Pharmacology Biochemistry and Behavior, Vol. 64, No. 4, pp. 803–812, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00168-9

Gender Differences in Dopaminergic Function in Striatum and Nucleus Accumbens

JILL B. BECKER

Psychology Department, Biopsychology Area, Reproductive Sciences Program and Neuroscience Program, The University of Michigan, 525 E. University, Ann Arbor, MI 48109

BECKER, J. B. *Gender differences in dopaminergic function in striatum and nucleus accumbens.* PHARMACOL BIOCHEM BEHAV **64**(4) 803–812, 1999.—In female rats the gonadal hormones estrogen and progesterone modulate dopamine (DA) activity in the striatum and nucleus accumbens. For example, there is estrous cycle-dependent variation in basal extracellular concentration of striatal DA, in amphetamine (AMPH)-stimulated DA release, and in striatal DA-mediated behaviors. Ovariectomy attenuates basal extracellular DA, AMPH-induced striatal DA release, and behaviors mediated by the striatal DA system. Estrogen rapidly and directly acts on the striatum and accumbens, via a G-protein–coupled external membrane receptor, to enhance DA release and DA-mediated behaviors. In male rats, estrogen does not affect striatal DA release, and removal of testicular hormones is without effect. These effects of estrogen also result in gender differences in sensitization to psychomotor stimulants. The effects of the gonadal hormones on the striatum and ascending DA systems projecting to the striatum and nucleus accumbens are hypothesized to occur as follows: estrogen induces a rapid change in neuronal excitability by acting on membrane receptors located in intrinsic striatal GABAergic neurons and on DA terminals. The effect of these two actions results in enhanced stimulated DA release through modulation of terminal excitability. These effects of gonadal hormones are postulated to have important implications for gender differences in susceptibility to addiction to the psychomotor stimulants. It is suggested that hormonal modulation of the striatum may have evolved to facilitate reproductive success in female rats by enhancing pacing behavior. © 1999 Elsevier Science Inc.

Amphetamine Cocaine Estrogen Progesterone Sensitization Sexual behavior

THERE is substantial evidence that gonadal hormones modulate behavioral and neurochemical indices of activity in the striatum and nucleus accumbens, and there are gender differences in this regard [e.g., (10,11,14,41,42,44,49,58,64,67,70, 127)]. For example, during naturally occurring behavioral estrus, amphetamine (AMPH)-induced striatal dopamine (DA) release and AMPH-induced behaviors are greater than on other days of the estrous cycle (13,14,16). AMPH and other drugs that act via these DA systems have been important tools in studying these effects of gonadal hormones. After receiving AMPH or other DA-mimetic drugs, the behavioral syndrome that results is predominantly mediated by the activity of DA in the striatum and nucleus accumbens. This has been repeatedly demonstrated in experiments in which these DA systems are either lesioned or blocked pharmacologically [e.g., (2,35,55,124,125)]. Thus, it is interesting to note that ovariectomy attenuates while estrogen treatment in ovariectomized (OVX) female rats rapidly enhances both AMPH-induced striatal DA release and AMPH-induced behaviors (9,14,31,111,137). Furthermore, the effects of estrogen are sexually dimorphic. In the male rat, estrogen does not produce the same effects (9,31). This article will review the author's interpretation of the results of research on this topic and propose a model for how gonadal steroid hormones may be acting in females to produce the observed results. Finally, the relevance of these effects of ovarian hormones for gender differences in more naturally occurring behaviors will be discussed.

GONADAL HORMONES INFLUENCE BEHAVIORAL AND NEUROCHEMICAL INDICES OF DOPAMINE FUNCTION IN STRIATUM AND NUCLEUS ACCUMBENS

Estrous Cycle

During the estrous cycle, ovarian hormone fluctuations induce variation in behavioral and neurochemical responses to psychomotor stimulant drugs. Female rats show a greater behavioral response (e.g., rotational behavior, stereotyped behaviors) when the striatal DA system in stimulated, pharmacologically or electrically, on the evening of behavioral estrus (6–12 h after the surges of estrogen and progesterone) than they do 24 h later on diestrus 1 (13,16,71,112). Female rats also show enhanced sensorimotor function on estrus compared with diestrus (19). Striatal DA metabolism and AMPH-stimulated release of DA either in vitro or in vivo are greater during estrus than on diestrus (8,13,69), while striatal DA uptake sites are highest on the morning of proestrus (91). The basal extracellular concentrations of DA in the striatum, determined by quantitative microdialysis, are greater on estrus than on diestrus (134). There is also estrous cycle-dependent

variation in striatal DA receptors (40,82). Thus, coincident with the endogenous surges of estrogen and progesterone, there is enhanced presynaptic DA activity, as indicated by enhanced DA release, metabolism, and reuptake. To determine the roles of the ovarian hormones, it is important to see what happens when these hormones are removed and subsequently replaced.

Effect of OVX

Rotational behavior induced by AMPH or electrical stimulation of the ascending DA projection decreases within 2–3 weeks after OVX (11,27,111). OVX also decreases basal extracellular DA concentrations in striatum (134), AMPH-stimulated striatal DA release (14,15), and striatal DA transporter density (23). Striatal DA-stimulated adenylate cyclase activity is lower, and D_1 DA receptor density is decreased in OVX relative to intact females (78,82). By contrast, OVX-induced supersensitivity of striatal D_2 DA receptor binding sites develops over 2–3 months (65) [c.f. (58)]. Furthermore, there is an increase in the ratio of high:low affinity D_2 DA agonist binding sites following OVX (40). This is apparently followed by an increase in D_2 DA receptor B_{max} at 3 months post-OVX (58). So, OVX results in a decrease in behavioral and neurochemical indices of presynaptic DA functions and induces a decrease in D_1 DA receptor function, while D_2 DA receptor binding is increased.

Effects of Acute Estrogen Treatment

The acute administration of estrogen to OVX rats induces a rapid (within 30 min) increase in AMPH-induced striatal DA release as detected by in vivo microdialysis (9,17,31). Estrogen also induces an increase in striatal DA turnover (43) and downregulates D_2 class DA receptors (3). These effects are thought to be due to the direct effect of estrogen on the striatum, as physiological concentrations of estrogen in vitro enhance the AMPH- or K^+-induced release of DA from striatal tissue (8), and interfere in vitro with the GTP-induced affinity shift of D_2 DA receptors (81). Furthermore, the pulsatile administration of physiological concentrations of estradiol to striatal slices directly stimulates DA release in vitro (8). Thus, estrogen acts directly on the striatum to induce changes in DA release and DA receptor activity. Estrogen has also been shown to act directly on the nucleus accumbens to enhance K^+-stimulated DA release (121). Local injection of 20–50 pg 17β-estradiol, but not 17α-estradiol, produces a rapid (within 2 min) and dramatic increase in stimulated DA overflow in nucleus accumbens detected by in vivo voltametry. Although there has been less research on estrogen–DA interactions in the nucleus accumbens, the work of Thompson and Moss (121) suggests that the mechanism(s) mediating the effects of estrogen in the nucleus accumbens and striatum are similar.

In cultured striatal neurons from an embryonic mouse, estrogen induces changes in adenylate cyclase activity stimulated by D_1 and D_2 DA receptor agonists by apparently modifying the G-protein coupling process (83,84). This effect is prevented by inhibition of protein synthesis (84), suggesting that classical estrogen receptors may be involved in this phenomenon (although second-messenger induction of protein synthesis also occurs). Estrogen receptor mRNA is present in the striatum during development at postnatal days 10–12 in the female rat, and there is specific binding to estrogen receptors at this time (123). Therefore, the effect reported by Maus et al. (83,84) may reflect the early developmental stage of the neurons obtained for culture. It is also possible that the culture system in some way affected protein expression, and consequently, the time course of the expression of the response to estrogen. In the adult rat, there are few, if any, classical estrogen receptors (ERα) in the striatum (93). Nor is the newly cloned estrogen receptor, ERβ (77) found in the striatum of the adult female rat (118). Furthermore, because the effects of estrogen reported in the adult striatum occur within minutes or seconds, it seems unlikely that the rapid effects of estrogen in the adult rat striatum are mediated by genome-activating estrogen receptors.

Electrophysiological studies have shown that estrogen can induce rapid changes in the response of striatal neurons to D_1 and D_2 DA agonists (38). Results from experiments using whole-cell clamp electrophysiology in acutely dissociated striatal neurons indicate that there are also rapid effects of estrogen on L-type Ca^{2+} channels in striatal neurons (89). In this preparation the acute application of 17β-estradiol decreases Ca^{2+} currents. The effects are rapid (within seconds), reverse as soon as estrogen delivery ceases, are sex specific (cells from females show a greater response than males), and are seen at physiologically relevant concentrations of estrogen (i.e., pM). Furthermore, estrogen conjugated to bovine serum albumin (BSA, prevents estrogen entry onto cells) is also effective. Interestingly, estrogen applied internally to cells through the electrode is not effective at reducing Ca^{2+}-currents, nor does it block the effect of 1 pM estrogen applied externally. Collectively, these results suggest that the effect of estrogen occurs externally at the membrane surface. In the presence of GTPγS (which prevents inactivation of G-protein–mediated events) the effect of 17βestradiol does not reverse when hormone delivery ceases. Thus, the effect of estrogen on striatal neurons is apparently dependent upon a G-protein–coupled receptor. Finally, the effect of 17βestradiol is stereospecific—as 17α-estradiol does not mimic the modulation—and steroid-specific, as 100 pM estrone and 3-methoxyestriol were ineffective while estriol or 4-hydroxy-estradiol mimic the effect of 17β-estradiol. The striatal neurons used in these studies were medium spiny neurons, which are primarily GABAergic (57,133). It is concluded, therefore, that estrogen has rapid stereospecific effects on striatal GABAergic neurons that alter signaling pathways independent of genome-activating estrogen receptors (89).

In in vitro superfusion experiments we find that the effects of estrogen on AMPH-induced striatal DA release are mimicked by the catechol–estrogens or estrogen–BSA, but not by the nonsteroidal estrogen agonist, diethylstilbestrol (DES), or by estriol or estrone (137). Furthermore, the effect of estrogen to enhance AMPH-induced DA release from striatal tissue in vitro is blocked by the steroidal estrogen receptor antagonist ICI 182,780, but not by the nonsteroidal estrogen antagonist, tamoxifen (136). Thus, the pharmacology of the effects of estrogen in the striatum indicate that it is steroid specific with characteristics distinct from ERα: 1) a rigid steroidal conformation is necessary for efficacy; and 2) hydroxylation of the A-ring does not inhibit, while modification of the D ring prevents, efficacy of a compound in the striatum. In addition, it is not necessary for estrogen to enter a cell to produce its effect in the striatum, as estrogen–BSA mimics the effect of estrogen to enhance AMPH-induced DA release. Finally, there is a rapid downregulation of D_2 DA receptor binding within 30 min following estrogen administration (3).

The rapid effects of estrogen on D_2 DA receptors and DA release in striatum and nucleus accumbens are associated with an enhancement of sensorimotor function and DA-mediated

behaviors (9,19,31). During the estrous cycle, however, the female rat is exposed to estrogen repeatedly. Therefore, if hormonal modulation of the striatum and nucleus accumbens are important for naturally occurring behaviors, it is important to determine how both estrogen and progesterone affect DA function in these brain regions.

Effects of Estrogen and Progesterone Treatments

Estrogen and progesterone are the hormones released during the estrous cycle that have been found to affect striatal DA function. Effects of physiological doses of estrogen on the striatum have a rapid onset, but there are also long-term effects of repeated hormone treatments that vary with the time after cessation of treatment. When testing occurs 1–4 h following the last dose of estrogen (2–4 days of estrogen within the physiological range), or after repeated estrogen followed by progesterone treatment, the AMPH- or K^+-stimulated release of DA from striatal tissue in vitro is potentiated (11,12,14,44) as are AMPH-induced behaviors (11). On the other hand, 24 h after 3 days of estrogen treatments, there is a significant decrease in the high/low affinity states of the striatal D_2 DA receptor (33). The behavioral effects of DA mimetics, 24–48 h after estrogen, are either attenuated or unchanged (11,20,52,58,59). Recently, however, we have found that 24 h after the last of 4 days of estrogen treatment (5 μg/day) AMPH-induced DA in dialysate and AMPH-induced stereotyped behaviors are significantly greater than that seen in OVX rats that do not receive estrogen treatment, but significantly lower than the responses of rats that are tested 30 min after the last of four daily estrogen treatments (17). Finally, 2–8 days after the termination of estrogen treatment there is a second phase when the behavioral response to AMPH or apomorphine is again enhanced (11,58,59,67,70). The first two phases of this response have only been reported in female rats. The third phase has been reported to occur in both males and females. This sex difference indicates that phase 3 can occur independently of the first two phases, and suggests that more than one mechanism is involved.

A very different response to estrogen treatment is obtained when high doses of estrogen are administered or when estrogen treatment is extended for more than 4 days. With chronic estrogen treatment, or with high doses of estrogen, presynaptic DA activity is decreased, and D_2 DA receptor supersensitivity is reported (39,42,63,67). The mechanism(s) through which the effects of prolonged estrogen treatments affect striatal DA activity have not been investigated to a great extent. In one experiment, intrastriatal implants of estradiol were found to enhance rotational behavior, but only after the striatum had been exposed to estradiol for 4 days (113). Roy et al. (113) did not determine the extent of estradiol diffusion from the site of the unilateral implant, however, so whether the enhanced rotational behavior is due to the actions of estradiol in the striatum, or at an adjacent site, is not known. Nevertheless, these results, and other findings discussed above, raise the possibility that estrogen may also have actions on the striatum mediated by genome-activating estrogen receptors. Whether these effects are mediated by a small number of classical estrogen receptors (ERα or ERβ) in the striatum or indirectly by estrogen receptors in adjacent/afferent brain regions remains to be determined.

Progesterone has also been shown to enhance DA release in striatal tissue from estrogen-primed OVX female rats (44,45,47,48,50). Furthermore, after estrogen priming, a membrane-associated protein with high affinity for progesterone has been isolated from the striatum (74,100). The effect of progesterone on striatal DA release is not seen without estrogen priming. Thus, there are acute effects of estrogen on striatal neuronal activity, striatal DA receptor binding, and striatal DA release, as well as a long-term effect that primes progesterone receptors. Recently, we directly compared the effect of repeated estrogen with acute estrogen or progesterone treatment on striatal DA activity. We find that prior exposure to estrogen enhances the effects of subsequent estrogen or progesterone treatments on AMPH-stimulated DA in dialysate from dorsolateral striatum (17). This confirms previous reports that progesterone, without estrogen priming, is ineffective in this regard (45). Behaviorally, AMPH-induced rotational behavior and stereotyped behaviors are enhanced by a single dose of estrogen, repeated estrogen treatment, or during the evening of behavioral estrus (6–12 h after the estrogen surge) (9,11,13,17). The enhancement of AMPH-induced DA detected in dialysate is greater following repeated treatments than with a single acute treatment, suggesting that physiological doses of estrogen produce both acute and long-term effects in the striatum (17).

Males

It has been reported that there are no differences between intact and castrated (CAST) males in the efficacy of AMPH or apomorphine to induce stereotyped behaviors (114,128). Other studies have reported that CAST increases AMPH-induced stereotypy (6) or prolongs chlorpromazine-induced catalepsy (90). However, it is difficult to dissociate these increases in drug-induced behaviors from the decreased rate of liver microsomal enzyme activity that accompanies CAST (34). When intact male and CAST male rats are given the same dose of AMPH (1.25 mg/kg, IP), brain concentrations of AMPH are significantly higher in the CAST group at 30 and 60 min after injection (unpublished results from the Becker laboratory). Therefore, the differences that Beatty et al. (6) find in stereotypy after CAST may be attributable to different brain concentrations of AMPH. In fact, when different systemic doses are used to produce equivalent brain concentrations in CAST and intact males, the two groups do not differ in AMPH-induced rotational behavior or stereotypy (27). In addition, CAST does not alter rotational behavior induced by unilateral electrical stimulation of the ascending nigrostriatal bundle (112). In contrast, spontaneous shuttle box activity is reported to be increased following CAST compared to intact males (46), although open-field activity is not reported to be affected by CAST (5).

Gender Differences

Intact female rats show more intense and prolonged stereotyped behavior after AMPH or apomorphine administration (6,66), a greater decrease in activity in response to chlorpromazine or haloperidol (7,90) and more AMPH-stimulated rotational behavior than do males (109). Although there are gender differences in drug metabolism, the gender difference in rotational behavior persists even when brain levels of AMPH are equivalent (16). This suggests that although most reported gender differences in response to AMPH may be greater in magnitude than would be found if brain levels of the test drugs were equalized, there are underlying gender differences in the organization of the striatal DA system. This idea is supported by research on gender differences in the behavioral response to cocaine, where males and females do not differ in cocaine metabolism (25). Female rats also exhibit

greater locomotor activation in response to cocaine than do male rats (126).

In addition to gender differences in the behavioral response to psychomotor stimulants, there are more D_1 DA receptors in the striatum of male rats than in intact female or OVX rats, but no gender difference in striatal D_2 DA receptors (65,80). In vitro, the AMPH-stimulated increase in striatal DA release is comparable in intact male rats and intact female rats in estrus (14). Females, however, are found to have a higher density of DA transporter mRNA in striatum than do males (23). There are also gender differences in basal and AMPH-stimulated striatal DA release in the absence of gonadal hormones. Following OVX, the AMPH-induced increase in striatal DA release is significantly less than the response of tissue from CAST (14). Finally, results from in vivo microdialysis in freely moving rats indicate that the basal extracellular concentrations of DA are twice as high in striatum of CAST males as in OVX females (134). These sex-related differences in striatal DA release and receptors likely reflect an underlying sexual dimorphism in the organization of the striatum (30).

A MODEL FOR ESTROGEN–DOPAMINE INTERACTION IN STRIATUM AND NUCLEUS ACCUMBENS

Figure 1 illustrates schematically our current working hypothesis on how estrogen is acting acutely in the striatum to enhance DA release in female rats. It is hypothesized that estrogen can affect DA release in two ways. First, estrogen acts on intrinsic medium spiny striatal neurons (89), which have recurrent collaterals onto DA terminals, to inhibit Ca^{+2} current in these neurons. Because medium spiny striatal neurons are primarily GABAergic neurons, we speculate that the effect of reduced Ca^{+2} current is to decrease GABA release. This, in turn, results in a decreased response to GABA at the DA terminals and increased stimulated DA release. Second, estrogen is hypothesized to act directly on DA terminals to downregulate D_2 DA autoreceptors. This also results in a release from the inhibitory action of these receptors and increased stimulated DA release.

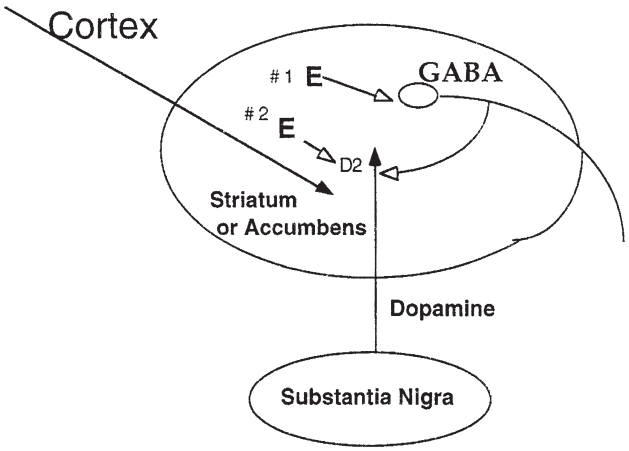

FIG. 1. Two mechanisms are postulated to contribute to the effect of E on stimulated DA release in female rats: #1—Estrogen acts to inhibit intrinsic GABA neurons that have recurrent collaterals onto DA terminals. This results in greater DA release. #2—Estrogen acts on DA terminals to enhance DA release by downregulating presynaptic D_2 DA receptor function.

The first component of this model is supported by data that indicates GABA inhibits K^+-stimulated DA release from nigrostriatal terminals by its action on GABA-B receptors (24,101). Thus, if estrogen inhibits GABA release, this would result in an enhancement of stimulated DA release. This, in turn, could cause enhanced activation of pre- and postsynaptic DA receptors. The effect of DA at presynaptic DA receptors results in enhanced activity at the DA transporter (86). Therefore, the effect of DA at both pre- and postsynaptic DA receptors results in downregulation of the D_2 DA receptor (32).

We postulate further that there is a separate, independent, effect of estrogen on presynaptic D_2 DA receptors. This idea is supported by research indicating that estrogen in a synaptosomal preparation prevents the GTP-induced affinity shift of D_2 DA receptors (81). Further research is needed to determine whether the rapid changes in D_2 DA binding (3), and the changes in DA binding and DA transporter activity during the estrous cycle (40,91), are directly caused by the effects of estrogen on presynaptic DA terminals or indirectly mediated by the effect of estrogen on striatal neurons.

This model assumes that these effects are sexually dimorphic, in that the GABAergic neurons and DA terminals in male rats do not contain (or contain lower concentrations of) the receptors mediating these responses to estrogen. Finally, the mechanism(s) through which the effects of repeated estrogen treatment result in an enhanced rapid response to estrogen remain to be determined. As discussed above, the long-term effects of estrogen may be mediated by other mechanisms. There could be cumulative effects of estrogen mediated within the striatum via cumulative effects of activation on specific second messengers. Alternatively, estrogen could be acting at sites external to the striatum to further enhance the striatal response to estrogen.

A ROLE FOR GENDER DIFFERENCES IN BEHAVIORS MEDIATED BY THE STRIATUM

Implications for the Behavior of the Rat

What are the implications of these gender differences in the effects of estrogen on the striatum for other species, and how are they manifest in functions associated with the natural behavior of rats? Two examples are presented.

First, gender differences in the striatum result not only in an enhanced acute response to psychomotor stimulants, but also in an enhancement in sensitization to psychomotor stimulants. Behavioral sensitization refers to an increase in drug effect with repeated drug administration. Typically, behavioral sensitization is quantified as a progressive increase in the behavioral response to a drug with successive injections of a constant dose of that drug. Gender differences in sensitization may have important implications for gender differences in addiction in humans.

Second, gender differences in the striatum are important for the reproductive success of the female rat. In the female rat, estrogen in the striatum enhances specific components of sexual behavior (i.e., pacing behavior), thereby increasing fertility. Thus, it is suggested that the gender differences discussed above have important consequences for the female rat in the wild.

Behavioral Sensitization

So far we have dealt solely with gender differences in the acute effects of psychomotor stimulants. It is well established,

however, that the effects of drugs change with repeated administration, and these changes take two general forms: tolerance or sensitization (76,120). Historically, tolerance (i.e., the progressive decrement in responses induced by subsequent exposures to a drug), and its role in the development of physical dependence, have been a central focus of research on addiction (68,76,122,129,132). There is increasing evidence, however, that sensitization-related neuroadaptations may play an important role in the process of addiction (21,37,61, 62,79,97,106,110,115,120). It is beyond the scope of this article to completely review the sensitization literature. Sensitization has been, however, the topic of a number of review articles to which the reader is referred [e.g., (72,99,104,105,107, 116,117,131)]. Some critics have argued that sensitization is merely a phenomena of pharmacokinetic changes; however, behavioral sensitization to cocaine clearly occurs in the absence of altered brain cocaine levels (22). For additional discussion of how behavioral sensitization can be dissociated from pharmacokinetics the reader is referred to the reviews cited above and to the work of Stewart and colleagues (119,120).

The literature on gender differences in sensitization of AMPH- and cocaine-induced psychomotor behavior is both convincing and problematic. If one considers sensitization of AMPH or cocaine-induced psychomotor behavior to be the absolute increase in the behavioral response exhibited when the results of two behavioral tests are compared, females exhibit more robust sensitization than do intact males (28, 29,56,103,108,126). The studies looking at AMPH-induced behaviors are confounded, however, by gender differences in AMPH metabolism (16). Robinson (103) attempted to control for metabolic differences by giving females a lower dose than males (2.6 vs. 3.0 mg/kg). These doses were calculated from previous research based on brain concentration of AMPH at 30 min and 1 h postinjection (16); however, rotational behavior was recorded for 2 h post-AMPH. Because males exhibit more rapid AMPH metabolism, and gender differences become more pronounced with time postinjection, it is not really possible to determine from these data the magnitude of the gender difference in sensitization to AMPH. Camp and colleagues (28) attempted to address this problem by giving females a substantially lower dose of AMPH on a challenge test. Females received 2.6 mg/kg AMPH during the sensitizing regimen and 1.78 mg/kg on the challenge test, while males received 3.0 mg/kg AMPH on all tests. Stereotyped behavior exhibited by females on the challenge test was significantly greater than for males on the challenge test, supporting the idea that gender differences in AMPH metabolism are not the only cause of the gender differences in behavior reported. Thus, females apparently exhibit more robust behavioral sensitization to AMPH than do males, but the magnitude of the difference has not been addressed by the research to date. Finally, it has been reported that there are gender differences in sensitization of AMPH-induced rotational behavior at a high dose of AMPH, but not at a low dose (103). This suggests that there may be gender differences in the dose–effect curve for the induction and/or expression of sensitization.

Research on gender differences in the sensitization of cocaine-induced behavioral activity is less problematic, as cocaine metabolism is the same in males and females (25), and yet females again exhibit greater behavioral sensitization (126). Research on sensitization to cocaine has been problematic in intact female rats, as cocaine has been shown to disrupt neuroendocrine function in rats (102) and other species (87). Thus, the specific roles for ovarian hormones in sensitization has been difficult to parcel out.

In general, OVX of female rats does not affect the induction or expression of sensitization (28,29,56,103,108), although in one report OVX females did not exhibit sensitization of cocaine-induced locomotor activity when intact females did (126). Interpretation of reports that intact and OVX females do not differ in behavioral sensitization to AMPH or cocaine is further complicated by reports that estrogen treatments enhance sensitization of locomotor activity induced by AMPH or cocaine (56,92). These apparently conflicting results suggest that variability in the behavior of intact female rats across the estrous cycle may obscure the effects of ovarian hormones on the induction and/or expression of sensitized psychomotor behaviors.

Castration of male rats has been reported to enhance sensitization of AMPH- or cocaine-induced psychomotor behavior [e.g., (28,29,103)], although this result has not been found consistently (56,126). It has been hypothesized that if castration enhances the induction and/or expression of behavioral sensitization, then 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 (56). Thus, the role of testicular hormones in sensitization to psychomotor stimulants remains an open question.

Behavioral sensitization has important implications for gender differences in susceptibility to cocaine addiction. According to a recent report, 9% of women age 12 and over have used cocaine. The only illicit drug used more by women is marijuana (28% have used marijuana) (73). Among women who have used cocaine, the prevalence of lifetime dependence for cocaine is 14.9 $\pm$ 2.0% (mean $\pm$ SD). This is in contrast to alcohol where 79% have used alcohol, but only 9.2 $\pm$ 0.8% have developed a lifetime dependence (73). The use of all illicit drugs has been increasing among women in the past decade, and cocaine dependence among women, in particular, is a growing public health concern (130).

It is unlikely, however, that these gender differences in the brain evolved to make individuals more susceptible to drug addiction.

Pacing of Sexual Behavior

Demonstrating that estrogen in female rats modulates the sensorimotor function and DA-induced behaviors through its effects on the striatum has been important for understanding how estrogen affects this neural system. However, our understanding of the role this phenomena plays in the behavior of the rat in the wild remains relatively speculative. One report suggests that estrogen acting in the striatum enhances sensorimotor behavior, allowing female rats to traverse narrow pieces of wood with greater precision during estrus (19). Yet, although it may be adaptive for a female rat to be able to traverse the environment more efficiently when she is in behavioral estrus, the strength of this relationship is weak. Evolutionary biologists argue that biological functions that vary with the reproductive cycle are likely to play a role in reproduction. Therefore, my laboratory began to look for a role for the ascending DA systems in sexual behavior.

Research on the role of the ascending DA systems in sexual behavior of the male rat suggests that the nucleus accumbens is important for anticipatory or motivational components, while the striatum is important for consummatory aspects of sexual behavior (36,94–96). In male rats, extracellular DA concentrations, as detected by microdialysis or voltam-

metry in the nucleus accumbens, increase when a sexually receptive female rat is presented. Increases in extracellular DA occur in the striatum as well as the nucleus accumbens during copulation (36,94,96,98). Furthermore, infusion of the DA antagonist, haloperidol, into the striatum increases the number of ejaculations that males display in a 20-min period, while haloperidol in the nucleus accumbens attenuates anticipatory sexual behavior (95).

In female rats, DA antagonists abolish the soliciting/proceptive behaviors of hopping and darting, while enhancing the receptive lordosis posture (53,54). Similarly, bilateral DA and norepinephrine depletions enhance lordosis while decreasing the incidence and duration of soliciting behaviors (26). Conversely, lesions of the ascending ventral norepinephrine pathway attenuate lordosis behavior, but do not affect proceptive behavior (60). Hansen et al. (60) suggest that lesions of the ventral norepinephrine pathway result in a loss of inhibition of nigrostriatal/mesolimbic DA activity, which causes a decrease in passive responses, such as lordosis, and an increase in active responses, including proceptive behaviors. Different neural systems, therefore, mediate lordosis and proceptive behaviors in the female rat, and the ascending DA system is implicated in the later.

To study the possible role of the ascending DA system in proceptive sexual behaviors of the rat, testing conditions need to be optimized for the expression of these behaviors. Sexual behavior in the female rat has typically been studied in the laboratory under conditions where the male rat is able to copulate with the female rat at will, resulting in low levels of female proceptive behaviors [e.g., (4)]. In seminatural conditions, however, the female rat will actively control the pace of copulatory behavior by exhibiting proceptive behaviors and actively withdrawing from the male (85). The optimal rate of intromissions for males and females are different. For the male rat, a rapidly paced series of intromissions (about 1 min between intromissions) is optimal to induce ejaculation in the fewest number of intromissions (1). The female rat, on the other hand, requires behavioral activation of a progestational response to facilitate pregnancy. When intromissions are spaced 2–15 min apart, the chance that insemination will result in pregnancy is significantly enhanced (1). A female rat will "pace" the rate of intromissions if there is a barrier behind which she can escape from the male rat (51,85). Within one or two intromission a naive sexually receptive female rat will take advantage of a barrier in the testing apparatus and begin pacing (personal observation). The rate at which the female withdraws from the presence of the male after a copulatory contact (percent exits) and the time before she returns to the male after a contact (return latency in minutes), are used to objectively define the behavior referred to as pacing. A female that is pacing shows higher rates of percent exits and a longer return latency after an ejaculation than after an intromission or mount. These sexually dimorphic mating strategies are optimal for the reproductive success of both males and females, because in the wild, mating occurs within a group of animals rather than in individual male–female pairs (85). With rapid intromissions and ejaculation, the mating strategy of the male maximizes the number of females it is possible to inseminate. The pacing behavior of the female increases the probability that pregnancy will occur.

The Role of Dopamine in Pacing Behavior

The possible role of the ascending DA systems in female rodent sexual behavior has been a recent topic of investigation in this laboratory and others. We find that there is enhanced DA in dialysate from striatum and nucleus accumbens during sexual behavior in female rats that are pacing sexual behavior, compared with females that are engaging in sex but not pacing (88). In the striatum and nucleus accumbens, the increase in DA concentrations in dialysate of estrogen and progesterone-primed OVX rats pacing copulation is significantly greater than that of nonpacing animals or behaviorally receptive animals tested without a male rat (88). Similarly, in hamsters, DA in the nucleus accumbens increases in dialysate of females engaging in copulation, but only when the male can achieve intromission. Females tested with vaginal masks that prevent intromission by the male do not show an increase in DA in dialysate from nucleus accumbens (75). In rats, DA in dialysate from striatum and nucleus accumbens has been found to increase in animals pacing sexual behavior and in animals where the male rat is introduced by the experimenter at the female's previously determined preferred pace, relative to animals engaging in sexual behavior but not pacing or those prevented form receiving coital stimulation by the presence of a vaginal mask (18). These results together support the notion that DA in the striatum and nucleus accumbens is important for coding specific aspects of the coital stimuli received, rather than being related to specific motor behaviors.

Support for the functional dissociation of the roles of the striatum and nucleus accumbens in pacing behavior comes from studies in which female rats were induced into behavioral estrus via bilateral ventromedial hypothalamus (VMH) hormone treatments and then received estrogen bilaterally into the striatum or nucleus accumbens (135). Intrastriatal estrogen was found to facilitate exits from the male after a copulatory contact (percent exits), while intranucleus accumbens implants increases the time to return to the male (return latency). Conversely, the antiestrogen ICI 182,780 applied to the striatum decreased percent exits, while in the nucleus accumbens it decreased return latency (135). Thus, the results together suggest that the striatum and nucleus accumbens differentially modulate specific components of pacing behavior, and that the effects of estrogen on dopamine in these brain areas enhances these functions.

CONCLUSIONS

The evidence reviewed indicates that there are gender differences in the acute response to psychomotor stimulants and in sensitization of psychomotor behavior induced by AMPH or cocaine. The neural systems mediating the behavioral response to psychomotor stimulants are sexually dimorphic, and are modulated by the gonadal steroid hormones in the female rat. Estrogen enhances the acute behavioral and neurochemical responses to psychomotor stimulants in female rats, and female rats exhibit a greater sensitization of psychomotor behaviors in response to these drugs than do males. These effects of gonadal hormones are postulated to have important implications for gender differences in susceptibility to addiction to the psychomotor stimulants. It is suggested that hormonal modulation of the striatum may have evolved to facilitate reproductive success in female rats by enhancing pacing behavior.

A model is proposed for the mechanisms through which estrogen produces the effects described above. It is suggested that estrogen induces rapid changes in neuronal excitability by acting on membrane receptors located on intrinsic striatal neurons and on DA terminals. The effects on intrinsic striatal GABAergic neurons result in decreased firing of recurrent

collaterals that synapse on GABA-B receptors found on DA terminals, and this decrease in GABA-B receptor stimulation enhances stimulated DA release. Estrogen also affects presynaptic DA terminals by downregulating D_2 DA autoreceptors, which also results in enhanced simulated DA release. The behavioral consequence of these actions is enhanced sensorimotor efficiency, pacing during sexual behavior, and enhanced behavioral responses to psychomotor stimulant drugs. Thus, the hormonal stimuli that are important for behavioral estrus also induce enhanced nucleus accumbens and striatal DA activity, thereby facilitating specific components of pacing behavior in the female rat.

ACKNOWLEDGEMENTS

This research has been supported by grants from the National Science Foundation and the University of Michigan Rackham Graduate School.

REFERENCES

1. Adler, N. T.: On the mechanisms of sexual behavior and their evolutionary constraints. In: Biological determinants of sexual behavior. Hutchinson, J. B., ed. New York Wiley and Sons; 1978: 657–694.
2. Arbuthnott, G. W.; Crow T. J.: Relation of contraversive turning to unilateral release of dopamine from the nigrostriatal pathway in rats. Exp. Neurol. 30:484–491; 1971.
3. Bazzett, T. J.; Becker, J. B.: Sex differences in the rapid and acute effects of estrogen on striatal D_2 dopamine receptor binding. Brain Res. 637:163–172; 1994.
4. Beach, F. A.: Sexual attractivity, proceptivity, and receptivity in female mammals. Horm. Behav. 7:105–138; 1976.
5. Beatty, W. W.: Gonadal hormones and sex differences in nonreproductive behaviors in rodents: Organizational and activational influences. Horm. Behav. 12:112–163; 1979.
6. Beatty, W. W.; Dodge, A. M.; Traylor, K. L.: Stereotyped behavior elicited by amphetamine in the rat: Organizational and activational effects of the testes. Pharmacol. Biochem. Behav. 16:565–568; 1982.
7. Beatty, W. W.; Holzer, G. A.: Sex differences in stereotyped behavior in the rat. Pharmacol. Biochem. Behav. 9:777–785; 1978.
8. Becker, J. B.: Direct effect of 17β-estradiol on striatum: Sex differences in dopamine release. Synapse 5:157–164; 1990.
9. Becker, J. B.: Estrogen rapidly potentiates amphetamine-induced striatal dopamine release and rotational behavior during microdialysis. Neurosci. Lett. 118:169–171; 1990.
10. Becker, J. B.; Bazzett, T.; Albin R. L.: Sex differences in striatal dopamine receptor binding. Soc. Neurosci. Abstr. 17:269; 1991.
11. Becker, J. B.; Beer, M. E.: The influence of estrogen on nigrostriatal dopamine activity: Behavioral and neurochemical evidence for both pre- and postsynaptic components. Behav. Brain Res. 19:27–33; 1986.
12. Becker, J. B.; Beer, M. E.; Robinson, T. E.: Striatal dopamine release stimulated by amphetamine or potassium: Influence of ovarian hormones and the light–dark cycle. Brain Res. 311:157–160; 1984.
13. Becker, J. B.; Cha, J.: Estrous cycle-dependent variation in amphetamine-induced behaviors and striatal dopamine release assessed with microdialysis. Behav. Brain Res. 35:117–125; 1989.
14. Becker, J. B.; Ramirez, V. D.: Sex differences in the amphetamine stimulated release of catecholamines from rat striatal tissue in vitro. Brain Res. 204:361–372; 1980.
15. Becker, J. B., Ramirez, V. D.: Experimental studies on the development of sex differences in the release of dopamine from striatal tissue fragments in vitro. Neuroendocrinology 32:168–173; 1981.
16. Becker, J. B.; Robinson, T. E., Lorenz, K. A.: Sex differences and estrous cycle variations in amphetamine-elicited rotational behavior. Eur. J. Pharmacol. 80:65–72; 1982.
17. Becker, J. B.; Rudick, C. N.: Rapid effects of estrogen or progesterone on the amphetamine-induced increase in striatal dopamine are enhanced by estrogen priming; A microdialysis study. Pharmacol. Biochem. Behav. (in press).
18. Becker, J. B.; Rudick, C. N.; Jenkins, W. J.; Hummer, D. L.: Dopamine in dialysate during pacing of sexual behavior: Stimulus or response? Soc. Neurosci. Abstr. 24:356; 1998.
19. Becker, J. B.; Snyder, P. J.; Miller, M. M.; Westgate, S. A.; Jenuwine M. J.: The influence of estrous cycle and intrastriatal estradiol on sensorimotor performance in the female rat. Pharmacol. Biochem. Behav. 27:53–59; 1987.
20. Bedard, P.; Boucher, R.; Di Paolo, T.; Labrie, F.: Biphasic effect of estradiol and domperidone on lingual dyskinesia in monkeys. Exp. Neurol. 82:172–182; 1983.
21. Berridge, K. C.; Robinson, T. E.: The mind of an addicted brain: Neural sensitization of wanting versus liking. Curr. Direct Psychol. Sci. 4:71–76; 1995.
22. Bonate, P.; Swann, A.; Silverman, P.: Behavioral sensitization to cocaine in the absence of altered brain cocaine levels. Pharmacol. Biochem. Behav. 57:665–669; 1997.
23. Bosse, R.; Rivest, R.; Di Paolo, T.: Ovariectomy and estradiol treatment affect the dopamine transporter and its gene expression in the rat brain. Mol. Brain Res. 46:343–346; 1997.
24. Bowery, N. G.; Hill, D. R.; Hudson, A. L.; Doble, A.; Middlemiss, D. N.; Shaw, J.; Turnbull, M.: (−)Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. Nature 283:92–94; 1980.
25. Bowman, B.; Vaughan, S.; Walker, Q.; Davis, S.; Little, P.; Scheffler, N.; Thomas, B.; Kuhn, C.: Effects of gender and gonadectomy on cocaine metabolism in the rat. J. Pharmacol. Exp. Ther. (in press).
26. Caggiula, A. R.; Herndon, J. G.; Scanlon, R.; Greenstone, D.; Bradshaw, W.; Sharp, D.: Dissociation of active from immobility components of sexual behavior in female rats by central 6-hydroxydopamine: Implications for catecholamine involvement in sexual behavior and sensorimotor responsiveness. Brain Res. 172:505–520; 1979.
27. Camp, D. M.; Becker, J. B.; Robinson, T. E.: Sex differences in the effects of gonadectomy on amphetamine-induced rotational behavior in rats. Behav. Neural. Biol. 46:491–495; 1986.
28. Camp, D. M.; Robinson, T. E.: Susceptibility to sensitization. I. Sex differences in the enduring effects of chronic D-amphetamine treatment on locomotion, stereotyped behavior and brain monoamines. Behav. Brain Res. 30:55–68; 1988.
29. Camp, D. M.; Robinson, T. E.: Susceptibility to sensitization. II. The influence of gonadal hormones on enduring changes in brain monoamines and behavior produced by the repeated administration of d-amphetamine or restraint stress. Behav. Brain Res. 30:69–88; 1988.
30. Castner, S. A., Becker, J. B.: Sex differences in the effect of amphetamine on immediate early gene expression in the rat dorsal striatum. Brain Res. 712:245–257; 1996.
31. Castner, S. A.; Xiao, L.; Becker, J. B.: Sex differences in striatal dopamine: In vivo microdialysis and behavioral studies. Brain Res. 610:127–134; 1993.
32. Chang, C. J.; Ishii, H.; Yamamoto, T.; Spatz, M.: Effects of cerebral ischemia on regional dopamine release and D_1 and D_2 receptors. J. Neurochem. 60:1483–1490; 1993.
33. Clopton, J. K.; Gordon, J. H.: In vivo effects of estrogen and 2-hydroxyestradiol on D-2 dopamine receptor agonist affinity states in rat striatum. J. Neural Transm. 66:13–20; 1986.
34. Conney, A. H.: Pharmacological implications of microsomal enzyme induction. Pharmacol. Rev. 19:317–366; 1967.
35. Costall, B.; Naylor, R. J.: Mesolimbic and extrapyramidal sites

for the mediation of stereotyped behavior patterns and hyperactivity by amphetamine and apomorphine in the rat. In: Ellinwood, E. H.; Kilbey, M. M., eds. Cocaine and Other Stimulants. New York: Plenum Press; 1977:47–76.
36. Damsma, G.; Pfaus, J. G.; Wenkstern, D.; Phillips, A. G.; Fibiger, H. C.: Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: Comparison with novelty and locomotion. Behav. Neurosci. 106:181–191; 1992.
37. Deminiere, J. M.; Piazza, P. V.; Le Moal, M.; Simon, H.: Experimental approach to individual vulnerability to psychostimulant addiction. Neurosci. Biobehav. Rev. 13:141–147; 1989.
38. Demotes-Mainard, J.; Arnauld, E.; Vincent, J. D.: Estrogens modulate the responsiveness of in vivo reorded striatal neurons to iontophoretic application of dopamine in rats: Roles of D_1 and D_2 receptor activation. J. Neuroendocrinol. 2:825–832; 1990.
39. Di Paolo, T.; Dupont, A.; Daigle, M: Effect of chronic estradiol treatment on dopamine concentrations in discrete brain nuclei of hypophysectomized female rats. Neurosci. Lett. 32:295–300; 1982.
40. Di Paolo, T.; Falardeau, P.; Morisette, M.: Striatal D-2 dopamine agonist binding sites fluctuate during the rat estrous cycle. Life Sci. 43:665–672; 1988.
41. Di Paolo, T.; Levesque, D.; Daigle, M.: A physiological dose of progesterone affects rat striatum biogenic amine metabolism. Eur. J. Pharmacol. 125:11–16; 1986.
42. Di Paolo, T.; Poyet, P.; Labrie, F.: Effect of chronic estradiol and haloperidol treatment on striatal dopamine receptors. Eur. J. Pharmacol. 73:105–106; 1981.
43. Di Paolo, T.; Rouillard, C.; Bedard, P.: 17 beta-Estradiol at a physiological dose acutely increases dopamine turnover in rat brain. Eur. J. Pharmacol. 117:197–203; 1985.
44. Dluzen, D. E.; Ramirez, V. D.: Bimodal effect of progesterone on in vitro dopamine function of the rat corpus striatum. Neuroendocrinology 39:149–155; 1984.
45. Dluzen, D. E., Ramirez, V. D.: Intermittent infusion of progesterone potentiates whereas continuous infusion reduces amphetamine-stimulated dopamine release from ovariectomized estrogen-primed rat striatal fragments superfused in vitro. Brain Res. 406:1–9; 1987.
46. Dluzen, D. E., Ramirez, V. D.: Effects of orchidectomy on nigrostriatal dopaminergic function: Behavioral and physiological evidence. J. Neuroendocrinol. 1:285–290; 1989.
47. Dluzen, D. E., Ramierz, V. D.: Progesterone effects upon dopamine release from the corpus striatum of female rats. I. Evidence for interneuronal control. Brain Res. 476:332–337; 1989.
48. Dluzen, D. E.; Ramirez, V. D.: In vitro progesterone modulates amphetamine-stimulated dopamine release from the corpus striatum of castrated male rats treated with estrogen. Neuroendocrinology 52:517–520; 1990.
49. Dluzen, D. E.; Ramirez, V. D.: In vitro progesterone modulation of amphetamine-stimulated dopamine release from the corpus striatum of ovariectomized estrogen-treated female rats: Response characteristics. Brain Res. 517:117–122; 1990.
50. Dluzen, D. E.; Ramirez, V. D.: Modulatory effects of progesterone upon dopamine release from the corpus striatum of ovariectomized estrogen-treated rats are stereospecific. Brain Res. 538:176–179; 1991.
51. Erskine, M. S.; Solicitation behavior in the estrous female rat: A review. Horm. Behav. 23:473–502; 1989.
52. Euvrard, C.; Labrie, F.; Boissier, J. R.: Effect of estrogen on changes in the activity of striatal cholinergic neurons induced by DA drugs. Brain Res. 169:215–220; 1979.
53. Everitt, B. J.; Fuxe, K.; Hokfelt, T.: Inhibitory role for dopamine and 5-hydroxytryptamine in the sexual behavior of the female rat. Eur. J. Pharmacol. 29:187–191; 1974.
54. Everitt, B. J.; Fuxe, K.; Hokfelt, T.; Jonsson, G.: Role of monoamines in the control of hormones of sexual receptivity in the female rat. J. Comp. Physiol. Psychol. 89:556–572; 1975.
55. Fink, J. S.; Smith, G. P.: Relationships between selective denervation of dopamine terminal fields in the anterior forebrain and behavioral responses to amphetamine and apomorphine. Brain Res. 201:107–127; 1980.
56. Forgie, M. L.; Stewart, J.: Sex difference in amphetamine-induced locomotor activity in adult rats: Role of testosterone exposure in the neonatal period. Pharamcol. Biochem. Behav. 46:637–645; 1994.
57. Gerfen, C. R.; The neostriatal mosaic: Multiple levels of compartmental organization in the basal ganglia. Annu. Rev. Neurosci. 15:285–320; 1992.
58. Gordon, J. H.; Modulation of apomorphine-induced stereotypy by estrogen: Time course and dose response. Brain Res. Bull. 5:679–682; 1980.
59. Gordon, J. H.; Diamond, B. I.: Antagonism of dopamine supersensitivity by estrogen: Neurochemical studies in an animal model of tardive dyskinesia. Biol. Psychiatry 16:365–371; 1981.
60. Hansen, S.; Stanfield, E. J.; Everitt, B. J.: The effects of lesions of lateral tegmental noradrenergic neurons on components of sexual behavior and pseudopregnancy in female rats. Neuroscience 6:1105–1117; 1981.
61. Horger, B. A.; Giles, M. K.; Schenk, S.: Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. Psychopharmacology (Berlin) 107:271–276; 1992.
62. Horger, B. A.; Shelton, K.; Schenk, S.: Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav. 37:707–711; 1990.
63. Hruska, R. E.: Elevation of striatal dopamine receptors by estrogen: Dose and time studies. J. Neurochem. 47:1908–1915; 1986.
64. Hruska, R. E.: 17βEstradiol regulation of DA receptor interactions with G-proteins. Soc. Neurosci. Abstr. 14:454; 1988.
65. Hruska, R. E.; Ludmer, L. M.; Pitman, K. T.; De Ryck, M.; Silbergeld, E. K.: Effects of estrogen on striatal dopamine receptor function in male and female rats. Pharmacol. Biochem. Behav. 16:285–291; 1982.
66. Hruska, R. E.; Pitman, K. T.: Hyperphysectomy reduces the haloperidol-induced changes in striatal dopamine receptor density. Eur. J. Pharmacol. 85:201–205; 1982.
67. Hruska, R. E.; Silbergeld, E. K.: Increased dopamine receptor sensitivity after estrogen treatment using the rat rotation model. Science 208:1466–1468; 1980.
68. Jaffe, J. H.: Drug addiction and drug abuse. In: The pharmacological basis of therapeutics. Gilman, A. G. et al., eds. New York: Pegamon Press; 1990: 522–573.
69. Jori, A.; Cecchetti, G.: Homovannilic acid levels in rats striatum during the oestrus cycle. J. Endocrinol. 58:341–342; 1973.
70. Joyce, J. N.; Smith, R. L; Van Hartesveldt, C.: Estradiol suppresses then enhances intracaudate dopamine-induced contralateral deviation. Eur. J. Pharmacol. 81:117–122; 1982.
71. Joyce, J. N.; Van Hartesveldt, C.: Estradiol application to one striatum produces postural deviation to systemic apomorphine. Pharmacol. Biochem. Behav. 20:575–581; 1984.
72. Kalivas, P. W.; Stewart, J.: Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16:223–244; 1991.
73. Kandel, D. B.; Warner, M. P. P.; Kessler, R. C.: The epidemiology of substance abuse and dependence among women. In: Drug addiction research and the health of women. Wetherington, C. L.; Roman, A. R., eds. Rockville, MD: U.S. Department of Health and Human Services; 1995: 105–130.
74. Ke, F. C.; Ramirez, V. D.: Binding of progesterone to nerve cell membranes of rat brain using progesterone conjugated to 125I-bovine serum albumin as a ligand. J. Neurochem. 54:467–472; 1990.
75. Kohlert, J.; Rowe, R.; Meisel, R.: Intromissive stimuli from the male increases extracellular dopamine from fluoro-gold-identified neurons within the midbrain of female hamsters. Horm. Behav. 32:143–154; 1997.
76. Koob, G. F., Bloom, F. E.: Cellular and molecular mechanisms of drug dependence. Science 242:715–723; 1988.
77. Kuiper, G.; Enmark, E.; Pelto-Huikko, M.; Nilsson, S.: Gustafsson, J.: Cloning of a novel estrogen receptor expressed in rat

prostrate and ovary. Proc. Natl. Acad. Sci. USA 93:5925–5930; 1996.
78. Kumakara, K.; Hoffman, M.; Cocchi, D.; Trabucchi, M.; Spano, P. F.; Muller, E. E.: Long-term effects of ovariectomy on dopamine-stimulated adenylate cyclase in rat striatum and nucleus accumbens. Psychopharmacology (Berlin) 61:13–16; 1979.
79. Lett, B. T.: Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. Psychopharmacology (Berlin) 98:357–362; 1989.
80. Levesque, D.; Di Paolo, T.: Rapid conversion of high into low striatal D_2-dopamine receptor agonist binding states after an acute physiological dose of 17 beta-estradiol. Neurosci. Lett. 88:113–118; 1988.
81. Levesque, D.; Di Paolo, T.: Modulation by estradiol and progesterone of the GTP effect on striatal D-2 dopamine receptors. Biochem. Pharmacol. 45:723–733; 1993.
82. Levesque, D.; Gagnon, S.; Di Paolo, T.: Striatal D1 dopamine receptor density fluctuates during the rat estrous cycle. Neurosci. Lett. 98:345–350; 1989.
83. Maus, M.; Bertrand, P.; Drouva, S.; Rasolonjanahary, R.; Kordon, C.; Glowinski, J.; Premont, J.; Enjalbert, A.: Differential modulation of D_1 and D_2 dopamine-sensitive adenylate cyclases by 17β-estradiol in cultures styriatal neurons and anterior pituitary cells. J. Neurochem. 52:410–418; 1989.
84. Maus, M.; Cordier, J.; Glowinski, J.; Premont, J.: 17β-Oestradiol pretreatment of mouse striatal neurons in culture enhances the responses to adenylate cyclase sensitive tobiogenic amines. Eur. J. Neurosci. 1:1; 1989.
85. McClintock , M. K.: Group mating in the domestic rat as context for sexual selection: Consequences for the analysis of sexual behavior and neuroendocrine responses. Adv. Stud. Behav. 14:1–50; 1984.
86. Meiergerd, S.; Patterson, T.; Schenk, J.: D_2 receptors modulate the function of the striatal transporter for dopamine: Kinetic evidence from studies in vitro and vivo. J. Neurochem. 61:764–767; 1993.
87. Mello, N. K.: Cocaine abuse and reproductive function in women. In: Drug addiction research and the health of women. Wetherington, C. L.; Roman, A. R, eds. Rockville MD: U.S. Department of Health and Human Services; 1995: 131–150.
88. Mermelstein, P. G.; Becker, J. B.: Increased extracellular dopamine in the nucleus accumbens and striatum of the female rat during paced copulatory behavior. Behav. Neurosci. 109:354–365; 1995.
89. Mermelstein, P. G.; Becker, J. B.; Surmeier, D. J.: Estradiol reduces calcium currents in rat neostriatal neurons through a membrane receptor. J. Neurosci. 16:595–604; 1996.
90. Mislow, J. F.; Freidhoff, A. J.: A comparison of chlorpromazine-induced extrapyramidal syndrome in male and female rats. In: Lissak, K., ed. Hormones and brain function. New York: Plenum Press; New York: 1973: 315–326.
91. Morissette, M.; Di Paolo, T.: Sex and estrous cycle variations of rat striatal dopamine uptake sites. Neuroendocrinology 58:16–22; 1993.
92. Peris, J.; Decambre, N.; Coleman-Hardee, M.; Simpkins, J.: Estradiol enhances behavioral sensitization to cocaine and amphetamine-stimulated [^{3}H]dopamine release. Brain Res. 566: 255–264; 1991.
93. Pfaff, D.; Keiner, M.: Atlas of estradiol-concentrating cells in the central nervous system of the rat. Comp. Neurol. 151:121–158; 1973.
94. Pfaus, J. G.; Damsma, G.; Nomikos, G. G.; Wenkstern, D. G.; Blaha, C. D.; Phillips, A. G.; Fibiger, H. C.: Sexual behavior enhances central dopamine transmission in the male rat. Brain Res. 530:345–348; 1990.
95. Pfaus, J. G.; Phillips, A. G.: Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. Behav. Neurosci. 105:727–743; 1991.
96. Phillips, A. G.; Pfaus, J. G.; Blaha, C. D.: Dopamine and motivated behavior: Insights provided by in vivo analyses, In: Willmer, P.; Sheel-Krüger, J., eds. The mesolimbic dopamine system: From motivation to action. New York: John Wiley & Sons, Ltd; 1991: 199–224.
97. Piazza, P. V.; Deminière, J.-M.; Maccari, S.; Le Moal, M.; Mormède, P.; Simon, H.: Individual vulnerability to drug self-administration: Action of corticosterone on dopaminergic systems as a possible pathophysiological mechanism. In: Willner, P.; Scheel-Krüger, J., eds. The mesolimbic dopamine system: From motivation to action. New York: John Wiley & Sons Ltd; 1991:473–495.
98. Pleim, E. T.; Matochik, J. A.; Barfield, R. J.; Auerbach, S. B.: Correlation of dopamine release in the nucleus accumbens with masculine sexual behavior in rats. Brain Res. 524:160–163; 1990.
99. Post, R. M.; Weiss, S. R.; Pert, A.: The role of context and conditioning in behavioral sensitization to cocaine. Psychopharmacol. Bull. 23:425–429; 1987.
100. Ramirez, V. D.; Zheng, J.; Siddique, K. M.: Membrane receptors for estrogen, progesterone, and testosterone in the rat brain: Fantasy or reality. Cell. Mol. Neurobiol. 16:175–198; 1996.
101. Reimann, W.: Inhibition by GABA, baclofen and gabapentin of dopamine release from rabbit caudate nucleus: Are there common or different sites of action? Eur. J. Pharamacol. 94:341–344; 1983.
102. Roberts, D.; Bennett, S.; Vickers, G.: The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology (Berlin) 98:408–411; 1989.
103. Robinson, T. E.: Behavioral sensitization: Characterization of enduring changes in rotational behavior produced by intermittent injections of amphetamine in male and female rats. Psychopharmacology (Berlin) 84:466–475; 1984.
104. Robinson, T. E.: Stimulant drugs and stress: Factors influencing individual differences in the susceptibility to sensitization. In: Kalivas, P. W.; Barnes, C., eds. Sensitization of the nervous system. Caldwell, NJ: Telford Press; 1988:145–173.
105. Robinson, T. E.: The neurobiology of amphetamine psychosis: Evidence from studies with an animal model. In: Nakazawa, T., ed. Taniguchi symposia on brain sciences, vol. 14, Biological basis of schizophrenia. Tokyo: Japan Scientific Societies Press; 1991:185–201.
106. Robinson, T. E.: Persistent sensitizing effects of drugs on brain dopamine systems and behavior: Implications for addiction and relapse. In: Korenman, S. G.; Barchas, J. D., eds. Biological basis of substance abuse. New York: Oxford University Press; 1993:373–402.
107. Robinson, T. E.; Becker, J. B., Moore, C. J.; Castãneda, E.; Mittleman, G.: Enduring enhancement in frontal cortex dopamine utilization in an animal model of amphetamine psychosis. Brain Res. 343:374–377; 1985.
108. Robinson, T. E.; Becker, J. B.; Presty, S. K.: Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: Sex differences. Brain Res. 253:231–241; 1982.
109. Robinson, T. E.; Becker, J. B.; Ramirez, V. D.: Sex differences in amphetamine-elicited rotational behavior and the lateralization of striatal dopamine in rats. Brain Res. Bull. 5:539–545; 1980.
110. Robinson, T. E.; Berridge, K. C.: The neural basis of drug craving: An incentrive-sensitization theory of addiction. Brain Res. Rev. 18:247–291; 1993.
111. Robinson, T. E., Camp, D. M.; Becker, J. B.: Gonadectomy attenuates turning behavior produced by electrical stimulation of the nigrostriatal dopamine system in female but not male rats. Neurosci. Lett. 23:203–208; 1981.
112. Robinson, T. E.; Camp, D. M.; Jacknow, D. S.; Becker, J. B.: Sex differences and estrous cycle dependent variation in rotational behavior elicited by electrical stimulation of the mesostriatal dopamine system. Behav. Brain Res. 6:273–287; 1982.
113. Roy, E. J.; Buyer, D. R.; Licari, V. A.: Estradiol in the striatum: Effects on behavior and dopamine receptors but no evidence for membrane steroid receptors. Brain Res. Bull. 25:221–227; 1990.
114. Savageau, M. M.; Beatty, W. W.: Gonadectomy and sex differences in the behavioral responses of amphetamine and apomorphine of rats. Pharmacol. Biochem. Behav. 14:17–23; 1981.
115. Schenk, S.; Valdez, A.; McNamara, C.; Horger, B. A.: Blockade of sensitizing effects of amphetamine preexposure on cocaine self-administration by the NMDA antagonist MD-801. Soc. Neurosci. Abstr. 18:1237; 1992.

116. Segal, D. S.; Kuczenski, R.: Behavioral pharmacology of amphetamine. In: Cho, A. K.; Segal, D. S., eds. Amphetamine and its analogs: Psychopharmacology, toxicology and abuse. San Diego, Academic Press, Inc.; 1994: 115–150.
117. Segal, D. S.; Schuckit, M. A.: Animal models of stimulant-induced psychosis, In: Creese, I., ed. Neurochemical, behavioral and clinical perspectives. New York: Raven Press; 1983: 131–167.
118. Shughrue, P.; Lane, M.; Merchenthaler, I.: Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. J. Comp. Neurol. 388:507–525; 1997.
119. Stewart, J.: Tolerance and sensitization to the behavioral effects of drugs. In: Controllo farmacologico del comportamento. Firenze: Uses Edizioni Scientifiche, S.P.A.; 1992.
120. Stewart, J.; Badiani, A.: Tolerance and sensitization to the behavioral effects of drugs. Behav. Pharmacol. 4:289–312; 1993.
121. Thompson, T. L.; Moss, R. L.: Estrogen regulation of dopamine release in the nucleus accumbens; Genomic- and nongenomic-mediated effects. J. Neurochem. 62:1750–1756; 1994.
122. Tiffany, S. T.: A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. Psychol. Rev. 97:147–168; 1990.
123. Toran-Allerand, C. D.; Miranda, R. C.; Hochberg, R. B.; MacLusky, N. J.: Cellular variations in estrogen receptor mRNA translation in the developing brain: Evidence from combined [^{125}I]estrogen autoradiography and non-isotopic in situ hybridization histochemistry. Brian Res. 576:25–41; 1992.
124. Ungerstedt, U.: Striadal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. Acta Physiol. Scand. 82(Suppl.367):49–68; 1971.
125. Ungerstedt, U.: Functional dynamics of central monamine pathways. In: Schmitt, F. O.; Worden, F. G., eds. In: The neurosciences: third study program. Cambridge, MA: MIT Press; 1974:979–988.
126. van Haaren, F.; Meyer, M.: Sex differences in the locomotor activity after acute and chronic cocaine administration. Pharmacol. Biochem. Behav. 39:923–927; 1991.
127. Van Hartesveldt, C.; Cottrell, G. A.; Meyer, M. E.: Effects of intrastriatal hormones on the dorsal immobility response in male rats. Pharmacol. Biochem. Behav. 35:307–310; 1989.
128. Verimer, T.; Arneric, S. P.; Long, J. P.; Walsh, B. J.; Abou Zeit-Har, M. S.: Effects of ovariectomy, castration, and chronic lithium chloride treatment on stereotyped behavior in rats. Psychopharmacology (Berlin) 75:273–276; 1981.
129. Watson, S. J., Trujillo, K. A., Herman, J. P., Akil, H.: Neuroanatomical and neurochemical substrates of drug-seeking behavior: Overview and future directions: In: Goldstein, A., ed. Molecular and cellular aspects of the drug addictions. New York: Springer Verlag; 1989: 29–91.
130. Wetherington, C. L.; Roman, A. R., eds. Drug addiction research and the health of women. Rockville, MD: U.S. Department of Health and Human Services; 1995.
131. White, F. J.; Wolfe, M.E., Psychomotor stimulants. In: Pratt, J., ed. The biological bases of drug tolerance and dependence. New York: Academic Press; 1991: 153–197.
132. Wise, R. A.; Bozarth, M. A.: A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492; 1987.
133. Wong, A.; Shetreat, M.; Clarke, J.; Rayport, S.: D1- and D2-like dopamine receptors are co-localized on the presynaptic varicosities of striatal and nucleus accumbens neurons in vitro. Neuroscience 89:221–233; 1999.
134. Xiao, L.; Becker, J. B.: Quantitative microdialysis determination of extracellular striatal dopamine concentrations in male and female rats: Effects of estrous cycle and gonadectomy. Neurosci. Lett. 180:155–158; 1994.
135. Xiao, L.; Becker, J. B.: Hormonal activation of the striatum and the nucleus accumbens modulates paced mating behavior in the female rat. Horm. Behav. 32:114–124; 1997.
136. Xiao, L.; Becker, J. B.: Steroid-specific effects of estrogen agonists and antagonists on amphetamine-induced striatal dopamine released from superfused striatal tissue. Soc. Neurosci. Abst. 23:403; 1997.
137. Xiao, L.; Becker, J. B.: Effects of estrogen agonists on amphetamine-stimulated striatal dopamine release. Synapse 29:379–391; 1998.