



# Treating Chronic Fatigue states as a disease of the regulation of energy metabolism

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**Abstract** Chronic Fatigue Syndrome is a physiological state in which the patient feels high levels of fatigue without an obvious organic cause, which affects around 1 in 400 people in the developed world. A wide range of causes have been suggested, including immune or hormonal dysfunction, viral or bacterial infection, and psychological somatization. It is likely that several causes are needed to trigger the disease, and that the triggers are different from the mechanisms that maintain fatigue over months or years. Many treatments have been tested for CFS, with very limited success – a programme of combined CBT and graded exercise shows the most effect. I suggest that patients with CFS have a reduced ability to increase mitochondrial energy production when exertion requires it, with fewer mitochondria that are each more efficient, and hence nearer to their maximum energy output, than normal. A range of indirect evidence suggests that the renin-angiotensin system stimulates mitochondrial responsiveness and reduces mitochondrial efficiency: chronic under-stimulation of this system could contribute to CFS aetiology. If correct, this means that CFS can be successfully treated with RAS agonists (eg angiotensin mimetics), or adrenergic agonists. It also suggests that there will be a positive link between the use of adrenergic- and RAS-blocking drugs and CFS incidence, and a negative link between adrenergic agonist use and CFS.

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## Background

Chronic Fatigue Syndrome is a physiological state in which the patient feels high levels of fatigue without an obvious organic cause. Abnormal fatigue is known to be a pathological feature of many diseases. In a set of syndromes together called Chronic Fatigue Syndromes (CFS) fatigue is a defining symptom, and does not have an obvious organic cause, such as physical exertion or the metabolic effects

of another disease process [1,2]. Clinical diagnosis emphasises the presence of symptoms of fatigue and the absence of obvious causes [3–5]. For reasons of social acceptability, CFS is often called Myalgic Encephalomyelitis (ME) in the non-technical literature [2].

'Fatigue' in this context is not the same as 'weakness'. CFS patients usually have normal muscle strength [6–8] (although a few studies find loss of muscle power in CFS patients, possibly an effect of 'deconditioning', ie being 'out of shape' from prolonged lack of muscle use [9,10]), so CFS is caused neither by a failure of muscle power or a failure of motivation. It is also not caused by failure

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of the cardiovascular system to support muscle physiology [10] (although see [11] who finds some cardiovascular deconditioning). The chronic fatigue found in chronic heart failure patients is also metabolic rather than due to haemodynamic effects [12,13]. Rather, CFS is an inability to apply that power to sustained effort. This is usually taken to mean physical effort, but mental effort seems to be similarly impaired, independent of any depressive or other psychiatric disease [14].

CFS can be severely disabling [15]. The disease can last for years, while some patients recover on their own, others show resistance to recovery over a decade or more [16]. This variability of outcome, as well as the variability of symptoms and different diagnostic criteria, make comparison between studies and therapeutic approaches very hard [17].

Typical prevalence estimates suggest around 1/400 people are suffering from CFS at any one time [2,18–25]. Some studies have found lifetime risk of suffering prolonged, inexplicable fatigue as high as 33% [26].

## CFS causes and treatments

Most studies show that no single factor is necessary and sufficient to trigger CFS, and that a combination of triggering factors applies, such as allergy and psychological factors [27], heavy exercise and viral infection [28] or other muscle damage [29,30], or CNS and immunological factors [31]. Consequently, there has been little progress in finding a cure.

Several meta-studies of the trials literature show that graded exercise programmes and Cognitive Behavioural Therapy (CBT) are the only approaches which shows a consistently good track record of benefit in clinical trials [17,32,33]. There is no effective pharmacological treatment for CFS [33,34], although this is not for lack of searches – Whiting et al analysed found 350 trials, and in a meta-analysis of 44 of them found 31 different interventions [17,32]. A major issue is that the trigger for CFS is believed to be different from the mechanisms that sustain the disease [1,35], so searches for, and treatments of, triggering factors may say little to how to treat or cure the disease once it is established.

Suggested etiologies for CFS generally fall in the category of psychological/psychiatric [1,36], immunological/viral, or hormonal [37]. The disease is at least partly psychological [1,26], and it is often comorbid with psychiatric disease, especially depression [1,38–41]. But antidepressants are generally considered ineffective against all but the psychological sequelae of CFS [37,42,43], and a large trial

using treatments to enhance cognition [14] was not successful [44]. Association with immune and allergic disease and immune activation parameters [27,45] or abnormal immune regulation [46] has suggested immunological treatment, but these have not generally shown any objective value [47,48]. Anti-viral agents do not seem to help [2,49], and the symptomatic similarities to adrenal insufficiency are not supported by any more than mild impairment of the hypothalamic-adrenal axis [50–53], although these are the only consistent hormonal changes in CFS [52,54]. A wide range of other etiologies have been suggested for CFS (eg. [55–58]).

In part, the variability in trial outcome may be because 'CFS' is not one disease [2,4,59], or if a single disease (as Ciccone and Natelsson argue on epidemiological grounds [60]) that is has distinct sub-types [2]. So it is likely that, even if a treatment does work well for one sub-group of patients, it will not work as well for others.

## Metabolism in CFS

There are no obvious metabolic 'problems' that could cause CFS, but a common finding is a reduced level of oxidative metabolism [61] and increase in lactate production [9,10], which these workers attribute to deconditioning – loss of muscle tone and power from prolonged lack of use. (Lactate elevation could also be related to the reduction in post-exercise delivery of oxygen to tissues observed by McCully and Natelson [62], although this reduction does not in itself seem to alter muscle metabolism [63]). Mitochondrial abnormalities and degeneration are frequently [64] although not always [10] found.

## RAS, alarm response and CFS

A common (although not obvious) theme running through CFS is the involvement of the body's 'fight or flight' systems, and particularly the neurotransmitters and hormones of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS). Several indirect lines of evidence suggests that low RAS activation is related causally linked to CFS triggering or maintenance.

- Serum Angiotensin converting enzyme (ACE) is recognised as a marker for CFS [65].
- Gulf war veterans with the Tissue ACE gene I allele (high level expression) are less likely to be found to develop CFS as part of the 'Gulf War Syndrome' spectrum of disorders than veterans

who carry the D allele. DD veterans are 8 times as likely to suffer chronic fatigue as the whole population [66].

- Chronic heart failure is often accompanied by CFS-like fatigue (which is not designated CFS because of the co-morbidity with heart failure). Haemodynamic parameters do not explain this. The principle difference between the two patient sets is the extensive dosing of heart failure patients with AT-II inhibitors, beta blockers and ACE inhibitors, usually in combination [12].
- Vasopressin levels have been reported to be lower in CFS patients, suggesting relative inactivity of all blood pressure control systems [67].
- Oxygen delivery to muscles post exercise has been found to be reduced in CFS, which has been attributed to reduced autonomic control of vasodilation in CFS [62].

## RAS, SNS and mitochondria

A mechanism for the effect of the RAS on fatigue is through mitochondrial efficiency and energy reserve. Several pieces of evidence suggest that RAS and SNS activation reduce the efficiency of mitochondrial energy production, and increase mitochondrial number.

- Beta-3 agonist induce UCP-1, through mechanism involving rB protein, in fat (turning white to brown fat) [68,69] and muscle [70]. Beta adrenoreceptor knockouts depress brown fat formation [71]. The same pathways stimulate mitochondrial biogenesis via CaMK and PGC-1 [72].
- AT-II antagonists increase the duration and energy of sperm swimming. Sperm are almost totally dependent on mitochondrial metabolism of externally supplied sugars for their energy. AT-II antagonists increase this power generation, ie increase the efficiency with which the sperm generate energy. [73,74].
- RAS blockade is associated with increased ability to build muscle mass. There are several pieces of evidence of this type, from cachexic patients, training athletes and high altitude mountaineers [75–77]. This may seem a contrary piece of evidence. However, any body builder knows that muscle mass is best increased through intense anaerobic exercise, not through aerobic exercise. If RAS blockade reduces the ability of mitochondria to upregulate their energy generation, then a given level of activity would exhaust the aerobic energy generation capacity of low-RAS individuals before it exhausted the aerobic capacity of high-RAS individuals.

Consistent with this hypothesis (but with many others as well) is that CFS symptoms are increasingly being shown to be associated with, and possibly caused by, increased oxidative stress [78], which would be expected of long-term loss of adequate mitochondrial function as other systems took up the task of balancing muscle redox balance [79,80].

## RAS, SNS and mitochondrial responsiveness in CFS

Why should the same hormonal system increase mitochondrial number yet decrease mitochondrial efficiency? I hypothesise that this is due to an inverse correlation between mitochondrial efficiency and the ability of mitochondria to increase energy output on demand, and that this links the same systems to CFS.

For rapid response to shock or stress (such as caused by psychological shock, such as activates the SNS, or haemodynamic shock such as activates the RAS), mitochondrial energy production must be capable of being upregulated in seconds. One of the more common ways of enabling metabolic pathways to respond rapidly to changes in control, and to provide greater response than feedback inhibition and substrate activation mechanisms can allow, is to use substrate cycles at key points in the metabolic pathway concerned [81]. Such a cycle in mitochondria would have the effect of making the mitochondria 'inefficient', ie causing it to oxidise substrate to H<sub>2</sub>O and CO<sub>2</sub> without generating maximal energy. Uncoupling proteins allow precisely this to happen: other mechanisms can also be imagined to achieve this in oxidative phosphorylation.

The physiological benefit of such cycles is that the body can respond rapidly to increased energy demand. The downside is that you need more mitochondria at rest (because each is less efficient), and some resting energy is 'wasted', ie dissipated as heat.

The paradoxical effects of RAS and the SNS can therefore be seen as the cell's response to chronic stimulation from hormonal systems that alert the body to the need for immediate, substantial energy demand, through increasing mitochondrial number and mitochondrial responsiveness. Blockade of these systems signals a reduction in stress demand and hence the need for fewer, more efficient and less potentially responsive mitochondria. This relates to muscle mass because mitochondrial cycling is not something that can be switched on and off on a matter of minutes – protein synthesis, and creation of new mitochondria take hours or days. If a

patient has their RAS chronically blocked, genetically or pharmacologically, then the number of mitochondria will fall and their ability to rapidly increase energy output will fall. When such muscle is exercised, it will rapidly reach its limit of oxidative phosphorylation and move into a glycolytic metabolism, typical of sprint rather than marathon training regimes. This will result in more muscle build-up, as it does in more conventional training. For patients suffering severe muscle wasting (cachexia), even everyday tasks would become sprint training tasks, resulting in muscle build-up (or slowing of muscle decline).

### Hypothesis: chronic lack of ras/sns stimulation maintains CFS

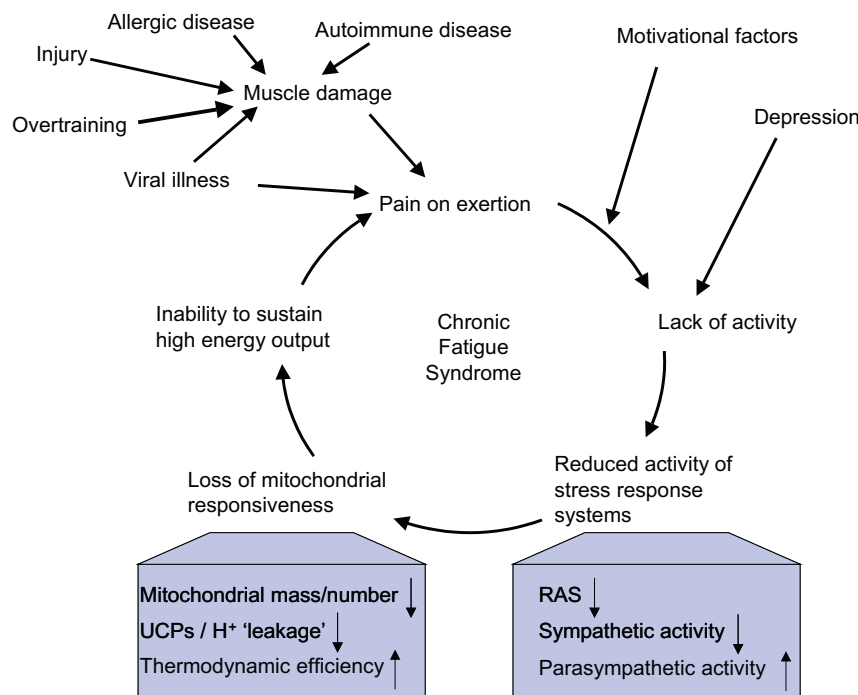
My hypotheses is that the failure of CFS patients to maintain power output in physical or mental activities is due to an inability of their metabolism to deliver increased energy in response to increased demand. This is a key component of the maintenance of CFS. Any event that causes the patient to reduce their exertion to a low level might trigger the state: the likelihood that it did so would be influenced by other physiological and genetic fac-

tors. Once the capacity to increase energy production on demand has been reduced, any exercise will be 'felt' to be like heavy exertion, and will rapidly cause the muscle to become hypoxic, generating lactic acid, and sometimes causing muscle damage more normally associated with over-exercise. Depending on other physiological and psychological factors, this may be sufficient to deter the individual from exercising, maintaining a vicious cycle. This is illustrated in [Figure 1](#).

This means that treating the initial, triggering causes of CFS – viral infection, injury, inflammation, depression – are very unlikely to be cure the disease: this is found to be the case. The only two approaches likely to be effective are

- i. increasing physical activity: this is the only therapeutic approach presently shown to have an effect
- ii. increasing mitochondrial mass and responsiveness

I propose to treat CFS through the second of the two options above. The pharmacology for doing this could include use of stimulants of the renin-angiotensin system, or sympatheticomimetic agents, especially beta adrenergic agonists such as salbutamol, thiotropium or ephedrine. In practice, because



**Figure 1** Cartoon of the mechanism of the proposed hypothesis (A wide range of insults can result in a patient reducing activity over a substantial period of time (weeks or months). This leads to reduced RAS and sympathetic activity, and hence to an decrease in mitochondrial number and increase in efficiency which leads to an inability to sustain high power output levels, and hence exertional pain on even mild exercise).

of the redundancy of biological circuitry and the need to avoid unwanted pharmacological effects, combinations of low doses of these compounds are likely to be the best approach.

I note that this is unlikely to be a 'universal cure'. In some groups of patients other factors than cell-level power generation may be a dominant maintaining factor, and in particular in some defects in neuromuscular transmission or inappropriate psychological attitudes are strongly suspected to be important in the disease [59]. However it is plausible to suggest that this approach will be of some use to a lot, maybe a majority of patients, and as it is very easy to administer and should have a rapid effect, if proven successful it could be used as a 'first line' treatment, with more costly and time-consuming psychological and exercise approaches being brought in subsequently.

## Predictions and tests

Testable predictions flow from this hypotheses. Most obviously, it suggests that a suitable combination of RAS and adrenergic agonists will be an effective treatment for CFS. However proving this is a long-term prospect. In the more immediate term, the following experimental tests are available.

- In any cycling system, as flux through the pathway is increased, back flux through the cycle becomes less a factor in the overall flux (although it never reaches 0). One would expect that the 'efficiency' of mitochondria in cells that were being energetically exercised would be higher than the same cells under resting conditions. This could be tested with cultured muscle cells.
- Tissue (specifically muscle) in chronically-RAS-stimulated or RAS-blocked animals would be expected to have more or less mitochondria per unit mass than average, respectively, and less or more efficient mitochondria respectively.
- Other agents associated with the 'fight or flight' response might be expected to have similar effects: The effect of  $\alpha$ -adrenergic agonists would be interesting in this regard, as the  $\alpha$ -adrenergic system does not activate RAS: in this respect I note that Naschitz et al [82] report that Miodrine, an  $\alpha$ -adrenergic agonist, was effective in one case of CFS.
- Other agents associated with tissue growth, and with muscle bulk, such as growth hormone or I-GF, would however not be expected to have these effects.

- Other agents associated with the clinical control of blood pressure, but acting other than through the RAS, such as the thiazide diuretics, would not have these effects.

The measurement of mitochondrial number can be done by electron microscopy. Mitochondrial mass may be estimated from assay of any one of several mitochondrion-specific enzymes, or measuring relative amount of mitochondrial DNA [83,84]. 'Efficiency' can be measured by three approaches – measuring the net amount of oxygen and glucose consumed by resting cells (assuming that drug treatment has not altered the cells' energy requirements), measuring intracellular ATP pools compared to oxygen and glucose consumption, and measuring mitochondrial membrane potential. This last is most direct, and can be achieved by using dyes such as rhodamine 123 [85] or JC-1 [86].

In addition, there is a clear epidemiological prediction of the logic above, that patients treated with RAS or SNS antagonists will be more prone to develop long-term, disabling fatigue than patients treated for the same diseases with other classes of drugs. The obvious comparison is in cardiovascular disease, where the sequelae of the use of ACE inhibitors, AT-II antagonists, and beta-blockers can be compared to those arising from use of diuretics,  $Ca^{2+}$  blockers, cardiotonics, or nitrates. Conversely, patients treated with adrenergic agonists might be expected to have a lower than normal level of fatigue syndromes. Asthmatics are an interesting case here, being treated with inhaled beta adrenergic agonists that act primarily topically but which do have a low level of systemic penetration [87–89]. Very extensive academic databases of cardiovascular medicine treatments and outcomes have been compiled over the last two decades. These databases could be tested by suitable 'data mining' of these patient and clinical trial databases for these predicted outcomes.

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