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Preclinical evidence for the addiction potential of highly palatable foods: Current developments related to maternal influence

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ABSTRACT

It is well established that obesity has reached pandemic proportions. Over the last four decades the prevalence of obesity and morbid obesity have risen substantially in both men and women worldwide. Although there are many causative factors leading to excessive weight gain including genetics and sedentary lifestyle, the transformation of the food environment has undoubtedly contributed to the dangerously high rates of obesity. The current food landscape is inundated with food engineered to contain artificially high levels of sugar and fat. Overconsumption of these types of food overrides the homeostatic mechanisms, which under normal circumstances regulate appetite and body mass, leading to hedonic eating. Evidence from the animal literature has illustrated nutrition-influenced perturbations that occur within the mesolimbic dopamine pathway, as well as maladaptive behavioral responses that result from chronic ingestion of highly palatable foods. These neurobehavioral adaptations are similar to what is observed in drugs of abuse. Recent evidence also supports that maternal exposure to these foods is capable of provoking neurobehavioral alterations in offspring. Therefore the purpose of this review is to summarize the current developments on the addictive potential of highly palatable foods, as well as illuminate the impact of maternal hyperphagia and obesity on the reward-related neurocircuitry and addiction-like behaviors in the offspring.

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1. Introduction

Obesity remains a major public health problem in the United States, with growing prevalence in children (Ng et al., 2014; Swinburn et al., 2011). Several established mechanisms contributing to the increased rates of obesity include changes in dietary patterns (Chaput, Klingenberg, Astrup, & Sjodin, 2011; Mozaffarian, Hao, Rimm, Willett, & Hu, 2011; Popkin, Adair, & Ng, 2012), sedentary lifestyles (Myers, Gibbons, Finlayson, & Blundell, 2016), genetic susceptibility (Farooqi & O'Rahilly, 2006; Llewellyn & Wardle, 2015), and gene-environment interactions resulting in epigenetic modifications (Rooney & Ozanne, 2011; Skinner, 2011). It is undeniable that the current food environment encourages excessive consumption of highly processed foods due to exaggerated levels of sugar and fat in these foods. The chronic consumption of highly palatable foods results in neuroadaptations within the mesolimbic dopamine (DA) reward pathways (Avena, Rada, & Hoebel, 2008; Rada, Avena, & Hoebel, 2005; Willuhn, Burgeno, Groblewski, & Phillips, 2014), leading to neurochemical and behavioral alterations mirroring those seen in drug addiction (Murray, Tulloch, Gold, & Avena, 2014). Given the alarmingly high rates of pediatric obesity, researchers have begun to postulate that prenatal or intrauterine influences may contribute to obesity risk later in life. Preclinical evidence suggests appetite regulation begins in the prenatal and perinatal period (Ashino et al., 2012; Muhlhausler, Adam, Findlay, Duffield, & McMillen, 2006; Shalev et al., 2010; Sun, Purcell, Terrillion, Yan, & Moran, 2012), when homeostatic and hedonic appetite centers within the brain are sensitive to the maternal nutritional environment. Indeed, maternal drug abuse can predispose offspring to future drug addiction (Pinheiro et al., 2015) as well as impaired behavior (Richardson, Hamel, Goldschmidt, & Day, 1996). This has led to the exploration of underlying mechanisms of addictive-like eating observed in offspring that may occur in response to maternal ingestion of a highly palatable diet during gestation and lactation.

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Therefore, the focus of this paper is to provide an update on intrauterine nutritional experiments in animal models and to review preclinical data on nutritional programming. We focus on the impact of maternal hyperphagia and obesity on the neurohormonal circuitry related to addiction-like behaviors in the offspring. “Junk food” and “highly palatable” are terms used to describe highly processed combinations of fat, sugar, and salt, resembling contemporary Westernized convenience foods.

2. Hypothalamus & hormones

The arcuate nucleus (ARC) is thought to be the integration site of appetite-related signals in the hypothalamus. Blood-borne signals including glucose, triglyceride, insulin, and leptin contribute information to the ARC (see review by Bauer, Hamr, & Duca, 2015). An individual's metabolic state will profoundly influence the reward system by linking homeostatic mechanisms (governed by the hypothalamus) with reward pathways in the midbrain and cortex (see reviews by De Araujo, Ferreira, Tellez, Ren, & Yeckel, 2012; Coll, Farooqi, & O'Rahilly, 2007). In the ARC, orexigenic hormones such as neuropeptide Y (NPY) and agouti-related protein (AgRP) are produced to stimulate food intake, while anorexigenic neurons such as proopiomelanocortin (POMC) inhibit food intake (Hahn, Breininger, Baskin, & Schwartz, 1998). It has been established that the appetite-regulating neural network is present before birth in animal models (Muhlhausler et al., 2006). Hormones such as insulin and leptin are implicated in the programmed hyperphagia observed in offspring overfed during pregnancy. A recent review summarized the role of various hormones in the hypothalamic appetite-signaling pathway, concluding that the rise in obesity rates could at least in part be explained by early life nutritional imbalances (Ramamoorthy, Begum, Harno, & White, 2015).

2.1. Insulin

Insulin promotes the absorption of glucose from the blood and into both muscles and fat tissue. Insulin can cross the blood brain barrier to influence orexigenic and anorexigenic neurons in the ARC (see reviews by Kleinridders, Ferris, Cai, & Kahn, 2014; Schwartz, Woods, Porte, Seeley, & Baskin, 2000). Indeed, that excess adipose tissue resulting from chronic intake of a highly palatable diet can cause insulin resistance and impaired insulin utilization, leading to diminished insulin secretion (Kahn & Flier, 2000), which impacts both homeostatic and hedonic feeding circuitry. Insulin and DA work together to orchestrate both the motivation to engage in consumptive behavior, and to calibrate the associated reward, particularly related to hedonic feeding (Mebel, Wong, Dong, & Borgland, 2012). More specifically, insulin-mediated decreases in DA concentration in the ventral tegmental area (VTA) via increased DA reuptake through DA transporter (DAT) may explain suppressed salience of food, once satiety is reached. Insulin can act on the ARC to reduce food intake and body weight, however there is evidence of central insulin resistance in obese patients (see review by Ye, 2013). Diet induced maternal obesity has a detrimental effect on insulin secretion and metabolic dysfunction, as well as elevated leptin levels in offspring (Zambrano et al., 2016).

2.2. Leptin

Leptin is produced and secreted by adipose tissue to increase metabolic rate. Leptin signals the individual to reduce energy intake and increase expenditure, generally by inhibiting orexigens such as NPY and stimulating anorexigens such as POMC (see reviews by Morton, Meek, & Schwartz, 2014; Shan & Yeo, 2011). Fulton et al. (2006) showed that leptin administration to leptin-deficient mice decreased DA activity in the VTA, supporting the hypothesis that that these animals compensate for a deficit in NAc DA by increasing food intake. Furthermore, reduced expression of leptin receptors in the VTA and hypothalamus lead to increased food intake via modulation of mesolimbic DA neurons and associated effort-based feeding (motivation) (Hommel et al., 2006). Taken together, it appears that leptin-mediated modulation of DA circuits generate an overall behavioral response.

It has been reported that maternal leptin can cross the placenta and be a significant source of fetal leptin (Smith & Waddell, 2003). Not surprisingly, neonatal overfeeding is associated with elevated juvenile and adult plasma leptin levels in rats (Stefanidis & Spencer, 2012). High-fat diets (HFD) can induce leptin resistance and is emerging as a cause and consequence of weight gain (Pandit, Mercer, Overduin, la Fleur, & Adan, 2012). The combination of perinatal and post-weaning HFD leads to an elevated fasting plasma glucose and leptin resistance in offspring (Shalev et al., 2010). These authors found that increased potential for leptin resistance in the postnatal period can result in abnormal appetite regulation, glucose intolerance, altered reward sensitivity, and obesity.

2.3. Ghrelin

Ghrelin is stomach-derived hormone, which decreases after eating and contributes to satiety. Ghrelin has been shown to increase the intake of high-calorie food including sugar and fat (King, Isaacs, O'Farrell, & Abizaid, 2011; MacKay et al., 2016). Similar to the hormones leptin and insulin, ghrelin is also implicated in homeostatic appetite regulation, and data suggest its implication in hedonic eating (Abizaid et al., 2006; Naleid, Grace, Cummings, & Levine, 2005). In addition to its action on orexigenic neurons in the hypothalamus, ghrelin receptors have also been identified in the VTA, hippocampus, and amygdala (Abizaid et al., 2006; Zigman, Jones, Lee, Saper, & Elmquist, 2006). The ghrelin system increases the motivation to eat by altering the set point of dopaminergic neurons in the VTA thereby enhancing the ability of rewarding substances to activate the midbrain DA system (Dickson et al., 2011; Skibicka, Alvarez-Crespo, Friberg, & Dickson, 2011). Perello et al. (2010) found that ghrelin is involved in certain rewarding aspects of eating (HFD) and requires the presence of intact orexin signaling, distinct from homeostatic mechanisms that promote food intake in response to reduced energy stores. It has been suggested that the mesoaccumbal DA pathway (designed to promote survival in times of food scarcity) is targeted by the ghrelin/growth hormone secretagogue receptor type 1A (GHSR-1A) system and is a driver in the overconsumption of palatable foods beyond metabolic need (see Perello & Dickson, 2015). Recently it has been shown that GHSR knockout rats eat less of palatable dessert following a meal (MacKay et al., 2016).

Just as maternal diet influences leptin levels in offspring, a maternal HFD during prenatal and lactation increases ghrelin levels in offspring when compared to offspring from dams fed standard chow (Slupecka, Romanowicz, & Wolinski, 2016). Thus, observable neurobehavioral adaptations in the HFD offspring are not surprising given that the central ghrelin signaling system interfaces with neurobiological circuits involved in reward from both food (Vengeliene, 2013) and chemical drugs including cocaine (Davis, Wellman, & Clifford, 2007) and alcohol (Jerlhag et al., 2009; Leggio et al., 2011). Some investigators have concluded that ghrelin primarily exerts motivational effects on feeding, rather than hedonic or opioid-related effects (Overduin, Figlewicz, Bennet-Jay, Kittleson, & Cummings, 2012) while others have identified the *mu* or *kappa* opioid system (in the VTA) as being modulated by ghrelin (Kawahara et al., 2013). The precise role of ghrelin in the

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