In this article we review the evidence that activation of airway sensory receptors by pollutants can reflexly influence the cardiovascular system, as well as other systems that may cause secondary cardiovascular changes.

A number of studies in humans show that chronic inhalation of pollutants can induce changes in the electrocardiogram (ECG) (1–4), but the sensory receptors and neural pathways involved in these changes have not been established. By comparison many studies in experimental animals have allowed identification of sensory receptors and afferent and motor pathways (5–10).

The mucosae and epithelia of the airways, from nares to bronchioles and alveoli, contain afferent (sensory) nervous receptors that respond to a large variety of pollutant and irritant inhaled substances (Table 1) (5–11,12), and on activation set up profound reflex changes involving breathing and the autonomic nervous system (Table 2) (5–10). Although the sensory receptors have been studied mainly with respect to breathing, we concentrate in this review on the reflex cardiovascular changes.

Table 1 lists the airway receptor types that have been identified and which are sensitive to pollutants and irritants. There are some disagreements in the literature for example, on the relative sensitivity of C fiber and of rapidly adapting receptors (RARs) to various endogenous mediators (5,6,13–15), but a majority view is presented in Tables 1 and 2. Most of the experiments have been acute and have been performed on anesthetized experimental animals. Experiments on humans suggest we have similar sensory systems and reflex responses. However, we must use caution when applying the animal experiments, unlike those with humans, have been performed using general anesthesia, with irritants administered in high concentrations, and often to a restricted part of the respiratory tract. Species differences in the response to irritants are well established. We must be even more careful when applying the results of acute experiments in animals to the pathophysiologic changes observed in prolonged exposure to environmental pollution in humans. Key words: afferent receptors, afferent sensitization, airway reflexes, bronchi, cardiac dysrhythmias, cardiovascular responses, larynx, nose, trachea. — Environ Health Perspect 109(suppl 4):579–584 (2001).

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effect of nasal inhalation of cigarette smoke in an unanesthetized rabbit (A) and during anesthesia with pentobarbital (B). Smoke causes a rise in blood pressure, a fall in heart rate, and a fall in aortic flow. During anesthesia the changes in heart rate and in aortic flow are attenuated. Data are from White and McRitchie (23).

### Table 1. Respiratory receptors and their stimuli.

| Site            | Receptor | Stimulus          |
|-----------------|----------|-------------------|
| Nose            | Touch    | Mechanical        |
|                 | Cold/flow| Cold              |
|                 | Pressure | Mechanical        |
|                 | C fiber  | Irritants         |
| Epipharynx      | Touch    | Mechanical        |
|                 | ? C fiber| ? Irritants       |
| Larynx          | Pressure | Mechanical        |
|                 | Cold/flow| Cold              |
|                 | Drive    | Inspiratory drive |
|                 | C fiber  | Irritants         |
| Trachea/bronchi | SAR      | Lung inflation    |
|                 | RAR      | Touch, irritants  |
|                 | C fiber  | Irritants         |
| Alveoli         | C fiber  | Irritants         |

Abbreviations: SAR, slowly adapting pulmonary stretch receptor; NEB, neuroepithelial body.

### Table 2. Respiratory and cardiovascular responses from different airway sites.

| Site            | Respiration | Blood pressure | Heart rate |
|-----------------|-------------|----------------|------------|
| Nose            | Sneeze/apnea| Increase       | Decrease   |
| Nasopharynx     | Gasp/sniff  | Increase       | Increase   |
| Larynx          | Cough/apnea/expiration| Increase/Decompression | Decrease |
| Trachea/bronchi | Cough/apnea/hyperpnea| Increase/Decompression | Decrease |
| Alveoli         | Apnea       | Decrease       | Decrease   |

Apnea may be replaced or followed by rapid shallow breathing.

### Dysrhythmias

Human inhalation of pollutants can cause changes in the heart, based on evidence from complex statistical analysis of the pattern of the ECGs (1–4). In animal experiments, inhalation of strong concentrations of irritant vapor can cause dysrhythmias. Kratschmer and colleagues (20,21) noted if one allows one of the stimulating substances to act upon the nasal mucosa, there occurs almost always, in addition to the increase in blood pressure, a peculiar cessation of the heart beat; there is a distinct slowing of the heart rate in combination with a strange irregularity, reminiscent, perhaps, of pulsus bigeminus (Traube). (22)

More recent studies support this possibility; laryngeal irritation in humans can cause cardiac dysrhythmias with depression of the ST complex of the ECG (27) (Figure 3). Before use of local anesthetics in the larynx, cardiac dysrhythmias and even cardiac arrest were not uncommon responses to laryngeal intubation (31). It has long been assumed, but with little evidence, that “restaurant death,” the sudden death caused by inhalation of food, is due to dysrhythmia, possibly ventricular fibrillation, and set up by a reflex from the larynx. In humans, the role of the vagus nerves in dysrhythmias caused by inhalation of pollutants has been much discussed (1–4). It should be...
noted that even with strong chemical irritation of the lower respiratory tract (below the larynx) and with pronounced cardiovascular reflex changes in experimental animals, dysrhythmias have not been described.

**Sensitization, Inhibition, and Interactions**

An important property of the sensory receptors responding to pollutants is their plasticity (17,29,32). This has recently been studied both by recording reflexes and by single nerve fiber recordings of action potentials, in vivo and in vitro. A sensitization to chemical and mechanical stimuli has been shown on a short-term basis—minutes or hours—for RARs with histamine (33), immunologic reactions (34), and by agents such as substance P and lobeline (15,35,36). Longer lasting sensitization—several days to a week—has been shown with ozone (37). Similar sensitization of C-fiber receptors has been established (29) with ozone (38), histamine (39), prostaglandin E₂ (40), and in experimental airways disease (41). Some of the sensitizations occur at the receptor level in the periphery, but interactions between different groups of receptors at the level of the vagal nodose and jugular ganglia have also been established (42).

None of these sensitizations has been established for the cardiovascular reflexes but they potentially exist. A sensitized cough reflex after respiratory viral infection, often persisting for months, is a common condition that must depend on sensitized RARs in the airways, as these mediate the cough reflex (14). In addition, there has been much speculation and a number of studies to determine whether the hyperresponsiveness of asthma is due to the sensitization of sensory receptors in the lungs.

Some neural pathways will inhibit the responses from others. A good example is the stimulation of pulmonary C-fiber receptors, which can inhibit cough induced by activation of RARs (14,43). Whether a similar inhibitory mechanism exists for the cardiovascular reflexes is not known. If an irritant at one site (e.g., the nose) causes hypertension, and at the same time at another site (e.g., the lungs) causes hypotension, the result must depend on the interaction of the two afferent pathways. For heart rate, most but not all reflexes from the respiratory tract responding to irritants cause bradycardia, so there may be the possibility of summation or synergy rather than inhibition. Studies are limited on these phenomena but could be important.

A further consideration is that, apart from primary reflexes from irritation of the respiratory tract, the cardiovascular system may be secondarily affected. The changes in breathing, usually apneas, hyperventilation, or cough, will have a mechanical effect on the cardiovascular system, change blood gas tensions with cardiovascular effects via the peripheral chemoreceptors, and alter the discharge of lung receptors (RARs and slowly adapting pulmonary stretch receptors), which in turn may affect the heart and vasculature. For example, in Figure 2 (25) one cannot determine the extent to which the hypertension and tachycardia are influenced by the respiratory changes, cough, and tachycardia, or are primary reflex actions. The hypertension seen in anesthetized cats with mechanical stimulation of the respiratory tract from nose to trachea are much larger in spontaneously breathing animals than in those paralyzed and artificially ventilated (23). The whole-body mechanisms are very complex.

**Application of Animal Results to Humans**

Most experiments with inhaled pollutants—nearly all those that analyze nervous pathways and all of those based on single nerve fiber recordings—have been conducted on experimental animals. It has yet to be determined to what extent they are applicable to the mechanisms of cardiovascular responses to inhaled environmental pollutants in humans.

**Size of Stimulus**

When animals are exposed to chemical irritants, pollutants, and biologic mediators in aerosols, the concentrations are usually far greater than those to which humans are exposed. With some stimuli (water, hyper- and hyposmolar solutions, cold and...
touch), the stimuli may be similar in size. There have been few or no comparisons of the same stimulus in humans and in unanesthetized animals.

Localization of Stimulus

In the majority of animal experiments, the stimulus has been localized to one site, e.g., nose or lungs. Humans exposed to environmental pollutants inhale them into the entire respiratory system unless the nose, which is the most sensitive reflexogenic zone in most animals, is mechanically blocked. In human experiments inhalation is usually through a mouthpiece. The potential importance of interactions between reflexes arising from different parts of the respiratory system has already been mentioned. Most of the animal species used are rodents—guinea pigs, rats, and mice—which are obligatory nose breathers, unlike humans. The balance of the reflexes from different sites in the respiratory tract may be quite different.

Duration of Stimulus

Most animal experiments are acute, lasting minutes or hours, whether reflexes or afferent nervous activities are being studied. Acute experiments have also been conducted with pollutants in humans, but for natural environmental pollution the period of exposure required for pathologic changes may be months or years.

Anesthesia

Many of the animal experiments have been performed using general anesthesia, and even when the anesthesia is light, it can profoundly change the pattern and size of irritant responses, including those responses in humans. Volatile anesthetics affect, by a peripheral action, the sensitivity and discharge of airway receptors that respond to irritants (5, 9), and centrally acting anesthetics act on the brainstem pathways for their reflexes. In humans light general anesthesia enhances the respiratory responses due to stimulation of the larynx (expiratory efforts and cough), whereas deeper anesthesia converts the response to apnea (26, 44) (Figure 6). However, anesthesia seems to have little effect on the reflex laryngospasm due to laryngeal stimulation. In experimental animals, anesthesia may depress the reflex respiratory changes from the larynx (23) (Figure 1). Blood pressure and heart rate changes have not been studied in this context.

It should be emphasized that the brainstem neural pathways for reflexes elicited by inhalation of pollutants have not been mapped out in detail, although the first-order pathways into the nucleus of the solitary tract and adjacent areas have been (45–47). This lack of detailed knowledge may not be sufficient to enable precise prediction of the effects of pollutants on natural respiratory reflexes.
surprising in view of the complexity of the brainstem respiratory rhythm generator into which airway afferent pathways feed. Thus, there is much uncertainty as to precisely how, in neuronal terms, general anesthetics affect these reflexes.

Sensitization and Reflex Interactions

These interactions have been mentioned previously. In experimental animals they can occur in the very short term—seconds or minutes. Clinically they can be illustrated by the sensitized cough after respiratory tract infection, and by the hyperresponsiveness observed in subjects with asthma (48). In subjects exposed to pollution for months or years they are certain to exist, but comparison with acute animal and human experiments must be quantitatively uncertain. Cardiac changes in human chronic exposure to pollutants have been well described (1-4), but it is difficult to establish whether the neural mechanisms identified in the more acute experiments in animals apply to humans.

Conclusion

Abundant evidence exists about reflexes, including those to the cardiovascular system, activated by inhalation of pollutants in experimental animals. Nearly all the studies have been acute or short term. Similar experiments suggest that humans have the same reflexes, but they have not been extensively analyzed, especially with regard to the cardiovascular system. The applicability of this large body of research to the pathophysiologic results of long-term exposure to atmospheric pollutants is at present very tenuous.

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Figure 5. Possible neurogenic inflammation in asthmatic airways via retrograde release of peptides from sensory C-fiber receptors via an axon reflex. Substance P (SP) causes vasodilatation, plasma exudation, and mucus secretion, whereas neurokinin A (NKA) causes bronchoconstriction and enhanced cholinergic reflexes, and calcitonin gene-related peptide (CGRP) causes vasodilatation. Data are from Barnes (49).

Figure 6. Respiratory responses to laryngeal stimulation with distilled water in (A) an awake subject, showing expiratory efforts and cough; (B) a lightly anesthetized subject with the same stimulus, showing vigorous coughs; and (C) with further deepening of anesthesia for the same subject showing cough replaced by an apneic response. Data modified from Nishino et al. (26).
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