Multiple Chemical Sensitivity - The End of Controversy

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Multiple chemical sensitivity (MCS), where people report being exquisitely sensitive to a wide range of organic chemicals, is almost always described as being "controversial." The main source of this supposed controversy is that there has been no plausible physiological mechanism for MCS and consequently, it was difficult to interpret the puzzling reported features of this condition. As discussed below, this is no longer true and consequently the main source of such controversy has been laid to rest. There still are important issues such as how it should be diagnosed and treated and these may also be allayed by further studies of the mechanism discussed below.

The descriptions of MCS made by a several different research groups are remarkably consistent. MCS sufferers report being hypersensitive to a wide variety of hydrophobic organic solvents, including gasoline vapor, perfume, diesel or jet engine exhaust, new or remodeled buildings where building materials or carpeting has outgassed various solvents, vapors associated with copy machines, many solvents used in industrial settings, cleaning materials and cigarette and other smoke. Each of these is known to have volatile hydrophobic organic compounds as a prominent part of its composition. The symptoms of MCS sufferers report having on such solvent exposure include multiorgan pain typically including headache, muscle pain and joint pain, dizziness, cognitive dysfunction including confusion, lack of memory, and lack of concentration. These symptoms are often accompanied by some of a wide range of more variable symptoms. The major symptoms reported on chemical exposure in MCS are strikingly similar to the chronic symptoms in chronic fatigue syndrome (CFS) and may be explained by mechanisms previously proposed for the CFS symptoms (1). Perhaps the best source of information on the properties and science of MCS is the Ashford and Miller book (2). Many individual accounts of MCS victims have been presented in an interesting book edited by Johnson (3). Most MCS sufferers trace their sensitivity to chemicals to a chemical exposure at a particular time in their life, often a single, high level exposure to organic solvents or to certain pesticides, notably organophosphates or carbamates. Some MCS cases are traced to a time period where the person lived or worked in a particular new or newly remodeled building ("sick building syndrome") where the outgassing of the organic solvents may have had a role in inducing MCS. One of the most interesting examples of MCS/sick building syndrome occured about 15 years ago when the U. S. Environmental Protection Agency remodeled its headquarters and some 200 of its employees became chemically sensitive. The obvious interpretation of this pattern of incidence of MCS is that pesticide or high level or repeated organic solvent exposure induces cases of MCS. This interpretation has been challenged by MCS skeptics but they have, in my judgement, no plausible alternative explanation.

MCS in the U. S. appears to be surprisingly common. Epidemiologists have studied how commonly MCS occurs in the U. S. and roughly 9 to 16 % having more modest sensitivity. Thus we are talking about perhaps 10 million severe MCS sufferers and perhaps 25 to 45 million people with more modest sensitivity. From these numbers, it appears that MCS is the most common of what are described as "unexplained illnesses" in the U. S. Those suffering from severe MCS often have their lives disrupted by their illness. They often have to move to a different location, often undergoing several moves before finding an tolerable environment. They may have to leave their place of employment, so many are unemployed. Going out in public may expose them to perfumes that make them ill. They often report sensitivity to cleaning agents used in motels or other commercial locations. Flying is difficult due to jet fumes, cleaning materials, pesticide use and perfumes.

The exquisite sensitivity of many MCS people is most clearly seen through their reported sensitivity to perfumes. MCS people report becoming ill when a person wearing perfumes walks by or when they are seated several seats away from someone wearing perfume. Clearly the perfume wearer is exposed to a much higher dose than is the MCS person and yet the perfume wearer reports no obvious illness. This strongly suggests that MCS people must be at least 100 times more sensitive than are normal individuals and perhaps a 1000 or more times more sensitive.

Thus a plausible physiological model of MCS must be able to explain each of the following: How can MCS people be 100 to 1000 times more sensitive to hydrophobic organic solvents than normal people? How can such sensitivity be induced by previous exposure to pesticides or organic solvents? Why is MCS chronic, with sensitivity typically lasting for life? How can the diverse symptoms of MCS be explained? Each of these questions is answered by the model discussed below.

Elevated Nitric Oxide/Peroxynitrite/NMDA Model of MCS:

My own interest in MCS stems from the reported overlaps among MCS and chronic fatigue syndrome (CFS), fibromyalgia (FM) and posttraumatic stress disorder (PTSD). These have overlapping symptoms, many people are diagnosed as having more than one of these and cases of each of these are reported to be preceded by and presumably induced by a short term stressor such as infection in CFS and chemical exposure in MCS. The overlaps among these have led others to suggest that they may share a common causal (etiologic) mechanism. Having proposed that elevated levels of nitric oxide and its oxidant product, peroxynitrite are central to the cause of CFS, it was obvious to raise the question of whether these might be involved in MCS. We proposed such a role in a paper published in the Annals of the New York Academy of Sciences (4) and in a subsequent paper, I list 10 different types of experimental observations that provide support for the view that elevated levels of these two compounds have an important role in MCS (5). These 10

observations are listed in the table below (from ref. 5).

Table 1

Types of Evidence Implicating Nitric Oxide/Peroxynitrite in MCS

1. Several organic solvents thought to be able to induce MCS, formaldehyde, benzene, carbon tetrachloride and certain organochlorine pesticides all induce increases in nitric oxide levels.
2. A sequence of action of organophosphate and carbamate insecticides is suggested, whereby they may induce MCS by inactivating acetylcholinesterase and thus produce increased stimulation of muscarinic receptors which are known to produce increases in nitric oxide.
3. Evidence for induction of inflammatory cytokines by organic solvents, which induce the inducible nitric oxide synthase (iNOS). Elevated cytokines are an integral part of a proposed feedback mechanism of the elevated nitric oxide/peroxynitrite theory.
4. Neopterin, a marker of the induction of the iNOS, is reported to be elevated in MCS.
5. Increased oxidative stress has been reported in MCS and also antioxidant therapy may produce improvements in symptoms, as expected if the levels of the oxidant peroxynitrite are elevated.
6. In a series of studies of a mouse model of MCS, involving partial kindling and kindling, both excessive NMDA activity and excessive nitric oxide synthesis were convincingly shown to be required to produce the characteristic biological response.
7. The symptoms exacerbated on chemical exposure are very similar to the chronic symptoms of CFS (1) and these may be explained by several known properties of nitric oxide, peroxynitrite and inflammatory cytokines, each of which have a role in the proposed mechanism.
8. These conditions (CFS, MCS, FM and PTSD) are often treated through intramuscular injections of vitamin B-12 and B-12 in the form of hydroxocobalamin is a potent nitric oxide scavenger, both in vitro and in vivo.
9. Peroxynitrite is known to induce increased permeabilization of the blood brain barrier and such increased permeabilization is reported in a rat model of MCS.
10. 5 types of evidence implicate excessive NMDA activity in MCS, an activity known to increase nitric oxide and peroxynitrite levels.

However, although one can make a substantial case for this theory for an elevated nitric oxide/peroxynitrite etiology (cause) in MCS, this does not explain how the exquisite chemical sensitivity may be produced - which has to be viewed as the most central puzzle of MCS. By what mechanism or set of mechanisms can such exquisite sensitivity to organic chemicals be generated?

Another theory of MCS was proposed earlier by Iris Bell (6,7) and coworkers

and adopted with modifications by numerous other research groups. This was the neural sensitization theory of MCS. What this theory says is that the synapses in the brain, the connections between nerve cells by which one nerve cell stimulates (or in some cases inhibits) another become hypersensitive in MCS. This neural sensitization theory is supported by observations that many of the symptoms of MCS relate directly to brain function and that a number of studies have shown that scans of the brains of MCS people, performed by techniques known as PET scanning or SPECT scanning are abnormal. There is also evidence that electrical activity in the brains of MCS people, measured by EEG's, is also abnormal. Neural sensitization is produced by a mechanism known as long term potentiation, a mechanism that has a role in learning and memory. Long term potentiation produces neural sensitization but in the normal nervous system, it does so very selectively - increasing the sensitivity of certain selected synapses. In MCS, it may be suggested, that a widespread sensitization may be involved that is somehow triggered by chemical or pesticide exposure. This leaves open the question as to why specifically hydrophobic organic solvents or certain pesticides are involved and, most importantly, how these can lead to such exquisite chemical sensitivity as is seen in MCS. So the neural sensitization theory is a promising one but it leaves unanswered the central puzzles of MCS.

The question that I raised in my key paper (5), published in the prestigious publication of the Federation of American Societies for Experimental Biology, The FASEB Journal, is what happens if both of these theories are correct? The answer is that you get a fusion theory that, for the first time, answers all of the most puzzling questions about MCS. The fusion theory is supported by all of the observations supporting the nitric oxide/peroxynitrite theory, all of the observations supporting the neural sensitization theory plus several additional observations that relate specifically to the fusion.

How can we understand this fusion theory? When you look at the two precursor theories together, you immediately see ways in which they interact with each other. Long term potentiation, the mechanism behind neural sensitization, involves certain receptors at the synapses of nerve cells called NMDA receptors. These are receptors that are stimulated by glutamate and aspartate and when these receptors are stimulated to be active, they produce in turn, increases in nitric oxide and its oxidant product, peroxynitrite. So immediately you can see a possible interaction between the two theories. Furthermore, nitric oxide can act in long term potentiation, serving as what is known as a retrograde messenger, diffusing from the cell containing the NMDA receptors (the post-synaptic cell) to the cell that can stimulate it (the pre-synaptic cell), making the pre-synaptic cell more active in releasing neurotransmitter (glutamate and aspartate). In this way, NMDA stimulation increases the activity to the pre-synaptic cell to stimulate more NMDA activity. Thus we have the potential for a vicious cycle in the brain, with too much NMDA activity leading to too much nitric oxide leading to too much NMDA activity etc (see Figure 1, below). There is also a mechanism by which peroxynitrite may act to exacerbate this potential vicious cycle. Peroxynitrite is known to act to deplete energy (ATP) pools in cells by two different

mechanisms and it is known that when cells containing NMDA receptors are energy depleted, the receptors become hypersensitive to stimulation. Consequently nitric oxide may act to increase NMDA stimulation and peroxnitrite may act to increase the sensitivity to such stimulation. With both nitric oxide and peroxynitrite levels increased by NMDA receptor activity, an overall increase in these activities may lead to a major, sustained increase in neural sensitivity and activity. The only thing left is to explain how hydrophobic organic chemicals or pesticides can stimulate this whole response. I'll discuss that below.

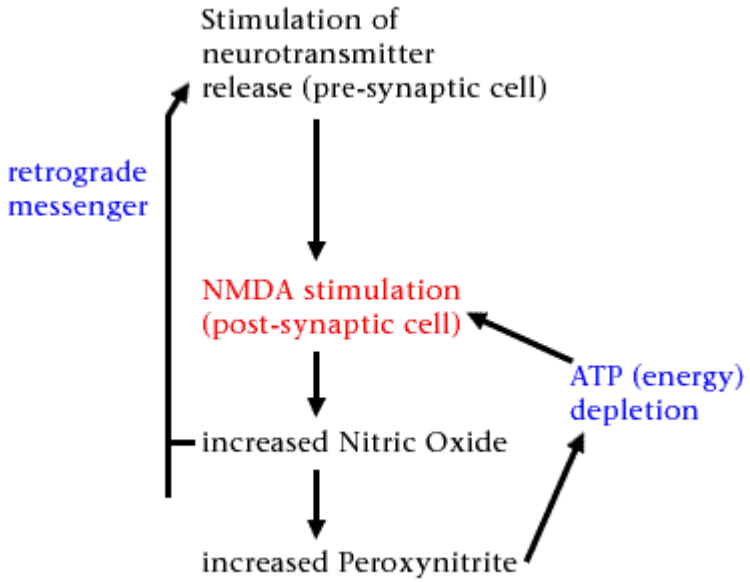

Figure 1

I have also proposed two additional, accessory mechanisms in MCS. One is that peroxynitrite is known to act to break down the blood brain barrier - the barrier that minimizes the access of chemicals to the brain. By breaking down this barrier, more chemicals may accumulate in the brain, thus producing more chemical sensitivity. It has been reported that an animal model of MCS shows substantial breakdown of the blood brain barrier. Nitric oxide is also known to inhibit the activity of certain enzymes that degrade hydrophobic organic solvents, known as cytochrome P-450's. By inhibiting these enzymes, nitric oxide will cause more accumulation of these compounds because they are broken down much more slowly. Consequently there are four distinct mechanisms proposed to directly lead to chemical sensitivity:

- Nitric oxide acting as a retrograde messenger, increasing release of neurotransmitters (glutamate and aspartate) that stimulate the NMDA receptors.
- Peroxynitrite depleted energy (ATP) pools, thus making the NMDA receptors more sensitive to stimulation.
- Peroxynitrite acts to break down the blood brain barrier, thus allowing greater chemical access to the brain.

- Nitric oxide inhibits cytochrome P-450 activity, thus slowing degradation of hydrophobic organic chemicals.

It is proposed to be the combination of all four of these mechanisms, each acting at a different level and therefore expected to act synergistically with each other, that produces the exquisite chemical sensitivity reported in MCS.

So how do organophosphate pesticides or hydrophobic organic chemicals initiate this sensitivity and trigger symptoms of MCS? Both are proposed to stimulate the potential vicious cycle involving too much nitric oxide/peroxynitrite and too much NMDA activity (figure 1). Organophosphates and carbamate pesticides, often reported to be involved in inducing cases of MCS, are both acetylcholinesterase inhibitors, acting to increase acetylcholine levels which stimulate muscarinic receptors in the brain. It is known that stimulating of certain muscarinic receptors produces increases in nitric oxide! Thus these two pesticides should be able to act to stimulate the proposed nitric oxide/peroxynitrite/NMDA vicious cycle mechanism. Hydrophobic organic solvents are proposed to act by three possible mechanisms, two producing increases in nitric oxide and one producing energy depletion and therefore NMDA stimulation. These three mechanisms are documented in the scientific literature but none have been tested yet for involvement in MCS. So both the pesticides, organophosphates and carbamates, and the hydrophobic organic solvents have known mechanisms which should be able to initiate the proposed vicious cycle centered on excessive NMDA/nitric oxide/peroxynitrite and thus initiate MCS. Once MCS has been initiated, by simulating this same cycle, they are predicted to produce the symptoms of chemical sensitivity.

Explanations for the most puzzling features reported for MCS:

If this theory is correct, it provides answers to all of the most difficult questions about MCS.

1. How do pesticides (organophosphates and carbamates) and hydrophobic organic solvents act to induce cases of MCS? Each acts to initiate a vicious cycle mechanism involving NMDA receptors, nitric oxide and peroxynitrite in the brain, with organophosphates/carbamates acting via one known mechanism and hydrophobic organic solvents acting by another mechanism.
2. How do hydrophobic organic solvents act to trigger the symptoms of MCS? They act by the same mechanism proposed for such solvents in #1 above.
3. Why is MCS chronic? Presumably for two reasons: Because of the several positive feedback loops that maintain the elevated nitric oxide/peroxynitrite/NMDA activity and also because changes in the synapses of the brain may be long term.
4. How can MCS victims be so exquisitely sensitive to organic solvents? Because there are four different mechanisms by which nitric oxide or peroxynitrite act to produce the response, with the combination of all four acting synergistically to produce such exquisite sensitivity. The

mechanisms of all four are well documented although their relevance to MCS can be questioned.

5. How are the symptoms of MCS generated? Possibly by the same mechanisms proposed earlier for the symptoms of chronic fatigue syndrome.
6. How can we explain the overlaps of MCS with chronic fatigue syndrome, fibromyalgia, posttraumatic stress disorder and Gulf War syndrome? All of these are proposed to involve excessive nitric oxide and peroxynitrite and all may also involved excessive NMDA activity.

References:

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