

Dopamine and serotonin: influences on male sexual behavior

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Abstract

Steroid hormones regulate sexual behavior primarily by slow, genomically mediated effects. These effects are realized, in part, by enhancing the processing of relevant sensory stimuli, altering the synthesis, release, and/or receptors for neurotransmitters in integrative areas, and increasing the responsiveness of appropriate motor outputs. Dopamine has facilitative effects on sexual motivation, copulatory proficiency, and genital reflexes. Dopamine in the nigrostriatal tract influences motor activity; in the mesolimbic tract it activates numerous motivated behaviors, including copulation; in the medial preoptic area (MPOA) it controls genital reflexes, copulatory patterns, and specifically sexual motivation. Testosterone increases nitric oxide synthase in the MPOA; nitric oxide increases basal and female-stimulated dopamine release, which in turn facilitates copulation and genital reflexes. Serotonin (5-HT) is primarily inhibitory, although stimulation of 5-HT_{2C} receptors increases erections and inhibits ejaculation, whereas stimulation of 5-HT_{1A} receptors has the opposite effects: facilitation of ejaculation and, in some circumstances, inhibition of erection. 5-HT is released in the anterior lateral hypothalamus at the time of ejaculation. Microinjections of selective serotonin reuptake inhibitors there delay the onset of copulation and delay ejaculation after copulation begins. One means for this inhibition is a decrease in dopamine release in the mesolimbic tract.

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1. Introduction

In this review we summarize the current understanding of the primarily excitatory roles of dopamine and primarily inhibitory roles of serotonin in the regulation of male sexual behavior. We begin by discussing the means by which slow genomically mediated effects of steroid hormones are translated into rapid, moment-to-moment control of copulation. Subsequently, first for dopamine, then for serotonin, we describe the effects of systemically administered dopaminergic and serotonergic drugs, discuss the primary sites at which dopamine and serotonin exert their effects, and review some of the regulators that govern their release in those sites. Throughout, we describe effects on sexual motivation, copulatory patterns, and genital reflexes. We

conclude with a summary and a series of questions that remain unanswered and that may guide future research.

2. Model of central control of male sexual behavior

Sexually relevant stimuli elicit a complex cascade of genital and somatomotor patterns. In male rats this precisely timed motor sequence includes locomotor pursuit, mounting, pelvic thrusting, penile erection and insertion, ejaculation, postejaculatory grooming, and quiescence. Steroid hormones facilitate this process by biasing sensorimotor integration so that a sexually relevant stimulus is more likely to elicit a sexual response. Most steroid effects that are important for the elicitation of sexual behavior are mediated by slow genomic actions [1–5], although steroids also have rapid, nongenomic effects (reviewed in Refs. [6,7]). Among the important targets of steroid action are synthetic enzymes, receptors, or other proteins affecting neurotransmitter function.

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One step in the translation of long-term steroid effects into rapid behavioral events is a change in the release or effectiveness of one or more neurotransmitters. One candidate neurotransmitter is dopamine, since dopaminergic drugs have long been known to facilitate masculine sexual function clinically [8–11]. A newer sublingual formulation of the classic dopamine agonist apomorphine has been effective in treating erectile dysfunction with fewer side effects (such as nausea) than previous orally administered drugs (reviewed in Ref. [12]). Recent studies in animals have confirmed the general facilitative effect of systemically administered dopaminergic drugs (reviewed in Ref. [13]). For example, systemically injected apomorphine activated copulatory behavior in male mice with a targeted deletion of the gene encoding the estrogen receptor alpha (ER α); saline-treated ER α “knock out” males failed to copulate [14]. Similarly, apomorphine elicited penile erections and genital grooming in mice; the effect was blocked by the centrally acting dopamine antagonist haloperidol, but not by the peripherally active antagonist domperidone [15]. Apomorphine also partially restored mounting behavior in socially stressed rats [16]. Selective D₂/D₃ agonists (7-OH-DPAT and B-HT 920) increased the numbers of noncontact erections in sexually experienced males [17]. In addition, a selective D₁ agonist, SKF-38393, increased the number of copulatory behaviors, as well as the time spent in a goal compartment with an estrous female, suggesting that dopamine enhances sexual motivation as well as copulatory behavior [18]. Conversely, the dopamine antagonist haloperidol increased the latency to run to an estrous female in a straight alley, without affecting latency to reach an empty goalbox [19]. In another study, haloperidol administered before males’ first copulatory experience diminished their motivation to approach an estrous female on a subsequent drug-free test, even though all males did ejaculate on their first experience [20]. Thus, several studies report effects of dopaminergic drugs on both motivation and copulatory ability, even in situations in which motoric behavior was not significantly affected. However, there is one report that dopaminergic drugs failed to influence the choice by sexually naïve males to spend time near a female, unless motoric behavior was also affected [21].

Gonadal steroids regulate dopaminergic innervation in both hypothalamic and extra-hypothalamic structures at various developmental stages. Sexual dimorphism of the anteroventral periventricular nucleus (AVPV) is well documented [22,23]. This loss of dopaminergic cells and fibers during the perinatal period is testosterone- [23] and ER α -dependent [24]. In adult rats, removal of circulating gonadal steroids increases dopaminergic innervation in AVPV [23,25], but decreases such innervation in A13 [26]. In extra-hypothalamic dopamine systems, dopamine innervation to frontal cortex is influenced by gonadal steroids. Estradiol appears to up-regulate dopamine levels in the

frontal cortex during the perinatal period [27]. In adulthood, estradiol has been reported to increase, while androgens decrease, dopaminergic fibers in prefrontal cortex [28–30]. Similarly, the restoration of copulation by apomorphine in ER α “knock out” males, noted above, suggests that one function of estrogen at ER α receptors is to increase dopaminergic stimulation (see Section 3.6, below).

Dopamine is released before and/or during copulation in several key integrative sites, described below. One means by which dopamine may act is by removing tonic inhibition, thereby enhancing sensorimotor integration (reviewed in Refs. [31,32]). Thus, steroid hormones may prime neurons to be responsive, but the neurons cannot actually respond unless the tonic inhibition is first removed. Therefore, dopamine may not elicit behavior directly but may allow sexually relevant stimuli to have easier access to hormonally primed output pathways. It may also facilitate the release of excitatory neurotransmitters, such as glutamate.

Three major integrative systems control sexual motivation and genital and somatomotor responses in male rats. A key factor in this model is that sensory input from a receptive female and/or the act of copulation elicits the release of dopamine in each of the three main integrative systems. Output from these systems controls the expression of sexual motivation, genital reflexes, and somatomotor patterns of copulation. The nigrostriatal system enhances the motoric readiness to respond to stimuli; the mesolimbic system is critical for appetitive behavior and reinforcement; and the medial preoptic system contributes to genital reflexes, as well as to specifically sexual motivation and the motor patterns of copulation (reviewed in Refs. [13,33]).

2.1. *The nigrostriatal integrative system*

The nigrostriatal system enhances readiness to respond to stimuli [34,35]. Dopamine in the striatum disinhibits pathways through which the cortex elicits movements [31,32]; loss of nigrostriatal dopamine in Parkinson’s disease impairs response initiation. Bilateral lesions of the substantia nigra slowed the rate of copulation and decreased the number of ejaculations [36], consistent with its importance for motor initiation and coordination. Nigral dopamine neurons respond with short latencies to a variety of stimuli that have “attention-grabbing properties” but do not provide specific information about those stimuli [37]. Dopamine is released in the striatum during copulation, but not during precopulatory exposure to a receptive female, suggesting that striatal dopamine is important for motoric aspects of copulation, but not sexual motivation [38]. Indeed, a subset of dopamine transients, recorded with fast cyclic voltammetry, immediately preceded intromissions [39]. This system may contribute to the execution of “consummatory” movements [35], including pursuit of the female and mounting.

2.2. The mesolimbic integrative system

The mesolimbic system is critical for appetitive behavior and reinforcement. It is activated before or during a variety of motivated behaviors, including eating, drinking, copulating, drug self-administration, and intracranial self-stimulation [40,41]. There is disagreement as to whether mesolimbic dopamine is more important for reward processes (e.g., Ref. [42]), the behavioral activation elicited by reinforcers (e.g., Refs. [34,43,44]), “wanting” (as opposed to “liking,” e.g., Ref. [45]), or incentive learning (reviewed in Refs. [46,47]). However, there is agreement that the mesolimbic system is crucial for appetitive behavior.

2.3. The medial preoptic area (MPOA) integrative system

The MPOA is critical for male sexual behavior in all vertebrate species in which its role has been studied (reviewed in Ref. [13]). Even in unisexual lizards, expression of male-like behavior is associated with increased activity in the MPOA, whereas expression of female-like behavior is associated with ventromedial hypothalamic activity [48]. Because the specific sexual stimuli and motor patterns differ greatly among species, the universal regulatory role of the MPOA suggests that it occupies a very high position in the hierarchy of control. Furthermore, dopamine in the MPOA facilitates male sexual behavior in many species, suggesting that it, too, plays a central role in this process. (See the articles by Ball et al. and Woolley et al. in this issue regarding neural control of male sexual behavior in birds and in reptiles and amphibians, respectively.)

The MPOA receives indirect sensory input from virtually every sensory modality [49]. Reciprocal connections with each source of input provide a means for the MPOA to modulate sensory processing [50]. Steroid hormone receptors in the MPOA and its afferent connections allow hormones to promote the processing of sexually relevant stimuli. Dopamine input to the MPOA arises from the periventricular system, including cell bodies in the medial portion of the MPOA [49,51].

Efferent projections from the MPOA are critical for the initiation of copulation. Males with MPOA lesions may still exhibit appetitive behavior to be with a female, but they are unable to trigger the stereotypic mounting and thrusting pattern [52,53]. The major efferent projections of the MPOA are to hypothalamic, midbrain, and brain stem nuclei that regulate autonomic or somatomotor patterns and motivational states (reviewed in Refs. [13,50,54,55]). A major output is to the paraventricular nucleus (PVN) of the hypothalamus, which is also important for the control of noncontact erections and copulation (see review by Argiolas and Melis in this issue). MPOA dopamine may remove the tonic inhibition on these patterns and thereby allow sensory stimuli to elicit a motor response. The causes and con-

sequences of MPOA dopamine release are discussed in depth below.

2.4. Roles of the MPOA and mesolimbic dopamine systems in sexual behavior

Everitt [53] suggested that the MPOA is important for copulatory performance, whereas the mesolimbic system provides the motivational impetus. Manipulations of the mesolimbic system affected responding for a secondary reinforcer that had been associated with a receptive female, but did not affect copulatory performance [56]. On the other hand, MPOA lesions abolished copulation, but did not affect lever pressing for the secondary reinforcer. Thus, there may be a double dissociation between mesolimbic and MPOA influences, with the mesolimbic system contributing appetitive responses and the MPOA controlling performance. However, this dichotomy may be too simplistic. The MPOA can influence sexual motivation, and the mesolimbic tract can affect copulatory performance. Decreasing mesolimbic dopamine activity delayed the onset and slowed the rate of copulation [57]. It also led to general inactivity and poorly organized copulatory patterns, but did not affect specifically sexual motivation [58,59]. Thus, general activation, but not specifically sexual motivation, may be affected by mesolimbic activity.

On the other hand, microinjections of dopamine antagonists into the MPOA decreased sexual motivation, measured in an X-maze [60] or in a bi-level apparatus in which the male changed levels in search of a female [61]. MPOA lesions decreased the male's preference for an estrous female [62,63] and decreased pursuit of the female [64]. In addition, some MPOA neurons in rats [65] and monkeys [66] increased firing only during approach behavior before copulation, while others increased firing only during copulation. Furthermore, different sub-areas of the MPOA are associated with appetitive vs. consummatory behavior patterns in birds [67]. Finally, our finding that dopamine in the MPOA is elevated during a precopulatory period, when the female is inaccessible, also suggests a role for MPOA dopamine in sexual motivation [68]. Thus, MPOA dopamine and neural activity may contribute to sexual motivation as well as performance.

3. Activation of dopamine release in the MPOA

3.1. MPOA dopamine release and copulation

We have observed a very consistent relationship between MPOA dopamine release during a precopulatory period (female behind a perforated barrier) and the subsequent ability of the male to copulate [68] (see Fig. 1). The presence of a male, rather than a female, behind the barrier did not elicit dopamine release, nor did voluntary running in an activity wheel. Moreover, eating a highly palatable food

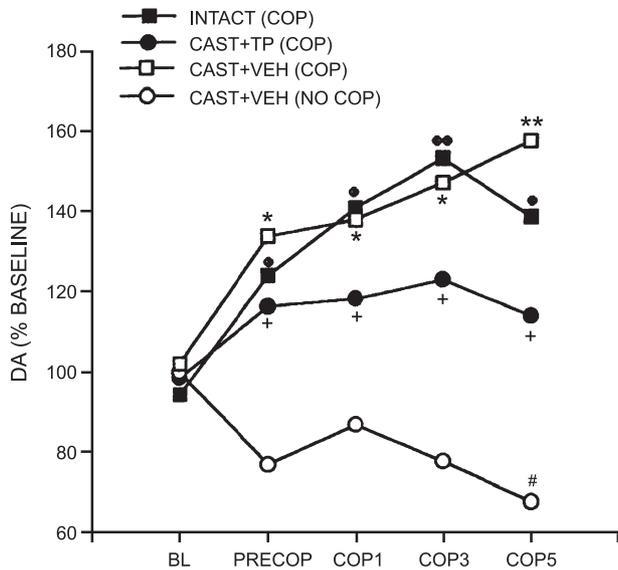


Fig. 1. Extracellular dopamine in the MPOA of male rats during baseline, a precopulatory period (estrous female behind a perforated barrier), and three 6-min periods after the barrier was removed and the animals were free to copulate. All gonadally intact males and all castrates treated with testosterone propionate (TP, 200 μ g/day) showed a significant increase in dopamine during the precopulatory period and during copulation; all these animals did copulate. A total of nine of 14 oil-treated 1-week castrates also showed the precopulatory dopamine response and copulated after the barrier was removed. The remaining 1-week and all four 2-week oil-treated castrates failed to show the precopulatory dopamine response and failed to copulate; data from these two groups are combined. * $P < 0.05$ compared to final baseline for intact males or for 1-week vehicle-treated castrates that copulated. ** $P < 0.01$ compared to final baseline for intact males or for 1-week vehicle-treated castrates that copulated. + $P < 0.05$ compared to baseline for testosterone-treated castrates. # $P < 0.05$ compared to final baseline for vehicle-treated castrates that failed to copulate. (Reprinted from Hull et al. [68], with permission.)

did not increase dopamine metabolites [69]. Thus, there is behavioral specificity to the MPOA dopamine response, in contrast to the variety of stimuli that elicit dopamine release in the mesolimbic system. There is also site specificity, in that no drug effects were associated with cannulae that were located anterior, lateral, or dorsal to the MPOA [70–72], and misplaced microdialysis probes did not detect dopamine increases in response to a female [68].

3.2. The role of testosterone

The recent presence of testosterone is permissive for the precopulatory dopamine response and for copulation [68]. All gonadally intact males, all testosterone-replaced castrates, and two-thirds of oil-treated animals that had been castrated 1 week previously showed a precopulatory dopamine response, and all of them copulated. All 2-week oil-treated castrates and one-third of the 1-week oil-treated castrates failed to show a precopulatory dopamine response, and all failed to copulate when the barrier was removed. Every animal that showed at least some precopulatory increase in dopamine was able to copulate, and no animal

that failed to show such a response could copulate. Therefore, recent testosterone may facilitate copulation, in part, by permitting increased MPOA dopamine release in response to a female.

A similar pattern was seen with 2-, 5-, and 10-day regimens of testosterone restoration in males castrated 3 weeks earlier [5]. All males had lost copulatory ability before hormone restoration was begun. As in the previous study, there was a consistent relationship between precopulatory dopamine release and the ability of the male to copulate. None of the 2-day, but all of the 10-day castrates showed at least some dopamine increase and copulated. Five of the nine 5-day castrates ejaculated, three intromitted but did not ejaculate, and one failed to copulate. All but the noncopulator (i.e., eight of the nine) showed at least some precopulatory dopamine response. Furthermore, there were significant partial correlations between precopulatory dopamine increases and every copulatory measure. (Partial correlations tested for significant correlations between behavior and dopamine, after the effects of hormone treatment were statistically removed.) Therefore, there was again a compelling link between MPOA dopamine release and the ability to copulate. These data are also consistent with those of McGinnis et al. [4], who reported that 5 days was a threshold time for testosterone restoration to activate behavior.

3.3. How general is the dopamine deficit in castrates?

Is the deficit in extracellular dopamine of castrates a general one, or is it specific to the sexual context? The no-net-flux technique was used to measure absolute levels of extracellular dopamine [73]. Briefly, if excess dopamine is added to the dialysate, some of it will diffuse out of the probe into the brain, and the loss can be detected. If there is less dopamine in the dialysate than in the brain, or if there is none, as is always the case in normal dialysis, then dopamine will diffuse from the brain into the dialysate, and the gain can be detected. A regression line is drawn, and the point at which the line crosses from loss to gain of dopamine in the dialysate (no net flux out of or into the dialysate) is taken as the actual level of extracellular dopamine. Basal levels of extracellular dopamine were indeed lower in castrates than in intact males. Thus, there is a general deficiency of extracellular dopamine in the MPOA of castrates, both in basal conditions and in response to a female.

3.4. Synthesis or release problem?

A decrease in extracellular dopamine could result from either a decrease in stored dopamine or a decrease in release. Therefore, we measured dopamine in MPOA tissue punches, in which almost all neurotransmitter is stored in vesicles. In contrast to their low extracellular levels, castrates actually had more stored dopamine than did intact

males [73]. This suggests that synthesis and storage were at least normal, and perhaps enhanced, in castrates. This finding was confirmed when amphetamine elicited greater dopamine release in castrates than in intact males. Amphetamine causes storage vesicles to become “leaky” and also reverses the transporter, thereby evoking dopamine release [74]. Since there is more stored dopamine in castrates, there is more available for release. These data may explain a puzzling phenomenon in recently castrated animals. In the weeks following castration, the latency to begin copulating increases progressively [2]. However, if the male does initiate copulation, he will ejaculate prematurely, with fewer intromissions and in less time than an intact male. The increased latency to begin copulating may be explained by the increasing difficulty of castrates to release MPOA dopamine. However, if they do begin, castrates have more stored dopamine to be released. We have suggested that high levels of dopamine, acting on D₂-like receptors, shift the autonomic balance to favor ejaculation [71,72].

3.5. Does testosterone influence DA synthesis in MPOA?

The increased intracellular dopamine in castrates could result from decreased release, increased synthesis, or both. However, there was no difference in immunoreactivity for tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine synthesis, between castrates and intact males [75]. Furthermore, there was little co-localization of TH and androgen receptors or ER α in neurons in several dopaminergic cell groups in the preoptic area and hypothalamus [76]. Therefore, it appears that testosterone has little influence on the synthesis of dopamine in the MPOA; its effects on intra- and extracellular dopamine are primarily on release.

3.6. The role of nitric oxide (NO)

Dopamine release may be affected by influences on axon terminals, as well as changes in the firing rate of dopamine neurons. One likely mediator of steroid influence on dopamine release is nitric oxide (NO). NO has been reported to enhance catecholamine release (reviewed in Refs. [77,78]) and to inhibit reuptake, possibly by reversing the transporter [79]. NO, a soluble gas, is given off when L-arginine is converted to citrulline by the enzyme NO synthase (NOS). Administration of the NO precursor L-arginine through a microdialysis probe increased the mount rate of sexually experienced male rats, whereas administration of a NOS inhibitor reduced mount rate [80]. In addition, a NOS inhibitor (L-nitroarginine methyl ester, L-NAME), when microinjected into the MPOA, prevented copulation in sexually naïve males and impaired copulation in sexually experienced animals [81]. Finally, L-NAME, microinjected into the MPOA before each of seven exposures to an inaccessible estrous female, also blocked the facilitative influence of those exposures, which was seen in saline-injected animals, compared to males that were not

pre-exposed to females. Thus, NO in the MPOA may be important for sensitization to sensory cues that elicit copulatory behavior as well as for copulation.

At least some of the effects of NO in the MPOA may be mediated by dopamine. Reverse dialysis of L-arginine, but not its inactive isomer D-arginine, into the MPOA increased extracellular dopamine [82]. This increase was blocked by a NOS inhibitor, which also decreased basal dopamine release when administered alone. Furthermore, a NOS inhibitor, administered through the dialysis probe, prevented the increase in MPOA dopamine seen in controls during copulation [83]. Only animals that copulated were analyzed, although specific behavioral measures were not recorded. Apparently, the volume dialyzed by the probe was small enough that dopamine in the remaining MPOA was sufficient to support copulation. Thus, NO may act at dopamine terminals to enhance dopamine release in response to an estrous female. Alternatively, it may increase firing of dopamine-containing cells in the periventricular system.

The most common second messenger of NO is 3',5'-cyclic guanosine monophosphate (cGMP). Alterations of cGMP in the MPOA influenced both extracellular dopamine in the MPOA and copulation [84]. Furthermore, the steroid-dependent luteinizing hormone (LH) release in both male and female rats was dependent on NMDA glutamate receptors, NO, and cGMP in the MPOA [85]. Thus, NO in the MPOA may play an integral role in the regulation of both reproductive behavior and neuroendocrine control, and cGMP may mediate some of those effects.

Nitric function in the MPOA appears to depend on gonadal hormones. For example, there were fewer NOS immunoreactive (NOS-ir) neurons in the medial preoptic nucleus (MPN) of oil-treated castrates than in intact males or testosterone-replaced castrates [75]. Furthermore, 2-, 5-, and 10-day regimens of testosterone replacement in long-term (3-week) castrates produced progressive increases in the numbers of intromissions and ejaculations and in the density of NOS-ir with longer treatments [86]. There was also a significant negative correlation between NOS-ir density and mount latency. Thus, the greater the NOS-ir density, the shorter was the mount latency. In addition, co-localization of neuronal NOS and steroid receptors in the MPOA has been reported in hamsters [87], mice [88] and rats [89,90]. Together, these experiments suggest that one means by which testosterone, or one of its metabolites, promotes copulation is by up-regulating NO production in the MPOA, which then increases both basal and female-stimulated dopamine release. Dopamine, in turn, facilitates genital reflexes, sexual motivation, and copulatory efficiency (see below).

3.7. Which metabolites of testosterone maintain dopamine release, NOS-ir, and copulation?

Testosterone (T) is primarily a prohormone, which is either aromatized to estradiol (E) or reduced to dihydrotest-

tosterone (DHT) in target tissues, including the brain. The importance of E in the MPOA, and of androgens in the periphery and in the brain, has received considerable attention over the years (e.g., Refs. [13,91–95]). Accordingly, we have examined the roles of T metabolites in the effects of T manipulations discussed above. Sexually experienced male rats were castrated and immediately began a 3-week regimen of hormone maintenance with daily injections of T, E, DHT, E+DHT, or oil [96] (see Fig. 2). E+DHT- and T-treated animals had normal basal dopamine levels, showed a precopulatory dopamine response, and copulated normally. E-treated castrates had high basal dopamine levels but failed to show a female-stimulated increase; most intromitted, but none ejaculated. DHT- and oil-treated groups had low basal levels of extracellular dopamine that did not increase during copulation testing; most failed to mount and none ejaculated. These results suggest that E maintains normal basal levels of extracellular dopamine in the MPOA, which are sufficient for suboptimal copulation, but that androgen is required for the female-stimulated increase in dopamine release and for facilitation of ejaculation. Conversely, we found an inverse relation between tissue (intracellular) dopamine levels and the ability to copulate [97]. E, T, and E+DHT animals had low levels of tissue dopamine and did copulate. Vehicle- and DHT-treated animals had high levels of dopamine in tissue and did not copulate. In additional animals, E maintained a

variable number of NOS-ir neurons in the MPN and variable copulatory ability; there were several significant partial correlations between NOS-ir and copulatory measures [98]. T and E+DHT maintained both copulatory ability and high numbers of NOS-ir neurons, whereas neither DHT nor oil vehicle maintained copulation or numbers of NOS-ir neurons. Furthermore, ER α “knock out” mice had less NOS-ir in the MPOA than did wild-type males [88]; tissue dopamine content was not affected by the gene disruption [14]. In addition, microinjections of low doses of the classic dopamine agonist apomorphine into the MPOA increased copulatory behaviors in ER α “knock out” mice [99]. The authors suggested that, since MPOA apomorphine restored copulation in the “knock out” mice, a major function of the ER α may be to up-regulate NOS, which facilitates MPOA dopamine release, which in turn enhances copulatory ability. Therefore, it appears that activation of estrogen receptors in the MPOA is critical for maintenance of NOS-ir, dopamine release, and copulation; but there is no direct effect of hormones on dopamine synthesis. Dopamine accumulates in tissue in castrates because so little can be released. Androgens, on the other hand, seem to act at peripheral tissues and other areas of the brain to modulate sensory input and motor output.

3.8. What triggers the dopamine release in response to a female?

The medial amygdala (MeA) provides a major source of input to the MPOA [13,100–102]. It receives sensory information from the olfactory bulbs and vomeronasal organ, processes it, and relays it to the MPOA and other sites. The MeA and MPOA (as well as other sites) are activated by copulation, as measured by an increase in Fos-ir (e.g., Refs. [103–105]). Combined lesions of the MeA (which removed chemosensory input) and of the central tegmental field (which removed genital sensory input) blocked the induction of Fos-ir in the MPOA [103]. Lesions of the MeA also impaired copulation [106] and blocked the facilitative effect of pre-exposure to a receptive female immediately before copulation [107]. Microinjections of the dopamine agonist apomorphine into the MPOA restored copulatory ability in males with large amygdala lesions [108] (Fig. 3). Smaller MeA lesions also impaired copulation and completely prevented the MPOA dopamine response to a female, although basal dopamine levels in the MPOA were not affected [108] (Fig. 4). Therefore, MeA lesions removed an important stimulus for DA release in the MPOA and for copulatory ability. Furthermore, as with E-treated castrates, normal basal MPOA dopamine levels were apparently sufficient for suboptimal copulation, whereas an additional increase in response to a female was associated with more efficient copulation. In addition, chemical stimulation of the MeA with glutamate plus a glutamate reuptake inhibitor (L-trans PDC) elicited an increase in extracellular dopamine in the MPOA [109]. The size of the

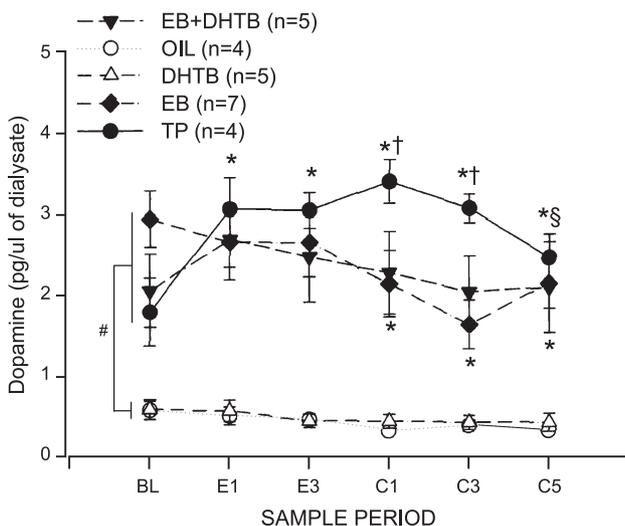


Fig. 2. Levels of extracellular dopamine in 6-min microdialysate samples from the MPOA of male rats during baseline conditions (BL), during exposure to an estrous female behind a barrier (EST), and during copulation testing (COP). Castrates treated with testosterone propionate (TP, 500 μ g/day) or with estradiol benzoate (EB, 20 μ g/day) plus dihydrotestosterone propionate (DHT, 500 μ g/day) showed increased extracellular dopamine during EST or COP conditions. All these males copulated to ejaculation. Castrates treated with EB alone showed high basal levels of dopamine but no increase in response to the female or during copulation. All these males intromitted, but none ejaculated. Castrates treated with DHT alone or with vehicle had low basal levels of extracellular dopamine and no increase during EST or COP conditions; none of these animals copulated. (Reprinted from Putnam et al. [96], with permission.)

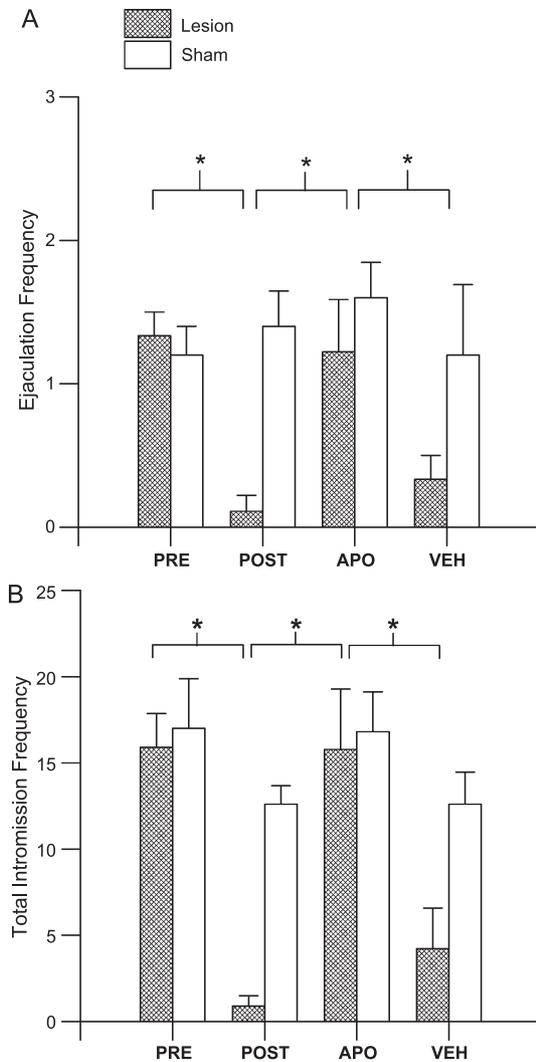


Fig. 3. Ejaculation frequency and total intromission frequency for animals with amygdalar lesions or sham lesions. There were no significant differences in ejaculation frequency or total intromission frequency for animals with sham lesions. Animals with amygdalar lesions displayed significantly fewer ejaculations and fewer total intromissions after surgery (POST) compared with before surgery (PRE). Microinjections of apomorphine (APO), but not vehicle (VEH), restored measures of copulation for animals with amygdalar lesions. Values are expressed as mean \pm SEM ($*P < 0.05$). (Reprinted from Dominguez et al. [108], with permission.)

increase (~150%) approximated that seen with exposure to an estrous female and during copulation. Therefore, a major input from the MeA to the MPOA both mediates the dopamine response to a female and enhances copulatory ability.

3.9. Influence of glutamate on dopamine release

There are no dopamine cell bodies in the MeA of male rats; therefore, any change in dopamine release in the MPOA after lesions or stimulation of the MeA must be due to changes in stimulation of periventricular dopamine neurons, either at the soma or axon terminals in the MPOA. We propose that MeA influences MPOA dopamine via

release of glutamate in MPOA. Glutamate is the major excitatory transmitter in the brain. It has been reported to increase dopamine release by activating dopamine-containing cell bodies [110–113] and to have variable effects on terminals [114–120] of the nigrostriatal and mesolimbic dopamine systems. The MPOA contains both cell bodies and terminals of periventricular dopamine neurons [51,121]. One likely stimulus for the female-stimulated increase in extracellular dopamine is excitatory input from one or more sources of sexually relevant sensory input, including the MeA. Furthermore, microinjection of glutamate into the MPOA elicited erectile responses in male rats [122], demonstrating the physiological relevance of glutamate in the MPOA for sexual function.

Two studies provide evidence for glutamatergic input from the MeA to the MPOA. First, [3 H]D-aspartate, microinjected into the MPOA and taken up by glutamate-containing terminals, was retrogradely transported to the sources of glutamatergic input, including the MeA and the bed nucleus of the stria terminalis (BNST), a major relay station between the MeA and the MPOA [123]. In addition, preliminary results from a very recent study using anterograde tract tracing from the MeA and BNST showed that a few axons from the MeA contained immunoreactivity for the vesicular glutamate transporter, a marker for glutamatergic axons [124]. In addition, numerous axons from the BNST were immunopositive for the vesicular glutamate

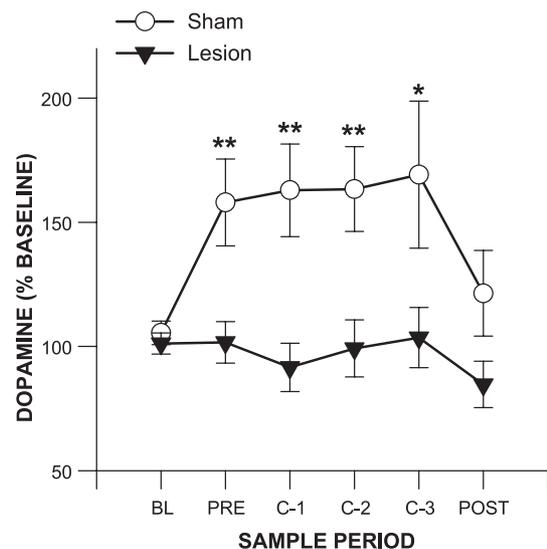


Fig. 4. Levels of dopamine in dialysate from the MPOA of animals with medial amygdala lesions. Levels represent percent changes from baseline (BL) in response to precopulatory exposure to an estrous female (PRE), during copulation (C1–C3), and after copulation (POST). Extracellular levels of dopamine significantly increased during the precopulatory and copulatory stages of testing for animals with sham lesions but not for animals with medial amygdalar lesions. The baseline value used for computation was obtained by dividing the value of the last baseline by the mean of all three baselines. Values are expressed as mean \pm SEM ($*P < 0.05$; $**P < 0.01$). (Reprinted from Dominguez et al. [108], with permission.)

transporter. Thus, axons from the MeA may synapse upon excitatory neurons in the BNST, which in turn relay glutamatergic input to the MPOA.

In a test of the effects of glutamate in the MPOA, reverse dialysis was used to administer glutamate into the MPOA while extracellular dopamine was measured [125]. Glutamate increased extracellular DA, which returned to baseline after the glutamate was removed. This increase was blocked by co-administration of L-NAME, but not by the inactive isomer, D-NAME. In contrast, extracellular concentrations of the major metabolites of dopamine were decreased by glutamate. Because metabolism occurs following transport into the terminal, the increase in dopamine, combined with decreases in its metabolites, suggests that the dopamine transporter was inhibited. These decreases in metabolites were also inhibited by L-NAME, but not D-NAME. As noted above, one means by which NO can increase dopamine levels is by inhibiting the dopamine transporter. Thus, glutamate may elicit the female-induced increase in extracellular DA in the MPOA, at least in part, via NO activity.

4. Effects of sexual experience

4.1. *Fos-ir in the medial preoptic nucleus*

Previous sexual experience increased the numbers of cells in the MPN that were immunoreactive for Fos following one ejaculation [104]. This increase was observed in spite of the fact that experienced males required fewer intromissions to trigger an ejaculation. A D₁ antagonist administered before copulation partially blocked the Fos-ir response to copulation. Previous sexual experience also increased the number of NOS-ir neurons in the MPN [126]. Indeed, the mere exposure of males to the odor of receptive females for 10 half-hour periods increased NOS-ir neurons in the MPN [127]. Thus, sexual experience increases the responsiveness of Fos-ir neurons to sexual stimuli, and that increased responsiveness may be mediated in part by increased stimulation of D₁ receptors, resulting from enhanced DA release, mediated by increased NO production.

4.2. *Effects of sexual experience on responsiveness to drugs*

We have also tested the influence of the glutamate NMDA receptor antagonist MK-801 (dizocilpine), administered systemically before copulation tests. MK-801 significantly impaired copulation [128]. We then administered the lowest effective dose of MK-801 to a group of sexually naive males before each of seven exposures to an estrous female in a wire-bottom cage placed directly over the male's cage. All animals were tested drug-free on the eighth day. The pre-exposures did improve copulatory behavior in vehicle-treated males, compared to animals

given no odor exposure; MK-801 abolished that effect. The drug-treated males spent similar amounts of time sniffing at the female, so the lack of improvement did not result from decreased exposure to the odor. Therefore, repeated exposures to an inaccessible estrous female are sufficient to improve copulatory behavior of male rats, and that improvement appears to be mediated, at least in part, by NMDA receptors.

We have more recently tested the effects of micro-injections of MK-801 into the MPOA in experienced and inexperienced males [129]. MK-801 completely blocked intromissions and ejaculations in sexually naive animals and decreased the numbers of intromissions and ejaculations in sexually experienced males. Furthermore, microinjection of MK-801 before each of seven noncopulatory exposures to a receptive female blocked the facilitation of copulation observed in saline-treated animals, compared to nonexposed controls. Thus, glutamate, acting via NMDA receptors, may produce long-term facilitation of processing within the MPOA. Malenka and Nicoll [130] have suggested that "LTP (long-term potentiation) is a fundamental property of the majority of excitatory synapses in the mammalian brain and, as such, is likely to subserve many functions..." Perhaps one of those functions is enhanced copulatory ability due to glutamatergic activity in the MPOA. These results mirror those of the NOS inhibitor L-NAME, microinjected into the MPOA, as discussed above. Both drugs blocked copulation in naive males, impaired copulation in experienced animals, and prevented the improvement due to repeated noncopulatory exposures to a receptive female. This similarity of effect likely reflects the fact that calcium, admitted via NMDA receptors, activates calmodulin, which in turn activates NOS. Thus, glutamate, acting via NMDA receptors in the MPOA, increases production of NO, resulting in increased DA release and/or inhibition of DA uptake and facilitation of copulation.

5. Consequences of dopamine release in the MPOA

5.1. *Does dopamine in the MPOA influence behavior?*

Early data showed that dopamine in the MPOA is important for copulation. Microinjections of the classic dopamine agonist apomorphine into the MPOA increased the rate and efficiency of copulation [70] and also increased the numbers of ex copula erections [131]. Blocking dopamine's access to receptors slowed the rate of copulation, decreased ex copula erections, and decreased sexual motivation [60]. More recently, it was demonstrated that reverse-dialysis of the dopamine reuptake inhibitor bupropion into the MPOA increased endogenous dopamine levels and increased both reflexive and noncontact erections [132]. Thus, endogenous dopamine in the MPOA facilitates copulation and enhances genital reflexes and sexual motivation.

The microinjection and reverse-dialysis data are critical, because the information gained from standard microdialysis leaves open the question of whether the observed dopamine increase is a cause or an effect of copulation. The combination of microdialysis and microinjection studies verifies that not only is dopamine released in the MPOA before and during copulation, but it is actively involved in facilitating the reflexive, motoric, and motivational aspects of sexual behavior.

5.2. Different roles of D_1 and D_2 receptors

D_1 and D_2 families of receptors may regulate the progression of a copulatory bout (reviewed in Ref. [33]). Small increases in dopamine, acting via D_2 -like receptors, appear to disinhibit genital reflexes. A low dose of a D_3/D_2 agonist (quinelorane) decreased the latency to the first reflexive erection or seminal emission, but did not affect the numbers of erections or seminal emissions [133]. A moderate dose of a D_1 agonist (dihydroxyphenyl-tetrahydrothienopyridine, THP) or of a mixed D_1/D_2 agonist (apomorphine) increased the numbers of parasympathetically mediated erections and facilitated copulation, but the D_1 agonist also decreased the number of sympathetically mediated seminal emissions in ex copula reflex tests [72,134]. Finally, a high dose of the D_3/D_2 agonist, or of apomorphine combined with a D_1 antagonist, shifted the balance of autonomic influence to favor ejaculation and inhibit erection [71,72,133]. Therefore, increasing amounts of DA in the MPOA may first disinhibit and then facilitate erections, and finally promote ejaculation. It is not clear whether the pure disinhibitory effect of the low dose of the D_3/D_2 agonist is mediated by a different subtype of the D_2 family of receptors than the one that inhibits erections and increases seminal emissions; alternatively, the same receptor subtype may produce the two different effects by acting on different populations of neurons with different efficacies.

5.3. Summary of dopaminergic influences on male sexual behavior

Dopamine, released in several major integrative areas before and/or during copulation, facilitates sexual motivation, motor performance, and genital reflexes. Testosterone up-regulates NOS in the MPOA; the resultant increase in NO then increases basal and female-stimulated levels of extracellular dopamine, which in turn enhance copulation. The female-stimulated increase in MPOA dopamine is mediated largely by glutamatergic input from the BNST, a major relay station between the MeA and the MPOA, and is dependent on the activation of NOS in the MPOA. Small increases in dopamine in the MPOA disinhibit genital reflexes via a member of the D_2 family of receptors; moderate increases facilitate parasympathetically mediated erections and copulatory behavior via a D_1 -like receptor;

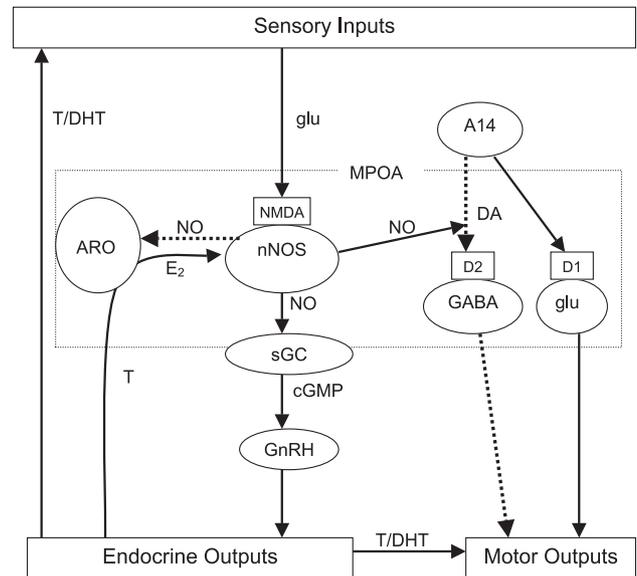


Fig. 5. Sensory input, transmitted from limbic and midbrain areas, results in activation of nNOS in the MPOA via glutamatergic NMDA receptors, resulting in NO release. NO, in turn, results in stimulation of several motor and endocrine outputs from the MPOA. (1) NO facilitates dopamine release from A14 periventricular neurons; dopamine either removes tonic inhibition by GABAergic cells or stimulates glutamatergic excitatory output. (2) NO, through the cGMP pathway, activates the hypothalamo-pituitary-gonadal (HPG) axis. This triggers release of gonadal hormones, which ensure the readiness of the circuitry involved in copulation. Estrogens maintain nNOS activity and, thus, dopamine release in the MPOA. Androgens exert their pro-copulatory effects on sensory, motor and integrative structures within the brain and in peripheral tissue. (3) NO may also mediate negative feedback by direct inhibition of aromatase. (T/DHT, testosterone/dihydrotestosterone; glu, glutamate; A14, periventricular dopamine neurons; MPOA, medial preoptic area; ARO, aromatase; NO, nitric oxide; NMDA, N-methyl-D-aspartate glutamate receptor; nNOS, neuronal nitric oxide synthase; D_2 , D_1 , dopamine receptor subtypes; sGC, soluble guanylyl cyclase; GnRH, gonadotropin releasing hormone; GABA, gamma-aminobutyric acid.)

large increases promote sympathetically mediated ejaculation and inhibit erections (Fig. 5).

6. The role of serotonin (5-HT) in male sexual behavior

6.1. Inhibitory effects of 5-HT

Dopamine is generally facilitative to male sexual behavior; however, 5-HT is regarded as inhibitory. Antidepressants of the selective serotonin reuptake inhibitor class (SSRIs, including Prozac and Zoloft) impair ejaculatory/orgasmic function and frequently inhibit erectile function and sexual interest as well [135,136]. Microinjection of large doses of 5-HT into the MPOA impaired male sexual behavior in rats [137,138]. Conversely, decreases in serotonergic activity, due either to lesions of cell bodies in the raphe nuclei [139–141] or to synthesis inhibition [142,143], facilitated male copulatory behavior; similar lesions also facilitated

ex copula genital reflexes [144,145] (reviewed in Ref. [13]). Furthermore, lesions of a major source of 5-HT to the spinal cord, the nucleus paragigantocellularis (nPGi) in the medulla, disinhibited the urethro-genital reflex (a model of sexual climax) [146] and reflexive erections and penile anteroflexions [147]. Such lesions also facilitated copulation [148].

6.2. Receptor subtype specificity

Different subtypes of 5-HT receptors appear to mediate the inhibitory effects of 5-HT on erection and on ejaculation. Systemic administration of the 5-HT_{1B} receptor agonist anpirtoline impaired ejaculation in male rats [149]. On the other hand, stimulation of 5-HT_{2C} receptors with mCPP impaired ejaculation but facilitated erections in male monkeys [150], suggesting an increase in parasympathetic influence. Similarly, mCPP increased the firing of cavernous nerves that innervate the penis and increased intracavernous pressure in anesthetized male rats [151]. Increased erections also resulted from systemic administration of either mCPP or a more selective 5-HT_{2C} agonist (R060-175) in awake rats [152]. The facilitative effect of 5-HT_{2C} agonists on erection is probably mediated by 5-HT_{2C} receptors on the visceromotor neurons of the sacral parasympathetic nucleus of the spinal cord, as well as on the dorsal gray commissure and ventral horn motor neurons [153]. On the other hand, a relatively nonselective 5-HT₂ agonist, DOI, inhibited copulation in male rats [154,155], increasing ejaculation latency and the PEI, while a 5-HT₂ antagonist facilitated copulation [156]. Thus, some 5-HT₂ receptors inhibit copulation, although the 5-HT_{2C} subtype appears to facilitate parasympathetically mediated erection, while inhibiting ejaculation.

6.3. Effects of 5-HT_{1A} receptor agonists

In contrast to the effects of 5-HT_{2C} agonists, stimulation of 5-HT_{1A} receptors, either systemically [137] or in the MPOA [157], facilitated ejaculation, and systemic administration of a 5-HT_{1A} agonist reversed sexual satiety [158]. Because decreases in 5-HT facilitate sexual behavior, it was suggested that 5-HT_{1A} agonists' beneficial effects may result from their stimulation of inhibitory autoreceptors in the raphe nuclei, which would decrease 5-HT levels [159]. However, the effects of a systemically injected 5-HT_{1A} agonist (8-OH-DPAT) were not prevented by lesions of 5-HT neurons, suggesting that inhibition of 5-HT release did not mediate the facilitative effects of the agonist [137]. Reverse-dialysis of 8-OH-DPAT into the MPOA facilitated copulation [157] and also increased levels of extracellular dopamine [160], possibly by inhibiting the dopamine transporter [161]. Furthermore, some of the facilitative effects on copulation of 8-OH-DPAT, microinjected into the MPOA, were partially blocked by the D₂ antagonist raclopride,

but not by the 5-HT_{1A} antagonist p-MPPI, at the doses used. Altered 5-HT levels were unlikely to mediate the effects of 8-OH-DPAT on copulation and MPOA dopamine levels. The behavioral facilitation was observed in the presence of both decreased 5-HT levels, due to stimulation of autoreceptors with systemic administration of the drug, and with increased 5-HT levels, due to inhibition of the transporter when the drug was reverse-dialyzed [160]. Therefore, the facilitative effects of the 5-HT_{1A} agonist may be mediated in part through its increase in extracellular DA in the MPOA. Further support for this hypothesis is provided by data showing that 8-OH-DPAT microinjections into the POA produce sympathetic responses (e.g., tachycardia, hypertension) [162]. We have suggested that stimulation of D₂-like receptors in the MPOA facilitates sympathetically mediated seminal emission and ejaculation (see above).

6.4. 5-HT release during ejaculation

Microdialysis studies, in which MPOA 5-HT was measured over the course of copulation, found no significant change in levels of the transmitter [160]. Furthermore, artificial elevation of MPOA 5-HT by microinjections of an SSRI did not significantly affect sexual behavior [160]. Impairment of sexual behavior by 5-HT microinjection into the MPOA has been reported, but only by large, supra-physiologic doses [137]. Taken together, it appears that, if serotonergic transmission in the MPOA does influence copulatory behavior, it does so with a subtlety that has eluded many analyses.

Mas et al. [163,164] suggested that 5-HT is released somewhat more laterally, in the preoptic area (POA), after ejaculation, and that these high levels of 5-HT may lead to the sexual quiescence that follows ejaculation. This suggestion was based on increased tissue levels of 5-HT in the POA [163] and increased extracellular levels of 5-HIAA (the major metabolite of 5-HT) in dialysate during the postejaculatory interval [164]. 5-HT was not detectable in dialysate in the latter study. However, we subsequently found no change in extracellular 5-HT levels in the MPOA or in the somewhat more lateral POA (Fig. 6) [165]. However, even farther lateral, in the anterior lateral hypothalamic area (LHA), 5-HT was released after ejaculation [165] (see Fig. 7). Because the observed elevation in 5-HT was coextensive with the postejaculatory interval (PEI), the possibility that it may be a causal determinant of the sexual quiescence was tested by microinjecting an SSRI (alaproclate) into the LHA. Alaproclate increased the latency to copulate, as though the animal had just ejaculated, and also increased the latency to ejaculate after the animal did start to copulate [165]. Similar microinjections into the MPOA were without significant effect. Therefore, the LHA may be one site where SSRI antidepressants produce their impairment of sexual function in humans.

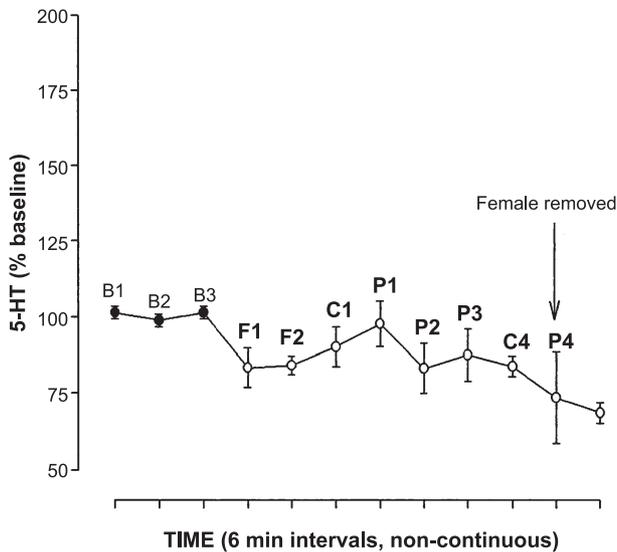


Fig. 6. Temporal changes in dialysate concentrations of serotonin (5-HT) collected from the MPOA of 16 subjects during copulatory activities. One sample was collected 30 min after removal of the female. Each data point represents the mean \pm SE from 6-min sampling intervals. No change in 5-HT release was observed during the sampling periods. Basal extracellular concentrations of 5-HT in the MPOA were estimated to be 1.4 ± 0.1 nM. (Reprinted from Lorrain et al. [165], with permission.)

6.5. Interaction between the LHA and the nucleus accumbens

The increase in latency to begin copulating observed with alaproclate suggested that sexual motivation had been dampened. Because dopamine release in the nucleus accumbens provides a major impetus for motivated behav-

ior, the effects of 5-HT, reverse-dialyzed into the LHA, on dopamine release in the nucleus accumbens was investigated. Indeed, 5-HT administered unilaterally into the LHA decreased basal levels of DA in the ipsilateral nucleus accumbens, beginning with the first 10-min sample [166]. Furthermore, reverse-dialysis of 5-HT prevented the usual increase in ipsilateral accumbens DA before and during copulation (see Fig. 8). Therefore, one way in which LHA 5-HT may promote sexual quiescence is by inhibiting activity in the mesolimbic DA tract, which is important for all types of motivated behavior.

6.6. 5-HT receptor subtypes in the LHA

We later performed behavioral experiments in order to infer which 5-HT receptor subtype was responsible for the decrements in copulatory behavior seen after microinjections of the SSRI into the LHA. Microinjection of a 5-HT_{2A/2C} agonist (DOI) into the LHA increased ejaculation latency and postejaculatory interval, an effect that was blocked by the 5-HT_{2A} antagonist LY-53,857, which did not affect copulation when administered alone [167]. DOI, at the doses used, did not affect locomotor activity. As we observed in the MPOA [157], microinjection of the 5-HT_{1A} agonist 8-OH-DPAT into the LHA facilitated ejaculation. As before, this effect was not blocked by the 5-HT_{1A} antagonist p-MPPI [167]. On the other hand, microinjection of a 5-HT_{1B} agonist (CGS-12066A maleate) into the LHA did not affect copulation at moderate doses, but abolished copulation at a high dose that also produced considerable motoric slowing in an open field test [167]. Thus, the copulatory deficit produced by the 5-HT_{1B} agonist may

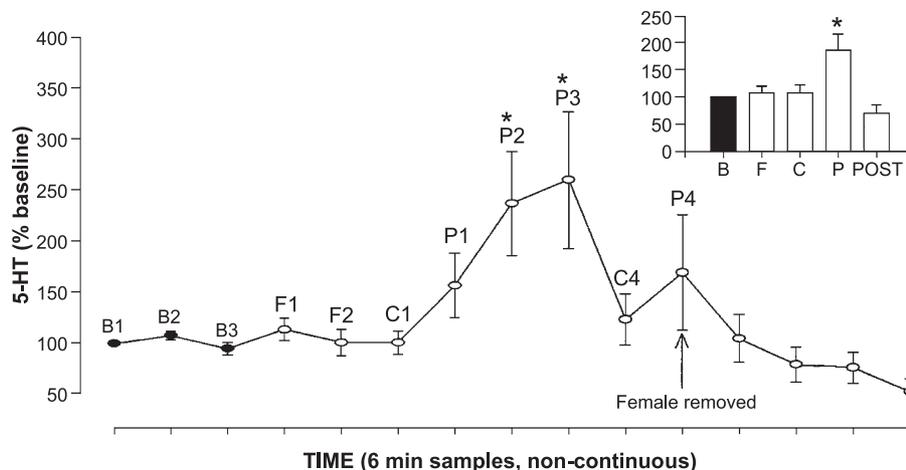


Fig. 7. Temporal changes in dialysate concentrations of serotonin (5-HT) collected from the anterior lateral hypothalamic area (LHA) of seven subjects during copulatory activities. Each data point represents the mean \pm SE for 6-min samples collected during baseline (B), in the presence of an estrous female (F), during copulation (C), during the postejaculatory interval (P), and after the female was removed (expressed as a percentage of baseline levels). Four samples were collected after removal of the female at 30-min intervals. Serotonin levels increased during the second (P2) and third (P3) postejaculatory intervals (PEIs), compared to the final baseline (B3), female behind barrier (F1, F2), and the first active copulation series (C1). Levels during the third PEI (P3) were also significantly greater compared with series 4 active copulation (C4). Samples collected during the second and third copulation series were not analyzed, because most animals ejaculated before a full 6-min sample could be collected. The summary graph (inset) represents the mean \pm SE for data from the 15 sample periods collapsed into five groups, based on behavioral condition. Samples collected during PEIs show enhanced 5-HT concentrations. (* $P < 0.05$ versus B, F, C, and POST) Basal extracellular concentrations in the LHA were estimated to be 1.6 ± 0.1 nM. (Reprinted from Lorrain et al. [165], with permission.)

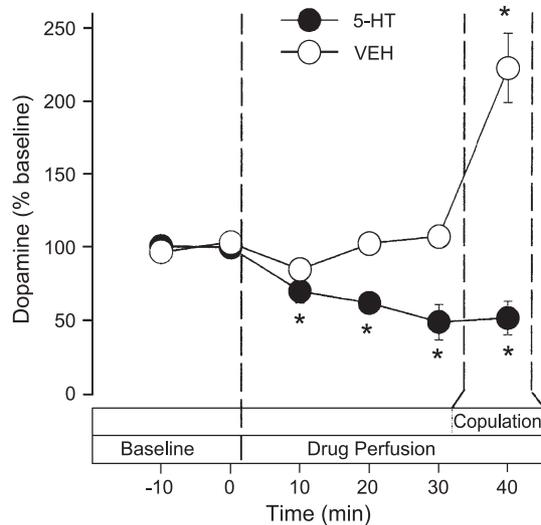


Fig. 8. Temporal change in dopamine concentration in dialysate collected from the nucleus accumbens before and during 40 min of serotonin (5-HT) perfusion into the anterior lateral hypothalamic area (LHA) of six male rats. Samples were collected at 10-min intervals. An estrous female was introduced to the male, and copulation was allowed during collection of the final sample during 5-HT perfusion. A significant decrease in dopamine occurred throughout the entire 5-HT perfusion period. This treatment blocked the increase in dopamine release seen in control (vehicle, VEH) animals ($*P < 0.05$ relative to baseline). (Reprinted from Lorrain et al. [166], with permission.)

have been secondary to the motor impairment. Thus, the receptor that may be most directly and specifically linked to the inhibitory effects of 5-HT in the LHA is the 5-HT_{2A} subtype.

6.7. The role of the LHA in arousal

The LHA generally, and its anterior and posterior poles in particular, is a classic site for the control of arousal and accompanying behavioral output [168]. These structures and their associated circuitry have been conceptualized as controllers of “behavioral state” which fulfill broad regulatory influence on various behaviors through their reciprocal connections with wake-active aminergic nuclei of the mid-brain and brainstem [169]. Appropriate arousal states and behavioral and autonomic output [170] may then be elaborated by the LHA as it affects (and is affected by) monoaminergic transmission in the medial forebrain bundle that traverses the LHA [171–174].

Data presented above may present a glimpse of some of the workings of this under-characterized system. For example, following ejaculation the anterior LHA appears to coordinate behavior and arousal state appropriate to the postejaculatory interval, at least in part by its afferents to the ventral tegmental area and nucleus accumbens [174,175]. This response includes a 5-HT signal in the LHA that takes nucleus accumbens dopamine “off-line” to diminish goal-directed behavior and immediate attempts at copulation [166].

The potential breadth of this system’s control across behaviors is apparent from the literature on feeding, which contains parallels to copulation. For example, during feeding, 5-HT in the anterior (Muschamp, unpublished observation) and posterior [176] LHA rises, as after ejaculation. Also, systemic or intra-hypothalamic administration of 8-OH-DPAT creates hyperphagia—perhaps a behavioral homolog of the pro-sexual effects observed with the drug [177,178]. Similarly, SSRIs cause hypophagia [179] that may be equivalent to the sexual indifference and anorgasmia the drugs also produce. The factors that contribute to the different temporal profiles of 5-HT release during feeding and after copulation must be reconciled, though, before 5-HT can be considered to play a unified role in different modes of behavioral expression.

7. Unanswered questions and future directions

The very progress that has answered previous questions now leads to further questions. These fall into several categories. First, the sources of the excitatory inputs to the MPOA should be confirmed and extended. In addition, the neurotransmitter signatures of MPOA neurons that contain D₁- or D₂-like receptors should be determined, as well as their efferent connections. The intracellular messengers and ionic conductances in MPOA neurons that mediate the excitatory and inhibitory effects of dopamine, NO, glutamate, GABA, and other neurotransmitters are largely unknown. Possible interactions between MPOA neurons that regulate male sexual behavior and those that control maternal behavior and temperature regulation should be explored. What neurotransmitters are released from MPOA efferents into the major downstream integrative nuclei? With regard to serotonergic influences, what is the source of neural input to the LHA that triggers the 5-HT release at the time of ejaculation? What neurotransmitter is released from LHA axons into the nucleus accumbens that inhibits dopamine release there? Confirmation is needed for the 5-HT receptor subtypes in the LHA that mediate the inhibitory actions of 5-HT on sexual behavior. What are the efferent connections and neurotransmitter contents of LHA neurons that contain 5-HT_{2A}, 5-HT_{1A}, and 5-HT_{1B} receptors? In general, how do the facilitative and inhibitory influences on male sexual behavior interact with those that control other social and homeostatic behaviors and processes?

8. Summary

Steroid hormones regulate male sexual behavior primarily by genomically mediated influences on sexually relevant sensory processes, on neurotransmitter synthesis, release, and receptors, and on the responsiveness of appropriate motor effectors. One means by which steroid hormones facilitate male sexual behavior is by up-regulating NOS in

the MPOA; NO increases both basal and female-stimulated dopamine release in the MPOA, which in turn enhances sexual motivation, genital reflexes, and copulatory motor patterns. Conversely, 5-HT is released in the LHA at the time of ejaculation and promotes sexual quiescence during the postejaculatory interval, at least in part by inhibiting dopamine release in the mesolimbic tract.

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