Prenatal Pollutant Exposures and Hypothalamic Development: Early Life Disruption of Metabolic Programming

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Environmental contaminants in ambient air pollution pose a serious risk to long-term metabolic health. Strong evidence shows that prenatal exposure to pollutants can significantly increase the risk of Type II Diabetes (T2DM) in children and all ethnicities, even without the prevalence of obesity. The central nervous system (CNS) is critical in regulating whole-body metabolism. Within the CNS, the hypothalamus lies at the intersection of the neuroendocrine and autonomic systems and is primarily responsible for the regulation of energy homeostasis and satiety signals. The hypothalamus is particularly sensitive to insults during early neurodevelopmental periods and may be susceptible to alterations in the formation of neural metabolic circuitry. Although the precise molecular mechanism is not yet defined, alterations in hypothalamic developmental circuits may represent a leading cause of impaired metabolic programming. In this review, we present the current knowledge on the links between prenatal pollutant exposure and the hypothalamic programming of metabolism.

Keywords: prenatal environmental exposures, air pollution, hypothalamic development, neuroinflammation, metabolic programming, metabolic syndrome, diabetes

INTRODUCTION

Air pollution is one of the leading environmental concerns and poses a significant risk to the health of people around the world, despite advancements in medicine and technology. According to the World Health Organization, around 7 million deaths were prematurely caused by air pollution per year, including both ambient outdoor pollution and household pollution (1, 2). Of those deaths in 2016, the majority (4.2 million) were caused by outdoor air pollution including particulate matter (PM) (3, 4), ozone, nitrogen and sulfur dioxide, and carbon monoxide (5). Exposures to air pollution during early life and adulthood have been shown to propagate adverse health effects (6–13). Still, less is known about the impact of early-life exposures during gestation and the neonatal period on metabolic syndrome (14). A growing body of literature suggests that environmental contaminants can predispose to metabolic syndrome and disease, which have steadily increased in recent decades and are projected to continue rising (8, 15–20). While an exact mechanism linking pollutant exposures with metabolic programming remains unclear, a combination of
factors likely determines the predisposition to impaired metabolism. Here we discuss a few of the possible routes by which air pollution could be contributing to metabolic disruption in offspring (Figure 1).

THE DEVELOPMENTAL PROGRAMMING OF THE HYPOTHALAMUS

In the CNS, the hypothalamus is the main region critical for the regulation of whole-body metabolism (21, 22). The hypothalamus is comprised of nuclei containing distinct neuronal populations that produce neuropeptides critical for the regulation of body core temperature, metabolic rate, satiety signals, sexual dimorphism and reproduction, circadian rhythm, energy homeostasis, and glucose metabolism (22–24). Recent studies in vertebrate genetic models have demonstrated that the development of hypothalamic neurocircuitry can be influenced by various nutritional and environmental cues in early life (25, 26). In humans, connectivity of a subset of these pathways occurs during gestation, while in rodents, refinement of connections occurs in early postnatal life (25). The rodent hypothalamus develops during a relatively long period, beginning early in gestation and continuing during the postnatal period (27). The developing hypothalamus is therefore exposed to two distinct environments: one in utero (around mid-gestation to birth) and the other extra utero (27–29). These developmental windows represent important intervals of vulnerability during which alterations in the maternal environment may lead to abnormal hypothalamic development and subsequent metabolic alterations.

The arcuate nucleus of the hypothalamus (ARC) contains pro-opiomelanocortin (POMC) neurons that produce the anorexigenic peptide melanocyte-stimulating hormone (MSH) and neurons that co-express the orexigenic peptides neuropeptide Y (NPY) and agouti-related protein (AgRP), which regulate food intake and energy expenditure (30–32). The POMC and NPY/AgRP neurons project to the paraventricular hypothalamic nucleus (PVN) and lateral hypothalamus (LH), as well as regions outside the hypothalamus, to regulate energy homeostasis and nutrient intake (22). Developmental abnormalities of these hypothalamic neurocircuits are associated with alterations in body weight, metabolic imbalance, chronic stress, and obesity (33). Importantly, the interaction of hypothalamic neurons with neighboring glial cells (especially astrocytes and microglia) is critical for sensing hormonal changes and various metabolites. Impairments in these interactions can have an impact on hypothalamic physiology and dysfunction in the context of systemic metabolism and metabolic disease.

GLIAL ROLE IN HYPOTHALAMIC DEVELOPMENT

Microglia, the resident parenchymal myeloid cells of the CNS, have been shown to play a vital role in hypothalamic development (34). Microglia are remarkably sensitive to external environmental stressors such as ozone, diesel exhaust, air pollution, and environmental contaminants (35–38) (39), causing them to interact with neighboring neurons and modulate inflammatory pathways (40–42). During both prenatal and postnatal development, microglia play a critical role in cross-talk between the nervous and immune systems and in many developmental processes (43). Activation of the immune

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**FIGURE 1** | Prenatal air pollution exposure induces hypothalamic and metabolic dysfunction.
system during pregnancy or early life has been shown to exert long-term effects on the wiring of neural circuits and may contribute to the etiology of neurodevelopmental and metabolic disorders (44–46). In humans, microglia colonize the developing brain between weeks 4 and 24 of gestation (47) while in rodents, it begins around embryonic day 8 (E8) (48). By birth, microglia normally transition from an amoeboid to a ramified “surveillant” state and remain this way until subjected to an immune challenge (49). Maternal exposure to persistent stressors during pregnancy can lead to maternal immune activation (MIA), forcing fetal microglia to remain activated, also known as microglial priming (50, 51). Upon subsequent immune challenges later in life, these cells can inappropriately react with excessive cytokine release as a result of immune memory (51). The early embryonic development of immune-sensing microglia potentially plays a role in the sensitivity of the developing CNS (52). The distribution and function of embryonic microglia in the developing brain was covered in detail elsewhere (53). While the role of microglia in the developmental stages of hypothalamic neurocircuits is still emerging, embryonic microglia can influence gliogenesis within the developing hypothalamus (54). Specific depletion of microglia in mice during embryonic development caused a decrease in hypothalamic POMC neurons postnatally and accelerated weight gain in early postnatal life (34), emphasizing the necessity of microglia for the development of the hypothalamic satiety signals. Hypothalamic embryonic microglia are very sensitive to insults and can coordinate innate immune response following an insult via microglial TAM receptors (55), providing additional insights into the role of microglia in hypothalamic developmental programming.

Astrocytes, the most abundant glial cell type in the brain, are largely produced during gliogenesis (53). Astrocyte development begins around E18 and lasts until roughly P7 in mice, although adult astrocytes retain the ability to divide and differentiate (53, 56). Microglia have been proposed to influence the transition from neurogenesis to astrogenesis (57). Like microglia, astrocytes significantly regulate synaptogenesis, mostly postnatally in mice, by secreting factors such as brain-derived neurotrophic factor (BDNF) and gp4 and 6 (Gpc4 and Gpc6) and through the generation of lipids (58–60). Under normal physiologic conditions, astrocytes support the nutritional needs of the neurons by producing and shuttling metabolites such as lactate and ketone bodies (61, 62). More recently, astrocytes have been proposed to help maintain the integrity of the blood-brain barrier (63, 64) and synaptic transmission between neurons through the protection of gap junctions (64). Hypothalamic astrocytes sense glucose and fatty acids and express receptors for several peripheral hormones such as leptin and insulin (65). During development, hypothalamic astrocytes express unique clusters of genes critical for growth and development (66). Microglia and astrocytes are in constant crosstalk, thereby influencing the activity of one another. Early-life microglial activation as a result of pollution exposure may thereby alter astrocyte function later in life (67), inducing the activation of astrocytes and microglia and subsequent neuroinflammation (58). Considering the critical roles microglia and astrocytes play during hypothalamic development, understanding the interaction between these cells and their responsiveness to the early-life insults, can provide insights into the pathogenesis of metabolic disease.

HYPOTHALAMIC RESPONSE TO POLLUTANTS: NEUROINFLAMMATION AND ALTERED DEVELOPMENT

A growing body of evidence now implicates that exposure to air pollutants and toxins leads to hypothalamic neuroinflammation and subsequent metabolic dysregulation (55, 68–71). For example, when pregnant mice were exposed to diesel exhaust (DE) inhalation from E9-17, the fetal brains of the offspring showed altered cytokine and chemokine levels at E18, including increased pro-inflammatory IL-6 and decreased anti-inflammatory IL-10 (71). In adulthood, DE-exposed offspring fed a high-fat diet (HFD) had increased microglial activation in several brain regions, including the hypothalamus, indicative of long-term microglial priming from the prenatal exposure (71). Additionally, DE-exposed offspring demonstrated increased weight gain, energy intake, and insulin levels, either before or after HFD feeding, with males exhibiting a more severe phenotype (71). Thus, prenatal DE exposure triggers neuroinflammatory responses during gestation that lead to microglial priming, predisposing offspring to adult diet-induced metabolic imbalance and neuroinflammation (71, 72). Similarly, male offspring of pregnant dams treated with intermittent doses of diesel exhaust particles (DEP) from E2-17 demonstrated increased expression of IL-1β in serum and brain tissue following an immune challenge with LPS (69). However, only male offspring of DEP-exposed dams exhibited exaggerated weight gain, insulin resistance, and anxiety-like behavior when challenged with HFD compared with male control offspring (69). In support, we have previously demonstrated that maternal exposure to inhaled benzene throughout pregnancy was associated with hyperglycemia, insulin resistance, reduced energy expenditure, and increased hepatic inflammation in the adult male offspring (73). Similarly, exposure to benzene in adulthood was also associated with a metabolic imbalance in male but not female mice (74).

Harmful environmental conditions can pose a serious threat to the development of hypothalamic neurocircuits (75–80). Exposing rats to various endocrine-disrupting polychlorinated biphenyls (PCBs) during gestation (77) and a subsequent postnatal immune challenge (78), alters hypothalamic neuropeptide gene expression and cytokine levels in the serum in a sexually dimorphic manner (78). During gestation, hypothalamic microglia also show strong sensitivity to exposure to the endocrine-disrupting chemical (EDC) bisphenol A (BPA). In mouse studies, offspring prenatally exposed to BPA had early hypothalamic neurogenesis (81), altered embryonic microglia (82), reduced anorexigenic hypothalamic projections, central leptin resistance, and a delayed postnatal leptin surge (79). Similarly, BPA exposure in
pregnant dams induced a significant increase in microglia numbers and the expression of inflammatory genes in the fetal hypothalamus (83). Thus, gestational BPA exposure in mice negatively impacts the development of embryonic hypothalamic microglia, associated with increased microglia numbers, expanded microglial process ramification, and increased numbers of microglial phagocytic cups (82). Studies in rats have also demonstrated the influence of exposure to toxins on postnatal hypothalamic development through lactation (84–86). A recent review presented a series of experiments where rats were exposed to a nicotine level equivalent to heavy smokers during lactation (84). Nicotine-exposed male offspring exhibited increased body weight, adiposity, insulin resistance, and central leptin resistance in adulthood (86, 87). However, the time frame and the route of exposure may differentially impact the metabolic outcomes in young animals and animals exposed to nicotine in adulthood (88). At PN180, nicotine-exposed male offspring had increased expression of α-MSH, corticotrophin-releasing hormone (CRH), and NPY along with decreased cocaine- and amphetamine-regulated transcript (CART) in the PVN (86). Additionally, nicotine-exposed offspring had increased hypothalamic microgliosis and astrogliosis (84, 89). When offspring were exposed to cigarette smoke during lactation, this resulted in impaired development of hypothalamic circuits leading to hyperphagia, obesity, and neuroinflammation in the adult offspring (85).

MECHANISMS LINKING HYPOTHALAMIC METABOLIC PROGRAMMING AND POLLUTION

How can air pollution and specific particles exert deleterious effects on the hypothalamus during development? It is becoming increasingly accepted that pollution triggers an inflammatory response in peripheral tissues that is associated with an elevation in cytokine secretion. In turn, circulating cytokines produced in systemic inflammation can enter the brain, causing neuroinflammation and neurotoxicity (90, 91).

Maternal inflammation and maternal immune activation (MIA) are known to be harmful to a developing fetus (44, 92–96). A recent study indicates that exposure of pregnant African American women to air pollution was associated with inflammation in the mothers by mid-pregnancy (97). This study focused on ambient exposure to BTEX (benzene, toluene, ethylbenzene, and xylene) and measured maternal inflammatory markers during the second trimester. A positive association was found between the levels of BTEX exposure and inflammatory cytokines IL-1β and TNF-α (97). Maternal exposure to benzene during pregnancy was found to be associated with low birth weight and head circumference (98–100). As shown in rodent models, gestational immune activation can disrupt hypothalamic neurocircuits of maternal care behavior (101), alter the hypothalamic epigenome in the offspring (102), and decrease hypothalamic dopamine neurotransmission (103). Additionally, evidence from rodents has shown that maternal inflammation can result in altered offspring metabolism, such as increased food intake, body weight, and impaired insulin sensitivity (104). Thus, it is likely that maternal exposure to pollution via alterations in hypothalamic developmental circuits may contribute to metabolic disease in the offspring.

A key factor that must be considered when determining how the maternal environment influences the offspring is the placenta. The placenta is a vital organ that acts to provide a supportive and protective environment for the developing fetus and as a point of interaction between the mother and fetus (105). However, while some molecules are not able to cross the placenta and act directly on the fetus, they can potentially exert indirect influence via inflammation or hypoxia (106). Modulation of plental function by maternal inflammation could, in turn, alter the environment of the fetus and possibly impact its development (107). A pilot study looking at the effects of household air pollution (HAP) on pregnant Nigerian women found that exposure to air pollution was associated with increased markers of chronic hypoxia in the placenta, which was implicated as a mechanism for adverse pregnancy outcomes associated with HAP (108). Conversely, molecules with the ability to cross the placenta can directly interact with the fetus and lead to adverse health effects on brain development (106). Various toxins and chemicals can cross the placenta, as indicated by measurable levels in umbilical cord serum, including multiple organohalogen compounds (OHCs) such as polybrominated diphenyl ethers (PBDEs), phencyclidine (PCP), and polychlorinated biphenyls (PCBs) (109, 110). Other chemicals with the known ability for transfer are BPAs, nicotine from tobacco smoke, phthalate monoesters, and the polycyclic aromatic hydrocarbon (PAH) benzo(a)pyrene (81, 82, 111). BPAs have been found in human placental tissue, umbilical cord blood, and fetal plasma (112–114). Volatile organic compounds (VOCs) such as benzene, ethylbenzene, xylene, carbon tetrachloride, and chloroform can also cross the placenta during pregnancy and have an impact on the developing fetus (115). Once the pollutants and particles reach the developing brain, there is considerable debate as to what are the precise mechanisms of toxicity. One potential mechanism by which gestational exposure to pollutants may cause impaired health outcomes is via neuroinflammation mediated by the activation of the brain’s innate immune system in response to an inflammatory challenge, which leads to adverse neural adaptations and neurotoxicity (40, 41, 116). Developmental abnormalities in the hypothalamus and neuroendocrine system induced by air pollution (117) and the stimulated innate immunity in the brain can provide a potential mechanistic link for peripheral chronic disease susceptibility.

Given the chronic nature of human exposure to environmental toxins over an entire lifetime, including the critical periods of hypothalamic development, this could alter later life metabolism, contributing to metabolic disease (29). Although there is a lack of information on the hypothalamic consequences of pollutant exposure in humans, epidemiological studies indicate that air pollution increases the risk of metabolic
disease, which may be worsened by poor lifestyle choices such as lack of exercise, alcohol consumption, and obesity (118). Observational studies in humans have linked exposures to various pollutants including PM 2.5 and ozone with higher rates of T2DM in populations across the globe (119–123). Healthy mothers living near busy streets at preconception had increased fasting blood glucose levels, suggesting that air pollution exposure contributes to metabolic imbalance (124). Disturbances in hypothalamic development could result in metabolic impairments, which may explain why rising cases of childhood diabetes are associated with highly polluted areas.

CONCLUSION AND FUTURE PERSPECTIVES

As the onset of metabolic disorders steadily increases in children and young adults, there is a great need to understand this etiology. Significant associations have been found between prenatal exposure to environmental pollutants and the heightened risk for metabolic impairments (69, 71, 73, 125). One potential mechanism is an increase in neuroinflammation, particularly affecting the hypothalamus. This is especially relevant considering the known neurotoxicity of air pollutants. Here, we propose a current gap highlighting the susceptibility of the hypothalamus during sensitive perinatal periods and how environmental insults may impact the hypothalamic programming of metabolism. Neuroinflammation may have a larger effect on hypothalamic development than previously thought, thus predisposing future generations to metabolic syndrome. Further research is needed to elucidate the molecular mechanisms that predispose offspring to metabolic disease. While it is clear that some particles and compounds can cross the placenta and have an impact on fetal development, the direct effect of these pollutants on hypothalamic development is unclear. Similarly, the direct or indirect impact of pollution-triggered maternal inflammation on the offspring’s metabolic health remains to be defined. While previous studies have assessed the outcomes of prenatal pollution on brain development, few have focused on the role of hypothalamic developmental circuits during fetal development on the later life metabolic outcomes. Finally, as research into prenatal pollution-induced neuroinflammation as a potential cause for metabolic dysfunction is limited, studies looking into therapeutic interventions remain scarce. Overall, significant challenges remain in understanding how pollution exposures impact fetal neurodevelopment and later life metabolism.

AUTHOR CONTRIBUTIONS

MS conceptualized the study, revised, and critically reviewed the manuscript. LK and SS drafted and revised the manuscript. GM critically reviewed the manuscript. All authors agree to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

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