Published in final edited form as:

Psychoneuroendocrinology. 2013 September ; 38(9): 1923–1927. doi:10.1016/j.psyneuen.2013.06.017.

Stress and Addiction

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Abstract

Appetitive behaviors such as substance use and eating are under significant regulatory control by the hypothalamic-pituitary adrenal (HPA) and hypothalamic pituitary gonadal (HPG) axes. Recent research has begun to examine how these systems interact to cause and maintain poor regulation of these appetitive behaviors. A range of potential molecular, neuroendocrine, and hormonal mechanisms are involved in these interactions and may explain individual differences in both of risk and resilience to a range of addictions. This manuscript provides a commentary on research presented during the International Society of Psychoneuroendocrinology's mini-conference on sex differences in eating and addiction with an emphasis on how HPG and HPA axis interactions affect appetitive behaviors in classic addictions and may be used to help inform the ongoing debate about the validity of food addiction.

Introduction

The purpose of this commentary is to provide a summary of the research presented at International Society for Psychoneuroendocrinology (ISPNE)'s satellite conference, “Sex Differences in Eating and Addiction: What does Stress Have to Do with It? Our goal is twofold: (1) highlight how interactions between the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary adrenal (HPA) axes influence motivation-reward processes; (2) apply this information to better understand individual differences in addiction risk and consequences. The research reviewed in this paper utilizes a range of the genetic, molecular, and neuroendocrine tools to study HPG-HPA axes effects on motivation-reward behaviors including addiction to synthetic substances as well as natural reinforcers such as food. The latter reinforcer provides a controversial, but important, example of where the interplay of HPG-HPA axes can be used to understand sex differences in risk for eating disorder psychopathology and the validity of food addiction.

Sex Differences in Stress and Learning

Research indicates that there are sex differences in the ability to learn under stress which are predominantly related to hippocampal functioning. Under stressful circumstances, learning acquisition typically increases in males and decreases in females (Wood and Shors 1998). This has been linked to sex-specific changes in cellular structures in the hippocampus as well as distinct learning circuitry in males and females. Specifically, males engaging in a trace eyeblink conditioning paradigm under stressful conditions show an increase in

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dendritic spine density, whereas females in the same paradigm evidence decreased density ((Shors, Chua et al. 2001; Waddell, Bangasser et al. 2008). Learning circuitry for both sexes involves the hippocampus and amygdala (Bangasser and Shors 2007; Waddell and Shors 2008); however, only learning under stress in females requires communication between the amygdala and the medial prefrontal cortex (mPFC), whereas learning in males distinctly involves the bed nucleus of striatum terminals (BNST) (Maeng, Waddell et al. 2010). The hormonal environments of males and females are likely responsible for these differences. For example, research suggests that post-partum female mice evidence a sustained, enhanced ability to learn under stress, similar to their male counterparts, presumably from hormonal changes caused by pregnancy and childbirth (Maeng and Shors 2012).

Learning is an essential component to the motivation-reward system and specifically to the encoding of cued associations (Tracy, Jarrard et al. 2001) and the reinforced behaviors that drive appetitive responses (Morita, Morishima et al. 2013). One interesting approach to studying the effects of stress-learning on this system has been to examine hippocampal neurogenesis. Shors et al (2012) have documented how effortful learning increases the survival of new cells in the hippocampus and this survival correlates with ability to learn under various conditions. Moderate drinking, however, reduces the survival of these neurons in the dentate gyrus of the hippocampus (Anderson, Nokia et al. 2012), although these changes do not appear to have significant impact on short-term measures of associative learning. An important line of questions evolving from this line of research are whether these effects of alcohol (and presumably other substances) on neurogenesis are moderated by gonadal hormones and whether these same effects influence key aspects of reward and stress learning. Gonadal hormones, in particular estrogen, have been shown to affect cell survival in models of neurogenesis and learning (McClure, Barha et al. 2013). Cortisol also regulates hippocampal neurogenesis through glucocorticoid receptor (GR) signaling (Anacker, Cattaneo et al. 2013), but it remains unclear how these two systems (glucocorticoid and estrogenic) interact to affect neurogenesis in conditions of reward or stress learning.

Stress caused Adaptations to Motivation-Reward System

It has long been recognized that stress, in certain contexts, is reinforcing, but also works to suppress the reward value of synthetic reinforcers in the development of drug dependence (Koob 2009). The mechanisms for these effects are partially mediated by a number of systems including the dynorphin-kappa opioid receptor (KOR) system (Wee and Koob 2010) and mounting evidence suggests that genetic or epigenetic effects of the *OPK1* or *PDYN* genes can explain risk and resilience to the development of drug dependence (Butelman, Yuferov et al. 2012). Dynorphin activation of KOR can reinstate drug seeking via stress-like effects in the amygdala (Redila and Chavkin 2008), reduces the rewarding impact of intracranial self-stimulation (Todtenkopf, Marcus et al. 2004), and mediates anxious behavior in rodents (Bruchas, Land et al. 2009). Thus, the dynorphin-KOR system functions in a counter-regulatory manner to offset elevated hedonic tone, but also mediates stress-induced seeking of reward (Bruchas, Land et al. 2010).

The influence of gonadal hormones on dynorphin-KOR system is just beginning to be understood. Gonadal hormones potentially catalyze organizational effects on KOR neurocircuitry or activate acute changes in KOR distribution, function, and localization (Rasakham and Liu-Chen 2011). For instance, recent evidence suggests a unique KOR-mu receptor heterodimer mediates pro-estrous antinociception in females (Chakrabarti, Liu et al. 2010), suggesting an estrogen specific mechanism responsible for nociception differences between men and women. Whether similar effects occur in the brain remains unclear. Alternatively, the reinforcing effects of androgens are likely to be mediated by the opioid system (Wood 2008), but have been theorized to have a specific role in the reinforcing

value of exercise-stress among anabolic steroid users (Hildebrandt, Yehuda et al. 2011). For instance, animal models of anabolic-androgenic steroid abuse suggest synthetic androgens up-regulate KOR density and suppress dynorphin production in the ventral tegmental area (VTA) and nucleus accumbens (Schlussman, Zhou et al. 2000). Critical questions remain, however, regarding gonadal hormones' effect on HPA functioning. For example, the molecular mechanisms by which androgens modify dynorphin metabolism or stimulate endorphin production remain unknown. Investigating these processes may help explain sex differences in learning under stress and why specific types of stressors (e.g., exercise) appear more reinforcing for men than women.

Gonadal Hormones' influence on Motivation-Reward in Substance Use Disorders

The direct effect of gonadal hormones on motivation and reward has also become an area significant development, largely because of an increasing literature documenting gender differences in expression, course, and outcomes of substance use disorders (Wetherington 2010). These differences are, in part, mediated by direct effects of gonadal hormones on reward value, but are also likely interacting with the HPA axis to moderate these effects. For example, females evidence an enhanced HPA axis response to cocaine (Walker, Francis et al. 2001; Evans and Foltin 2010) contributing to the increased escalation of cocaine use observed among women (Anker and Carroll 2011). Estradiol has also been linked to cocaine use; ovariectomized rats demonstrate a reduction in self-administration of cocaine, whereas rats with enhanced levels of estrogen evidence an increase in overall cocaine administration (Hu, Crombag et al. 2004), motivation to administer cocaine (Becker and Hu 2008), and an increase in the length of their initial cocaine binge (Fagergren and Hurd 1999). Electrophysiological research indicates that estradiol increases amphetamine-induced dopamine (DA) release in the striatum of females via attenuated GABA release (Xiao and Becker 1998). More specifically, estradiol binds to the alpha estrogen receptor, which activates the glutamate receptor (mGluR), and attenuates depolarization – triggered GABA release in the striatum. This results in an attenuated release of GABA and subsequently an increase in DA release. This relationship between estradiol and DA release is likely be U shaped (Hu and Becker 2008), and suggestive of different mechanisms by which estradiol affects behavioral responses to drugs of abuse (Becker and Hu 2008). For instance, the time-course effects of estradiol on GABA release in the striatum indicate changes that occur too quickly for classic genomic receptor effects (Schultz, von Esenwein et al. 2009), suggesting a specific role for nonclassical estrogen receptor effects on acute modulation of DA release.

Gonadal Hormones as a Contributor to Eating Pathology

Food is a natural reinforcer that is subject to developmental changes and significant regulation by both the HPG and HPA axes. For instance, eating behavior is very similar between boys and girls until the early stages of puberty when gonadal hormones begin to exert sexually dimorphic effects on hypothalamic regulators of weight and appetitive drive (Brown and Clegg 2010). Recent evidence however has begun to link gonadal hormones to pathological expressions of eating behavior (Klump, Keel et al. 2008; Culbert, Burt et al. 2009) and points to a moderating effect of puberty on genetic risks for eating disorders (Klump, Culbert et al. 2012). Prior to puberty, genetics accounts for 0% variance of eating disorders in females, whereas over 50% of variance is accounted for by genetics in their post-pubertal counterparts ((Klump, McGue et al. 2003; Klump, Burt et al. 2007; Culbert, Burt et al. 2009). The genetic variance in post-pubertal females occurs only in individuals with high estradiol levels, suggesting that estradiol may trigger an underlying genetic risk for eating disorders in post-pubertal females ((Klump, Keel et al. 2010). In contrast, genetics account for approximately 50% variance of males with eating disorders pre and post-puberty and the variance is not related to estradiol. Individual differences in the expression of eating disorder symptoms are correlated with high estradiol levels and are likely to interact with

progesterone (Klump, Keel et al. 2013). Other sources of variation include prenatal exposure to gonadal hormones as indirect measures of prenatal androgen exposure have been found to moderate risk for eating disorder symptoms (Culbert, Breedlove et al. 2013). A number of critical questions remain about what specific effects gonadal hormones are having on the brain to affect feeding behavior and which genes they are interacting with to confer eating disorder risk. The HPA axis is likely to be a significant source for understanding these effects.

Food as an Addictive Substance

Although food is a natural reinforcer, its status as an addictive substance remains a heavily debated topic as does the distinction of food addiction. Proponents of an addiction model assert that the overconsumption of sugars and fats leads to addictive-like behaviors, namely tolerance, withdrawal, craving, and drug cross-sensitization. Compared to controls, rats that binge daily on sucrose evidence greater consumption of sucrose, increased, sustained release of DA in the nucleus accumbens and downregulation of D2 receptors (Rada, Avena et al. 2005; Johnson and Kenny 2010). Sugar-bingeing rats also evidence symptoms consistent with opiate withdrawal, namely anxious behavior (i.e., reduced time spend on an elevated maze), enhanced levels of extracellular acetylcholine (ACh) and decreased levels of DA in the nucleus accumbens shell (Avena, Bocarsly et al. 2008). "Craving" behavior is also evident in rats that overconsume sucrose, as they engage in increased consumption of this substance subsequent to deprivation. Moreover, motivation to obtain food is enhanced in binge eating rats; they are more willing to cross a shock grid in order to obtain food (Oswald, Murdaugh et al. 2011) and will work harder than controls to obtain access to cues associated with sugar (Grimm, Fyall et al. 2005). Cross-sensitization to other drugs has also been reported; rats that binge on sugar evidence sensitization to amphetamine and increased consumption of alcohol (Avena and Hoebel 2003; Avena, Carrillo et al. 2004).

Critics of the food addiction model contend that the evidence supporting the clinical and neurobiological overlap between chronic overeating and other addictive behaviors is inconclusive and therefore widespread acceptance of a food addiction model of obesity/eating disorders is premature (Ziauddeen and Fletcher 2013). The neurobiological basis of this critique suggests that findings are generally inconsistent and that they suggest a more complex regulation of feeding behavior. For instance, PET imaging data do not consistently show a strong relationship between D2 receptor availability and body mass (Wang et al., 2001), or evidence of genetic contributions from DA polymorphisms (Munafo et al., 2009; Smith et al., 2008). Furthermore, there appears to be no specificity to the relationship between sugar abusing rats and weight, but rather this involves consumption of both sugar and fat (Avena, Rada et al. 2009) suggesting more complex relationships exist between preference and consumption of reinforcing food and the resulting effects on weight.

Eating disorders have a higher prevalence in females than males (20:1 to 2:1) depending on the diagnosis and study sampled (Hudson, Hiripi et al. 2007; Smink, van Hoeken et al. 2012). The neurobiological contributions to this discrepancy remain unclear, in part, because sex differences in clinical populations are rarely studied. Approaching this discrepancy with evolving methodologies and findings from the study of HPA-HPG interactions utilized in other disciplines, such as those reviewed above, are likely to contribute greatly to the resolution of the food addiction debate. It is clear that food is reinforcing and can be "abused" in either discrete contexts (i.e., binge eating) or chronically in the form of overconsumption. However, the sources of inconsistency in different approaches to food addiction may be aided by dissection of the neuroendocrine and associated molecular mechanisms that affect the behavior. For instance, one critical question would be whether food reward undergoes the same stress-mediated suppression via the dynorphin-KOR

system characteristic of other addictions and whether this allostatic regulation of hedonic tone is moderated by gonadal hormones.

Summary and Conclusions

The HPG and HPA axes have direct regulatory control over a range of appetitive behaviors, either through maintenance of hedonic tone or altering sensitivities to different types of rewards. The primary interactions between these two systems have largely focused on the hypothalamus (Viau 2002), but as described in much of the work reviewed in this manuscript there are likely interactions occurring in other areas of the brain that are relevant to addiction. Particularly interesting are the possible molecular mechanisms by which one set of hormones sensitize target neurons or neurocircuits to the effects of other hormones. Such interactions may explain gender differences in stress-induced appetitive behaviors and to some degree the specificity of addiction type (e.g., drug vs. food). In particular, this line of research may also help to develop more targeted interventions for the types of addictive behavior and identify robust biomarkers for risk and resilience to a range of addictions.

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