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Testosterone, Preoptic Dopamine, and Copulation in Male Rats

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ABSTRACT: Steroid hormones prime neural circuits for sexual behavior, in part by regulating enzymes, receptors, or other proteins affecting neurotransmitter function. Dopamine facilitates male sexual behavior in numerous species and is released before and/or during copulation in three integrative neural systems. The nigrostriatal system enhances readiness to respond; the mesolimbic system promotes many appetitive behaviors; the medial preoptic area (MPOA) contributes to sexual motivation, genital reflexes, and copulation. We have reported a consistent relationship between precopulatory dopamine release in the MPOA, when an estrous female was behind a perforated barrier, and the ability to copulate after the barrier was removed. Recent, but not concurrent, testosterone was necessary for the precopulatory dopamine response and copulation. The deficit in MPOA dopamine release in castrates was observed in basal conditions as well as the sexual context. However, dopamine in tissue punches from castrates was higher than in intact males. Because tissue levels represent primarily stored neurotransmitter, dopamine appeared to have been synthesized normally, but was not being released. Amphetamine induced greater dopamine release in castrates, again suggesting excessive dopamine storage. The decreased release may result from decreased activity of nitric oxide synthase in the MPOA of castrates. A marker for this enzyme showed lower activity in castrates than in intact males. Finally, blocking nitric oxide synthase in intact males blocked the copulation-induced release of dopamine in the MPOA. Therefore, one means by which testosterone may promote copulation is by upregulating nitric oxide synthesis in the MPOA, which in turn enhances dopamine release. © 1997 Elsevier Science Inc.

KEY WORDS: Nitric oxide, MPOA, Microdialysis, HPLC-EC.

STEROID PRIMING OF NEURAL CIRCUITS

Genomic actions of steroid hormones prime neuronal circuits that regulate sexual behavior in most mammals. However, hormonal effects on gene transcription are relatively slow and long lasting, whereas the complex cascade of copulatory behavior is rapidly executed and intricately coordinated with a partner. Hormones facilitate sexual behavior by biasing sensorimotor integration, so that a sexually relevant stimulus is more likely to elicit a sexual response. The means by which hormones prime specific neural circuits undoubtedly includes the up (or down) regulation of neurotransmitter synthesis, release, receptors, or other proteins that affect neurotransmitter function.

ROLES OF DOPAMINE IN MALE SEXUAL BEHAVIOR

One candidate for a central role is dopamine, because dopaminergic drugs have long been known to facilitate masculine, and probably also feminine, sexual behavior (reviewed in [2,25]). Dopamine is released in several key integrative sites. A common feature of dopaminergic action is enhancement of sensorimotor function, probably achieved by removing tonic inhibition [5]. Thus, steroid hormones may prime neurons to be responsive, but the neurons cannot respond fully unless the tonic inhibition is first removed (Fig. 1).

Therefore, dopamine does not elicit behavior directly, but allows stimuli to have easier access to hormonally primed output pathways. Dopamine's short-term biasing is similar to the longer term biasing of steroid hormones, in that certain neuronal circuits may be preferentially facilitated. This preferential facilitation may enable the expression of the hormonal effects.

Three major integrative systems control sexual motivation and genital and somatomotor responses in male rats [12] (Fig. 2). 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 these systems [3,15,23]. The largest system, innervated by the nigrostriatal dopamine tract, enhances the initiation and execution of movements. Degeneration of this tract in Parkinson's disease results in difficulty initiating movements, slowness of actions, and tremor. Therefore, the nigrostriatal system is thought to contribute to the somatomotor patterns of pursuit and mounting of the female [36].

The second system, innervated by the mesolimbic dopamine tract, is critical for appetitive behavior and reinforcement. It has been implicated in feeding, drinking, brain stimulation reward, drug addiction, sexual behavior, and active avoidance of noxious stimuli (reviewed in [3,4,26,35,37]). Blocking dopamine receptors in the nucleus accumbens, a major terminal of this tract, decreased anticipatory level changing in search of a female in a bilevel apparatus [33]. Conversely, stimulating dopamine receptors in the same area restored conditioned lever press responding for a female, which had been disrupted by lesions of the amygdala [10]. However, both lever pressing and level changing are composite measures that confound specifically sexual motivation with motor activity and general motivational arousal. An X-maze (also called a plus-maze) allows dissociation of these measures. A receptive female and a stud male are in opposite goal boxes, and the other two goal boxes are empty. The male is placed into the center of the apparatus and must run to one of the four goal boxes. Sensorimotor activation (speed of running to any goal box or number of trials in

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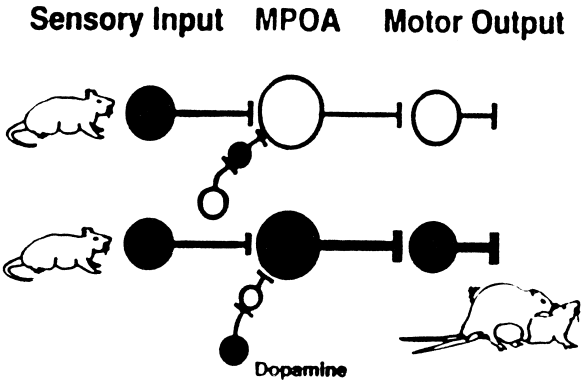

FIG. 1. Effects of dopamine on steroid-primed pathways. Inhibitory GABAergic neurons prevent the full responsiveness of steroid-primed neurons. Dopamine may enhance the responsiveness of those neurons by inhibiting the inhibitory neurons, thereby disinhibiting the relevant output pathways. This increases the probability that a sexually relevant stimulus will elicit a sexual response.

which the animal fails to choose a goal box) can be differentiated from specifically sexual motivation (percent of trials on which the female is chosen). Manipulations of either the ventral tegmental area (the site of cell bodies of the mesolimbic tract) [13,19] or the nucleus accumbens (a major terminal area) [29] suggest that this system subserves sensorimotor activation, but not specifically sexual motivation. Because the mesolimbic system energizes so many motivated behaviors, there must be some other means of focusing a diffuse motivational state specifically on sexual behavior.

The MPOA as an Integrative Site for Sexual Motivation and Performance

That focusing may be attributed to the third system, the medial preoptic area (MPOA). This area is critical for male sexual behavior in all vertebrate species that have been studied (reviewed in [24]). Even in unisexual lizards, expression of male-like behavior is associated with increased activity in the MPOA (measured as uptake of radiolabeled 2-deoxyglucose), whereas the expression of female-like behavior is associated with ventromedial hypothalamic activity [34]. 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 facilitates male sexual behavior in many species, suggesting that it, too, plays a central role in the process.

The MPOA receives sensory input from virtually every sensory modality (reviewed in [39]). Reciprocal connections with each source of input provide a means for the MPOA to modulate sensory processing. Steroid hormone receptors in the MPOA and all of its afferent connections allow hormones to promote the processing of sexually relevant stimuli. Dopaminergic input to the MPOA arises from the periventricular system, including cell bodies in the medial portion of the MPOA [27,38]. We have shown that stimulation of dopamine receptors in the MPOA enhanced the rate of copulation [14] and increased the number of ex copula genital reflexes [32], whereas blocking those receptors impaired copulatory rate and genital reflexes [40]. In an X-maze study, blocking MPOA dopamine receptors also specifically decreased sexual motivation (percent choice of the female's goal box), without affecting sensorimotor activation (latencies to any goal box or the number of no-response trials) [40]. We have presented evidence that small or brief increases in dopaminergic stimulation may act through the D_1 family of dopamine receptors to facilitate

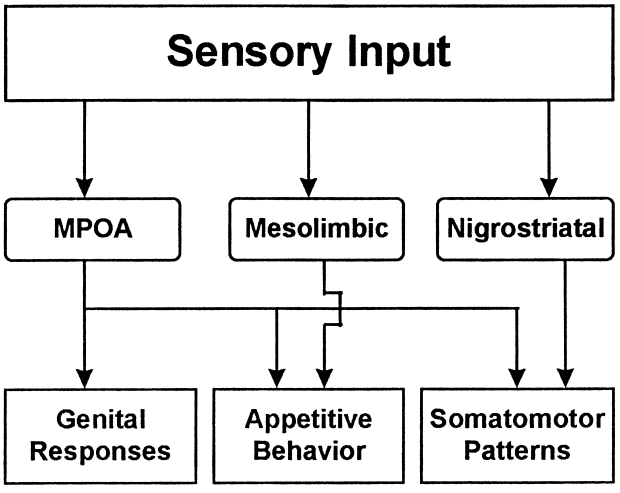

FIG. 2. Effects of dopamine in three integrative neural systems. Stimuli from an estrous female and/or the act of copulation elicits dopamine release in each system. Dopamine in the nigrostriatal tract promotes the initiation of somatomotor patterns of copulation. Dopamine in the mesolimbic system enhances general appetitive behavior. Dopamine in the medial preoptic area (MPOA) facilitates genital reflexes, enhances specifically sexual motivation, and promotes somatomotor copulatory patterns. (Modified from Hull, 1995.)

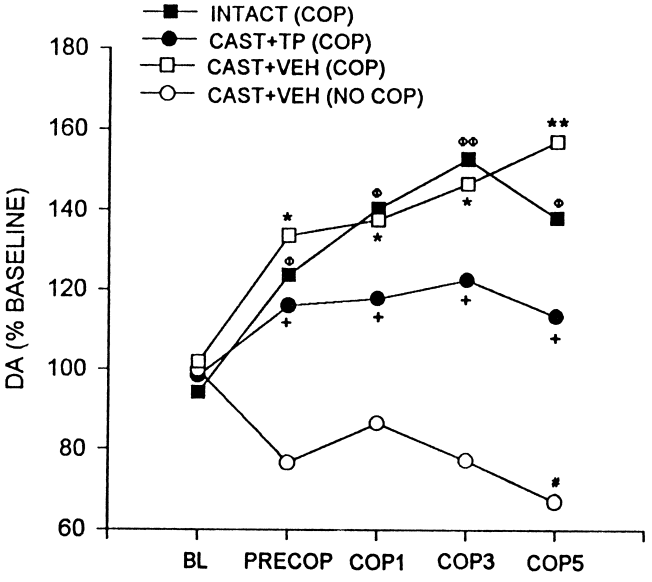

FIG. 3. Extracellular dopamine in the medial preoptic area (MPOA) of male rats during baseline, a precopulatory period (estrous female behind a perforated barrier), and three 6-min periods after the barrier was removed and the animals were free to copulate. All gonadally intact males and all castrates treated with testosterone propionate (200 μg/day) showed a significant increase in dopamine during the precopulatory period and during copulation; all of these animals did copulate. 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. (From Hull et al., 1995, with permission.)

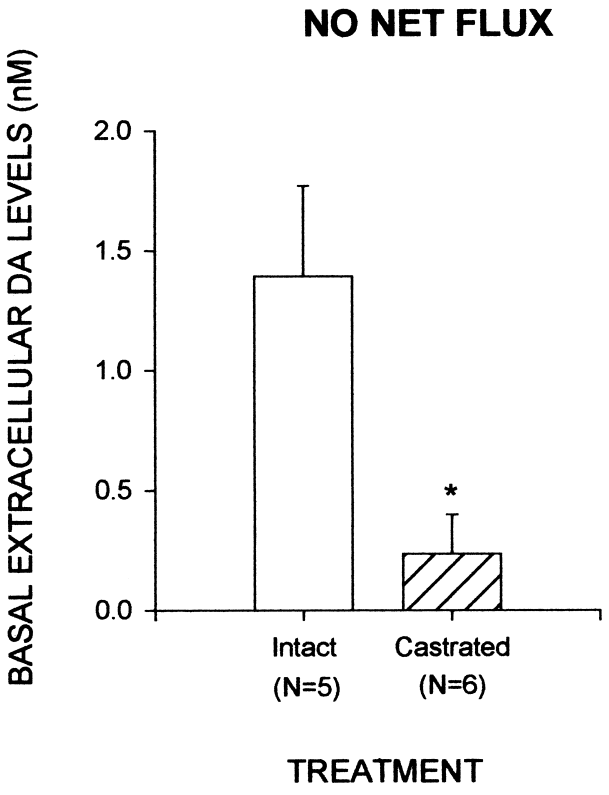

FIG. 4. Basal levels of extracellular dopamine in MPOA of 1-month castrates and gonadally intact males. Absolute levels were determined, using the no-net-flux method (see text). Intact males had significantly higher dopamine levels than did castrates. (From Du et al., in press.)

erection, whereas larger or longer increases, acting through the D_2 family of receptors, may shift the autonomic balance to favor ejaculation [16,18]. Therefore, shifting levels of dopamine in the MPOA may regulate the autonomic influences on genital reflexes and may also focus the male's motivation on specifically sexual pursuits and enhance the rate and efficiency of copulation.

MPOA DOPAMINE RELEASE BEFORE AND DURING COPULATION

We have recently developed a very sensitive assay for detecting dopamine in microdialysate samples from the MPOA. Briefly, artificial cerebrospinal fluid is pumped very slowly into a probe, which ends in a 1-mm long, 210-μm diameter dialysis tube. While the fluid is within the dialysis tube, transmitters and their metabolites can diffuse into the fluid. Because the end of the probe is plugged, the fluid exits up through a concentric silicon tube and is collected. The contents are analyzed, using high-performance liquid chromatography with electrochemical detection (HPLC-EC).

We have observed a very consistent relationship between MPOA dopamine release during a precopulatory period (with a receptive female behind a perforated barrier) and the subsequent ability of the male to copulate [15] (Fig. 3, see page 328). The presence of another male, rather than a female, did not increase dopamine release, nor did voluntary running in an activity wheel. Eating a highly palatable food did not increase dopamine metabolites in the MPOA in a previous experiment [17]. Therefore, there is some behavioral specificity to the MPOA dopamine response, in contrast to the variety of stimuli that elicit dopamine release in the mesolimbic system.

Castration Impairs MPOA Dopamine Release in Response to a Female

The recent presence of testosterone is permissive for the precopulatory dopamine release and for copulation [15]. Sexually experienced male rats were castrated either 1 or 2 weeks before testing, and were injected daily with either 200 μg testosterone propionate (TP) or oil vehicle. All of the TP-treated animals showed the precopulatory dopamine response, and all of them copulated after the barrier was removed (Fig. 3). Nine of the 14 1-week castrates also showed the precopulatory dopamine response and subsequently copulated. The rest of the 1-week and all of the 2-week castrates failed to show the anticipatory dopamine increase and failed to copulate when the barrier was removed. The relationship between the precopulatory dopamine response and the ability to copulate was very consistent. Every animal that showed at least some precopulatory increase in dopamine was able to copulate, and no animal that failed to show such an response could copulate. The consistency of this relationship suggests that the MPOA dopamine response is intimately connected with the ability to copulate. Thus, testosterone may facilitate copulation, in part, by permitting increased MPOA dopamine release in response to a female.

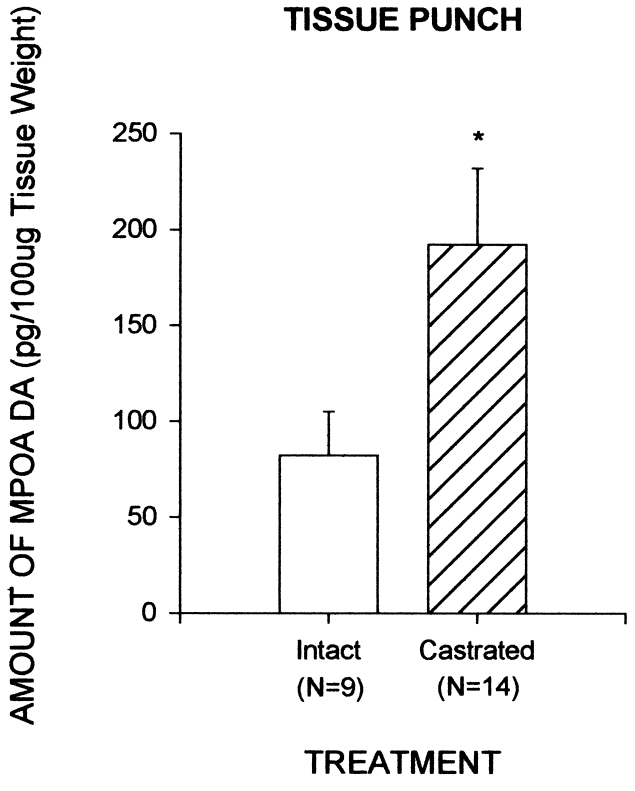

FIG. 5. Dopamine levels in tissue punches from the MPOA of 1-month castrates or gonadally intact males. This, together with the previous finding, suggests that castrates synthesize and store dopamine normally or excessively, but have difficulty releasing it. (From Du et al., in press.)

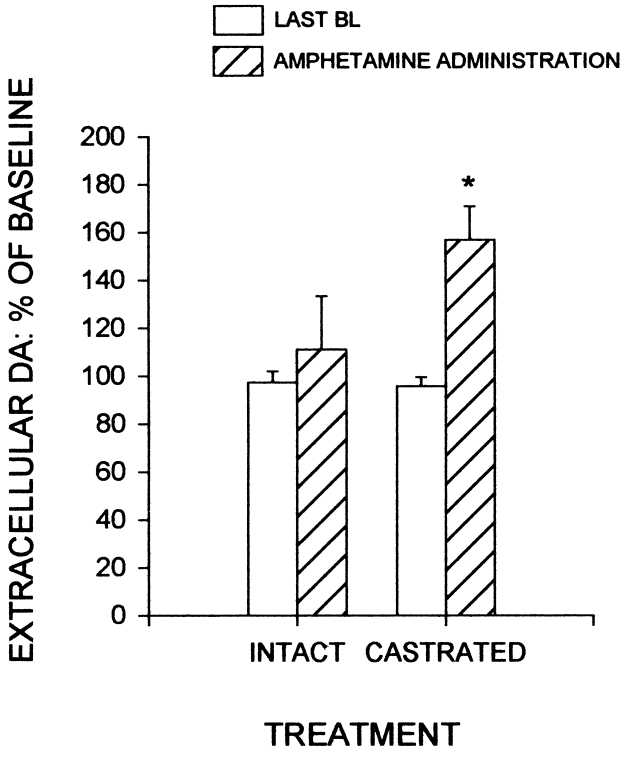

FIG. 6. Amphetamine-induced dopamine release in the MPOA of 1-month castrates or gonadally intact males. Castrates showed greater amphetamine-evoked release of dopamine than did intact males. Levels were measured in microdialysate collected following systemic amphetamine (1 mg/kg). (From Du et al., in press.)

Castration Decreases MPOA Dopamine Release During Basal Conditions

We next asked whether there was a general problem with dopamine release in the MPOA, or whether the deficit was specific to the sexual context. If there were a general problem, then the basal levels of extracellular dopamine should be lower in castrates. To measure absolute levels of extracellular dopamine, we used the no-net-flux technique [31]. Briefly, if excess dopamine is added to the dialysate, some of it will diffuse out of the dialysate into the brain, and the loss can be detected. Similarly, if there is less dopamine in the dialysate than in the brain, or if there is none, as is usually the case in microdialysis, then dopamine will diffuse into the dialysate from the brain. A regression line is drawn, and the point at which the line crosses from loss to gain in dopamine in the dialysate (no net flux out of or into the dialysate) is taken as the absolute level of extracellular dopamine.

Basal extracellular dopamine levels in castrates were indeed lower than in intact males [8] (Fig. 4). This suggests that there is a general decrease in dopamine release in the MPOA of castrates, and that the impaired response to a female in the previous experiment was not specific to the sexual context. The decreased release could be due to decreased synthesis of dopamine, so that there was less dopamine available for release; alternatively, synthesis could be normal and only release impaired. Therefore, we assayed the levels of dopamine in tissue punches from the MPOA in 1-month castrates and intact males. The neurotransmitter found in tissue punches is almost exclusively intracellular, because released amines are rapidly transported back into the terminal and/or metabolized. In contrast to the low extracellular levels in castrates, there was more dopamine in MPOA tissue punches from castrates than from intact animals [8] (Fig. 5). This suggests that synthesis and storage were at least normal, or even enhanced, in castrates. This suggestion was confirmed by administering amphetamine sulfate (1 mg/kg) systemically and measuring the drug-induced dopamine release. Amphetamine causes leakage of dopamine from its storage vesicles into the cytoplasm and reverses the transporter, thereby evoking dopamine release from the axon (reviewed in [1]). Consistent with our finding of increased tissue levels of dopamine in castrates, there was also greater amphetamine-induced release of dopamine in castrates [8] (Fig. 6). These experiments suggest that castrates synthesize and store at least as much dopamine as intact animals, but that they have a generalized difficulty releasing it (Fig. 7).

These data may help to explain a puzzling phenomenon in recently castrated animals. In the weeks following gonadectomy, the latency to initiate copulation increases progressively [6]. However, if the animal is able to begin copulating, he will ejaculate prematurely, with fewer intromissions and a shorter latency. Eventually, ejaculation latency increases; then ejaculation and intromissions are lost; finally, the animal stops mounting. It has been difficult to explain the conjunction of increased latency to initiate copulation with the decreased latency to ejaculate in the early weeks following castration. One possible explanation for the increased latency to begin copulating may be that dopamine in the MPOA becomes progressively harder to release. However, castrates appear to have more dopamine stored, so that if it can be released, there is sufficient dopamine to shift the autonomic balance to favor ejaculation.

NITRIC OXIDE PROMOTES MPOA DOPAMINE RELEASE

One factor that may regulate dopamine release is the gaseous messenger molecule nitric oxide (NO). NO has been implicated in many physiological processes, including killing of nonself cells by macrophages, vasodilation, long-term potentiation, excitotoxic

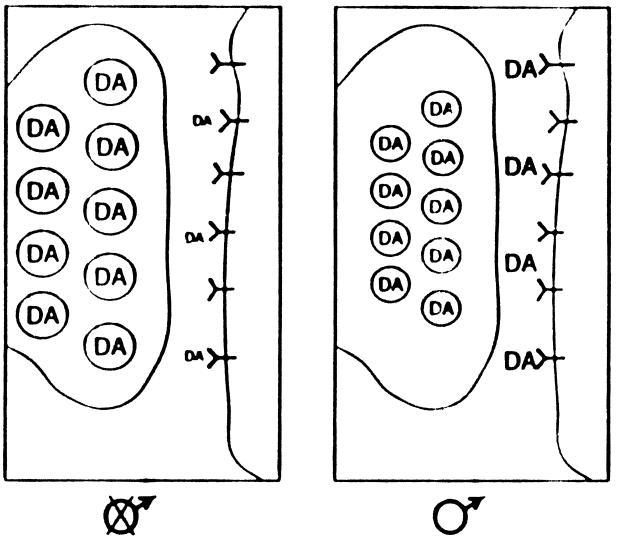

FIG. 7. A depiction of intra- vs. extracellular dopamine levels in 1-month castrates, compared with gonadally intact males. Castrates synthesize and/or store more dopamine than do intact males; however, they release less dopamine into the extracellular space.

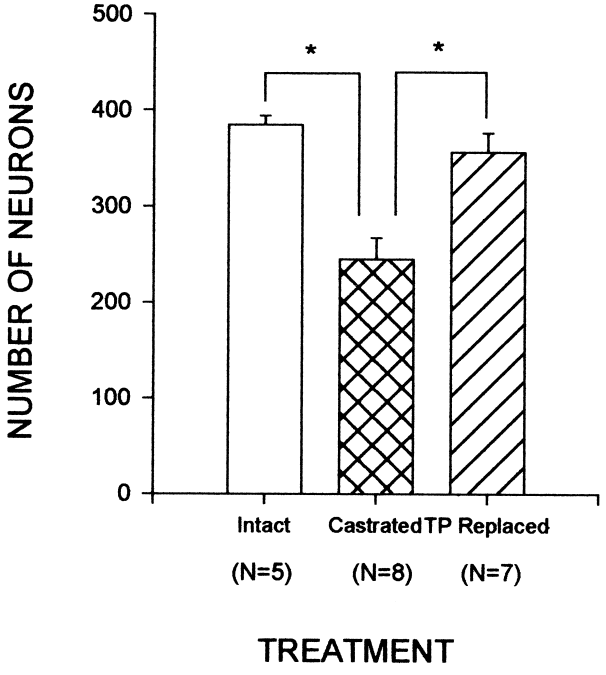

FIG. 8. Activity of NADPH diaphorase (a marker of nitric oxide synthase activity) in the MPOA of 1-month castrates treated with oil vehicle, 1-month castrates treated with testosterone propionate (200 μg/day), and gonadally intact males. There were more cells that stained positive for NADPH diaphorase in intact males and in testosterone-treated castrates than in oil-treated castrates.

damage, and neurotransmitter release (reviewed in [7,20]). NO is formed by NO synthase in the process of converting L-arginine to L-citrulline. We have shown that administration of L-arginine through the microdialysis probe increased dopamine release in the MPOA [21]. This increase was blocked by an inhibitor of NO synthase, which lowered basal levels of dopamine when administered alone. Furthermore, NO synthase has been reported to be reduced in the MPOA of both ovariectomized female rats [30] and castrated male hamsters [11]. Therefore, we examined a marker of NO synthase activity, NADPH diaphorase, in brain sections from 1-month castrates or sham-operated animals [9]. As predicted, there was less NADPH diaphorase activity in the MPOA of castrates than in intact animals (Fig. 8). However, there were no differences between castrated and intact males in several other sites, including the paraventricular nucleus and the amygdala. Therefore, testosterone may promote dopamine release in the MPOA by upregulating nitric oxide synthase, and this effect may be relatively site specific.

Finally, we tested whether an inhibitor of NO synthase, dialyzed into the MPOA through the probe, would inhibit the dopamine release that usually accompanies copulation [22]. Gonadally intact, sexually naive males were tested with an estrous female behind a perforated barrier and then with the barrier removed. Data were analyzed only from animals that copulated. Animals received either the NO synthase inhibitor nitro-L-arginine methyl ester (L-NAME, 400 μM), or its inactive isomer D-NAME (400 μM), for 3 h before the introduction of a female and throughout the precopulatory and copulatory periods. Animals tested with the inactive isomer D-NAME showed the typical elevation of dopamine during copulation (Fig. 9). However, inhibition of NO synthase with L-NAME abolished this increase. Therefore, nitric oxide appears to be essential for the MPOA dopamine release during copulation.

There were no behavioral deficits in L-NAME–treated animals in this experiment, even though dopamine release was inhibited in the area of the probe. The lack of behavioral effects probably reflects the small volume of tissue perfused by the probe. Large lesions of the MPOA are typically required to impair copulation (reviewed in [24]). Similarly, Moses and Hull [28] observed a copulatory impairment only in inexperienced males that received a large dose of an NO synthase inhibitor (400 μg monomethyl-L-arginine in 1 μl) microinjected into the MPOA. That dose is far larger than the amount administered through the microdialysis probe. Therefore, copulation in the microdialysis experiment could have been facilitated by dopamine released outside the volume of tissue perfused by the probe.

There was not a significant increase in extracellular dopamine during the precopulatory period in these animals. The reduction in the precopulatory dopamine response, compared with the previous experiments, is probably due to the use of sexually naive males. Preliminary data from our lab has shown a more meager dopamine response when a male first encounters an estrous female across the barrier, compared with sexually experienced males. Dopamine levels during copulation were comparable for experienced and inexperienced animals.

CONCLUSIONS

A consistent picture of MPOA function has emerged. One of the numerous effects of testosterone is the upregulation of NO synthase activity in the MPOA (Fig. 10). As a result, both basal and copulation-induced dopamine release are enhanced. Dopamine promotes sensorimotor integration in the MPOA, probably through

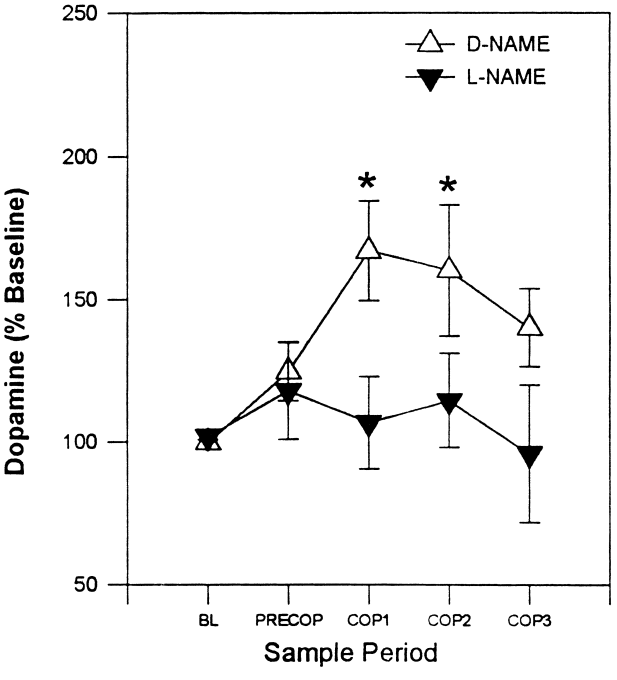

FIG. 9. Levels of extracellular dopamine in the MPOA of animals treated with an inhibitor of nitric oxide synthase (L-NAME) or its inactive isomer (D-NAME). L-NAME prevented the increase in dopamine release during copulation that was observed in animals treated with D-NAME. (From Lorrain et al., 1996, with permission.)

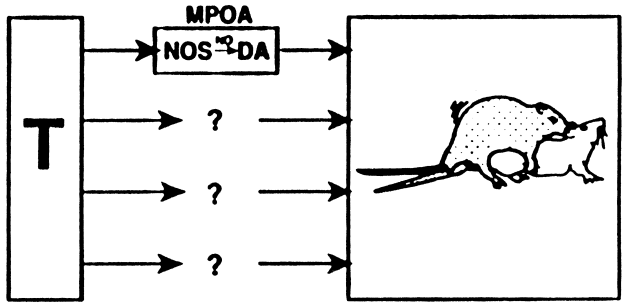

FIG. 10. One means by which testosterone may facilitate male sexual behavior. Testosterone upregulates nitric oxide synthase (NOS) in the MPOA; as a result, NO production is increased. NO promotes the release of dopamine in both basal and sexual contexts. The increased MPOA dopamine release enhances responsiveness to stimuli from an estrous female and increases the probability, rate, and efficiency of copulation.

disinhibition. As a result, stimuli from an estrous female are able to enhance sexual interest and to elicit appropriate copulatory responses. Early and/or small dopamine increases promote parasympathetically mediated erection, whereas larger and/or later increases shift autonomic balance to favor sympathetically mediated ejaculation. Similarly, dopamine released in the mesolimbic system increases general motivational fervor, while dopamine in the nigrostriatal system increases motoric initiative and the execution of motor patterns. Therefore, one means by which testosterone's long-term neural priming is translated into short-term neural processes, may be through enhancement of dopamine release in one or more neural integrative systems that coordinate motivation and behavior.

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