new metabolites were made after exercise, in ME/CFS they were not (they were used up instead (Baraniuk 2025)
- lack of the normal parasympathetic surge after exercise stops (in HC this will lead to normalization of heart rate 10 minutes after the end of exercise – which does not occur in ME/CFS patients (Wüst 2025)

One example from Glass 2024, who measured the urine metabolome

- Before exercise there were only very few differences between ME/CFS patients and healthy controls (HCs)
- What about 24 hours after exercise?
  In the HCs: 255 compounds were significantly altered. All but 5 increased in abundance – see figure:



What was measured in the ME/CFS patients?



No change, <u>not in one single compound</u>

Here is the adaptive response to stress in ME/CFS patients:

And what about the brain?
same story:

- lack of adjustment of cerebral blood flow (CBF) in response to orthostatic stress (van Campen 2020 and 2021; Medow 2014) (and this reflects a problem of the CNS vasculature, not a peripheral cardiovascular one; van Campen 2020 and 2024)
- lack of oxygen level adaptations in the brain after cognitive exercise (Schönberg 2024)
- lack of adjustment of the “resting state” network: in response to physical exercise, the Default Mode Network (DMN) remains activated (Rayhan 2021)

So here again, instead of adjusting, the body remains in the “chill mode”.

This is a problem – but why?

The stress response has 2 arms:

- Arm 1: „Release the troops“. The body is being primed for action - through immune activation which includes inflammatory signals, oxidative stimuli, adrenergic signalling etc.
- Arm 2: „Release the guardian angels“. This arm helps the tissues to adapt to the noxious effects of this machinery. This part is about *protection and repair.*

The stress response is indeed a balancing act between aggression and protection

PEM may represent a dysbalace between the two arms of the stress response:

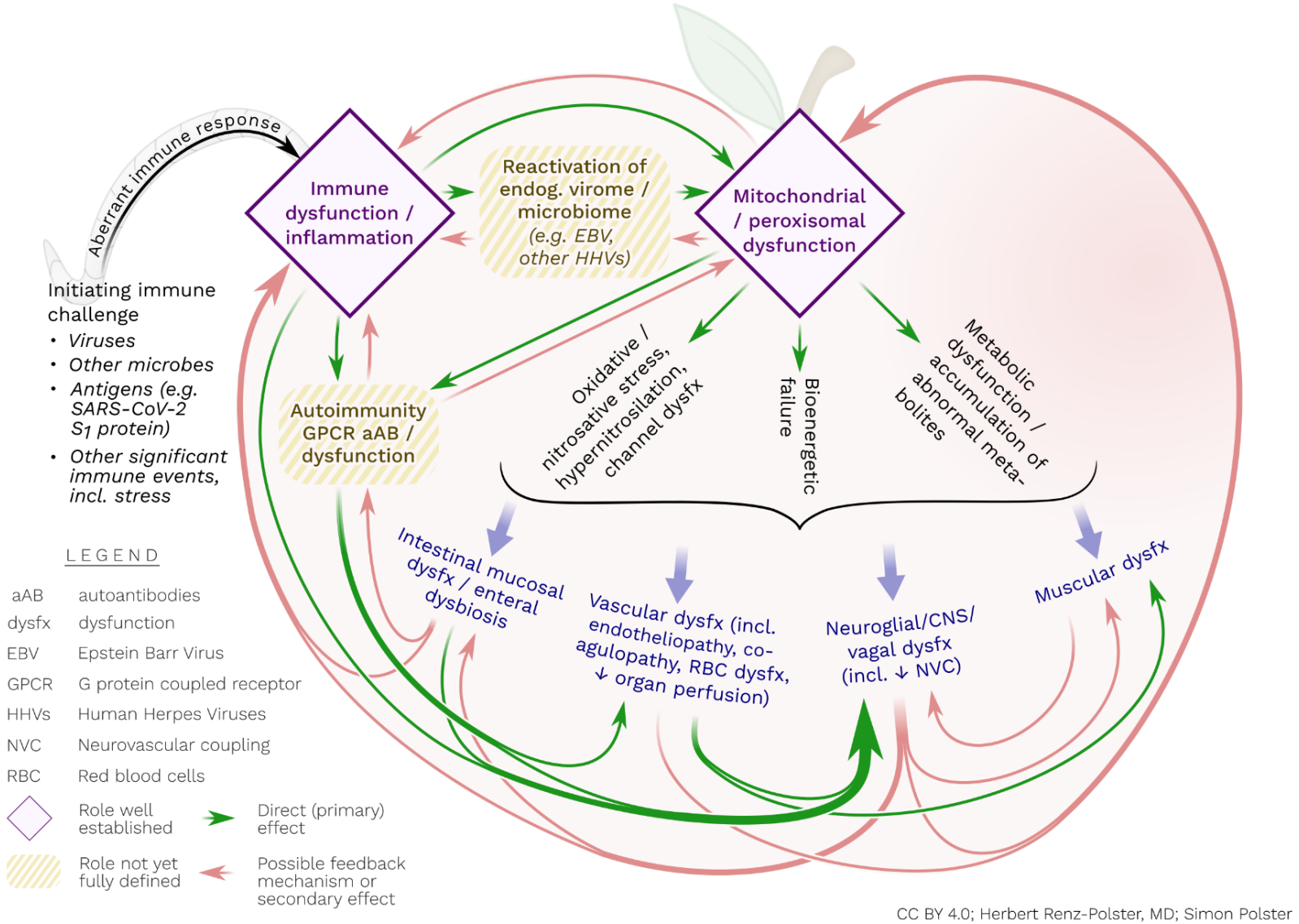
- The effects of exertion (immune activation, including inflammatory, oxidative and adrenergic load) cannot be resolved
- The tissues get hammered without protection and lose their ability to recover and repair

Injured by friendly fire?

If exertion hits the body unprepared and unbuffered, the following can happen:

- … tissue damage from inflammation and oxidative stress
- … viral reactivation
- … mitochondrial dysfunction
- … immune dysfunction (if chronic and associated with inflammation: autoimmunity)
- … endothelial dysfunction (perfusion failure, barrier dysfunction)
- … metabolic dysfunction
- … CNS dysfunction: autonomic failure, neuroinflammation
- … ineffective use of CNS ressources (→ fatigue)

In short, the whole ME/CFS zoo



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… including

some possible vicious cycles:

- oxidative stress → endothelial dysfunction → leaky blood brain barrier and/or reduced CBF → neuroinflammation → inadequate stress response

- viral reactivation in endothelial cells → endothelial dysfunction → reduced cerebral blood flow → neuroinflammation → inadequate stress response

- endothelial dysfunction → reduced tissue perfusion → mitochondrial dysfunction (+/- → toxic metabolites like ammonia) → neuroinflammation → inadequate stress response

- immune dysfunction → viral reactivation → mitochondrial dysfunction → dysfunction of affected tissues (including endothelial cells and immune cells) → …

- immune dysfunction → viral reactivation → immune exhaustion → lower threshold for viral reactivation → …

What does this have to do with the brain(stem)?

- The stress response is the result of intense collaboration between certain CNS regions/nuclei and the functional networks to which they are connected
- A coordinated stress response thus requires normal connectivity ("communication") and normal "hardware" (e.g. functioning brain nuclei)
- CNS regions/nuclei implicated in arousal and stress adaptation include: the limbic system including hippocampus, amygdala, parts of the cingulate cortex, the insular and thalamic regions, subdivisions of the prefrontal cortex and, most centrally, some brainstem centers like the locus coeruleus and the circumventricular organs
- The brainstem is indeed thought to have a central and coordinating role in the stress response (no surprise: the brainstem is part of a functional connectome linking 58 brainstem nuclei with the midbrain, pons, medulla and the cortex) (Hansen 2024)

The ME/CFS „brain findings“ ?

… the abnormal findings identified in ME/CFS basically point to all the brain hubs, nuclei and networks relevant to the stress response:

- „broken connections“ – there is altered connectivity between the brainstem, the cerebellum and „higher“ nuclei/networks relevant to stress adaptation
- abnormal perfusion, oxygen content or metabolic function in several brain areas relevant to stress adaptation (e.g. locus coeruleus, cingulate cortex, hypothalamus, insula…)
- abnormalities in the brainstem itself may be key (reduced control of systemic inflammation? Reduced norepinephrine signalling? Vagal dysfunction? Others?)

A central role of the brainstem?

… is possible and plausible:

- brain connectivity is heavily influenced by brainstem nuclei
- the brainstem is a recognized regulator of our „peripheral“ biology (including the immune system and the systemic inflammatory response)
- The brainstem is THE relay station of peripheral signals
- A central role of the brainstem would explain the clinical and pathobiological overlap between ME/CFS and traumatic brain injury
- It would also explain why chronic mechanical effects on the brainstem can trigger ME/CFS (CCI, possibly hEDS)

And what about the muscles? Many researchers consider ME/CFS a muscular disorder…?

There is evidence that the muscle problems actually „follow“ CNS dysregulation:

- Muscle fatigue is most prononced in those who hardly use their muscles (severe patients)
- In ME/CFS, muscle fatigue clinically always goes hand in hand with CNS symptoms: the more pronounced the latter the more pronounced the former
- Muscle fatigue can be triggered by mental exertion alone
- Muscle fatigue in ME/CFS can be relieved by centrally acting medications (like lorazepam)
- A „brain-muscle signaling axis“ was discovered through which the brain regulates muscle performance: Brain Inflammation can explain muscle fatigue ((Yang 2024))
- a major finding in the NIH intramural study was: “central fatigue” was driving the fatigue of the muscles ((Nath 2024))
- In an animal model it can even be shown that mitochondrial dysfunction in certain brain areas can cause mitochondrial dysfunction in the muscles ((Zhang 2024))

Summary: a challenged brain has a solid reach into the muscles…

And what about the muscles? (2)

Rob Wüst´s team showed that heavy exercise can literally trash the muscle tissue in ME/CFS patients (Appelman/Wüst 2024). Could this represent „harm by friendly fire“?

- Maureen Hanson´s team showed that, in healthy people, exercise causes a rise in several proteins which are thought to induce repair processes in muscle cells and thus protect muscles against damage from exercise (Giloteaux, 2024)
- This surge seems to be lacking in ME/CFS patients - this may open the door for the muscle damage seen after exercise.

And what about endothelial dysfunction (ED) – could this be „centrally“ mediated, too?

- There is intense crosstalk between the autonomic nervous system and blood vessels ((Sheng 2018))
- The brainstem's inability to regulate autonomic functions can therefore directly impact endothelial function.
- Indee, ED is part of dysautonomia syndromes like POTS ((A. Chopoorian, 2021))
- Chronic sympathetic activation as well as chronic inflammation (both features of ME/CFS) can induce inflammation and oxidative damage to the vascular endothelium
- ED can happen from sleep deprivation ((Cherubine 2021))
- The endothelium is a harbor for latent viruses like EBV which could be reactivated in periods of immune dysfunction

All this may indicate that brainstem functions are closely tied to endothelial functions (including endothelial inflammation)

What could be the root cause of all this ?

- **Infections could induce connectivity changes in the brain** (Fernandez-Castaneda 2022): mild SARS-CoV-2 infection → persistently impaired neurogenesis in certain brain regions, decreased activity of oligodendrocytes/ myelin loss → dysfunctional connectivity (e.g. between brainstem and “higher” networks und vice versa)
- **Infections could induce autoimmunity against CNS targets** (Jernbom 2024) - depending on the target, this could mess up the arousal system (e.g. when affecting the nucleus coeruleus) (Iwasaki 2025) or the aCC
- **Infections could go along with viral persistence in certain brain tissues** (however, evidence is lacking so far)
- **Infections could lead to reactivation of latent viruses in certain brain tissues affecting their function**
- **Infections could induce inflammation of the vagus nerve** → dysregulation of the brainstem (Papadopoulou 2022, vanElzakker 2013)
- **Infections could induce endothelial dysfunction** → leaky BBB and/or dysfunctional neurovascular coupling → neuroinflammation → dysfunctional connectivity

If you want to read on (including the references):

https://tinyurl.com/3b52we79

Guardian angels off duty? ME/CFS is Sustained by an Impaired Stress Response in the Central Nervous System

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Herbert Renz-Polster, MD