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Stretching the stress boundary: Linking air pollution health effects to a neurohormonal stress response☆,☆☆

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ABSTRACT

Inhaled pollutants produce effects in virtually all organ systems in our body and have been linked to chronic diseases including hypertension, atherosclerosis, Alzheimer's and diabetes. A neurohormonal stress response (referred to here as a systemic response produced by activation of the sympathetic nervous system and hypothalamus–pituitary–adrenal (HPA)-axis) has been implicated in a variety of psychological and physical stresses, which involves immune and metabolic homeostatic mechanisms affecting all organs in the body. In this review, we provide new evidence for the involvement of this well-characterized neurohormonal stress response in mediating systemic and pulmonary effects of a prototypic air pollutant — ozone. A plethora of systemic metabolic and immune effects are induced in animals exposed to inhaled pollutants, which could result from increased circulating stress hormones. The release of adrenal-derived stress hormones in response to ozone exposure not only mediates systemic immune and metabolic responses, but by doing so, also modulates pulmonary injury and inflammation. With recurring pollutant exposures, these effects can contribute to multi-organ chronic conditions associated with air pollution. This review will cover, 1) the potential mechanisms by which air pollutants can initiate the relay of signals from respiratory tract to brain through trigeminal and vagus nerves, and activate stress responsive regions including hypothalamus; and 2) the contribution of sympathetic and HPA-axis activation in mediating systemic homeostatic metabolic and immune effects of ozone in various organs. The potential contribution of chronic environmental stress in cardiovascular, neurological, reproductive and metabolic diseases, and the knowledge gaps are also discussed. This article is part of a Special Issue entitled Air Pollution , edited by Wenjun Ding, Andy Ghio and Weidong Wu.

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1. Introduction: air pollution and extrapulmonary health effects

The field of air pollution health effects has expanded in recent years as reports have emerged indicating effects in virtually all organ systems and association of air pollution with many chronic diseases. Prior to the 1990s, most air pollution studies centered on the respiratory effects. The primary focus was air pollutants in occupational settings. Unique occupational exposures that led to pollutant-specific respiratory diseases, such as asbestosis, coal miner's disease, metal fume fever, pneumonitis, silicosis, foundry workers pulmonary disease, and lung diseases linked to cigarette smoke, dominated the field as high level exposures to these pollutants produced profound respiratory effects while extrapulmonary effects remained unnoticed. The establishment of the Clean Air Act in 1970 generated interest in examining how ambient pollution can affect health. Numerous epidemiological studies have emerged associating air pollution from anthropogenic and natural sources to not only pulmonary effects but also cardiovascular diseases [1–5]. This recognition generated interest in the mechanisms by which pollutants encountered by the lung may affect the organs distant from lung.

In the past decade, it has become increasingly apparent that air pollution effects are not restricted to the cardiopulmonary system, rather various organs can be impacted. Organs affected by inhaled pollutants include the lung [6], brain [7], heart and vasculature [8–10], liver [11], kidneys [12,13], and gonads [14]. Effects on bone marrow have also been noted after exposure to particulate matter [15–17]. Likewise, air pollution has been linked to chronic disease conditions, including hypertension [18], ischemic heart diseases [19,20], steatohepatitis

Abbreviations: ACTH, adrenocorticotropic hormone; CGRP, calcitonin gene-related peptide; CNS, central nervous system; CRH, corticotropic releasing hormone; HPA, hypothalamus–pituitary–adrenal; LPS, lipopolysaccharide; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus; RARS, rapidly adapting receptors; SARS, slowly adapting receptors; TRP, transient receptor potential cation channel; TRPA1, transient receptor potential cation channel, subfamily A, member 1; TRPV1, transient receptor potential cation channel, subfamily V, member 1 (capsaicin receptor or vanilloid receptor).

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[21], central nervous system disorders, such as autism spectrum-disorder, and neurodegenerative diseases [22], diabetes [23] and poor reproductive and developmental outcomes [24]. More recently, air pollution has also been shown to affect developmental programming [25], however, the mechanisms remain poorly understood. Although air pollutants exist as a mixture of many components, which will have distinct mechanisms at the molecular and cellular level, this review will not focus on components and component specific mechanisms, or address systemic translocation of particles or soluble components. This review instead will highlight new evidence that provides a novel, and likely a common, mechanism involving activation of a neurohormonal stress response and subsequent extrapulmonary, and even pulmonary, health effects of inhaled pollutants (Fig. 1). The neurohormonal stress response in the context of this paper is referred to as a systemic response produced by the activation of central hypothalamic stress responsive regions and resulting stimulation of sympathetic nervous system and hypothalamus–pituitary–adrenal (HPA)-axis.

2. Neurohormonal stress response

The activation of HPA and sympathetic nervous system after psychological or physical stress and mediation of flight-or-fight response involving homeostatic derangement have been very well characterized for decades [26,27]. Although the question as to how different stressors might mediate this response by involvement of distinct brain areas remains an active area of research, it is well established that metabolism and immune response, two fundamental and well conserved survival mechanisms, are activated in orchestrating the homeostatic derangement. A variety of physical stressors, such as confinement, fear, organ specific injury, infection, burn-related injuries or site-specific inflammatory activation, have been shown to induce the HPA-mediated hormonal stress response and changes to metabolism and immune function.

The hormonal stress response begins with a stress being sensed by the central nervous system (CNS) leading to the stimulation of hypothalamus and amygdala leading to activation of the efferent arms of the sympathetic and parasympathetic nervous systems to mediate HPA-axis activation [28,29]. First, the stimulated efferent arm of sympathetic nerves innervating the adrenal medulla activates the synthesis and release of catecholamines, including epinephrine (adrenalin) and nor-epinephrine (nor-adrenalin), which is responsible for initiating a fight-or-fight response involving major peripheral metabolic and cardiovascular activation. Although epinephrine is primarily made and released from adrenal medulla, nearly 80% of norepinephrine is released upon sympathetic activation at the nerve endings in various organs producing local effects [30]. The follow-up event that occurs after receiving a stress signal to the hypothalamus is the local release of corticotrophin releasing hormone (CRH), which activates the pituitary gland to release adrenocorticotropic hormone (ACTH) in the circulation. ACTH subsequently activates the adrenal cortex to produce and release glucocorticoid and mineralocorticoid hormones. The corticosteroid hormones mediate a slower homeostatic response to stress, involving some of the similar but longer actions by binding to their respective receptors, which have a dynamic tissue distribution. CNS feedback control of these stress hormones maintains the longevity of changes such that reestablishment of homeostasis is assured after a stress situation. The parasympathetic arm of the autonomic system is also activated to counter the effects of sympathetic activation.

The activation of sympathetic system and HPA-axis leads to release of catecholamines and glucocorticoids [31,32]. The adrenergic and glucocorticoid receptors, once activated by respective stress hormones, play a central role in mediating systemic innate immune and metabolic changes in dynamic manner, such that the energy source and immune cells mobilized from their depots are directed to the affected tissues to combat injury or danger signals such as tissue damage, burn, or infection, and reestablish normal homeostasis. This paradigm of CNS-mediated stress response is modulated by age, sex, diet and environmental factors [33–36]. The stress response mechanisms are conserved throughout the animal kingdom from molecular to whole organism levels [37,38].

Although exposure to air pollution has been linked to effects in many different organs, this stress response has not been widely implicated in systemic effects. Our recent studies provide new evidence to support the role of hormonal stress response in ozone and acrolein effects in the lung and extrapulmonary organs [39,40]. These studies support

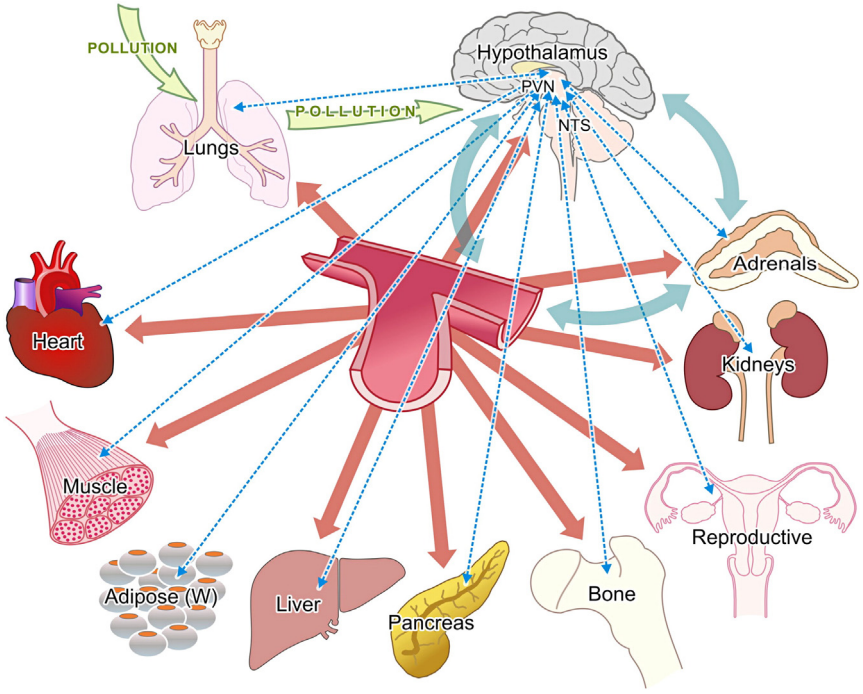

Fig. 1. Schematic showing effects of the activation of sympathetic and hypothalamus-pituitary-adrenal axis on virtually all peripheral organs. Dotted arrows indicate likely direct sympathetic effect. Solid unidirectional arrows indicate stress hormone-mediated regulation of metabolic and immune processes in different organs. Double directional curved arrows indicate how stress hormones mediate feedback inhibition on the brain. NTS, nucleus tractus solitarius; PVN, paraventricular nucleus.

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