Elevated Nitric Oxide/Peroxynitrite Theory of Multiple Chemical Sensitivity: Central Role of *N*-Methyl-D-Aspartate Receptors in the Sensitivity Mechanism

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The elevated nitric oxide/peroxynitrite and the neural sensitization theories of multiple chemical sensitivity (MCS) are extended here to propose a central mechanism for the exquisite sensitivity to organic solvents apparently induced by previous chemical exposure in MCS. This mechanism is centered on the activation of *N*-methyl-D-aspartate (NMDA) receptors by organic solvents producing elevated nitric oxide and peroxynitrite, leading in turn to increased stimulating of and hypersensitivity of NMDA receptors. In this way, organic solvent exposure may produce progressive sensitivity to organic solvents. Pesticides such as organophosphates and carbamates may act via muscarinic stimulation to produce a similar biochemical and sensitivity response. Accessory mechanisms of sensitivity may involve both increased blood–brain barrier permeability, induced by peroxynitrite, and cytochrome P450 inhibition by nitric oxide. The NMDA hyperactivity/hypersensitivity and excessive nitric oxide/peroxynitrite view of MCS provides answers to many of the most puzzling aspects of MCS while building on previous studies and views of this condition. *Key words:* excitatory neurotransmitters, glutamate, long-term potentiation, muscarinic, organic solvents, oxidative stress, reactive nitrogen species, retrograde messenger, synaptic transmission. *Environ Health Perspect* 111:1461–1464 (2003). doi:10.1289/ehp.5935 available via http://dx.doi.org/ [Online 9 April 2003]

Cases of multiple chemical sensitivity (MCS) are characterized by a series of puzzling features described by multiple research groups and individuals (Ashford and Miller 1998; Cullen 1987; Johnson 2000; Miller and Mitzel 1995; Rea 1992; Sorg 1999; Ziem and McTamney 1997). Although they are typically preceded by and presumably induced by exposure of the individual to one or more chemicals, there is no accepted view as to how those chemicals may act in inducing MCS. Chemical sensitivity appears to be progressive, increasing with increasing chemical exposure; however, there is no accepted mechanism by which such progressive sensitization may occur. The symptoms reported to be induced by chemical exposure in MCS patients are similar to those characteristic of chronic fatigue syndrome (CFS), but no plausible mechanism has been proposed as to how those symptoms are generated by such chemical exposure. Sensitivity to a wide variety of chemicals has been reported in MCS, most notably volatile organic solvents and organophosphates and other acetylcholinesterase inhibitors, but it is unclear why these types of compounds produce such sensitivity. Sensitivity is chronic, apparently decreasing slowly over time when MCS individuals avoid chemical exposure; however, there is no indication that this leads to a complete recovery for the condition, leaving the puzzle of why MCS is chronic. There are multiple overlaps between MCS and three related conditions—CFS, fibromyalgia (FM), and posttraumatic stress disorder (PTSD)—with both overlapping symptoms and the number of people being diagnosed with more than one of these disorders (Pall 2001b, 2002b). However, it is not clear why these overlaps occur.

In this article, I discuss a proposed etiologic mechanism that provides attractive solutions to each of the above-described puzzles. Such solutions do not allow us to infer that this proposal is necessarily correct, but they do suggest that we should look at it carefully. This mechanism was discussed previously in a different context (Pall 2002b) and goes to the heart of the most central puzzle of MCS: How can previous chemical exposure generate the exquisite chemical sensitivity reported in MCS, often two or more orders of magnitude greater sensitivity than is seen in normal people? Such sensitivity is shown, for example, when an MCS patient reports sensitivity to the perfume worn by someone walking by them, but the perfume wearer herself shows little sensitivity. Cullen (1987) suggested a sensitivity of two orders of magnitude as a diagnostic feature of MCS. The previous lack of any physiologically plausible mechanism for generating such exquisite sensitivity has been one of the weak points of the CFS literature.

The exquisite chemical sensitivity mechanism proposed here is not only an extension of the previous elevated nitric oxide/peroxynitrite theory of MCS, but also shares the central tenets of the neural sensitization theory of MCS etiology (Bell et al. 1992, 1996, 1999) that were the focus of the recent New York Academy of Science volume on neural sensitization and MCS (Bell and Sorg 2001).

The Elevated Nitric Oxide/Peroxynitrite Theory

The most wide-ranging theory of MCS and related conditions CFS, FM, and PTSD is the elevated nitric oxide/peroxynitrite theory, which was first proposed for CFS (Pall 2000a, 2000b, 2001a, 2002a; Smirnova and Pall 2003), and later extended to the other three conditions (Pall 2001b; Pall and Satterlee 2001). The theory as it applies to CFS will be briefly discussed, followed by a discussion of how it may extend to these other overlapping conditions. Most CFS cases are preceded by an infectious episode. The infection is proposed (Pall 2000a) to induce inflammatory cytokines, which induce, in turn, the inducible nitric oxide synthase, which produces elevated levels of nitric oxide. Nitric oxide reacts with superoxide to form the potent oxidant peroxynitrite. Peroxynitrite acts, in turn, through known biochemical mechanisms to increase the levels of both its precursors, nitric oxide and superoxide, thus generating chronically elevated peroxynitrite (Pall 2000a). In this way, a biochemical vicious cycle may be initiated and maintained, characterized by excessive levels of nitric oxide and peroxynitrite. The classic symptoms of CFS can be generated by plausible mechanisms involving nitric oxide, peroxynitrite, and other consequences of this proposed mechanism (Pall 2000b). Furthermore, the proposed mechanism is supported by 13 different biochemical/physiological observations (Pall 2000a, 2000b, 2001a, 2002a; Smirnova and Pall 2003). One treatment commonly used to treat CFS and also used to treat some cases of FM and MCS involves intramuscular or subcutaneous vitamin B_{12} and vitamin B_{12} in the form of hydroxocobalamin, a potent nitric oxide scavenger both *in vitro* and *in vivo* (Pall 2001a).

A pattern of evidence derived from studies of patients and animal models suggests that the elevated nitric oxide/peroxynitrite theory can be extended to MCS, FM, and PTSD (Pall 2001b; Pall and Satterlee 2001). Where differences in symptoms occur, these may be

caused partly by variation in tissue distribution of the underlying biochemistry.

Fusion of the Nitric Oxide/Peroxynitrite Theory with the Neural Sensitization Theory of MCS

As discussed above, neural sensitization was first proposed by Bell et al. (1992, 1996, 1998, 1999) as a central mechanism in MCS, and such neural sensitization is produced by the process of long-term potentiation (LTP). LTP has been most studied in the hippocampus, where it involves stimulation of the *N*-methyl-D-aspartate (NMDA) receptors. It is well known that NMDA stimulation produces increased levels of both nitric oxide and peroxynitrite (Haley et al. 1990; Lafon Cazal et al. 1993; Murray et al. 1991; Reynolds and Hastings 1995). It may be immediately seen from this that the neural sensitization theory overlaps with the nitric oxide/peroxynitrite theory. Furthermore, nitric oxide has an important role in LTP, acting as a retrograde messenger (Bliss and Collingridge 1993; Prast and Phillipu 2001; Snyder 1992), increasing the release of neurotransmitters including glutamate, which in turn stimulate the NMDA receptors. Thus, we have a potential vicious cycle in the nervous system, with excessive NMDA activity producing excessive nitric oxide leading to excessive NMDA activity (Figure 1). Furthermore the peroxynitrite product of nitric oxide depletes ATP pools via
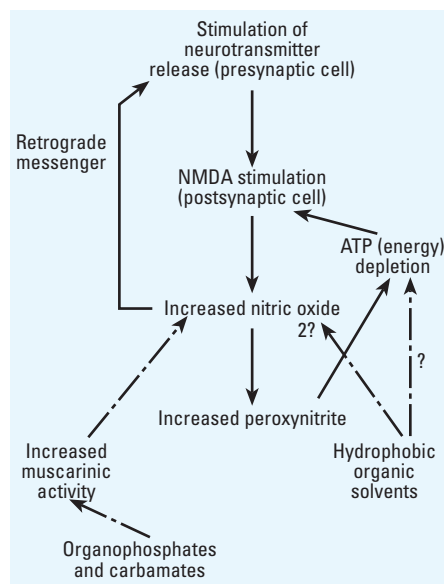

Figure 1. Potential vicious cycle mechanism and MCS. The top two-thirds of the figure represents the potential stimulatory interactions leading to a potential vicious cycle involving excessive NMDA sensitivity and stimulation and excessive nitric oxide and peroxynitrite. Arrows leading from the lower regions represent proposed actions of chemicals leading into the potential vicious cycle.

two different mechanisms (Boczkowski et al. 2001; Szabo and Billiar 1999), and when cells containing NMDA receptors become ATP depleted, these receptors become hypersensitive to stimulation (Novelli et al. 1988; Schultz et al. 1997; Turski and Turski 1993). Thus, there is potential for additional input into the proposed vicious cycle, with nitric oxide producing increased NMDA stimulation and peroxynitrite producing increased NMDA receptor sensitivity (Figure 1).

Normally, LTP is thought to be triggered on a highly selective basis in learning and memory, increasing the sensitivity and activity of specific synapses. If chemical stimulation produces increased nitric oxide and peroxynitrite in large regions of the brain, the diffusion of these compounds over several cell diameters from their sites of synthesis could lead to massive neural hyperactivity and hypersensitivity.

So how may chemicals feed into these proposed mechanisms? As discussed above, two classes of chemicals are implicated in the initiation of cases of MCS: organophosphate and carbamate pesticides and hydrophobic organic solvents. The pesticides here are known acetylcholinesterase inhibitors, leading to increased levels of acetylcholine. Acetylcholine stimulation of muscarinic receptors will produce increases in nitric oxide, as discussed earlier (Pall 2002b; Pall and Satterlee 2001), thus feeding into the proposed NMDA mechanism (Figure 1). There are three suggested roles for hydrophobic organic solvents; two are predicted to produce increases in nitric oxide, and one is predicted to lead to decreased ATP synthesis (Pall 2002b), any of which may lead into the proposed mechanism (Figure 1, arrows with question marks). Thus, although the target(s) of action of hydrophobic organic solvents is uncertain, several plausible targets are consistent with the overall mechanism discussed above.

The major evidence supporting the above-described mechanism includes 10 types of evidence supporting the nitric oxide/peroxynitrite theory of MCS (Pall 2002b; Pall and Satterlee 2001); 10 "remarkable similarities" between neural sensitization and MCS (Ashford and Miller 1998); and five types of evidence suggesting NMDA hyperactivity in MCS (Pall 2002b).

Two accessory mechanisms are also suggested to be involved in MCS, one involving nitric oxide and the other peroxynitrite:nitric oxide inhibition of cytochrome P450 activity and peroxynitrite-mediated increased permeability of the blood–brain barrier (BBB) (Pall 2002b; Pall and Satterlee 2001). Each of these is expected to lead to increased chemical sensitivity through decreased metabolism of hydrophobic chemicals and increased accessibility of chemicals to the central nervous system (CNS), respectively. Consequently, after initiation of increased NMDA receptor activity, nitric oxide levels, and peroxynitrite levels by

organic solvent exposure, four mechanisms are expected to act synergistically to produce the exquisite chemical sensitivity reported in MCS:

- Increased neurotransmitter (glutamate) release stimulated by nitric oxide acting as a retrograde messenger
- Increased NMDA sensitivity, produced by peroxynitrite via postsynaptic 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 BBB permeability, leading to increased access of chemicals to the CNS.

It should be noted that Abou-Donia et al. (2001) reported increased permeability of the BBB in an animal model of MCS.

Relation to Other Previous Hypotheses of MCS

As mentioned above, the NMDA/nitric oxide/peroxynitrite view of MCS is derived partly from both the elevated nitric oxide/peroxynitrite and the neural sensitization theories of MCS. However, it may also be compatible with evidence supporting two other views of MCS.

The nitric oxide/peroxynitrite biochemistry proposed to underlie the current mechanism is basically inflammatory, i.e., induced by inflammatory cytokines and found at the sites of inflammation in many overtly inflammatory conditions. Therefore, the mechanism proposed above may be related to and possibly linked to the neurogenic inflammation mechanism suggested by Meggs and coworkers to be involved in MCS (Bascom et al. 1997; Meggs 1993, 1995). Evidence for a causal role of nitric oxide in such neurogenic inflammation has been reported by several groups (Kajekar et al. 1995; Ruocco et al. 2001; Yonehara and Yoshimura 1999), providing important support for this view. Furthermore, mast cell degranulation, an important aspect of the neurogenic inflammation mechanism, is reported to be stimulated by nitric oxide and/or peroxynitrite (Deschoolmeester et al. 1999; Forsyth et al. 2001; Kawauchi et al. 2001; Konopka et al. 2001). These observations provide some support for the view that a possible role of neurogenic inflammation in MCS may be seen as a consequence of elevated nitric oxide and peroxynitrite.

An additional type of aberrant biochemistry that may be implicated in MCS concerns evidence for elevated levels of porphyrin pathway intermediates and their products, as well as possible low levels of porphyrin pathway enzymes (Downey 2001; Matthews 1998; Morton 1997; Ziem and McTamney 1997; see also Hahn and Bonkovsky 1997). These observations have led to the proposal that

MCS may be a form of porphyria. My comments here will be limited to two of the more puzzling features of the porphyrin/MCS observations—apparently several intermediates of the porphyrin pathway tend to accumulate in MCS, and several of the pathway biosynthetic enzymes tend to be low (Downey 2001; Matthews 1998; Morton 1997; Ziem and McTamney 1997). This pattern is distinguished from what may be viewed as classical porphyria produced either by mutation of one of the genes encoding a biosynthetic enzyme in the porphyrin pathway or in lead toxicity (Jacob et al. 1999), each of which are limited to lowered activity of a single enzyme in the pathway. Is there a mechanism whereby elevated nitric oxide/peroxynitrite might be expected to lead to a deficiency in several porphyrin biosynthetic enzymes? There may be such a mechanism. Most porphyrin synthesis is located in either the liver or blood-forming tissue, and blocks in either of these may lead to symptoms of porphyria. Reports show that nitric oxide leads to loss of some of these porphyrin biosynthetic enzymes (Kim et al. 1995; Rafferty et al. 1996), suggesting that nitric oxide may interact with a regulatory mechanism regulating the synthesis of these enzymes. One specific mechanism that may be particularly relevant to the blood-forming cells is the control of the initiation factor eIF2 by phosphorylation, which is stimulated by nitric oxide, thus leading to decreased protein synthesis, presumably including the porphyrin biosynthetic enzymes (Uma et al. 2001). The nitric oxide/eIF2 mechanism cited here may be accompanied by a more specific mechanism. The last enzyme in the porphyrin biosynthetic pathway is ferrochelatase, an iron-sulfur protein (Dailey et al. 2000), and such iron-sulfur proteins are inactivated by peroxynitrite. It is possible, therefore, that a combination of mechanisms involving nitric oxide and peroxynitrite may lead to lowered levels of several porphyrin biosynthetic enzymes, leading, in turn, to accumulation of porphyrin precursors and their side products.

Evidence supporting four different views of MCS centered on nitric oxide/peroxynitrite, neural sensitization, neurogenic inflammation, and porphyrin pathway aberrations may be compatible with the NMDA/nitric oxide/peroxynitrite view presented here, and this may be a way of integrating a variety of observations into a single view of this condition.

Explanations for Puzzling Features of MCS

This hypothesis involving excessive nitric oxide and peroxynitrite and NMDA hyperactivity provides answers to many of the most puzzling questions about MCS:

- How is the exquisite sensitivity to chemicals produced in MCS? Previous chemical exposure produces increases in nitric oxide and peroxynitrite in the nervous system, leading to four interacting and synergistic mechanisms of sensitivity: *a*) nitric oxide inhibition of cytochrome P450 activity; *b*) peroxynitrite-mediated increased permeability of the BBB; *c*) nitric oxide stimulation of neurotransmitter (glutamate) release, leading to increase NMDA activity; and *d*) peroxynitrite-mediated ATP depletion and consequent increased sensitivity of NMDA receptors.
- How do chemicals initiate MCS and exacerbate the symptoms characteristic of MCS? Such chemicals act via two neurotransmission systems, both of which increase nitric oxide levels, with organic solvents acting through the nitric oxide/peroxynitrite, and NMDA receptors and pesticides including organophosphates and carbamates acting through the muscarinic receptors. These same neurotransmitter systems may act both in initiation of MCS and in upregulating the symptoms of MCS.
- Why is MCS chronic? The multiple positive feedback loops are proposed to act such that once peroxynitrite levels are elevated, they may remain elevated. Synaptic changes produced by LTP are also long-lasting and therefore these may produce chronic effects as well.
- How does chemical exposure generate the characteristic symptoms of MCS? These symptoms are similar to the chronic symptoms of CFS and may be generated by the same mechanisms proposed for CFS—by elevated levels of nitric oxide, peroxynitrite, and other associated biochemical changes (Pall 2000b).
- Why does MCS overlap with other conditions, including CFS, FM, and PTSD? These may all be proposed to have an identical central etiologic mechanism involving elevated nitric oxide/peroxynitrite, albeit with somewhat different tissue distribution, leading to some variation in symptoms.
- How should MCS be treated? In addition to avoidance of chemical exposure, treatments might include the use of antioxidants to lower the consequences of peroxynitrite elevation and lower action of the positive feedback loops; drugs and nutrients to lower the activity of NMDA and muscarinic receptors; and oxygen and other therapies that could possibly improve mitochondrial function and ATP generation.

Hypothesis-Driven Research on MCS

Our knowledge of MCS has been mainly a product of observational studies by a number of dedicated physicians who described in detail the case histories of thousands of patients. These studies have raised many of the puzzling issues discussed above. However, unlike most areas of modern medicine, there has been very little in the way of hypothesis-driven research, largely because of a lack of any overarching hypothesis or theory susceptible to experimental test. The lack of such a theory has also led some to disparage the inferences drawn from careful observational studies. Various predictions of the proposed nitric oxide/peroxynitrite/NMDA view of CFS are testable, and it is my hope that they will help motivate hypothesis-driven research to test some of these predictions.

As stated by Alfred North Whitehead, mathematician and philosopher, "Seek simplicity but distrust it." We may have made a start in seeking here, but have not yet proceeded to distrust.

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