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Neurogenic Inflammation and Sensitivity to Environmental Chemicals

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Neurogenic inflammation as a pathway distinct from antigen-driven, immune-mediated inflammation may play a pivotal role in understanding a broad class of environmental health problems resulting from chemical exposures. Recent progress in understanding the mediators, triggers, and regulation of neurogenic inflammation is reviewed. Evidence for and speculations about a role for neurogenic inflammation in established disorders such as asthma, rhinitis, contact dermatitis, migraine headache, and rheumatoid arthritis are presented. The sick building syndrome and multiple chemical sensitivity syndrome have been defined as clinical entities in which exposure to chemical inhalants gives rise to disease. Current data on the existence of chemical irritant receptors in the airway and skin are discussed; neurogenic inflammation arising from stimulation of chemical irritant receptors is a possible model to explain many of the aspects of chemical sensitivities. *Key words:* asthma, indoor air pollution, multiple chemical sensitivity syndrome, neurogenic inflammation, neutral endopeptidase, reactive airways dysfunction syndrome, reactive upper airways dysfunction syndrome, rhinitis, substance P, sick building syndrome. *Environ Health Perspect* 101: 234–238(1993)

Sensitivity to environmental chemicals in general, and in particular to volatile organic chemicals (VOCs) in indoor air, needs to be elucidated. The lack of an established mechanism to explain how exposure to concentrations of VOCs that are well tolerated by the population at large can produce the array of symptoms seen in sensitized individuals has hampered progress in understanding these disorders. Over the past few years progress has been made in understanding neurogenic inflammation, chemical irritant receptors, and the regulation of neurogenic inflammation. Here I review these topics, emphasizing those aspects that may be applicable to elucidating the mechanism of chemical sensitivity as a disorder of the regulation of neurogenic inflammation. Possible application to specific clinical entities is discussed, with suggestions for clinical research to study the association.

Neurogenic Inflammation

Inflammation is an abnormal condition of redness, swelling, heat, and pain localized to a tissue. Histologically, inflammation is characterized by edema, vasodilatation, and infiltrates of leukocytes. A number of chemical mediators of inflammation have been identified biochemically. Inflammation may be triggered by the immune system, in which foreign materials interact with leukocyte receptors created after a sensitizing exposure to trigger an inflammatory cascade. Neurogenic inflammation is a well-defined process by which inflammation is triggered by the nervous system.

Early in the study of neurogenic inflammation, chemical stimulation was recognized as a trigger of neurogenic inflammation. As early as 1910, it was recognized that the application of mustard oil to the conjunctival sac in experimental models produces inflammation that can be blocked by sensory nerve ablation (*1,2*). The neuropeptides substance P (SP), neurokinen A (NA), and calcitonin gene-related peptide (CGRP) are now known to coexist in sensory neurons and to have potent vasodilatory properties (*3–6*). Direct stimulation of sensory nerves produces vasodilatation (*7,8*), which can be blocked by depletion of substance P with capsaicin (*9–11*). The sensory fibers involved in neurogenic inflammation have been identified as C-fibers with a slow velocity of 1–2 m/sec (*12*).

Progress has been made in understanding the regulation of neurogenic inflammation (*13*). A cell-surface enzyme, neutral endopeptidase (NEP), downregulates neurogenic inflammation by degradating substance P. In the lung this enzyme is inhibited by cigarette smoke, viral infections, and toluene diisocynate, whereas corticosteroids increase NEP.

Neurogenic inflammation is now a well-defined physiological mechanism by which mediators are directly released from sensory nerves to produce vasodilatation, edema, and other manifestations of inflammation. The nerve fibers have been identified as slow velocity C-fibers, and the regulation of neurogenic inflammation has been studied.

Chemical Irritant Receptors

The common chemical sense is a nasal sensation provoked by airborne chemicals which is distinct from taste and smell (*14*). This sense is experienced as a burning and painful sensation in the upper airways and eyes upon exposure to irritant

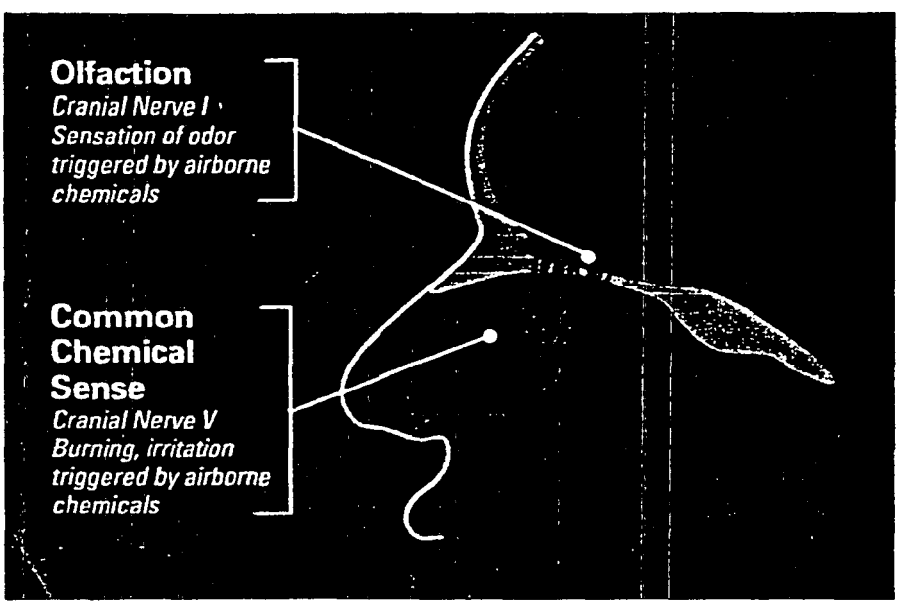

Figure 1. Olfaction and the common chemical sense. Olfaction is the sensation of odor, transmitted by cranial nerve I, the olfactory nerve. The common chemical sense is a sensation of burning and irritation in the airway, produced by irritant chemicals and transmitted by cranial nerve V, the trigeminal nerve.

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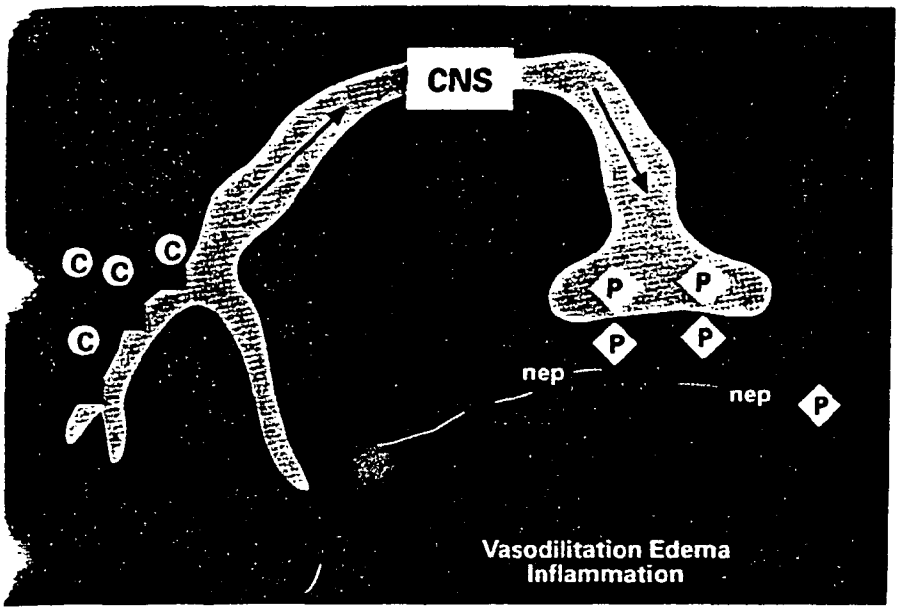

Figure 2. Schematic diagram of neurogenic inflammation triggered by chemical irritants. Chemical irritants (C) bind chemical irritant receptors on sensory nerves to release substance P (P) and other mediators from nerve endings. Substance P binds receptors on effector cells to trigger inflammation. Neutral endopeptidase (nep), an enzyme located on the membranes of effector cells, degrades substance P and downregulates neurogenic inflammation. It is proposed that chemical sensitivity syndromes are disorders of the regulation of neurogenic inflammation.

substances and results from exposure of trigeminal nerve endings to the irritants. The skin and other mucous membranes have similar responses to irritant chemicals. Recent studies in anosmic subjects have separated the common chemical sense from olfaction (*15*). The common chemical sense and olfaction are depicted in Figure 1. There is evidence that protein receptors on cell membranes are the activation site for chemical irritants. It is thought that sensory nerves act as both afferent and efferent nerves for neurogenic inflammation triggered by chemical irritants. In the nose, substance P release has been verified for exposures to nicotine, capsaicin, ether, formaldehyde, and cigarette smoke (*16,17*). Hence, stimulation of the chemical irritant receptors leads to neurogenic inflammation. The relationship among chemical irritants, sensory nerves, substance P, and NEP is summarized in Figure 2.

Regulation of Neurogenic Inflammation

Neutral endopeptidase degrades substance P (*13*). NEP is located on the surfaces of cells with substance P receptors, i.e., the target cells of substance P. Substances that decrease neutral endopeptidase levels increase neurogenic inflammation, while substances that increase neutral endopeptidase suppress neurogenic inflammation. Human recombinant NEP suppresses neurogenic inflammation (*18–20*). Exogenous substances that inhibit NEP include cigarette smoke (*21*), respiratory viruses (*22–25*), and the volatile organic chemical toluene diisocyanate (*26*).

Possible Roles of Neurogenic Inflammation

Neurogenic inflammation may play a role in a variety of disorders, from asthma and rhinitis to migraine headache, rheumatoid arthritis, and fibromyalgia. Such a role is supported by a combination of animal studies, pharmacological responses of these disorders, and circumstantial evidence. At the current time these associations are somewhat speculative, but there is sufficient evidence to justify investigations.

It is now known that the neuropeptides of neurogenic inflammation reproduce the pathology of asthma (*27*), and the role of neurogenic inflammation has been documented in animal models of asthma (*28*). Barnes (*29*) has recently reviewed the current evidence for the role of neurogenic inflammation in asthma and has suggested strategies for reducing neurogenic inflammation in this disease. It is increasingly recognized that respiratory irritants such as VOCs and environmental tobacco smoke can exacerbate asthma and rhinitis (*30–32*). A number of studies have documented an increase in the incidence of asthma in industrialized countries, over both the long term and during the 1980s (*33*). In addition, studies during the 1980s established that the American population is exposed to VOCs in the indoor air (*34*).

The role of neurogenic inflammation and chemical irritants in these respiratory disorders and the upregulation of neurogenic inflammation by inhalant irritants discussed above indicate that there may be a relationship between indoor air pollution with VOCs and the worsening asthma epidemic. Pursuit of this relationship should be a research priority. In the past asthma was divided into extrinsic asthma, triggered by protein aeroallergens, and intrinsic asthma of unknown cause. This distinction was made before the role of neurogenic inflammation in asthma was appreciated. It may be that asthma would be better classified as immunogenic or neurogenic (Table 1). The distinction between neurogenic and immunologic asthma is limited to the catalysts because the two types cross over after the release of mediators, in that the mediators of neurogenic inflammation trigger mast cell degranulation, and mast cell mediators stimulate peripheral nerves. This "bidirectional regulatory circuit" has recently been reviewed (35).

This crossover phenomenon does not mean that neurogenic inflammation and immunologic inflammation are clinically identical in all cases. In the upper airways and skin, the initial complaint associated with exposure to chemical irritants is burning or pain, whereas itching is the initial complaint associated with immune-mediated exposures. It may be that there is individual variability in the degree to which crossover is clinically manifested. The two mechanisms might be differentiated by testing patients with challenging doses of antigens and nonallergenic chemical irritants while monitoring clinical

Table 1. Immunogenic versus neurogenic asthma

	Immunogenic	Neurogenic
Triggered by	Protein aeroallergens	Volatile organic chemicals
Interacting with	IgE antibody	Chemical irritant receptors
Located on	Mast cells	Sensory nerve C-fibers
Releasing	Histamine, leukotrienes, prostoglandins, chemotactic factors	Neuropeptides: substance P, naurokinen A, calcitonin gene-related peptide
Stimulating	Sensory nerve C-fibers	Mast cell degranulation
Producing	Bronchial inflammation	Bronchial inflammation
Manifesting as	Asthma	Asthma

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symptoms and measuring mediators. This research would best be carried out by studying upper airway responses, as nasal washings can be easily obtained for quantifying mediators.

Another disorder that increased significantly during the 1980s is migraine headaches (*36*). Headache is an early and consistent consequence of exposure to VOCs. On the basis of pharmaceutical responses of migraine and animal experiments, Nicolodi and Sicuteri proposed that neurogenic inflammation plays a role in the pathophysiology of migraine headaches (*37*). Silberstein argued that both tension headaches and migraine may be generated by neurogenic inflammation (*38*). Buzzi and Moskowitz demonstrated that stimulation of trigeminal sensory fibers leads to changes consistent with those of migraine in a rat model, and these changes can be blocked by the antimigraine drugs sumatriptan and dihydroergotamine (*39*). Hardebo has pointed out that the postulate that neurogenic inflammation mediates migraine provides a rational explanation for why serotonin antagonists are effective in treating migraine (*40*). Challenge studies with VOCs on migraine patients, with and without specific pharmacological blockage of relevant receptors, is needed to elucidate the role of neurogenic inflammation and chemical irritants in migraine.

A comparison of neuropeptide staining in the synovium of patients with rheumatoid arthritis, osteoarthritis, and controls found weaker staining in the nerve filaments of the rheumatoid arthritis group (*41*). The authors suggest that this weaker staining is evidence of release from nerve fibers in rheumatoid arthritis, and neurogenic inflammation may play a role in this disorder. Zimmerman has suggested that neurogenic inflammation may play a role in fibromyalgia (*42*).

Role of Neurogenic Inflammation in Chemical Sensitivity Syndromes

"Sick building syndrome" (SBS) is a term used to designate an outbreak of illness associated with indoor air contaminants in new and tightly sealed buildings. Symptoms include irritation of the eyes, nose, and throat, skin irritation, and neurotoxic symptoms including mental fatigue and difficulty concentrating (*43*). The syndrome is an acquired disorder with onset related to moving into a new or renovated building, and there is wide individual variability in onset and symptoms after exposure.

Multiple chemical sensitivity syndrome (MCS) is a related syndrome with onset related to an environmental exposure, most commonly a solvent or pesticide. After the initial exposure, individuals become sensitive to low-level chemical exposures with symptoms involving more than one organ system. Though this syndrome was de-scribed four decades ago (*44,45*), it re-mains highly controversial.

Reactive airways dysfunction syndrome (RADS) is an asthmalike illness that develops within minutes to hours after an acute exposure to dust, smoke, or solvent. There is persistent bronchial hyperreactivity with positive methacholine challenge. The asthma becomes chronic after the initial exposure and can be difficult to treat (*46*).

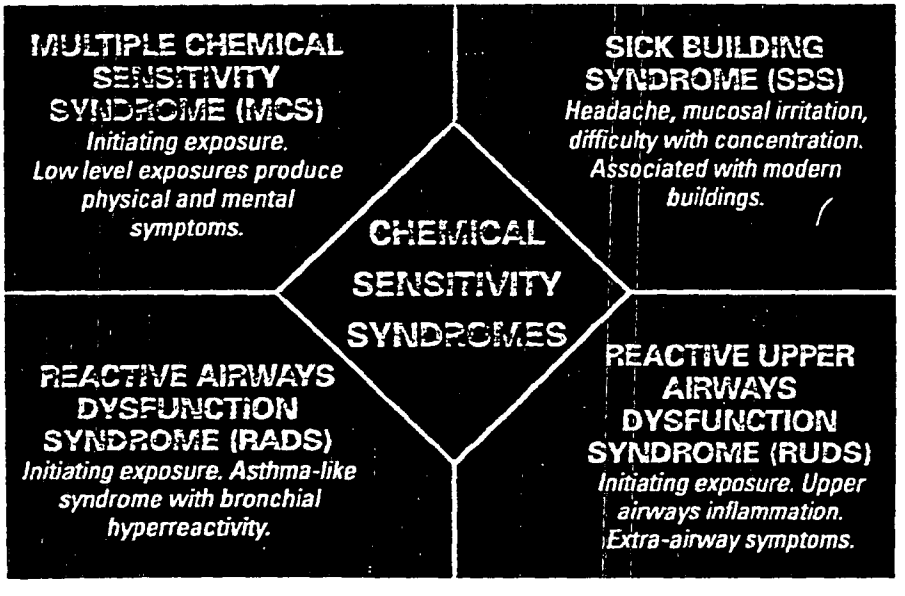

Figure 3. Chemical sensitivity syndromes. The multiple chemical sensitivity syndrome (MCS), sick building syndrome (SDS), reactive airways dysfunction syndrome (RADS), the reactive upper airways dysfunction syndrome (RUDS) have many features in common. These syndromes may all be disorders of the regulation of neurogenic inflammation.

Reactive upper-airways dysfunction syndrome (RUDS) also follows a chemical exposure, and there is persistent chronic rhinitis. The chief complaint of patients with RUDS is chemical sensitivity (*47*). Unlike patients with RADS, medical attention is not sought on the day of exposure, which probably reflects the fact that breathing is compromised in RADS but not in RUDS. Preliminary study of the nasal mucosa found lymphocytic infiltrates, and electron microscopy has shown thickening of the basement membrane and desquamation of the respiratory epithelium (*48*).

There are many similarities between SBS, MCS, RADS, and RUDS (Fig. 3). In each snydrome, a high-dose exposure induces the syndrome, and subsequent exacerbations are associated with low-level exposures. SBS and MCS include symptoms involving more than one organ system, with the respiratory mucosal and central nervous system being prominently involved. The major difference between SBS and MCS is that SBS refers to a cluster of cases associated with a building, while MCS patients have more generalized complaints. RADS and RUDS have prominent airway involvement, with the difference between the two being that RADS involves the lower airway (asthma), and RUDS involves the upper airway (rhinitis). In one small series, 100% of patients with RUDS had extra-airway manifestations and met the Cullen case definition (*49*) for MCS.

These syndromes may be related at a deeper level. All of these illnesses may be disorders of the regulation of neurogenic inflammation. The inducing exposure may alter the respiratory mucosa in one or more ways. The regulation of neurogenic inflammation may be disturbed by the depletion of NEP or other enzymes, which would result in a heightened response to subsequent exposures. The desquamation of the respiratory epithelium seen in RUDS may remove a barrier to chemical irritants, so that chemical irritants may reach and trigger the irritant receptors at lower concentrations.

Patients with these illnesses complain of symptoms in organ systems in addition to the airways, and some patients have no airways symptoms at all. Mechanisms to explain how airway irritants can trigger systemic symptoms must be considered. First, it is common for inflammatory illnesses primarily arising in one organ or tissue to produce systemic manifestations (e.g., the extra-articular manifestations of rheumatoid arthritis and the systemic manifestations of Crohn's disease). Viral infections of the upper airway produce systemic symptoms, including myalgias, fever, fatigue, and malaise.

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Both the mediators and regulators of inflammation may be released from the site of inflammation and affect distant sites. Two important regulators of inflammation, interleukin 1 and interleukin 2, suppress central nervous system activity (*50,51*). Another possibility is that some form of neural switching may take place. That is, triggering of chemical irritant receptors in one organ could lead to an efferent signal traveling to another site through an aberrant or conditioned crossing of the pathways. A combination of these two mechanisms may be operative.

The hypothesis that neurogenic inflammation is the mechanism of chemical sensitivity syndromes is amenable to scientific study. Biopsies of the airways of chemically sensitive individuals should be abnormal, with signs of inflammation. Immunofluorescent monoclonal antibodies could be used to detect NEP, which should be decreased, and substance P, which should be elevated relative to controls. Nasal washings should contain increased levels of the mediators of neurogenic inflammation relative to controls, and the levels should increase after chemical challenge in patients but not controls. Heightened neuronal firing of sensory fibers should occur after chemical challenges.

Discussion

Neurogenic inflammation leads to inflammation independent of the immune system. Polypeptide mediators are stored in nerve endings and released when irritant receptors on nerves are stimulated by chemicals. The role of neurogenic inflammation in a number of inflammatory conditions is currently under investigation. There is strong evidence that neurogenic inflammation is operative in asthma and rhinitis. There is circumstantial evidence that neurogenic inflammation may play a role in migraine headache. Evidence for a role in rheumatoid arthritis and fibromyalgia is not as compelling at this time. The significance of these associations for environmental health is that neurogenic inflammation can be triggered in the airways by environmental chemicals such as cigarette smoke and solvents. Hence, any disorder mediated by neurogenic inflammation can potentially be exacerbated by environmental chemicals. Study of the hypothesis that chemical sensitivity syndromes such as SBS and MCS may result from neurogenic inflammation arising from stimulation of irritant receptors by environmental chemicals may lead to an understanding of these disorders. It is of interest that the symptoms of headache, myalgia, arthralgias and arthritis, and airway symptoms reported by MCS patients overlap with those disorders for which a role for neurogenic inflammation has been reported.

The hypothesis that neurogenic inflammation triggered by environmental chemicals plays a role in human health is amenable to scientific study. Research should focus on noninvasive methods for detecting biomarkers of neurogenic inflammation. Are there degradation products of substance P or other mediators of neurogenic inflammation that are elevated in the urine or serum of patients with activation of this system? Are there evoked potentials or nerve conduction parameters that can be used to detect activation of neurogenic inflammation? Two groups of patients should be studied with challenge tests: patients with disorders in which neurogenic inflammation is suspected to play a role (i.e., asthma, rhinitis, migraine, rheumatoid arthritis, fibromyalgia) and patients with chemical sensitivity syndromes. These patients should be isolated from VOCs in a specially constructed clinical research unit and monitored for resolution of their symptoms. Chemical challenges should be conducted while patients are monitored for provoked symptoms. Biomarkers of neurogenic inflammation should be measured throughout the course of these challenges.

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