The Vanilloid Receptor as a Putative Target of Diverse Chemicals in Multiple Chemical Sensitivity

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ABSTRACT. The vanilloid receptor (TRPV1 or VR1), widely distributed in the central and peripheral nervous system, is activated by a broad range of chemicals similar to those implicated in Multiple Chemical Sensitivity (MCS) Syndrome. The vanilloid receptor is reportedly hyperresponsive in MCS and can increase nitric oxide levels and stimulate *N*-methyl-D-aspartate (NMDA) receptor activity, both of which are important features in the previously proposed central role of nitric oxide and NMDA receptors in MCS. Vanilloid receptor activity is markedly altered by multiple mechanisms, possibly providing an explanation for the increased activity in MCS and symptom masking by previous chemical exposure. Activation of this receptor by certain mycotoxins may account for some cases of sick building syndrome, a frequent precursor of MCS. Twelve types of evidence implicate the vanilloid receptor as the major target of chemicals, including volatile organic solvents (but not pesticides) in MCS.

<Key words: mold, multiple chemical sensitivity, nitric oxide, NMDA, peroxynitrite, vanilloid receptor>

THE ORIGIN of this article was an interchange between the 2 authors of this study at the 2003 Chemical Injury Information Network professional meeting at Fairfax, Virginia, during October 3–5, 2003. One of the authors (MLP) presented extensive evidence[1–3] that supported the view that excessive levels of nitric oxide and its oxidant product peroxynitrite, as well as excessive activity of *N*-methyl-D-aspartate (NMDA) receptors in the brain, are centrally involved in the etiology of multiple chemical sensitivity (MCS). The remaining author (JHA) presented evidence that the vanilloid receptor (TRPV1 or VR1) is the primary target for xenobiotic chemicals in MCS. Many chemicals that elicit MCS activate this receptor, and symptoms produced by vanilloid activation are similar to many of the symptoms reported in MCS. Repeated exposures to chemical irritants have led to increased apparent vanilloid receptor activity in mice[4–8]; presumably, similar changes could occur in humans.

The question raised in our interchange was whether these 2 views are compatible, i.e., whether vanilloid stimulation can be linked to the proposed nitric oxide/peroxynitrite/NMDA mechanism. This article contains several areas of review in the scientific literature that address the aforementioned question, and it contains reviews from which we gleaned evidence that suggested the important vanilloid receptor role in MCS. We also have reviewed the closely related phenomena of peripheral chemical sensitivity; the activity of formaldehyde, chlorine, and other diverse chemicals in MCS; the "masking" of sensitivity responses after chronic, low-level chemical exposures; and the role of mold toxins in the initiation of some cases of MCS.

Nitric Oxide/Peroxynitrite/NMDA Theory for MCS

The nitric oxide/peroxynitrite/NMDA theory focuses on excessive levels of nitric oxide (NO) and its oxidant product, peroxynitrite, and a set of positive feedback mechanisms that may act to maintain these excessive levels. The process is purportedly initiated by several short-term stressors, reported to precede a group of

overlapping illnesses, including chronic fatigue syndrome, fibromyalgia, MCS, and posttraumatic stress disorder. Each of these stressors increase NO levels.[1–3, 9–17] Several chemicals that initiate MCS[18,19] increase NO levels, including organophosphate/carbamate pesticides and a variety of volatile organic solvents.[1–3] The aforementioned theory has been verified by observations of physiological correlates of these illnesses, and explanations exist for many of the most common symptoms of these illnesses.[2,3,10,12] Investigators have proposed 4 mechanisms that explain the exquisite chemical sensitivity seen in some cases of MCS, and each involved well-documented mechanisms involving NO or peroxynitrite.[2,3] The role of organophosphate/carbamate pesticides in the initiation of this sequence likely involved their known role as acetylcholinesterase inhibitors and consequently increased stimulation of muscarinic receptors and, therefore, led to increased NO levels and indirectly increased NMDA activity.[1–3] Although 3 possible targets of hydrophobic chemicals have been posited,[2] the major target of organic solvents has remained unclear under this theory.

The theory was most predictive when fused with an earlier theory of MCS developed by Sorg, Bell, and collaborators.[19–24] Their neural sensitization theory[19–24] focuses on long-term potentiation (LTP), a mechanism known to involve increased NMDA receptor activity in the brain, where such activity produces an increase in NO and peroxynitrite. In addition, NO often acts as a retrograde messenger, diffusing to the presynaptic cell, where it increases release of the neurotransmitter glutamate.[2,25] There are considerable overlaps between the two theories, allowing the development of a theory fusing the two. Twenty-four types of observations[2] provide support for the fusion theory, including ten that provide support for an NO/peroxynitrite mechanism. Animal model data, clinical observations, pesticide mechanisms, and a genetic study provide support for a role of excessive NMDA activity in MSC.[2]

The NO/peroxynitrite/NMDA theory, linked to LTP, focuses on the central nervous system (CNS) in the pathogenesis of MCS and provides a mechanistic basis for the earlier suggestion of Ashford and Miller,[18] as well as the previously cited studies by Bell et al.,[21–24] that MCS involves the limbic region of the brain. The 2 phases of the proposed mechanism—initiation of sensitivity on initial chemical exposure followed by chemical sensitivity in the chronic phase of the illness, with both phases involving increased nitric oxide, peroxynitrite, and NMDA activity—are essentially proposed as explanations of the 2 phases of MCS described previously by Ashford and Miller,[18] termed *initiation* and *elicitation*.

There are, however, several hypersensitivity conditions that apparently involve the peripheral tissues, rather than the central nervous system. Meggs and colleagues[26–29] and other investigators[30–32] emphasized the similarities between MCS and asthma and other forms of peripheral sensitivity, including reactive airways dysfunction syndrome (RADS), a form of asthma initiated by chemical exposure; reactive upper airways dysfunction syndrome (RUDS), rhinitis induced by chemical exposure; and skin contact sensitization.[26–29] Many forms of asthma involve excessive responses in the airways to a series of diverse chemicals[33–39] that are similar to those implicated in MCS. Meggs has suggested that many asthmatics may be viewed as having MCS, arguing that any asthmatic with nonrespiratory symptoms on chronic exposure to chemicals meets the Cullen[40] case definition for MCS.[26] In RADS, RUDS, contact sensitivity, and in some cases of MCS, the process cannot be easily explained by the CNS mechanism outlined earlier. Meggs and colleagues emphasized the important role of neurogenic inflammation in these peripheral chemical sensitivity conditions.[26–29] Neurogenic inflammation is caused by activation of the vanilloid receptor, as well as by increased NO levels.[2] How, then, can the similarities between peripheral chemical sensitivity and central mechanisms of MCS be explained?

Vanilloid Receptor Family

The vanilloid receptor (i.e., TRPV1 or VR1) is the primary receptor for the compound capsaicin, the "heat" in hot *Capsicum* peppers, as well as for several other "hot" foods and spices and other irritants.[41–44] Information on vanilloid receptor properties has exploded during the last decade.[41–44] As we describe selected features of this protein, we will indicate how they may help to explain important properties of MCS and related conditions. The receptor is one of the major mechanisms by which animals interact with xenobiotics.[45,46] It is a critical component in the "common chemical sense," located in the small C-fibers of the trigeminal nerve, which innervates a large part of the face, eyes, and upper airways, and provides an early warning or sensory irritation (SI [a conscious sensation of burning or pain in the facial area]) that the organism has entered a zone of irritant chemicals. It is also widely distributed in the central and peripheral nervous systems and in some nonneuronal cells.

The vanilloid receptor is part of the receptor family designated as the transient receptor potential (TRP), the members of which are involved in all the major senses—temperature, touch, vision, and taste.[47] There are 6 members of this receptor family (TRPV1, TRPV2, among others), but only the vanilloid receptor, TRPV1, is highly sensitive to a wide range of xenobiotics, and it is the only 1 sensitive to capsaicin; several members of this receptor family—including the vanilloid receptor—are sensitive to pH or temperature.[43,44] Menthol reacts with 1 of the other members of this receptor family[48–50] and produces a cold, rather than heat, sensation. The vanilloid

receptor can also be activated by heat and protons, and these responses may be important in its role in pain, inflammation,[51] and gastrointestinal responses to intraluminal acid.[52,53]

Vanilloid receptor function has been studied in intact animals and receptor gene-knockout mice and in in vitro techniques. In studies, investigators have focused on sensory irritation (SI)[6–8,54–56] in trigeminal nerves using firing rates,[57,58] on cells using fluorescent probes responding to calcium influxes,[51,59,60] and on cell membrane fragments using patch-clamp techniques.[51,59,60] Strong agonists (capsaicin and resiniferatoxin) and strong antagonists (i.e., capsazepine, ruthenium red, and iodoresiniferatoxin) facilitate pharmacological studies.[41–44] The ability of capsaicin treatments to desensitize the receptor to other agonists has been very useful. Such diverse studies have provided a fairly coherent picture of the function and roles of the vanilloid receptor.

Vanilloid receptor distribution. The vanilloid receptor is distributed widely in neuronal and nonneuronal cells. In many studies, the role of the vanilloid receptor has been demonstrated in the spinal cord, dorsal root ganglia, and trigeminal ganglia.[61] In the brain, it is present in the hippocampus, where much of the neural sensitization is thought to occur.[41,62–69] The vanilloid receptor also has been demonstrated in the olfactory nuclei; cerebral cortex; dentate gyrus; thalamus; hypothalamus; periaqueductal grey matter; superior colliculus; locus coeruleus; cerebellar cortex; the preoptic area; amygdala; substantia nigra; reticular formation; and inferior olive.[61,64–69] C-fibers of the autonomic nervous system carry vanilloid receptors along blood vessels into every organ throughout the body. In addition, it has been found in lung epithelial cells; the prostate; macrophages; bladder smooth muscle; kidney; mast cells; skin keratinocytes; and liver cells.[43,44]

Although the vanilloid receptor appears to have similar chemical properties in the peripheral and the central nervous systems, pH buffers and antioxidants may protect the brain and brain vanilloid receptors from some adverse effects of some xenobiotics. For example, chlorine, an oxidant, and acetic acid have marked peripheral effects,[27] in part because of vanilloid activation, but they have little effect on the central nervous system (presumably because buffers and antioxidants are present).

Xenobiotics as vanilloid agonists. Much of the evidence suggesting that the vanilloid receptor is a major target for xenobiotics comes from SI studies. SI can be elicited by alkanes, alkyl benzenes, halogenated benzenes, halogenated alkylbenzenes, alcohols, ketones, ethers, aldehydes, formaldehyde, isocyanates, and chlorine.[46] Studies in which apparent vanilloid receptor stimulation has occurred via diverse xenobiotics are summarized in Table 1.[70–78]

The results of several studies suggest that SI is produced primarily through the action of a single receptor,[46,79] and the review by Nielsen summarizes much of the evidence that this receptor is the vanilloid receptor.[46] For example, the effects of SI with mixtures of formaldehyde, acrolein, and acetaldehyde are less than additive—a result consistent with a model involving competition for a common receptor on the trigeminal nerve.[80] However, there is 1 major exception to this otherwise simple picture: Symanowicz et al.[56] demonstrated SI from acrolein in knockout mice lacking vanilloid receptor activity and lack of inhibition of SI by a potent vanilloid antagonist in C57BL/6J mice. These studies suggest the likelihood that vanilloid stimulation is not the entire explanation for chemical stimulation of SI. This conclusion also is supported by the specific action of the irritant menthol as a stimulant of 1 of the other members of the TRP family of receptors,[48–50] as discussed previously. It follows that the vanilloid receptor may be the most important target of irritants in the SI response, but it is not the only such target.

The vanilloid receptor binds ligands in a stereospecific manner,[81] thus implying at least 3 points of interaction. The results of studies with capsaicin have resulted in the identification of 3 important regions in the binding site: (1) the homovanillyl aromatic group, (2) a hydrogen bonding group, and (3) an aliphatic chain group.[42] A series of alkyl benzenes showed increased apparent affinity with increasing length of the aliphatic alkyl

Table 1.—Compounds with Vanilloid Agonist Activity

Compound	Reference no.
Hydrophobic	
Toluene, xylene, and other alkylbenzenes	46, 71–73
Benzene	74
Ether	46
Cyclohexanone	46
Chloracetophenone	46
o-Chlorobenzylidene malononitrile	46
Amyl acetate	46
Aliphatic alcohols	46,70,73
Eugenol	*
Methyl anthranilate	75
Aldehydes	
Formaldehyde	*
Hydrophobic dialdehydes	76
Others	
Low pH, HCl, acetic acid, propionic acid	46,77
Sulfur dioxide	46,78
Toluene diisocyanate	*
Chlorine	87

*Most of these compounds have been identified as apparent vanilloid agonists, using presumed specific assays that include effects of capsaicin pretreatment on their response and the effects of vanilloid antagonists capsazepine and ruthenium red, the latter of which is likely the less specific of the 2. The references for eugenol, formaldehyde, and toluene diisocyanate are provided in relation to specific discussion of these compounds in the text of this article.

group, a result that implicates both the aromatic benzene group and the aliphatic tail in binding.[79] A series of alcohols showed increasing activity with the length of their aliphatic tails, again implicating both the hydroxyl hydrogen bonding group and the aliphatic tail in binding.[79] The ability of a series of related compounds to stimulate vanilloid activity suggested that hydrophobicity is critically important in binding agonists.[82]

Capsaicin produces an irritant response followed by a period of desensitization during which receptor activity is less responsive to subsequent stimulation by vanilloid agonists.[41,42] This desensitization response to capsaicin is thought to be specific and has been used to identify formaldehyde, cigarette smoke, ether, cyclohexanone, amyl acetate, and propionic acid[46] as presumed vanilloid agonists. Other irritants may be inferred to act via the same receptor because they show competitive antagonism with each other (e.g., propanol vs. d-limonene, formaldehyde vs. acrolein).[46] Chlorine gas, an irritant, leads to reciprocal desensitization to formaldehyde,[83] suggesting that chlorine gas itself is a vanilloid agonist.

Biochemical/physiological functions of the vanilloid receptor. The vanilloid, like many other receptors, resides in the plasma membrane and makes the cell responsive to certain external stimuli. Its 838 amino acids[51] are arranged in 6 transmembrane segments with both the N- and C-terminal ends extending into the cytoplasm, where they complex with macromolecule scaffolds.[44] The primary site for capsaicin binding is on an intracellular loop[44,84] between the second and third transmembrane segments, but there may be additional agonist binding sites on the extracellular side of the membrane.[85,86] Four units associate to form a tetrameric[87,88] nonspecific cation channel; the subunits interact, producing ligand cooperativity.[51]

Activation of this receptor leads to a conformational change allowing rapid influx of extracellular calcium. The rising intracellular calcium levels produce nerve cell action potentials and nerve cell firing, activation of NO synthesis, which in turn results in increased intracellular NO and activates synthesis of cyclic GMP. There is also release of Substance P, CGRP (calcitonin gene-related peptide), VIP (vasoactive intestinal polypeptide), and adenosine.[88,89]

The extracellular products of vanilloid activation can affect numerous physiological processes. Substance P, CGRP, and VIP are potent vasodilators and neuronal cotransmitters.[88,89] Release of these vasoactive peptides at nerve axon terminals leads to local changes termed *neurogenic inflammation*. Substance P is one of the major agents in the development of asthma. The receptor is important in the control of blood pressure,[90] gastrointestinal secretion,[52,53] bladder voiding,[91] pain sensation,[59] and response to inflammation.[92,93] Vanilloid activity in the area postrema influences blood pressure, heart rate, and renal sympathetic nerve firing.[94]

Control of vanilloid activity. Control of vanilloid activity is a complex process that involves regulation at several different levels.[41–43,92–105] These include control of vanilloid gene expression,[92,93] regulation by phosphorylation/dephosphorylation,[95–103] and regulation by direct binding of regulatory ligands.[104,105] Vanilloid receptor regulation specifically involves a number of protein kinases. Protein kinase C activity appears to be the most commonly involved,[41–43,95–102] with the cyclic-AMP–dependent protein kinase (protein kinase A) and Ca2+ calmodulin kinase II also involved.[42,43,102,103] Protein kinase-C–dependent phosphorylation leads to increased vanilloid activity, whereas dephosphorylation by the Ca2+ calmodulin phosphatase calcineurin leads to decreased activity.[43,95–102] Changes in the phosphorylation state are likely involved in the desensitization (tachyphylaxis) frequently seen in vanilloid studies,[42,43] which was discussed previously. Nerve growth factor (NGF) is produced by a variety of cell types, especially under inflammatory conditions,[106–111] and NGF increases vanilloid activity by increasing protein kinase C activity.[99,101,111–114]

There are 2 potentially important roles for such control of vanilloid activity in MCS. Ironically, they influence the activity of the vanilloid receptor in opposite directions.

Desensitization of the vanilloid receptor develops during some, but not all, exposures to xenobiotics.[41,42,115–117] Typically, modest doses of agonists produce this response either in response to chronic or repeated exposure. There is but a minimal relationship between the irritant response produced by such compounds and their desensitization potential. For example, capsaicin can produce both strong activation and desensitization, but there are other potent irritants that produce very minor desensitization, and there are weak irritants that produce potent desensitization.[42] Desensitization could be achieved by changes in the phosphorylation state[42,43,60,102] and/or by endocytosis[99] of the receptor protein.

Vanilloid desensitization may account for 2 features of MCS: (1) the "masking" phenomenon—previous xenobiotic exposure reportedly causes a decreased response to subsequent xenobiotic exposures in MCS patients, and a 4-d abstinence from exposure leads to a return to full (heightened) sensitivity[18]; and (2) the desensitization of MCS patients on deliberate exposure to very small amounts of xenobiotics as part of a therapeutic program.[118,119] Our goal herein is not to endorse such treatment but to simply provide an attractive explanation for the observations.

Vanilloid regulatory mechanisms may also help explain part of the increased chemical sensitivity seen in MCS—both during the initiation of illness and in the high level of sensitivity seen in those with MCS. High level vanilloid stimulation shows a reciprocal regulatory

relationship with inflammation. Such high-level stimulation can lead to inflammatory responses[120–125] through several mechanisms, including the stimulation of neurogenic inflammation and the actions of Substance P and CGRP released on vanilloid stimulation, as discussed previously. Inflammation, in turn, has been widely reported to lead to increased vanilloid activity.[42,93–97,99,102,114,126] Part of this inflammatory increase in activity is reportedly involved in the stimulation of vanilloid activity by oxidants, including superoxide.[127,128] Given the reported increased level of oxidants in MCS, this influence may possibly be relevant to this condition.[129] Another part involves the influence of NGF (discussed previously). Both NGF and oxidants may be expected to increase vanilloid activity by stimulating protein kinase C-dependent phosphorylation.[100,112,130,131] Inflammation also acts to increase vanilloid gene expression, which leads to increased levels of the receptor protein.[93,94] The role of inflammatory biochemistry in up-regulating vanilloid activity is suggested because it provides a partial explanation for the increased chemical sensitivity in MCS. Inflammation induced by initial high-level chemical exposure may cause increased vanilloid activity, in turn leading to increased chemical sensitivity. Increased vanilloid activity may act concurrently with other previously proposed mechanisms to generate chemical sensitivity.

Mold toxins and vanilloid stimulation. Many cases of MCS occur in occupants of specific buildings, often referred to as examples of the Sick Building Syndrome (SBS). For example, Miller and Mitzel[132] studied a group of SBS sufferers as 1 group in a study of MCS, and they compared them with MCS sufferers whose illnesses appeared to have been induced by pesticide exposure. MCS has also reportedly occurred in other SBS conditions.[133–135] Berglund et al.[136] reported that individuals reacted to air piped in from such a "sick building" in a blinded fashion, but they did not react to uncontaminated air, thus demonstrating that these individuals reacted to chemicals in the sick building air—and not to some sort of psychological trauma associated with being physically located in the building.

There are 2 main types of SBS conditions: (1) those associated with volatile organic solvents out-gassing from building materials of several types; and (2) those associated with mold-contaminated buildings—mainly involving molds that grow on moist plasterboard materials in buildings that have leakage or water-condensation problems.[18,137–140] Sufferers from mold-contaminated buildings were also reported to have MCS symptoms.[137] Although the stimulation of mechanisms purportedly involved in MCS via vanilloid receptor stimulation or other targets may explain the role of organic solvents in MCS, no mechanistic explanation has previously been established for the possible role of molds in the initiation of cases of MCS. Accordingly, it may be important that 1 group of toxins that stimulates the vanilloid receptor—the hydrophobic dialdehydes[76,141–144]—is produced by several different fungi.[76,141] In addition, the mold *Stachybotrys*, which has been associated with several SBS situations and grows readily in moist plasterboard,[139,140,145] could possibly produce similar hydrophobic dialdehyde toxins,[146] although these specific toxins have not been tested as possible vanilloid agonists. Another class of fungal toxins, triprenyl phenols, has also been reported to stimulate the vanilloid receptors.[147] Given the similarities between MCS and asthma that have been discussed here, it is not surprising that mold-infested buildings are also reported to be an important risk factor in the development of asthma.[139,140,148–151]

Molds produce many additional chemicals that may activate the vanilloid receptor. They produce a number of additional unusual organic metabolites (i.e., MVOCs), including alcohols, terpenes, ketones, aldehydes, esters, aromatic compounds, amines, and sulfur-containing compounds. The chemicals produced depend on the species of mold, the substrate (food) for growth, and the phase of the life cycle of the mold colony.[138] The ability of MVOCs to produce SI has been studied in mice. SI can be produced by individual MVOCs, as well as by mixtures of MVOCs[152]; extracts of *Stachybotrys chartarum*[153]; and extracts of *Aspergillus versicolor*.[154]

Perhaps the MCS response to mold-contaminated buildings may be produced by vanilloid stimulation in response to dialdehyde or other mycotoxins, or by MVOC irritants that may work by activating the vanilloid receptor pathway. It should be noted that mold-infested examples of SBS have also been reported to generate inflammatory responses in exposed individuals[155]; therefore, one may also expect mold toxins to act via the inflammatory process to raise vanilloid activity, and such response may be expected to act synergistically with vanilloid agonists in generating MCS responses.

Links between the vanilloid receptor and NMDA/NO. Vanilloid biochemistry and physiology provide 2 links to the previous proposal that MCS involves NO/peroxynitrite/NMDA pathology. First, vanilloid activation increases NO levels[69,156–160] in a manner similar to the NO increase caused by activation of NMDA receptors. Each of these receptors opens membrane channels that allow calcium influx into cells, thus stimulating the 2 forms of NO synthases known to be calcium dependent (nNOS and eNOS). Thus, xenobiotic activation of vanilloid receptors would be expected to elevate NO/peroxynitrite levels—factors previously described as central components of MCS pathology.[2,3] Second, vanilloid activation leads to NMDA receptor stimulation, in part through glutamate release, as seen in the paraventricular nucleus,[161] nucleus tractus soltarius,[162] and elsewhere.[163–170] Vanilloid stimulation is linked to NMDA stimulation in antinociception functions of the

periaqueductal grey matter,[171] inflammation in rat paw[172] and dorsal horn of the spinal cord,[173] and in allodynia reactions in monkey tails.[174] Thus, vanilloid stimulation by xenobiotics may be linked to the proposed fusion theory mechanism for MCS (i.e., excessive NMDA activity with excessive NO and peroxynitrite levels, particularly in brain tissues) discussed previously.

Clinical Investigations of MCS and Related Conditions

Two types of clinical investigations provide supporting evidence that vanilloid activity is increased in MCS. In several studies, investigators have reported capsaicin hypersensitivity in MCS individuals. Compared with normals, individuals with MCS develop excess coughing after inhalation challenges with aerosols of capsaicin.[175–178] Such data indicate that increased vanilloid activity occurs in the lower airways (i.e., vagus nerves and/or lung epithelial cells) in these individuals with MCS.

Elevated serum markers indicative of vanilloid stimulation were reported in a group of MCS patients. Specifically, they had 10-fold increases in serum NGF, which increases vanilloid activity, as discussed previously, and 10-fold increases in serum Substance P (a product of vanilloid stimulation).[179] These levels further increased by approximately 50% following brief inhalation challenges to paint fumes. The investigators used various control groups to demonstrate that these features were linked to MCS. The increased Substance P and the increased response of Substance P to paint fumes clearly indicated increased vanilloid activity in these individuals with MCS. Further research is required if (a) the source of NGF is to be determined, and (b) to determine whether the NGF elevation is a primary or secondary phenomenon. Serum NGF or Substance P levels are also elevated in asthma,[110] lupus erythematosus,[180] atopic dermatitis,[181] juvenile chronic arthritis,[182] and rheumatoid arthritis[183]; therefore, these are not unique serum markers for MCS, although increases in response to chemical exposure(s) may be unique.

Vanilloid activity is also involved in the pathophysiology of several conditions that are closely related to MCS.

Peripheral chemical sensitivity conditions. Peripheral chemical sensitivity mechanisms, including RADS, RUDS, and contact sensitivity mechanisms, are important components in many cases of MCS. RADS is a form of chemical sensitivity that focuses on the lower airways (bronchi and bronchioles). The classic chemical sensitizer, toluene diisocyanate, is a potent vanilloid agonist[184–188] that can induce RADS, as well as the contact sensitivity of the skin.[189–195] Capsaicin, the classic vanilloid agonist, also induces peripheral chemical sensitivity.[196–200] Eugenol, another vanilloid agonist,[201,202] produces both skin sensitization[203–207] and lung sensitization (RADS or asthma).[208] Formaldehyde, another vanilloid agonist, can produce peripheral chemical sensitivity[208–211] and, in some of these studies, vanilloid stimulation appeared essential in producing such sensitivity.[209,211] Both RUDS and RADS include mechanisms of neurogenic inflammation involving Substance P elevation and, therefore, presumably vanilloid stimulation.[26] Vanilloid hyperactivity is also implicated in psoriasis[212–214] and atopic dermatitis[181]—other forms of peripheral chemical sensitivity. The aforementioned diverse studies link vanilloid agonists and the vanilloid receptor itself to production of peripheral chemical sensitivities, several of which are elements in many cases of MCS.

Why might some cases of MCS involve such peripheral sensitivity but not others? Researchers think that the elevated NO/PRN mechanism may be centered on local mechanisms because of the limited diffusion of NO, PRN, and superoxide, as well as the cellular nature of the proposed positive feedback loops in the vicious cycle. Consequently, if an MCS sufferer expresses this proposed mechanism in peripheral tissues, it is expected that he or she will show peripheral sensitivity in the peripheral tissues that are impacted in that particular individual.

It should be noted that peripheral sensitivity typically involves sensitivity to the presence of mechanical stress, antigens, pH, or temperature and is, therefore, considerably broader than sensitivity to relatively simple organic chemicals.

Fibromyalgia. This condition, which involves chronic intermittent pain in fibrous connective tissues, overlaps with and presumably shares etiologic similarities with MCS.[12,215] Vanilloid hyperresponsiveness occurs in fibromyalgia,[216–218] and Substance P, a marker of vanilloid activity, is increased in the cerebrospinal fluid in fibromyalgia.[219,220] These data strongly implicate increased vanilloid activity in fibromyalgia, a condition with presumed etiologic similarities to MCS.

Conclusions

Although the results of previous studies have suggested a role for the "irritant receptor" in MCS,[4,5,175–178,221,222] the specific role of the vanilloid receptor in MCS has not been clarified, and the possible interactions with other mechanisms in MCS and closely related conditions were not explored.

The central conclusion of this review is that the vanilloid receptor, which appears to play a central role in the irritant response, is the putative major target for organic solvents and certain other compounds in MCS. Its widespread distribution in both the central and peripheral nervous systems, as well as in certain other tissues, suggests a possible important role for this receptor as the main target of diverse chemicals in both

central and peripheral chemical sensitivity mechanisms. Twelve types of observations provide support for this inference.

1. The pattern of chemicals that appears to stimulate the vanilloid receptor is similar to the diversity of chemicals implicated in MCS.
2. Excessive stimulation of the vanilloid receptor is implicated in peripheral chemical sensitivity mechanisms, which are important aspects in a high fraction of MCS cases.
3. MCS sufferers are reportedly hypersensitive to capsaicin, a classic and specific vanilloid agonist.
4. Substance P levels, which are known to be increased on vanilloid stimulation, are elevated in MCS, as well as being increased upon chemical exposure in MCS.
5. The vanilloid receptor stimulation produces increases in NO, an important predicted property for the target of chemicals in MCS.
6. The vanilloid receptor produces increased NMDA receptor stimulation, another important predicted property.
7. The vanilloid receptor appears to be involved in an animal model of MCS as the putative target of diverse irritants.
8. Vanilloid hyperactivity reportedly occurs in fibromyalgia, a related illness that is comorbid with MCS and may have etiologic similarities to MCS.
9. The vanilloid receptor is reported to be stimulated by certain mold toxins, thus providing an explanation for the initiation of MCS cases by mold-infested buildings.
10. Neurogenic inflammation, a reported feature of MCS, is caused by vanilloid stimulation.
11. Inflammation acting in part through oxidants increases vanilloid receptor activity, providing a partial explanation for the increased vanilloid activity in MCS, given the reported role of oxidative stress in that condition. The elevated receptor activity also provides a partial explanation for the chemical sensitivity.
12. Exposure to many vanilloid agonists produces a down-regulation of vanilloid activity, and provides an explanation for the masking/desensitization phenomenon in MCS.

Although the vanilloid receptor may be the major target of organic solvents in MCS, it is not the only target of chemicals in this illness. As noted here and elsewhere,[1–3] organophosphate and carbamate pesticides almost certainly act via a different pathway. Although the reported up-regulation of vanilloid activity provides a partial explanation for the chemical sensitivity in this illness, *it is only partial*, and other multiple mechanisms are likely involved.[2,3]

None of the individual types of evidence listed previously may be viewed as being definitive evidence for a central role of vanilloid activity in MCS. Indeed, the whole list may well be viewed as not definitive. However, when considered concurrently with the explanations derived from a vanilloid mechanism, a substantial case can be made. The following mechanistic explanations for MCS properties have long been sought, and all have been developed in the previous discussion: (a) a role for both central chemical sensitivity in MCS, as documented by Sorg, Bell, and colleagues[19–24] and for peripheral chemical sensitivity, as documented by Dr. William Meggs and colleagues[26–29] is the consequence of the putative role of the vanilloid receptor in increasing NMDA activity and nitric oxide levels in both types of sensitivity; (b) the masking/desensitization phenomenon can be viewed as a consequence of the mechanisms of vanilloid regulation; (c) part of the induction of chemical sensitivity resulting from previous chemical exposure in MCS can be interpreted as a consequence of vanilloid up-regulation by inflammation and oxidants; (d) the similarities of sensitivity responses to chemicals with the SI response in an animal model can be seen as a reflection of a central role of the vanilloid receptor in both; and (e) the role of mold-contaminated buildings in initiating cases of MCS could originate from the action of mold toxins and some volatile organic compounds in stimulating the vanilloid receptor.

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