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Dopamine, the medial preoptic area, and male sexual behavior

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Abstract

The medial preoptic area (MPOA), at the rostral end of the hypothalamus, is important for the regulation of male sexual behavior. Results showing that male sexual behavior is impaired following MPOA lesions and enhanced with MPOA stimulation support this conclusion. The neurotransmitter dopamine (DA) facilitates male sexual behavior in all studied species, including rodents and humans. Here, we review data indicating that the MPOA is one site where DA may act to regulate male sexual behavior. DA agonists microinjected into the MPOA facilitate sexual behavior, whereas DA antagonists impair copulation, genital reflexes, and sexual motivation. Moreover, microdialysis experiments showed increased release of DA in the MPOA as a result of precopulatory exposure to an estrous female and during copulation. DA may remove tonic inhibition in the MPOA, thereby enhancing sensorimotor integration, and also coordinate autonomic influences on genital reflexes. In addition to sensory stimulation, other factors influence the release of DA in the MPOA, including testosterone, nitric oxide, and glutamate. Here we summarize and interpret these data.

Keywords: Dopamine; Medial preoptic area; Testosterone; Nitric oxide; Glutamate; Copulation

1. Introduction

The neurotransmitter dopamine (DA) is important for male sexual behavior. One region where DA may act to facilitate male sexual behavior is the medial preoptic area (MPOA), a region at the rostral end of the hypothalamus, which is important for endocrine activity and essential for the expression of male sexual behavior. In this review we summarize and interpret data that indicate that DA in the MPOA facilitates male sexual behavior; also, we describe sensory and hormonal factors that might regulate release of DA in the MPOA.

2. Dopamine facilitates male sexual behavior

2.1. Human studies

2.1.1. Dopamine agonists and antagonists

Evidence supporting the hypothesis that dopamine enhances male sexual behavior comes from studies of drugs that relieve symptoms of Parkinson's disease or schizophrenia. DA-mediated enhancement of sexual behavior was first recognized when administration of L-dopa (3,4-dihydroxy-L-phenylalanine), the precursor to DA, to men suffering from Parkinson's disease resulted in increased libido and sexual potency [1–4]; this increase was not related to improvements in locomotor function [5]. More recently, other DA agonists, including apomorphine (a D_1/D_2 DA receptor agonist), have also been used to potentiate human erectile function (reviewed in Ref. [6]). Whereas treatments with DA agonists enhanced male sexual behavior, treatments with DA antagonists impaired behavior. For instance, common side effects of treatment for schizophrenia with antipsychotic drugs included sexual dysfunction and decreased libido (reviewed in Refs. [7,8]). Collectively, the human data indicate that stimulation or inhibition of DA receptors enhances or impairs male sexual behavior, respectively.

2.2. Non-human animal studies

2.2.1. Dopamine agonists

In agreement with the above conclusion, non-human animal studies also indicate that increased DA activity

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facilitates male sexual behavior. Earlier studies showed that systemic administration of L-dopa resulted in more rats displaying sexual behaviors, compared with controls [9,10]. Administration of apomorphine also resulted in decreased ejaculation threshold, with rats requiring less time to reach an ejaculation and a larger percentage of them achieving ejaculations [10].

More recent studies indicate that DA agonists can also restore sexual behavior in animals displaying sexual impairments. For instance, apomorphine treatment partially restored mounting behavior in socially stressed rats [11]; SDN 919, a potent D_2/D_3 dopamine receptor agonist, restored sexual arousal and ejaculatory ability in rats that were previously categorized as sexually sluggish [12]; and apomorphine partially restored sexual activity in animals with sexual deficits resulting from castration [13,14] and fully restored copulation in mice lacking the gene for the estrogen receptor-alpha [15].

Finally, in addition to enhancing the consummatory phase of sexual behavior, DA agonists also enhanced psychogenic erections and sexual motivation. Specifically, animals that received 7-OH-DPAT or B-HT 920, selective D_2/D_3 DA receptor agonists, displayed higher frequencies of noncontact, or "psychogenic" erections in the presence of an inaccessible estrous female, when compared with rats receiving vehicle control [16]. Furthermore, SKF 38393, a D_1 DA receptor agonist, increased the number of copulatory behaviors and prolonged the time spent in a goal compartment with a sexually receptive female, suggesting that DA also facilitates sexual motivation [17].

2.2.2. Dopamine antagonists

Studies that used DA antagonists similarly indicate a DA-mediated enhancement of male sexual behavior; specifically, blocking DA receptors impairs male sexual behavior. In adult male rats, administration of haloperidol decreased the number of mounts, intromissions, and ejaculations, and increased mount and intromission latencies [18]. Administration of several DA antagonists (clozapine, haloperidol, pimozide, or SCH 23390) also inhibited anticipatory sexual behavior, as sexually experienced male rats receiving drugs displayed fewer anticipatory level changes, before the introduction of a sexually receptive female [19], in a bi-level chamber that is used as an assay of sexual motivation [20]. Finally, it appears that central, not peripheral, DA receptors facilitate erectile function, because erections and erection-like responses elicited by systemically administered apomorphine were blocked by haloperidol (a centrally active DA antagonist) but not domperidone (a peripherally active DA antagonist) in mice [21] and rats [22]. Together, these and other pharmacological experiments indicate that increased DA activity enhances male sexual behavior. However, an inherent problem with systemic manipulations is that the administered drugs may affect numerous brain systems simultaneously. Therefore, it is not clear which brain regions mediate the drug effects. The resultant question is, "Where in the brain does DA act to enhance male sexual behavior?"

2.2.3. Dopaminergic systems important for the control of male sexual behavior

DA activity increases in several sex-relevant brain regions before and/or during copulation (reviewed in Ref. [23]). However, the specific functions that DA plays in regulating male sexual behavior are not entirely understood. One hypothesis is that, once released, DA acts by removing tonic inhibition in brain regions that are important for male sexual behavior, thereby enhancing sensorimotor integration, in the presence of a sexually exciting stimulus or during copulation. Indeed, a common feature of dopaminergic action in the nigrostriatal and mesolimbic dopamine systems is enhancement of sensorimotor integration, achieved by removing tonic GABAergic inhibition (reviewed in Refs. [24,25]).

As to the issue of site specificity, studies indicate that DA acts in the nigrostriatal, mesolimbic, and incertohypothalamic (including the MPOA) systems to facilitate male sexual behavior (reviewed in Refs. [26–29]). Hull [30] and others have proposed a model for the central control of male sexual behavior, in which these three major integrative systems [the nigrostriatal, mesolimbic, and incertohypothalamic systems] work in concert to control sexual motivation and genital and somatomotor responses in male rats. A key factor in this model is that DA release is elicited in each of the three integrative systems as a result of sensory cues from a sexually exciting stimulus and/or the act of copulation. Briefly, in this model, increased DA in the nigrostriatal system enhances the motoric readiness to respond to sexual stimuli; increased DA in the mesolimbic system is important for motivation and reinforcement; and increased DA in the MPOA is important for genital reflexes, motor patterns of copulation, and possibly sexual motivation. In this network, however, the MPOA plays a central integrative role, via its connections with regions of the brain that are important for the assimilation of sensory information, and with regions that are important for sexual motivation and somatomotor patterning.

3. The medial preoptic area is important for male sexual behavior

3.1. Ablation of the MPOA

The MPOA is perhaps the most important site for the regulation of male sexual behavior in all vertebrate species. It receives indirect input from every sensory modality [31] and sends projections to structures that are critical for the initiation and patterning of copulation [32]. The MPOA's role as a central integrative site for the regulation of male sexual behavior is confirmed by ablation studies, in which damage to the MPOA impaired male sexual behavior; this

effect is observed in all studied species, including rats, monkeys, goats, dogs, cats, mice, guinea pigs, hamsters, ferrets, gerbils, snakes, birds, lizards, and fish (reviewed in Ref. [23]). The severity of sexual impairment by MPOA lesions is dependent on the lesion's size and location. Smaller MPOA lesions have variable and less severe effects than larger lesions [33,34]. Lesions of the caudal MPOA, including the rostral anterior hypothalamus, impaired copulation more severely than did those of the rostral MPOA [35].

3.2. Stimulation of the MPOA

Experiments performing MPOA stimulation also indicate that the MPOA is important for male sexual behavior. In rats, electrical stimulation of the MPOA reduced the number of intromissions preceding ejaculation, the time required to reach an ejaculation, and the postejaculatory interval [36,37]. However, MPOA stimulation did not restore copulation in males that reached sexual satiety [37], suggesting that sexual inhibition due to satiety is not mediated by the MPOA. Finally, stimulation of the MPOA also elicits erections [38] and the urethrogenital reflex, a model for orgasm [39].

3.3. Measuring mating-induced activity in the MPOA

Electrophysiological recordings in the MPOA of sexually experienced monkeys showed increased neural activity both when the animal bar-pressed to bring a conspecific female closer and during copulation, whereas activity ceased after ejaculation [40]. Other experiments, using similar recording techniques in rats, showed that different cells within the MPOA play specific roles in regulating appetitive versus consummatory aspects of behavior; specific neurons in the MPOA showed increased activity preceding copulation, while other neurons showed increased activity only during copulation [41]. Immunohistochemical data similarly indicate that neural activity in the MPOA increases with mating. Results from studies using Fos-immunoreactivity (ir) as a measure of cellular activity showed that exposure to the odor of an estrous female increased Fos-ir in the MPOA. Furthermore, when comparing Fos-ir in the MPOA of copulating animals, versus controls, studies found that increasing amounts of copulation induced increasing amounts of Fos-ir in the MPOA of male rats [42–45], hamsters [46] and gerbils [47]. Noncontact erections and exposure to the bedding of an estrous female also induced Fos-ir in the MPOA of male rats, but the effects were less dramatic than those observed following copulation [48]. In one subregion, the posterodorsal preoptic nucleus, Fos-ir was significantly increased only following ejaculation in male rats [49], hamsters [46] and gerbils [47], again suggesting that subregions within the MPOA may play different roles in regulating copulation.

3.4. Hormonal activity in the MPOA is important for male sexual behavior

Neuroendocrine interactions play a major role in the regulation of various behaviors. Male sexual behavior is no exception to this rule. For example, androgen activity is important for male sexual behavior to take place, as evidenced by the fact that castration impairs copulation to a greater or lesser extent in all studied species (reviewed in Ref. [23]). Studies indicate that the MPOA may be important for this androgen-induced enhancement of male sexual behavior (reviewed in Ref. [23]). In castrated hamsters, for example, postoperative implants of testosterone into the MPOA partially restored male sexual behavior (reviewed in Ref. [50]). Additionally, androgen-sensitive neurons are activated in the MPOA after sexual activity [51]. These data indicate that androgen-induced enhancement of sexual behavior occurs, at least in part, at the level of the MPOA, via activation of androgen-sensitive neurons indigenous to the MPOA. Neuroendocrine interactions at different levels of the nervous system, including the MPOA, have been a source of great interest to many scientists for many years (reviewed in Ref. [52]); details of these interactions are beyond the scope of this review, for a thorough review of these interactions see e.g. Refs. [27,53].

3.5. Role of the MPOA in regulating male sexual motivation

Together, the aforementioned studies provide strong evidence that the MPOA is important for the consummatory aspects of male sexual behavior. Everitt [54] has suggested that the ventral striatal system regulates sexual motivation, whereas the MPOA controls mainly copulatory performance and is not important for sexual motivation. This postulation is supported by reports that male rats with MPOA lesions pursued estrous females and investigated their anogenital region similarly to animals with sham lesions [34,55], suggesting that animals with lesions maintain sexual interest. Similar patterns of behavior were observed in cats [56] and dogs [57] with MPOA lesions. Furthermore, MPOA lesions did not affect the frequency of masturbation in monkeys [58] or noncontact erections, a measure of psychogenic erections, in rats [59]. In contrast to those studies, lesions of the MPOA diminished preference for a female partner in rats [60–62] and ferrets [63,64], decreased pursuit of a female by male rats [65], and inhibited precopulatory behavior in marmosets [66], suggesting that the MPOA may indeed be important for the appetitive aspects of sexual behavior. Therefore, the MPOA contributes to, but is not essential for, sexual motivation.

The ablation, immunohistochemical, and electrophysiological data provide overwhelming evidence to indicate that the MPOA is important for the regulation of male sexual behavior. Additional studies have assessed how neurotransmitters in the MPOA might function to regulate copulation, genital reflexes, and sexual motivation. The

following is a summary of studies that examined how DA in the MPOA might function to regulate these behaviors.

4. Dopamine in the MPOA is important for male sexual behavior

4.1. Dopamine input to the MPOA

DA-containing cell bodies are concentrated in two major dopaminergic cell groups, the substantia nigra (A9), which sends axons to the caudate-putamen and comprises the nigrostriatal dopamine pathway, and the ventral tegmental area (A10), which sends axons to the nucleus accumbens septi and several other areas and comprises the mesolimbic dopamine pathway (reviewed in e.g. Ref. [67]). A9 cells play a major role in the regulation of motor functions, whereas A10 cells are important for motivation (reviewed in e.g. Refs. [68,69]). However, there are other minor cell groups distributed throughout the brain, several of which reside in the hypothalamus. Two DA cell groups within the incertohypothalamic DA system are the periventricular cell group (A14), whose cells lie along the edge of the 3rd ventricle and send axons laterally into the adjacent medial preoptic nucleus and the anterior hypothalamus (reviewed in Ref. [70]), and the rostral zona incerta (A13), which sends projections to MPOA and lateral preoptic area [71]. A13 and A14 projections are the major source of DA in the MPOA. Although there are also a small number of afferent projections from A10 to the MPOA, these are probably not dopaminergic [71,72].

4.2. Pharmacological manipulations

4.2.1. Neurotoxic lesions

Partial lesions of DA fibers in the MPOA (using 6-OHDA, 1 week before testing) combined with acute depletion of DA synthesis in A14 [using alpha-methyl *p*-tyrosine methyl ester (AMPT)] resulted in fewer ejaculations, longer ejaculation latencies and longer PEIs, compared with controls [73], suggesting that MPOA DA is indeed important for copulation. The neurotoxic lesions alone (without AMPT) were ineffective in tests 1 week after the lesion; however, DA was depleted by only 23% at that time. A subsequent experiment showed that the lesions alone impaired behavior in tests conducted 4 h after the lesion, but not at 24 h postlesion [74]. Apparently, increased DA synthesis in remaining neurons and/or increased receptors was able to compensate for the effects of the lesion within 24 h.

4.2.2. Microinjection of dopamine antagonists

The conclusion that MPOA DA is important for copulation was further supported by studies in which microinjections of DA antagonists into the MPOA impaired copulation and genital reflexes. Specifically, following microinjections of *cis*-flupenthixol fewer male rats copulated, and those that copulated achieved fewer ejaculations [75]; *cis*-flupenthixol also blocked the facilitative effects of apomorphine on ejaculations [75,76]. In addition to inhibiting copulation, DA antagonists also impaired penile reflexes. There are different tests for measuring penile reflexes; one test places a rat in the supine position, where it is restrained and its penile sheath is retracted; this test allows the experimenter to readily distinguish between penile reflexes (ex copula erections and flips) and seminal emissions. Using such a test, it was observed that microinjection of *cis*-flupenthixol also decreased ex copula penile reflexes [76], again suggesting that activation of DA receptors in the MPOA facilitates copulation and genital responses.

4.2.3. Microinjection of dopamine agonists

While DA antagonists impaired male sexual behavior, conversely, microinjections of DA agonists enhanced it. Specifically, apomorphine microinjections increased the number of ejaculations and the intromission ratio (number of intromissions/number of intromissions plus mounts), and decreased the time required to achieve an ejaculation and the time spent in PEI [77]. Apomorphine microinjections also partially restored copulation in long-term castrates that failed to copulate on two successive tests [14]. Finally, apomorphine microinjections also decreased latency to the first penile reflex and increased the number of erections in a timed test [78], showing an enhanced penile response following DA receptor stimulation.

Combined, the behavioral data obtained after central administration of apomorphine into the MPOA suggest a primarily excitatory role for MPOA DA in regulating male sexual behavior. However, at the cellular level, D_1 and D_2 activation may result in opposite postsynaptic effects; generally, receptors in the D_1 family (D_1 and D_5) stimulate adenylyl cyclase, while those in the D_2 family (D_2, D_3, and D_4) inhibit this enzyme and may open potassium channels and inhibit calcium entry (reviewed in Refs. [79,80]). Therefore, it is important to distinguish between the specific contributions of D_1 and D_2 activity in the MPOA to male copulatory behavior.

By administering drugs that selectively alter these two families of receptors, it was determined that stimulation of D_1 and D_2 receptors in the MPOA has some synergistic and some opposing behavioral effects (see Fig. 1). A low dose of the D_2/D_3 agonist quinelorane shortened the latency to the first ex copula genital reflex but did not affect the numbers of parasympathetically mediated erections or sympathetically mediated seminal emissions [81]. Thus, stimulation of D_2-like receptors may disinhibit genital reflexes (i.e., remove the “brakes”) without directly stimulating them. Though the nature of this disinhibition is not known, one possibility is that D_2 dopamine receptors exist on GABA containing neurons in the MPOA; therefore stimulation of these D_2 receptors would inhibit GABA

release downstream from the MPOA. Stimulation of D_1 receptors using dihydroxyphenyl-tetrahydrothienopyridine (THP; a D_1 receptor full agonist) increased the number of ex copula erections but decreased the number of seminal emissions; conversely a D_1 antagonist (SCH-23390) had the opposite effects, decreased erections and increased seminal emissions [82]. Therefore, stimulation of D_1-like receptors may provide the "engine" for erections. In this same study, a low dose of apomorphine increased erections, and this effect was fully blocked by the D_1 antagonist SCH-23390 and partially blocked by the D_2 antagonist raclopride, suggesting that both receptor types contributed to apomorphine's effects, but that the D_1 receptor was more efficacious. On the other hand, a high dose of apomorphine increased seminal emissions, and this effect was blocked by the D_2 antagonist raclopride and slightly enhanced by the D_1 antagonist SCH-23390 [82], suggesting that potent stimulation of D_2-like receptors may shift the autonomic balance to favor seminal emission and inhibit erection. Therefore, D_1 and D_2 receptors in the MPOA have different thresholds of activation and different effects on autonomic control of genital reflexes. Finally, microinjections of THP into the MPOA facilitated copulation [83], whereas a high dose of the D_2 agonist quinelorane (LY-163502) delayed the start and slowed the rate of copulation but also decreased the number of intromissions required to trigger an ejaculation [84] (i.e., favored ejaculation at the expense of erection and the early stages of copulation). Therefore, synergy between D_1 and D_2 receptors in the MPOA occurs, in that activation of D_2 receptors may be required to disinhibit erections, which are then activated by stimulation of D_1 receptors by low to moderate levels of DA. In contrast, intense or more prolonged stimulation of D_2 receptors may shift the autonomic balance to favor seminal emissions and ejaculations.

4.2.4. Dopamine in the MPOA and sexual motivation

Next, we shift our focus to the role that DA in the MPOA might play in regulating sexual motivation. Experiments using an X-maze to measure motivation suggest that stimulation of DA receptors in the MPOA enhances sexual motivation. An X-maze contains four arms with a box at each end; one box (the goal box) contains a sexually receptive female; other arms contain a male, a nonreceptive female, or are empty. During training, the male rat learns which box contains the receptive female. Sexual motivation is measured as the percentage of times a male chooses the goal box or the difference in running speed to the receptive female, compared to the other boxes. Motor activity is recorded as the running speed to all goal boxes and the number of times that the male fails to leave the start box. Using this apparatus, it was observed that *cis*-flupenthixol microinjections directly into the MPOA reduced the percentage of trials that males chose the receptive female's goal box (% choice of female) [76]. Neither running speed nor number of non-running trials was affected, suggesting that sexual motivation, and not motoric activity, was affected. Similarly, Pfaus and Phillips [19] reported that microinjection of haloperidol into the MPOA decreased anticipatory level changing in a bi-level chamber, presumably in search of a female, although there was no independent measure of motor activity in that experiment. Therefore, DA in the MPOA contributes to copulation, genital reflexes, and sexual motivation, although other structures also contribute to these measures.

4.3. Microdialysis studies

By performing pharmacological manipulations it is possible to examine which receptors and receptor subtypes are important for copulation and sexual motivation. However, by using microdialysis, combined with high performance liquid chromatography with electrochemical detection (HPLC-EC), it is possible also to measure in vivo changes in levels of neurotransmitters before, during, and after copulation. By using this technique, it was determined that DA in the MPOA indeed increased in male rats during precopulatory exposure to an estrous female and during copulation [85–89], as suggested by data obtained from the microinjection experiments. Increases in DA release in the microdialysis experiments were noted only in response to a female; exposure to another male or voluntary running in a running wheel did not evoke this response [85], and eating a highly palatable food did not alter the levels of the dopamine metabolite DOPAC in an earlier experiment [90]. Furthermore, an increase in DA activity in the MPOA of male hamsters (measured as an increase in the DA metabolite DOPAC) in response to female odor occurred only after puberty, when males became able to copulate [91], even though MPOA Fos-ir responses to female odors occurred before puberty [92]. Therefore, the ability of sexual stimuli to elicit a DA response in the MPOA is correlated with the ability of a male to copulate. Finally, hamsters with bulbectomies ipsilateral to the probe within the MPOA or bilateral bulbectomies did not show mating-induced release of DA in the MPOA; while those with sham lesions or contralateral bulbectomies displayed normal DA response, suggesting that chemosensory cues are essential for the release of DA in the MPOA during mating [93].

4.3.1. Testosterone mediates MPOA DA release in response to a female and during copulation

Testosterone may promote copulation in part through permissive actions on DA release in the MPOA. Gonadally intact male rats showed an increase in extracellular DA during precopulatory exposure to an inaccessible estrous female, and all intact males copulated; males castrated 2 weeks previously showed no DA release in response to the female, and none copulated [85] (see Fig. 2). Two-thirds of males castrated 1 week earlier showed a DA response and were able to copulate; the remaining one-third showed no

DA release and were unable to copulate. Because plasma testosterone declines to undetectable levels within 24 h after castration [94], the concurrent presence of testosterone is not necessary for copulation or for the MPOA DA response to a female. However, recent testosterone is required to produce long-lasting permissive effects. The major finding of this study was that the post-castration loss of the MPOA DA response was tightly correlated with the loss of copulatory ability. That initial experiment measured only increases from baseline; in order to measure absolute values of extracellular DA in the MPOA, a subsequent experiment used the no-net flux microdialysis technique [95]. With this technique, different amounts of DA are added to the dialysate solution (artificial cerebrospinal fluid) that flows in the microdialysis probe; if the dialysate contains more DA than the tissue, some of it will diffuse into the brain, down its concentration gradient, and the loss will be detectable. Conversely, if the brain contains more DA than the dialysate, DA will diffuse into the dialysate, and the increase can be measured. A regression line is drawn, plotting the loss or gain of DA for each concentration of DA in the dialysate; the point at which the line crosses from loss to gain (the point of no net flux into or out of the microdialysis probe) is taken as the extracellular level of DA. Using this technique, it was observed that castrates had lower basal levels of extracellular DA, compared with gonadally intact rats; however, systemic amphetamine injections, which induce DA release, resulted in greater DA release in castrates, compared with intact rats [95]. These results suggested that DA synthesis and storage in the MPOA of castrates were actually normal; therefore, deficits in extracellular levels of DA observed in castrates were related to release and not synthesis [95].

While the above studies focused on castration-induced loss of copulation and MPOA DA, other studies focused on restoration of the same, following testosterone replacement [88]. As with Hull et al. [85], the increased release of DA in the MPOA during precopulatory exposure to an estrous female predicted an animal's subsequent ability to copulate [88]. Additionally, the threshold period for restoration of both the MPOA DA response and copulation after testosterone replacement was five days; two days of testosterone replacement did not restore copulation in castrates, nor did it restore the MPOA DA response to a receptive female [88]. Five days of testosterone replacement restored both copulation and the precopulatory MPOA DA response in most animals, while 10-day replacement fully restored both in all animals [88].

Testosterone is primarily a prohormone that is either aromatized to estradiol or reduced to dihydrotestosterone

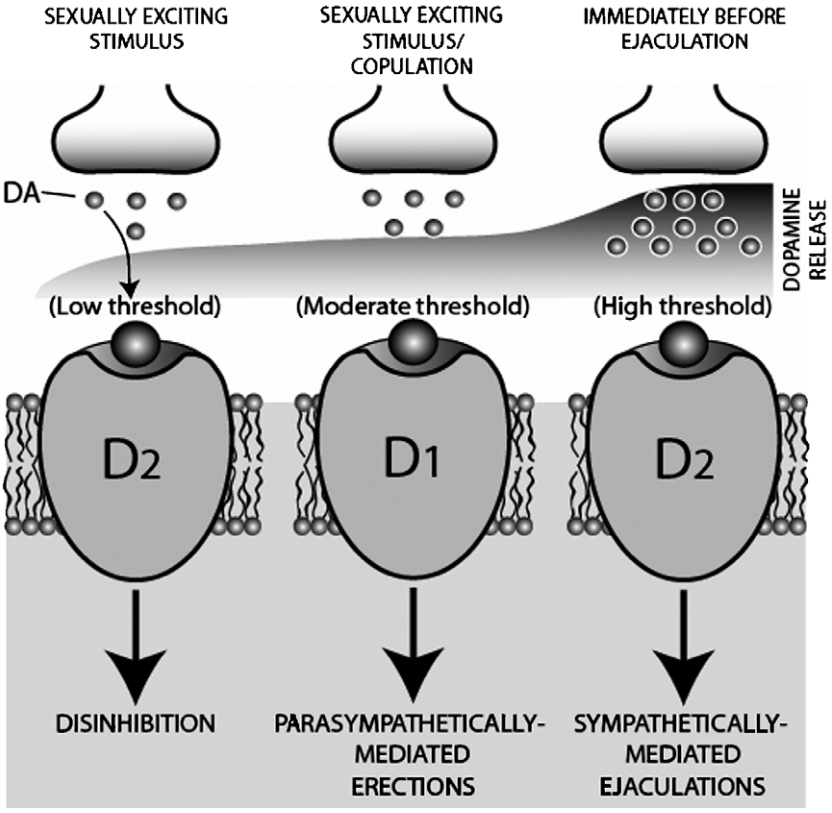

Fig. 1. Model showing possible effects of D_1 versus D_2 stimulation in the MPOA, as a result of a sexually exciting stimulus and/or sexual activity. In this model, a low-threshold mechanism mediated by D_2 receptors disinhibits genital reflexes. A moderate threshold mechanism facilitates penile erections, after activation of D_1 receptors. A high threshold mechanism, activated by stimulation of D_2 receptors, facilitates seminal emissions and inhibits erections. These mechanisms may be activated successively by increasing levels or longer duration of DA activity.

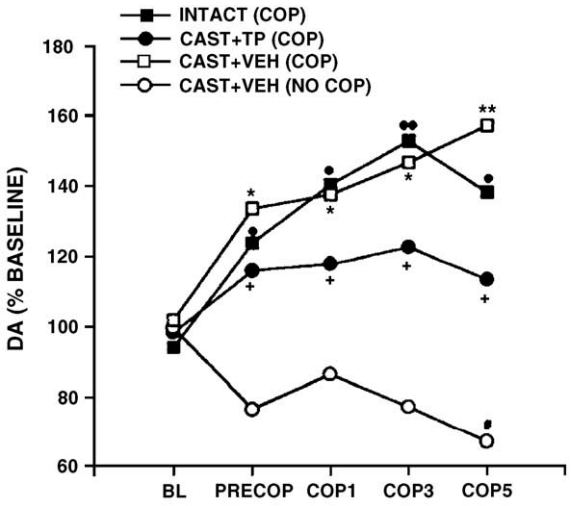

Fig. 2. Testosterone-mediated enhancement of sexual activity may occur in part through increased DA release in the MPOA. Gonadally intact male rats showed an increase in extracellular DA during precopulatory exposure to an inaccessible estrous female, and all intact males copulated; males castrated 2 weeks before showed no DA release in response to the female, and none copulated. Values are expressed as mean ± SEM, $*P<0.05$, compared to final baseline for intact males or for one-week vehicle-treated castrates that copulated; $**P<0.01$, compared to final baseline for intact males or for one-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 Ref. [85], with permission).

within target cells. Comparison of the effectiveness of estradiol and dihydrotestosterone revealed that testosterone's metabolites play synergistic roles in the testosterone-mediated enhancement of copulation and MPOA DA release. Specifically, castrates treated with estradiol benzoate had high levels of basal DA but failed to show a female-stimulated increase; most intromitted, but none ejaculated [89]. Males treated with dihydrotestosterone benzoate and oil-treated groups had low basal levels of extracellular DA that did not increase during copulation; most failed to mount, and none ejaculated [89]. This suggests that estrogen maintains normal basal levels of extracellular DA in the MPOA, which is sufficient for suboptimal copulation, but androgen is required for the female-stimulated increase in DA release and for the facilitation of ejaculation (via stimulation of D_2 receptors).

These studies provide strong evidence indicating that increased DA release in the MPOA facilitates male sexual behavior, and that testosterone may mediate this effect. We next asked what factors elicit release of DA in the MPOA, and how do gonadal hormones mediate this release? Neuronal firing is undoubtedly one factor regulating release; another factor may be nitric oxide (NO).

4.3.2. Interactions between NO and DA in the MPOA

Numerous studies support the above hypothesis. NO has been reported to increase the release of DA from striatal slices [96–98]. Reverse dialysis of L-arginine, the NO precursor, through the microdialysis probe into the MPOA increased basal levels of extracellular DA; this increase was blocked by the nitric oxide synthase (NOS) inhibitor, *N*-monomethyl-L-arginine (L-NMMA), which also decreased basal DA levels when administered alone [99]. Furthermore, reverse dialysis of a different NOS inhibitor, nitro-L-arginine methyl ester (L-NAME), into the MPOA three hours prior to the introduction of a female prevented the increase of DA normally observed in the presence of a receptive female and during copulation; animals receiving D-NAME, the inactive isomer of L-NAME, showed normal DA responses [100]. The importance of NO in the MPOA for copulation was demonstrated when reverse dialysis of L-arginine increased the rate of mounting by male rats, and similar administration of L-NMMA decreased mount rate [101].

Additionally, NOS may be hormonally regulated in the MPOA. For example, in the male Syrian hamster, castration reduced NOS-positive neurons in the medial preoptic nucleus [102]. Also, castrated male rats had fewer NOS-positive neurons in the MPOA than did gonadally intact rats or testosterone-treated castrates [103]. Thus, the effects of gonadal steroid hormones on DA release in the MPOA may be through their actions on NOS. As with DA release, the two major metabolites of testosterone, estradiol and dihydrotestosterone were differentially effective in maintaining NOS immunoreactivity. Estradiol maintained a variable number of NOS-ir neurons in the MPN and variable copulatory ability, with several significant partial correlations between NOS-ir and copulatory measures [104]. However, dihydrotestosterone alone was no more effective than oil control treatment in maintaining NOS-ir, although the combination of estradiol and dihydrotestosterone was as effective in this regard as testosterone itself. In addition, tissue levels of DA were affected in the opposite direction than NOS-ir by the two metabolites, suggesting that NO-stimulated release decreased the amount of DA stored in tissue. Therefore, estradiol, testosterone, and the combination of estradiol and dihydrotestosterone maintained high extracellular and low intracellular dopamine, whereas dihydrotestosterone and oil treatments resulted in low extracellular and high intracellular dopamine. The low intracellular dopamine in the former animals probably resulted from greater dopamine release, mediated by increased NOS activity, and conversely the latter animals would have had less NO-stimulated dopamine release, resulting in higher tissue dopamine. These data suggest that a major means by which testosterone's primarily slow, genomically mediated effects facilitate sexual behavior is via up-regulation of NOS, which in turn increases basal extracellular dopamine levels and mediates the female-stimulated MPOA dopamine release.

4.3.3. Interactions between glutamate and DA in the MPOA

The above experiments suggest that basal and copulation-stimulated DA release in the MPOA is regulated, at

least in part, by NO. However, nonhormonal factors "upstream" of NO had not been determined. Because glutamate is the major excitatory neurotransmitter in the CNS (reviewed in e.g. Ref. [105]), and it regulates the release of DA in several other brain regions both in vitro and in vivo [106–111], we hypothesized that it may play a key role in enhancing release of DA in the MPOA.

To assess whether glutamate mediates DA activity in the MPOA, we reversed dialyzed glutamate through the microdialysis probe, while concurrently collecting extracellular DA. We observed that exogenous glutamate increased levels of extracellular DA by nearly three times that of basal levels [112], suggesting glutamate as a possible candidate for regulating MPOA DA release. Interestingly, however, while exogenous glutamate evoked increased DA release, it also inhibited levels of DA metabolites [homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC)] [112]. This may seem perplexing; however, these results are likely a function of NO activity rather than direct glutamatergic regulation (see below). To determine whether NO was responsible for the aforementioned results, we performed a similar experiment, in which we co-administered L-NAME along with glutamate through the microdialysis probe. L-NAME did decrease basal DA levels and completely blocked the glutamate-evoked increase in extracellular DA, as well as the glutamate-evoked attenuation of DOPAC and HVA levels observed in animals receiving glutamate alone [112] (see Fig. 3). D-NAME was ineffective,

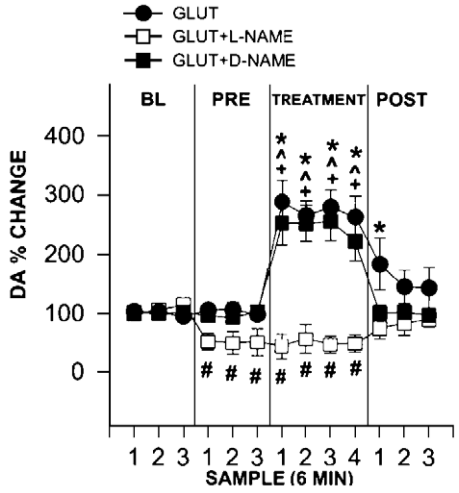

Fig. 3. Nitric oxide mediates glutamate evoked DA release in the MPOA. Extracellular levels of DA significantly increased for animals receiving reverse dialysis of glutamate or glutamate+D-NAME, but not for animals receiving glutamate+L-NAME. These levels returned to baseline after glutamate was removed. Additionally, reverse dialysis of L-NAME alone decreased levels of DA, compared with baseline. The baseline measure was obtained by dividing the value of the last baseline by the mean of all three baselines. Values are expressed as mean±S.E.M. (*$P<0.05$, compared with baseline, for glutamate-alone; $^{\#}P<0.05$, compared with baseline, for L-NAME+glutamate; $^{\wedge}P<0.05$, compared with baseline, for D-NAME+glutamate; $^{+}P<0.05$, for glutamate-alone and glutamate+D-NAME, compared with glutamate+L-NAME). (Reprinted from Ref. [112], with permission).

indicating that L-NAME's effects were stereospecific. These data indicated that NO mediates the glutamate-evoked release of DA in the MPOA.

The following summary will discuss the cellular mechanisms that might be responsible for the results seen in the above experiments (see Fig. 4). Glutamate, acting via *N*-methyl-D-aspartate (NMDA) receptors, opens Ca^{2+} channels; the resultant increase in intracellular Ca^{2+} can then activate calcium calmodulin, which in turn activates NOS in some neurons. NOS is linked to the carboxy-terminal tail of the NMDA receptor, via a PSD-95 protein–protein interaction domain (reviewed in Ref. [113]), thereby coupling NOS with the NMDA receptor. Studies (reviewed in Refs. [114,115]) suggest that NO increases calcium-dependent [98,116–118] and/or calcium-independent [119–121] vesicular release. NO may also inhibit the DA transporter (DAT) [122–125], thereby prolonging DA's synaptic life. In addition, NO may increase extracellular DA indirectly by increasing the release of glutamate or via other neurotransmitter systems (reviewed in Refs. [114,115]). The pattern of increased extracellular DA, together with decreased metabolites, observed in the above experiments suggests that inhibition of DAT activity contributed to the glutamate-induced increase in extracellular DA in the MPOA. Metabolism of DA to DOPAC requires transport into the axon terminal, where monoamine oxidase is located on mitochondrial membranes. DOPAC, in turn, may be metabolized to HVA by catechol-*O*-methyl transferase, which may be located in glia or neurons. Thus, inhibition of the DAT would decrease the formation of DOPAC and HVA as well as prolong DA's presence in the extracellular fluid, explaining the results observed in these experiments.

Finally, more recent data further support the importance of glutamate and NO in the MPOA for the release of DA and copulation. Microinjection of either the NMDA receptor antagonist MK-801 [126,127] or the NOS inhibitor L-NAME [126] prevented copulation in sexually naïve male rats and impaired copulation in sexually experienced animals. In addition, microinjections of either drug before each of 7 daily exposures to an inaccessible estrous female blocked the improvement in copulatory ability that was seen in similarly exposed saline-treated males, compared to nonexposed males [127,128]. Therefore, both NMDA glutamate receptors and NO are important for both the expression of copulation and the experience-induced sensitization to sexually relevant stimuli.

4.3.4. Inputs from the medial amygdala (direct or indirect) that mediate MPOA DA release may be glutamatergic

Finally, we switch focus to the medial amygdala (MeA) and its possible role in regulating DA activity in the MPOA. The MPOA receives indirect input from every sensory modality [31], including direct and indirect input from the MeA, a nucleus in the amygdaloid complex that is important for, among other things, the assimilation of chemosensory information and hormonal regulation of sexual behavior

(reviewed in Refs. [23,50,129]). The MeA is the recipient of major olfactory input from the main olfactory bulb and the vomeronasal organ via the accessory olfactory bulbs (reviewed in Refs. [50,130,131]). In turn, MeA efferents project to a variety of sex-relevant regions that are important for the control of sexual behavior, including the MPOA. The MeA, particularly the posterior region, is also important for the androgen-induced enhancement of male sexual behavior, and the posterior dorsal subnucleus (MeApd) is part of a circuit that is specific for control of ejaculation and, perhaps, sexual satiety (reviewed in Refs. [23,129]). In castrated hamsters, postoperative implants of testosterone into the MeA partially restored sexual behavior; in rats, MeA testosterone implants also delayed the onset of sexual deficits (reviewed in Ref. [23]). These data suggest that androgen-induced enhancement of sexual behavior occurs, in part, via activation of androgen-sensitive neurons indigenous to the posterior MeA. Moreover, a high concentration of androgen-sensitive neurons in the posterior MeA were activated (Fos-ir) after sexual activity and projected to the MPOA [132]. Thus, hormonal enhancement of male sexual behavior may occur at the level of the posterior MeA, in cells with projections to the MPOA.

Because the MPOA receives major direct and indirect input from the MeA, which is important as an integrative site for olfactory and endocrine information, we hypothesized that MeA activity mediates DA release in the MPOA resulting from exposure to a female and mating. To test this hypothesis we performed two sets of experiments. In the first set, we performed sham or excitotoxic lesions of the amygdala in sexually experienced animals. Lesions significantly decreased all aspects of copulation. Microinjections of apomorphine, but not vehicle, into the MPOA of animals with amygdala lesions restored copulation [87]. This finding suggests that the amygdala facilitates copulation by increasing DA activity in the MPOA. Alternatively, it is possible that enhancement of copulation by apomorphine, seen in animals with lesions, offset a nondopaminergic effect in the MPOA or elsewhere. Therefore, in the second set of experiments, using microdialysis and HPLC-EC, we measured mating-induced DA activity in the MPOA of animals with MeA lesions or sham lesions. Results showed that MeA lesions again impaired copulation, as animals with lesions displayed fewer ejaculations and required more time and more intromissions to reach an ejaculation; these animals also displayed longer PEIs [87]. Analyses of dialysate samples collected from the MPOA of animals with sham lesions showed increases of extracellular DA in the MPOA during exposure to an estrous female and during copulation, consistent with previous reports (see above); however, analyses of samples from animals with lesions did not reveal such an increase, although basal DA levels were normal [87] (see Fig. 5). Combined, these findings suggest that the MPOA DA response during exposure to a receptive female and during copulation is regulated, in part, by inputs from the MeA.

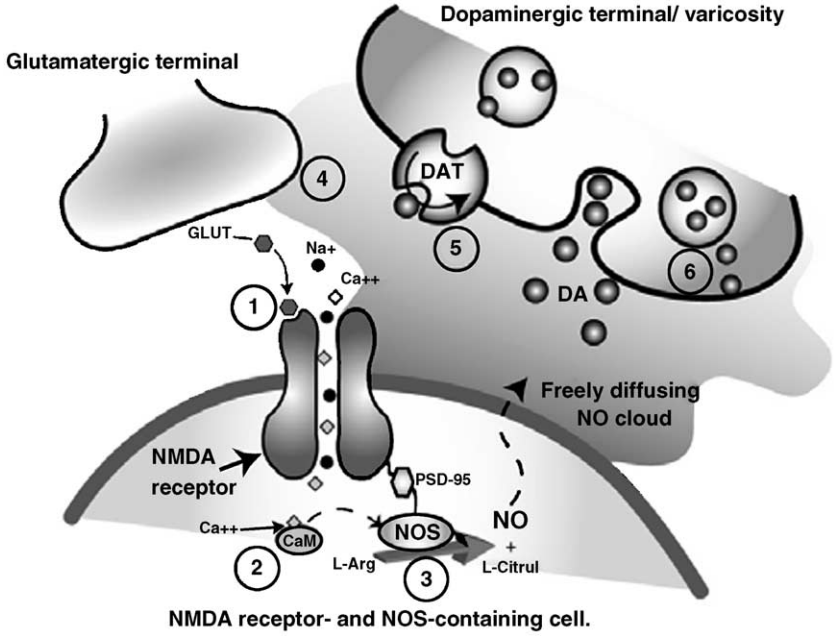

Fig. 4. Model showing possible interactions between glutamate, NO, and DA in the MPOA. (1) Glutamate (GLUT; gray hexagon) release activates NMDA receptors, which opens calcium channels. (2) The resultant increase in intracellular calcium (gray diamonds) then activates calcium calmodulin (CaM), (3) which in turn activates the enzyme NOS, this leads to an immediate production of NO. NOS links to the carboxy-terminal tail of the NMDA receptor, via a PSD-95 protein–protein interaction domain. Once synthesized, NO freely diffuses from cell to cell, (4) where it can alter activity in the presynaptic neurons. (5) Additionally, in DA producing neurons, NO has been shown to inhibit the dopamine transporter (DAT), (6) and increase calcium-dependent and/or calcium independent vesicular release. Therefore, increased NO in the MPOA, after glutamate release, would increase levels of extracellular DA and prolong the presence of DA in the synapse.

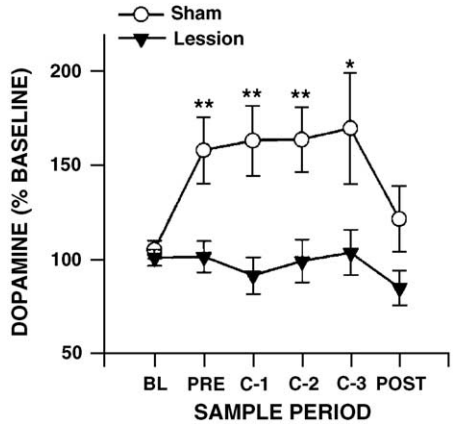

Fig. 5. Lesions of the MeA inhibit the release of DA in the MPOA resulting from exposure to an estrous female and copulation. Levels represent percent changes from baseline (BL) in response to precopulatory exposure to an estrous female (PRE) during copulation (C1–C3) and after copulation (POST). Extracellular levels of DA significantly increased during the precopulatory and copulatory stages of testing for animals with sham lesions but not for animals with MeA 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 ± SEM, $*P<0.05$; $**P<0.01$ (Reprinted from Ref. [87], with permission).

A role for the MeA in regulating MPOA DA activity was also supported by experiments using chemical stimulation of the MeA. Specifically, stimulation of the MeA with glutamate and L-trans-2,4-PDC (a glutamate uptake inhibitor) resulted in increased extracellular DA in the MPOA [133]. The increase in DA release following MeA stimulation (~150%) was similar to increases observed with exposure to an estrous female and during copulation.

There are no DA cells in the MeA of rats [134]. Therefore any changes in DA release in the MPOA after lesion or stimulation of the MeA are likely a result of changes in stimulation of DA soma in A14 or terminals in the MPOA. As a result, it is reasonable to infer that MeA activity mediates MPOA DA release through direct or indirect excitatory input to the MPOA. Glutamatergic input from the MeA to the MPOA was revealed using [3H]D-aspartate, as a retrograde tracer selectively taken up by glutamate-containing terminals [135]. Sources of glutamate to the MPOA included the lateral septum, the bed nucleus of the stria terminalis (a major relay station between the MeA and MPOA), the MeA, the MPOA itself, and paraventricular, suprachiasmatic, ventromedial, arcuate, ventral premammillary, supramammillary, and thalamic paraventricular nuclei [135]. These results are in line with preliminary observations that some anterogradely labeled axons from the MeA and many anterogradely labeled axons from the bed nucleus of the stria terminalis were immunoreactive for the vesicular glutamate transporter, an indicator of glutamatergic terminals, in the MPOA [126]. Thus, glutamatergic axons from areas that are involved in processing endocrine and/or sensory cues, such as olfactory cues processed by the MeA via the bed nucleus of the stria terminalis, may be responsible for regulating dopaminergic activity in the MPOA.

5. Summary

In summary, both systemically administered and intra-MPOA DA agonists facilitate copulation, genital reflexes, and sexual motivation, whereas DA antagonists impair those measures. Small increases in DA in the MPOA may disinhibit genital reflexes via D_2-like receptors, and slightly larger increases may promote parasympathetically mediated erection and the early stages of copulation, via D_1-like receptors. Larger amounts of DA or of D_2 agonists in the MPOA may shift the autonomic balance to favor seminal emission and ejaculation. DA is released in the MPOA of male rats as soon as they detect the presence of a receptive female. Testosterone is important for maintaining both basal DA levels and female-stimulated increases, as well as copulatory ability. Estradiol is the major metabolite that maintains basal DA levels and sub-optimal copulation, but the additional presence of dihydrotestosterone is required for the female-stimulated increase and optimal copulation; however, dihydrotestosterone alone is ineffective. A major way in which testosterone and its metabolites maintain MPOA DA and copulation is by up-regulating the production of NO, which in turn is important for both basal and female-stimulated DA release. A major stimulus for the female-stimulated DA release is glutamate from the MeA, bed nucleus of the stria terminalis, and other structures. Glutamate's effects are mediated in part by NMDA receptors in the MPOA, which activate NOS and other cellular messengers. Finally, NMDA receptors and NO are important for copulatory behavior and for sensitization to sexually relevant stimuli. Future research will further explore the neurotransmitter interactions, intracellular messengers, and neural circuitry that provide the basis for male sexual behavior.

Acknowledgements

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