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SHORT COMMUNICATION

Stress and addiction

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Summary 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 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.

1. 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.

2. 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 dendritic spine density, whereas females in the same paradigm evidence decreased density (Shors et al.,

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2001; Waddell 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 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 et al., 2001) and the reinforced behaviors that drive appetitive responses (Morita 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 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 et al., 2013). Cortisol also regulates hippocampal neurogenesis through glucocorticoid receptor (GR) signaling (Anacker et al., 2013), but it remains unclear how these two systems (glucocorticoid and estrongenic) interact to affect neurogenesis in conditions of reward or stress learning.

3. 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 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 et al., 2004), and mediates anxious behavior in rodents (Bruchas 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 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 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 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 tagmental area (VTA) and nucleus accumbens (Schlussman 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.

4. 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 of 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 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 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

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