Neurogenic Inflammation: Additional Points

William Meggs’s recent article, “Neurogenic Inflammation and Sensitivity to Environmental chemicals” (EHP 101:234–238), provides a useful introduction to a rapidly growing area of knowledge in physiology and poits a number of interesting hypotheses regarding the health effects of airborne chemicals. Some specific technical points, however, merit comment.

Meggs describes the common chemical sense as “a nasal sensation provoked by airborne chemicals” (p. 234, my emphasis). This statement is correct as far as it goes, but it neglects to mention that the trigeminal nerve also innervates the oral cavity and that ingested irritants (e.g., capsaicin, the irritant in hot peppers, and allyl isothiocyanate, the irritant in horseradish) trigger some of the same reflexes as inhaled irritants. Thus, so-called gustatory rhinitis involves rhinorrhea, nasal congestion, and facial sweating after ingestion of “hot” (spicy) foods (1). As to whether the common chemical sense was only “recently separated” from olfaction as a sensory modality (p. 235), the 1990 study of odor and nasal pungency in anosmics cited by Meggs (2) is but the latest in a series stretching back over 80 years and utilizing various tools to separate the two sensory systems (3).

Neuropeptide release occurs in relation to other types of airway reflexes, some of which do, indeed, involve an efferent limb coming from the central nervous system, as portrayed in Meggs’s Figure 2. Gustatory rhinitis, for example, involves afferent trigeminal sensory fibers and efferent facial nerve cholinergic fibers and is blocked by the preadministration of atropine (1). In contrast to Figure 2, however, the axon reflex (whereby neuropeptides are released) is a primarily afferent process, involving release of neuropeptides from varicosities in sensory nerves (4). Thus, neuropeptide release can be thought of as a local, as opposed to a central, reflex. What is clear is that a complex interrelationship exists between local (neuropeptide-mediated) and central (adrenergic, cholinergic, and nonadrenergic/noncholinergic) airway reflexes. Each of these mechanisms, as well as mast-cell degranulation (atopy), is subject to various regulatory factors, ultimately influencing upper and lower airway reactivity to environmental stimuli.

Meggs briefly mentions the variety of neuropeptides documented in human airways (substance P, calcitonin gene-related protein, neurokinin A, and others), but then goes on to focus on the role of substance P. The relative distribution of neuropeptides and their physiological actions appear to vary across species, making generalizations difficult at this time (5). For example, whereas substance P promotes neurophil and eosinophil chemotaxis and adhesion, its role in mast cell function appears to be that of potentiating other stimuli, rather than as an independent stimulus for degranulation, as Meggs suggests (6).

One aspect of the relationship between neurogenic and immunogenic inflammation not touched upon in the article is the fact that individuals with a history of atopy seem to be at higher risk of reactivity to airborne irritants, even when there is no evidence of an allergic mechanism of response. Thus, while both Bascom et al. (5) and Cummings et al. (7) observed a higher prevalence of environmental tobacco smoke (ETS)-related upper airway symptoms among subjects with a history of atopy, neither assays for allergic mediators in nasal lavage fluid (5) nor skin test reactivity to tobacco leaf extracts or tobacco smoke condensates (8) suggests an allergic mechanism of response. These data are consistent with a role for neuropeptides in the genesis of ETS-related nasal symptoms, as well as a modulatory effect of atopy upon neuropeptide release (9). Thus, atopy may constitute one of the most important “disorders of regulation of neurogenic inflammation” referred to by Meggs (p. 236).

An understanding of respiratory tract responses to irritant chemicals requires familiarity with concepts in allergy/immunology, sensory science, and toxicology. Meggs has made an important and accessible contribution to the literature by discussing neurogenic inflammation as a component of the airway response.

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Neurogenic Inflammation: Literature on Toluene Diisocyanate

I am writing in regard to the article by William Meggs in the August 1993 edition of EHP (101:234–238). I was surprised to see that in a review article of this type, the author made no mention of the work of our group on the well-known chemical sensitizer toluene diisocyanate and its action on capsaicin-sensitive primary afferents. For your information, I enclose a list of papers in question:

Mapp CE, Boniotti A, Graf PD, Chitano P, Fabbri LM, Nadel JA. Bronchial smooth muscle responses are inhibited by ruthenium red and by indomethacin. Eur J Pharmacol 200:73 (1991).”

Mapp CE, Boniotti A, Graf PD, Plebani M, Maisiero M, Fabbri LM, Ciaccia A. Role of metabolites of arachidonic acid in toluene diisocyanate-induced contraction on guinea-pig bronchi. Respir J 4:355 (1991).

Mapp CE, Boniotti A, Papi A, Chitano P, Cesar E, Di Stefano A, Saetta M, Ciaccia A, Fabbri LM. The effect of compound 48/80 on contractions induced by toluene diisocyanate in isolated guinea-pig bronchi. Eur J Pharmacol 248:67–73 (1993).

Mapp CE, Boniotti A, Papi A, Chitano P, Saetta M, Di Stefano A, Ciaccia A, Fabbri LM. The effect of phosphoramidon and epithelium removal on toluene diisocyanate-induced contractions in guinea-pig bronchi. Eur Respir J 5:331–338 (1992).

Mapp CE, Boniotti A, Papi A, Maggi CA, Di Stefano A, Saetta M, Giaccia A, Fabbri LM. Effect of bumetanide on toluene diisocyanate-induced contraction in guinea-pig airways. Thorax 48:63–67 (1993).
Mapp CE, Chitano P, Fabbri LM, Patacchini R, Maggi CA. Pharmacological modulation of the contractile response to toluene diisocyanate in the rat isolated urinary bladder. Br J Pharmacol 100:886–888 (1990).

Mapp CE, Chitano P, Fabbri, LM, Patacchini R, Santicioli P, Geppetti P, Maggi CA. Evidence that toluene diisocyanate activates the efferent function of capsaicin-sensitive primary afferents. Eur J Pharmacol 180:113 (1990).

Mapp CE, Graf PD, Boniotto A, Nadel JA. Toluene diisocyanate contracts guinea-pig bronchial smooth muscle by activating capsaicin-sensitive sensory nerves. J Pharmacol Exp Ther 256:1082–1085 (1991).

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Response to Shusterman and to Mapp

There has been an explosion of investigations into the basic science of neurogenic inflammation and its regulation in recent years, and it was beyond the scope of my review to give an exhaustive bibliography of the field. I apologize to those investigators whose excellent and relevant works were not included in the discussion. I am grateful to Dennis Shusterman for his clarifying remarks. The relationship between sensitivity to airway irritants and atopy is a complicated one that needs further study.

In my clinical experience, there are patients with chemical irritant rhinitis or asthma who are not atopic, atopic individuals who are not sensitive to chemical irritants, and an overlap group. Study of these groups may clarify this issue. It is my opinion that over the next few years we will move beyond the basic science of neurogenic inflammation to learn that it plays a major role in clinical medicine and environmental health and that a number of disorders are exacerbated by environmental chemicals interacting through sensory nerves to produce neurogenic inflammation. This knowledge will be useful to patients and clinicians as well as to regulators.

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Whose Sperm?

This letter is prompted by the illustration accompanying a news item, "Sperm: Down for the Count," (EHP 101:283) with substantial attribution to Sharpe and Skakkebaek. The problem is not with the content of the text, but with the illustration. It is evident that the illustration on page 283 is a portion of a seminiferous tubule from a rat and not a human. This is readily discernible by the hook-shaped nuclear morphology of the spermatids, near the lumen and elsewhere in the illustration. The appearance of a human seminiferous tubule is very different, although certainly illustrations of a human seminiferous tubule could have been provided by Skakkebaek or individuals resident at NIEHS. I recognize that the caption to the illustration includes the words "and animals," but association of the illustration with a text devoted primarily to humans strikes me as imprudent.

I considered ignoring this inconsistency, but thought it appropriate to call it to your attention because of the otherwise excellent quality of Environmental Health Perspectives.

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Editor's Note: The forum article on sperm counts was not derived directly from Sharpe and Skakkebaek, but merely synthesized a report authored by them. Unfortunately, we were unable to obtain a photomicrograph of human sperm in time for publication and used the photomicrograph of rat sperm as an alternative. The photomicrograph was kindly provided by Bob Chapin of the Systems Toxicity Branch of NIEHS.