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Sexual Differentiation of Motivation: a novel mechanism?

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Abstract

Sex differences in motivation are apparent for the motivation to engage in sexual behavior, the motivation to take drugs of abuse, and the motivation to engage in parental behavior. In both males and females there is an increase in NAcc DA associated with motivated behaviors. Here it is proposed that sex differences in the regulation of DA activity in the ascending mesolimbic projections may underlie sex differences in motivation. In particular, sex differences in the neuroendocrine regulation of this brain system plays a role in the expression of sex differences in motivated behaviors. Here it is proposed that sexual differentiation of motivation is mediated, at least in part, by a novel mechanism in which ovarian hormones secreted at puberty in the female actively feminize the DA system.

Keywords

sexual motivation; drug abuse; sex differences; nucleus accumbens; striatum; dopamine; maternal behavior

Introduction

In 1959, Phoenix and colleagues proposed that during the prenatal period gonadal hormones “organize” the development of brain regions important for mating behavior. In the adult, hormones were thought to “activate” functions that were established during development to allow mating behavior to occur. The authors concluded with a discussion of the concept that behavior could be treated as a dependent variable that can be described as having been shaped by the organizational effects of hormone exposure on the brain (Phoenix, et al., 1959). This was a novel concept at the time, but many behaviors are now known to be sexually dimorphic due to developmental exposure to gonadal hormones. As we learn more about sex differences in the brain we also begin to see that not all behaviors are “organized” in the same way. Here we discuss the idea that an important component of mating behavior, motivation, is organized through a mechanism different from the prenatal androgen-driven sexual differentiation of mating behavior.

Motivation is the internal state of an individual that induces or drives someone to engage in a specific behavior. Some behaviors are what we think of as “naturally motivated” because we

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engage in these behaviors in order to survive and reproduce, and the consequence of engaging in the behavior is intrinsically rewarding. This is true for eating, drinking, and engaging in sexual behavior, where the food, water or sexual encounter are considered 'primary' reinforcers. Motivation to engage in other behaviors is learned or acquired through experience with either primary reinforcers or 'secondary' reinforcers (items that have acquired value as a reinforcer through association with primary reinforcers). On the other hand, when individuals take drugs of abuse, it is thought that these drugs tap into the endogenous reward system. Sex differences in motivation could be due to learning differences, differences in the neural systems mediating reward mechanisms, or a combination of factors.

Sex differences in motivation are apparent for the motivation to engage in sexual behavior, the motivation to take drugs of abuse, and the motivation to engage in parental behavior. In a recent chapter, Jane Taylor and I proposed that the neural systems mediating the motivation to engage in behaviors that are essential for reproductive success are different for males and females (Becker and Taylor, 2008). For most mammals, reproductive success of males depends on a reproductive system that is always ready to reproduce: motivation and sperm production are 'on' all the time. On the other hand, motivation in females varies with reproductive status (i.e., estrous cycle or pregnancy) and is, therefore, modulated by gonadal, placental and lactational hormones. There are also neuroanatomical sex differences in the motivational systems important for attachment to offspring. We proposed that sex differences in motivation occur as a result of the neural system that mediates the rapid onset of maternal motivation, causing females to form rapid and strong attachments to their young, as well as rapid attachments to other desired items with enhanced motivation to obtain the item (Becker and Taylor, 2008). This brief review will begin with an overview of some of the evidence for sex differences in motivation, then follow with a proposed mechanism for sexual differentiation of the neural systems important for this sex difference.

The Neurobiology of Reward: The Role of Dopamine (DA)

Over 50 years ago, Olds and Milner (Olds and Milner, 1954) reported that rats would press a bar to receive electrical stimulation in certain areas of the brain. Studies that followed using 'intracranial self-stimulation' found that the medial forebrain bundle was critical for the reinforcing effects of electric shock (Olds and Olds, 1969). These studies lead to the idea that there are "rewarding" areas in the brain, and the concept of a 'reward system' was derived from this concept. Subsequent research found that it was stimulation of the DA axons in the medial forebrain bundle that was critical for rewarding effects of intracranial self-stimulation (Anden, et al., 1966; Ungerstedt, 1971; Ungerstedt, 1973; Ungerstedt, 1974; Ungerstedt, et al., 1974).

As the concept of a reward system became generally accepted, the evidence was accumulating that the reinforcing properties of intracranial self-stimulation, drugs of abuse, and natural rewards were mediated by activation of the ascending DA pathway, and in the absence of DA these things were not rewarding. As Wise summarized (Wise, 1984), "The notion that cocaine and amphetamine can centrally activate natural reward mechanisms and that they owe their reinforcing action to such activation ... is consistent with the fact that these agents have the traditional properties of conventional reinforcers ... In both cases the central reinforcer can be more powerful than more "natural" reinforcers, even in cases of acute need; access to psychomotor stimulant reinforcement ... or to electrical brain stimulation ... can cause self starvation to the point of severe weight loss."

We know now that DA is not the only neurotransmitter involved in reward. As summarized in a recent review (Becker and Meisel, 2007), activation of DA, and nucleus accumbens (NAcc) DA in particular, is thought to be an internal cue that tells an animal that something is desirable, that something desired is available, or that something desirable is soon to be available.

Glutamate and GABA neurons modulate DA release, providing input related to context and motivational state. GABA and endogenous opioids also provide qualitative information about the hedonic value of a stimulus.

Sex Differences in Sexual Motivation

Male Sexual Behavior

Sexual behavior has both appetitive (motivational) and consummatory components (sexual ability) as do many behaviors (Pfaus and Phillips, 1991b). This has been elegantly demonstrated in experiments from the Everitt laboratory with male rats (Everitt, 1990; Everitt and Stacey, 1987). Everitt and collaborators demonstrated that male rats could be trained to bar press for access to a sexually receptive female rat, with the number of bar presses made by the male used as an objective measure of sexual motivation. The ability to engage in sexual behavior was measured in terms of mounts by the male when the female was delivered into the testing chamber. In this model, castration reduced both bar pressing for the female (i.e., sexual motivation) and sexual behavior (i.e., sexual ability). As would be predicted from a large body of research (reviewed in (Hull and Dominguez, 2007)), lesions of the medial preoptic area (POA) resulted in a severe impairment of male copulatory behavior, but had little effect on operant responding for access to the female. On the other hand, lesions of the basolateral amygdala (blAMY) reduced bar pressing for access to the female rat (i.e., sexual motivation), but failed to affect sexual ability (Everitt, 1990; Everitt and Stacey, 1987).

The results of these experiments demonstrate that there are distinct neural substrates for sexual motivation vs. sexual ability in the male. Furthermore, when amphetamine (AMPH) was delivered to the NAcc of male rats with a blAMY lesion, bar pressing for access to the female was reinstated. (Everitt, 1990). Since there are projections from the blAMY to the NAcc, DA in the NAcc released by AMPH was implicated in sexual motivation. Subsequently, a number of investigators have demonstrated that DA increases in the NAcc of male rats in anticipation of gaining access to a sexually receptive female rat as well as during sexual behavior. (Damsma, et al., 1992; Pfaus, et al., 1990; Pfaus and Phillips, 1991a; Pleim, et al., 1990). Thus, DA in the NAcc is playing an important role in sexual motivation in males.

It should be noted that the medial POA has also been shown to contribute to sexual motivation in male rats, ferrets, and marmosets (Hull and Dominguez, 2007). DA increases in the POA in anticipation of sexual contact in male rats (Hull and Dominguez, 2007). In the Japanese quail, sub-regions of the medial POA are implicated in sexual motivation while other regions are associated with sexual ability (Balthazart and Ball, 2007).

Female Sexual Behavior

Both male and female rats exhibit an increase in extracellular concentrations of DA in the NAcc during sexual behavior (Mermelstein and Becker, 1995; Pfaus et al., 1990; Pfaus, et al., 1995). In the female, however, the increase in NAcc DA depends upon the context in which the sexual behavior occurs. Laboratory experiments on sexual behavior in rodents have historically been studied in a small chamber. The male initiates contacts and engages in a rapid series of mounts and intromissions that ultimately lead to ejaculation (Adler, 1969; Bermant, 1961; Bermant, 1967). These conditions are not rewarding for a female rat; for the female the context and timing of the sexual encounter is critical to whether sexual behavior is rewarding (Jenkins and Becker, 2003b; Martinez and Paredes, 2001; Oldenberger, et al., 1992; Paredes and Alonso, 1997; Paredes and Vazquez, 1999).

If sexual behavior takes place in a chamber where the female can escape from the male, she will establish and maintain longer latencies between sexual contacts (Adler, 1969; Adler, 1978; Erskine, et al., 1989; McClintock, 1984). For laboratory rodents, the female will remove

herself from the presence of the male after an intromission and return to the male about 2 min later (Jenkins and Becker, 2003b). A similar behavior occurs in the wild, but with multiple partners both females and males are able to obtain their preferred pattern of contacts during the sexual encounter (McClintock, 1984). Achieving the preferred rate of copulation is important for the female rodent to optimize the rate of vaginocervical stimulation received from a male which activates a neuroendocrine reflex that is necessary for pregnancy to occur (Adler, 1969; Adler, 1978; Erskine, 1989; McClintock, 1984; McClintock and Adler, 1977).

The female's repeated approach and withdrawal from the male during a sexual encounter is known as pacing behavior (Erskine et al., 1989). Pacing behavior allows the female to control both the rate and duration of the copulatory contacts during mating. Importantly, sexual behavior is rewarding to the female rat when she achieves her preferred rate of copulation (Jenkins and Becker, 2003b; Martinez and Paredes, 2001; Paredes and Alonso, 1997; Paredes and Vazquez, 1999), whether or not she is actively pacing the rate of copulation (Jenkins and Becker, 2003a).

In females it has not been as easy to dissociate sexual motivation from sexual ability, since a test comparable to the operant paradigm used by the Everitt laboratory in male rats (Everitt, 1990; Everitt and Stacey, 1987), has not yet been developed for the female rat. Studies of feminine sexual ability usually assess lordosis intensity and/or quotient as the dependent measure (McCarthy and Becker, 2002). In females, lordosis can be activated by implants of estradiol followed by progesterone into the ventromedial hypothalamus (VMH), where this hormonal activation of the VMH is necessary and sufficient for lordosis to be exhibited (Meisel, et al., 1987; Rubin and Barfield, 1983). Of course other areas of the brain contribute to feminine sexual ability (McCarthy and Becker, 2002; Pfaff, 1980; Pfaff and Schwartz-Giblin, 1988). Studies have assessed female motivation using conditioned place preference (CPP), partner preference tests, or tests of pacing behavior, but these different tests don't always provide the same results about the neural basis of sexual motivation. In general, the NAcc and POA are both implicated in female sexual motivation, although there is some disagreement (Jenkins and Becker, 2001; Rivas and Mir, 1990; Xiao and Becker, 1997; Yang and Clemens, 2000). There is also some disagreement about the neurotransmitter systems mediating sexual motivation in females, as discussed below.

Within the NAcc, in support for a role for DA in sexual motivation in females, NAcc DA increases only when female rats are receiving copulatory stimulation at their preferred rate of intromissions, and not when they receive similar numbers of intromissions a rate faster or slower than their preferred rate (Becker, et al., 2001; Mermelstein and Becker, 1995). Female hamsters also exhibit an increase of DA in dialysate during sexual behavior (Meisel, et al., 1993). Increases in NAcc DA are not induced by coital stimulation, instead, the NAcc DA increases occur in anticipation of coital stimulation that occurs at a specific interval. These data support the hypothesis that DA increases in the NAcc signal the impending receipt of coital stimulation at the female's preferred pacing interval, and that NAcc DA plays a role in sexual motivation.

The increase in DA in the NAcc is apparently not always necessary for a female to find sexual behavior rewarding, and may shed light on what it is that DA is doing in 'reward'. Paredes and co-workers have found that pretreatment with the DA antagonists flupentixol or raclopride did not block conditioned place preference induced by paced mating in female rats (Garcia-Horsman and Paredes, 2004). In contrast the μ -opiate antagonist naloxone prevented establishment of conditioned place preference induced by paced mating (Paredes and Martinez, 2001). In these studies, animals are placed into the test apparatus for conditioned place preference training immediately after receiving an ejaculation, not during the paced mating. The rewarding value of the post-ejaculatory context is blocked by an opiate antagonist, but not

by DA antagonists. On the other hand, pretreatment of female hamsters with D2-DA receptor antagonist raclopride blocked conditioned place preferences for the place in which mating occurred (Meisel, et al., 1996). So, DA may be important for development of conditioned place preferences when sexual behavior occurs in the testing environment being conditioned. This may reflect the role DA plays in signaling that a reward is imminent (Schultz, 2001; Schultz, 2004). Alternatively, the testing environment may develop increased saliency as a consequence of this DA release, and so testing in the environment is necessary to see the dependence on DA (Berridge, 2007). A role for the endogenous opiates in the reward system is also seen in other systems (Smith and Berridge, 2007). These results suggest that activation of D2 DA receptors is not necessary for all aspects of sexual behavior to be rewarding, and that μ -opioid receptor mediated activation is also important for sexual motivation in the female rat.

Sex that is rewarding has been shown to be associated with the triggering of a neuroendocrine reflex necessary for pregnancy (Adler, 1974; Erskine et al., 1989; Gilman, et al., 1979). One possibility is that the changes in DA observed during paced mating represent a coupling of the sexual interaction and its physiological consequences, both of which are necessary for sexual behavior to be rewarding in the female. In other words, increases in DA predict the receipt of coital stimulation, but DA only increases after the initiation of the sexual encounter when the coital stimulation is occurring at a rate that triggers the neuroendocrine reflex necessary for successful pregnancy to occur. Coital stimulation is also known to induce the release of oxytocin in rats and other species (Flanagan, et al., 1993), and we infer from the studies by Paredes and colleagues that the enkephalins are also released. The coordinated release of DA, enkephalins, and oxytocin during paced sexual behavior is postulated to mediate the rewarding value of this behavior in the female.

Summary—In both males and females there is an increase in NAcc DA associated with motivational components of sexual behavior. In females, context determines whether a sexual encounter is rewarding and neuroendocrine events may contribute to the determination of the rewarding nature of the context.

Maternal Motivation: a Sexually Dimorphic Behavior

The neuroendocrinology and neurochemistry of maternal motivation has recently been reviewed quite thoroughly (Lonstein and Morrell, 2007), so the reader is referred to this excellent review for additional details. The hormones of pregnancy and parturition prime the brain for the onset of maternal behaviors, which begin at parturition as a consequence of the exposure to pups. Once maternal behaviors have been induced by the presence of the pups, expression of maternal behavior continues to occur without additional hormones as long as the pups are present. Maternal behavior is also induced more rapidly by exposure to pups during subsequent pregnancies, indicating that establishment of maternal behaviors results in long term changes in the brain. As is true of sexual behavior, there are brain regions important for the ability to engage in the behaviors that comprise maternal behavior and other brain regions important for the motivation to engage in these behaviors.

Female rats will cross electrified grids to gain access to pups (Lonstein and Morrell, 2007), and recently parturient female rats will readily learn to bar-press for access to pups, bar-pressing for hours, retrieving hundreds of pups (reviewed in (Lonstein and Morrell, 2007)). Operant responding has also been used to identify the areas of the brain that are necessary for bar-pressing for access to pups. Lesions of the POA or BLAMY reduced bar pressing for access to pups whereas lesions of the NAcc did not (Lee, et al., 2000). All lesions disrupted pup retrieval in the home cage (Lee et al., 2000). In other paradigms, lesion of the NAcc have been shown to decrease sensitivity to changes in the delivery of reinforcers (Acheson, et al., 2006), so it is possible that after NAcc lesions the bar pressing by parturient rats may reflect a learning deficit,

rather than lack of involvement of NAcc in maternal motivation. The finding that lesions of the NAcc shell disrupt pup retrieval, but not locomotor activity, argues that the NAcc is involved in some aspect of maternal motivation (Li and Fleming, 2003).

Morrell and colleagues have shown that cues associated with pups in a conditioned place preference task result in activation of neurons in the POA, prefrontal cortex, NAcc, and the BLAMY, but not the dorsal striatum (Mattson and Morrell, 2005; Mattson, et al., 2003). Based on their analysis of the neural systems mediating maternal motivation, Lonstein and Morrell (Lonstein and Morrell, 2007) propose that increased DA activity in the ascending mesolimbic circuits is necessary for many of the active components of maternal behavior.

What is unique about the motivation to retrieve pups in rats, and the positive valence of pup-associated cues, is that in adults this is primarily a trait of females. Adult male rats can be induced to exhibit parental behaviors, but it usually takes many more days to induce this response to pups in males, than it does for females (Lonstein and De Vries, 2000), and motivation to care for pups has not been examined. Sex differences in the regulation of DA activity in the ascending mesolimbic projections may underlie sex differences in motivation to engage in parental behavior, in addition to sex differences in the neuroendocrine regulation of this brain system.

Sex Differences in Drug Abuse

More men use drugs than women, but this sex difference is rapidly disappearing. In fact, the current sex difference may reflect historical differences in opportunity to experience drugs, rather than vulnerability to drug use (Van Etten and Anthony, 2001; Van Etten, et al., 1999). Use of cocaine and other stimulants in particular, have increased in the last decade among young girls so that more girls abuse stimulants in grades 8–12 than do boys (Johnston, et al., 2008). According to a recent report, among users 12–17 years old 51.5% are women, in the 18–25 age group 42.0% are women, and among cocaine users 26 years and older 38.8% are women (Johnston, et al., 2006). The use and dependence of women on stimulant drugs is steadily increasing and a growing public health concern (Carroll, et al., 2004; Lynch, et al., 2002; Wetherington and Roman, 1995).

Drug taking patterns are sexually dimorphic. Women tend to increase their rate of consumption of alcohol, marijuana, opioids and cocaine more rapidly than do men (Brady and Randall, 1999; Hernandez-Avila, et al., 2004; Lynch et al., 2002; Mann, et al., 2005; Randall, et al., 1999). Furthermore, once addicted to a drug, women can find it more difficult to quit than men do (Back, et al., 2005; Breese, et al., 2005; Carpenter, et al., 2006; Lynch et al., 2002). Among women in a residential treatment program, women tend to have greater lifetime use and greater current use of cocaine than their male counterparts (Lejuez, et al., 2007).

Of necessity, the information regarding drug use and addiction in men and women is observational or statistical in nature. Some investigators have been able to investigate the effect of ovarian hormones on the subjective effects of stimulants, which have been found to vary across the menstrual cycle (Justice and de Wit, 1999; Justice and de Wit, 2000; Justice and De Wit, 2000). Euphoria, desire, increased energy and intellectual efficiency induced by amphetamine are enhanced during the follicular phase (when estradiol levels are low at first and rise slowly; progesterone levels are low) relative to the luteal phase (when estradiol levels are moderate and progesterone levels are high). If estradiol is administered during the follicular phase of the menstrual cycle the subjective effects of amphetamine are enhanced further (Justice and De Wit, 2000). In contrast, the subjective effects of psychomotor stimulant drugs are negatively correlated with salivary progesterone levels in women (White, 2002), and progesterone administered during the follicular phase has been reported to attenuate the subjective response to repeated self-administered cocaine (Evans and Foltin, 2006; Evans, et

al., 2002; Sofuoglu, et al., 2002). Thus, ovarian hormones modulate the reward value of psychomotor stimulants in women.

Sex Differences in Response to Psychomotor Stimulants in Rats—Cocaine and other drugs of abuse act by increasing DA in the nucleus accumbens, so understanding sex differences in the effects of these drugs on the brain may provide insight into sex differences in the neural basis of reward. The acute behavioral response to psychomotor stimulants in rodents reflects both sex differences and the modulatory role of gonadal hormones in females. Research on rats and humans indicates that the behavioral effects of drugs of abuse, and the psychomotor stimulants in particular, are both sexually dimorphic and modulated by the gonadal steroid hormones (e.g., (Bazzett, et al., 2000; Becker and Beer, 1986; Becker and Ramirez, 1981b; Carroll et al., 2004; Di Paolo, et al., 1986; Di Paolo, et al., 1981; Dluzen and Ramirez, 1984; Dluzen and Ramirez, 1990; Gordon, 1980; Hruska, 1988; Hruska and Silbergeld, 1980; Joyce, et al., 1982; Lynch et al., 2002; Sell, et al., 2002; Van Hartesveldt, et al., 1989; Walker, et al., 2001).

Sensitization of AMPH or cocaine-induced psychomotor behavior can be defined as the absolute increase in the behavioral response exhibited when two tests are compared. Using this definition, gonad-intact females exhibit more robust sensitization than do intact males (Camp and Robinson, 1988a; Camp and Robinson, 1988b; Forgie and Stewart, 1994; Robinson, 1984; Robinson, et al., 1982; van Haaren and Meyer, 1991). Following ovariectomy (OVX) of female rats the expression of sensitization to AMPH is attenuated (Camp and Robinson, 1988a; Camp and Robinson, 1988b; Forgie and Stewart, 1994; Robinson, 1984; Robinson et al., 1982) or suppressed all together (Sircar and Kim, 1999; van Haaren and Meyer, 1991). Estradiol treatments in OVX rats enhance sensitization of locomotor activity induced by AMPH or cocaine (Forgie and Stewart, 1994; Peris, et al., 1991). These studies demonstrate that the neurobiological response to stimulant drugs is sexually dimorphic, but they do not address how this biological difference impacts sex differences in the motivation to take drugs.

Sex Differences in Stimulant Self-Administration in Animals—The animal model of human drug taking behavior that has the most face-validity is self-administration. In self-administration studies, animals are trained to bar-press or nose poke in order to receive access to a drug (usually by i.v. infusion). The animal's pattern of drug taking can be studied during acquisition, maintenance and relapse. It is also possible to manipulate the schedule of reinforcement in order to determine motivation to take a drug.

Sex differences have been reported during all phases of the addiction process as assessed using various self-administration paradigms (see (Becker and Hu, 2008; Carroll et al., 2004; Lynch et al., 2002; Roth, et al., 2004). When a low dose of drug is used, female rats acquire cocaine self-administration at a faster rate than do males (Davis, et al., 2008; Hu, et al., 2004; Lynch, 2006; Lynch and Carroll, 1999; Lynch et al., 2002). Estradiol treatment enhances acquisition of cocaine self-administration in OVX female rats (Hu et al., 2004; Lynch, et al., 2001).

During maintenance conditions, when given a choice between two doses of cocaine, female rats in estrus preferred higher doses of cocaine compared with females in other phases of the estrous cycle or male rats (Lynch, 2006; Lynch, et al., 2000). When the role of estradiol in 'binge' cocaine intake and subsequent motivational changes is examined, estradiol benzoate treatment increases the initial binge length and total levels of cocaine self-administration (Lynch and Taylor, 2005). In another experiment, OVX rats treated with estradiol also consumed more cocaine than vehicle treated controls (Lynch, 2006). When responding for low doses of cocaine is assessed under a schedule in which the number of responses required in order to obtain a cocaine infusion progressively increases with each dose received, motivation for access to a drug can be assessed. Under this 'progressive ratio schedule' intact female rats

reach much higher final ratios than do males, indicating that females are more motivated to obtain cocaine (Roberts, et al., 1989). Females also work harder for access to cocaine during the phase of the estrous cycle when estradiol is elevated, indicating that ovarian hormones modulate the motivation to obtain cocaine (Roberts et al., 1989). In fact, estradiol treatment enhances responding for cocaine on a progressive ratio schedule (Becker and Hu, 2008). These results show that estradiol influences both acquisition of cocaine self-administration and that there are *motivational* effects of estradiol on cocaine intake.

In contrast to estradiol, progesterone treatment given concurrently with estradiol counteracts the effect of estradiol on acquisition of cocaine self-administration behavior (Jackson, et al., 2006). We have recently confirmed this finding and find that progesterone alone does not affect cocaine self-administration, but that progesterone enhances cocaine intake in EB primed OVX rats (Yang, et al., 2007). Taken together, ovarian hormones contribute to sex differences in cocaine self-administration and estradiol in particular is a key factor influencing the reinforcing effects of cocaine in female rats. So, over the course of the estrous cycle, there are peaks and valleys during which females are more or less susceptible to the reinforcing properties of cocaine.

Castration (CAST) of males has been reported to enhance sensitization of AMPH- or cocaine-induced psychomotor behavior (e.g., (Camp and Robinson, 1988a; Camp and Robinson, 1988b; Robinson, 1984), although this result has not been found consistently (Forgie and Stewart, 1994; van Haaren and Meyer, 1991). It has been hypothesized that if CAST enhances the induction and/or expression of behavioral sensitization, that testosterone treatment should reverse this effect. This is not the case, however, as testosterone treatment has not been found to affect behavioral sensitization in CAST males (Forgie and Stewart, 1994). Furthermore, there is no effect of CAST on acquisition of cocaine self-administration behavior and a dose of estradiol that enhances self-administration in female rats has no effect on cocaine self-administration behavior in male (Jackson et al., 2006). Thus, testicular hormones do not affect self-administration in males, and the effects of estradiol on the acquisition of cocaine self-administration are sexually dimorphic.

Neural Mechanisms Mediating Sex Differences in the Ascending DA System

The sex differences in the motivation to take drugs of abuse and engage in sexual behavior or pup-related behaviors, discussed above, are most likely due at least in part to sex differences in the ascending mesotelencephalic DA systems. Basal extracellular concentrations of DA, as determined by the no net flux method, are twice as high in striatum of CAST males as in OVX females, and varies with the estrous cycle (Xiao and Becker, 1994). In experiments with *in vivo* voltammetry, cocaine or haloperidol induce a greater increase in electrical stimulation evoked extracellular DA in intact females than in males, possibly due to greater autoreceptor control of the DA transporter (DAT) (Walker, et al., 2006; Walker, et al., 2000). Following OVX, the AMPH-induced increase in striatal DA release is significantly less than the response of tissue from CAST (Becker, 1990b; Becker and Ramirez, 1981b), and estradiol treatment results in greater AMPH-induced DA in dialysate from OVX vs. CAST males (Castner, et al., 1993). A rapid effect of estradiol on the striatum of females is seen *in vitro* as well as *in vivo* (Becker, 1990b; Becker, 1990c). So, basal DA tone is chronically higher in males than in females, while the stimulated release of DA is modulated by estradiol in females, but not in males. In many systems an increase in tone is characteristic of greater basal activity within the system, but this does not appear to be the case here. In general, the male is less responsive than the female to drugs or other stimulation. This suggests that the chronic high DA signal results in down regulation of activity throughout the feedback network. Thus, when DA release is stimulated, the relative increase is less in males than in females and the behavioral response is proportionally less as well.

DA receptors are also sexually dimorphic. There are 10% more D1 DA receptors in the striatum and Nacc of male rats than in intact female rats (Andersen, et al., 1997; Hruska, et al., 1982). In one experiment intact female rats had fewer D2 receptors than males (Miller, 1983), while we have reported greater D2 binding in OVX vs. CAST in the dorsolateral striatum (Bazzett and Becker, 1994). Others have reported no sex differences in D2 binding when the entire striatum is considered (Andersen et al., 1997; Hruska et al., 1982). Additionally, in females, estradiol rapidly down-regulates D2 DA receptor binding in dorsolateral striatum of female rats (Bazzett and Becker, 1994).

Our knowledge of how estradiol acts in the striatum and NAcc of females to influence DA function is rapidly evolving. ER α and ER β are thought to associate with chaperone proteins of the caveolin family to act in concert with metabotropic glutamate receptors (mGluR) to induce second messenger signaling (Boulware, et al., 2007; Dewing, et al., 2007; Micevych and Mermelstein, 2008). Depending on which caveolin protein (caveolin-1 chaperones ER α with mGluR5 and caveolin-3 chaperones ER α or ER β with mGluR3), different intracellular signaling processes are activated (Boulware et al., 2007; Dewing et al., 2007; Micevych and Mermelstein, 2008). These effects are clearly “membrane” effects of estradiol, although the distinction between “rapid” indicating membrane effects and “slow” indicating nuclear ER activation is eroding the more we learn about the membrane effects. For example, in cells that have both membrane and nuclear ER receptors there is a synergistic interaction resulting in amplification of the effects of estradiol (Pedram, et al., 2002). Since there are some cells in the NAcc with nuclear ERs (ER α and ER β) (Shughrue, et al., 1997) it is possible that some of the effects of estradiol on motivation are mediated by a combined effect of membrane and nuclear ERs.

There is, however, one functional difference in the membrane effects of ER activation and nuclear ER activation, at least in the striatum, and from behavioral data it is inferred that this is also the case in the NAcc. The membrane ER is activated most strongly by physiological concentrations of the hormone delivered intermittently. High concentrations of estradiol, or prolonged delivery of physiological concentrations of estradiol, shut down the rapid signaling response. This is seen behaviorally where physiological doses of estradiol enhance cocaine self-administration and high doses of estradiol do not (Hu and Becker, 2008). It is also seen *in vitro* where physiological concentrations of estradiol delivered in pulses induce DA release, physiological concentrations also enhance AMPH-induced DA release but high doses of estradiol do not have this effect (Becker, 1990a). This sensitivity of the ascending DA system to estradiol is sexually dimorphic, as discussed above, and is hypothesized to underlie the sex differences in motivation.

Ontogeny and Sexual Differentiation of the Ascending DA System

As demonstrated by (Phoenix et al., 1959), the brains of mammals undergo sexual differentiation during sensitive periods of development. In rats this occurs during the perinatal period and again during the peripubertal period. Exposure to testosterone (which is converted to estradiol in some areas of the brain) during the perinatal period, influences neuronal survival, differentiation and connectivity resulting in masculinization (Becker, et al., 2005; Breedlove and Hampson, 2002). Additionally, during the peripubertal period, hormone exposure can influence neuronal and dendritic pruning (Zehr, et al., 2006), so that reorganization occurs when the brain is exposed to ovarian or testicular hormones (Sisk and Foster, 2004; Sisk and Zehr, 2005). Unlike its actions during the perinatal period, estradiol does not masculinize the female brain at puberty. As reviewed by Bakker and Baum (Bakker and Baum, 2008), evidence from the aromatase knockout mouse, taken with findings from previous research, indicates that estradiol exposure between birth and puberty is important for feminization of sexual behavior in females.

Phoenix et al., (1959) also noted that sex differences in brain function can be produced in response to exposure to gonadal hormones in the adult, or “activational” effects of hormones. This second type of sex difference can be due either to the effects of gonadal hormones acting on sexually dimorphic brain regions, or as a result of the different effects induced by ovarian vs. testicular hormones that in some neural regions may decrease differences between the sexes (McCarthy and Konkle, 2005). In the ascending DA system, it is hypothesized that both of these processes are involved, and there is sexual differentiation of the system during the perinatal period as well as an active feminization of the system by exposure to estradiol at puberty in females which induces sex differences in the activational effects of estradiol (Figure 1).

During late prenatal development of the rat, female striata are reported to display higher densities of both tyrosine hydroxylase immunoreactive (TH-IR) axons and GABA-IR cell body profiles than are seen in striata from male rats at embryonic days 16, 18, 20, and 21 (Ovtscharoff, et al., 1992). In the adult, if TH-IR in the substantia nigra (SN) and ventral tegmental area (VTA) are analyzed by stereotaxic level, the distribution of DA cells is sexually dimorphic and females have 15% more DA neurons than do males (McArthur, et al., 2007). Interestingly, if dams are given dexamethasone during the late prenatal or early postnatal period, the numbers of neurons and the 3-D architecture of the VTA and SN is de-masculinized in the male and the number of neurons is even greater in the female (McArthur et al., 2007). Since stress hormone exposure during this period of development inhibits the secretion of androgens by the male testes, these results may indicate the effects of perinatal androgen on sexual differentiation of these neurons.

Postnatally, it is known that in male rats there is over-production of D1 and D2 DA receptors in the striatum and NAcc of male rats, with a peak around postnatal day (PND) 40 with subsequent pruning (Andersen et al., 1997). In females, the over-production of DA receptors is attenuated, relative to males (Andersen et al., 1997). Gonadectomy of males or females prior to puberty does not alter the sex differences in pattern of DA receptor binding, indicating that neither the over-production or pruning are regulated by peri-pubertal hormones (Andersen, et al., 2002).

When DA concentrations in dialysate from NAcc were measured from males at PND 38 or 76 there was no difference between the ages in extracellular DA determined by the no net flux method, nor were there age differences in cocaine-induced increases in DA in NAcc (Frantz, et al., 2007). In another study there was a difference between PND35 males and adult males in cocaine-induced increases in DA in dialysate and DA reuptake in NAcc, with adolescent males exhibiting more rapid DA reuptake (Badanich, et al., 2006). If rats are gonadectomized at PND 15 (prior to puberty), males show a typical pattern of AMPH-induced DA release, while females show a more male-typical pattern of AMPH-induced DA release *in vitro*. From this it is inferred that exposure to ovarian hormones during the prepubertal period may play a role in feminizing the ascending DA system (Becker and Ramirez, 1981a).

The role of gonadal hormones in the ontogeny of sex differences in mesotelencephalic DA-mediated behaviors has not been investigated systematically. In one study, perinatal or prepubertal OVX partially masculinized dodging to protect a food item (Field, et al., 2004), a behavior that has been shown to be mediated by striatal DA activity (Field, et al., 2000). In another study, female rats exhibit greater exploratory activity in a large novel open-field than do males (Stewart and Cygan, 1980). This enhanced activity in the open-field is seen in females if animals are not exposed to gonadal hormones during the perinatal period **and** if they are exposed to estradiol during the period prior to weaning (days 10–20 when there is an endogenous surge of estradiol in females) or during the peripubertal period (days 30–40). Male rats gonadectomized at day 1 (GDXd1) and treated with estradiol on days 10–20 or 30–40

show higher levels of open-field activity than animals GDXd1 but not treated with estradiol (Stewart and Cygan, 1980). A model for this pattern of sexual differentiation is presented in Figure 1.

Enhanced activity in a novel-environment is a trait that predicts rapid acquisition of self-administration of cocaine or AMPH in rats and higher rates of AMPH- and cocaine-induced locomotor activity (Piazza, et al., 1998) It is possible, therefore, that the more rapid acquisition of drug taking seen in female rats is due to the absence of exposure to hormones perinatally plus exposure to estradiol prior to weaning and/or at puberty.

In male rats, prenatal stress during the third week of gestation attenuates testicular hormone release and masculinization of sexual behavior (Meisel, et al., 1979). Prenatal stress during the third week of gestation also enhances the acute response to AMPH and the amount of AMPH that animals will self-administer (Deminiere, et al., 1992). In pilot studies, prenatal stress enhances acquisition of cocaine-self administration in males but not females (Thomas, et al., submitted).

So, the available data suggest that **feminization** of the ascending midbrain DA neurons, novelty-induced locomotor behavior, and drug taking behavior, occurs if animals are NOT exposed to gonadal hormones during the perinatal period and are subsequently exposed to estradiol during the peripubertal period. In other words, it is hypothesized that there are at least two active processes working at cross-purposes during ontogeny of the ascending DA systems. Testicular hormones perinatally induce masculinization of neuronal architecture and neuronal survival in the VTA/SN and peripubertal estradiol feminizes the system, perhaps acting on GABAergic cells and/or DA terminals in the striatum and NAcc to change the basal set-point of the system and induce permanent sensitivity to estradiol. It is also possible that testicular hormones at puberty further reduce the sensitivity to estradiol in males (Figure 1).

Since this is a fairly new concept in the field of sexual differentiation of the brain, there are no data regarding apparently permanent changes in the brain induced by exposure to estradiol during the peripubertal period. From the breast cancer literature there are data that estrogenic exposure during the peripubertal period can result in epigenetic changes that result in reprogramming of the mitogen activated protein kinase (MAPK), and caveolin-1 genes in mammary tissue (De Assis and Hilakivi-Clarke, 2006) that have long term effects on the likelihood of a woman getting breast cancer due to enhanced sensitivity to estradiol exposure. Since estradiol's effects in the striatum/NAcc are thought to be dependent on caveolin 1 to facilitate the association between ER α and mGluR5, one possibility is that estradiol at puberty is inducing epigenetic changes that result in a reprogramming of the striatal/NAcc response to estradiol. This is proposed to have functional consequences for the ascending DA system resulting in sexual differences in the motivational system.

Summary

Sex differences in the DA system of the NAcc and striatum are thought to mediate the sex differences in motivation. We have previously hypothesized that the presence of the neural circuits that mediate maternal motivation, and in particular the greater oxytocin projection to the NAcc in females, may contribute to this sex difference (Becker and Taylor, 2008). In addition, there are effects of gonadal hormones that modulate the reward system. Developmental events that lead to sex differences in motivation have not been investigated systematically, and may provide insight into the neurobiology of this system and lead to novel gender-specific approaches for treatment of drug abuse and other motivational disorders. Here it is proposed that sexual differentiation of the motivational system is mediated by a novel mechanism in which ovarian hormones secreted at puberty in the female can actively feminized the DA system.

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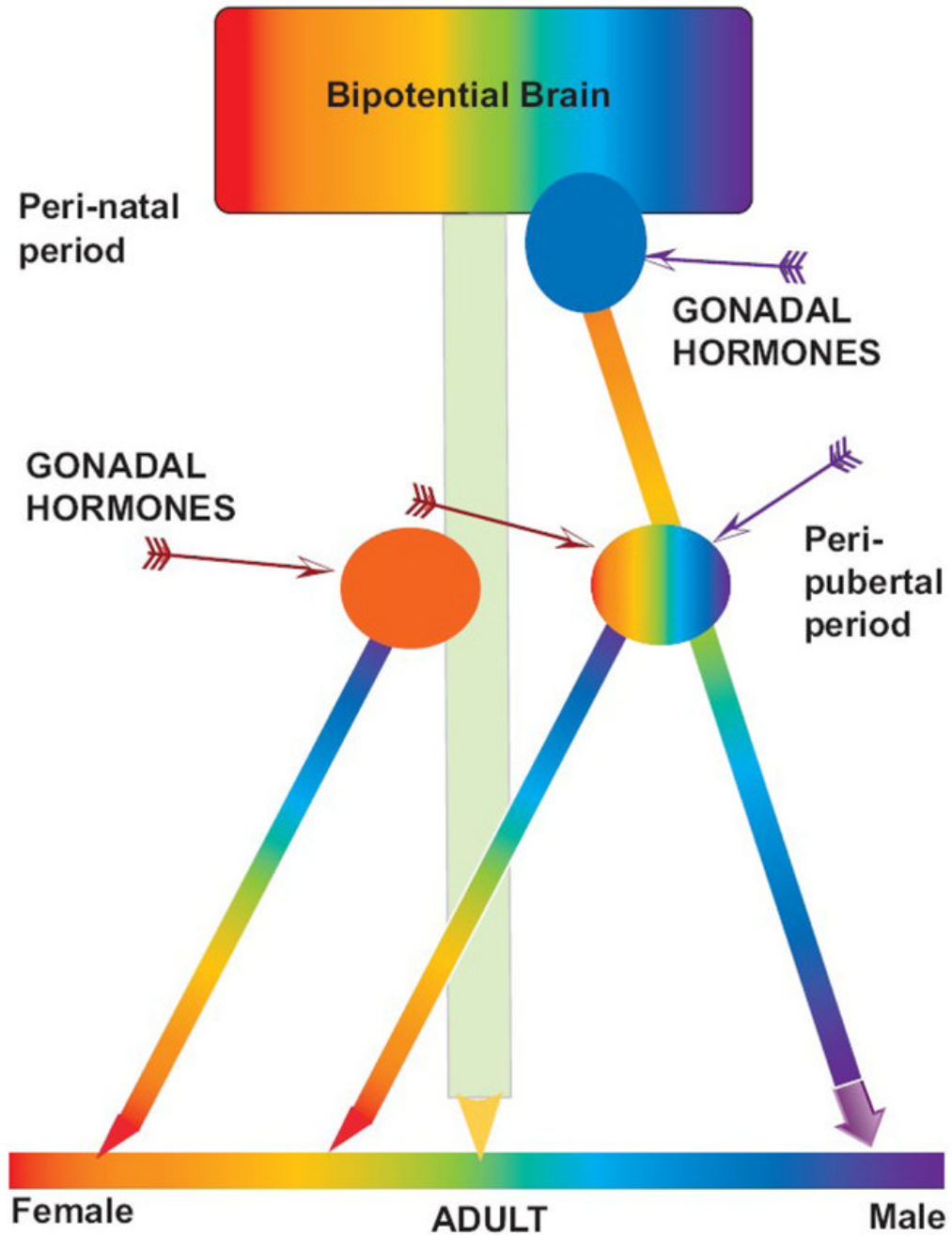


Fig 1. Schematic of hypothesized events determining sexual differentiation of motivation mediated by the ascending DA system

Gonadal hormones act in the rat brain during the sensitive perinatal period and again during the peripubertal period to result in adult sex differences.

During the peri-natal period in the rat, testicular hormones (Blue oval, purple arrow) act on the bipotential brain to induce masculinization of the brain (rainbow colored heavy arrow on the right). In the absence of testicular hormones the brain remains feminine (green arrow in center). During the peri-pubertal period, estradiol (red arrows), released from the ovary (orange oval) and possibly if given exogenously to a CAST male, permanently feminizes the neural response

to estradiol. Testicular hormones may further masculinize the system at puberty or have no effect.