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Role of Autonomic Reflex Arcs in Cardiovascular Responses to Air Pollution Exposure

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Abstract The body responds to environmental stressors by triggering autonomic reflexes in the pulmonary receptors, baroreceptors, and chemoreceptors to maintain homeostasis. Numerous studies have shown that exposure to various gases and airborne particles can alter the functional outcome of these reflexes, particularly with respect to the cardiovascular system. Modulation of autonomic neural input to the heart and vasculature following direct activation of sensory nerves in the respiratory system, elicitation of oxidative stress and inflammation, or through other mechanisms is one of the primary ways that exposure to air pollution affects normal cardiovascular function. Any homeostatic process that utilizes the autonomic nervous system to regulate organ function might be affected. Thus, air pollution and other inhaled environmental irritants have the potential to alter both local airway function and baro- and chemoreflex responses, which modulate autonomic control of blood pressure and detect concentrations of key gases in the body. While each of these reflex pathways causes distinct responses, the systems are heavily integrated and communicate through overlapping regions of the brainstem to cause global effects. This short review summarizes the function of major pulmonary sensory receptors, baroreceptors, and carotid body chemoreceptors and discusses the impacts of air pollution exposure on these systems.

Keywords C fibers · RARs · SARs · Baroreceptors · Carotid body · Air pollution

Abbreviations

ANS	Autonomic nervous system
BRS	Baroreflex sensitivity
COPD	Chronic obstructive pulmonary disease
HRV	Heart rate variability
HVR	Hypoxia ventilatory response
NTS	Nucleus tractus solitarius
OSA	Obstructive sleep apnea
PM	Particulate matter
RARs	Rapidly adapting pulmonary receptors
SARs	Slowly adapting pulmonary receptors
TRPA1	Transient receptor potential ankyrin 1
TRPV1	Transient receptor potential vanilloid 1

Introduction

Epidemiological studies have shown that air pollution exposure increases cardiovascular morbidity and mortality [1], especially in individuals made more susceptible by advanced age or chronic cardiovascular and lung disease. In fact, air pollution exposure has been shown to exacerbate cardiac and vascular pathophysiology attendant to

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hypertension, ischemia, heart failure, diabetes, coronary artery disease, and other pathophysiological conditions of the cardiovascular system [1]. Key components of air pollution associated with adverse health effects include fine and ultra-fine particulate matter ($PM_{2.5}$ and UFP, with diameters less than 2.5 and 0.1 μm, respectively), and gases including ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) [2]. For example, exposure to $PM_{2.5}$ concentrations of as little as 10–20 $\mu g/m^3$ caused significant increases in the risk of myocardial infarction 24 h after exposure [3]. In addition, individuals who had been hospitalized for coronary artery disease showed increases in T wave area (suggesting impairment in myocardial repolarization) after exposure to ambient levels of black carbon [4]. PM inhalation has also been associated with myocardial ischemia [5–7] and arrhythmias [7–9], especially in susceptible populations such as aged adults, the medically fragile, and those with underlying cardiovascular disease.

Our understanding of the pathophysiological mechanisms underlying air pollution-induced adverse clinical cardiovascular events has increased substantially since the first epidemiological studies discovered associations between PM exposure and increased cardiovascular morbidity and mortality. Currently, there are three mechanisms of action hypothesized that could explain the health effects of gaseous and particulate pollutants [1]. One theory posits that health effects result from the translocation of PM and/or its components into the systemic circulation resulting from the direct interaction of the pollutant with blood vessel walls and/or the myocardium and causing attendant changes in vascular, mechanical, and electrical function. The second mechanism suggests that air pollution exposure elicits its effects by triggering pulmonary oxidative injury and systemic inflammation with an increase in pro-inflammatory biomarkers [1]. This local response can lead to systemic oxidative stress and inflammation characterized by an increase in activated white blood cells, platelets, and cytokine expression. Perhaps the major consequence of air pollutant-induced systemic inflammation is injury of the vascular endothelium, the inner lining of the blood vessel wall, thus promoting vasoconstriction, thrombosis, and inflammation [10]. The third mechanism for air pollution-induced cardiovascular dysfunction posits that pollutant inhalation activates airway sensory nerves, which due to neural plasticity, even in the short-term, can modify autonomic nervous system (ANS) control of cardiovascular function. Importantly, these three mechanisms can overlap, as seen in studies showing that oxidative stress can lead to changes in autonomic function [11, 12]. While evidence exists for all three mechanisms, changes in cardiac autonomic tone are often the most immediate consequences of air pollution exposure [1] and involve several different reflex arcs.

The ANS controls many of the visceral functions and is composed of two branches, the sympathetic branch that is responsible for the "fight or flight" response and the parasympathetic branch that is responsible for maintaining a homeostatic baseline. The body has a complex and multifaceted system that responds to environmental stressors or anything that causes fluctuation in normal function on a moment-to-moment basis, by triggering autonomic reflexes. This includes pulmonary pathways that respond to sensory activation/irritation, baroreceptor reflexes that respond to changes in blood pressure (BP), and chemoreceptor-initiated reflex responses to changes in pCO_2, pO_2, pH, and temperature. Given the growing interest in mechanisms that mediate short-term cardiovascular effects of air pollution, this review will discuss (1) the impacts of autonomic modulation on cardiovascular function, (2) evidence linking these three prominent autonomic reflex arcs to the cardiovascular effects associated with exposure to air pollution, and (3) how these responses are integrated.

Changes in Heart Rate Variability: Evidence for Altered Autonomic Tone

Much of the evidence linking changes in cardiac autonomic tone with exposure to air pollution comes from studies of heart rate variability (HRV). HRV is the degree of difference in the inter-beat intervals of successive heartbeats and is an indicator of the balance between the sympathetic and parasympathetic branches of the ANS [13]. High HRV is traditionally considered positive because the heart has the ability to respond to rapidly changing environments. Low HRV, reflecting increased sympathetic tone [13], is associated with an increased risk of cardiac arrhythmia [14] and an increased risk of mortality in people with heart disease [15, 16]. While low HRV has been reported with exposure to PM [17–21] and ozone [4, 22, 23], other studies have demonstrated associations between PM exposure and increased HRV [24–26]. Importantly, increased HRV may also have links to adverse health outcomes. Increased parasympathetic tone is a precursor to drug-induced *torsade de pointes* [27] (a precursor arrhythmia to ventricular fibrillation [28]) and is associated with increased apnea severity in obese patients [29], adverse cardiovascular events in type II diabetics [30], and increased mortality in heart failure [31]. While the mechanisms triggering changes in HRV, and thus autonomic tone, have not been fully delineated and are likely numerous and diverse in nature, the best studied mechanism with respect to acute air

Table 1 Summary of locations, effects of activation, and activating air pollutants in the body's reflex responses

Receptor	Location	Irritant/pollutant	Effect
C-nerve fibers TRPA, TRPV, J receptors	Nose, larynx, trachea/ bronchi alveoli [34]	Cigarette smoke [40, 41], SO_2 [41], acrolein [39], PM [41]	Apnea, dyspnea, cough, bronchoconstriction, lung inflation, injury, acute pulmonary vascular congestion [35–38]
Rapidly adapting pulmonary receptors (RARs)	Larynx, trachea/ bronchi [47]	Cigarette smoke, acrolein, ozone [42–44]	Cough, bronchoconstriction, mucus secretion, lung inflation, deflation, congestion of pulmonary vascular bed, prolonged inspiration [34, 37, 38, 48, 50]
Slowly adapting pulmonary receptors (SARs)	Trachea/ bronchi, visceral pleurae [34]	Lung inflation [34]	Changes heart rate and cardiac output [55–58]
Baroreceptors	Carotid sinus, aortic arch [59]	PM [67–69, 73], cigarette smoke [76], concentrated ambient particles [78]	Increased diastolic blood pressure [74], reduced HRV [74], increased sympathetic nerve activity [81], decreased baroreflex sensitivity [72, 75]
Chemoreceptors–carotid body	Bifurcation of carotid artery [87]	PM [91–94], acrolein [99]	Increased likelihood of arrhythmias [98], increased systolic, diastolic, and mean arterial blood pressure [99]

pollution-induced effects is the activation of pulmonary neural reflexes.

Airway Receptors

The respiratory system is innervated with multiple vagal sensory nerve types to "sense" the presence of various environmental irritants as well as stretch receptors that respond to changes in lung inflation (Table 1). The cell bodies of the sensory nerve fibers are located in the jugular and nodose ganglia; upon activation, these fibers send afferent signals to the nucleus tractus solitarius (NTS) in the brainstem, which initiates both higher central nervous system signals and an efferent flow of information via the autonomic nerves (Fig. 1) [32]. There are three major types of receptors by which the sensory nerve fibers are characterized in the airways: C-nerve fibers, rapidly adapting pulmonary receptors (RARs or irritant receptors), and slowly adapting pulmonary receptors (SARs or stretch receptors) [33]. The receptor types have overlapping locations in the airways and are designed to respond to different stimuli (Table 1).

C-nerve fibers exist throughout the respiratory tract including the nose, larynx, trachea/bronchi, and alveoli [34]. These unmyelinated afferent fibers are activated by environmental pollutants and initiate chemoreflex responses that result in cough, bronchoconstriction, and dyspnea through both local and central pathways [35]. C-nerve fiber activation causes local responses with the release of Substance P as well as reflex bronchospasm and mucus secretion, and centrally mediated responses that trigger apnea followed by rapid shallow breathing [36]. A type of C fiber receptor known as juxtapulmonary capillary receptors (J receptors) have also been shown to be sensitive to lung inflation and will cause apnea if severely stimulated [37, 38]. Acrolein [39], cigarette smoke [40], and SO_2 [41] potentiate C-nerve fiber airway chemoreflex responsiveness and result in prolonged apnea and increased bronchoconstriction. Some of these responses may be further augmented due to increased neuropeptide release and initiation of neuroinflammatory mechanisms as in the case of cigarette smoke exposure [41].

In recent years, increased attention has been paid to the direct targets of air pollutants, particularly the gaseous irritants. Bautista et al. [42] initially showed that the transient receptor potential ankyrin 1 (TRPA1) cation channel mediated the activation of C-nerve fiber by pungent substances like garlic and mustard oil, but also ubiquitous air pollutants like acrolein. Ozone was also found to stimulate C-nerve fibers through TRPA1 [43]. It is now quite clear that nasal, bronchial, and pulmonary C-nerve fiber subtypes play a role in the response to certain air pollution components through the activation of not only TRPA1 [43], but also transient receptor potential vanilloid 1 (TRPV1) [44], and purinergic P2X channels [45]; these receptors act like innate environmental sensors and initiate sensory nerve excitation.

C-nerve fiber activation often coincides with RAR activation [46], as the two sensory receptors have been shown to respond to similar irritants. RARs are myelinated fibers located in the larynx, trachea, and bronchi [47].

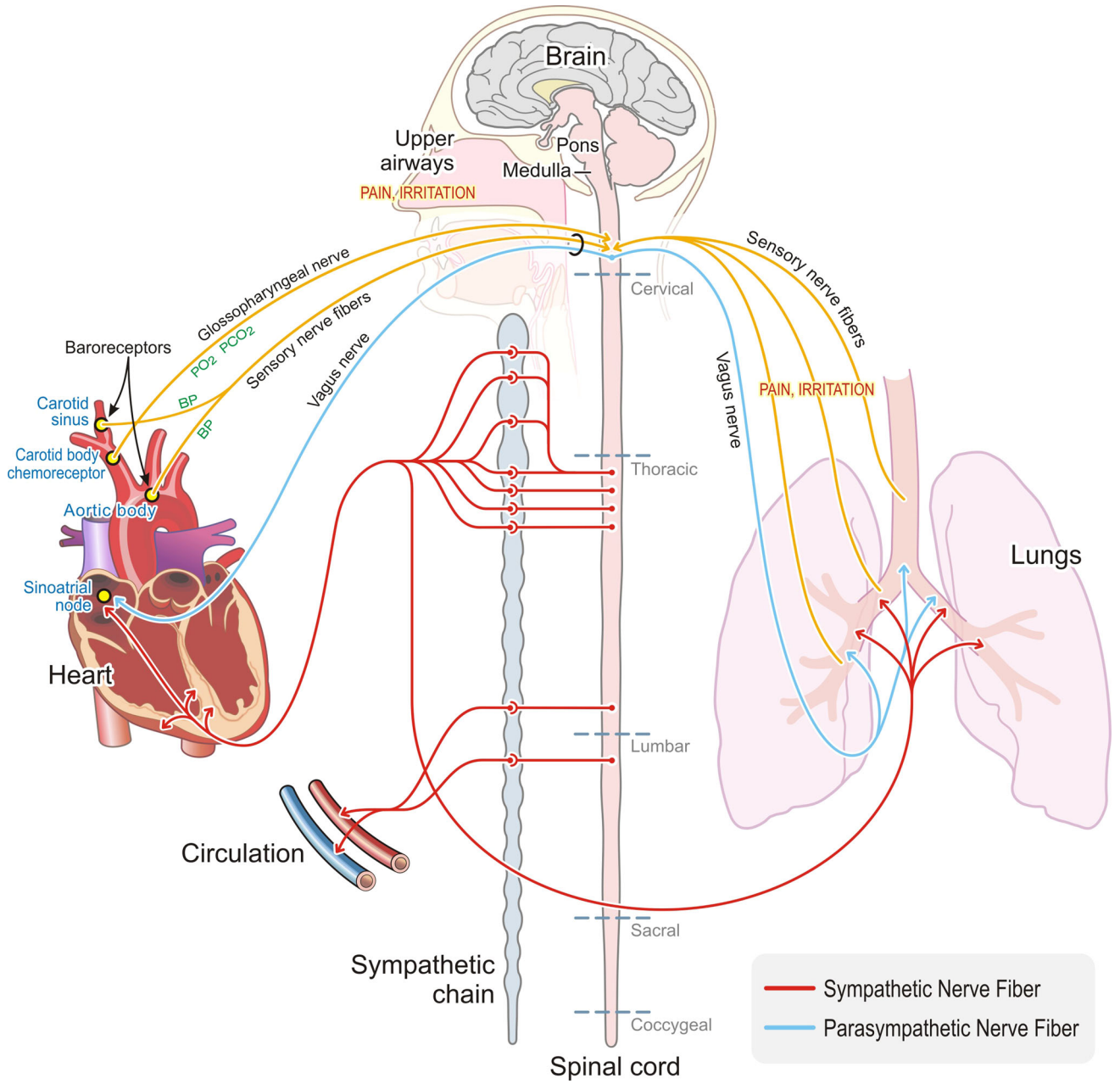

Fig. 1 Airway, baroreceptor, and chemoreceptor responses in the body. Multiple autonomic and neural pathways control the body's response to stimuli, including air pollution. The ANS is composed of the sympathetic and parasympathetic branches that innervate the major organs of the body including the heart and lungs. The sympathetic nervous system communicates through sympathetic nerve fibers (shown in *red*) and is responsible for the "fight or flight" response while the parasympathetic nervous system communicates through the vagus nerve (shown in *blue*) and is crucial in homeostatic control and regulation. The ANS communicates with the lungs through multiple efferent pathways while signals from the lung are then transmitted back to the brain through sensory nerve fibers (shown in *yellow*). The ANS also innervates the heart, and signals from the heart are transmitted back to the brain through sensory organs including the baroreceptors and carotid body chemoreceptors via sensory nerve fibers, specifically the afferent fibers of the glossopharyngeal nerve in the case of the carotid body (shown in *yellow*). The ANS is a complex system with multi-organ control, and exposure to air pollution can trigger responses through multiple levels of neural communication including pulmonary nerve fibers, baroreceptors, and the carotid body (Color figure online)

Similar to C-nerve fibers, activation of RARs leads to bronchoconstriction, cough, and increased mucus secretion [48]. However, RARs respond to both mechanical and chemical irritation depending on the location of the receptor and have an additive effect on the pulmonary reflex response when stimulated simultaneously with

C-nerve fibers [49]. Although RAR and C-nerve fiber activation are similar in many respects, including their responses to air pollution, C-nerve fiber activation causes apnea and then recovery through rapid shallow breathing, while RAR activation more commonly causes cough and augmented breathing [34]. In addition to the varied changes in tidal volume and breathing frequency, stimulation of C-nerve fibers and RARs alters cardiovascular function due to global (i.e., not restricted to the respiratory system) autonomic modulation resulting from activation of the pulmonary chemoreflex. Inhalation of irritants in the nose, nasopharynx, and pharynx stimulates reflex bradycardia coupled with subsequent increases or decreases in HR depending on the location of activation in the airways [34]. In the lower airways, C-nerve fibers and RARs will respond strongly to inhaled irritants and lead to pronounced bradycardia and hypotension [50]. On the other hand, airway reflexes originating in the larynx have been shown to cause cardiac arrhythmia and ST depression, a non-specific electrocardiographic change often associated with myocardial ischemia [51]. Similarly, we demonstrated that the TRPA1 channels expressed on these fibers mediate increased cardiac arrhythmogenesis one day after diesel exhaust exposure [44]. In addition, RARs respond to changes in the fluid volume of the airways and play a role in respiratory reflexes during heart failure and may contribute to increased heart failure hospitalization and mortality associated with acute exposure to air pollution [52, 53].

Only the lower airways contain stretch receptors called SARs that, unlike C-nerve fibers and RARs, are likely not as sensitive to irritants. While clear evidence links air pollution exposure to C-nerve fiber and RAR activation, SARs do not, for the most part, respond to chemical stimuli and are not major drivers of pulmonary reflex responses to air pollutants. They are, however, extremely important regulators of breathing, as they are sensitive to lung inflation [34] and have an important role in controlling changes in HR and cardiac output as well as stimulating the cough reflex [54]. SARs have been shown to be critical mediators of respiratory sinus arrhythmia (RSA) [55], a naturally occurring variation in HR where HR increases during inspiration and decreases during expiration [56]. SARs control of RSA is critical in maintaining normal functioning of the cardiovascular system since it has been shown that disordered breathing can cause life threatening ventricular arrhythmias [57], while paced breathing can actually reduce BP in hypertensive individuals through improvement of another homeostatic reflex called the baroreflex [58]. The baroreceptor reflex is another important component of autonomic regulation and overlaps with airway reflexes to induce cardiovascular responses after air pollution exposure.

Baroreceptors

The baroreceptor reflex controls BP and is critical to maintaining normal cardiovascular function and perfusion throughout the body. Baroreceptors are stretch-sensitive mechanoreceptors located in the carotid sinus and aortic arch (Fig. 1) that are innervated by the glossopharyngeal and vagus nerve, respectively; these nerves transmit afferent signals to the nucleus of the solitary tract (NTS) in the brainstem [59] (Table 1). Baroreceptor reflex function is regulated through a negative feedback mechanism characterized by opposing activation/inhibition of the parasympathetic and sympathetic branches. An increase in BP causes the baroreceptors to fire more rapidly, which results in the inhibition of the sympathetic branch and contemporaneous activation of the parasympathetic branch causing a reflex decrease in HR with an attendant decrease in systemic BP. On the other hand, decreases in systemic BP decrease baroreceptor firing, which reduces the inhibitory effect on the sympathetic branch; this results in an increase in HR and subsequently BP. Studies using isolated carotid sinuses found that a reflex increase in systemic arterial BP and HR occurred when pressure was lowered in the sinus [60]. Upon receiving input from the baroreceptors, the NTS communicates with regions of the brain controlling the ANS and leads to an inhibition of the sympathetic nervous system and an activation of the parasympathetic nervous system [61]. Because the baroreceptor reflex is crucial in day-to-day, and indeed moment-to-moment, homeostatic control [62], abnormal functioning of this reflex may significantly increase the risk of adverse cardiovascular events [63, 64]. Studies have shown that desensitization of the baroreceptor reflex contributes to the development and progression of cardiovascular diseases [65] and is believed to contribute to cardiovascular disease in rats with hypertension [66].

Multiple studies have reported significant changes in BP following air pollution exposure. In a cohort of German citizens, individuals living in close proximity to high traffic had higher arterial BP and greater prevalence of hypertension than individuals living in low traffic areas [67]. Long-term exposure to PM, SO_2, O_3, and black carbon causes increases in arterial BP and incidence of hypertension [68–71], potentially suggesting increased sympathetic tone and baroreceptor desensitization [72]. Exposure of research volunteers to concentrated ambient fine PM caused significant increases in diastolic BP in healthy adults, and this increase was coupled with decreases in HRV (increased sympathetic tone) [73]. Similarly, a controlled human exposure by Huang et al. [74] found that exposure to $PM_{2.5}$, black carbon, and NO_2 significantly decreases HRV and increases BP in patients with underlying cardiovascular disease. Air pollution-induced

increases in BP have also been coupled with baroreflex desensitization [72], showing that the baroreceptor reflex responses are likely involved during air pollution exposure. Although this study was performed in rats, the results provide key insight into the effect of air pollution on baroreflex responses.

Most studies that directly examined baroreflex sensitivity (BRS) activity following air pollution exposure point to a reduction in BRS. In humans, for example, exposure to 200 ppb SO_2 was associated with decreased BRS [75]. The national standard for SO_2 is 75 ppb for 1 h, and decreases in BRS at realistic exposure concentrations reveal the importance of measuring baroreceptor response when studying the effects of air pollutants. We previously demonstrated that whole-body exposure to acrolein causes baroreflex desensitization in both normotensive and hypertensive rats [72]. In addition, exposure to cigarette smoke in rats decreased BRS [76]. Rats instilled with carbon nanotubes, engineered nanomaterials that share many properties with the ultrafine component of air pollution, decreased arterial baroreceptor function after exposure [77]. By contrast, exposure to concentrated ambient particles (CAPs) in dogs increased arterial BP and BRS, which were reversed with alpha-adrenergic blockade [78]. These opposing findings by Bartoli et al. [78] may be due to the fact that the dogs were exposed via the trachea, bypassing irritant mechanisms of the upper airways and potentially modifying BRS responses. An additional possibility is that sympathetic activation resulted in increased HR and peripheral vascular resistance which caused increases in BP, while concurrent increases in parasympathetic tone blunted the HR response and resulted in only small HR changes [78]. These results highlight the complex nature of the autonomic response with both the sympathetic and parasympathetic branches working to regulate BP through opposing mechanisms. Low BRS has been associated with increased sympathetic modulation, including responses during intermittent hypoxia [79]. While low HRV (i.e., increased sympathetic tone) has been linked to increased cardiac morbidity and mortality, studies have shown that low BRS is an even stronger predictor [80] and may represent a shift toward sympathetic dominance [81]. Thus, cardiovascular effects of air pollution may in part be mediated by BRS-driven changes in autonomic tone. The precise cause of BRS desensitization related to air pollution exposure is uncertain although evidence suggests that factors associated with endothelium and endothelial dysfunction play a role. For instance, air pollution exposure alters prostacyclins, nitric oxide (NO), and factors released from aggregating platelets. Each of these factors is known to modulate baroreceptor nerve activity [82–84]. Even reactive oxygen species (ROS), which are increased in macrophages after acrolein exposure [85], can blunt baroreflex responses [86].

Chemoreceptors

There are two categories of chemoreceptors: (1) central chemoreceptors located in the brainstem and (2) peripheral chemoreceptors located in the aortic and carotid bodies [87] (Table 1). In mammals, the response to changes in oxygen, carbon dioxide, pH, and temperature is controlled by the carotid body, a major sensory organ located at the bifurcation of the carotid artery (Fig. 1). Activation of the carotid body initiates reflex cardiopulmonary changes that serve to maintain homeostasis. In response to hypoxia, for example, the carotid body triggers increases in sympathetic tone that result in elevations in BP and HR, as well as increased ventilation [88–90]. Such shifts in autonomic tone may be detrimental if they persist given that increased sympathetic tone is associated with elevated cardiovascular risk, which includes increased mortality rate in people with heart disease [16]. However, increased sympathetic modulation has been reported with PM and ozone exposure [1]; whether it occurs due to chemoreflex activation remains to be determined. Parallels between carotid body-mediated effects and cardiovascular responses associated with air pollution exposure suggest a linkage is plausible.

Although it is known that the carotid body is a key component of cardiovascular reflex responses, there is relatively little evidence linking carotid body activation with air pollution exposure. While the effects were small, several studies have reported changes in oxygen saturation, an important parameter of carotid body sensing, with exposure to air pollution including older individuals with cardiopulmonary disease [91], 80-year-old males [92], healthy adults with long-term traffic exposure [93], and healthy elderly volunteers [94, 95]. Furthermore, exposures to environmental tobacco smoke [96], SO_2, and NO_2 [97] were linked to abnormal cardiopulmonary sensitivity responses to hypoxia, indicating modified activity of the carotid body. In heart failure mice, Wang et al. [98] recently found that cardiac arrhythmias associated with exposure to particulate matter were in part due to altered sensitivity of the carotid body. In addition, our laboratory found that pretreatment with an inhibitor of carotid body signal transduction in rats prevented several adverse cardiovascular responses associated with acrolein exposure (i.e., increased systolic, diastolic, and mean arterial BP during exposure, and decreased cardiac contractility 1 day after exposure). In the same study, we found that acrolein exposure caused significant decreases in pO_2 and significant increases in pCO_2 during exposure, suggesting that carotid body activation may have been triggered by hypercapnia and/or hypoxia [99]. While we did not perform direct measurements of carotid body activation during acrolein exposure, changes in the concentrations of pO_2 and pCO_2 are known to activate carotid body signaling.

Importantly these responses appeared to be mediated by carotid body-triggered changes in autonomic tone, suggesting that this may be a potential mechanism for the cardiovascular effects of air pollution.

Integration of Reflex Responses and Conclusions

While evidence exists that exposure to air pollution is associated with the activation of each of these autonomic reflex arcs in cardiovascular effects, in reality, these responses do not function independently and are highly integrated (Fig. 1). A striking example of the degree of interconnectedness between the reflex responses can be seen in the hypoxia ventilatory response (HVR) in obstructive sleep apnea. In OSA, obstruction of the upper airway during sleep causes both hypoxia and hypercapnia, which stimulate the carotid body chemoreceptors. This causes a reflex increase in ventilation, sympathetic tone, and arterial BP. The stimulation of these pathways is accompanied by both chemoreceptor and pulmonary mechanoreceptor activation, restoring normal ventilation, often causing individuals to awake from sleep [100]. In addition to immediate reflex responses, approximately half of all people who suffer from OSA will develop systemic hypertension, while others develop pulmonary hypertension affecting cardiac output [101], with potential alteration of BRS. The HVR shows that the reflex pathways are not only involved in exposure situations but also influence responses in multiple target locations.

Moreover, activation of the chemoreflex response has been shown to cause a resetting of the baseline function of the baroreflex [102], further displaying the interaction between reflex responses after stimulation. Exposure to hypoxia causes increases in HR and sympathetic nerve activity [103], and these changes are accompanied by baroreflex resetting to higher pressures and higher HRs [104]. These effects were largely independent of breathing changes and tidal volume and were instead attributed to peripheral chemoreceptor activation [102]. While breathing changes were not responsible for baroreflex resetting, exposure to hypoxia caused a rapid increase in ventilation [89], further displaying the interaction between the various reflexes responses. Moreover, pulmonary, baro-, and chemoreflexes have extensive influence over the ANS as well as overlapping pathways in the brainstem, making interaction and integration between the system not only plausible but highly likely [102]. Thus, as future research better defines the roles of unique reflex responses in modulating autonomic control of the heart, the constant interplay among pulmonary, baroreceptor, and chemoreceptor responses together likely determines the overall physiological response to an inhaled air pollutant.

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