Review Article

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Neurological susceptibility to environmental exposures: pathophysiological mechanisms in neurodegeneration and multiple chemical sensitivity

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Abstract: The World Health Organization lists air pollution as one of the top five risks for developing chronic non-communicable disease, joining tobacco use, harmful use of alcohol, unhealthy diets and physical inactivity. This review focuses on how host defense mechanisms against adverse airborne exposures relate to the probable interacting and overlapping pathophysiological features of neurodegeneration and multiple chemical sensitivity. Significant long-term airborne exposures can contribute to oxidative stress, systemic inflammation, transient receptor subfamily vanilloid 1 (TRPV1) and subfamily ankyrin 1 (TRPA1) upregulation and sensitization, with impacts on olfactory and trigeminal nerve function, and eventual loss of brain mass. The potential for neurologic dysfunction, including decreased cognition, chronic pain and central sensitization related to airborne contaminants, can be magnified by genetic polymorphisms that result in less effective detoxification. Onset of neurodegenerative disorders is subtle, with early loss of brain mass and loss of sense of smell. Onset of MCS may be gradual following long-term low dose airborne exposures, or acute following a recognizable exposure. Upregulation of chemosensitive TRPV1 and TRPA1 polymodal receptors has been observed in patients with neurodegeneration, and chemically sensitive individuals with asthma, migraine and MCS. In people with chemical sensitivity, these receptors are also sensitized, which is defined as a reduction in the threshold and an increase in the magnitude of a response to noxious stimulation. There is likely damage to the olfactory system in neurodegeneration and trigeminal nerve hypersensitivity in MCS, with different effects on olfactory processing. The associations of low vitamin D levels and protein kinase activity seen in neurodegeneration have not been studied in MCS. Table 2 presents a summary of neurodegeneration and MCS, comparing 16 distinctive genetic, pathophysiological and clinical features associated with air pollution exposures. There is significant overlap, suggesting potential comorbidity. Canadian Health Measures Survey data indicates an overlap between neurodegeneration and MCS ($p < 0.05$) that suggests comorbidity, but the extent of increased susceptibility to the other condition is not established. Nevertheless, the pathways to the development of these conditions likely involve TRPV1 and TRPA1 receptors, and so it is hypothesized that manifestation of neurodegeneration and/or MCS and possibly why there is divergence may be influenced by polymorphisms of these receptors, among other factors.

Keywords: air pollution; multiple chemical sensitivity; neurodegeneration; oxidative stress; transient receptor potential channels.

Introduction

All humans are regularly exposed to thousands of chemicals in the air we breathe, the water we drink, the food we eat, and the products we buy and use [1, 2]. Our exposures are ubiquitous, complex and dynamic mixtures [3, 4]. To understand the many potential exposures that affect health over the life span, the concept of the exposome has been developed [5]. With knowledge of beneficial and adverse effects of exposures, the exposome captures the cumulative hazards, from preconception to death, associated with multiple environmental exposures, including the microbiome, according to one's genome and epigenetic features

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and the intracellular, metabolic, inflammatory and stress pathway responses [6]. Our most common route of exposure to toxicants is inhalation [7].

There is potential for any organ system to be impacted by the systemic absorption and response to pollutants. The purpose of this review is to focus on the potential biological impacts of air pollution exposure on the central nervous system (CNS), and in particular to compare and contrast the pathophysiology of neurodegeneration and multiple chemical sensitivity (MCS).

Literature review search criteria

Pubmed/Medline was searched using the terms "oxidative stress", "systemic inflammation", "blood-brain barrier", TRPV1, TRPA1, upregulation, sensitization, "air pollution", translocation, olfactory, trigeminal, "neurodevelopmental disorder", neurodegeneration, detoxification, "central sensitization", "multiple chemical sensitivity", "capsaicin challenge", and related terms (see Supplementary Material – Glossary), alone and combined. Articles from 1991 to January 2021 were selected based on the purpose of this review. We also reviewed pertinent publications found on the website of the World Health Organization.

Airborne pollutant exposures

Diverse air pollutants are ubiquitous in both outdoor and indoor environments.

Sources – outdoors

The urban outdoor air is contaminated with a complex mixture of numerous pollutants, such as airborne particulate matter (PM) and gases, including carbon monoxide, polyaromatic hydrocarbons, sulfur dioxide, nitrogen oxides, ozone and volatile organic compounds (VOCs) [8, 9].

Most studies showing increased risks of developing chronic disease with outdoor air pollution consider the effects of long-term exposure. Many studies demonstrate adverse health effects associated with residing in proximity to major roadways [10]. It is noteworthy, however, that we spend more than 90% of our time indoors [11], with 70% at home [12]. The building envelope of our homes and workplaces may reduce our exposures somewhat but we still remain exposed to outdoor air pollution while indoors [13]. Indeed, about 65% of PM from outdoor sources is inhaled while indoors [14].

PM originates from both natural and anthropogenic sources, and is a heterogeneous mixture of solid and liquid particles suspended in the air, varying in concentration, size, chemical composition and surface area [15–17]. PM is categorized according to size: particles between 2.5 and 10 μm diameter (PM10) is defined as 'coarse'; 2.5 μm or smaller (PM2.5) is 'fine'; and PM <0.1 μm or 100 nm is defined as 'ultrafine' (UFP) or nanoparticles [18]. In contrast to PM10 and PM2.5, UFPs have negligible mass but they are the dominant contributor to the total number of particles in ambient air, typically 80–90% of all particles [4, 19]. The highest UFP concentrations in urban areas are observed in proximity to traffic, particularly when vehicles are idling and accelerating [20]. There is no recognized threshold for health effects of outdoor PM2.5 regardless of whether the exposure occurs indoors or outdoors, and there is evidence that adverse health effects occur at cur- rent levels of exposure [21].

Airborne PM tends to adsorb harmful substances on its surface, such as heavy metals, polyaromatic hydrocarbons, and volatile and semi-volatile organic compounds (VOCs and SVOCs) [22–26]. VOCs and SVOCs equilibrate between vapour and adsorbed states, with SVOCs in greater preponderance on particles. The partitioning of VOCs onto nanoparticles is less studied [27], but they readily partition and adsorb to surfaces too, including on and within irregular and porous PM [28].

Exposure can also occur to exogenous free radicals and reactive oxygen species (ROS) that are formed outdoors through photochemical reactions (between NOx, carbon monoxide, formaldehyde and VOCs) [29]. ROS are particle-bound [30, 31], and can be transported into buildings. ROS are also generated in the indoor environment, where they are produced via the interaction of ozone and airborne chemicals, such as terpenes [32]. The levels of ROS on particles in the indoor environment generally mirrors the ROS on particles outdoors [29].

Sources – indoors

Total VOC concentrations are approximately four times higher indoors than in outdoor air, [I would delete: according to indoor sources,] with higher VOC concentrations observed from building materials in new or renovated locations [13, 33]. Other common indoor sources of VOCs include household cleaning and laundry products, air fresheners, fragrances, and cooking odors [34–36]. There is also considerable, ubiquitous indoor exposure to SVOCs,

many of which are high production volume chemicals used in plastics, detergents, synthetic musks, pest control products, building components and furnishings (e.g. flame retardants and stain repellents) [37, 38].

Being semi-volatile, SVOCs continuously vaporize and re-condense, redistributing from their original source to the indoor air and interior surfaces, including surfaces of airborne particles [39]. Inhaled SVOCs on smaller particles (e.g. nanoparticles) are likely to penetrate deeper into the respiratory tract and to linger and interact longer with contacted tissues [40, 41].

As a gas, the bulk of inhaled VOCs are exhaled immediately; however, desorption of VOCs from PM maintains elevated VOC concentrations on the surface of the bronchial tubes and alveoli for an extended period of time [42]. VOCs emanating from particles may diffuse from the extracellular space into the cellular membrane and into the cells themselves [42]. Thus the toxicities of PM are magnified by transport and release of both VOCs and SVOCs [42].

The burden of disease from air pollution appears to be due to the combined effects of indoor and outdoor ambient exposures [8]. See Table 1.

Toxicodynamics

Air pollution is now recognized as a fifth major risk factor for developing non-communicable diseases by the World Health Organization, joining tobacco use, harmful use of alcohol, unhealthy diets and physical inactivity [47, 48]. Scientific consensus continues to build that inhaled pollutants induce oxidative stress [49], which occurs when the cellular or organism detoxification systems are overwhelmed or deficient [50]. Oxidative stress is a phenomenon caused by an imbalance between the production of

Table □: Common sources of ambient air pollutants.

Air pollutants	Outdoor air	Indoor air
Particulates, PM	Fossil fuel combustion, forming liquid droplets or solids in the atmosphere.	Cooking at high heat, especially meat, combustion activities (including gas stoves, burning of candles, use of fireplaces, use of unvented space heaters or kerosene heaters, cigarette and cannabis smoking, and domestic burning of solid fuels).
Ground level ozone ($O_□$)	Chemical reactions between oxides of nitrogen (NOx) and volatile organic compounds (VOCs) in the presence of sunlight.	Some indoor air cleaners, photocopiers and printers.
Sulfur dioxide ($SO_□$)	Burning of sulphur-containing fossil fuels in power plants and other industrial facilities, and by heavy machinery.	Largely from outdoor sources.
Nitrogen dioxide ($NO_□$)	Burning fossil fuels at high temperatures.	Domestic burning of solid fuels
Carbon monoxide (CO)	Incomplete combustion of fossil fuels.	Tobacco smoke, gas stove ranges, domestic burning of solid fuels .
Volatile organic compounds (VOCs)	Scented exhaust from clothes dryers and indoor air in cities. Fossil fuels, industrial emissions, asphalt paving [□□].	Fragrances, scented products (personal care, “deodorizers,” cleaning and laundry products, disinfectants), dry-cleaned clothes, building materials, fumes from attached garage.
Semi-volatile organic compounds (SVOCs)	Pesticides, fumes from paving, diesel fuel.	Carpets, textiles, electronics, furniture, building materials, cleaning products, personal care products, cosmetics, pesticides.
Polyaromatic hydrocarbons, PAHs	Naturally occurring in heavy petrochemicals and asphalt. Thermal and industrial processes such as incomplete burning of coal (coking), oil, waste. Burning tobacco or cannabis and charbroiling meat.	Burning tobacco or cannabis and charbroiling meat.
Aldehydes e.g. formaldehyde	Not significant.	Ozone reactions with terpenes, cigarette and cannabis smoke and vape, fresh paints, varnish and floor finishes.
Microbes	Not significant.	Water damaged buildings: mould, bacteria and very small arthropods such as mites.
Antimicrobial agents	Disinfectants (including pool chemicals) and pesticides.	Cleaning and disinfection products, and pesticides.

Adapted from US Centers for Disease Control and Prevention [□□]; Mannan M et al. Indoor Air Quality in Buildings: A Comprehensive Review of the Factors Influencing Air Pollution in Residential and Commercial Structures [□□]; Lucattini L. et al. A review of semi-volatile organic compounds (SVOCs) in the indoor environment: occurrence in consumer products, indoor air and dust [□□].

oxidants and antioxidants leading to an accumulation of reactive oxygen species (ROS) and other free radicals in cells and tissues [10]. It causes molecular damage to cells due to adverse modifications of cell components, such as lipids, proteins and DNA [51], which can eventually lead to many chronic diseases [52].

Studies examining the effects of air pollution exposure in cell culture, animal models, and human patients repeatedly demonstrate changes in oxidative stress and inflammatory markers [53–55]. Elevated circulating levels of inflammatory biomarkers define systemic inflammation [56]. Oxidative stress and systemic inflammation are intricately linked [57], and both play key roles mediating the hazardous effects of environmental stressors [58]. It has been repeatedly demonstrated that oxidative stress occurs with exposures to a wide range of ubiquitous indoor and outdoor pollutants [59–63], including PM; especially UFPs from major traffic [64], photocopiers or laser printers used in the workplace [65], and even the by-products formed by the effects of ozone on house dust [66]. VOCs can induce oxidative stress at levels typically found in the indoor air [67–70]. Oxidative stress has been demonstrated in individuals complaining of poor indoor air quality associated with "sick building syndrome." [71–73].

The brain is particularly vulnerable to oxidative stress because it has naturally high oxygen requirements and is high in polyunsaturated fatty acids, which are readily oxidized [74]. Long-term oxidative stress is a key component of neurotoxicity mechanisms and plays a causal role in a range of brain pathologies [75]. Systematic reviews and meta-analyses have established strong associations between air pollution exposures and neurodegeneration [76, 77].

Host defense mechanisms

The body uses many mechanisms and responses to defend itself against foreign substances, microorganisms, viruses, toxins, and non-compatible living cells [78]. Defense against air pollutants is such a prominent factor in preventing chronic, complex, environmentally-linked conditions, that for the purposes of this paper, we review the mechanisms for this defense. These include respiratory tract defenses, the blood-brain barrier, transient potential receptor family and detoxification systems.

Respiratory tract defenses

A large fraction of inhaled PM will be removed via mucociliary clearance in the upper airways or through engulfment by macrophages, predominantly residing in the alveolar regions [79]. Epithelial cells also form a barrier with tight junctions, which regulate the paracellular movement of ions and macromolecules [80]. Components of air pollution, such as ozone and PM can disrupt the integrity of tight junctions [81]. Particles or their components can reach underlying cells and exert effects, including oxidative stress and inflamma- tion [82–84].

Of most relevance are the UFPs that, because of their small size, are better able to enter cells and exert toxic effects [85–88]. Geometry dictates that smaller particles have proportionately greater surface area, and this greater contact area for transfer of toxicants magnifies their potential toxicity [89, 90]. Some UFPs can still be absorbed from the lungs to the blood stream [91], and potentially penetrate the blood-brain barrier (BBB). Moreover, some reach the brain directly by neuronal trans-synaptic transport (translocation) [92–94]. These neurons originate within the olfactory epithelium, and pass through the skull, ultimately terminating in the olfactory bulb. Translocation enables UFPs to bypass the BBB and to gain access to the brain directly through the nasal olfactory mucosa, migrating via the olfactory nerve, to reach the olfactory bulb and beyond [94–99]. Once UFPs reach the brain they can migrate and be deposited in more distal regions, causing damage and disruption of function and morphology, including in the hippocampus, corpus callosum and olfactory cortex [100–102]. Multiple adverse effects can be observed, including inflammation, oxidative stress and neurodegeneration [100, 103, 104].

Blood-brain barrier

The BBB is a complex structure that regulates and controls the diffusion and transport of substances into the brain [105]. The barrier refers to the unique properties of the capillary blood vessels that vascularize the CNS, which include tight junctions, a much lower rate of pinocytosis, and a lack of intracellular fenestrations [106]. It is critical for protecting the brain from metabolic waste products, toxins and xenobiotics [107]. Xenobiotics are defined as molecules not naturally produced by or expected to be present in an organism, including environmental pollutants, drugs, food additives, pesticides, and microbial-derived metabolites [108].

When considering the effects of inhaled particles and pollutants on the CNS, a fundamental question is whether they reach the brain. Despite the tightness of the BBB, it has been demonstrated that some blood-borne particles may

translocate through an intact BBB [109]. More importantly, exposure to particulate matter can also damage the BBB [92, 110–114], which enhances the potential for exposure of the CNS to circulating xenobiotics. Alterations of BBB properties are recognized as a significant component of the pathophysiology mechanisms and progression of different degenerative diseases, including Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis and others [107, 115].

Transient receptor potential (TRP) family

Transient receptor potential (TRP) receptors are a group of unique, polymodal ion channels widely expressed in the nervous system [116]. They function as cellular sensors and can detect a wide spectrum of potentially harmful physical stimuli, such as temperature and mechanical or osmotic stress. More relevantly, they respond to biochemical stimuli, including mediators of inflammation and oxidative stress [117–120]. In particular, they are fundamentally involved in the molecular physiology of chemical perception [121]. This article is focussed on two particular TRP receptors: subfamily vanilloid 1 (TRPV1) and subfamily ankyrin 1 (TRPA1).

Under normal physiological conditions, regulated TRPV1 activity contributes to many basic neuronal functions including resting membrane potential, neurotransmitter release, synaptic plasticity and mitochondrial function, and promotes various processes, such as resistance to oxidative stress [122]. The TRPA1 receptor plays a crucial role as a sensory receptor in several physiological and pathophysiological processes, such as pain sensation and inflammation [123].

Both channels function as chemosensory receptors. The TRPV1 channel senses environmental pollutants and is activated by various common volatile compounds, such as m-xylene, toluene, styrene, benzene, ethylbenzene, acetone, diethyl ether, hexane, heptane and cyclohexane and formaldehyde [124–126], plus particulate matter pollution [127, 128].

The TRPA1 channel is robustly activated by a multitude of environmental chemical substances, including isocyanates, heavy metals, oxidizing agents, styrene, naphthalene, formaldehyde, tobacco smoke and multiple other VOCs [127, 129, 130]. This receptor is the most broadly-tuned chemosensory channel known. To date, more than 130 different chemicals have been identified as activators of TRPA1 receptors [131].

These receptors are highly expressed in the olfactory and trigeminal nerve endings, which extend within a few microns of the surface of the nasal epithelium, just below the tight junctions, thereby giving lipid soluble chemical stimuli almost direct access [132, 133]. They are also expressed in the brain, including such areas as the dopaminergic neurons of the substantia nigra, hippocampal pyramidal neurons, hypothalamus, locus coeruleus and cortex [123, 134].

Multiple *in vitro* and *in vivo* studies have demonstrated that both types of receptors can be activated by air pollution [135–137], oxidative stress [138–141], and systemic inflammation [142–146]. When inflammation is induced, a systemic response of the body is required to redirect energy-rich fuels to the activated immune system [147]. Primary afferent sensory nerve fibers are activated to inform the CNS of the peripheral inflammation. TRPV1 and TRPA1 receptors play important roles in both initiating and maintaining activation of the systemic immune response [117].

TRPA1 and TRPV1 receptors are extensively co-localized. While 30% of TRPV1-positive neurons co-express TRPA1, TRPA1-positive neurons co-express TRPV1 97% of the time [148]. The functional properties, and therefore the pathophysiological roles, of TRPA1 receptors are regulated by their almost universal co-expression with TRPV1 [131]. TRPV1 and TRPA1 function together [134, 149], and their co-expression result in unique activation profiles that can be distinct from those of cells expressing only TRPA1 or TRPV1 [150]. Jointly, they modulate sensitivity, and they can sensitize each other [151, 152]. For example, sensitization of TRPA1 receptors via repeated low dose exposures to acrolein can enhance sensitization of TRPV1 receptors to its well known agonist, capsaicin [203]. In fact, the sensitization of each of these receptors is dependent on co-expression with each other [153, 154]. When activated simultaneously, the effect can be synergistic [155].

Of major interest is the fact that repeated, chronic activation of TRPA1 and TRPV1 receptors can lead to upregulation and sensitization [140, 141, 156–160]. In the current work, "upregulation" refers to a greater number or density of cell surface receptors and their activity, which may result in a stronger cellular response to an activating substance [161]. Sensitization involves receptor hyperexcitability and the perception of an input as noxious, even if it is from a normal, or even subthreshold, generally innocuous stimulus [162].

Sensitization encompasses a lowered threshold for activation plus increased firing of action potential (sending of a signal along a neuron) with stimulation. TRP receptors can become sensitized following repetitive noxious stimuli or inflammation [162]. This may be related to the fact that TRPV1 and TRPA1 can form complex units (TRPA1V1) in

sensory neurons, called heterotetramers, which have distinct properties that are different from the individual channels [149]. When cells co-expressing these channels are challenged with chemicals, the TRPA1V1 heterotetramer is more commonly activated than either TRPA1 or TRPV1 alone [150]. In other words, the more oxidative stress and systemic inflammation, the more there is upregulation of these receptors. When they are both upregulated by shared triggers, they are co-expressed in close proximity [163], and thus they are more likely to form heterotetramers. This results in a lower threshold for a cellular response to chemical stimuli and enhances the strength and duration of the reactions [149].

Detoxification

The impact of chemical exposures is related to both the level of exposure and the ability to detoxify and eliminate the substances [164]. Detoxification is a fundamental and essential component of the defense mechanism inherent in every cell. Being deficient in nutritional support [165], or being overwhelmed by xenobiotic exposures can contribute to inadequate detoxification. Furthermore, genetic polymorphisms and epigenetic changes can reduce the capacity to metabolize xenobiotics and may thereby enhance their toxic effects [166]. Some people have more effective detoxification systems than others [167–169], which can help to explain the inter-individual variations in disease susceptibility.

Potential consequences: neurodegeneration

When the protective mechanisms are insufficient or overloaded, air pollution can affect the CNS through a variety of cellular, molecular, and inflammatory pathways that can potentially lead to a predisposition to neurological diseases or damaged brain structures [95]. In fact, associations between air pollution exposures and neurodegeneration are well established [76, 77]. There is a significant body of evidence demonstrating a strong correlation between air pollution exposure and cognitive decline [170, 171], such as that found in Parkinson's disease [76, 172, 173], as well as Alzheimer's and other dementias [174–178].

Even at levels below the recommended upper limit, chronic exposure to PM can be associated with physical reductions in grey and white matter mass [179, 180]. According to studies conducted in the United Kingdom, both PM exposure and living in proximity to major roadways are associated with reductions in the volume of the left hippocampus, thalamus and prefrontal cortex [181–183]. Brain atrophy is associated with neurodegener- ative disorders [184, 185].

Environmental exposures of the CNS can be increased due to alterations of the BBB properties, which are recognized as a significant component of the pathophysiology mechanisms and progression of different degenerative diseases [107, 115]. Furthermore, systematic reviews provide strong evidence of the association of genetic detoxification polymorphisms with susceptibility to neurodegeneration [186, 187], likely related to increased oxidative stress. Long-term oxidative stress is a key component of neurotoxicity mechanisms and plays a causal role in neurodegenerative disorders [75, 188, 189].

Reduced olfactory function, such as deficits in odor identification and recognition and increased olfactory threshold, are commonly associated with neurodegeneration [190–194]. Olfactory loss can appear years before the development of any motor symptoms and cognitive decline [195, 196], and is considered an early sign for the diagnosis of neurodegenerative disorders [197, 198]. This could be the result of direct exposure to polluted air on the olfactory nerve via the olfactory epithelium [132], and/or the translocation of pollutants [94].

Another sensory dysfunction commonly seen in patients with neurodegenerative conditions is chronic pain. The prevalence of pain ranges from 38 to 75% in Alzheimer's and from 40 to 86% in Parkinson's disease [199]. It can be an early symptom in Parkinson's and precede the motor symptoms by two to 10 years [200, 201]. The pathogenesis of chronic pain in these conditions is complex, multifactorial and poorly understood [202]. It can appear as nociceptive, neuropathic, or miscellaneous pain [203], but there is evidence for hyperalgesia and allodynia, which is convincing evidence for TRPV1 and TRPA1 sensitization [206], even before the onset of any movement dysfunction in Parkinson's [207, 208]. These channels are involved in the development and perpetuation of chronic pain [157, 209]. Therefore, given that these channels are involved in the progression of neurodegenerative diseases and have a role in pain, it is feasible to propose that these channels could act as central players common to both processes [199].

Sensitivity to noxious stimulation is increased in patients with Parkinson's with or without pain symptoms. Although not consistent in all cases, numerous clinical studies have reported reduced thermal, electrical, cold or mechanical pain thresholds in Parkinson's disease

patients, reflective of hypersensitivity [188]. This suggests that hypersensitive TRPV1 and TRPA1 receptors may be playing a role. There is support for this concept from animal studies [210]. Increased pain responses and/or greater pain sensitivity is found in cognitively impaired patients with widespread brain atrophy or neural degen- eration [211]. Sensitization of TRPV1 receptors is also suggested by the finding of thermal hyperalgesia and mechanical allodynia in a mouse model of Alzheimer's disease [212].

Calcium in neurons

TRPV1 and TRPA1 are calcium channels and when stimulated, they facilitate the transmembrane entry of calcium ions (Ca^{2+}) into cells [213, 214]. These ions contribute to the electrochemical gradient in cells and are critical to cellular excitability. The regulation of TRPV1 and TRPA1 activity is complex [215], and over-activation of these channels under pathological conditions can lead to elevated levels of intracellular Ca^{2+} causing subsequent mitochondrial damage and apoptosis [216].

Deregulated TRPV1 activation promotes the loss of hippocampal neurons and an impairment of cognitive functions and has been directly implicated in cell death [217]. To reduce this excitability and maintain cell homeostasis, tight control of intracellular Ca^{2+} levels in neurons is crucial to prevent neurodegeneration [218]. Most important in this regard are the Ca^{2+} pumps, which export Ca^{2+} ions out of the cell within milliseconds to restore physiological homeostasis promptly [219, 220]. Disruption of this precise regulation of intracellular Ca^{2+} is considered to be a final common pathway leading to neuron dysfunction and cell death [221], and may also possibly play a role in nociception [222].

Vitamin D and protein kinase

Vitamin D also plays a significant role in maintaining the plasma membrane expression of the Ca^{2+} pumps and buffers that reduce intracellular Ca^{2+} levels [223]. The vitamin D status is defined by the total 25-hydroxy vitamin D (25OHD), which is the sum of the concentra- tions of $25(OH)D_3$ and $25(OH)D_2$ [224]. Low vitamin D status is a global problem and is associated with dementia, Alzheimer's and Parkinson's diseases [225, 226], and disorders of nociception [227]. Vitamin D modulates the function of TRPV1; for example, it antagonizes the stimulatory effects of TRPV1 agonists like capsaicin because it binds to TRPV1 within the same vanilloid binding pocket and reduces trigeminal signalling mediated by TRPV1 [228]. This suggests that when vitamin D levels are low this protection could be reduced. Another example of modulation is the effect of 25OHD on protein kinase C (PKC), which sensitizes but does not activate TRPV1 [229]. Enhanced activity of PKC is associated with neurodegeneration [230], but 25OHD reduces the PKC effect on TRPV1 sensitization [231].

Protein kinases regulate diverse cellular functions. They are also activated by oxidative stress and pollutants [214, 232, 233], and their overexpression has been implicated in various diseases, including neurological disorders [234, 235]. There are several hundred kinases encoded in the human genome, comprising 1.7% of human genes [236]. There are genetic links between kinases and neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, due to mutations, epigenetic changes, enhanced activation or altered expression [237]. Protein kinases can sensitize TRPV1 and TRPA1 receptors [238–241].

Central sensitization

TRPV1 and TRPA1 also contribute to central sensitization (CS) [242–245], which is defined by the International Association for the Study of Pain as an "increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input" [246]. CS is also characterized by hyperalgesia and allodynia [247].

CS has also been defined as a state in which the CNS amplifies sensory input from many organ systems [248]. It is a common pathophysiological mechanism in several overlapping syndromes, such as chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome [249]. A systematic literature review of the definitions of CS found that the one main theme is the hyperexcitability of the CNS to sensory input [247]. Individuals with a central sensitivity syndrome may find other normally innocuous stimuli, such as touch, heat, cold, sight, sound, smell, to be noxious as well [250]. Chronic nociceptive pain and the cardinal features of CS are also commonly found in neurodegenerative disorders [207, 251, 252].

Potential consequences: multiple chemical sensitivity (MCS)

There is a significant body of evidence that many individuals are observing sensitivity to common chemicals. A 2015 national survey in the U.S.A. measured the prevalence

of self-reported sensitivity to chemicals and medically diagnosed multiple chemical sensitivity (MCS) at 25.9 and 12.8% respectively [253].

MCS is an acquired condition in which the person experiences a range of recurrent symptoms attributed to exposures to low levels of chemicals that most people regard as unproblematic, and which the person used to tolerate previously as well [254]. Almost half of MCS patients have comorbid migraines, up to 70% are asthmatic, and almost 90% report adverse effects from exposure to fragranced consumer products [253].

Up to 60% of asthmatics report that odors of perfumes and cleaning sprays provoke asthma symptoms [255], and 70% of migraine patients report that headaches are triggered by the odors of perfume, paints and gasoline [256]. Having migraine headaches increases the likelihood of being an asthmatic, and vice versa [234, 257], and one common denominator for this bidirectional association is the sensitivity to chemical odors. Both conditions are also impacted by air pollutants, including PM, nitrogen dioxide, ozone, and carbon monoxide [258, 259]. Furthermore, TRPV1 and TRPA1 channels are implicated in their triggering mechanisms [260, 261].

Several case definitions for MCS were proposed in the 1980s and 90s, with differing characteristics other than one feature in common: that symptoms were linked to low levels of chemical exposures [262]. The most widely Accessed case definitions are those proposed by Cullen in 1987 [263], and the MCS consensus proposed in 1999 [264]. Cullen defined MCS as an acquired disorder characterized by recurrent symptoms referable to multiple organ systems and occurring in response to exposure to chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. The MCS consensus definition was validated in 2000 [265], and includes the following [264]:

(1) The symptoms are reproducible with [repeated] chemical exposure.
(2) The condition is chronic.
(3) Low levels of exposure [lower than previously or commonly tolerated] result in manifestation of the symptoms.
(4) The symptoms improve or resolve when the incitants are removed.
(5) Responses occur to multiple chemically unrelated substances.
(6) Symptoms involve multiple organ systems.

Interestingly, in a study by McKeown-Eyssen et al. it was found that symptoms which most commonly distinguished patients with MCS from controls involved the CNS, and included having a stronger sense of smell than others, feeling "spacey", feeling dull or groggy, and having difficulty concentrating [262]. In 2005, Lacour suggested an extension of the criteria, opining that multiple symptoms in other body systems be mentioned, but this would decrease specificity of the definition [266].

Similar to neurodegenerative disorders, genetic polymorphisms predisposing to less efficient metabolism and excretion of commonly encountered environmental chemicals are more common in people who meet the criteria for MCS [267–272]. These findings have not been completely consistent [273, 274] however, a regression analysis published in 2019 reinforces the concept that a genetic risk related to phase I and II liver enzymes involved in xenobiotic detoxification can play a role in the pathophysiological route towards sensitization to olfactory compounds in MCS [275]. Nevertheless, even in the absence of an abnormality among detoxification polymorphisms, oxidative stress and systemic inflammation are universally observed in MCS patients [276, 277]. There is also evidence suggesting that the BBB may be dysfunctional in MCS [278], which would enable greater chemical exposures in the CNS.

A strong association between pollutant exposure and MCS is evidenced by the onset. Many published papers report the onset of MCS following recognized or well-defined chemical exposures [279], such as in new or renovated homes or nonindustrial offices because of the gassing off of construction materials such as paints, solvents and new carpets, or immediate or lingering effects of pesticides [280, 281]. The most commonly reported factors associated with the onset of MCS (estimates in brackets) include [282, 283]:

- exposure to indoor air contaminants caused by new construction or renovation of a home or office (63.2%)
- exposure to various solvents and cleaners (54%)
- indoor air contaminants (45%)
- pesticides or agricultural chemicals (27.4%) and
- chemicals encountered at work or used in hobbies (26.3%).

Other clinical studies similarly describe exposures at the onset of symptoms. Initiating agents include organic solvents, hydrocarbon compounds and pesticides, and chemicals described as irritating or having an odor. Clusters of cases may emerge in what have been described as "sick buildings" with chemical mixtures and/or molds and other agents generated within or infiltrating poorly ventilated structures [284–290].

The initiation of MCS is more likely to be associated with identified exposures and differs from neurodegenerative disorders, which begin more insidiously with

non-specific symptoms, such as chronic pain and loss of olfaction, perhaps years before the hallmark symptoms and signs of the specific disease.

TRPV1 and TRPA1 sensitization in MCS

TRPV1 receptors are heat sensitive and respond to capsaicin [291], the pungent ingredient in hot chili peppers that produces the sensation of heat [292]. Capsaicin is also a well-known cough-inducing agent when inhaled because it provokes cough in a safe, reliable and dose-dependent manner [273, 293], by stimulating the TRPV1 receptors [294]. The more sensitive the receptors on the sensory neurons lining the bronchial tubes, the more easily coughing can be provoked with capsaicin inhalation [295]. Capsaicin has been used in clinical research for more than three decades [296].

Capsaicin inhalation challenge and chemical sensitivity

In 1996, a small study was performed in Sweden on nine patients with at least a two-year history of airway symptoms as well as headache, fatigue, dizziness and chest pain [297]. Demonstrable bronchial obstruction and IgE-mediated allergy had been ruled out and there was no benefit from prescribed beta-agonist or steroid inhalers. Symptoms were purported to be induced by chemical odors, such as house paint and perfume. The patients were challenged with inhalations of perfume or a saline placebo and a nasal clamp was used to prevent the detection of the scent of perfume. The patients' observations of symptom provocation by perfume were verified by blinded perfume inhalation and were reproduced in a second round of testing at least one week later. Since the patients could not detect the odor of perfume, the authors concluded that the symptoms were not transmitted via the olfactory nerve but may have been induced by a trigeminal response via the respiratory tract or the eyes.

This same research group then tested a similar group of patients claiming to have asthma-like symptoms provoked by multiple chemical exposures [298]. The respiratory symptoms included heavy breathing, difficulties in getting air, pressure over the chest, coughing, phlegm, hoarseness, stuffy nose and eye irritation. Many were on long term disability. As in their first study, the authors demonstrated that asthma and allergies were ruled out by normal methacholine challenge testing and negative skin prick tests. These patients also alleged to have other symptoms in multiple systems, including eye irritation, fatigue and headache. Since the authors had postulated symptom induction by a trigeminal reflex, the patients were challenged with capsaicin inhalation. Compared to controls, the patients with purported sensitivity to chemical odors with asthma-like symptoms coughed more after capsaicin inhalation in a dose-dependent manner and were provoked at lower doses. Furthermore, the same respiratory and non-respiratory symptoms were also provoked yet the pulmonary function tests remained normal.

Since 1998, this research group has produced multiple other papers supporting the finding of respiratory hyperreactivity in those who also meet the criteria for MCS, even when asthma has been ruled out by methacholine challenge [284, 299–303]. The non-respiratory symptoms included headaches, lightheadedness, nausea and/or fatigue. These patients have respiratory sensory hyperreactivity probably due to the sensitization of TRPV1 receptors and follow-up after five and 10 years later showed no reduction in sensitivity to inhaled capsaicin [304, 305]. Similar findings of capsaicin inhalation hypersensitivity in patients meeting the criteria for MCS have been published by other centres in Denmark [306], and Japan [307]. MCS patients consistently demonstrate TRPV1 sensitivity with capsaicin inhalation challenge, which is a reliable clinical research tool with good short- and long-term reproducibility [293].

We identified one single-blind inhalant challenge study in MCS patients using acrolein [308], that also demonstrated greater cough sensitivity than in controls, suggesting that TRPA1 receptor sensitization may be contributing to chemical hypersensitivity as well.

The evidenced sensitization of TRPV1 and TRPA1 receptors in MCS provides the explanation for the multitude of structurally unrelated chemicals to which these patients observe and attribute sensitivity reactions [309].

Olfactory sensitivity and MCS

Having a stronger sense of smell than others since the onset of MCS is a very frequent subjective complaint that distinguishes MCS patients [262, 310–313]; however, a number of studies have not found any difference in odor detection thresholds [310, 314–316], or odor identification [317]. In other words, there was no direct evidence of olfactory nerve dysfunction. Nevertheless, some objective support for the patients' observed increased sense of smell experience comes from a brain imaging study showing that the responses at the recognition threshold level are stronger in those with MCS, and perceived intensity and

unpleasantness of odors are significantly higher [318]. This may be because the capacity to detect and react to volatile chemicals is mediated by both the olfactory and trigeminal systems, which interact [319–321]. Most odorants also stimulate the trigeminal nerve; even anosmics are able to distinguish between odorants based on their trigeminally-mediated sensitivity [319]. Central processing of olfactory and trigeminal stimuli activate synonymous somatosensory and primary olfactory regions [322]. The perceived increase in olfaction sensitivity reported by those with MCS may be related to the lower stimulation threshold of the trigeminal nerve in MCS, as demonstrated in numerous studies using capsaicin inhalation challenge. This differs from neurodegeneration, in which there frequently is loss of olfaction.

CNS dysfunction in MCS

Unfortunately, studies in which MCS patients are challenged directly with chemicals [323], such as perfume, have not been consistent because of multiple problems with design [324]. As a result, the focus of MCS research more recently has shifted from experimental models of chemical stimulation and symptom provocation to searching for and measuring neurological dysfunction to understand the clinical aspects of MCS. MCS patients frequently attribute neurocognitive symptoms to chemical exposures [262, 266, 325]. This observation is supported by a 2010 chemical challenge study using simultaneous single photon-emission computed tomography brain scan imaging, which found an association of simultaneous dysfunction processing odors with cognitive impairment [326]. Abnormalities in brain imaging in patients with MCS at rest have been described since 1994 [327–329], although differences are not consistently found at baseline [330]. There is no loss of brain mass observed, in contrast to neurodegeneration, but multiple studies employing functional brain scan imaging provide measurable evidence that patients with MCS process odors differently compared with normal, healthy controls, including the finding of prolonged recovery time after exposure [314, 318, 331–334]. It is noteworthy that when challenged with chemical exposures, compared to controls, MCS patients demonstrate a stronger signal-intensity reaction in magnetic resonance imaging (MRI) of the limbic system [335], and particularly in odor-processing areas such as the hippocampus, amygdala, and thalamus [326]. Functional MRI has also demonstrated that MCS patients do not habituate to repeated sensory stimulation when compared to healthy controls, but instead show evidence of sensitization, as evidenced by increased reactivity to repeated, consistent stimulation [336, 337].

The evidence is compelling that there is CNS dysfunction in MCS patients. A 2018 systematic review found consistent evidence that MCS patients have altered processing of ascending sensory pathways with over-activation in the limbic system, and olfactory and cognitive manifestations [338]. A 2019 systematic review identified nine studies that used functional imaging to assess cerebral responses to several different odorous stimuli and all demonstrated that odors are processed differently by MCS patients compared with controls [339]. In addition, EEG measurements of olfactory event-related potentials provides evidence for TRPV1 sensitivity to carbon dioxide [340], which may help to explain why MCS patients may experience panic attacks when provoked by carbon dioxide challenge [341].

Central sensitization has also been evidenced in MCS [342], which is not surprising given that central sensitization involves the action of TRPV1 receptors. This may help to explain why fibromyalgia and MCS are frequently co-morbid [343, 344]. Interestingly, increased hyperalgesia and temporal summation of pain can be observed in MCS patients, even without other comorbid disorders [342, 345].

There are as yet no published studies on MCS examining a potential relationship with low vitamin D levels or increased protein kinase activity, despite the evidence for TRPV1 modulation and sensitization respectively [228, 229].

Comparison of neurodegeneration and MCS

The major risks to the CNS from chronic air pollution exposure are the development of neurodegenerative disease and/or MCS (Table 2). There are both similar and distinctive associated exposures, and genetic, pathophysiological and clinical features of neurodegenerative disorders and MCS (Table 2). Shared features include associated risks for adverse effects from airborne chemical pollutants according to one's genotype for detoxification and dysfunctional BBB; adverse effects on a cellular level, including oxidative stress, systemic inflammation and changes in polymodal TRPA1 and TRPV1 receptor function; and chronic pain and central sensitization. Neurodegenerative conditions involve olfactory nerve dysfunction, and MCS most likely involves the trigeminal nerve. The conditions diverge in how the TRPV1 and TRPA1 channels respond. Intriguingly, while people with neurodegeneration or MCS are more likely to experience

Table □: Associations of exposures and markers of neurodegeneration vs. MCS.

	Neurodegeneration	Multiple chemical sensitivity
Air pollution exposure	✓	✓
Genotype for detoxification	✓	✓
Oxidative stress	✓	✓
Systemic inflammation	✓	✓
Disruption of BBB	✓	✓
Chronic pain	✓	✓
Central sensitization	✓	✓
Decreased cognition	✓	✓
Loss of brain mass	✓	None
Olfactory dysfunction	Loss of function	Dysfunctional processing
Trigeminal dysfunction	None	✓
TRPV□ upregulation	✓	✓
TRPA□ upregulation	✓	✓
TRPV□ chemical sensitivity	None	✓
TRPA□ chemical sensitivity	None	✓
Onset with chemical exposure	Insidious	✓
Low vitamin D	✓	Unknown
Protein kinase activity	✓	Unknown

hyperalgesia and allodynia [206, 342, 345], due to receptor upregulation and sensitization, symptomatic responses to low-dose chemical exposures are reported only by those with MCS. Reasons for this difference are unknown but may possibly be a reflection of receptor phenotypes.

Sensitization to multiple unrelated chemicals is diagnostic for MCS; a condition that has been evidenced by multiple studies of capsaicin challenge tests and functional MRIs. Unlike neurodegenerative disorders, MCS patients do not demonstrate loss of olfactory nerve function or CNS mass, but do show olfactory processing dysfunction. The reason for this divergence of the pathophysiologic pathways to dysfunction and damage is not clear. Despite the overlapping exposures and mechanisms, there is no robust published evidence for comorbidity of neurodegeneration with MCS.

A clue to possible comorbidity is offered by the 2015-16 Canadian Community Health Survey (CCHS) [346]; a cross-sectional survey that collects information about the health behaviors and health care use of the non-institutionalized household population aged 12 or older. Statistics Canada provided a tabulation from the CCHS 2015–2016, of Canadians aged 40 y or older (representing 745,700 people) who reported having MCS, or "Alzheimer's or other dementia" (Table 3). No information was gathered regarding other

Table □: Overlap between MCS and dementia in □□□□–□□□□ CCHS respondents over □□ years old.

	CCHS cohort > □□y	With MCS
No dementia	□□,□□□,□□□	□□□,□□□
Alzheimer's or other dementia	□□□,□□□ (□.□%)	□□,□□□ (□□%

p-value for difference in dementia prevalence in respondents with and without MCS=□.□□□

neurodegenerative disorders. People experiencing MCS are statistically significantly more likely to develop Alzheimer's or other dementia (p=0.046). Further research is required to corroborate these findings that there is an associated risk of neurodegeneration for patients with MCS, and if not, how the commonalities illustrated in Table 2 diverge such that those with MCS would be spared dementia.

Finally, a number of nonsynonymous single-nucleotide polymorphisms (SNPs) have been described in the human TRPV1 gene, associated with increases in both the response to capsaicin and the expression of TRPV1 on the cell surface [347, 348]. Genetic mutations in TRPV1 and TRPA1 have been found which are associated with increased sensitivity to chemicals [320, 349–351], as well as an enhanced perception of odorous stimulants that is likely trigeminal [351]. MCS patients may have TRPV1 and/or TRPA1 polymorphisms that predispose them to develop sensitization to pollutant exposures and odors.

Conclusion

There are interacting and overlapping pathophysiological features of responses to environmental exposures that are associated with neurodegeneration and MCS. These include genotypes for detoxification, oxidative stress, systemic inflammation, disruption of the BBB, chronic pain, central sensitization, decreased cognition and upregulation of TRPV1 and TRPA1 receptors.

TRPA1 is the most promiscuous sensor of chemicals known. While much less literature examines sensitization of TRPA1 than TRPV1 receptors in MCS, it is clear that these receptors are frequently co-expressed and can sensitize and provoke responses in each other when stimulated. They can combine to form a complex unit (which is the structure most commonly activated when challenged with chemicals *in vitro*) and they can interact synergistically. TRPA1 and TRPV1 sensitization explains the myriad of chemicals to which MCS patients attribute reactions and observe sensitivities. Co-expression of TRPA1 and TRPV1 and formation of complex units may contribute to the

severity of MCS. Further research on MCS should investigate TRPA1 sensitization, singularly and in conjunction with TRPV1. This may assist in finding a clinical marker for the diagnosis of MCS. Identifying TRPV1 and TRPA1 polymorphisms in neurodegenerative disorders and MCS may help to understand how air pollution influences the divergent development of these conditions and provide targets for management and treatment beyond placing a high priority on air pollution prevention and abatement.

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