

**Important paper which explains multiple chemical sensitivity (MCS)**

**Review by Margaret Williams**

**(August 2002)**

*Reviewer's note:*

- (i) MCS is now included in the WHO International Classification of Diseases (ICD-Germany)*
- (ii) the term "CFS" needs great care in interpretation as it means different things to different people: most international researchers equate it with myalgic encephalomyelitis (ME) in which there is neurogenic fatigue similar to that seen in multiple sclerosis, but certain UK psychiatrists (in defiance of significant biomarkers of organic pathology in ICD-classified CFS and using their own criteria for patient selection for their studies) use the same term "CFS" to refer to somatoform disorder. In this review, "CFS" does not refer to psychogenic fatigue states*
- (iii) NMDA (N-methyl-D-aspartate) is a neuroreceptor in the brain and spinal cord for the neurotransmitter glutamate (the most important excitatory transmitter in the brain) and is involved in the toxic effects of excessive glutamate. NMDA is not only a neuroreceptor but is also an ion channel and is involved in the neurobiology of chronic pain*
- (iv) ATP (adenosine triphosphate) is the main energy-releasing source of the cell*
- (v) a synapse is a junctional area between two nerves, or between a nerve and a muscle fibre; nerve impulses are transmitted across a synapse by means of a chemical neurotransmitter (such as acetylcholine). Synapses allow impulses to pass in one direction only; a single brain cell has more than 15,000 synapses with other cells*
- (vi) a mitochondrion is the site of the cell's energy production*
- (vii) free radicals are produced naturally by the body during metabolism of foods but are also produced in connection with exposure to pollution. They are extremely reactive chemical compounds which if produced in excess can be very damaging to DNA (deoxyribonucleic acid, the genetic material of nearly all living organisms), proteins and fat in cell membranes, where a free radical chain reaction can be set up. They are normally mopped up by antioxidants such as vitamins E and C and by selenium, but they can acquire new properties, for example, becoming insoluble. An accumulation of free radicals in the body is known as oxidative stress.*

*(viii) an allele is one of alternative forms of a gene, in which it may differ in DNA sequence from normal*

A significant paper is about to be published in the prestigious Journal of the Federation of American Societies for Experimental Biology: it is authored by Professor Marty Pall from the School of Molecular Biosciences at Washington State University, Washington, USA, whose work in this area is well-known to medical scientists

The paper has a shortened title: “Exquisite Chemical Sensitivity Mechanism in MCS”, the full title being “NMDA Sensitization and Stimulation by Peroxynitrite, Nitric Oxide and Organic Solvents as the Mechanism of Chemical Sensitivity in Multiple Chemical Sensitivity” (*ref: The FASEB Journal, September 2002: 16: 1407-1417*).

It contains 164 references and describes a compelling set of four interacting mechanisms, all previously validated in their own right (each based on known physiological mechanisms), which when acting synergistically, provide explanations for the most puzzling aspects of MCS, notably (i) how people with MCS can be so exquisitely sensitive to chemical exposure (ii) why hydrophobic organic solvents and organophosphate pesticides are implicated in MCS (iii) why MCS is chronic and (iv) how previous chemical exposure can lead to the induction of chemical sensitivity.

### Introduction

Multiple chemical sensitivity (MCS) is a condition which in many cases appears to be preceded by and induced by exposure to various organic solvents or certain pesticides; after such exposure, MCS sufferers report being hypersensitive to a wide range of organic chemicals. The hypersensitivity is often exquisite, being apparently at least two orders of magnitude greater than that of normal individuals, and sufferers often report being sensitive to perfumes worn by people seated several seats away or even walking past them. MCS results in greatly reduced quality of life for sufferers.

MCS has multiple overlaps with three other medical conditions: chronic fatigue syndrome (CFS), fibromyalgia (FM) and post-traumatic stress disorder (PTSD) and many people are diagnosed as having more than one of these disorders. Gulf War Syndrome (GWS) can be viewed as a combination of all four disorders, with several research groups proposing that they may share a common aetiological mechanism. To Pall’s knowledge, the only such overall common mechanism is the elevated nitric oxide / peroxynitrite mechanism (*see below*).

For each of these four conditions, many cases appear to be preceded by a short term stress whilst being followed by a chronic condition which typically lasts for decades. There is considerable evidence that stressors commonly preceding development of these overlapping conditions (most notably infection, physical trauma and severe psychological stress) may act to increase nitric oxide levels.

Epidemiological studies report that MCS is surprisingly common in the US, being of similar prevalence to diabetes (but funding for MCS is probably less than one thousandth of that available for diabetes research).

More symptoms of MCS may be attributed to central nervous system (CNS) dysfunction than to dysfunction of any other organ or organ system; however, there are MCS symptoms which are not attributed to a CNS origin, such as cardiovascular, respiratory, gastro-intestinal, genito-urinary, musculoskeletal and dermatologic origin. Thus whilst many of the symptoms seen in MCS appear to be of neurologic origin, various other organs appear to be impacted also.

### THE FOUR MECHANISMS

1. Nitric oxide acts as a retrograde messenger, stimulating the presynaptic cells to become more active in releasing the neurotransmitter glutamate
2. Peroxynitrite depletes ATP pools via two different mechanisms, causing NMDA receptors in depleted cells to be hypersensitive to stimulation
3. Peroxynitrite increases permeability of the blood brain barrier (BBB), increasing accessibility of organic chemicals to the central nervous system (CNS)
4. Nitric oxide inhibits cytochrome P450 metabolism of organic compounds, producing increased levels of organic compounds which may stimulate NMDA activity

### Elevated Nitric Oxide / Peroxynitrite and Neural Sensitization

There is evidence that acute short-term stress produces increases in nitric oxide; this reacts with superoxide to form the potent oxidant peroxynitrite, which can act through six different positive feedback loops to increase the levels of both nitric oxide and superoxide, which in turn form more peroxynitrite. In this way, a biochemical vicious circle is initiated and maintained, which produces the chronic nature of these conditions. Extensive supporting evidence is provided for this mechanism.

The theory of neural sensitization (originally proposed by Iris Bell and co-workers) is based on the evidence for neurological dysfunction in MCS, the underlying mechanisms being that of long-term potentiation (LTP), a central mechanism involving learning and memory where the synapses show long term increases in sensitivity to stimulation. Central nervous system dysfunction in MCS has been confirmed by SPECT and PET scans of the brain of MCS patients, as well as changes in EEG patterns. Both nitric oxide and the NMDA excitatory neurotransmission system are implicated in LTP. Excessive NMDA activity leading to excessive levels of nitric oxide and peroxynitrite has been

implicated in several neurodegenerative diseases including Parkinson's disease and Alzheimer's disease.

The combination of nitric oxide-mediated increased neurotransmitter release and peroxynitrite-mediated increased sensitivity of the NMDA receptors, acting synergistically, is proposed to be the central mechanism of chemical sensitivity in MCS

### Pesticides in MCS

In addition to the role of volatile organic solvents, cases of MCS appear to be initiated through the action of pesticides, particularly organophosphates and carbamate pesticides, which are known inhibitors of acetylcholinesterase, producing elevated levels of acetylcholine. The action of acetylcholine, especially on receptors of the vascular endothelium, is known to induce nitric oxide. In this way excessive muscarinic activity may initiate the same biochemical consequences as excessive NMDA activity. A study of Gulf War veterans specifically implicated an organophosphate in the induction of chronic neurological symptoms (because of the association of a specific genetic polymorphism of a gene encoding the enzyme PON1 which is involved in the metabolism of cholinesterase inhibitors, like organophosphate compounds) with the occurrence of such symptoms.

### Increased Blood Brain Barrier Permeability and Decreased Cytochrome P450 Activity

Nitric oxide and peroxynitrite may act via two other known mechanisms, both of which may be expected to increase chemical sensitivity.

Many reports have been published which greatly strengthen the evidence that peroxynitrite increases the permeability of the blood brain barrier, thereby allowing increased chemical access to the central nervous system (CNS) and thus increase chemical sensitivity generated in the CNS. Evidence that this occurs in (ME) CFS has been reviewed.

Nitric oxide is a known inhibitor of cytochrome P450 metabolism, which is widely involved in the metabolism of hydrophobic molecules; such P450 inhibition will slow the metabolism of these compounds and thus cause them to be found in higher levels in the body.

### Evidence for Excessive NMDA Activity in MCS and Organic Solvent Stimulation of NMDA Activity

There is evidence that NMDA activity is involved in this overlapping group of medical conditions and not only in MCS. One organic compound that is often implicated in MCS is formaldehyde, which is known to stimulate NMDA activity: many studies have

confirmed this, and they also demonstrate that pain can be produced by excessive NMDA activity (and consequent elevated nitric oxide levels).

Those with MCS are often reported to have low magnesium pools, and magnesium is known to lower NMDA sensitivity.

Organic solvents may act by directly stimulating NMDA receptor activity via three possible mechanisms, two involving increased nitric oxide synthesis leading to NMDA hyperactivity and one involving a mitochondrial mechanism. A large number of hydrophobic solvents are thought to act by disrupting mitochondrial membrane structure and function, whilst also increasing the generation of superoxide radical (a precursor, with nitric oxide, of peroxynitrite). This response appears to produce a prolonged generation of free radicals and other oxidants in the brain. The actions of a wide array of organic solvents may induce NMDA hyperactivity in MCS.

NMDA receptors are widely distributed in the central and peripheral nervous systems, but other cell types are not known to carry such receptors, so it is necessary to consider mechanisms by which central neural sensitization and CNS nitric oxide / peroxynitrite elevation may impact various tissues. Several mechanisms have been suggested. Inflammatory cytokines are thought to be part of the mechanism leading to increased nitric oxide; such cytokines that have been reported to be induced by organic solvents will reach a variety of tissues via the systemic circulation. Furthermore, nitric oxide itself has been shown to bind to some heme groups of haemoglobin and when stabilised by such binding, can circulate to various regions of the body. Thus both inflammatory cytokine elevation and nitric oxide transport may be mechanisms whereby elevated nitric oxide in the CNS may spread to other tissues.

Other mechanisms of spread beyond the CNS include autonomic dysfunction, neurogenic inflammation and neuroendocrine dysfunction (including HPA axis dysfunction, which is well-documented in ME/CFS).

A recent genetic study may provide another link between MCS and NMDA activity: it has been reported that a particular allele (encoding the CCK-B receptor) was significantly associated with increased MCS prevalence. It is known that the CCK-B receptor modulates NMDA activity; a genetic susceptibility for the development of MCS thus seems likely.

## Conclusion

This paper presents an explanation for the biological basis of the specific symptom pattern found in MCS (including the “spreading phenomenon”) associated with chemical exposure and injury. When the elevated nitric oxide / peroxynitrite theory, together with the neural sensitization theory, are put together, the four mechanisms (nitric oxide-mediated stimulating of neural transmitter release; peroxynitrite-mediated stimulation of post-synaptic NMDA sensitization; peroxynitrite-mediated blood brain barrier

permeabilization and nitric oxide inhibition of cytochrome P450 metabolism) would all be expected to act synergistically in line with the well-determined properties of LTP and the NMDA receptor system, thus producing the exquisite sensitivity found in MCS. All four mechanisms are individually well-documented. Sceptics have been wont to scoff at MCS sufferers, claiming that “there is no known mechanism whereby low levels of chemicals of widely varied chemical structure can interact adversely with numerous organ systems”; thanks to Pall, such disbelief and dismissal will no longer be tenable.