Airway Reflexes, Autonomic Function, and Cardiovascular Responses

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In this article, we review the cardiovascular responses to the inhalation of irritants and pollutants. Many sensory receptors in the respiratory system, from nose to alveoli, respond to these irritants and set up powerful reflex changes, including those in the cardiovascular system. Systemic hypotension or hypertension, pulmonary hypertension, bradycardia, tachycardia, and dysrhythmias have all been described previously. 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 results to humans. Most 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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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. It seems certain that the list of sensory receptors is an oversimplification, but it may provide a framework for discussion of the role of airway receptors in modulating cardiovascular responses. Functional subgroups of RARs are well established (*7*); it is likely that subgroups will also be identified for the C-fiber receptors (*6,16,17*). Single nerve fiber recordings show that many of the groups responding to irritants can be subdivided. Thus, some C-fiber receptors in the nose respond to nicotine but not to ammonia, whereas for others the pattern is vice versa (*11*). Similar differences in sensitivities to a range of irritants and biologic mediators are seen for tracheobronchial C-fiber receptors and for RARs (*5,6,12,16*). Although it is known that various RAR subgroups in the lower respiratory tract have different respiratory reflex actions (*7,8,17,18*), it is uncertain whether this is true for the C-fiber receptors and whether subgroups of RARs and C-fiber receptors also have different cardiovascular reflex actions.

In this review we refer to receptors in their original physiologic sense as nervous or sensory endings which receive stimuli and set up reflex responses. In the pharmacologic sense the nervous endings have chemical receptors on their membranes that when activated set up generator and action potentials in the sensory end organ and nerve fibers. There is an extensive literature on these pharmacologic receptors in airway sensory receptors or end organs (*6,17,19,20*).

Cardiovascular Reflex Responses to Pollutants

The classical and seminal study was conducted by Kratschmer in 1870 (*21,22*), who showed that chemical irritants such as ammonia applied to the nose and larynx caused profound hypertension and bradycardia. He also analyzed the afferent and motor pathways. He worked only on experimental animals but realized the significance of his studies for humans. (He later occupied the first Professorial Chair in Public Hygiene in Vienna, Austria.) He wrote

> We are only repeating the experiments which Nature carries out daily on Man and animals, and thus we can obtain information about processes which, quite apart from their theoretical interest, are of immediate practical significance (*22*).

Since Kratschmer's work, an extensive literature has documented that irritants inhaled into the upper respiratory tract cause cardiovascular reflex changes that are predominantly bradycardiac and include either hyper- or hypotension (*8–10*) (Table 2). Nasal inhalation of cigarette smoke in rabbits causes hypertension and bradycardia (*23*) (Figure 1). Because the bradycardia is prevented by administration of atropine (*5,8*) it is mainly vagally mediated, but studies are limited on the possible additional involvement of the sympathetic innervation of the heart. Receptors in the nasopharynx and pharynx do not seem to be very chemosensitive, possibly because the epithelium in these areas is squamous cell in nature and may be relatively impermeable, but the sites can give rise to powerful cardiovascular reflexes, especially hypertension (*8,10,24*). Laryngeal irritation can cause a variety of cardiovascular changes, but systemic hypertension has usually been reported, including in humans (*25–27*) (Figure 2); in addition, there may be either bradycardia or tachycardia and pulmonary hypertension (*27*) (Figure 3).

For the lower respiratory tract, RARs and C-fiber receptors occur in and under the epithelium (*6,28*) (Figure 4). These latter receptors, as well as C-fiber receptors in the alveolar wall, are very sensitive to irritants and

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pollutants (*29*) and reflexly cause pronounced bradycardia and hypotension. As Table 2 indicates, an irritant pollutant distributed throughout the entire respiratory system could activate many reflexes, with diverse actions on blood pressure and heart rate.

Acute cardiovascular reflex responses to inhaled irritants and mechanical stimuli have been reported in humans (*25,27*) (Figures 2, 3), and in general the patterns are similar to those described for animals, although the stimuli have naturally been much weaker. Assessing neural mechanisms has seldom been practical.

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
	RAR/Irritant	Touch, irritants
	C fiber	Irritants
Trachea/bronchi	SAR	Lung inflation
	RAR	Touch, irritants
	C fiber	Irritants
	NEB	Hypoxia
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	Increase/ decrease
Trachea/ bronchi	Cough/apnea/ hyperpnea	Increase/ decrease	Increase/ decrease
Alveoli	Apnea	Decrease	Decrease

Apnea may be replaced or followed by rapid shallow breathing.

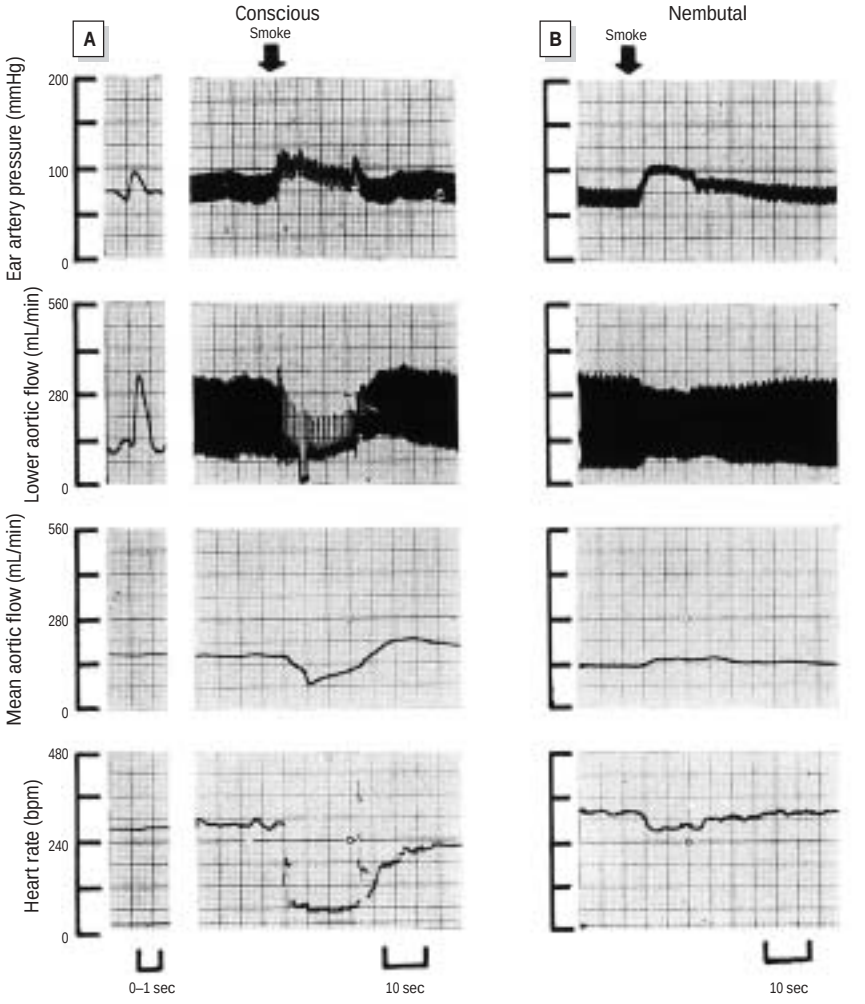

Figure 1. Effect of nasal inhalation of cigarette smoke in an unanesthetized rabbit (*A*) and during anesthesia with pentobarbitone (*B*). Smoke causes a rise in blood pressure, a fall in heart rate, and a fall in aortic flow. During anesthesia the changes in heart rate and in aortic flow are attenuated. Data are from White and McRitchie (*23*).

The receptors for these reflexes have been identified in animals by single nerve fiber recording and in humans and animals by histology. They lie in and under the airway epithelium from nose to alveoli (*6,28*) (Figure 4). They are polymodal, responding to many chemical and mechanical irritants, and nociceptive, responding to a variety of pathologic conditions that activate airway reflexes. Their morphology is not well mapped out (*6*). When stimulated, they release tachykinins such as substance P and neurokinin A, which cause the local axon-reflex effects known as neurogenic inflammation (*30*) (Figure 5). This includes mucosal vasodilatation. However, airway neurogenic inflammation has not been convincingly established in humans (*30*).

Thus, inhaling a chemical irritant will potentially stimulate a large number of airway afferent receptors. Presumably the reflex cardiovascular response will depend on the integration of the reflexes from individual anatomic zones and therefore will in turn depend on the sites of deposition of the pollutant. The integrative mechanisms of such a reflex response have seldom been studied in experimental animals, and not at all in humans.

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 E_2 (*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 then 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 hypertensions 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.

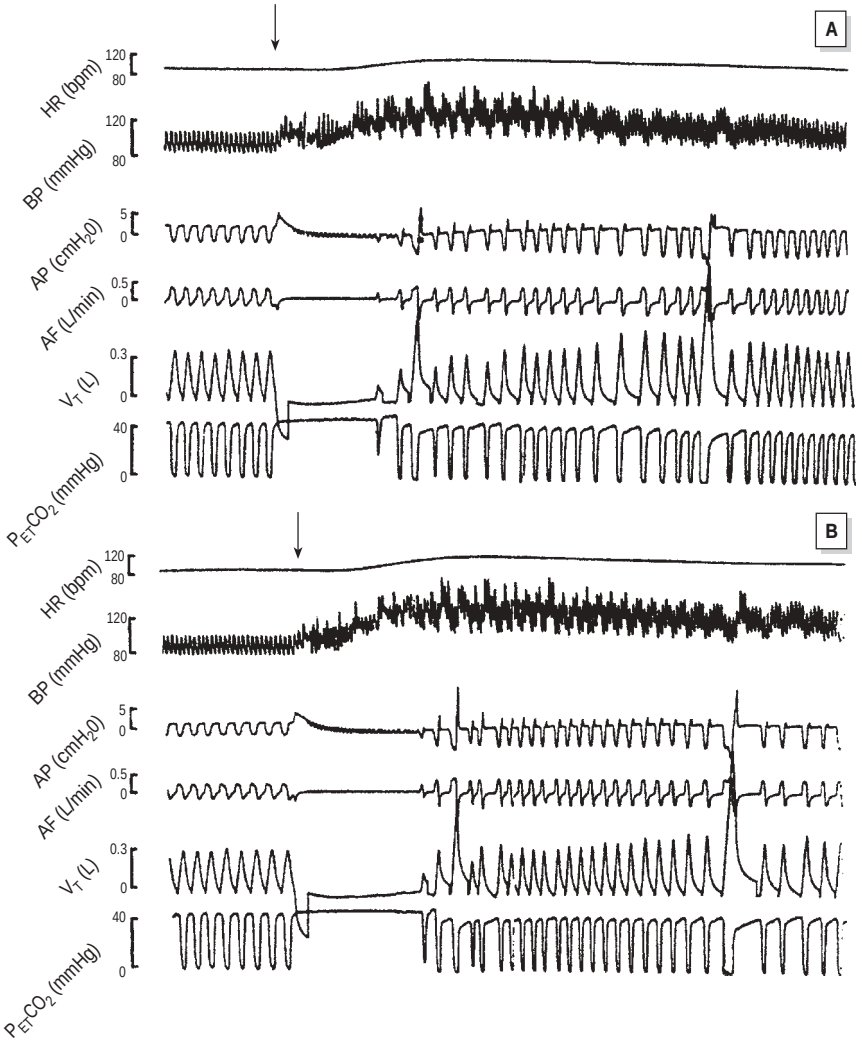

Figure 2. Respiratory responses to stimulation by distilled water (arrows) of different sites of the respiratory tract in an anesthetized human. HR, heart rate; BP, arterial blood pressure; AP, airway pressure; AF, airflow; V_T, tidal volume; $P_{ET}CO_2$, end tidal CO_2. (*A*) Stimulation of the larynx causes apnea, cough, and increases in blood pressure and heart rate. (*B*) Stimulation of the trachea causes similar responses. Data modified from Nishino et al. (*26*).

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 stimulants (water, hyper- and hyposmolar solutions, cold and

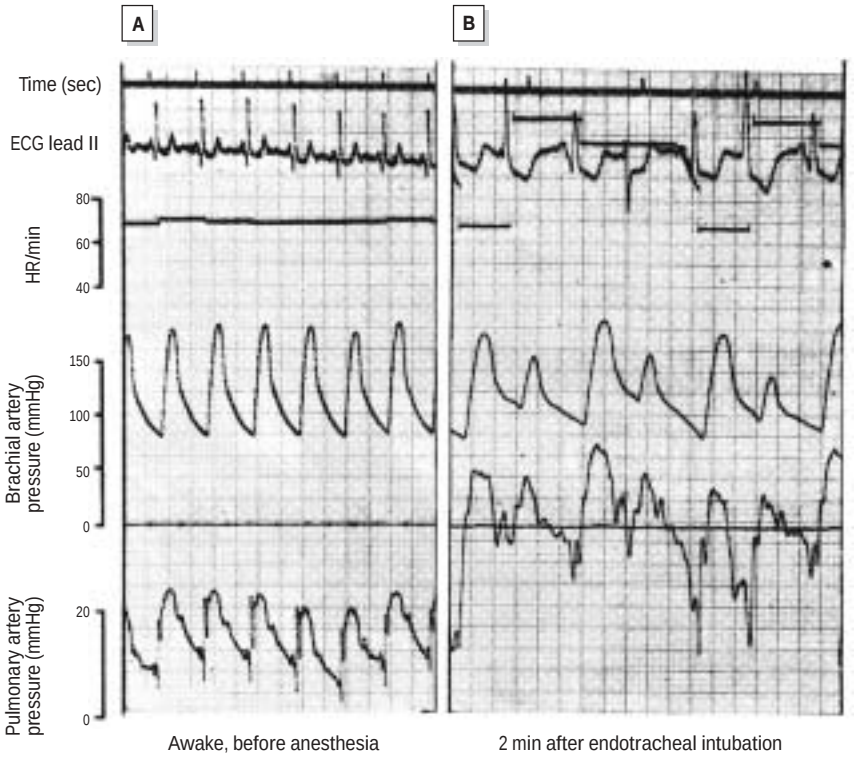

Figure 3. Circulatory changes in a patient during and after laryngoscopy and tracheal intubation. (*A*) Values during the awake control period, with systemic hypertension. (*B*) Effects of endotracheal intubation with ventricular bigeminy, maintained hypertension, pulmonary hypertension, and ECG changes: depression of the S-T segment and T-wave inversion, possibly indicating myocardial ischemia. Data are from Prys-Roberts et al. (*27*).

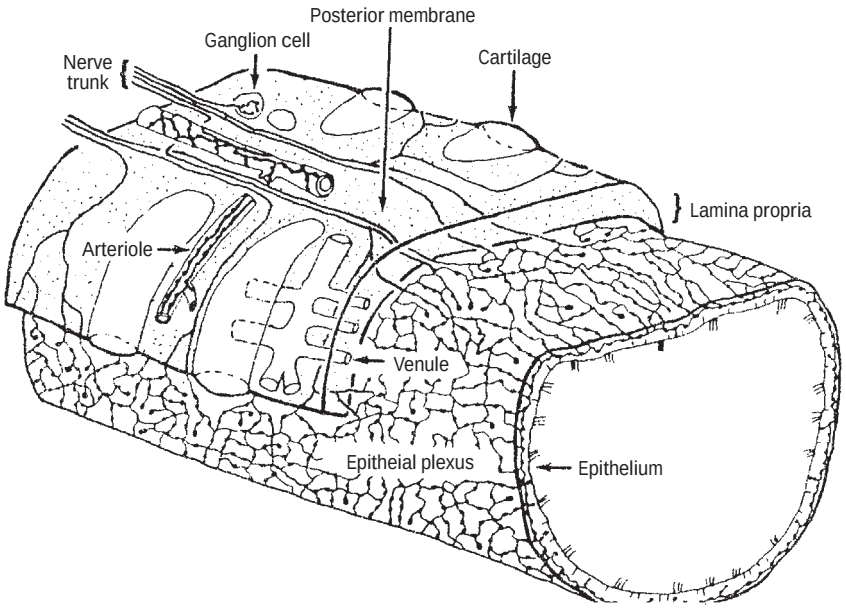

Figure 4. Schematic diagram of the innervation of rat trachea by substance P–immunoreactive axons. Most of the varicose terminal portions of substance P–immunoreactive axons are found in the epithelium, but a few are associated with arterioles and small parasympathetic ganglia of the posterior membrane. Bundles of smooth nonterminal axons run through the lamina propria. Data are from Baluk et al. (*28*).

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

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.

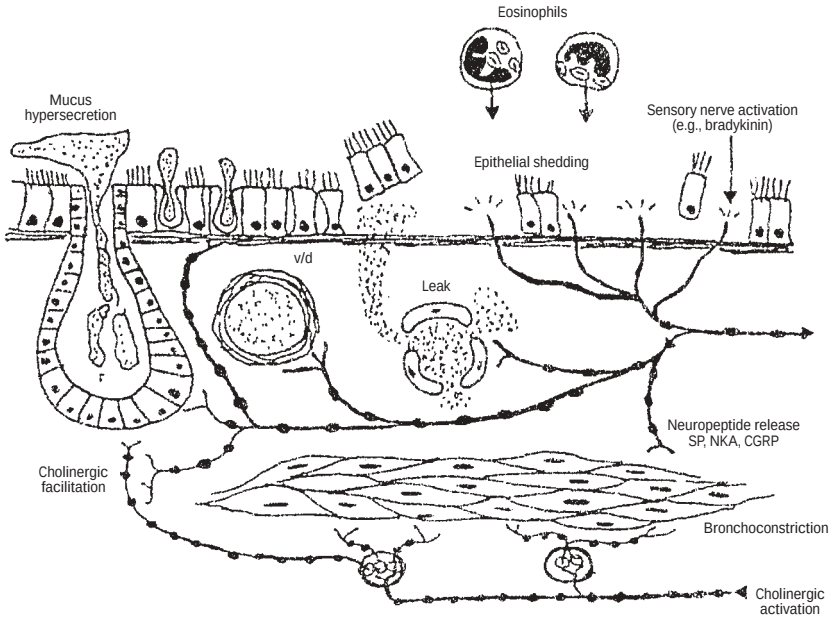

Figure 5. Possible neurogenic inflammation in asthmatic airways via retrograde release of peptides from sensory C-fiber receptors via an axon reflex. Substance P (SP) causes vasodilatation, plasma exudation, and mucus secretion, whereas neurokinin A (NKA) causes bronchoconstriction and enhanced cholinergic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

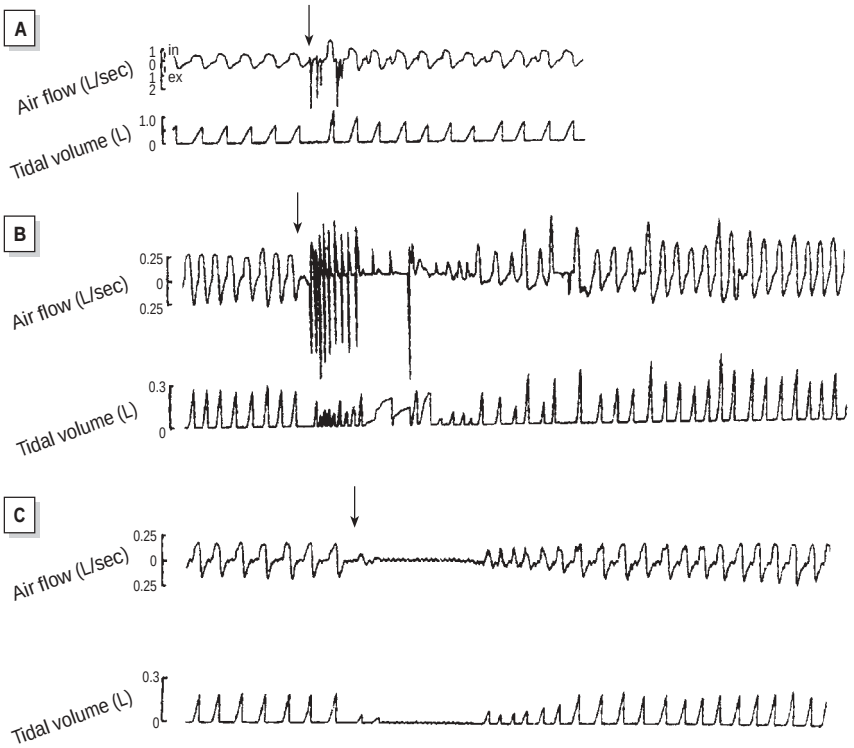

Figure 6. Respiratory responses to laryngeal stimulation with distilled water in (*A*) an awake subject, showing expiratory efforts and cough; (*B*) a lightly anesthetized subject with the same stimulus, showing vigorous coughs; and (*C*) with further deepening of anesthesia for the same subject showing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

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.

References and Notes

1. Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Gold DR, Dockery DW. Heart rate variability associated with particulate air pollution. Am Heart J 138:895–899 (1999).
2. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 107:521–525 (1999).
3. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. Circulation 101:1267–1273 (2000).
4. Zareba W, Nomura A, Couderc J-P. Cardiovascular effects of air pollution: what to measure in ECG? Environ Health Perspect 109(suppl 4):533–538 (2001).
5. Coleridge HM, Coleridge JCC. Reflexes evoked from the tracheobronchial tree and lungs. In: Handbook of Physiology, Section 3: the Respiratory System, Vol II: Control of Breathing, Part I (Cherniack NS, Widdicombe JG, eds). Washington, DC:American Physiological Society, 1986;395–429.
6. Widdicombe JG. Airway receptors. Respir Physiol 125:3–15 (2001).
7. Sant'Ambrogio G, Widdicombe JG. Reflexes from airway rapidl adapting receptors. Respir Physiol 125:33–45 (2001).
8. Widdicombe JG. Reflexes from the upper respiratory tract. In: Handbook of Physiology, Section 3: the Respiratory System, Vol II: Control of Breathing, Part I (Cherniack NS, Widdicombe JG, eds). Washington, DC:American Physiological Society, 1986;363–394.
9. Widdicombe JG. Respiratory reflexes. In: Handbook of Physiology, Section 3: Respiration, Vol I (Fenn WO, Rahn H, eds). Washington, DC:American Physiological Society, 1964;585–630.
10. Widdicombe JG. Vagal reflexes in the airways. In: Neural Regulation of the Airways in Health and Disease (Kaliner M, Barnes PJ, eds). New York:Marcel Dekker, 1988;187–202.
11. Sekisawa S, Tsubone H. Nasal receptors responding to noxious chemical irritants. Respir Physiol 96:37–48 (1994).
12. Widdicombe JG. Receptors in the trachea and bronchi of the cat. J Physiol (Lond) 123:71–104 (1954).
13. Karlsson J-A, Fuller RW. Pharmacological regulation of the

cough reflex—from experimental models to antitussive effect in man. Pulm Pharmacol Ther 12:215–228 (1999).
14. Widdicombe JG. Afferent receptors in the airways and cough. Respir Physiol 114:5–15 (1998).
15. Widdicombe JG. Sensory mechanisms. Pulm Pharmacol 9:383–388 (1996).
16. Riccio MM, Kummer W, Biglari B, Myers AC, Undem BJ. Interganglionic segregation of distinct vagal afferent fiibre phnotypes in guinea pig airways. J Physiol (Lond) 496:521–530 (1996).
17. Undem BJ, McAlexander M, Hunter OD. Neurobiology of the upper and lower airways. Allergy 54(suppl 57):81–93 (1999).
18. Widdicombe JG. Respiratory reflexes from the trachea and bronchi of the cat. J Physiol (Lond) 123:71–104 (1954).
19. Spina D, Matera MG, Riccio MM, Page CP. A comparison of sensory nerve function in human, guinea-pig, rabbit and marmoset. Life Sci 63:1629–1643 (1998).
20. Kajekar R, Proud D, Myers AC, Meeker SN, Undem BJ. Characterization of vagal afferent subtypes stimulated by bradykinin in guinea pig trachea. J Pharmacol Exp Ther 289:682–687 (1999).
21. Kratschmer F. Uber Reflexe von der Nasenschleimhaut auf Athmung und Kreislauf. Sitzber Akad Wiss Wien 62:147–170 (1870).
22. Kratschmer F. On refflexes from the nasal mucous membrane o respiration and circulation [translation by Elizabeth Ullmann]. Respir Physiol (in press).
23. White SW, McRitchie RJ. Nasopharyngeal refflexes: integrativ analysis of evoked respiratory and cardiovascular effects. Exp Biol Med Sci 51:17–31 (1973).
24. Tomori Z, Widdicombe JG. Muscular, bronchomotor and cardiovascular refflexes elicited by mechanical stimulation of the repiratory tract. J Physiol (Lond) 200:25–49 (1969).
25. Nishino T, Kochi T, Ishii M. Differences in respiratory reflex responses from the larynx, trachea, and bronchi in anesthetized female subjects. Anesthesiology 84:70–74 (1996).
26. Nishino T, Tagaito Y, Isono S. Cough and other refflexes on iritation of airway mucosa in man. Pulm Pharmacol 9:285–292 (1996).
27. Prys-Roberts C, Greene LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension. II: Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 43:531–547 (1971).
28. Baluk P, Nadel JA, McDonald DM. Substance P immunoreactive sensory axons in the rat respiratory tract: a quantitative study of their distribution and role in neurogenic inflammation. J Comp Neurol 319:586–598 (1992).
29. Lee L-Y, Widdicombe JG. Modulation of airway sensitivity to inhaled irritants: role of infllammatory mediators. Environ Healt Perspect 109(suppl 4):585–589 (2001).
30. Barnes PJ. Neurogenic inflammation in the airways. Respir Physiol 125:165–154 (2001).
31. Colon-Yordan E, Mackrell TN, Stone HH. An evaluation of the use of thiopental and decamethonium bromide for rapid endotracheal intubation. Anesthesiology 14:255–261 (1953).
32. Lee L-Y, Pisarri TE. Afferent properties and reflex functions of bronchopulmonary C-fiibres Respir Physiol 125:47–65 (2001).
33. Sellick H, Widdicombe JG. Stimulation of lung irritant receptors by cigarette smoke, carbon dust, and histamine aerosol. J Appl Physiol 31:15–19 (1971).
34. Riccio MM, Myers AC, Undem BJ. Immunomodulation of afferent neurons in guinea-pig isolated airway. J Physiol (Lond) 491:499–509 (1996).
35. Fox AJ. Mechanisms and modulation of capsaicin activity on airway afferent nerves. Pulm Pharmacol 9:207–214 (1996).
36. Fox AJ. Modulation of cough and airway sensory fibres. Pulm Pharmacol 9:335–342 (1996).
37. Joad JP, Kott KS, Bonham AC. Exposing guinea pigs to ozone for 1 week enhances responsiveness of rapidly adapting receptors. J Appl Physiol 84:1190–1197 (1998).
38. Ho CY, Lee L-Y. Ozone enhances excitabilities of pulmonary C fiibers to chemical and mechanical stimuli in anesthetized rats J Appl Physiol 85:1509–1515 (1998).
39. Lee L-Y, Morton RF. Histamine enhances vagal pulmonary C-fibre responses to capsaicin and lung inflation. Respir Physiol 93:83–96 (1993).
40. Lee L-Y, Morton RF. Pulmonary chemoreflex sensitivity is enhanced by prostaglandin E_2 in anesthetized rats. J Appl Physiol 79:1679–1686 (1995).
41. Long NC, Martin JG, Pantano R, Shore SA. Airway hyperresponsiveness in a rat model of chronic bronchitis: role of C fibers. Am J Respir Crit Care Med 155:1222–1229 (1997).
42. Myers AC. Transmission in autonomic ganglia. Respir Physiol 125:99–111 (2001).
43. Tatar M, Webber SE, Widdicombe JG. Lung C-fibre receptor activation and defensive reflexes in anaesthetized cats. J Physiol (Lond) 402:411–420 (1988).
44. Nishino T, Honda Y. Refflex respiratory responses to stimulatio of tracheal mucosa in enflurane-anesthetized humans. J Appl Physiol 65:1069–1074 (1988).
45. Shannon R, Beekey DM, Morris KF, Lindsey BG. Ventrolateral medullary respiratory network and a model of cough motor pattern generation. J Appl Physiol 84:2020–2035 (1997).
46. Jordan D. Central nervous pathways and control of airways. Respir Physiol 125:67–81 (2001).
47. Widdicombe J. Upper airway reflexes. Curr Opin Pulm Med 4:376–382 (1998).
48. Spina D, Page CP. Airway sensory nerves in asthma—targets for therapy? Pulm Pharmacol 9:1–18 (1996).
49. Barnes PJ. Airway neuropeptides. In: Asthma and Rhinitis (Busse WM, Holgate ST, eds). Boston:Blackwell Scientific Publications, 1995;667–685.