Multiple Chemical Sensitivity: Towards the End of Controversy

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There are nine well accepted paradigms of human disease. The tenth may explain the features of multiple chemical sensitivity (MCS) and a group of related illnesses including chronic fatigue syndrome (CFS), fibromyalgia (FM) and posttraumatic stress disorder (PTSD); Gulf War syndrome appears to be a combination of all four. The elevated nitric oxide/peroxynitrite vicious cycle paradigm explains most of the most puzzling features of this group of previously unexplained illnesses (1-16) that afflict tens of millions of people in the U.S. and elsewhere. These illnesses have multiple overlaps with each other (2-5,13,16). They share many common symptoms and signs. They are repeatedly reported to be comorbid conditions. Cases of each of them typically show a common pattern of case initiation, with cases being preceded by and presumably induced by a short term stressor, only to be followed by a chronic illness that usually persists for life. These similarities have led many different researchers to propose that two, three or all four of them may share a common etiologic mechanism (3,5,16), but they were unable to suggest what that mechanism might be.

The short term stressors reported to initiate these illnesses are very diverse. Six have very well documented roles as initiators, viral infection, bacterial infection, physical trauma (particularly head and neck trauma), organophosphate/carbamate pesticide[*] exposure, volatile organic solvent exposure and severe psychological stress. There are six additional stressors that are less well documented as initiators of these illnesses and thus may be viewed as candidate initiators. These latter six include pyrethroid pesticide exposure, organochlorine (chlordane or lindane) pesticide exposure, a protozoan infection (toxoplasmosis), ciguatoxin poisoning[#], carbon monoxide poisoning and thimerosal exposure. All 12 of these are known to be able to initiate a sequence of events leading to increases in nitric oxide levels. Thus they all have a common biochemical end point, suggesting that they may act to initiate these illnesses through a common mechanism (1-5,7,13,16). The three classes of infection all act to raise nitric oxide levels primarily by inducing the inducible nitric oxide synthase (iNOS) whereas most of the others are known to act by increasing NMDA[@] receptor activity and such NMDA activity is

[*]The pesticides involved fall into discrete classes, based both on their chemical structure and biochemical mode of action in both insects and in humans. Organophosphate and carbamate pesticides both act as inhibitors of the enzyme acetylcholinesterase, the enzyme that gets rid of acetylcholine. The pyrethroid pesticides act to open sodium channels in the brain. The organochlorine pesticides act to inhibit what are known as GABAa receptors, sites at which the compound GABA acts in the brain. The interesting thing here is that although these all act at different targets in the brain, they all can produce a common response, involving excessive activity of the NMDA receptors in the brain and excessive nitric oxide.

[#] Ciguatoxin is a toxic compound produced by certain tropical organisms which when eaten by tropical fish, make the fish toxic to people who eat them. The toxin called ciguatoxin or ciguatera toxin acts somewhat like the pyrethroid pesticides, leaving open sodium channels in the brain.

[@] The NMDA receptors are receptors for glutamate found primarily in the central and peripheral nervous system. They are called NMDA receptors because they are specifically stimulated by the compound **N-m**ethyl-**D-a**spartate whereas other

known to produce, in turn, increases in nitric oxide and its oxidant product, peroxynitrite. The NMDA activity is known to act by allowing an influx of calcium into the cell, leading to increased activity of the calcium dependent neural nitric oxide synthase (nNOS) activity (5). Thus the stressors do not all share a common pathway or common enzyme producing nitric oxide. What they do appear to share is a common response of increased nitric oxide and its oxidant product peroxynitrite[@].

So how might elevated levels of nitric oxide and peroxynitrite[**] initiate these chronic illnesses? The proposed mechanism is that they initiate a biochemical/physiological vicious cycle mechanism which is responsible for both the chronic nature of these illnesses and is responsible for generating their diverse symptoms and signs. That vicious cycle mechanism is diagrammed in the figure on the following page. The arrows in the figure represent a total of 22 distinct mechanisms, 18 of which are quite well documented (1,5,7,13,16). The other 4 are based on what appear to be solid data, but are less established. The overall vicious cycle is quite plausible but what needs to be questioned is its physiological significance to these illnesses. One needs to focus, then, on the role of the various elements of this cycle in the chronic phases of these illnesses and that has been the focus of many of my own papers on this subject (1-7,10,12,13,16). Each of the following has been reported to occur in from two to four of these illnesses and typically when it has not been reported, it has not been studied: Elevated levels of nitric oxide, oxidative stress, elevated NF-κB activity, elevated levels of inflammatory cytokines, elevated NMDA activity, and increased vanilloid sensitivity[#&]. Intracellular calcium levels have not been studied but some properties produced by such calcium increase have been reported. A pattern of mitochondrial dysfunction characteristic of peroxynitrite-mediated damage has been reported in CFS and FM (1,16). So although it may certainly be argued that further studies are needed on many of these areas, the pattern of evidence that is available is supportive of the predictions of the vicious cycle mechanism. Many of the predictions of the cycle are also supported by studies of certain animal models of these illnesses. There is, for example, convincing published evidence for a key role of both NMDA activity and nitric oxide in certain animal models of MCS and substantial but less convincing evidence in PTSD models as well. There is an animal model of CFS that fits very well with the proposed mechanism but where some of the important predictions have never been tested. While there is no explicitly stated animal model for FM, whose characteristic symptom is widespread pain hypersensitivity, the mechanism of hyperalgesia in animals is known to involve all of the elements of the proposed vicious cycle (16). So in general, although the biochemical and physiological experimental data on these illnesses is limited, what data is available is in good agreement with the predictions of the cycle.

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glutamate receptors are not. While the NMDA receptors appear to have the most important role of the glutamate receptors in these illnesses, in some cases other glutamate receptors may also have a role.

[@] Nitric oxide is a compound found in the body that has important functions, particularly in controlling the circulatory system (it dilates the blood vessels), in the brain and in the immune system. However when its levels are too high, it can produce substantial pathophysiological effects, impacting the body in many negative ways. These elevated levels are proposed to be important in these illnesses and also occur a wide variety of chronic inflammatory diseases and in acute inflammatory responses such as sepsis. Much of the damage produced by excessive nitric oxide is actually a consequence of its oxidant product, peroxynitrite.

[**] Peroxynitrite is a potent oxidant formed by the reaction of nitric oxide with another compound superoxide. It is a potent oxidant that is thought to break down to produce a number of reactive free radicals and cause various types of oxidative damage.

[#&] The vanilloid receptor is the receptor for the "hot" compound in hot peppers, known as capsaicin. We have argued in reference 7 that this receptor has a complex role in MCS and specifically that it is the likely target for volatile organic solvents that produce sensitive responses in that illness. It also is reported to have a role in fibromyalgia and in irritable bowel syndrome but has not been studied in these other illnesses.

Figure 1

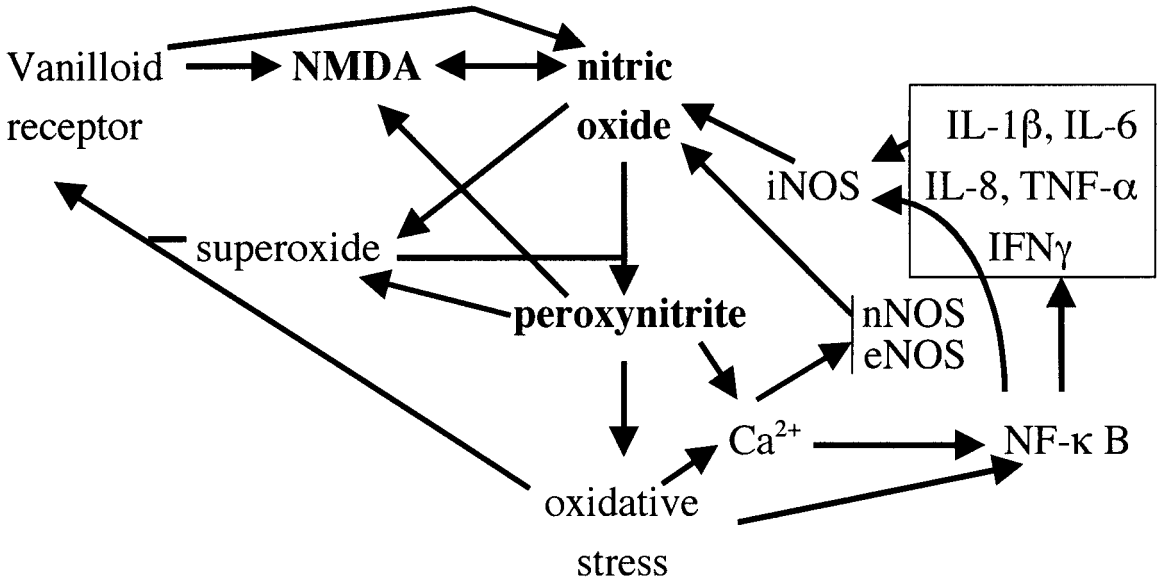

Fig. 1 legend. Vicious cycle diagram. Each arrow represents one or more mechanisms by which the variable at the foot of the arrow can stimulate the level of the variable at the head of the arrow. It can be seen that these arrows form a series of loops that can potentially continue to stimulate each other. An example of this would be that nitric oxide can increase peroxynitrite which can stimulate oxidative stress which can stimulate NF-κB which can increase the production of iNOS which can, in turn increase nitric oxide. This look alone constitutes a potential vicious cycle and there are a number of other loops, diagrammed in the figure that can collectively make up a much larger vicious cycle. The challenge, according to this view, in these illnesses is to lower this whole pattern of elevations to get back into a normal range.

There are two types of puzzles surrounding the symptoms and signs of these illnesses. One is that they are very diverse, involving neuronal, neuroendocrine, circulatory, immune, biochemical and psychiatric properties. This has raised the question of how any understandable mechanism might be able to generate such a diverse group of symptoms and signs? A second puzzle is that these symptoms and signs are highly variable from one individual to another so both the pattern and the variability require satisfactory explanations. In my book (16) and elsewhere (2), I have provided explanations for 16 different symptoms and signs that are found with reasonable frequency, based on one or more elements of the vicious cycle. It should be noted that these explanations are put forth as plausible mechanisms, not as established mechanisms. They include such things as orthostatic intolerance, possibly caused by nitric oxide effects both as a vasodilator and its effects on the sympathetic nervous system; sleep dysfunction such as non-refreshing sleep, caused by elevated cytokines, by elevated nitric oxide and by elevated NF-κB activity; low NK cell activity, caused by oxidants and specifically by superoxide; fatigue which is found in all conditions with low energy metabolism may be caused by peroxynitrite mediated mitochondrial dysfunction. Even such psychiatric symptoms as anxiety

(excessive NMDA activity in the amygdala) and depression (nitric oxide effects on the brain, locations still undetermined) may be explained by this mechanism.

The variability of the symptoms and signs may be explained by variation in tissue distribution of the underlying biochemistry. Nitric oxide, superoxide and peroxynitrite have limited diffusion in tissues (16) and the basic mechanisms outlined in the vicious cycle are cellular. It follows that one tissue may be impacted by this biochemistry whereas an adjacent tissue may be largely unaffected. The vicious cycle may propagate the tissue distribution into the future, thus producing a relatively stable pattern of symptoms and signs which varies from one patient to another. An example of this is that if the amygdala is impacted by this biochemistry, a patient will be expected have symptoms of anxiety and possible panic attacks, but not otherwise. Similarly, if certain regions of the GI tract are impacted you may have irritable bowel syndrome (IBS) symptoms; note that IBS is reported to involve both excessive vanilloid activity and excessive nitric oxide.

Multiple Chemical Sensitivity (MCS):

Multiple chemical sensitivity is reported to be both the most common of these illnesses and it also has been the most puzzling. It is characterized by exquisite chemical sensitivity to a wide variety of chemicals, with such sensitivity being apparently induced by previous chemical exposure (4,5). There has not previously been an understanding as to how these chemicals act or how the exquisite sensitivity reported, on the order of 1000 times that of normals, can be generated. It has been clear, for some time, that MCS is not caused by an IgE-based allergy or fundamentally by an immune response of any kind, but rather involves neuronal dysfunction.

There are four classes of chemicals reported to commonly produce MCS and also trigger symptoms in those already sensitized. These are the organophosphate/carbamate pesticides, volatile organic solvents, pyrethroid pesticides, and organochlorine (chlordane and lindane) pesticides. The three groups of pesticides acting at their major site of action can each initiate a control sequence that lead to increases in NMDA activity and consequent increases in nitric oxide (4-6, 14,16). The putative target for organic solvents, the vanilloid receptor (7), is also known to be able to produce increases in NMDA activity and nitric oxide (7). Thus, we see a common response to each of these four classes of chemicals as possibly being central to the action of these chemicals in MCS. How then, might this response lead to an understanding of chemical sensitivity? Apparently through a striking convergence of this mechanism with that proposed earlier by Dr. Iris Bell (17-20). Bell proposed that MCS is centered on the process of neural sensitization, providing substantial support for this view. Her ideas were the focus of a New York Academy of Science meeting (Ann N Y Acad Sci, vol. 933). The major mechanism of neural sensitization is thought to be long term potentiation (LTP) a mechanism thought to be involved on a highly selective basis in strengthening of synaptic transmission in the central nervous system, during learning and memory. LTP is known to involve NMDA receptors in the postsynaptic cell and also nitric oxide which diffuses back to the presynaptic cell, acting as what is known as a retrograde messenger[%%] to increase release of glutamate neurotransmitter (5). Thus, immediately you can see a striking convergence of these two theories. Each class of chemicals can act to stimulate the neural sensitization process proposed to be central to MCS. In addition, it is possible

[%%] A retrograde messenger is a compound which does just this--it diffuses from the post-synaptic neuron to the presynaptic neuron, causing the latter to release more neurotransmitter. In this way it can increase the activity of a synapse, thus producing LTP. Nitric oxide is not the only known retrograde messenger but it may be the most important one.

to propose a vicious cycle mechanism (actually part of the larger such mechanism diagrammed in Fig.1) that involves both excessive nitric oxide through the retrograde messenger role already discussed and peroxynitrite, through its ability to inhibit mitochondrial function and therefore ATP generation (5). It is known that when cells containing NMDA receptors become energy-deprived, those receptors become hypersensitive to stimulation (5). ATP-depletion in the glial cells may also have a role in increasing NMDA activity because of decreased transport of extracellular glutamate, that main NMDA agonist acting in the brain.

It can be seen from the above, how high level chemical exposure may be able to initiate a vicious cycle mechanism involving excessive NMDA activity, nitric oxide and peroxynitrite that would render areas of the brain hypersensitive to further chemical exposure. There are also three other well-documented mechanisms that may also have a role: Increased vanilloid activity due to oxidants (7); breakdown of the blood-brain-barrier (BBB) due to the action of peroxynitrite (5), thus allowing increased chemical access to the brain; and decreased chemical metabolism due to inhibition of cytochrome P450 activity by nitric oxide (5,6). The notion is that the total of six proposed mechanisms will act synergistically with each other to produce the exquisite sensitivity reported in MCS. Of these mechanisms, there is experimental support for a role of the NMDA receptors and of nitric oxide (4-6), for the breakdown of the BBB in both an animal model of MCS and in humans (6,13), and for excessive vanilloid activity in MCS (7). The overall mechanism is supported by at least 38 different types of observations, 24 documented in ref. 5, 12 more in ref. 7 and two additional ones in ref. 13.

There is often also, what may be described as peripheral sensitivity mechanisms involved in MCS, as emphasized by the work of William Meggs (21-25). Meggs has discussed the role of such peripheral sensitivity responses as reactive airways dysfunction syndrome or RADS, a form of asthma initiated by chemical exposure, reactive upper airways dysfunction syndrome or RUDS, chemical sensitivity in the upper respiratory tract, again initiated by chemical exposure and induced skin hypersensitivity. Several of the mechanisms involved in peripheral sensitivity are likely to be similar to those involved in central sensitivity but others, notably BBB breakdown and possibly the role of nitric oxide acting as a retrograde messenger will not be involved in such peripheral sensitivity. Each of these sensitivity responses are likely to be local, with local inflammatory responses such as mast cell sensitization (26) and neurogenic inflammation[%$#] (25) having important roles in the sensitivity mechanisms.

This model of MCS based on a vicious cycle mechanism centered on excessive nitric oxide, peroxynitrite and NMDA activity provides explanations for each of the previously puzzling features of that illness (5,13,16): Its initiation by three classes of pesticides and by volatile organic solvents (5,7,13); its chronic nature (4-6); the generation of exquisite sensitivity to these same classes of chemicals (5,7,13); the reported changed in porphyrin metabolism (6); the central and peripheral sensitivity mechanisms (5-7); and the masking/desensitization phenomenon in MCS (7). It also is consistent with the recent report by Kimata of some possible specific biomarkers for MCS (27), biomarkers consistent with the apparent vanilloid receptor role in MCS (7).

Overall Perspective of the Elevated Nitric Oxide/Peroxynitrite Vicious Cycle Mechanism:

[%$#] Neurogenic inflammation has been reported by Meggs and coworkers in peripheral sensitivity regions involved in MCS. It is an overt inflammatory response at the nerve endings involving several inflammatory messengers. It should be noted that the peripheral sensitivity responses seen in MCS are overt inflammatory responses.

It can be seen from the above discussion that the etiologic mechanism discussed here provides a detailed and relatively complete explanation of both MCS and of several other related illnesses, including CFS, FM, PTSD and Gulf War syndrome. It provides an explanation of how the various diverse stressors may initiate these illnesses, why they are chronic and how many of the diverse symptoms and signs of these illnesses may be generated.

The putative role of the nitric oxide/peroxynitrite vicious cycle mechanism with variable tissue distribution in these illnesses suggests that we can answer in the affirmative the question raised by Miller (28): "Are we on the threshold of a new theory of disease?"

Therapy:

The proposed mechanism of these illnesses suggests a number of approaches to therapy that will be discussed in more detail elsewhere (16). These include the use of various antioxidants acting as peroxynitrite scavengers, acting to lower NF-κB activity, acting a chain-breaking antioxidants to decrease oxidative chain reactions and acting as superoxide scavengers. They also include such agents as magnesium supplements, and the drugs dextromethorphan or memantine with both of these acting to lower NMDA activity. The vitamin B12 form hydroxocobalamin acts as a nitric oxide scavenger (8) and may be used either as an IM injection or as a nasal spray or as an inhalant to lower nitric oxide levels. Additional therapeutic approaches may be aimed at helping restoring mitochondrial function in the face of peroxynitrite or superoxide-mediated damage, through the use of L-carnitine (29) or of complex nutritional mixtures (30,31) or coenzyme Q10 supplements. These and other therapeutic approaches should be based, in addition, on attempts to minimize exposure of patients to anything that might otherwise exacerbate the basic biochemistry/physiology central to the putative etiology. Such exacerbation may be a consequence of chemical exposure in MCS, excitoxin exposure in FM and possibly other illnesses and excessive exercise leading to "post-exertional malaise" in CFS, as well as exposure to food antigens in individuals suffering from food allergies.

Combinations of therapeutic approaches based on this mechanism may well be more effective in the treatment of these illnesses than have been treatments mainly aimed at the lessening of symptoms that have been used in the past.

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