

Chemical Toxicology in Multiple Chemical Sensitivity: A Common Mechanism Involved in Environmentally Initiated Illnesses

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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 scientific literature reports that complete recoveries from CFS and FM do occur but are relatively rare. Only about 10% of the CFS and FM patients have a full recovery, although this typically take several years. Full recoveries from MCS rarely if ever occur, although MCS sufferers do report improved symptoms if they are able to avoid exposures to the classes of chemicals that produce sensitivity symptoms and environmental medicine treatment can often produce substantial improvements in MCS cases.



Much but not all of this presentation comes from information from my book 'Explaining 'Unexplained Illnesses': Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others'.



This talk will focus on MCS and other diseases that share with MCS the same group of chemicals that initiate cases of these diseases.



Epidemiological studies have shown that MCS is amazingly common. In the U.S., about 3.5% of the population suffers from severe MCS with great difficulties in maintaining employment and finding tolerated housing. Moderately effected people are a much larger percentage, perhaps 15 to 20% of the population. Figures for Canada, Germany, Sweden and Denmark are roughly similar.

The economic losses for the severely affected group have not been studied much but are clearly immense. I estimated the U.S. figures to be perhaps 200 billion dollars per year, due simply to unemployment or underemployment.

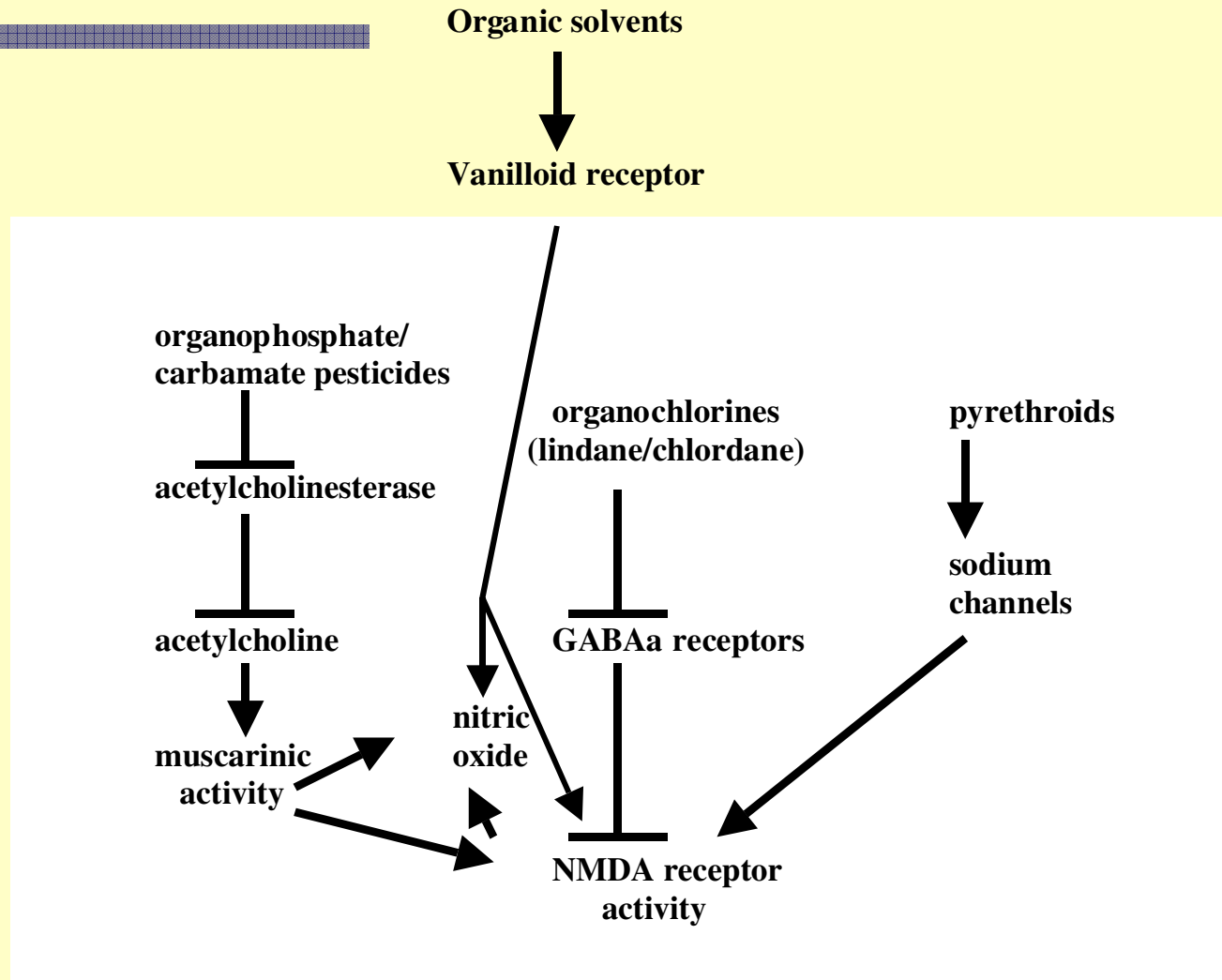
Chemicals reported to initiate cases of MCS include the following:

- **Organic solvents and related compounds.**
- **Organophosphorus/carbamate pesticides.**
- **Organochlorine pesticides**
- **Pyrethroid pesticides**

but also:

- Hydrogen sulfide
- Carbon monoxide
- Mercury

Chemical Action in MCS



We also know that members of each of these four classes of chemicals, the organic solvents and the three classes of pesticides, when tested in experimental animals, the following has been shown:

One can greatly lower their toxicity in the body by treating with an NMDA antagonist. This shows not only that increased NMDA activity is produced by these chemicals but that this increased activity has a major role in producing the toxic responses in the body!

What about the other three chemicals that also initiate cases of MCS??

These are also known to have similar toxicological properties:

Hydrogen sulfide, carbon monoxide and mercury (acting through its product, methylmercury) can each produce increased NMDA activity; and one can use NMDA antagonists to lower the toxic responses to all three of these!

Six other observations supporting an NMDA role in MCS:

1. MCS patients are sensitive to monosodium glutamate and glutamate is the physiological agonist of the NMDA receptors.
2. An allele of the CCK-B receptor gene that produces increased NMDA activity is associated with increased prevalence and therefore incidence of MCS.
3. The NMDA antagonist dextromethorphan is reported from clinical observations to produce lowered response to chemical exposures in MCS patients.
4. Bell and others have proposed that neural sensitization has a key role in MCS and the probable mechanism for such neural sensitization, called long term potentiation, is known to involve increased NMDA activity.
5. Elevated NMDA activity has been shown to play an essential role in several animal models of MCS.
6. Elevated NMDA activity appears to play a role in such related illnesses as fibromyalgia, chronic fatigue syndrome and post-traumatic stress disorder, with the most extensive evidence for such a role being found in fibromyalgia (Pall, 2006 and 2007a).

Compelling evidence for a common toxicological response

Table 1 Genetic polymorphisms influencing MCS susceptibility

Gene	Study	Function – chemical metabolism	Comments
PON1	H, M	Detoxification of organophosphorus toxicants	
CYP2D6	M	Hydroxylation of hydrophobic compounds	Hydroxylation of compounds without hydrogen binding group may be expected to lead to greater activity as a TRPV1 agonist
NAT2	M, S	Acetylation	May produce more or less activity depending on the specific compound involved
GSTM1	S	Provide reduced glutathione for conjugation	Should increase detoxification and excretion
GSTT1	S	Glutathione conjugation	Should increase detoxification and excretion
GSTP1	S	Glutathione conjugation	Should increase detoxification and excretion; only statistically significant role was in conjunction with specific alleles of other genes

H = Haley et al, 1999; M = McKeown-Eyssen et al, 2004; S = Schnakenberg et al, 2007.

NMDA receptor activation



channels allow calcium
entry into cell



nNOS and eNOS activation



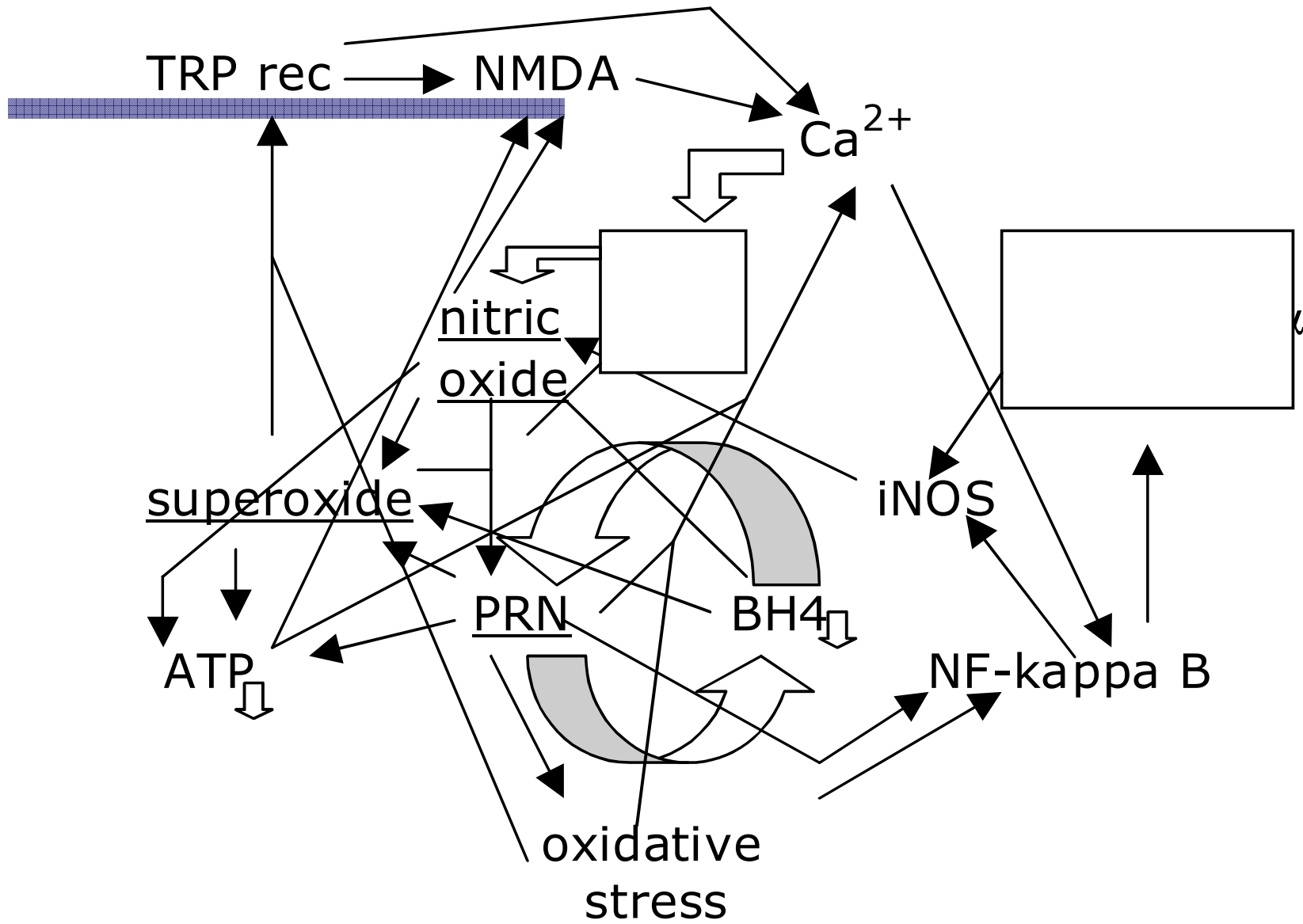
nitric oxide increase



react with superoxide to
form peroxynitrite

Table 1: The stressors implicated in the initiation of these illnesses are summarized.

Illness	Stressors Implicated in Initiation of Illness
Chronic fatigue syndrome	Viral infection, bacterial infection, organophosphorus pesticide exposure, carbon monoxide exposure, ciguatoxin poisoning, physical trauma, severe psychological stress, toxoplasmosis (protozoan) infection, ionizing radiation exposure
Multiple chemical sensitivity	Volatile organic solvent exposure, organophosphorus/carbamate pesticide exposure, organochlorine pesticide exposure, pyrethroid exposure; hydrogen sulfide; carbon monoxide; mercury
Fibromyalgia	Physical trauma (particularly head and neck trauma), viral infection, bacterial infection, severe psychological stress, pre-existing autoimmune disease
Post-traumatic stress disorder	Severe psychological stress, physical (head) trauma



We call this vicious cycle the NO/ONOO- cycle based on the structure of nitric oxide (NO) and peroxyntirite (ONOO-) but pronounced no, oh no! because this is the way people suffering from these diseases feel when suddenly or slowly they are afflicted with these wide-ranging diseases.

There are 47 distinct types of evidence for a NO/ONOO- cycle mechanism for MCS. These come from:

- Studies of basic mechanisms including the toxicological mechanisms discussed above.**
- Studies of MCS patients and their properties.**
- Studies of neural sensitization, a process that interacts with the NO/ONOO- cycle in MCS.**
- Genetic studies of susceptibility to MCS.**
- Animal model studies of MCS.**
- Studies of related diseases, including studies of therapy of these related diseases.**

There are **7 mechanisms** that may have important roles in generating the chemical sensitivity reported in MCS:

Chemical action to increase NMDA activity in regions of brain where the NO/ONOO- cycle is already up-regulated due to previous chemical exposure.

Nitric oxide acting as a retrograde messenger, increasing NMDA stimulation.

Peroxynitrite acting to decrease energy metabolism, producing increased NMDA sensitivity to stimulation.

Peroxynitrite acting to decrease energy metabolism, producing less transport of glutamate, leading to increased NMDA stimulation.

Nitric oxide, acting to inhibit cytochrome P450 metabolism of chemicals, leading to increased chemical accumulation.

Peroxynitrite, producing breakdown of the blood brain barrier, leading to increased chemical access to the brain.

Oxidants and superoxide, leading to increased vanilloid activity, producing increased sensitivity to organic solvents.

Table 14-1 Major Disease Paradigms

1. Infectious diseases.
2. Genetic diseases.
3. Nutritional deficiency diseases.
4. Hormone dysfunction diseases.
5. Allergies.
6. Autoimmune diseases.
7. Somatic mutation/selection (cancer).
8. Ischemic cardiovascular diseases.
9. Amyloid (including prion) diseases.
10. **NO/ONOO- cycle diseases**

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10. **NO/ONOO- cycle diseases**

1. Tinnitus
2. Post-Radiation Syndrome
3. **Multiple Sclerosis (MS)**
4. **Autism**
5. Overtraining Syndrome
6. Silicone Implant Associated Syndrome
7. Sudeck's Atrophy
8. Post-Herpetic Neuralgia (Pain)
9. Chronic Whiplash Associated Disorder
10. **Amyotrophic Lateral Sclerosis (ALS)**
11. **Parkinson's Disease**
12. Alzheimer's Disease
13. **Asthma**
14. Irritable Bowel Syndrome

The coloured diseases also are initiated by solvents and pesticides.

We have, then, a broad ranging role for organic solvents and three classes of pesticides in many environmentally initiated diseases, as well as an explanation of how these diverse chemicals can produce a common toxicological response in the body. This topic, is therefore, a very important topic in environmental medicine.

I have, therefore, three recommendations to make to the Parliament regarding this important topic.

1. We need to develop a bioassay test for the activity of organic solvents and related compounds in this process. This is needed in order to assess the activities of different chemicals in this very broad chemical class in this process and also to determine how these diverse chemicals may act together in this process. Without this information it will be difficult to regulate these chemicals effectively because we have little information on their individual or collective activities in the process of initiating environmentally caused disease. Organic solvents are by far the most common environmental toxicants, emphasizing the importance of this recommendation.

2. We need to establish several specific biomarker tests for MCS. In other words, with most diseases (i.e., asthma, lupus, multiple sclerosis) the disease is initially diagnosed based on symptoms, but then there are specific biomarker tests (specific tests for that specific disease) that can be used to confirm the diagnosis. There are attractive approaches to develop such tests described in the scientific literature for MCS but these have not been studied and validated sufficiently. Some of these tests only test chemical sensitivity in certain tissues and may only detect certain MCS cases. Such tests are essential both to the scientific study of MCS and to improve clinical practice on this disease.

3. The Parliament should move ahead with approval for an EU-wide specialty in Environmental Medicine. Some of the complexities of these areas of medicine should be clear from my earlier comments and the areas I have touched on represent only part of these complexities.

We have a great need, therefore, for well-trained clinicians in this area of medicine. By approving such a specialty, it should be possible for Europe to take the world wide leadership role in Environmental Medicine.