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Hormone-neurotransmitter interactions in the control of sexual behavior

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Abstract

The stimuli from a receptive female and/or copulation itself leads to the release of dopamine (DA) in at least three integrative hubs. The nigrostriatal system promotes somatomotor activity; the mesolimbic system subserves numerous types of motivation; and the medial preoptic area (MPOA) focuses the motivation onto specifically sexual targets, increases copulatory rate and efficiency, and coordinates genital reflexes. The previous (but not necessarily concurrent) presence of testosterone is permissive for DA release in the MPOA, both during basal conditions and in response to a female. One means by which testosterone may increase DA release is by upregulating nitric oxide synthase, which produces nitric oxide, which in turn increases DA release. Hormonal priming in females may also increase DA release in the MPOA, and copulatory activity may further increase DA levels in females. One of the intracellular effects of stimulation of DA D_1 receptors in the MPOA of male rats may be increased expression of the immediate-early gene c-fos, which may mediate longer term responses to copulation. Furthermore, increased sexual experience led to increased immunoreactivity to Fos, the protein product of c-fos, following copulation to one ejaculation. Another intracellular mediator of DA's effects, particularly in castrates, may be the phosphorylation of steroid receptors. Finally, while DA is facilitative to copulation, 5-HT is generally inhibitory. 5-HT is released in the LHA, but not in the MPOA, at the time of ejaculation. Increasing 5-HT in the LHA by microinjection of a selective serotonin reuptake inhibitor (SSRI) increased the latency to begin copulating and also the latency to the first ejaculation, measured from the time the male first intromitted. These data may at least partially explain the decrease in libido and the anorgasmia of people taking SSRI antidepressants. One means by which LHA 5-HT decreases sexual motivation (i.e. increases the latency to begin copulating) may be by decreasing DA release in the NAcc, a major terminal of the mesolimbic system. Thus, reciprocal changes in DA and 5-HT release in different areas of the brain may promote copulation and sexual satiety, respectively.

Keywords: Testosterone; Dopamine; Medial preoptic area; Nitric oxide; c-fos; Steroid receptors; Serotonin; Lateral hypothalamic area; SSRI

1. Model of central control of male sexual behavior

Sexually relevant stimuli elicit a complex cascade of genital and somatomotor patterns. Steroid hormones facilitate this process by biasing sensorimotor integration, so that a sexually relevant stimulus is more likely to elicit a sexual response. One step in the translation of long term steroid effects into rapid behavioral events is probably a change in the release or effectiveness of one or more neurotransmitters. One candidate for a central role is dopamine (DA), since dopaminergic drugs have long been known to facilitate masculine, and probably also feminine, sexual behavior (reviewed in [7,66,101,109]). DA is released before and during copu-

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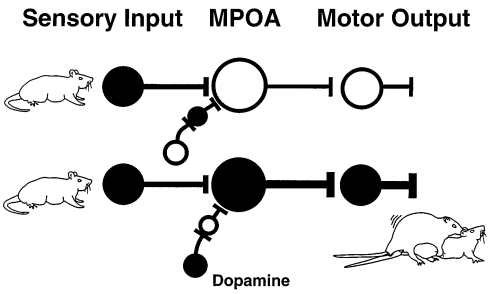

Fig. 1. Effects of dopamine on steroid-primed pathways. Inhibitory GABAergic neurons (small black interneuron in top part of figure) prevent the full responsiveness of steroid-primed neurons (three horizontal neurons in top and bottom halves of figure). Dopamine (small black neuron in lower part of figure) may enhance the responsiveness of those neurons by inhibiting the GABAergic neurons, thereby disinhibiting the relevant output pathways. This increases the probability that a sexually relevant stimulus will elicit a sexual response. Black neurons are active; white neurons (open circles) are inactive. (From Hull et al. [37], with permission.)

lation in several key integrative sites, described below. DA generally enhances sensorimotor integration by removing tonic inhibition [10]. Therefore, although steroid hormones increase the responsiveness of certain neurons, those neurons cannot fully respond to stimuli unless the tonic inhibition is first removed (Fig. 1). Thus, DA does not directly elicit behavior; rather, it allows hormonally primed output pathways to have easier access to sexually relevant stimuli.

Three major integrative systems control sexual motivation and genital and somatomotor responses in male rats (Fig. 2). Sensory input from a receptive female and/or the act of copulation elicits the release of DA in each of the three integrative systems. Output from these systems controls the expression of sexual motivation, genital reflexes, and somatomotor patterns of copulation. The nigrostriatal system enhances both the readiness to respond to stimuli and motor integration; the mesolimbic system is critical for appetitive behavior and reinforcement. The medial preoptic system may focus the male's motivation on sexually relevant stimuli, coordinate the genital reflexes necessary for erection and ejaculation, and enhance species-typical motor patterns of copulation (reviewed in [33]). Because of space limitations, this review will concentrate primarily on the roles of the medial preoptic system in male sexual behavior.

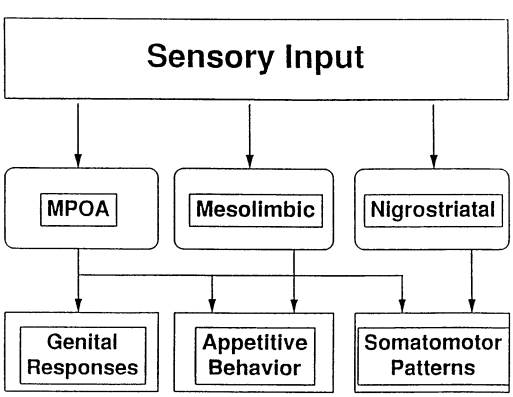

Fig. 2. Conceptual model of the dopamine systems that regulate male sexual behavior. Sensory stimuli from a female and from copulation elicit dopamine release in the MPOA and in the mesolimbic and nigrostriatal dopamine systems. MPOA dopamine influences genital responses, appetitive behavior, and somatomotor patterns; mesolimbic dopamine influences appetitive behavior; and nigrostriatal dopamine facilitates the somatomotor patterns of copulation. (From Hull [33], with permission.)

1.1. The nigrostriatal integrative system

The nigrostriatal system enhances readiness to respond to stimuli [2,87,89]. DA in the striatum disinhibits pathways through which the cortex elicits movements [10,108]. Loss of nigrostriatal DA in Parkinson's disease impairs response initiation and slows movement. DA neurons respond with short latencies to a variety of stimuli that have 'attention-grabbing properties,' but do not provide specific information about those stimuli [93]. This system may contribute to the execution of 'consummatory' movements [87], including pursuit of the female and mounting. DA is released in the dorsal striatum only after the male begins to copulate, suggesting that DA levels here reflect primarily motor activation, rather than motivational aspects of copulation [12].

1.2. 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. There is some disagreement as to whether mesolimbic DA is more important for reward processes [111] or the behavioral activation elicited by reinforcers [43,89,110]. However, there is agreement that the mesolimbic system is crucial for appetitive behavior. Extracellular DA increased in the nucleus accumbens (a major mesolimbic terminal field) when an estrous female was presented behind a barrier, as well as during copulation, suggesting that mesolimbic DA levels contribute to motivational aspects of behavior [12]. Furthermore, although numerous motivated behaviors may elicit DA release in the nucleus accumbens, there is some specificity. For example, a non-estrous female did not elicit DA release [25,62,106], nor did mild tail pinch [80], forced locomotion, or exposure to a novel chamber [12]. Exposure to the odor of an estrous female elicited accumbens DA release, measured by in vivo voltammetry [52], but did not initiate DA release in another study, using in vivo microdialysis [12]. It has been suggested that mesolim-

bic DA contributes to the initiation of various adaptive behavioral sequences [8,62].

1.3. The medial preoptic area integrative system

The medial preoptic area (MPOA) is critical for male sexual behavior in all vertebrate species that have been studied [67]. Even in parthenogenetic lizards, which display both female-like behavior (under the influence of estrogen early in the reproductive cycle) and male-like behavior (under the influence of progesterone after ovulation), activity in the MPOA is associated with male-like behavior, and activity in the ventromedial nucleus is associated with female-like behavior [86]. Because there is such variety among species in the stimuli that elicit sexual behavior and in the motor patterns that express it, the universal regulatory role of the MPOA suggests that it occupies a very high position in the hierarchy of control. Furthermore, DA facilitates male sexual behavior in several species, suggesting that it also plays an important role in this process.

The MPOA receives indirect sensory input from virtually every sensory modality and sends reciprocal connections back to those sources [96]. Therefore, MPOA neurons can modify the processing of sensory stimuli. Furthermore, steroid hormone receptors in the MPOA and its afferent connections allow hormones to bias sensory processing to favor sexually relevant stimuli. DA input to the MPOA arises from the periventricular system, including cell bodies in the medial portion of the MPOA and the anterior portion of the incertohypothalamic tract [70,95].

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 [21,31]. 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 [97,112]). The MPOA may remove the tonic inhibition on these patterns and thereby allow sensory stimuli to elicit a motor response.

1.4. Roles of the medial preoptic area and mesolimbic system in sexual behavior

Everitt [21] 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 [22]. 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 DA activity delayed the onset and slowed the rate of copulation [34]. It also led to general inactivity and poorly organized copulatory patterns, but did not affect the percentage of choices of the female in an X-maze, a measure of sexual motivation [41,72]. Thus, general activation, but not specifically sexual motivation, may be affected by mesolimbic activity.

On the other hand, microinjections of DA antagonists into the MPOA decreased sexual motivation, measured in an X-maze [105] or in a bilevel apparatus in which the male changes levels in search of a female [79]. Microinjection of an opioid antagonist into the MPOA, but not the nucleus accumbens, blocked the establishment of ejaculation-induced conditioned place preference [1]. MPOA lesions decreased the preference of male rats [20,76] or ferrets [42,75] for an estrous female and decreased pursuit of the female [76]. In addition, some MPOA neurons in male rats increased firing only before copulation, while others increased firing only during copulation [94]. Neural firing in the MPOA of male monkeys was greatest when they were pressing a lever to bring a female close to them; firing decreased slightly during copulation, and ceased following ejaculation [74]. Finally, the elevation of DA levels in the MPOA during a precopulatory period also suggests a role for MPOA DA in sexual motivation [36]. Thus, MPOA DA and neural activity may contribute to sexual motivation as well as performance.

2. Activation of dopamine release in the medial preoptic area

We have observed a consistent relationship between MPOA DA release during a precopulatory period, with a receptive female behind a perforated barrier, and the subsequent ability of a male to copulate [36] (Fig. 3). An increase in DA release, measured in microdialysate, was not elicited by the presence of another male behind the barrier or by voluntary running in an activity wheel. The amount of activity exerted in the running wheel was considerably greater than the motoric effort of copulation. Therefore, neither purely social stimuli nor motor activity can account for the DA increase that was observed before and during copulation. Furthermore, eating a highly palatable food did not increase DA metabolites in the MPOA in a previous experiment [39]. Thus, there is considerable behavioral specificity to

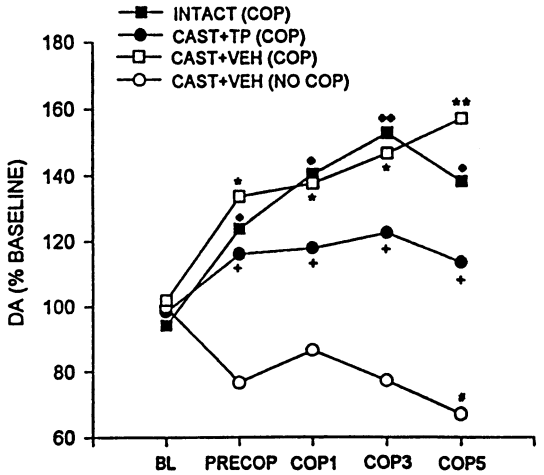

Fig. 3. Extracellular dopamine in the MPOA of male rats during baseline, a precopulatory period (estrous female behind a perforated barrier), and three 6-min periods after the barrier was removed and the animals were free to copulate. All gonadally intact males and all castrates treated with testosterone propionate (200 μg/day) showed a significant increase in dopamine during the precopulatory period and during copulation; all of 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. φ, $P < 0.05$ compared to final baseline for intact males; φφ, $P < 0.01$ compared to final baseline for intact males; +, $P < 0.05$ compared to final baseline for castrates treated with 200 μg testosterone propionate; *, $P < 0.05$ compared to final baseline for 1-week vehicle-treated castrates that copulated; **, $P < 0.01$ compared to final baseline for 1-week vehicle-treated castrates that copulated; #, $P < 0.05$ compared to final baseline for vehicle-treated castrates that failed to copulate. (From Hull et al. [36], with permission.)

the MPOA DA response, in contrast to the variety of stimuli that can elicit DA release in the mesolimbic system. There is also anatomical specificity, in that microdialysis probes located anterior, lateral, or dorsal to the MPOA did not show an increase in DA levels associated with an estrous female or copulation [36,39].

3. Consequences of dopamine release in the medial preoptic area

We shown that DA released in the MPOA is important for copulation. Microinjections of a DA agonist (apomorphine, APO) into the MPOA increased the rate and efficiency of copulation [35], and also increased the numbers of ex copula erections [78]. Furthermore, microinjection of APO into the MPOA reversed the impairment due to lesions of the medial amygdala [16]. Blocking DA's access to receptors slowed the rate of copulation, decreased ex copula erections, and decreased specifically sexual motivation [77,105]. Thus, endogenous DA facilitates copulation and enhances genital reflexes and sexual motivation.

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

We have presented evidence that small increases in MPOA DA may facilitate parasympathetically mediated erections by stimulating D_1-like receptors [38,59]. On the other hand, higher levels of DA may act via the D_2 family of receptors to shift the autonomic balance to favor sympathetically mediated ejaculation [6,40, reviewed in 33]. The opposing nature of these two families of receptors is also seen in the apparent ability of D_1-like receptors to inhibit seminal emission, perhaps thereby preventing 'premature ejaculation' [38] and in the ability of a relatively high dose of a D_2-like agonist to inhibit erections [6] and delay the onset of copulation [40], perhaps thereby contributing to the sexual quiescence of the postejaculatory interval. Thus, different levels of extracellular DA, acting through different families of receptors, may help control the timing of copulatory events.

4. Hormonal influences on medial preoptic area dopamine release

The recent presence of testosterone is necessary for the precopulatory DA release and for copulation itself [36]. All gonadally intact males, all testosterone-replaced castrates, and 2/3 of oil-treated animals that had been castrated 1 week previously showed a precopulatory DA response to a female behind a barrier, and all of them copulated (Fig. 3). All 2-week oil-treated castrates and 1/3 of the one-week oil-treated castrates failed to show a precopulatory DA response, and all of these failed to copulate when the barrier was removed. Every animal that showed at least some precopulatory DA increase 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 DA release in response to a female.

We have very recently tested the effects of 2-, 5-, and 10-day regimens of testosterone restoration in males castrated 3 weeks earlier [85]. As in the previous study, there was a perfect correlation between precopulatory DA release and the ability to copulate. None of the 2-day, but all of the 10-day animals showed the DA response and copulated. Half of the 5-day animals showed the DA response and copulated; the rest showed no DA response and did not intromit, although one mounted. Furthermore, the males that eventually

ejaculated had higher precopulatory DA release than did those that only intromitted. Therefore, we have again demonstrated a compelling link between MPOA DA release and the ability to copulate. We have also shown that 5 days is a threshold period for hormone replacement to restore the DA response and behavior.

4.1. How general is the dopamine deficit in castrates?

We next asked whether the deficit in extracellular DA of castrates is a general one or whether it is specific to the sexual context. We used the no-net-flux technique to measure absolute levels of extracellular DA [19]. Briefly, differing concentrations of DA are added to the dialysate. If there is more DA in the dialysate than in the brain, some of it will diffuse out of the probe into the brain, and the loss can be measured. If there is less DA in the dialysate than in the brain, or if there is none, as is always the case in normal dialysis, then DA will diffuse from the brain into the dialysate, and the gain can be measured. A regression line is drawn, and the point at which the line crosses from loss to gain of DA in the dialysate (no net flux out of or into the dialysate) is taken as the absolute level of extracellular DA. Basal levels of extracellular DA were indeed lower in castrates than in intact males (Fig. 4). Thus, castrates show a deficiency of extracellular DA in the MPOA, in both basal and estrous female conditions.

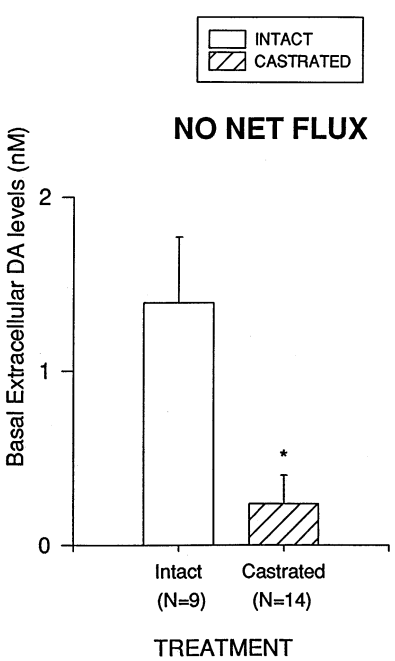

Fig. 4. Basal levels of extracellular dopamine in MPOA of 1-month castrates and gonadally intact males. Absolute levels were determined, using the no-net-flux method (see text). Intact males had significantly higher dopamine levels than did castrates. (Data from Du et al. [19]; figure from Hull et al. [37], with permission.)

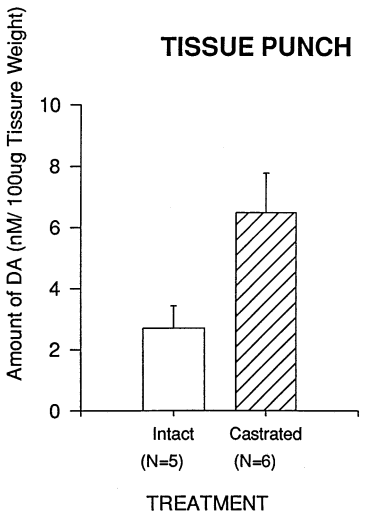

Fig. 5. Dopamine levels in tissue punches from the MPOA of 1-month castrates or gonadally intact males. Castrates had significantly more dopamine in tissue than did intact males. Because almost all dopamine in tissue is stored in vesicles, this suggests that castrates synthesize and store dopamine normally, or even excessively; the deficit in extracellular dopamine of castrates may be due to decreased release. (Data from Du et al. [19]; figure from Hull et al. [37], with permission.)

4.2. Synthesis or release problem?

A decrease in extracellular DA could result from either a decrease in stored DA or a decrease in release. We therefore measured DA in MPOA tissue punches, almost all of which is stored in vesicles. In contrast to the low extracellular levels, castrates actually had more stored DA than did intact males [19] (Fig. 5). This suggests that synthesis and storage were at least normal, and perhaps enhanced, in castrates. This finding was confirmed when amphetamine elicited greater DA release in castrates than in intact males. Amphetamine causes storage vesicles to become 'leaky' and also reverses the transporter, thereby evoking DA release [99]. Since there is more stored DA 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 [13]. However, if the male does initiate copulation, he will ejaculate prematurely, with fewer intromissions and less time than an intact male. The increased latency to begin copulating may be explained by the increasing difficulty of castrates to release MPOA DA. However, if they do begin, there is more stored DA to be released. We have previously suggested that high levels of DA, acting on D_2-like receptors, shift the autonomic balance to favor ejaculation [38,40].

5. The role of nitric oxide

DA release may be affected by influences on axon terminals, as well as changes in the firing rate of DA neurons. One particularly intriguing finding is that the gaseous messenger molecule, nitric oxide (NO), can enhance catecholamine release and inhibit reuptake, possibly by reversing the transporter [46,81]. NO, a highly reactive gas, is given off when L-arginine is converted to L-citrulline by the enzyme NO synthase (NOS). NO has been implicated in the regulation of DA release in striatal slices [30,45] and in the striatum of freely moving rats [92,107]. It is also important for a variety of neural and nonneural effects (reviewed in [14,44,98]. Furthermore, the steroid dependent luteinizing hormone (LH) release in both male and female rats was dependent on NMDA glutamate receptors, NO, and cGMP [84]. We reported that the NO precursor L-arginine, but not its inactive isomer D-arginine, increased extracellular DA in the MPOA, measured with microdialysis [47]. This increase was blocked by a NOS inhibitor, which decreased basal DA release when administered alone. We more recently reported that a NOS inhibitor, administered through the dialysis probe, prevented the increase in MPOA DA seen in controls during copulation [49] (Fig. 6). Only animals that copulated were analyzed; apparently the volume dialyzed by the probe was small enough that DA in the remaining MPOA was sufficient to support copulation. Microinjection of a large dose of a NOS inhibitor into the MPOA did inhibit the ability of sexually naïve males to copulate [71]. Furthermore, reverse dialysis of L-arginine into the MPOA increased the rate of mounting, whereas reverse dialysis of a synthesis inhibitor decreased mount rate [90]. Therefore, NO is an important mediator of DA release in the MPOA in both basal and sexual situations, and this may facilitate copulation.

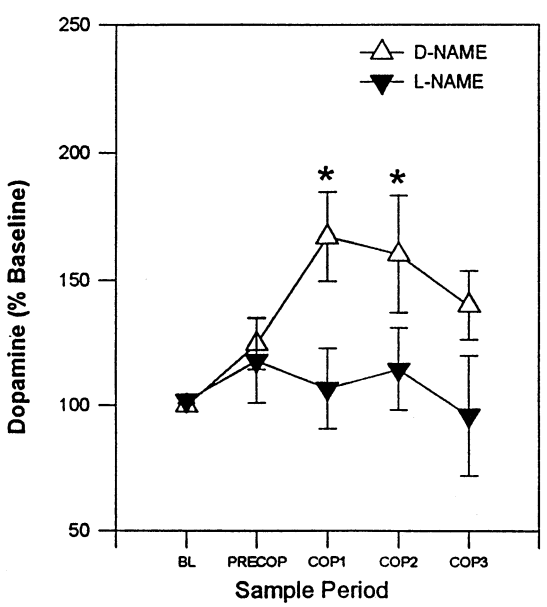

Fig. 6. Levels of extracellular dopamine in the MPOA of animals treated with an inhibitor of nitric oxide synthase (L-NAME) or its inactive isomer (D-NAME). L-NAME prevented the increase in dopamine release during copulation that was observed in animals treated with D-NAME. (From Lorrain et al. [49], with permission.)

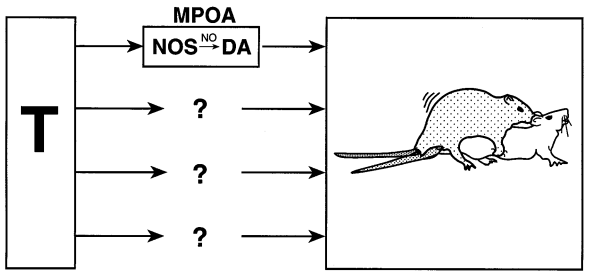

Fig. 7. One means by which testosterone may facilitate male sexual behavior. Testosterone upregulates nitric oxide synthase (NOS) in the MPOA. As a result, NO production is increased. NO promotes the release of dopamine in both basal and sexual contexts. The increased MPOA dopamine release enhances responsiveness to stimuli from an estrous female and increases the probability, rate, and efficiency of copulation. (From Hull et al. [37], with permission.)

We have now shown that testosterone upregulates NOS in male rats [18]. Animals castrated 1 or 2 months previously and injected daily with oil had fewer NOS immunoreactive (NOS-ir) neurons in the medial preoptic nucleus (MPN) than did gonadally intact males or castrates injected daily with testosterone propionate. Similarly, castration decreased NOS-positive neurons in the male hamster MPN [29]. Therefore, testosterone appears to increase NOS activity in the MPOA, which produces more NO, which in turn promotes DA release in both basal and sexual situations; DA, in turn, promotes sexual motivation, genital reflexes, and copulation (Fig. 7).

6. Medial preoptic area dopamine and female sexual behavior

We have recently asked whether DA may be released in the MPOA of females during sexual behavior [64]. In females injected with estradiol benzoate (EB, 2 μg) 48 h before testing and with progesterone (P, 500 μg) 4 h before testing, DA remained at baseline during the first 3 h and 20 min following P injection. However, the sample collected 3 h and 40 min after P showed a significant increase in DA. Furthermore, DA rose further at 4 h after injection, when a male was placed into the female's dialysis chamber and the animals began to copulate. Thus, increased extracellular levels of DA were observed at the time that the female would have become receptive and during actual copulation. However, the additional increase during copulation occurred

only if the male and female were confined in the same arena; in an apparatus that allowed the female to pace her contacts with the male, no copulatory increase was seen. This pattern is the opposite of that observed by Mermelstein and Becker [68], who reported that extracellular DA levels in the striatum increased significantly only if the female was allowed to pace her interactions with the male. In our experiment, there were significantly more mounts and a trend toward increased intromissions in the nonpaced condition. In summary, extracellular DA levels in the MPOA of females rose at the time that sexual receptivity would have been initiated by hormonal priming and may also reflect the number of sexual interactions with the male. While most studies of MPOA lesions in females have suggested an inhibitory influence of the MPOA on female receptive behavior [11,83,100], two reports have suggested that MPOA activity may facilitate sexual behavior in female rats [4] or musk shrews [103].

7. Fos: a possible intracellular mediator of some of dopamine's effects

Some of the longer term effects of neural activity may be mediated through the induction of immediate-early genes, which are expressed transiently in response to stimulation. The protein products of these genes may serve as transcription regulators for other genes, which may in turn affect neural activity or response to future stimulation.

The immediate-early gene c-fos and its protein product Fos are expressed in several hormone-concentrating brain areas, including the MPOA, following sexual behavior in male rats [5,88,102]. We tested whether D_1-like receptors mediate at least some of the Fos expression in the male rat's MPOA following copulation to ejaculation [53]. Systemic administration of the D_1 antagonist SCH-39166 to sexually naïve males before their first copulatory experience did decrease the number of Fos-immunoreactive (Fos-ir) neurons in the MPOA. Therefore, stimulation of D_1 receptors may be one means by which Fos is induced in the MPOA. However, the D_1 antagonist also decreased the number of intromissions preceding ejaculation. Therefore, the decreased Fos expression could have been secondary to the decrease in the number of intromissions.

Sexually experienced male rats copulate with greater speed and efficiency than sexually naïve males. We also tested whether sexually experienced male rats express more Fos-ir in the MPOA than do sexually naïve males following copulation to ejaculation [53]. There were more Fos-ir neurons in the MPOA of experienced than naïve males. Furthermore, experienced males had fewer intromissions preceding ejaculation than did naïve males. Thus, the increased Fos-ir in experienced males was associated with decreased numbers of intromissions. This finding suggests that the decrease in Fos-ir neurons in the first experiment was not due simply to fewer intromissions by the drug treated animals. Therefore, sexually experienced males show greater ejaculation-induced Fos expression in the MPOA than do sexually naïve animals, and at least some of this Fos expression may result from stimulation of D_1 receptors.

8. Hormonal influences on dopamine in other brain areas

There are contradictory reports concerning the effects of hormones on mesolimbic and nigrostriatal systems. For example, tissue levels of DA and its major metabolite in the nucleus accumbens were decreased by castration [3,69]. On the other hand, amphetamine-stimulated DA release in the ventral striatum (nucleus accumbens) was higher in castrates than in intact males [32,61]. In the dorsal striatum DA tissue levels were reported to be either unaffected [3,69] or increased [18] by castration, and castration increased DA efflux from striatal slices [15]. Finally, estrogen increased amphetamine-stimulated DA release in the striatum of ovariectomized females, but not in castrated males [9], and basal extracellular DA levels were affected by estrous cycle and ovariectomy in females, but not by castration in males [113]. These inconsistencies make it difficult to infer a common effect of castration on DA levels or release across brain areas.

9. Ligand-independent activation of steroid receptors by dopamine

The full elicitation of female sexual behavior in ovariectomized rats typically requires a regimen of estrogen injections, followed by progesterone. However, recent reports have shown that DA agonists are as effective as progesterone in eliciting lordosis in estrogen primed, ovariectomized female rats [56,58] and in wild-type, but not progesterone receptor knock-out, mice [57]. DA agonists, acting through the D_1 receptor cause the phosphorylation of progesterone receptors (PR), which in turn allows them to serve as transcription activators for various genes [82]. The classic DA agonist apomorphine can also partially restore male copulatory behavior in short-term [54] or long-term [91] castrated rats or in castrates with sub-optimal testosterone replacement [55,91]. We have recently completed an experiment in which apomorphine's ability to increase the number of mounts in long-term castrates was blocked by acute systemic administration of antagonists to the PR (RU-38486), the estrogen receptor (ER; tamoxifen), and the androgen receptor (AR; flutamide)

[17]. The reason that all three antagonists, injected individually 15 min before testing, inhibited mounting is not clear. A possible explanation is that all three steroid receptors, perhaps in different populations of cells, are needed for apomorphine's facilitative effects. Indeed, a D_1 agonist activated estrogen receptors in a human neuroblastoma cell line [26], and protein kinase A (PKA, which may be produced as a result of stimulation of D_1 receptors) activated androgen receptors in monkey kidney CV1 cells or human prostate PC-3 cells [73]. These findings suggest that DA may activate additional steroid receptors in a ligand-independent manner.

10. The role of serotonin (5-HT) in copulation

DA is generally facilitative to sexual behavior; however, 5-HT is usually regarded as inhibitory. Antidepressants of the selective serotonin reuptake inhibitor class (SSRIs, including Prozac and Zoloft) impair ejaculatory/orgasmic function, and frequently erectile function as well [27]. Microinjection of large doses of 5-HT into the MPOA impaired male sexual behavior [24,104]. Conversely, decreasing serotonergic activity, either by lesions or inhibition of synthesis, facilitated sexual behavior (reviewed in [7,28,109].

On the other hand, stimulation of 5-HT_{1A} receptors, either systemically or in the MPOA, facilitated ejaculation [24,65]. It was suggested that 5-HT_{1A} agonists may decrease 5-HT levels by stimulating inhibitory autoreceptors [23]. However, the effects of a systemically injected 5-HT_{1A} agonist were not prevented by lesions of 5-HT neurons [23]. We have very recently dialyzed a 5-HT_{1A} agonist into the MPOA, via the microdialysis probe, and observed a facilitation of copulation [65] and also increased levels of DA [51]. The drug did not consistently affect 5-HT levels; systemic administration of 8-OH-DPAT decreased 5-HT, and reverse dialysis increased 5-HT, but both methods of administration resulted in behavioral facilitation. Furthermore, some of the facilitative effects of 8-OH-DPAT microinjected into the MPOA were blocked by the D_2 antagonist raclopride, but the 5-HT_{1A} antagonist p-MPPI was totally ineffective. Therefore, the facilitative effects of the 5-HT_{1A} agonist administered into the MPOA may be mediated in part through its increase in DA release.

Mas and his colleagues [25,60,63] suggested that 5-HT is released in the POA and medial basal hypothalamus after ejaculation, and that these high levels of 5-HT may lead to the sexual quiescence following ejaculation. This suggestion was based on increased tissue levels of 5-HT in the POA and increased levels of 5-HIAA (the major metabolite of 5-HT) in dialysate; 5-HT itself was below detection limits in dialysate in their system. However, we recently reported that extracellular 5-HT in dialysate from the MPOA did not change during copulation or after ejaculation; however, 5-HT was released in the anterior lateral hypothalamus (LHA) after ejaculation [48] (Fig. 8). It is possible that the 5-HIAA that Mas et al. observed may have diffused from the LHA to the POA, since the acidic metabolites of monoamines diffuse much longer distances than do the monoamines themselves. Microinjection of an SSRI (alaproclate) into the LHA, but not into the MPOA of male rats, increased the latency to copulate and also increased the latency to ejaculate after copulation began. Therefore, the LHA may be one site where SSRI antidepressants produce their impairment of sexual function in humans.

We also found that administering 5-HT unilaterally via reverse dialysis into the LHA decreased basal levels of DA in the ipsilateral nucleus accumbens (NAcc), a major terminal field of the mesolimbic DA system [50]. Furthermore, there was no increase in NAcc DA before or during copulation during 5-HT administration. Apparently, DA release in the contralateral side allowed for normal copulation. Therefore, one way in which LHA 5-HT may promote sexual quiescence is by inhibiting activity in the mesolimbic DA tract, which is very important for all types of motivated behavior.

11. Summary

Stimuli from a receptive female elicit DA release in several integrative hubs that regulate different aspects of male sexual behavior. DA in the nigrostriatal system promotes the somatomotor patterns of copulation; in the mesolimbic system it facilitates numerous types of motivation; and in the MPOA it focuses motivation on sexual stimuli, coordinates genital reflexes, and increases the rate and efficiency of copulation. The recent presence of testosterone is permissive for DA release in the MPOA during both basal and sexual conditions. In females, as well as males, hormonal priming increases extracellular DA in the MPOA; copulation further increases DA levels, but only if the female is not allowed to pace the sexual interactions. One way in which testosterone may promote DA release is by upregulating NOS, which produces NO, which increases DA release. There are two possible intracellular mediators of some of DA's effects: Fos, the protein product of the immediate-early gene c-fos, and the phosphorylation of steroid receptors. Whereas DA is facilitative for male sexual behavior, 5-HT is generally inhibitory. 5-HT is released in the LHA at the time of ejaculation. Microinjection of an SSRI into the LHA delays the onset of copulation and also delays ejaculation even after the male begins to copulate. Therefore, this may be one site at which SSRI antidepresssants inhibit both libido and ejaculatory/orgasmic ability in humans. One

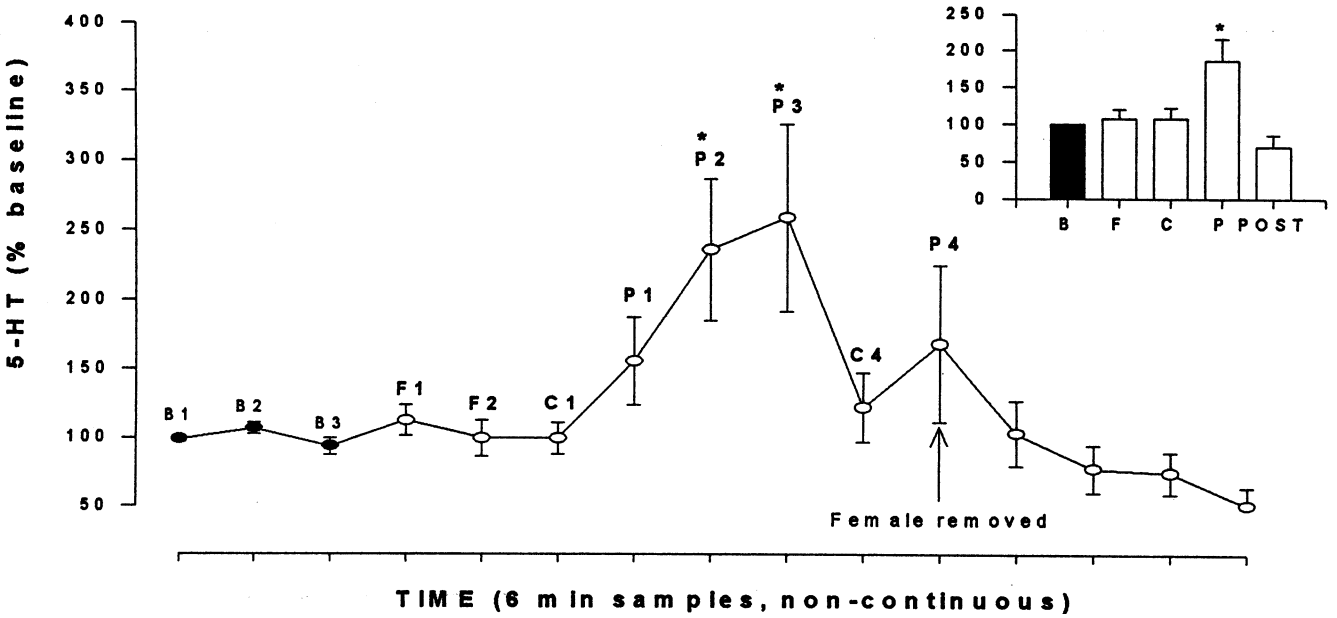

Fig. 8. Temporal changes in extracellular serotonin (5-HT) collected from the lateral hypothalamic area (LHA) of male rats before and during copulation. Each data point is the mean ($\pm$S.E.) for 6-min dialysate samples collected during baseline (B), in the presence of an estrous female (F), during copulation (C), during the postejaculatory interval (P), and after the female was removed (expressed as a % of mean baseline levels). A total of four samples were analyzed after the female was removed, at 30 min intervals. 5-HT levels increased during the second (P2) and third (P3) postejaculatory intervals, compared to final baseline (B3), female behind barrier (F2), and first copulation period (C1). 5-HT during P3 was also higher than during the fourth copulation interval (C4). Samples collected during the second and third copulation series were not analyzed, because most males ejaculated before a full 6 min sample could be collected. The summary graph (inset) represents the mean ($\pm$S.E.) for data from the 15 sample periods collapsed into 5 groups, based on behavioral condition. Samples collected during the postejaculatory intervals showed higher 5-HT levels compared to all other conditions. Basal extracellular concentrations of 5-HT in the LHA were calculated to be 1.6 ± 0.1 nM. (From Lorrain et al. [48], with permission.)

means by which LHA 5-HT may decrease sexual motivation is by decreasing DA release in the NAcc, a major terminal field of the mesolimbic system. Thus, reciprocal changes in DA and 5-HT release may differentially promote copulation and sexual satiation.

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