Organizational and Activational Effects of Dopamine on Male Sexual Behavior

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This chapter will summarize evidence that the neurotransmitter dopamine can affect both the developmental organization and the adolescent/adult activation of male rat sexual behavior. Furthermore, these effects are at least partially independent of hormonal influence. Specifically, evidence will be presented that (1) dopaminergic drugs administered perinatally can affect sexual differentiation without altering fetal or adult testosterone levels; (2) dopaminergic drugs, even in the absence of testosterone, can activate male-typical behavior in adult rats; (3) dopamine is released in the medial preoptic area (MPOA) of the basal forebrain of male rats before and during copulation; and (4) MPOA dopamine release in the presence of a receptive female depends on the recent, but not concurrent, presence of testosterone.

It is a central dogma of our field that testosterone and its metabolites masculinize mammalian brains and genitals during early development and activate male-typical behavior in adulthood (e.g., Ellis, 1996b, p. 36). The sex-determining region on the Y chromosome (Sry) of male mammals encodes a transcription factor, testis-determining factor (TDF), which induces the formation of testes from the primordial gonads and stimulates the secretion of testosterone (Gubbay et al., 1990; Sinclair et al., 1990). In male rats, a surge of testosterone on embryonic Days 18 and 19 (Weisz & Ward, 1980) is thought to initiate processes of masculinization and feminization of numerous brain structures, including those that regulate neuroendocrine control and reproductive behavior. Evidence for the central roles of gonadal hormones
in these processes is extensive, and will not be reviewed here. However, the assumption that hormonal influences are necessary and sufficient to organize the substrates and to activate male-typical behavior has recently been questioned (e.g., Hull, Nishita, Bitran, & Dalterio, 1984; Pilgrim & Hutchison, 1994; Reisert & Pilgrim, 1991; Scaletta & Hull, 1990).

PERINATAL MANIPULATION OF DOPAMINE RECEPTORS

In particular, the neurotransmitter dopamine may also have both organizational and activational effects on male rat sexual behavior. Dopamine agonists have long been known to enhance sexual function of men (Barbeau, 1969; Bowers, van Woert, & Davis, 1971; Lal, 1988; Pierini & Nusimovich, 1981) and of male rats (Malman, 1973; reviewed in Bitran & Hull, 1987; Melis & Arigiolas, 1995). Accordingly, some years ago we began to question whether perinatal treatments with dopaminergic drugs could modify the sexual differentiation of rats (Hull et al., 1984). To test this idea, we initially used a perinatal regimen that had been shown to affect dopamine receptors and behavioral sensitivity to dopaminergic drugs in adulthood. Rosengarten and Friedhoff (1979) had administered the dopamine antagonist haloperidol, a common antipsychotic drug, to mother rats during pregnancy or lactation. Haloperidol administered only during gestation decreased the numbers of dopamine receptors in the brains of the adult offspring and also decreased their behavioral sensitivity to dopamine agonists. On the other hand, postnatal treatment with haloperidol, via lactation, resulted in increased numbers of dopamine receptors and in supersensitivity of behavioral responses to dopamine agonists. Because dopamine agonists had been reported to impair the sexual behavior of male rats (Malman, 1973), we hypothesized that decreased numbers of dopamine receptors in adulthood, due to prenatal haloperidol, would also impair sexual behavior. Furthermore, since dopamine agonists had increased copulatory behaviors in male rats (Malman, 1973), we also hypothesized that increased dopamine receptors, due to postnatal haloperidol, would enhance sexual behavior.

We treated mother rats with either haloperidol or saline from Day 7 of gestation until postnatal Day 21 (Hull et al., 1984). Half the pups from each litter were cross-fostered to a mother given the opposite treatment, thereby forming four groups: those receiving haloperidol only prenatally, only postnatally, both prenatally and postnatally, or neither. Weekly copulation tests began on postnatal Day 65. As we expected, males treated prenatally with haloperidol showed fewer ejaculations than did saline/saline controls (Figure 5.1). Unexpectedly, the postnatally treated animals also showed impairments on the first test; however, on Tests 2 and 3 the postnatally treated animals were not different from controls.

The decrease in ejaculations reflected primarily a decrease in the number of males that were able to ejaculate within thirty minutes after the first intromission;
there was no difference in the number of tests on which an intromission occurred. Prenatal haloperidol-treated males ejaculated on only about 50 percent of all tests in which an intromission occurred, whereas postnatal haloperidol-treated males ejaculated on about 70 percent of such tests and control males ejaculated on almost 90 percent of those tests. Therefore, the primary deficit was in the ability to elicit an ejaculation, rather than in sexual arousal. There were no differences in female-typical behavior of the female littermates, or in body weights or maturational milestones of any animals. Furthermore, maternal behavior could not have been a factor in the demasculinization, since males treated both prenatally and postnatally with haloperidol showed deficits simi-
lar to those of males treated prenatally with haloperidol but cross-fostered to saline treated mothers at birth. There were also no differences in testosterone levels of male fetuses at Day 18 of gestation, the day of the major testosterone surge. Therefore, (1) blocking dopamine receptors at any time during early development demasculinized male sexual behavior, and (2) this demasculinization did not result from decreases in testosterone levels or body weight, or from retarded development or poor maternal behavior.

Since blocking dopamine receptors either pre- or postnatally had demasculinized sexual behavior, we next tested whether perinatal stimulation of dopamine receptors with the dopamine agonist apomorphine might enhance adult male sexual behavior (Hull et al., 1984). For contrast, we administered the dopamine synthesis blocker alpha-methyl tyrosine to a second group of dams. A third group received the combination of apomorphine and alpha-methyl tyrosine; control rats received saline. We predicted that stimulation of dopamine receptors with apomorphine would enhance masculine development, and that blocking dopamine synthesis would impair it. The effects of the combined agonist and synthesis inhibitor were expected to cancel out and have little effect on adult sexual behavior. In order to test whether improvement across tests was due to experience or to time since drug treatment, half the males in each group began weekly tests on Day 69, and the other half began on Day 90. There were no differences between the two series, and they were combined for statistical analysis. As in the perinatal haloperidol experiment, all drug treatments impaired ejaculatory ability on at least one test. There was a decrease in the number of ejaculations by all drug-treated males on the second and third tests (Figure 5.2). As in the haloperidol experiment, this decrease reflected fewer tests on which ejaculation occurred within thirty minutes after the first intromission (saline, 93%; apomorphine, 67%; alpha-methyl tyrosine, 55%; combination, 67%). In addition, those drug-treated animals that did ejaculate on Test 3 had longer latencies than controls. Again, there were no differences in body weights, developmental milestones, or female-typical behavior among groups.

We also measured adult testosterone levels in separate groups of animals that were given prenatal and postnatal treatments with haloperidol, apomorphine, or alpha-methyl tyrosine that were identical to those that produced behavioral deficits, to test whether the behavioral impairment of drug-treated males might be related to low levels of the hormone at the time of testing. However, no drug treatment produced significant alterations compared to controls at sixty days of age. In fact, the perinatal haloperidol-treated group had slightly (nonsignificantly) higher levels of testosterone than did saline-treated controls. Therefore, it is likely that these dopaminergic drugs produced a direct change in neural development, rather than acting simply by altering hormone levels.

A subsequent study of dopaminergic influence on sex differentiation reported somewhat similar results (Gonzalez & Leret, 1992). In that experiment, a relatively large dose of dopamine (2 mg/kg in 1 μl, or about 10 to 15 μg per pup) was
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Figure 5.2
Effects of Dopaminergic Drugs, Administered both Pre- and Postnataally, on Number of Ejaculations per Test

![Graph showing ejaculation frequency by treatment and test week](image)


administered intraventricularly on postnatal Day 1. Dopamine-treated males, tested in adulthood, showed fewer mounts and intromissions in a ten-minute test, compared to saline-treated animals. On the other hand, adult testosterone levels were actually higher in the dopamine-treated males than in controls. Therefore, the impairment of sexual behavior could not be attributed to a decrease in testosterone levels in adulthood. An injection of norepinephrine in a dose even higher than the dose of dopamine (20 mg/kg in 1 μl on postnatal Day 1) also increased testosterone levels in adulthood, but failed to affect sexual behavior. Therefore, the behavioral impairment produced by dopamine administration probably did not result from osmotic or other nonspecific effects of the injection, or from a decrease in adult testosterone levels.
SEX DIFFERENCES IN DOPAMINE NEURONS

These studies suggest that perinatal manipulation of dopaminergic systems can exert nonhormonal organizational effects on neurons that are destined to control male sexual behavior. There have also been reports that embryonic dopaminergic neurons can develop sex-differentiated morphology and function in the absence of sex steroids (Reisert & Pilgrim, 1991). In vitro cultures of midbrain or diencephalic (posterior part of forebrain) dopaminergic neurons, taken from Day 14 fetuses, were maintained for up to thirteen days. Because these cultures were obtained before gonadal differentiation and the resultant testosterone surge, hormones could not have mediated any differences that might be observed. Diencephalic neurons from female fetuses were smaller, but had greater activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, than did similar neurons from their male littermates. Female diencephalic neurons also had higher levels of dopamine and greater dopamine uptake than did comparable neurons from males. On the other hand, midbrain neurons from female fetuses had lower dopamine uptake but were more numerous than neurons from male fetuses. Therefore, there were region-specific and sex-specific differences in dopaminergic neurons in vitro in the absence of any hormonal treatment. The study found that addition of either estradiol or testosterone to the culture medium decreased dopamine levels and tyrosine hydroxylase activity in diencephalic cultures from both male and female fetuses, whereas estradiol, but not testosterone, increased dopamine uptake in midbrain cultures from female, but not male, fetuses. The authors suggested that sexual dimorphisms of some neural structures may develop under direct genetic control, not mediated by hormonal influences. Perhaps it is these dopaminergic neurons and/or their postsynaptic partners that are affected by perinatal dopaminergic drugs.

GENE INFLUENCES ON SEX DIFFERENTIATION

A gene on the Y chromosome induces the masculinization of XY individuals. This gene, termed the sex-determining region of the Y chromosome, encodes a protein, the testis-determining factor, which affects the transcription of other genes. TDF has been thought to affect only the primitive gonads, which then, via testosterone and its metabolites, masculinize the brain and external genitals. However, there are recent reports that Sry may be expressed as early as the two-cell stage of the mouse embryo (Zwingman, Erickson, Boyer, & Ao, 1993), long before the formation of testes. This early expression suggests that TDF may affect sex differentiation directly, rather than acting only through testosterone produced by the testes. One gene whose transcription may be affected directly by TDF is the gene coding for the aromatase enzyme, which converts testosterone to estrogen (Haqq, King, Donahue, & Weiss, 1993). There are sex differences in the expression of this
enzyme in cultures of embryonic mouse brains, obtained before differentiation of the testes and the subsequent testosterone surge (Beyer, Wozniak, & Hutchison, 1993).

There are additional genes on the short arm of the Y chromosome that may encode sex-specific transcription factors (reviewed in Graves, 1995; Pilgrim & Hutchison, 1994). Therefore, both Sry and other genes may contribute to sex differentiation in both hormone-dependent and hormone-independent ways. Figure 5.3 contrasts the classic view of sex differentiation, according to which masculinization and feminization of neurons are mediated entirely by hormones, with a more complex, partially hormone-independent model.

**DOPAMINERGIC INFLUENCES ON SEX DIFFERENTIATION OF THE BRAIN**

One particularly interesting possibility is that dopamine neurons may not only exhibit sex differences themselves, but may lead to sex differentiation of other neurons that possess dopamine receptors (reviewed in Lauder, 1993). For example, dopamine may suppress neurite outgrowth, acting through the

**Figure 5.3**
Alternative Pathways of Masculine Differentiation

![Diagram showing alternative pathways of masculine differentiation involving Sry, TDF, testosterone, estradiol, 5α-DHT, and other transcription factors.](image)

The top pathway represents the common view that the Sry gene causes the primordial gonads to become testes; testosterone and its metabolites masculinize and feminize the brain and genitals. The second pathway includes direct effects of neurotransmitters and other factors.
D_1 family of dopamine receptors (Lankford, DeMello, & Klein, 1988), or may enhance neurite outgrowth by stimulating the D_3 family of receptors (Todd, 1992). (Five subtypes of dopamine receptors have been cloned; however, they fall into two families, D_1-like and D_2-like, based on structural, pharmacological, and physiological criteria [Civelli et al., 1993].) Even within the D_1 family, there may be subtle differences. Stimulation of D_1 receptors increased the number and branching of neurites, but not neurite extension; stimulation of D_2 or D_3 receptors promoted both branching and extension of neurites (Swarzenski, Tang, Gh, O'Malley, & Todd, 1994). Therefore, cells with different distributions of subtypes of dopamine receptors may respond to the same neurotransmitter with a variety of responses. The effects of D_1-like receptor stimulation may be mediated in part by the activation of genes that code for transcription factors that in turn promote the expression of yet other genes (Liu, Takahashi, McKay, & Graybiel, 1995). Thus, increases or decreases in the amount of dopamine available to bind to D_2 or D_3-like receptors may have far-reaching repercussions. Both the physical growth of neurons and their expression of other regulatory factors may be affected. In summary, dopamine neurons show hormone-independent sexually dimorphic patterns of development, and they can, in turn, influence the development of other sexually dimorphic neural systems, through actions on D_1- or D_2-like receptors and regulatory genes.

ACTIVATIONAL EFFECTS OF DOPAMINE ON MALE SEXUAL BEHAVIOR

Dopamine also exerts activational effects on male sexual behavior (reviewed in Bitran & Hull, 1987; Melis & Argiolas, 1995). In some ways, dopamine’s effects parallel those of steroid hormones. Steroids enhance intracellular biochemical processes that increase the responsiveness of neurons to sexually relevant stimuli (Figure 5.4). This long-term enhancement is referred to as priming.

However, even with steroid priming, neurons may not be fully responsive to sexual stimuli. They are subject to ongoing inhibition by GABAergic neurons. (GABA, gamma amino butyric acid, is a common inhibitory neurotransmitter which dampens the responsiveness of other neurons.) Dopamine may be released over a period of minutes, or in some cases, an hour or more. It may diffuse some distance from sites of release, though levels outside the synaptic cleft may be markedly reduced compared to that inside the cleft (Gonon, Sucaud-Chagny, Mermet, & Buda, 1991). Dopamine acts, in part, by inhibiting those GABAergic interneurons, resulting in the disinhibition of the output neurons (Chevalier & Deniau, 1990). In this way, sensorimotor integration is enhanced and relevant stimuli can elicit a sexual response (Figure 5.5). Dopamine does not directly elicit behavior, but rather makes it easier for a stimulus to evoke a response.
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Figure 5.4
Activational Effects of Steroid Hormones on Neurons That Control Sexual Behavior

Sensory Input MPOA Motor Output

Gonadal steroids upregulate the responsiveness of neurons that process sexually relevant stimuli and responses; however, inhibitory GABAergic neurons prevent their full responsiveness.

INFLUENCES OF THREE DOPAMINERGIC BRAIN SYSTEMS

There are three main dopamine systems that influence male sexual behavior. Stimuli from the estrous female or from copulation increase the release of dopamine in each of three integrative hubs, brain areas that receive sensory input and elicit relevant motor output (Figure 5.6). The nigrostriatal dopamine tract, degeneration of which causes Parkinson's disease, prepares for the motor components of copulation (Robbins & Everitt, 1992).

The mesolimbic tract increases responsiveness to a variety of motivational stimuli (reviewed in Kiyatkin, 1995). The medial preoptic area (MPOA) is essential for male copulatory behavior of all vertebrate species that have been studied, from fish to primates (reviewed in Meisel & Sachs, 1994). Dopamine in the MPOA helps to orchestrate genital reflexes (Hull et al., 1992), and also contributes to specifically sexual motivation (Moses, Loucks, Watson, Matuszewich, & Hull, 1995; Pfau & Phillips, 1991; Warner et al., 1991) and
Dopamine neurons inhibit the GABAergic neurons, thereby disinhibiting the processing of sexual information; this increases the likelihood that a sexually relevant stimulus will evoke a sexual response.

probably also to stereotyped mounting and thrusting patterns (reviewed in Meisel & Sachs, 1994).

We have been especially interested in the MPOA, which receives dopamine innervation primarily from the A14 periventricular system (Simerly et al., 1986; reviewed in Moore & Lookingland, 1995). Briefly, certain levels of dopamine are necessary for normal sexual behavior. Stimulation of MPOA dopamine receptors, using the classic D₁/D₂ agonist apomorphine, facilitated copulation (Hull et al., 1986) and ex copula genital reflexes, measured in male rats restrained on their backs with the sheath surrounding the penis retracted (Pehek, Thompson, & Hull, 1989). Stimulation of D₁-family receptors within the MPOA facilitated the early stages of copulation (Markowski, Eaton, Lumley, Moses, & Hull, 1994) and increased the number of ex copula penile erections and anteroflexions (penile movements sometimes referred to as "flips") (Hull et al., 1992). On the other hand, high doses of apomorphine or a D₂-family agonist facilitated ejaculation (Hull et al., 1989) and increased the number of ex copula seminal emissions (Bazzett et al., 1991; Hull et al., 1992). Ejaculation and seminal emission are elicited by the sympathetic nervous system. Therefore, stimulation of low-threshold D₁-family receptors in the MPOA may promote parasympathetically mediated erections, whereas
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Figure 5.6
Effects of Dopamine in Three Integrative Hubs That Regulate Male Sexual Behavior

Sensory Input

MPOA

Mesolimbic

Nigrostriatal

Genital Responses

Appetitive Behavior

Somatomotor Patterns

Stimuli from an estrous female elicits dopamine release in each hub. Dopamine in the nigrostriatal tract promotes the initiation of somatomotor patterns of copulation. Dopamine in the mesolimbic tract enhances general appetitive behavior. Dopamine in the medial preoptic area facilitates genital reflexes, enhances specifically sexual motivation, and promotes copulatory motor patterns.

Consonant with the facilitative effects of dopamine agonists on male sexual behavior, dopamine antagonists microinjected into the MPOA impair those same functions. Blocking dopamine receptors in the MPOA using the classic D1/D2 antagonist cis-flupenthixol decreased the number of males that copulated and slowed the rate of those that did (Pehek et al., 1988). Cis-flupenthixol also decreased eX copula erections and anterolaxations and decreased sexual motivation, measured as the percent of trials on which the male chose the female’s goal box in an X-maze (Warner et al., 1991). Cis-flupenthixol did not affect measures of motor activity in the X-maze (Warner et al., 1991) or eating or locomotion in the home cage (Pehek et al., 1988); therefore, the
effect on sexual behavior was relatively specific. Both D₁ and D₂ families of receptors contributed to sexual motivation, since both types of antagonist mimicked the effects of cis-flupenthixol in the X-maze (Moses et al., 1995). On the other hand, decreasing activity of the mesolimbic dopamine tract, extending from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) and several other sites, decreased motor activation but did not affect specifically sexual motivation (Hull, Bazzett, Warner, Eaton, & Thompson, 1990; Hull et al., 1991; Moses et al., 1995).

These data suggest that dopamine has an important facilitative influence in the MPOA, which is a major integrative hub for the activation of male sexual behavior. Furthermore, MPOA dopamine appears to influence several aspects of sexual behavior, including sexual motivation, genital reflexes, and the rate and efficiency of copulation. On the other hand, dopamine in the mesolimbic tract appears to facilitate the appetitive aspects of numerous motivated behaviors and to promote general sensorimotor activation (reviewed in Kiyatkin, 1995).

**DOPAMINERGIC INFLUENCES IN CASTRATES**

Dopaminergic drugs can also partially restore copulatory behavior in castrated male rats. The classic D₁/D₂ dopamine agonist apomorphine was administered systemically, either 56 days after castration, at which time about a third of vehicle-treated animals were able to copulate (Malinas, 1977), or after suboptimal testosterone replacement (Malinas, 1973). Apomorphine increased the numbers of animals mounting, intromitting, and ejaculating in both experiments. We tested whether apomorphine could facilitate sexual behavior even in long-term castrates that had not mounted on two successive weekly tests (Scaletta & Hull, 1990). (Because a behavioral criterion was used to begin the counterbalanced drug tests, the actual number of days postcastration varied considerably; the numbers given here represent the mean days for all animals.) Systemically administered apomorphine dose-dependently increased the numbers of mounts and intromissions in animals tested between 80 and 108 days postcastration (Figure 5.7A). They were then given five weekly subthreshold testosterone injections (20 μg each) three days before weekly behavioral tests, which occurred on days 115 to 143 postcastration. Again, the number of mounts was increased by apomorphine; however, the testosterone alone slightly increased the number of intromissions, so that the comparison with the apomorphine and testosterone treatment was not statistically significant (Figure 5.7B). In order to test whether repeated hormone injections had an additive effect on behavior, mounts and intromissions within each test day were summed across treatments and compared statistically. However, there was no improvement in responsiveness to apomorphine over the four weeks of subthreshold testosterone tests and no decrease in responsiveness over the four weeks of steroid-free tests.

Those same animals were then surgically implanted with cannulae aimed at the MPOA and received apomorphine microinjections on tests between
Figure 5.7
Effects of Systemically Administered Apomorphine on Sexual Behavior of Long-Term Castrates

A. Apomorphine increased the number of mounts and intromissions per thirty-minute test. B. Apomorphine administered during a subthreshold testosterone regimen (20 µg/week, injected three days before testing) increased the number of mounts per thirty-minute test.
179 and 200 days postcastration. Apomorphine resulted in a significant dose-dependent increase in the numbers of mounts (Figure 5.8A), but no animal intromitted. An additional regimen of subthreshold testosterone revealed a nonsignificant apomorphine-related increase in mounts on days 207 to 228 postcastration (Figure 5.8B); two animals intromitted after apomorphine micro-injections. These data show that even in very long-term castrates, stimulation of dopamine receptors, either systemically or in the MPOA, could partially restore copulatory behavior. The lack of effectiveness of MPOA injections compared with systemic injections in restoring intromissions may have been related either to the greater length of time after castration that the animals were tested or to the requirement for stimulation in other brain areas in addition to the MPOA. In light of the lack of change in responsiveness to apomorphine across weeks of each experiment, it seems likely that the greater effectiveness of systemic apomorphine injections resulted from stimulation of dopamine receptors in multiple areas. In summary, a dopamine agonist, administered either systemically or into the MPOA, partially restored copulatory behavior in males tested approximately three to eight months after castration.

**DOPAMINE RELEASE IN THE MPOA BEFORE AND DURING COPULATION**

We have recently developed a very sensitive assay for dopamine in the MPOA, using microdialysis and high-performance liquid chromatography with electrochemical detection. In sexually experienced, gonadally intact males, dopamine levels increased in the first six-minute sample after an estrous female was placed across a perforated barrier from the male (Figure 5.5) (Hull, Du, Lorrain, & Matuszewich, 1995). Dopamine increased further when the barrier was removed and the animals were allowed to copulate. If the precopulatory period was lengthened to one hour, dopamine rose in the first two samples and then fell back toward baseline as the male lost interest in the female (Figure 5.10). When the barrier was finally removed, the animals immediately began to copulate and dopamine rose as before. Therefore, the level of extracellular dopamine in the MPOA may be a sensitive indicator of the male’s interest in the female.

If another male was placed across the barrier, instead of the estrous female, dopamine levels rose only slightly (nonsignificantly). Therefore, there is something special about the stimuli from the estrous female. We also tested whether the motor components of copulation could account for the dopamine increase. Animals received five weeks of daily access to an activity wheel; controls were allowed to explore a locked wheel but could not run until the test day. Voluntary running in a running wheel increased dopamine levels only slightly, and previous running experience did not affect the dopamine response to running on the test day. The motor activity exhibited by these males was greater than that required for copulation. Therefore, the motor components of copu-
Figure 5.8
Effects of Apomorphine Microinjected into the Medial Preoptic Area on Sexual Behavior of Long-Term Castrates


A. Apomorphine increased the number of mounts per thirty-minute test in animals tested without subthreshold testosterone. B. Apomorphine produced a nonsignificant increase in mounts when administered with subthreshold testosterone.
Figure 5.9
Extracellular Dopamine in the Medial Preoptic Area of Male Rats
(during a precopulatory period, with an estrous female across a perforated barrier, and during three six-minute periods after the barrier was removed and the animals were free to copulate)


lation cannot account for the increase in extracellular dopamine that we normally see during copulation.

We are currently investigating some of the biochemical factors that promote the dopamine response to the female. The first factor that we have studied is the recent or concurrent presence of testosterone (Hull et al., 1995). Castrates received either one or two weeks of testosterone propionate (TP) or oil injections. All TP-treated animals showed the precopulatory dopamine response, and all copulated after the barrier was removed (Figure 5.9). Nine of fourteen oil-treated one-week castrates also showed the precopulatory dopamine response, and all of these copulated after the barrier was removed. The remaining five of the oil-treated one-week castrates, and all of the oil-treated two-week castrates, failed to show the precopulatory dopamine response, and also failed to copulate when the barrier was removed. In every animal, the male’s precopulatory dopamine response predicted his subsequent copulatory behavior. Two conclusions can be drawn from this experiment: (1) The precopulatory MPOA dopamine response to the estrous female is a
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**Figure 5.10**

Extracellular Dopamine in the Medial Preoptic Area during a Prolonged Precopulatory Period Followed by Copulation

![Graph showing extracellular dopamine levels](image)


very consistent predictor of the ability and/or inclination of a male rat to copulate, and (2) the recent but not concurrent presence of testosterone may be necessary for both the dopamine response and copulation.

**CONCLUSION**

Stimuli from an estrous female elicit dopamine release in three integrative hubs in intact male rats. Dopamine in the nigrostriatal tract prepares the male for the motor components of copulation. Dopamine in the mesolimbic system increases responsiveness to a variety of environmental stimuli that have motivational significance. And dopamine in the MPOA increases responsiveness to sexual stimuli. This latter effect results in an increase in specific sexual motivation, a facilitation of genital reflexes, and coordination of stereotyped motor patterns of copulation. It may also be related to partner preference. Recent exposure to testosterone facilitates dopamine release in the MPOA and may thereby contribute to copulation.

Finally, it is important to emphasize the parallel effects of gonadal steroids and dopamine in the organization and activation of male sexual behavior. Undoubt-
edly, the steroid effects are more powerful and far reaching, while dopamine's effects are more subtle and may serve to fine tune or amplify integrative mechanisms of the sexual system. The organizational effects of dopamine appear to be at least partially independent of steroid influence. Sex differences have been reported in cultures of dopamine neurons obtained before the gonads differentiated and began to secrete hormones. These sex differences may derive from transcription factors coded by the Sr5 gene or other genes on the Y chromosome. Dopamine neurons may in turn influence the development of other neurons, either alone or in combination with other growth factors. In adulthood, dopamine agonists can facilitate several measures of sexual behavior in intact males and can partially restore copulatory behavior in long-term castrates. Furthermore, testosterone may facilitate the activation of male-typical sexual behavior, in part by promoting the release of dopamine in several integrative hubs, including the MPOA. Possible mechanisms of steroid influence on dopamine release are currently under investigation.

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