Chronic Fatigue Syndrome and Related Illnesses: An Overall Mechanism

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It has been the conventional wisdom that chronic fatigue syndrome is an unexplained illness and that even the symptoms are unexplained. Although several research groups have proposed that fibromyalgia and multiple chemical sensitivity and several other diseases/illnesses may share a common etiologic (causal) mechanism, the conventional wisdom has been that we don't understand what that mechanism is – indeed it is often stated that these illnesses are "baffling." In my recent book, "Explaining 'Unexplained Illnesses': Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others," Haworth Press, I challenge all of this conventional wisdom and much more. Indeed, many have argued that we need a new disease paradigm to understand this group of illnesses, and by providing such a paradigm, I argue that this part of conventional wisdom is correct.

The basic approach that I have used is based on the fact that cases of each of these illnesses are initiated (started) by certain short-term stressors, including viral, bacterial and even protozoan infections, exposure to several classes of chemicals, physical trauma, severe psychological stress and possibly even exposure to ionizing radiation. There are at least 12 or 13 such stressors that appear to initiate one or more of these illnesses and one needs to ask, therefore, how such stressors can cause chronic illness? I present evidence in my book that each of these stressors can start a sequence of events, leading to increased synthesis of nitric oxide in the body. So despite the diversity of these stressors, they may produce a common biochemical response. So how might the compound nitric oxide produce these chronic illnesses? By acting through its oxidant product peroxynitrite, which initiates a complex biochemical vicious cycle that is the cause of illness.

This vicious cycle is called the NO/ONOO- cycle, based on the structure of nitric oxide (NO) and peroxynitrite (ONOO-) but pronounced no, oh no! The core of the cycle is diagrammed in figure 1 from my web site. Please don't panic when you see many things in that figure that you may not be familiar with. There are two understandings that are most important. The arrows shown in the figure represent one or more mechanisms by which one element of the cycle can increase the levels of a second one. You can also see that these sequences of arrows make up a series of interacting cycles, such that once these cycles get going, the overall cycle, the NO/ONOO- cycle will propagate itself over time, producing chronic illness.

Figure 1

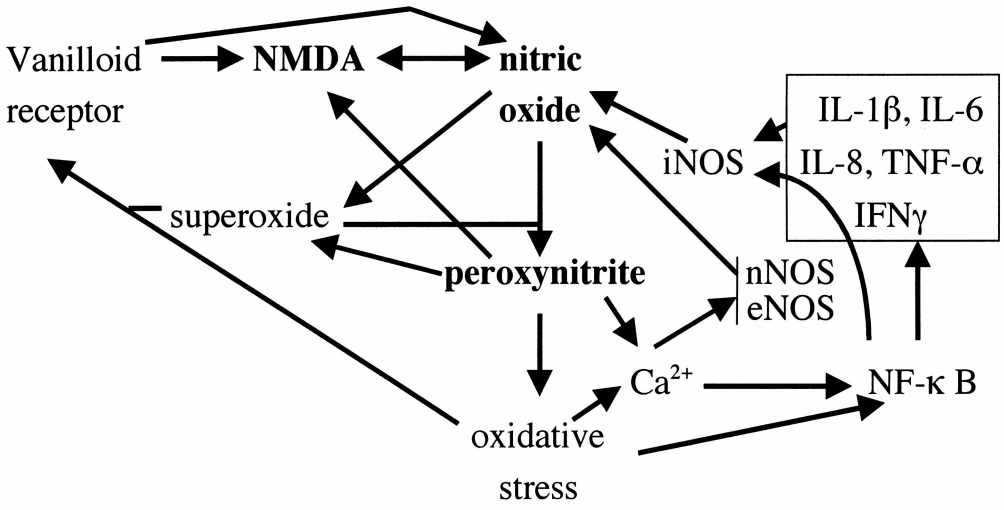

Figure 1. Stimulatory responses among various elements in proposed vicious cycle mechanism. Each arrow represents one or more mechanisms documented in the literature by which one element increases the level or activity of the next element.

Most of the mechanisms of the cycle are well-accepted biochemistry and physiology, and in my book, I lead the reader through these mechanisms, so that you can understand how they work and how extensive the evidence is for each of them.

There are three types of generic evidence presented in my book for the existence of the NO/ONOO- cycle as well as evidence for its role in each of these illnesses.

There are five principles outlined in my book that underlie the NO/ONOO- cycle as an explanatory model:
1. Illnesses can be initiated by stressors that increase nitric oxide or other cycle elements.
2. The chronic phase of illness is caused by the cycle and therefore, cycle elements will be elevated in the chronic phase of illness.
3. The symptoms and signs of illness are produced by one or more elements of the cycle.
4. The basic mechanisms of the NO/ONOO- cycle are local – that is they are localized to certain tissues in each individual. The reason for this is that the three compounds most central to the cycle, nitric oxide, superoxide and peroxynitrite have relatively short half-lives in biological tissue and the arrows – the mechanisms involved in the cycle act at the level of individual cells. The local nature of the cycle means that different sufferers may differ from each other in which tissues are impacted by the NO/ONOO- cycle, giving much variation of symptoms from one individual to another. Thus, one of the great

puzzles of these illnesses, the stunning variation in symptoms and signs, may be easily explained as being a consequence of the basic causal mechanism.
5. The way to treat these illnesses is to down-regulate the NO/ONOO- cycle biochemistry. That is we should treat the cause, not the symptoms.

Quite a number of the symptoms and signs of CFS are often shared by these other multisystem illnesses, including pain, cognitive dysfunction, fatigue, immune dysfunction such as low NK cell function, orthostatic intolerance, SPECT scan and PET scan abnormalities, depression and anxiety. These can all be explained as being produced by the NO/ONOO- cycle. The most characteristic feature of CFS, post-exertional malaise, may be explained by a CFS-specific change in HPA axis dysfunction, leading to changed control of cortisol in response to exercise. So a vast array of features of CFS may be explained by this model. And there are 14 distinct types of evidence which support a NO/ONOO- cycle etiology for CFS (a fifteenth was reported recently).

What about treatment? In Chapter 15 of my book, I discuss 30 different agents or classes of agents that are predicted to down-regulate the NO/ONOO- cycle biochemistry. Of these we have clinical trial data for effectiveness for 13 of them (only 12 of which had been reported when the book was written). There are several others, where we have clinical observations or anecdotal reports – less reliable types of evidence. In most cases, these individual agents produce only a modest improvement in these multisystem illnesses.

However, complex treatment protocols have been developed by several physicians/scientists, five of which are discussed in my book – those of Drs. Paul Cheney, Jacob Teitelbaum, Garth Nicolson, Nash Petrovic and the one developed by Dr. Grace Ziem and me. Each of these use at least 14 different agents or classes of agents predicted to down-regulate the NO/ONOO- cycle biochemistry. And each appears to be much more effective than are the individual agents. Most of these agents are nutritional supplements but some are conventional pharmaceuticals. The clinical trials and clinical observations supporting the efficacy of these treatments provide support for the NO/ONOO- cycle mechanism. Both these studies and the studies of single agents show that the NO/ONOO- cycle mechanism makes useful predictions in terms of therapy.

I think there are many different approaches to therapy that hold promise for the treatment of these illnesses. But we need to do many more clinical studies to compare them and hone their effectiveness. I would add that I developed a new protocol using only over-the-counter nutritional supplements through the Allergy Research Group (http://www.allergyresearchgroup.com/) which I feel will be both a useful and accessible approach to the down-regulation of the NO/ONOO- cycle. But let me remind the reader that I am a PhD, not an MD and nothing I say or write should be viewed as medical advice.

I think that this general approach – using multiple agents predicted to down-regulate the NO/ONOO- cycle biochemistry is very promising. Interestingly, it is almost diametrically opposite the approach that has dominated medicine for the last 60 years –

the search for “magic bullets” that will cure a disease. This magic bullet approach has not worked well for chronic disease as shown by the fact that we rarely cure chronic diseases.

I’d like to finish this by asking the question that I am often asked by people. Is my book understandable for lay people – those not extensively trained in science? I think my book is useful for educated lay people with a compelling need to understand one or more of this group of multisystem illnesses. Many of those people have educated themselves very well about these illnesses and often know much more than does the typical physician. They will find my book to be of interest, although they will also find it to take quite a bit of time and effort to go through. So don’t be intimidated by it, but don’t expect it to be easy going either.