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Review article

Perinatal exposure to endocrine disrupting compounds and the control of feeding behavior—An overview

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ABSTRACT

Endocrine disrupting compounds (EDC) are ubiquitous environmental contaminants that can interact with steroid and nuclear receptors or alter hormone production. Many studies have reported that perinatal exposure to EDC including bisphenol A, PCB, dioxins, and DDT disrupt energy balance, body weight, adiposity, or glucose homeostasis in rodent offspring. However, little information exists on the effects of perinatal EDC exposure on the control of feeding behaviors and meal pattern (size, frequency, duration), which may contribute to their obesogenic properties. Feeding behaviors are controlled centrally through communication between the hindbrain and hypothalamus with inputs from the emotion and reward centers of the brain and modulated by peripheral hormones like ghrelin and leptin. Discrete hypothalamic nuclei (arcuate nucleus, paraventricular nucleus, lateral and dorsomedial hypothalamus, and ventromedial nucleus) project numerous reciprocal neural connections between each other and to other brain regions including the hindbrain (nucleus tractus solitarius and parabrachial nucleus). Most studies on the effects of perinatal EDC exposure examine simple crude food intake over the course of the experiment or for a short period in adult models. In addition, these studies do not examine EDC's impacts on the feeding neurocircuitry of the hypothalamus-hindbrain, the response to peripheral hormones (leptin, ghrelin, cholecystokinin, etc.) after refeeding, or other feeding behavior paradigms. The purpose of this review is to discuss those few studies that report crude food or energy intake after perinatal EDC exposure and to explore the need for deeper investigations in the hypothalamic-hindbrain neurocircuitry and discrete feeding behaviors.

1. Introduction

The impacts of developmental endocrine disrupting compounds (EDC) exposures on energy homeostasis may be contributing to the increase in metabolic syndrome and its sequelae, type II diabetes and obesity, in children and adults. EDCs are widespread in both the work and home environment at concentrations potentially harmful to the developing fetus and neonate. EDC exert their effects by interacting with nuclear receptors including steroid receptors and xenobiotic receptors or by altering the production of steroid hormones. Exposure to EDCs such as diethylstilbestrol (DES) and bisphenol A (BPA) can lead to metabolic disruption in rodent models (Golden et al., 1998; vom Saal and Myers, 2008) and these effects are dependent on the concentration, duration, route, and developmental stage of exposure. Many studies have reported that a variety of EDCs including BPA, polychlorinated biphenyls (PCB), dioxins, and dichlorodiphenyltrichloroethane (DDT) cause disruption of energy or glucose homeostasis. These effects include elevated adult body weights, fat accumulation, triacylglycerol and cholesterol levels, and altered glucose and insulin homeostasis in both male and female adult offspring (Belcher et al., 2014; Kojima et al., 2013; La Merrill et al., 2014; Miyawaki et al., 2007; Newbold et al., 2007; Pillai et al., 2014; Rashid et al., 2013; Rubin et al., 2001; Suvorov et al., 2009; Xi et al., 2011; Xu et al., 2011). However, very few studies fully characterize the effects of perinatal EDC exposure on feeding behaviors and meal pattern (size, frequency, duration) opting instead to examine simple crude food intake over the course of the experiment or for a short period as adults.

The control of energy homeostasis and feeding behavior has been extensively reviewed (Cowley et al., 2001; Williams et al., 2001) and will be described briefly herein. Many of the central and peripheral regulators of energy homeostasis and feeding behavior are known. Food intake is controlled centrally through communication between the hindbrain and hypothalamus with inputs from the emotion and reward centers of the brain (Berthoud, 2002). The hypothalamus is regarded as the key center that regulates feeding behavior. Discrete hypothalamic nuclei project numerous reciprocal neural connections between each

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other and to other brain regions including the hindbrain. The hypothalamic nuclei involved include the arcuate nucleus (ARC), ventromedial nucleus of the hypothalamus (VMH), the dorsomedial hypothalamus (DMH), paraventricular nucleus (PVN), and lateral hypothalamus (LH) (Saper et al., 2002).

ARC neurons are in a unique position because their axonal terminals have direct contact with peripheral circulation (incomplete blood-brain barrier) and thus are accessible to peripheral satiety factors such as glucose, insulin, ghrelin, and leptin (Schwartz et al., 2000). ARC neurons integrate those peripheral signals with inputs from other brain regions regulating sensory attributes, reward expectancies, and emotional aspects of food (Cowley et al., 2001; Elmquist et al., 1999; Kalra et al., 1999; Schlingemann et al., 2003; Schwartz et al., 2000). At least two distinct ARC neuronal populations act in opposition to each other to control energy homeostasis. Neurons expressing neuropeptide Y (NPY) and agouti-related protein (AgRP) are orexigenic while neurons expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) are anorexigenic (Schwartz et al., 2000). Specifically, the posttranslational POMC product, α-melanocyte stimulating hormone (α-MSH), reduces food intake via activation of the melanocortin receptors (MC-3/4) expressed in other hypothalamic nuclei such as the PVN. NPY and AgRP also act on the same neurons to increase food intake with AgRP acting as an antagonist to melanocortin receptors, thus exerting an orexigenic influence (Saper et al., 2002).

The VMH is a satiety center of the hypothalamus (Williams et al., 2001). VMH neurons have direct connections with other nuclei such as the PVN and the DMH (Williams et al., 2001) and ablation of VMH steroidogenic factor 1 (SF1) neurons leads to an age-dependent increase in food intake in mice (Kinyua et al., 2016). The DMH expresses both the orexigenic peptide, NPY (Bi, 2007), and the anorexigenic peptide, CART (Elias et al., 2001; Williams et al., 2001). This nucleus controls thermoregulation (Dodd et al., 2014) and food intake through cholinergic neurons (Jeong et al., 2017), suggesting that it functions as an integrator of energy homeostasis and thermoregulation (Dimicco and Zaretsky, 2007). The PVN is a command center upon which the multiple signals from the LH and ARC converge to control energy expenditure and intake. The PVN is also the site where the hypothalamic control of stress (corticotropin-releasing hormone (CRH)) and metabolism (thyrotropin-releasing hormone (TRH)) intersects to control energy homeostasis and feeding (Arora and Anubhuti, 2006; Lechan and Fekete, 2006; Mastorakos and Zapanti, 2004; Williams et al., 2001). The LH, a downstream target of ARC POMC and NPY neurons, is also a feeding center of the hypothalamus given that stimulation of the LH induces food intake. The primary LH neurons that control feeding are melanin-concentrating hormone (MCH) and orexin neurons (Arora and Anubhuti, 2006; Horvath, 2006; Nahon, 2006; Williams et al., 2001). Orexin neurons primarily control sleeping behavior and arousal. Activation of MCH neurons induces hyperphagia and MCH neuron deficiency causes hypophagia (Mystkowski et al., 2000).

The other brain region involved in feeding behaviors is the hindbrain, specifically the nucleus tractus solitarius (NTS) and parabrachial nucleus (PBN). These two regions control ingestive or consummatory behaviors such as chewing, licking, and swallowing and have been extensively reviewed (Grill and Hayes, 2012; Riediger, 2012; Williams and Schwartz, 2011). Briefly, the NTS receives both hypothalamic (PVN, ARC, LH) and gastrointestinal vagal inputs to integrate both central and peripheral signals of energy status and meal ingestion (satiety). Neurons from the rostral NTS then project to the PBN and the parvocellular reticular formation leading to the control of feeding behaviors. One peripheral gut hormone that is a major satiety signal is cholecystokinin (CCK) (Schwartz and Moran, 1996) that is produced after gut distension. CCK triggers satiation and the cessation of feeding simultaneously with other signals such as serotonin (Hayes and Covasa, 2006; Mazda et al., 2004). Interestingly, 17β-estradiol via activation of ERα potentiates the NTS response to CCK and lipid ingestion in females (Asarian and Geary, 2007), opening the door to disruption by estrogenic EDC in females.

Because they elicit their effects through steroid and nuclear receptors that control feeding circuits, EDCs may alter the hypothalamic-hindbrain circuits and disrupt normal feeding behavior. Creation of these brain circuits begins during the early stages of development (E12) and, therefore, can be altered by adverse conditions like EDC exposure. The exposure window to EDC is critical as the central control of feeding behaviors develops both in utero and neonatally (Toda et al., 2017; Zhu et al., 2016). A previous review in this journal described the potential interplay between EDC and maternal programming on the control of energy homeostasis (Schneider et al., 2014). The authors also described the importance of sexual dimorphism that is programmed, in part, through steroid production at discrete developmental time periods during gestation, lactation, and puberty. In particular, the organization of the hypothalamic and extrahypothalamic centers that control feeding, reward, and motivation are key targets for the hormonally-driven programming of energy homeostasis that may be impacted by EDC exposure. However, few studies have directly examined the hypothalamic-hindbrain circuits after perinatal EDC exposure. Furthermore, there is little data on EDC's effects on meal patterns (size, frequency, duration), the feeding response to peripheral peptides (leptin, ghrelin, cholecystokinin, etc.) after refeeding, or other feeding behavior paradigms. The purpose of this review is to discuss a few studies that report crude food or energy intake after perinatal EDC exposure and to appeal for deeper investigations in the hypothalamic-hindbrain neurocircuitry and discrete feeding behaviors.

2. Bisphenol A

One of the most widely studied EDC, BPA is directly applied to metal or plastic products to prevent leeching of metals into food. The structure of BPA is similar to endogenous ligands and can activate transcription factors like peroxisome proliferator-activated receptor gamma (PPARγ), estrogen receptor (ER) α/β, and estrogen-related receptor gamma (ERRγ). Activation of these receptors by BPA may have adverse effects on feeding behavior (Anderson et al., 2013). Numerous studies have found changes in glucose homeostasis and activity, which are related to feeding behavior, but do not directly assess its connection with EDC.

Experiments that specifically examine food intake and perinatal BPA exposure are few. The studies discussed below have reported food intake or related endpoints. California mice are frequently used in studies to assess reproductive behaviors due to their preference in monogamous mating. Following perinatal exposure to BPA (50 mg/kg in diet) in pregnant California mice, male offspring were found to have the same exploratory behavior compared to females with no change in body weight (Williams et al., 2013). An experiment using the same animal model examined the effects of periconceptional and perinatal, diet-based, BPA exposure on metabolic and voluntary physical activity. Significant sex-dependent effects were found with body weight, water consumption, drinking episodes, and voluntary activity (Johnson et al., 2015). While there were no differences in overall food intake due to BPA exposure, BPA-exposed males failed to exhibit a distinct diurnal food intake pattern as was observed in the controls. Conversely, BPA-exposed females consumed less food during the dark cycle compared to the light cycle, which was not observed in the positive control (ethinyl estradiol) and spent the same amount of time eating in the light and dark cycle, unlike both negative and positive control groups (Johnson et al., 2015). Water consumption in BPA-exposed males increased significantly in both light and dark cycles, while no effect was seen in females. BPA exposure produced an opposite effect in drinking episodes with females exhibiting a decrease in episodes during the dark cycle and no change observed in males. The authors explained their sex-dependent findings by attributing the amount of time spent in spontaneous activity was a strong predictor of adiposity and weight gain, with evidence from other papers to support their conclusion (Perez-Leighton