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Sex differences in motivated behaviors in animal models

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Abstract

Sex differences exist in the motivation for sexual behavior, food, parental care and motivation to take drugs. There are also sex differences in the likelihood of exhibiting motivational disorders such as anhedonia, depression, addictive behavior, and eating disorders. This brief review summarizes recent studies on sex differences in all motivated behaviors in social and non-social contexts, focusing on animal models. We also discuss the roles of gonadal hormones and the nonapeptides (nine amino acid peptides) in modulating sex differences in motivation. We propose that sex differences in the neural mechanisms mediating endogenous motivation for food, sex, partners and care of offspring underlie sex differences in all motivated behaviors.

Introduction

Females and males differ in the incidence and expression of motivated behaviors. These differences may be qualitative, quantitative, population differences, and mechanistic [1]. There are also sex differences in the likelihood of exhibiting motivational disorders such as anhedonia, depression, addictive behavior, and eating disorders. Here we describe how sex differences in the neural mechanisms mediating endogenous motivation for food, sex, partners and care of offspring underlie sex differences in all motivated behaviors [2, 3]. In this brief review, we summarize recent advances in the studies on sex differences in motivated behaviors in both social and non-social contexts, focusing on mammalian animal models.

Sex differences in social motivation

Sexual motivation

According to evolutionary theory, a male is motivated to inseminate as many female conspecifics as possible. It follows then, the sexual motivation of a male mammal stays ‘on’ almost all the time (during the breeding season in seasonal breeders) to maximize mating opportunities. Females, however, must choose the best mate available, because after mating

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with the male they go through gestation, give birth, and provide care to the offspring. The cost of mating with low quality mates is high for females when offspring do not survive. Indeed, studies show males are highly motivated to engage in sexual behavior, as tested in a variety of paradigms involving operant lever pressing [4] and electrified grid crossing [5].

In contrast, contexts and timing are critical for sexual interactions to be rewarding in females. During a sexual encounter, females in the wild repeatedly withdraw from the male for short periods of time during the sex encounter. This repeated approach and withdrawal from the presence of the male during sexual encounters is known as paced mating or pacing behavior and it has been shown to significantly enhance fertilization. Females rats only form a conditioned place preference (CPP) for sex when it is at their preferred pacing intervals [6]. Furthermore, there is an increase in dopamine in the nucleus accumbens (NAc) only when coital stimulation occurs at the female's preferred pace of stimulation [7].

Parental motivation

In most rodent species, females provide care to their offspring and males do not, although there are some well studied exceptions such as the prairie vole and the California mouse. While specific components of parental behavior vary depending on the species, in rodents the behaviors include nest building, pup retrieval, licking and grooming. Sex differences in each component of parental behavior has been well-documented (for review on laboratory rodents [8]). There are, however, fewer studies on sex differences in the neural mechanisms mediating the motivation for parental care. Virgin male and female rodents usually do not find interactions with pups rewarding and thus do not perform spontaneous care to the pups. In fact, males in many species often attack and kill pups (infanticide) as an adaptive strategy to increase their own reproductive opportunities. Paternal behavior in mice can be induced by mating with a female and cohabitating with her after she becomes pregnant [9]. Male rats can be induced to paternal care by exposure to pups. However, it is generally believed that virgin females can be more readily induced to perform parental behavior and perform it more consistently compared with virgin male rats [10–12].

Females are motivated to care for the newborns immediately after parturition due to exposure estradiol during pregnancy [3]. Female rats will bar press to get access to pups and if pups are removed from the chamber, and will sustain motivation until hundreds of pups have been attained [13]. During the early postpartum period, a majority of rat dams show CPP for a chamber associated with pups over one associated with cocaine [14–16]. Functional magnetic resonance imaging (fMRI) studies indicate pup suckling stimulates more brain activities in the reward system than cocaine in lactating female rats [17]. There are very few data regarding the neural basis for paternal motivation. One study looking at proactive food sharing in marmoset monkeys suggests fathers and mothers have similar levels of motivation for parental care, at least in this biparental species [18].

Motivation for other social behaviors

Positive social interaction is beneficial for the survival and well-being of an individual as well as the species. Social play is a non-sexual and non-parental behavior that has been studied in juveniles of many species. Juvenile social play has long been documented as

rewarding in many laboratory species using T maze tests, CPP, and operant responding [19–23]. Non-sexual interactions among adult individuals have also been shown to be reinforcing [24–27]. Juvenile males generally play more often, though juvenile females respond more quickly for playing and they exhibit certain elements of play behavior at an earlier age [28]. Unfortunately, direct comparisons of motivation for non-sexual social interactions in adult females and males have not been possible as social motivation in adult females and males has not been investigated in the same study or using the same protocol.[e.g. 29, 30].

Sex differences in non-social motivation

Feeding

Sex differences exist in the preference and motivation for highly palatable foods in non-human animals and humans. Palatable foods seem to be inherently more rewarding for females compared to males. When tested in the CPP paradigm, palatable foods induce more robust place preference in female rats than in male rats [31]. Bouts of feeding behavior on palatable foods are longer in female rats than male rats. Studies also show that female rats work harder to obtain sucrose compared to males tested on a progressive ratio schedule that measures how many operant responses animal will exhibit to obtain the reward [32]. This sex difference in eating behavior from animal studies is consistent with the female biased prevalence of eating disorders that emerges at puberty in humans [33].

Addiction and addiction-like behavior

Psychostimulants such as cocaine act on the brain reward circuitry and thus are highly reinforcing/addictive. Drug addictions can be heuristically framed into four phases through which addicts process: acquisition, escalation, addiction, and relapse following abstinence. Sex differences are present in all phases of the addiction process in both humans and animal studies. Women have a faster escalation from initial use to addiction, a shorter interval between uses, and longer periods of use after abstinence [1, 34]. In rat studies, females acquire cocaine self-administration at a faster rate, are more highly motivated to take cocaine, and self-administer more cocaine during reinstatement [1, 34, 35]. As we discuss below, gonadal hormones, as well as the nonapeptide systems, including oxytocin and vasopressin, mediate sex differences in each phase of the addiction process.

Sex differences in neural mechanisms for motivation

The reward system and dopamine (DA)

The reward system is composed of, but not limited to, dorsal striatum (Str), ventral tegmental area (VTA), NAc, and ventral pallidum (VP). Although there are a number of neurochemicals involved in the reward system such as oxytocin and endogenous opioid peptides, DA plays an essential role in motivation. DA activation is necessary for the reinforcing properties produced by drugs of abuse and all motivated behaviors. Below we discuss how other systems (the gonadal hormone and nonapeptide systems) in males and females may interact with DA to mediate sex differences in motivation and how they may predispose certain patterns of sex differences across all motivated behaviors.

Hormonal Modulation of Motivated Behaviors

In addition to its primary role in reproduction, the ovarian hormone estradiol (E2) plays a key role in the regulation of motivation for sex, food and drug intake. E2 increases a female's willingness to approach a male and induces the production of pheromonal stimuli that make her more attractive to the male [36]. E2 exerts modulatory control over cost/benefit decision making in female rats [37]. Following ovariectomy (OVX), female rats shift their preference toward a high cost/high reward food option whereas E2 replacement subsequently reduce choice of the high effort reward. Interestingly, treatment with a selective ER α agonist (propyl pyrazole triol/PPT) or ER β agonist (DPN) alone increases preference for the high for the high effort/high reward food, whereas combination of these agonists mimics the effect of E2 [37]. E2 treatment also decreases meal size without an effect on meal frequency via acute activation of ER α [38, 39].

There are sex differences in the behavioral and neurochemical effects of acute and repeated exposure to drugs of abuse and these sex differences are modulated by gonadal hormones. E2 plays a key role in the acquisition of drug-taking behavior and motivation for drugs of abuse [1, 40] E2 also increases reinstatement of drug taking after forced abstinence. We have shown that basal DA, and the cocaine-induced DA increase in the NAc are lower in OVX females relative to CAST males. In the same animals E2 enhances cocaine-induced DA in the dorsolateral striatum (DLS) of female, but not male rats [26]. Studies in male rats have shown that when drug seeking becomes more avid, there is greater DA transmission in the DLS relative to the NAc [41]. We hypothesize that females acquire cocaine taking more rapidly and self-administer cocaine more avidly due to the lower cocaine-induced increase in DA from NAc, relative to DLS.

Interaction of oxytocin (OT) with DA

The role of OT in lactation and parturition was discovered more than a century ago. In the past several decades, OT has been found to promote sexual behavior, maternal behavior, and pair bonding by acting in a variety of brain areas including the hypothalamus, VTA, and NAc [42].

OT interacts with DA in the regulation of these behaviors as the brain areas that OT acts in are often crucial regions of the reward circuitry where DA is densely expressed (See Figure 1 for major interactions between OT and DA in a rodent brain). For instance, increased OT projections to VTA and higher DA signaling in the NAc are found in postpartum rats that perform high levels of maternal care compared to those perform low maternal care [43]. OT antagonism in the VTA abolishes these differences (both levels of maternal care and DA signaling) among postpartum rats.

Interestingly, OT acts in the VTA and the NAc to reduce palatable carbohydrate and sucrose intake in rats [44, 45]. OT damps the rewarding aspects of drugs of abuse, holding great potentials for treating drug addictions [46]. Our recent data show that OT treatment attenuates the motivation for methamphetamine (METH) intake in female rats that were highly motivated to self-administer METH [47]. How OT enhances the attachment to social stimuli while attenuating the motivation for other rewards is not known. It is possible that

OT acts on distinct groups of DA neurons depending on a social or non-social context. Indeed, a recent study reports that OT increases DA in the VTA while decreasing DA in the substantia nigra compacta (SNc) via different neuronal mechanisms [48]. It could also be that OT potentiates social motivation and by doing so reduces non-social motivation; the anxiolytic effects of OT could also play a role. On the other hand, vasopressin (VP), a closely related nonapeptide to OT, clearly mediates motivated behaviors such as pair bonding and aggression, but there is much less literature on the interaction of VP with DA in this regard.

OT and VP are differentially expressed in the CNS of males and females, which contribute to sex differences in different forms of motivation. The exact roles of these peptides in sex differences in motivation may depend on the specific forms of motivation as well as the differential effects of these peptides in the male and female systems (e.g. VP increases aggression in males and decreases it in female hamsters [49]).

Conclusions

Sexual differentiation begins after fertilization when genes on the sex chromosomes are starting to be expressed and influence the ontogeny of an organism. The differential expression of distinct genes on the sex chromosomes directly and indirectly (through differentially interacting with the whole genome) set up the cascade for sexual differentiation to influence virtually all aspects of life including all motivated behaviors. This review documents sex differences in motivated behaviors in social and non-social contexts and proposes that sex differences in the neurobiological mechanisms regulating some of the most primitive motivations such as sex and parental motivations underlie sex differences in all motivated behaviors including drug taking behaviors. Due to limits of space, we have only discussed the roles of E2 and OT (& VP) in mediating sex differences in animal models. We aim to better understand the differential prevalence of motivational disorders such as anhedonia, addictive behavior, and eating disorder in men and women, as well as provide convincing evidence to consider sex as an important variable when treating these disorders in humans.

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Highlights

Sex differences exist in motivated behaviors and prevalence of motivational disorders.

Oxytocin (a nonapeptide) enhances social motivations but attenuates food and drug motivations.

Nonapeptide systems and gonadal hormones interact with dopamine to impact motivation.

Estradiol contributes to more rapid escalation of and more avid drug taking in females.

Figure 1. Major interactions between oxytocin and dopamine in a rodent brain. (From [50] with permission)

NA, nucleus accumbens; ZI, zona incerta; MPOA, medial preoptic nucleus; PVN, paraventricular nucleus; SON, supraoptic nucleus; AMG, amygdala; VTA, ventral tegmental area; HC, hippocampus; PFC, prefrontal cortex; OB, olfactory bulbs; SC, spinal cord.