Literature on the stress response in ME/CFS

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In the last 2 years evidence gathered by ME/CFS researchers converges on a very peculiar finding: ME/CFS patients seem to be unable to adapt to stress – be it physical, cognitive, mental or even othostatic in nature. While healthy people respond to bouts of stress with profound biological changes on many levels – including on the metabolic, immunologic and epigenetic level -, ME/CFS patients stand out by the following findings:

- Lack of metabolic adaptation in response to exercise ("metabolic flatline"): https://www.mdpi.com/1422-0067/24/4/3685
- Lack of transcriptomic adaptation in response to exercise ("transcriptomic flatline"): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9916639/pdf/ijms-24-02698.pdf
- Lack of changes in circular RNA expression after exercise: https://www.sciencedirect.com/science/article/abs/pii/S0378111923004092
- Lack of adaptation of T- and NK cells after stress exposure: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9916639/pdf/ijms-24-02698.pdf
- Lack of changes in microRNA levels in peripheral blood mononuclear cells after exercise: https://pubmed.ncbi.nlm.nih.gov/32291908/
- A lacking acute phase response to luminal gut antigens translocated into the bloodstream during exercise: https://www.sciencedirect.com/science/article/pii/S2666354623000418?via%3Dihub
- no changes in the total concentration of extracellular vesicles (EVs) post-exercise (which is clearly seen in healthy controls) as well as a delayed increase in abundance of several EV proteins in response to exercise: https://www.biorxiv.org/content/10.1101/2023.08.28.555033v1.full.pdf
- lack of adjustment of cerebral blood flow in response to orthostatic stress: https://www.sciencedirect.com/science/article/pii/S2467981X20300044
- lack of cardiovascular and respiratory adjustment in response to exercise (inability to raise heart rate and respiratory rate to the levels demanded by exercise): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8923458/ and https://journal.chestnet.org/article/S0012-3692(23)00502-0/fulltext
- (Interestingly, a reduced capacity to respond to stress has recently also been found in monocytes and lymphocytes in patients with PASC: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(23)00294-3/fulltext)

This lack of immunologic, cardiovascular and metabolic adaptation to stress translates into **serious temporal vulnerability after exposure to stress conditions.** After all, all tissues of the body are left unprepared to meet the many profound challenges that physical , cognitive, mental or orthostatic stress brings along (e.g., inflammatory stress, oxidative stress, nitrosative stress, microbial translocation, adrenergic stress, increased or decreased blood flow). This unbuffered assault is bound

to trigger **a systemic inflammatory response and send a host of vulnerable cell populations and related functional units into dysfunction,** for example:

- Endothelial cells (which closely interact with the coagulation system) will stop working properly. This endothelial dysfunction in turn can result in limited perfusion (nutrient and oxygen supply) to all tissues, including the muscles, which then will also stop working properly (and, possibly, react with pain).
- Nerves may also become dysfunctional – especially those with high energy demand like small fibers. This can result in intermitten or permanent small fiber dysfunction/neuropathy.
- Other cell populations likely to be affected are the very sensitive cells in our brain (both neuronal and non-neuronal cells), leading to dysregulation of our brain and autonomous functions. (https://www.frontiersin.org/articles/10.3389/fncel.2022.888232/full) Some glial cells are also responsible for maintaining the nerve sheaths – their dysfunction may add to the dysregulation.
- Inadequately reacting immune cells will lead to temporary immune dysfunction. This can have serious effects on anti-microbial defence and/or tolerance. The stress-induced immune defect may, for example, allow for reactivation of endogenous microbes and/or genomically integrated retroviruses. Or it could cause flare-ups in auto-immunity

This assault can have even more consequences: unbuffered oxidative stress together with restricted tissue perfusion can lead to profound mitochondrial dysfunction. The mitochondria may then utilize amino acids as alternative fuel source and produce toxic by-products (like ammonia) – which in turn can have toxic effects especially in the brain. Also, endothelial cells (together with glial cells) constitute the blood-brain-barrier – if these cells don´t work properly the blood-brain-barrier becomes leaky and will allow for migration of peripheral immune cells into the central nervous system and thus for further disruption of CNS functions. Glial cells also constitute the immune system of our brain – if these cells are overactivated, a specific form of brain inflammation can occur ("neuroinflammation"). This neuroinflammation is problematic in itself but it can also "ignite" an inflammatory response in the whole body!
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4810977/)

A true multi-system disease

The many consequences that a lacking stress response can have on so many tissues and body functions explain why ME/CFS is called a multi-system disease. They also explain why researchers have identified so many different and apparently disparate pathological findings in ME/CFS – including muscle abnormalities, blood vessel abnormalities, red blood cell abnormalities, abnormalities of the small nerve fibers, malfunctioning mitochondria, immune system dysfunction, brain dysfunction like dysautonomia, viral reactivation, etc. But most importantly, these intertwined processes explain why symptoms in ME/CFS get worse or flare up after exercise and then need a very long time to quiet down again (ME/CFS patients need 2 weeks on average to recover to their previous baseline from a 2-day cardiopulmonary exercise test compared to 2 days in healthy controls: https://www.mdpi.com/1648-9144/59/3/571)