



Review

Stress responses and the mesolimbic dopamine system: Social contexts and sex differences

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ABSTRACT

Organisms react to threats with a variety of behavioral, hormonal, and neurobiological responses. The study of biological responses to stress has historically focused on the hypothalamic-pituitary-adrenal axis, but other systems such as the mesolimbic dopamine system are involved. Behavioral neuroendocrinologists have long recognized the importance of the mesolimbic dopamine system in mediating the effects of hormones on species specific behavior, especially aspects of reproductive behavior. There has been less focus on the role of this system in the context of stress, perhaps due to extensive data outlining its importance in reward or approach-based contexts. However, there is steadily growing evidence that the mesolimbic dopamine neurons have critical effects on behavioral responses to stress. Most of these data have been collected from experiments using a small number of animal model species under a limited set of contexts. This approach has led to important discoveries, but evidence is accumulating that mesolimbic dopamine responses are context dependent. Thus, focusing on a limited number of species under a narrow set of controlled conditions constrains our understanding of how the mesolimbic dopamine system regulates behavior in response to stress. Both affiliative and antagonistic social interactions have important effects on mesolimbic dopamine function, and there is preliminary evidence for sex differences as well. This review will highlight the benefits of expanding this approach, and focus on how social contexts and sex differences can impact mesolimbic dopamine stress responses.

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Introduction

Stressful experiences induce a powerful set of behavioral, hormonal, cellular and molecular responses that assist organisms in adapting to

the physical and social environment. Studies of physiological stress responses have historically focused on catecholamine responses and the hypothalamic-pituitary adrenal (HPA) axis (Herman et al., 2003; McEwen and Wingfield, 2003). However, physiological responses to stress are diverse, and over the past 30 years evidence has accumulated that dopamine neurons in the ventral tegmental area (VTA), (which project to limbic regions including the nucleus

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accumbens, amygdala, hippocampus, and frontal cortex) react strongly to stressful situations (Herman et al., 1982; Thierry et al., 1976; Tidey and Miczek, 1996). Reports that the mesolimbic dopamine system reacts to stress were initially slow to attract wide interest, perhaps because they run counter to prevailing views that the pathway is primarily activated by contexts associated with rewards. Despite these headwinds, interest in mesolimbic dopamine responses to stress and aversive contexts is growing. Recent discoveries suggest that there may be distinct populations of VTA neurons that are preferentially activated by rewards or stress. Furthermore individual variation in VTA stress responses has been linked to individual differences in coping responses to stress (Krishnan and Nestler, 2010). These discoveries are contributing to our still evolving understanding of the functions of mesolimbic dopamine neurons in behavior (Berridge, 2007; Bromberg-Martin et al., 2010; Hyman et al., 2006; Ikemoto and Panksepp, 1999; Wise, 2004).

How an individual responds behaviorally and physiologically to challenges is influenced by an array of factors including early life experience (Seckl and Meaney, 2004), seasonal cues (Nelson and Martin, 2007), social environment (DeVries et al., 2007), and sex (Goel and Bale, 2009). These factors are known to modulate how the HPA axis responds to stress. However, less is known about how these factors mediate mesolimbic dopamine responses to stress. Indeed, the majority of studies investigating dopaminergic responses to stress have focused on a few species of male rodents under relatively controlled laboratory conditions. Here, I will argue that there will be many benefits to diversifying the contexts in which the activity of the mesolimbic dopamine system is studied. The literature focusing on appetitive aspects of mesolimbic dopamine function has already started this process. A foundation of knowledge was formed by focusing on dopaminergic function in a few model species, under a limited set of controlled conditions (e.g. responses to food rewards or drugs of abuse) (Hyman et al., 2006; Wise, 2006). This set the stage for interpreting how the mesolimbic dopamine system functions in more complex social situations. For example, the formation of a pair bond between a male and a female prairie vole induces a dramatic upregulation of dopamine D1 receptors in the nucleus accumbens (NAc), which causes males to attack unfamiliar females (Aragona et al., 2006). These results contrast starkly from observations in rats. Unfamiliar female rats typically induce increased male sexual arousal (Wilson et al., 1963) and increase dopamine release in the NAc (Fiorino et al., 1997). Several lines of evidence suggest that dopamine receptors (including D1 receptors specifically) in the NAc facilitate male sexual motivation in rats (Bialy et al., 2010; Everitt et al., 1989; Liu et al., 1998; Pfaus and Phillips, 1991) but see (Moses et al., 1995). Thus, species differences in social organization are associated with divergent effects of dopamine receptors on male behavioral responses to novel females. This example highlights the value of comparative approaches.

This review will examine mesolimbic dopamine responses to aversive contexts (focusing on the VTA and NAc), and then focus on how social context and sex differences modulate these responses. Although most examples will come from a few widely used rodent model systems, this review will highlight the unique insights that can be gained from examining mesolimbic dopamine function under different social contexts, and in species with different social systems.

Mesolimbic dopamine system

Appetitive responses

The mesolimbic dopamine pathway consists of dopaminergic cell bodies in the VTA and its projections to striatal, limbic, and cortical regions. The NAc can be divided into two subregions: the core which has stronger connections to other nuclei within the basal ganglia (Zahm and Heimer, 1990) and the shell which has stronger connections to the amygdala and bed nucleus of the stria terminalis (Alheid and Heimer, 1988). Both natural rewards such as palatable foods (Baldo and Kelley,

2007) and artificial stimuli such as drugs of abuse (Di Chiara et al., 2004) stimulate dopamine release in the NAc. However, it appears the consequences of dopamine release in the NAc are more complex than indicating the presence of a reward. For example, several findings suggest that NAc dopamine release does not signal a hedonic (pleasurable) state. Inhibiting dopaminergic responses in the NAc, either via pharmacological lesion (Berridge et al., 1989) or through genetic inactivation of dopamine synthesis (Cannon and Palmiter, 2003), does not block behavioral preferences for rewards. Genetic deletion of dopamine synthesis in the NAc inhibits animals from seeking or working for rewards (Robinson et al., 2005), suggesting that dopamine released in the NAc may be more important for reinforcement (Berridge, 2007; Salamone et al., 2007). Electrical recordings of dopamine neurons in the VTA during learning tasks suggest these neurons also play a role in learning. The activity of dopamine neurons increases following unexpected rewards, and over time “burst” responses are stimulated by cues that predict the onset of the reward rather than the reward itself (Schultz et al., 1997). With these discoveries in male rats, mice, and rhesus monkeys, hypotheses on the role of dopamine function in the context of natural and artificial rewards have shifted. Focusing on a few species has facilitated these major advances, but as outlined below, considering species with different social systems can facilitate important insights. This is because the behavioral responses of dopamine neurons are context dependent, and examining species with different social systems expands the range of contexts that can be studied.

There is substantial evidence from a wide range of vertebrates that sexual behavior is perceived as a rewarding experience (Burns-Cusato et al., 2005; Domjan, 1992; Pfaus and Phillips, 1991; Tenk et al., 2009). However, there are some interesting species differences in how dopamine is released during mating. Rats live in complex social groups, and sexual behavior typically involves intense competition among males for mating opportunities (Calhoun, 1962). Under naturalistic conditions or cages in which females can avoid males, females control the pacing of sexual interactions by approaching and withdrawing from males (Erskine, 1989; McClintock and Anisko, 1982). This behavior has also been observed in *Mus musculus* (Garey et al., 2002). Intriguingly, dopamine release in the NAc of female rats increases during paced mating but does not increase when males have unrestricted access to females (Becker et al., 2001; Jenkins and Becker, 2003; Mermelstein and Becker, 1995). In contrast, female golden hamsters (*Mesocricetus auratus*) are solitary (Gattermann et al., 2001; Gattermann et al., 2008) and have increased NAc dopamine release during mating tests in which male hamsters have unrestricted access to females (Kohlert et al., 1997; Meisel et al., 1993). On the one hand, female hamster sexual behavior would appear to be a less dynamic process, as females often adopt the lordosis posture for several minutes at a time (Lisk et al., 1983). However, a closer examination showed that female hamsters can indeed pace mating bouts through perineal movements (Noble, 1980). This apparent pacing behavior in hamsters appears to increase the number of successful matings (Noble, 1980). Currently, it is unclear whether this more subtle pacing behavior in hamsters is critical for facilitating dopamine release, although there is some indirect evidence for a connection. Cytotoxic lesions of dopamine neurons of the basal forebrain (including nucleus accumbens) prevent increases in mating efficiency that occur with sexual experience in females (Bradley et al., 2005). It would be interesting to determine how female dopamine responses in the NAc vary across species with different levels of mating competition. One possibility is that in species with fewer mating partners, dopamine release might not be as tightly linked to mating behavior compared to other courtship cues. In monogamous zebra finches, male courtship behavior is positively correlated with the number of c-fos positive tyrosine hydroxylase (TH) neurons in the caudal VTA (Goodson et al., 2009), and electrophysiological recordings suggest that VTA neurons are more active during male courtship behavior (Huang and Nessler, 2008). It's not yet clear how these neurons respond to courtship behavior in females, and dopamine release following

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