

THE HYPERSUSCEPTIBLE INDIVIDUAL

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ABSTRACT

Sensitivity to low level chemical exposures is of increasing concern to patients, physicians, and regulatory agencies, among others. The hypothesis is presented that a primary mechanism for chemical sensitivity may involve the central nervous system, in particular, the limbic system, which may secondarily affect the immune system and other organ systems in a variety of ways. Adaptation and the overlapping effects of everyday exposures may make it necessary to place patients who report chemical sensitivities in a controlled environment for extended periods prior to provocative challenges. Cacosmia (feeling ill from odors) may affect one-third or more of the general population. Multiple chemical sensitivity (MCS) patients represent a tiny fraction of cacosmics, but both groups may experience cognitive impairment and other adverse effects with exposure to low levels of volatile organic compounds (LLVOCs).

INTRODUCTION

Chemical sensitivity or multiple chemical sensitivity (MCS) is a clinical phenomenon that is becoming more widely known and increasingly the subject of discussion and debate as more and more patients receive this label. Patients with multiple chemical sensitivity report becoming ill when they are exposed to common environmental chemicals, such as perfume, tobacco smoke, diesel exhaust, fresh paint, new carpeting, and a variety of low level volatile organic compounds (LLVOCs). Many of these individuals say they became ill following an initial, intense exposure to chemicals such as a pesticide or solvent. Others say they experienced repeated, daily exposure at much lower levels and gradually became ill, for example, in a sick building. Chemical sensitivity has been reported in several different demographic groups: industrial workers; occupants of tight buildings, including office workers and school children; residents of communities whose air or water has been contaminated by chemicals; and individuals who have had personal and unique exposures to domestic indoor air contaminants, pesticides, drugs or consumer products (1).

Some investigators attribute chemical sensitivity to underlying psychological problems, such as depression, to psychological conditioning, to stress, or to an inappropriate belief that chemicals are causing symptoms (2,3,4,5,6). However, these investigators have not ruled out possible chemical causes prior to making their diagnoses (7,8). Certainly stress or depression can produce some of the same symptoms that have been attributed to chemical sensitivity. The frequent presence of psychological symptoms in these patients, the current lack of a biological marker or accepted case definition and absence of a plausible biological mechanism have hindered serious scientific inquiry into this condition. Different meanings of the term "sensitivity" are at least in part responsible for the confusion

surrounding chemical sensitivity. MCS patients appear to be exhibiting a unique type of sensitivity. Like an allergy, chemical sensitivity appears to require an initiating exposure or series of exposures after which responses occur at extremely low doses. Unlike an allergy, however, substances chemically different from those that induced the sensitivity may subsequently provoke or "trigger" responses.

CLINICAL OBSERVATIONS

The limited data available at this time suggest that any mechanism or model that would purport to explain MCS would need to address the following chemical observations associated with this illness (1):

1. Symptoms involving virtually any system in the body or several systems simultaneously, most frequently, the central nervous system (fatigue, mood, memory and concentration difficulties).
2. Differing symptoms and severity in different individuals, even among those experiencing the same exposure.
3. *Induction* or sensitization by a wide range of environmental agents, including pesticides and solvents.
4. Subsequent *triggering* by lower levels of exposure than those involved in initial induction of the illness.
5. *Spreading* of sensitivity to other, often chemically dissimilar substances. Each substance may trigger a different, but reproducible, constellation of symptoms.
6. Concomitant food, alcohol and medication intolerances, estimated to occur in a sizeable percentage of MCS patients.
7. *Adaptation or masking*, that is, development of tolerance to environmental incitants (both chemicals and food) with continued exposure; loss of this tolerance with removal from the incitant(s); and augmented response with re-exposure after an appropriate interval. If the interval is too short, the patient may be adapted; if too long, sensitivity may wane. In either case, falsely negative challenges may ensue. Optimal timing of challenges for patients with occupational asthma presents similar difficulties.

Items 3 and 4 suggest a two-step process: (a) induction or sensitization resulting from an initial "major" exposure and (b) triggering of symptoms by subsequent, lower level exposures to many different incitants.

AN OLFATORY-LIMBIC MODEL FOR CHEMICAL SENSITIVITY

The olfactory nerves, with their receptors in the nose, link the external chemical environment to the amygdala, hippocampus, hypothalamus and other parts of the limbic system. The limbic system, or so-called "primitive smell brain", is a phylogenetically ancient part of the brain present in all mammals. There is no blood-brain barrier at this site, and various substances, including horseradish peroxidase, can enter the olfactory bulbs by via retrograde transport within the olfactory neurons. The olfactory bulbs lie in close proximity to the limbic area and supply much of its neural input. The limbic region governs the organism's interaction with its environment in many subtle ways essential for preservation of the individual and the species. The amygdala, popularly described as "emotion central", is involved in feelings and activities related to self-preservation, such as searching for food, feeding, fighting and self-protection. Lesions in the septal area may cause hyperresponsiveness to physical stimuli (such as touch, sound, or temperature changes), hyperemotionality, loss of motivation, excessive sugar and water intake, and fear of unfamiliar situations. The hippocampus is essential for laying down new memories and thus is essential for learning. Memory and concentration difficulties are among the most disabling symptoms patients with chemical sensitivities report (1).

In the hypothalamus, the immune, nervous and endocrine systems converge. The hypothalamus governs (a) body temperature via vasoconstriction, shivering, vasodilation, sweating and fever; (b) reproductive physiology and behavior; (c) feeding, drinking, digestive and metabolic activities, physical manifestations of emotion such as increased heart rate, elevated blood pressure, dry mouth and gastrointestinal responses. The hypothalamus is also the locus at which the sympathetic and parasympathetic nervous systems converge. Some symptoms of chemical sensitivity are suggestive of autonomic (sympathetic and parasympathetic) nervous system dysfunction, for example, altered smooth muscle tone producing Raynaud's phenomenon, diarrhea, constipation and other symptoms. The hypothalamus appears to influence anaphylaxis and other aspects of immunity. Conversely, antigens may affect electrical activity in the hypothalamus.

Lesions in the limbic region may be associated with irrational fears, feelings of strangeness or unreality, wishing to be alone and sadness. A sensation of being out of touch with or out of control of one's feelings and thoughts, not unlike that described by many patients with chemical sensitivity, may be perceived.

The dynamic involvement of the hypothalamus and limbic system in virtually every aspect of human physiology and behavior makes injury to these structures an intriguing hypothesis to explain chemical sensitivity's myriad manifestations. Sensitization or kindling of olfactory-limbic pathways by acute or chronic exposure to chemicals, such as solvents or pesticides, has been proposed as a putative mechanism for chemical sensitivity (7). Subsequently, lesser exposures to chemicals might trigger inappropriate firing of nerve cells in the limbic area. Genetic endowment, prior environmental exposures, psychological stress, hormonal variations and other factors may enhance neurological sensitization.

Animals primed by either high concentrations or chronic, lower concentrations of various chemicals, such as formaldehyde, ozone or a pesticide, and subsequently re-exposed to low concentrations of the same or different chemicals show an increased tendency toward paroxysmal electrical discharge in the amygdala, a kind of neurological sensitization (9,10,11). Chemicals used to sensitize animals may differ greatly in terms of their structure

and physical and chemical properties, yet their effects upon the limbic system are remarkably similar. Sensitivity, once induced, may be triggered by unrelated substances. In a parallel fashion, formerly well-tolerated, low-level exposures to tobacco smoke or perfume might trigger symptoms in individuals whose limbic areas have been sensitized by a prior pesticide or solvent exposure.

One intriguing aspect of the limbic system as a possible mechanism for multiple chemical sensitivities is the system's responsiveness to both chemical and cortical stimuli. Therefore, conscious thought processes and emotional states may influence limbic activity just as chemical stimuli can. The former may be under more or less conscious control of the individual, whereas the latter are almost entirely unconscious and automatic. However, the biological output or expression of chemical stimuli versus cortical stimuli would be indistinguishable, e.g., depression, sudden rage, memory difficulties, impaired concentration. One consequence of an olfactory-limbic mechanism, if correct, could be the unavailability of a convenient, blood-borne marker. If changes in limbic metabolism or blood flow cause MCS, these may only be observable using PET, SPECT or other brain functional imaging techniques.

ADAPTATION

Once limbic sensitization occurs, it appears to spread to other common chemical exposures. Thus, in order to diagnose this problem, it may be important for the sensitized individual to be removed both from the original exposure chemicals and from other chemicals that may be triggering adverse symptoms. Sorting out which exposures are perpetuating the illness may be very difficult: They are common exposures; their resultant symptoms may overlap in time; and, to varying degrees, individuals adapt as exposure continues. Adaptation is characterized by acclimatization (habituation, tolerance) with repeated exposures that result in a masking of overt symptoms. Symptoms may become chronic in nature and appear unrelated to any particular exposure. Adaptation has been recognized to occur for a variety of substances, for example, ozone, nitroglycerine, cigarette smoke, solvents and pharmaceuticals (tachyphylaxis) (12,13,14,15). Solvents are among the chemicals most frequently implicated by chemically sensitive patients as causing their symptoms. Withdrawal symptoms may occur if exposure is discontinued, a phenomenon recognized for solvents, tobacco smoke, caffeine and other substances. Once an individual has adapted, the effect of any single exposure may not be discernible because a kind of "saturation" effect has occurred. Background "noise" from many concurrent exposures may interfere with recognition of the "signal" from any particular exposure. Persons who are especially sensitive to certain chemicals, for example ozone, may adapt more slowly, adapt less completely or lose their adaptation more quickly than individuals with normal degrees of tolerance. Unravelling the effects of overlapping exposures and adaptation may require isolation of individuals in a hospital-like environment in which chemical exposures have been reduced to the lowest levels feasible. This approach was endorsed in a recent National Academy of Sciences report on chemical sensitivity, with the recommendation that it be given the highest priority for research in this area (16).

CONCLUSION

Individual susceptibility to chemicals may vary by orders of magnitude (17). MCS patients appear unique in that they report disabling symptoms at levels of exposure apparently well tolerated by most people. However, sensitivity to chemicals is in fact widespread in the population: The U.S. Environmental Protection Agency surveyed 4,000 of its employees and found that nearly one-third considered themselves "especially sensitive" to one or more common chemicals in indoor air (18). In a survey of more than 600 college students, two-thirds reported that one or more common chemical exposures made them ill (19). Thus, "cacosmia", feeling ill from odors, occurs in a sizeable percentage of the population. Given the disabling fatigue, depression and cognitive difficulties reported by MCS patients and the prevalence of these same problems among the population-at-large, which is similarly exposed, it would seem prudent to explore further the effects of LLVOC exposure upon humans using carefully designed provocative challenge testing in a controlled environment. Although costly, such studies in the future will be essential for understanding the precise linkages between chemical substances and clinical illness.

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