

Nitric Oxide/Peroxynitrite:

Mechanism for multiple chemical sensitivity (**MCS**), chronic fatigue syndrome (**CFS**), fibromyalgia (**FM**) and post-traumatic stress disorder (**PTSD**)

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A large number of research groups have proposed **that chronic fatigue syndrome (CFS), fibromyalgia (FM), multiple chemical sensitivity (MCS)** and, in some cases, **posttraumatic stress disorder (PTSD)** have multiple overlaps and may share a common etiology (cause). They have:

- overlapping symptoms
- many people are diagnosed as having more than one
- cases of each are commonly initiated by a short term stressor presumably inducing these chronic conditions.

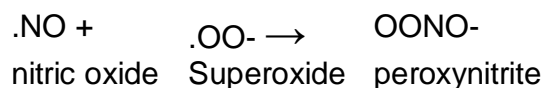
Gulf War syndrome exhibits elements of all four.

The notion that CFS, MCS, PTSD and FM and several other diseases may share a common etiology has been proposed by Miller, although the etiologic mechanism was uncertain. Miller asks "[Are we on the threshold of a new theory of disease?](#)" (Toxicol Indust Health 1999;15:284-294).

For example, Buchwald and Garrity concluded in a study of CFS, MCS and FM patients that: "[despite their different diagnostic labels, existing data, though limited, suggests that these illnesses may be similar if not identical conditions.](#)" (Arch Inter Med 1994;154:2049-2053).

Donnay and Ziem proposed that CFS, FM and MCS "[may simply reflect different aspects of a common underlying medical condition.](#)" (J Chronic Fatigue Syndr 1999;5:71-80).

The etiologic theory I will be discussing focuses on nitric oxide and its oxidant product peroxynitrite, a potent oxidant.



The two tissues that are reported to be the most active in synthesizing nitric oxide and probably superoxide are the brain and the immune system cells. These are also the tissues most often reported to be dysfunctional in this group of disorders.

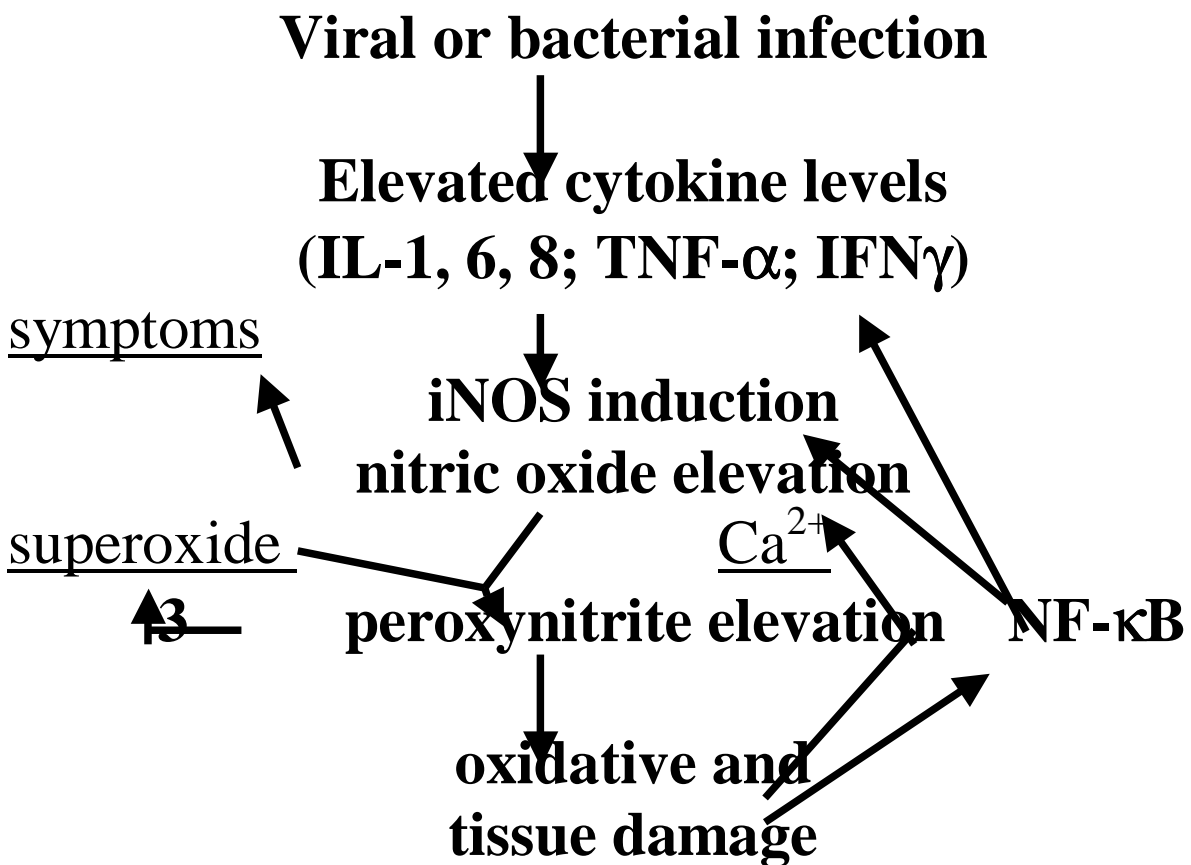
Short term stressors are known to produce increases in nitric oxide:

<u>Condition</u>	<u>Most common stressor</u>
CFS	infection
FM	physical trauma
MCS	chemical exposure
PTSD	psychological stress

Question: How does a short term stressor lead to a chronic medical condition?

Proposed Answer: It initiates a vicious cycle mechanism which perpetuates itself.

Example of vicious cycle mechanism:



Does such a vicious cycle act in living tissues?

A number of studies have been published in which drugs known to work via nitric oxide (nitroglycerine or nitroprusside) have been shown to increase nitric oxide synthesis in tissues. It follows that the proposed vicious cycle is not just theoretical but rather that this vicious cycle or one that acts like it must be able to act living tissues.

Animal Models:

There is **published evidence** from animal models of MCS and PTSD **that nitric oxide has an essential role** in producing the biological response observed. Certain animal models of CFS were reported to be cured by the drug thiacetarsamide and we have evidence showing **that this drug is a scavenger of both nitric oxide and peroxynitrite.**

There is also data from animal models of MCS and PTSD implicating excessive activity of the neurotransmitter system known as the NMDA system and it is known that NMDA activity leads to increased synthesis of nitric oxide and peroxynitrite.

**Proposed Symptom Generation:
(Probably Oversimplified)**

<u>Symptom:</u>	<u>Proposed Cause:</u>
Fatigue	Peroxynitrite attack on energy metabolism
Immune dysfunction	Inflamm. cytokines, nitric oxide, oxidative stress
Learning and Elevated brain nitric oxide;	
memory dysfunct.	circulatory dysfunction
Orthostatic intolerance	Nitric oxide-mediated vasodilation
Pain	Stimulation of nociceptors by nitric oxide
Depression	Inflamm. cytokines, nitric oxide
Panic disorder	Nitric oxide (amygdala)

Table 1: Summary of Observations on CFS, MCS, PTSD and FM

Type of Evidence:	CFS	MCS	PTSD	FM
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Evidence for nitric oxide/ peroxynitrite elevation?	yes	yes	yes	yes
Oxidative stress?	yes	yes	yes	yes
Induced by stressor Reported to induce nitric oxide?	yes	yes	yes	yes
Mitochondrial Dysfunction	yes	?	?	yes
Elevated inflamm. cytokines?	yes	?	yes	yes
NMDA involvement	yes	yes	yes	yes
Nitric oxide &/or inflamm. cytokines elevated in animal model?	Yes	yes	yes	?
Nitric oxide essential to animal model response?	?	yes	yes	?

(Evidence updated from Medical Hypoth 2001;57:139-145).

MCS Puzzles:

How does chemical exposure initiate cases of MCS?

Why are pesticides (organophosphates and carbamates) and hydrophobic solvents involved?

What mechanisms can generate the exquisite sensitivity reported in MCS?

Symptom generation?

Why is MCS chronic?

10 types of Evidence for Nitric Oxide/Peroxynitrite Mechanism for MCS

1. Several hydrophobic organic solvents reported to increase nitric oxide levels.
2. Sequence of action known for organophosphates/carbamates to increase nitric oxide levels.

3. Evidence for inflammatory cytokines.
4. Neopterin reported to be elevated.
5. Increase oxidative stress reported.
6. Nitric oxide causally involved in mouse model.
7. Symptoms explained by mechanism.
8. B-12 injections appear to be helpful.
9. BBB barrier permeabilization.
10. NMDA activity implicated.

However Nitric Oxide/Peroxynitrite Theory Does Not Explain Several Critical Aspects of MCS.

Specifically, it does not explain the exquisite sensitivity to hydrophobic organic solvents of about 1000-fold more sensitivity than that of normals nor does it explain what parts of the body are mainly impacted in MCS. By what mechanism can one obtain this tremendous increase in reported sensitivity??

Neural Sensitization Mechanism for MCS

An earlier mechanism for MCS was proposed by Dr. Iris Bell of the University of Arizona and adopted, with modifications by several other research groups - a neural sensitization mechanism. Dr. Bell proposed that the basic mechanism of MCS was the increased sensitivity of the synapses in the brain. The notion here is that chemicals act to make the synapses in parts of the brain hypersensitive and possibly hyperstimulated by neurotransmitter. Ashford and Miller list 10 different striking similarities between what is called time dependent (neural) sensitization and MCS. However neural sensitization leaves open the question as to how the chemicals reported to be involved in MCS can produce this sensitization or how this leads to the exquisite (circa 1000-fold) sensitivity reported in MCS.

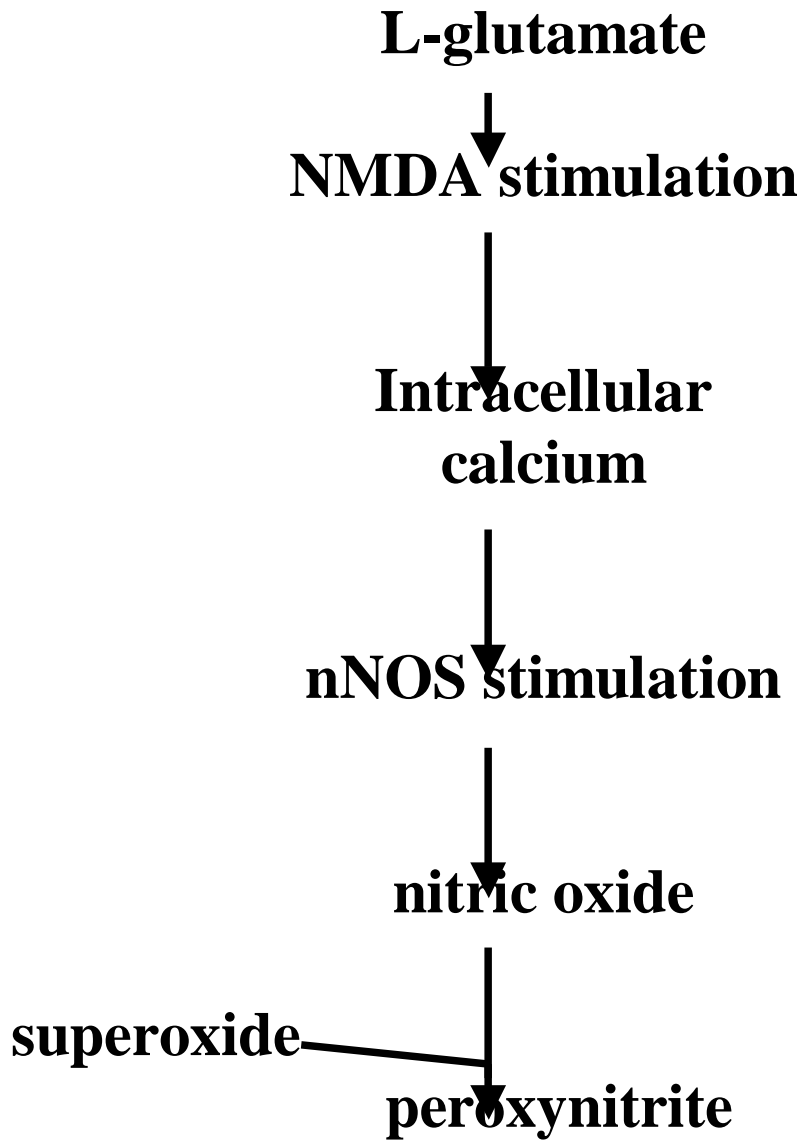
The Question Raised Here Is What Happens if Both Nitric Oxide/Peroxynitrite and Neural Sensitization Theories Are Correct?

The answer is that we have a fusion theory that provides answers to all of the most puzzling questions about MCS!

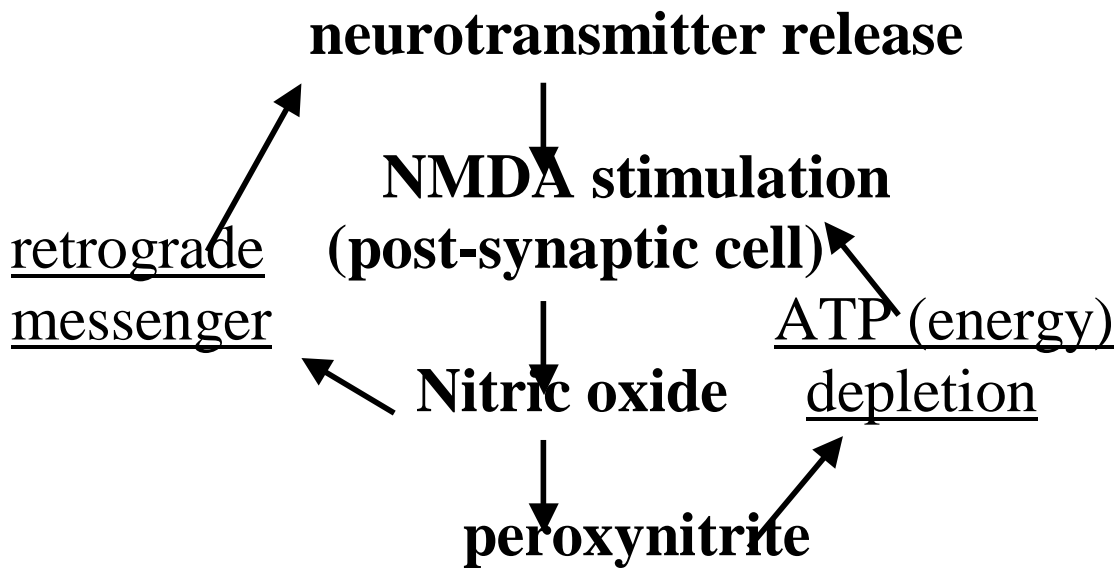
Neural sensitization and LTP

The mechanism of neural sensitization is a process known as long term potentiation (LTP), a mechanism thought to be involved on a highly selective basis in sensitizing neurons to stimulation during the process of learning and memory. LTP in several parts of the brain, including the hippocampus where much of learning and memory occur, involves

stimulation of the NMDA receptors and leads to sensitization of these receptors. It also involves, as we will discuss further, nitric oxide. It is known that stimulation of the NMDA receptors in the nervous system produces increases in nitric oxide and peroxynitrite.



Stimulation of



So how may chemicals initiate this proposed vicious cycle and trigger sensitivity responses. The two main classes of chemicals are **organophosphate and carbamate pesticides** and **hydrophobic organic solvents**.

Organophosphates and carbamates are known to act as **inhibitors of the enzyme acetylcholinesterase**, and such inhibition will lead to increases in acetylcholine levels. Acetylcholine is known to stimulate receptors in the brain known as muscarinic receptors and muscarinic stimulation produces **increases in nitric oxide levels**. So this known sequence of action can potentially stimulate the proposed vicious cycle mechanism.

Hydrophobic Organic Solvents:

The role of hydrophobic organic solvents is a more complex issue. There are three possible targets based on their reported chemical/biochemical properties, that could feed into the proposed mechanism.

- The protein PIN (protein inhibitor of nNOS) has a hydrophobic cleft in the molecule that binds a segment of nNOS on inhibition. It is plausible that solvent molecules could bind to the cleft, thus blocking the nNOS inhibition.
- Hydrophobic solvents are known to act as uncouplers of oxidative phosphorylation, thus depleting ATP (energy) pools.
- Hydrophobic organic solvents are known to open a calcium channel, allowing calcium entry into the cell and stimulating the calcium-dependent nNOS activity.

Two other "accessory mechanisms" for nitric oxide/peroxynitrite are also supported by the literature. Peroxynitrite is known to lead to permeabilization of the blood brain barrier (BBB) and such permeabilization is supported in both an animal model of MCS as well as in MCS patients. In addition, hydrophobic organic solvents are metabolized by cytochrome P450s and cytochrome P450s are known to be inhibited by nitric oxide. Thus one of these "accessory mechanisms" is predicted to produce increased chemical access to the brain and the other is predicted to decrease chemical metabolism, thus producing increased accumulation in the body. The combination of four mechanisms listed below, each acting synergistically with the others, are predicted to produce the exquisite chemical sensitivity found in MCS.

- Increased neurotransmitter (L-glutamate) release stimulated by nitric oxide acting as a retrograde messenger.
- Increased NMDA sensitivity, produced by peroxynitrite via post-synaptic ATP depletion and consequent increased sensitivity of NMDA receptors.
- Nitric oxide inhibition of cytochrome P450s, leading to decreased degradation of organic solvents.
- Peroxynitrite-mediated increased blood brain barrier (BBB) permeability, leading to increased access of chemicals to the CNS.

Meggs and coworkers have reported a series of observations suggesting that a process known as neurogenic inflammation has an important role in MCS. Neurogenic inflammation is reported to be stimulated by nitric oxide and one of the specific processes involved in neurogenic inflammation, mast cell degranulation, is also reported to be stimulated by nitric oxide. It follows that Meggs' observations may be consistent with the nitric oxide/peroxynitrite mechanism.

Four different research groups have reported that several enzymes involved in porphyrin synthesis appear to be low in MCS. It has been reported that nitric oxide lowers porphyrin synthesis and I have reported on two plausible mechanisms by which nitric oxide and its oxidant product peroxynitrite may lower the levels of several porphyrin biosynthetic enzymes. It follows that the porphyrin observations may also be consistent with the nitric oxide/peroxynitrite theory.

We have then a set of interacting mechanisms that provide explanations for the most puzzling features of MCS. Chemicals, both pesticides and hydrophobic organic solvents, act by initiating and stimulating a vicious cycle mechanism centered on nitric oxide, peroxynitrite and NMDA receptors. The chronic nature of MCS is explained by this vicious

cycle and by the long term effects it has on synapses (LTP). The high level sensitivity is explained by four different mechanisms acting synergistically with each other.

MCS therapy has been perhaps the most puzzling question of all. This theory suggests a number of approaches to therapy. Many physicians treating MCS patients have emphasized the role of chemical avoidance, however difficult that may be. There are several other possible approaches. Antagonism of NMDA receptors has some attractiveness although one must be aware of both their essential roles and also of the sometimes serious side effects of their use. Dextromethorphan has been used on an episodic basis, apparently blocking symptoms when taken after occasional chemical exposure. A minority of MCS patients may be intolerant of dextromethorphan. Other drugs that act directly or indirectly on NMDA activity including amantidine, memantine, neurontin and TSH should perhaps be considered. It may also be important to maintain normal vitamin B-6 levels.

Vitamin B12 injections, particularly hydroxocobalamin injections, have been widely used to treat these several illnesses and hydroxocobalamin is known act as a potent nitric oxide scavenger, leading to the suggestion that such scavenging is the mechanism of action of these injections. An early placebo-controlled study of patients with unexplained chronic fatigue reported statistically significant improvement with such injections .

A number of **antioxidants** have been reported to have some **peroxynitrite scavenging** activity as well as other antioxidant activity and may be useful for both of these reasons. These include a number of **flavonoids** and **carotenoids**, **selenium** compounds, **alpha-lipoic acid**, **α-tocopherol** and **carnosine**. These may concentrate differentially in different tissues and some are lipid soluble whereas others are water soluble. Furthermore they differ from each other in their antioxidant activities. It seems likely therefore that a combination of these may have the potential to be more effective than any single compound. The compound **uric acid** is a scavenger for breakdown products of peroxynitrite and **inosine**, a uric acid precursor, has been used to lower the consequences of elevated peroxynitrite.

As mentioned above, **mitochondrial/energy metabolism dysfunction** has been reported to occur in two of these illnesses and such dysfunction may be a consequence of the action of peroxynitrite and nitric oxide. It may be important to improve energy metabolism in order to restore a more normal energy balance and to avoid the effects of energy metabolism dysfunction in **stimulating NMDA hypersensitivity**. Three approaches to improving energy metabolism are:

a. **Oxygen therapy** to improve oxidative metabolism.

b. Use of **Coenzyme Q-10** (ubiquinone) to improve both mitochondrial function and antioxidant balance.

c. Use of **L-carnitine** to improve mitochondrial fatty acid oxidation and inhibit the mitochondrial inner membrane permeability transition. L-carnitine should not be confused with carnosine

Two of the proposed feedback loops proposed in Fig. 1 involved elevated **NF- κ B** activity and such activity is consistent with the reported increased levels of inflammatory cytokines in these illnesses. I am aware of only one study where NF- κ B was measured and it was inferred to be elevated. So it may be premature to suggest that inhibitors of NF- κ B function may be useful in treating these illnesses. Nevertheless, such **inhibitors (both conventional pharmaceuticals and herbal)** are available and are widely used to treat certain related illnesses, such as asthma and allergies.

A number of minerals have been reported to be low in one or more of these illnesses, including **magnesium, selenium and zinc**. It may be important to provide supplements of these minerals. Specifically magnesium acts to lower NMDA activity and selenium and zinc have some antioxidant properties. Several **B vitamins** are also reported to be marginally low in some patients with these illnesses. These may also be important to replete and a B multivitamin may be useful.

The nitric oxide/peroxynitrite theory provides an explanation of the etiology of MCS, CFS, FM and PTSD and provides answers to many of the most puzzling questions surrounding these previously unexplained illnesses. It is supported by many observations including many of which we have not had time to consider in this presentation. The listener is encouraged to look at the detailed information and not accept this overview without scrutiny. While I believe it may well be wrong in some specific details, its overall viewpoint provides unique insights into these illnesses, insights that I would argue should not be overlooked.

Documents ends.

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