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

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Abstract

Endocrine disrupting compounds (EDCs) 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 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.

Keywords

feeding behavior; food intake; hypothalamus; hindbrain; endocrine disruptors

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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 the 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., 2014a; 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 other and to other brain regions including the hindbrain. The hypothalamic nuclei involved include the arcuate nucleus (ARC), paraventricular nucleus (PVN), lateral hypothalamus (LH), the dorsomedial hypothalamus (DMH), and ventromedial nucleus of the hypothalamus (VMH) (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 controlled by peripheral satiety factors such as glucose, insulin, and leptin (Schwartz, 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, 17 β -estradiol via activation of ER α 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. Development of this area of the brain is formed 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-hinbrain neurocircuitry and discrete feeding behaviors.

Bisphenol A

One of the most widely studied EDCs, 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 (PPAR γ), estrogen receptor (ER) α/β , and estrogen response element gamma (ERR γ). 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 EDCs.

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 did not 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 et al., 2013; Perez-Leighton et al., 2012).

Rubin and Soto have written extensive reviews on the developmental effects of BPA and with their own studies have also confirmed perinatal exposure to both high and low doses of BPA through drinking water increase body weight in offspring compared to control (Rubin et al., 2001). They also showed females had a difference in mean body weight between high and low doses of BPA on day 28 compared to their male littermates (Rubin et al., 2001). However, Anderson et al., (2013) observed the opposite effect in energy expenditure and body weight from perinatal exposure to BPA (Anderson et al., 2013). Effects of maternal exposure to BPA recorded at 3, 6, and 9 months of age showed increased energy expenditure in females at all concentrations and a decrease in food intake compared to controls (Anderson et al., 2013). Males also had significant changes in increased energy expenditure at 3 and 9 months, which can be explained by the increase in ambulatory activity in males and horizontal activity in both sexes. Nevertheless, no significant effect on food intake was observed.

Recent publications by Abizaid and colleagues have elegantly demonstrated how developmental exposure to BPA through the maternal diet can influence the hypothalamic melanocortin neurocircuitry that control feeding behavior in CD-1 mice (MacKay et al., 2017; Mackay et al., 2013). Prior to the food challenge, high-dose BPA-exposed males exhibited elevated energy expenditure at 3 months of age compared to controls with no change in locomotor activity. BPA-exposed female mice gained more weight on a high-fat diet and consumed more calories daily compared to control without any effect on energy expenditure (Mackay et al., 2013). Conversely, males exhibited elevated energy expenditure before high-fat diet and reduced energy expenditure following the high-fat diet challenge, independent of locomotor activity. Males exposed to BPA exhibited reduced POMC fiber density in the PVN, while in females only DES reduced POMC fiber density. Interestingly, ER α expression in POMC neurons was increased in males and females exposed to BPA. These findings show that there is a sex-dependent effect following perinatal BPA exposure (Mackay et al., 2013).

In a follow-up study, Abizaid and colleagues examined how POMC and leptin influence feeding behavior from perinatal BPA exposure in mice (MacKay et al., 2017). Leptin is a adipokine hormone that is sensed by POMC and NPY/AgRP neurons in the ARC to regulate food intake. BPA-exposed male and female mice were more insensitive to the effects of leptin on POMC expression compared to controls and exhibited a reduction in POMC innervation of the PVN, which is rescued in females by postnatal administration of leptin (MacKay et al., 2017). Furthermore, both BPA-exposed males and females were resistant to the post-leptin injection effects of body weight. BPA-exposure also delayed the postnatal surge of leptin, which may alter the timing of development in the melanocortin neurocircuitry (MacKay et al., 2017). Without discrete measurements of meal patterns, it is unknown if these effects on the melanocortin circuitry have any effect of feeding behavior.

While perinatal BPA exposure may alter the melanocortin neurocircuitry in mice, many other studies have not found a clear effect on crude food intake. Using an isogenic mouse

model, perinatal BPA exposure through maternal diet increased energy expenditure due, in part, to increased horizontal and vertical activity and a decrease in food intake in females (Anderson et al., 2013). In a rat study, perinatal BPA exposure by oral gavage did not alter energy intake on a low-fat diet despite an increase in body weight indicating that the primary effect was a decrease in metabolism (Wei et al., 2011). A multi-generational study in Wistar rats explored the effects of low-dose perinatal BPA exposure (oral pipette) on flavor preference and food intake. In the unexposed F2 generation, body weight was higher without any clear effect on crude food or water intake (Boudalia et al., 2014). The F2 generation rats also preferred sweeter water solutions, salt, and fat compared to both F1 and control (Boudalia et al., 2014). Similar findings on food or flavor preference for high sucrose/saccharin solutions has also been observed after BPA (subcutaneous) injection in adolescent rats (Diaz Weinstein et al., 2013). Analysis of food intake by crude measurements is a common method in many studies that find no effect on food intake after perinatal BPA exposure (Somm et al., 2009). However, crude food intake determination may not capture subtle changes to meal pattern or food preferences.

Due to potential reproductive and metabolic disturbances by perinatal BPA exposure, the use of BPA in infant bottles, toys, and adult food and liquid storage containers has been reduced in the past decade. Industry has replaced BPA with closely related chemical substitutes such as bisphenol S (BPS) and bisphenol F (BPF). BPS and BPF are currently a concern because they are detectable in foodstuffs and human serum (Liao and Kannan, 2013). A few studies have examined the metabolic effects of these compounds in rodent models. In one study, CD-1 pregnant mice were orally dosed with BPS from gestation day (GD) 8 until postnatal day (PND) 21. BPS-exposed male mice exhibited reduced bodyweight until week 20 and increased mean velocity of movement compared to controls (Kim et al., 2015). In contrast, another study reported an increase in body weight in males exposed to 1.5 and 50 µg/kg bw/d BPS perinatal and chronically through adulthood when fed a high-fat diet (Ivry Del Moral et al., 2016). No effect on 24 h food intake was observed. Clearly, further investigation is needed to determine if BPS/F alters adult energy homeostasis, feeding behaviors, or the hypothalamic melanocortin circuitry like BPA.

Phytoestrogens

Phytoestrogens are the main ingredient in soy-based products and are another well-known EDC exerting their effects through interactions with ERs. Pregnant women that consume a high soy-based diet or bottle feed their infants a high soy-based formula are potentially at risk for adverse effects on fetal and neonatal development. Few studies that have focused on the effects of perinatal phytoestrogen exposure on feeding behaviors or crude food intake. To understand the influence of a high phytoestrogen diet on energy balance and metabolism, one study fed dams and offspring a high or low phytoestrogen diet with continuous phytoestrogen exposure from preconception (6 weeks prior to mating) through to adulthood. Continuous exposure led to lighter and more lean mice from 10 weeks onward (Cederroth et al., 2007). Mice fed the high phytoestrogen diet consumed more food at 3 and 6 months compared to the low phytoestrogen diet with an increase in metabolic rate and energy expenditure, but a decrease in respiratory exchange ratio (RER). These findings correlate with a decrease in AgRP expression and an increase in orexin A, MCH, and TRH (Cederroth

et al., 2007). Another study found that consumption of soy-based maternal diet led to an increase in crude food intake in male and female offspring compared to a casein-based maternal diet. When administered in conjunction with BPA during development, crude food intake was also elevated leading to greater body weight gain (Cao et al., 2015). Early life (PND1-22) oral doses of genistein, a common phytoestrogen, was conducted in rat pups mimicking blood levels in infants fed a soy formula. Post-weaning body weight was reduced in males and females despite an increase in energy intake. This effect was also observed when rats were challenged with a high-fat diet (Strakovsky et al., 2014). Interestingly, the low levels of phytoestrogens in the maternal diet can also disrupt energy and glucose homeostasis in offspring in a sex-dependent manner (Ruhlen et al., 2008). Nevertheless, no discrete measurement of food intake was collected.

Dioxins

Dioxins are a very potent and persistent environmental chemical that cause serious toxicity and teratogenicity in animal models. The most potent and well-studied dioxin is 2,3,7,8-tetrachlorodibenzodioxin (TCDD), which produces its effects through interactions with the aryl hydrocarbon receptor (AhR). In adult rodent models, intraperitoneal injection of TCDD reduced food and water intake and altered flavor and macronutrient preference (Pohjanvirta and Tuomisto, 1990; Pohjanvirta et al., 1998; Tuomisto et al., 2000). The aversion to food and water appears to involve changes in the hypothalamic-pituitary-adrenal axis, the melanocortin neurocircuitry, and the neuropeptides that control fluid intake (Moon et al., 2008; Seefeld et al., 1984). Interestingly, there are few reports on perinatal TCDD exposure and metabolism with little data on food intake or meal pattern despite an increase in body weight and adiposity (La Merrill et al., 2009; Sugai et al., 2014; van Esterik et al., 2015). In a study published in 2000, Schantz and colleagues reported that oral gavage dosing of TCDD (and PCB) to dams during gestation and lactation decreased saccharin consumption and preference in female rat offspring (Amin et al., 2000). These effects on saccharin consumption and preference may be due to metabolic disturbances, which were not examined by the authors, or by an impairment in the motivation and reward circuitries. While perinatal TCDD exposure disrupt energy homeostasis, the impacts on the hypothalamic-hindbrain feeding circuits and on meal patterns are largely uncharacterized and unknown.

Flame retardants

Flame retardants such as polybrominated diphenyl ethers (PBDE) and organophosphate flame retardants (OPFR) are EDC used in upholstery, building materials, electronics, and plastics. PBDE have been largely phased out of use over the past decade (Zota et al., 2013). Both PBDE and OPFR interact with steroid and nuclear receptors that control energy homeostasis and feeding behaviors including ER α , androgen receptors (AR), and PPAR γ (Kojima et al., 2013; Lu et al., 2014; Pillai et al., 2014). However, there are few studies that record food intake or feeding behavior from perinatal exposures to PBDE. One adult exposure study focused on the effects of PBDE-99 exposure by oral gavage on exploratory behaviors, locomotor activity, and spatial learning in male rats. The authors report finding no effects on food or water consumption (Daubie et al., 2011). OPFR, the successors to PBDE, interact with a range of nuclear and steroid receptors including ER, AR, and PPARs (Belcher

et al., 2014; Kojima et al., 2013; Pillai et al., 2014), which are all involved in the control of energy homeostasis and the melanocortin neurocircuitry (Barros and Gustafsson, 2011; Long et al., 2014). Again, few, if any studies characterize the effects of perinatal OPFR exposure on food intake or feeding behavior. In a recent study using a common OPFR mixture, Firemaster® 550, perinatal exposure to 100 or 1000 µg/day via food in rats increased body weight while decreasing exploratory activity in males and females without any determination of food intake or feeding behavior (Patisaul et al., 2013).

Perfluorooctanoic acid and Perfluorooctanesulfonic acid (PFOA/PFOS)

Perfluorinated compounds (PFC) are widely used as environmental surface protectants to reduce the occurrence of stains, friction, and waterproofing of furniture (Domingo and Nadal, 2017). Like other EDCs, PFCs are persistent in the environment due to slow degradation rates but do not bioaccumulate in adipose tissue. Two well-studied PFCs are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). When administered in adulthood, these compounds exert their effects on food intake through the PPAR α (Asakawa et al., 2007; Asakawa et al., 2008). Again, there are few studies that record food intake or feeding behavior from perinatal PFC exposure. In one perinatal exposure study, dams were dosed by gavage to four different concentrations of PFOA/PFOA from GD1-17 to determine any obesogenic effects. The only treatment to alter body weights was the highest PFOA dose (3.0 mg/kg/day), which reduced body weight with no change in food intake (Ngo et al., 2014).

Polychlorinated biphenyls

PCBs are mainly used as a lubricant, cooling fluid, plasticizer, and adhesive in commercial products and are persistent in the environment despite a ban in the US since the late 1970s. While there are numerous studies on the perinatal effects of PCB exposure (Boucher et al., 2009), few have closely examined food intake or feeding behavior. One perinatal study investigated how social behavior in adult offspring was impacted when dams were fed a diet containing PCBs. Exposure to 12.5 or 25 ppm PCB-47 and -77 reduced the area of the periventricular nucleus of the hypothalamus in male rats; however, there were no changes in food consumption or body weight (Jolous-Jamshidi et al., 2010). In a few studies, saccharin or sweet taste preference was examined. Males exposed perinatally to PCB in the maternal diet increased the preference for sweet (saccharin) taste but without an increase in overall food consumption (Hany et al., 1999; Kaya et al., 2002).

Organochlorines

Organochlorines (OC), like DDT, are a type of pesticide that act on the central nervous system to confer their toxicity. Their mechanism of action is through either the GABA A receptor (i.e. cyclodienes and toxaphene) or voltage-dependent potassium and sodium channels. Though DDT is labeled as moderately toxic compared to other organochlorines, it was banned by the Environmental Protection Agency (EPA) due to unintended toxicity in wildlife and humans (Li and Jennings, 2017). There are several studies investigating how perinatal DDT exposure influences metabolism in humans (de Cock and van de Bor, 2014). In animal models, there are few studies that directly measure or report food intake or feeding behavior. In mice, maternal DDT exposure from GD11.5 to PND5 via oral gavage reduced

energy expenditure and core body temperature and promoted adiposity in female offspring. DDT exposure also augmented the effects of a high-fat diet challenge leading to glucose intolerance, hyperinsulinemia, and dyslipidemia (La Merrill et al., 2014b). No effect on crude food intake was found during the study. Methoxychlor, a pesticide employed as a replacement for DDT and subsequently banned in the US, has also been implicated as an EDC (Padmanabhan et al., 2010). In a multi-generation exposure to methoxychlor, the two higher doses (500 and 1500 ppm), reduced growth rate during the growth period and body weight in males and females prior to weaning. Methoxychlor treatment via maternal diet also reduced crude food consumption, although the data was not shown (Aoyama et al., 2012). DDT, methoxychlor, or their metabolites are potential ligands for ER α (Kim et al., 2014; Wang et al., 2017), which is involved in the developmental programming of energy homeostasis, especially in females (Roepke et al., 2017).

Perinatal treatment of another organochlorine, the insecticide chlorpyrifos (CPO), from GD7-PND21 via gavage produced heavier male offspring after puberty and increased body volume (Lassiter and Brimijoin, 2008). No measurement of food intake or feeding behavior was noted. A similar study using the pesticide parathion (PTN) subcutaneously injected into neonatal rats from PND1-4 reported that treated mice exhibited weight gain on a low-fat diet, symptoms of pre-diabetes, and impaired fat metabolism (Lassiter et al., 2008). In another study by Lassiter and colleagues, neonatal PTN injection caused a reduction in weight gain in both sexes, but only in females at 0.2 mg/kg. All sexes fed a high-fat diet showed around a 37% reduction in food consumption. However, intake was found to be isocaloric since the high-fat diet has ~37% more calories per gram, even though mice gained more weight (Lassiter et al., 2010).

Tributyltin

Tributyltin (TBT) is a well-known, toxic biocide primarily used to prevent the growth of marine aquatic life on the hulls of large ships, buoys, docks, and fishnets. Perinatal TBT exposure impacts offspring metabolism and adiposity via interactions with PPAR γ and retinoid X receptor (RXR) (Kirchner et al., 2010). One such perinatal study attempted to understand how maternal TBT dosing via gavage from GD8 until birth combined with postweaning pup gavage until euthanasia at PND30 altered offspring homeostasis in rats. TBT exposure did not alter food consumption in females but produced a small increase in male offspring. Interestingly, feeding efficiency was augmented in females but suppressed in males (Cooke et al., 2004). It is unknown if the perinatal effects on food intake by TBT exposure involve developmental programming through PPAR γ and RXR.

Conclusions

While not exhaustive, this review has attempted to highlight the few studies that measured food or energy intake in rodent models perinatally-exposed to a range of EDC. A few of these studies report findings that were not consistent between them. These inconsistencies may be due to differences in species, dosages, routes of exposure or administration of EDC (oral (regular chow, novel food, or gavage); subcutaneous injection; fluid intake), or the developmental timing of exposures (gestational, lactational, pubertal). Future studies should

attempt to mimic human exposures, both in concentration and route, encompass all neuroendocrine developmental periods including puberty, and examine the steroidal control of feeding behaviors in adults (Schneider et al., 2014). Our review is a call for further investigation into the effects of EDC on developmental programming of feeding behaviors and the hypothalamic-hindbrain neurocircuitry that controls these behaviors. Few studies go beyond simple crude measurements of food or energy intake or measurements of melanocortin neuropeptides (α -MSH, CART, AgRP) of the hypothalamus. Two recent studies by Abizaid and colleagues are excellent examples of interrogating the impacts of perinatal EDC exposure on the hypothalamic melanocortin neurocircuitry and on peripheral peptide hormone (leptin) sensitivity. More studies on the wide array of EDC should incorporate similar endpoints while also employing behavioral instruments that measure meal patterns. Aside from crude food and liquid intake, there are other methods to record feeding behavior in rodents such as monitoring of feeding behaviors over a period of 7–14 days in instruments such as Research Diets Biological Data Acquisition (BioDAQ). This automated system can record food intake or preference, liquid intake or choice, place or taste preference, intermittent access, or a combination in up to 32 individually housed rodent models. The BioDAQ system documents the date, time, and duration of changes in weight per time period (bouts), which can be converted into meal size, duration, and frequency. Finally, another aspect of feeding behaviors that should be considered is incidence of eating disorders. If perinatal (or adult) exposures to EDC can alter feeding patterns, the neurocircuitry of feeding and reward, or the sensitivity to anorectic or orexigenic hormones, these compounds potentially increase the risk for anorexia nervosa or binge eating disorders. Any relation between EDC exposures and eating disorders is largely unknown.

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Highlights

- Perinatal exposure to EDC can disrupt energy homeostasis leading to obesity and diabetes.
- Most perinatal studies only report crude food or energy intake, if at all.
- Perinatal studies should analyze meal patterns and response to peripheral peptide hormones.
- These studies should also examine hypothalamic-hindbrain neurocircuitry.