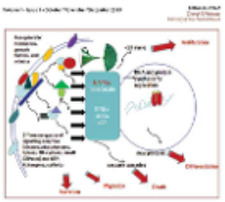
Endocrine Disruptors



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ISSN: (Print) 2327-3747 (Online) Journal homepage: informahealthcare.com/journals/kend20

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To cite this article: Errol M Thomson (2013) Neurobehavioral and metabolic impacts of inhaled pollutants, Endocrine Disruptors, 1:1, e27489, DOI: 10.4161/endo.27489

To link to this article: https://doi.org/10.4161/endo.27489

Endocrine Disruptors 1, e27489; 2013; © 2013 Landes Bioscience

Neurobehavioral and metabolic impacts of inhaled pollutants

A role for the hypothalamic-pituitary-adrenal axis?

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In addition to established effects on cardiovascular and respiratory systems, recent epidemiological studies show associations between air pollutants and impacts on the central nervous system such as depression and impaired cognitive ability, and on disease states associated with dysfunctional metabolism such as metabolic syndrome and type II diabetes. Although the relative risk attributed to air pollutants is small compared with established risk factors, the widespread exposure of the population translates into a substantial societal health burden. Controlled experimental studies support the notion that these associations have a biological basis. Recently, we reported that short-term exposure of rats to two pollutants associated with adverse health effects, particulate matter and ozone, activated the hypothalamic-pituitary-adrenal (HPA) stress response axis, resulting in increased circulating levels of the glucocorticoid corticosterone and systemic impacts on a variety of biological pathways. While effects were transient after a single exposure in this healthy animal model, chronic activation and dysfunction of the HPA axis is associated with adverse neurobehavioral, metabolic, cardiovascular, immune, reproductive, and developmental effects. Here I build upon the ideas presented in the original paper to discuss the potential role that activation and dysfunction of the stress axis, a common feature of neurobehavioral and metabolic disorders, may play in mediating adverse health effects associated with air pollution.

Keywords: air pollution, ozone, particulate matter, stress, hypothalamic-pituitary-adrenal axis, metabolic, neurobehavioural, glucocorticoid

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Submitted: 11/27/2013

Revised: 12/10/2013

Accepted: 12/10/2013

http://dx.doi.org/10.4161/endo.27489

Introduction

Air pollution is a complex mixture of gases and particulates that varies geographically and temporally. Despite this heterogeneity, epidemiological studies conducted worldwide over the past 20 or so years have shown small but significant associations between air pollution levels and respiratory and cardiovascular morbidity and mortality.[1-3] Recently, a number of epidemiological studies have found associations between air pollutants and health outcomes beyond the lungs and heart, including effects on the brain and metabolism. Neurological and neurobehavioral disorders associated with air pollution include headache,[4] cognitive decline,[5-8] Alzheimer disease,[9] hyperactivity,[10] depression,[11,12] and suicide.[13,14] Metabolic disorders associated with air pollution include type II diabetes[15] and the cluster of cardiometabolic abnormalities that make up metabolic syndrome.[16] Levels of polycyclic aromatic hydrocarbons in air pollution experienced by pregnant women are associated with childhood obesity[17] and anxiety,[18] indicating that impacts on metabolic and neurobehavioral disorders may begin in the prenatal period and extend to later life. Given the global prevalence of neurological and metabolic disorders,[19,20] and the near ubiquitous exposure of the population to air pollutants, even a modest air pollution-induced increase in the incidence of these diseases has significant implications for public health.

Neurological and metabolic effects: Underlying mechanisms

Animal studies in general support the notion of a causal link between exposure

to inhaled pollutants and extracardiopulmonary effects such as neurological and metabolic disorders,[21,22] but the biological mechanisms underlying these effects are less clear. Long-term exposure to high pollution levels is associated with impacts on neurodegenerative disease pathways, spatial learning, and behavioral deficits.[22] Exposure of 4-wk-old mice for 10 mo to concentrated fine particulate matter (mean aerodynamic diameter less than 2.5 μm) produced a phenotype with characteristics of depression, an effect accompanied by inflammation in the hippocampus.[23] Nanoparticles can translocate to the brain via olfactory neurons,[24] revealing one possible route of exposure for effects on the central nervous system. On the other hand, impacts on the central nervous system can arise also by indirect processes. For example, both acute and chronic exposure of adult rats to ozone, a reactive gas entirely consumed within the lungs, produces morphological changes to neurons and memory deficiency concurrent with increased oxidative stress.[25]

Metabolic effects of pollutant exposure have also been studied, particularly in the context of the pathogenesis of cardiovascular disease. Systemic inflammation and oxidative stress have long been postulated to be important drivers of cardiovascular effects of pollutant inhalation. Adult mice fed a high-fat diet and exposed for 24 wk to concentrated ambient particles displayed increased systemic and cellular inflammatory responses, insulin resistance, and visceral fat.[26] Treatment with statins was shown to abrogate circulating cytokine levels and reduce the progression of atherosclerosis in 12-wk-old rabbits exposed repeatedly by intratracheal instillation to particulate matter.[27] In an elderly cohort study in Taiwan, 1 y averages of particulate matter and ozone were independently associated with increased blood glucose, lipids, interleukin-6, and blood pressure, consistent with an impact of long-term exposure on metabolic, inflammatory, and cardiovascular endpoints.[28] A recent report[29] has also shown a relationship between short-term variation in ambient particulate pollution and insulin sensitivity in healthy adult subjects. This effect appeared unrelated to changes in the levels of inflammatory markers or vascular function, suggesting that effects other than increased systemic inflammation may be driving metabolic effects detected after sub-acute exposure in humans.[29]

Short-term pollution exposure and the HPA axis

To gain insight into biological mechanisms underlying extrapulmonary effects attributed to air pollution, we recently conducted a study[30] in which systemic changes in gene expression were evaluated after short-term exposure of adult male Fischer-344 rats to particulate matter and ozone. Rather than basing our analyses on a priori assumptions of the relative importance of any pathway or effect, we reasoned that a screening approach could be used to monitor systemic effects of pollutant exposure, with the pattern of effects then used to identify potential mediators. Genes involved in inflammation, xenobiotic metabolism, antioxidant-response, metal-response, and endothelial dysfunction, among others, were assessed in the lungs, heart, liver, kidney, spleen, brain, and pituitary, and the patterns of response were compared for each pollutant, organ, and time-point. Inhalation of either particles or ozone rapidly activated transcriptional pathways in all organs immediately after the 4 h exposure, with the majority of responses returning to control levels after 24 h recovery of the animals in filtered air. Despite certain organ-specific effects, a similar pattern of responses was observed for a subset of genes across all organs. Genes exhibiting similar responses to pollutant exposure in multiple organs included increased expression of metallothioneins, which in addition to scavenging metals and reactive oxygen species are responsive to glucocorticoids, and decreased expression of several inflammatory genes, a hallmark of glucocorticoid action. We measured plasma levels of adrenocorticotropic hormone and corticosterone and found both to be increased immediately after pollutant inhalation, returning to control levels after 24 h. Expression of known glucocorticoid-responsive genes was transiently increased in most organs, consistent with glucocorticoid activity. Together, the data indicate that acute exposure to both gaseous and particulate pollutants can rapidly activate the HPA axis, increasing circulating corticosterone levels concurrent with systemic changes in gene expression.

A role for HPA axis dysfunction in the adverse health impacts of air pollution?

The HPA axis is part of the stress response system of the body. Along with the sympathetic nervous system, it plays an essential role in the response to stress, and protects the host from deleterious effects of a sustained inflammatory immune response. As the effectors of the HPA axis, glucocorticoids (cortisol in humans, corticosterone in rodents) regulate a variety of processes, including glucose metabolism, immune response, adipocyte differentiation, and the action of other hormones.[31] They also exert profound effects on the central nervous system, contributing to the regulation of cognition, memory, mood, and sleep. Activation of the HPA axis is linked with a sympathetic nervous system response and with increased metabolism of serotonin, both of which also impact neurobehavioral and metabolic function.[32] A well-functioning HPA axis responds quickly but transiently when stimulated, with the magnitude and duration of the response critical to determining an adaptive or adverse effect.[33] In our study, the effect of a single brief exposure to air pollutants on corticosterone and most other endpoints was transient, consistent with an adaptive response in this healthy rat model.[30] Repeated or chronic stress, however, can lead to dysregulation of the HPA axis, hypercortisolemia, glucocorticoid resistance, and poor control of immune and inflammatory responses, and is associated with neurobehavioral, metabolic, immune, cardiovascular, and reproductive disease processes.[31,34] Effects of chronically elevated glucocorticoid levels, such as are observed in Cushing's syndrome, include obesity, hypertension, depression, hyperglycemia, impaired immune function, and osteoporosis.[33,35,36] In rats, repeated exposure to corticosterone is used to generate a model of depression,[37] and in conjunction with a high-fat diet a model of metabolic syndrome or type II diabetes,[38] establishing causal relationships of glucocorticoids with neurobehavioral and metabolic disorders.

Although there has been relatively little study of endocrine disruption by air pollution, constituents such as polycyclic aromatic hydrocarbons, polybrominated

diphenyl ethers, polychlorinated biphenyls, pesticides, phthalates, and heavy metals have been shown to interfere with endocrine functions.[39,40] There is considerable overlap between disorders associated with stress axis dysfunction and those associated with air pollution. For example, depression and suicide, both characterized by HPA axis disturbance,[32] are associated with short-term variation in pollutant levels.[11-14] Metabolic syndrome and type II diabetes, characterized by metabolic abnormalities common to Cushing's syndrome and thought to be mediated at least in part by glucocorticoid action,[34] are associated with long-term exposure to air pollution,[15,16] while increased blood glucose and insulin resistance are associated with short-term variation in pollutants levels.[29] Prenatal stress and elevated glucocorticoid levels are implicated in low birth weight and later development of metabolic and cardiovascular diseases,[41] and there is evidence of pollutant impacts on birth weight and development.[17,18,42] It is not known to what extent the HPA axis is involved in mediating pollutant effects. Although much of the research investigating mechanisms underlying extrapulmonary impacts of pollutants has focused on inflammatory pathways,[21,22,43] there is some evidence of a stress response to pollutant inhalation. Short-term exposure to 500 μg/m^3 fine particulate matter increased corticosterone levels in adult ovalbumin-sensitized Brown-Norway rats and saline controls, and increased norepinephrine levels in the paraventricular nucleus of the hypothalamus and the olfactory bulb.[44] Seven-week-old female Wistar rats exposed repeatedly to ozone (0.12 ppm, 6 h/day for 15 d) displayed increased corticosterone and behavioral changes including greater inactivity and decreased rearing.[45] Effects of ozone on behavior were similar during the first day of the protocol, albeit somewhat less pronounced, indicating a rapid response from even a single exposure. Short-term exposure of 6-wk-old male Wistar rats to ozone produced a pattern of neuronal activation that suggested a reflexive response to systemic stress.[46] A recent study in young and aged Brown Norway rats found that a 6 h exposure to ozone increased circulating epinephrine and impaired glucose tolerance.[47] These data in experimental models are consistent with an overall stress response that encompasses HPA axis and sympathetic nervous system activation. Given the interrelationships among pathways, these effects also imply impacts on acute phase and inflammatory responses.

Interdependent mechanisms underlying neuroendocrine, metabolic, and cardiovascular disorders: Relevance to effects of air pollutants

The breadth of health effects now associated with air pollution suggests the involvement of complex, multifactorial processes. System-wide approaches and transdisciplinary research may be needed to better understand the role played by air pollution in initiating or accelerating disease progression in the context of interrelated disease states and interactions with environment- and host-dependent factors that contribute to susceptibility. For example, exposure to chronic societal stressors, such as violence and poverty, may predispose individuals to the adverse effects of air pollution.[48] Depression is a common co-morbidity of metabolic syndrome, diabetes, obesity, atherosclerosis, and cardiovascular disease,[49,50] and there is a literature supporting a link between diseases of the central nervous system and peripheral diseases with a metabolic basis.[31,51] Dysfunction of several biological processes, notably inflammatory, endocrine, and metabolic, are common to these pathologies. In our study, increased corticosterone was measured immediately after the 4 h exposure,[30] indicating a rapid response, but it may nevertheless have been preceded, accompanied, or followed by sympathetic nervous system activation, an acute phase response, and an increase in circulating cytokines. For example, ozone-induced elevation of plasma epinephrine and reduced glucose tolerance were shown to precede an increase in circulating cytokines and acute phase proteins.[47] Our results should be interpreted with caution; it remains to be seen whether these transient effects, likely arising as part of a normal stress response, can with repeated exposure initiate or accelerate disease progression in healthy or susceptible animal models. Moreover, further research is needed to understand how interdependent processes such as oxidative stress, inflammatory, autonomic, and endocrine responses are involved in disease pathogenesis, and to what extent these effects observed in experimental animals model processes in humans.

Conclusion

The rising incidence of chronic cardiovascular, neurological, and metabolic disorders coincides with rapid changes to diet, lifestyle, and the environment. These diseases share a number of common underlying processes, including dysfunction of endocrine, inflammatory, and metabolic systems. Twenty years ago, McEwen and Stellar proposed the term "allostatic load" to describe how activation of the stress system, an adaptive response critical to managing acute threats and maintaining homeostasis, can with repeated or chronic stress accelerate disease processes.[52] Viewed in this light, relatively rapid effects of short-term exposure to pollutants, such as increased corticosterone[30] or possibly transient insulin resistance[29] may represent early adaptive responses in healthy subjects to short-term variation in pollutant levels. Repeated or chronic exposure, possibly in conjunction with other stressors (e.g., diet, noise, economic and societal burdens) and susceptibility factors (e.g., genetic polymorphisms, age, disease), could however lead to hyperactivation and dysfunction of the stress axis, resulting in increased probability of developing stress-related disorders such as depression, cognitive impairment, metabolic syndrome, obesity, type II diabetes, atherosclerosis, cardiovascular disease, immune dysfunction, and osteoporosis. Events and exposures during vulnerable windows of development can have profound and lasting impacts, as has been demonstrated in the programming of stress responses through epigenetic mechanisms.[53] Such processes may be relevant to early life effects of air pollutant exposure.[17,18,42] Given the considerable overlap between conditions arising from HPA axis dysfunction and those associated with air pollution, the relationship between stress axis regulation and adverse health effects of air pollutants warrants further study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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