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A Role for Preoptic Glutamate in the Regulation of Male Reproductive Behavior

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Although much progress has been made toward understanding the role of the medial preoptic area (MPOA) in the regulation of male reproductive behaviors, the precise mechanisms responsible for its activation during mating are largely unclear. Several studies implicate glutamate in this response. However, not until recently was there direct evidence supporting this hypothesis. Results obtained using in vivo microdialysis showed that levels of glutamate increased in the MPOA during mating, particularly with ejaculation. Levels then decreased rapidly following ejaculation, during a period of sexual quiescence. The magnitude of this decrease correlated with time spent in quiescence. Additionally, central administration of glutamate uptake inhibitors increased levels of glutamate and facilitated behavior. Glutamate activation of *N*-methyl-D-aspartate (NMDA) receptors in the MPOA is at least partly responsible for behavioral effects evoked by increase glutamate. This is evidenced by histological analysis of the MPOA, which shows that nearly all cells containing mating-induced Fos also contained NMDA receptors. Mating also increased phosphorylation of NMDA receptors, indicating receptor activation. Finally, bilateral microinjections of NMDA receptor antagonists inhibited copulation. This neurochemical, anatomical, and behavioral evidence points to a key role of preoptic glutamate in the regulation of sexual behavior in males. The implications of these findings are discussed.

Keywords: reproduction; preoptic area; glutamate; endocrine; NMDA receptor; limbic

Despite early discoveries demonstrating an excitatory effect of glutamate on the CNS (Curtis and Watkins 1960), several years passed before it was recognized as the principal excitatory neurotransmitter that we know today (Watkins 1986). This careful progression resulted largely from caveats associated with studying glutamate, including its ubiquitous distribution and high concentration throughout the nervous system. However, molecular, anatomical, and pharmacological approaches currently available to study its function are yielding a multitude of discoveries. Many of these findings demonstrate clear influences of glutamate on natural behavior and on disorders of motivation and cognition (Moghaddam and Wolf 2003). This update focuses on sexual behavior and specifically evidence that glutamate in the medial preoptic area (MPOA) is important for the expression of sexual behavior in males.

Why the Medial Preoptic Area?

The MPOA is not the only region of the brain that mediates the expression of male sexual behavior; however, it is an integrative site in this process. The MPOA is a region in the rostral end of the hypothalamus (Swanson 2004) that receives indirect input from every sensory modality (Simerly and Swanson 1986) and sends projections to structures vital for the patterning of sexual behavior (Simerly and Swanson 1988; Fig. 1). Although there are questions of whether the MPOA influences only appetitive and/or consummatory aspects of mating, there is little doubt that it is essential for the overt expression of sexual behavior (Hull and Dominguez 2003; Hull and others 2007; Hull and others 2006). Several studies have demonstrated this important role. Larsson and Heimer's seminal work (Heimer and Larsson 1966/67; Larsson and Heimer 1964) showed that lesions in the MPOA diminished or completely eliminated copulation in 88% of male rats (Larsson and Heimer 1964). Similar findings have been replicated in several species, including birds, cats, dogs, fish, ferrets, gerbils, goats, guinea pigs, hamsters, lizards, mice, monkeys, and snakes (Hull and Dominguez 2003; Hull and others 2002, 2006). These results are not redundant inasmuch as they not only support a role for the MPOA in mating but they also reveal that its role has been phylogenetically preserved across species.

Several nuclei comprise the MPOA, including the anterodorsal, anteroventral, median, and medial preoptic nuclei, with the medial nucleus further subdivided into medial, central, and lateral parts (Swanson 2004). With this assortment of cell clusters, it is not surprising that the severity of sexual impairments resulting from ablations is largely dependent on the size and location of the lesions. Namely, larger lesions and lesions at the caudal end of the MPOA have the most severe effects (Arendash and Gorski 1983; Heimer and Larsson 1966/67; Van De Poll and Van Dis 1979). This suggests that locus of transmitter or hormone action within the MPOA may be a critical factor in regulating behavior, with specific regions mediating aspects of behavior leading up to mating (appetitive phase) and others mediating copulation itself (consummatory phase). In this article the words appetitive and consummatory are used in reference to

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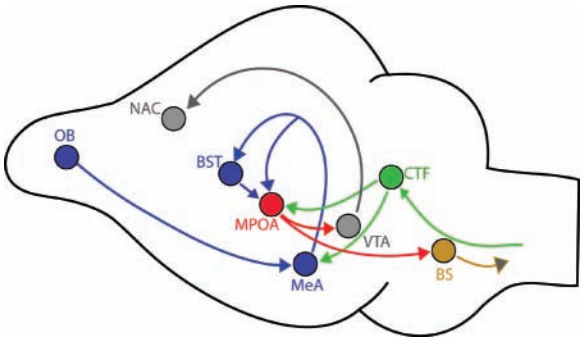

Figure 1. The medial preoptic area (MPOA) is a central integrative site for the regulation of sexual behavior. Olfactory information is relayed from the olfactory bulb (OB) and vomeronasal organ, via the medial amygdala (MeA) and bed nucleus of the stria terminalis (BST), to the MPOA. The MPOA and MeA receive somatosensory information via the central tegmental field (CTF). The MPOA, in turn, projects to the ventral tegmental area (VTA) and brain stem (BS). See Simerly and Swanson (1986, 1988) for a thorough description of MPOA afferent and efferent connections. Reprinted from Brain Research, 1126(1), Hull EM, Dominguez JM, Getting his act together: roles of glutamate, nitric oxide, and dopamine in the medial preoptic area, p 66–75, Copyright (2006), with permission from Elsevier.

behaviors leading up to copulation and behaviors occurring with copulation, respectively. For a thorough discussion of the history and appropriate use of this locution when describing sexual behavior, see previous publications (Ball and Balthazart 2007; Pfaus 1999; Pfaus and others 1990; Sachs 2007a, 2007b). Notwithstanding the locus-specific differences described above, results obtained with lesions point to an important role by the MPOA in mating.

Studies using central stimulation of the MPOA also point us in a similar direction (Hull and others 2007; Hull and others 2002; Hull and others 2006). Electrically stimulating the MPOA of rats increased the number of ejaculations in a timed test, reduced the number of intromissions preceding ejaculation, and decreased the time required to reach an ejaculation and the time spent in sexual quiescence following ejaculation (Malsbury 1971; Rodriguez-Manzo and others 2000; Vaughan and Fisher 1962). If the goal of sexual activity is procreation and natural outcrossing, then manipulations that facilitate the expression of ejaculations, as indicated by decreased latency to ejaculate or requiring less stimulation to reach ejaculation, can be interpreted as enhanced sexual performance.

Stimulation of the MPOA also increased intracavernous pressure, a measure of erections (Giuliano and others 1996). And in much the same way that lesions of the caudal MPOA produced the greatest sexual impairments, so did stimulations of the caudal MPOA produce the greatest response in penile activity (Giuliano and others 1996), pointing to a role by the MPOA in erectile function, and not just the overt expression of behavior. Finally, activity in the MPOA might also mediate orgasms. Stimulation of the MPOA that elicited the urethrogenital reflex, a model for orgasm as proposed by McKenna and colleagues (Marson and McKenna 1994), supports this conclusion.

Despite the evidence obtained with intracranial manipulations, that exogenous stimulation facilitates behavior does not indicate increased neural activity during normal mating conditions. To more closely examine whether this increased activity occurs, electrophysiological recordings of the MPOA were performed. Some of these studies found that in sexually experienced monkeys, bar pressing for a female or the act of copulation itself increased activity in the MPOA, but this activity ceased after ejaculation (Oomura and others 1988). Similar effects were observed in rats (Shimura and others 1994). Moreover, in rats, these increases were distributed in such a way that some cells depolarized immediately preceding ejaculation, whereas others did so only during copulation (Shimura and others 1994), again pointing to locus specificity in the MPOA in the regulation of behavior.

Histological analysis of the MPOA after different mating conditions dovetails the electrophysiological data. Induction of immediate early genes (IEG) provides investigators with a very useful tool for mapping neural activity. One such tool is Fos, specifically the protein by-product of the IEG *c-fos*, which is up-regulated with depolarization (Ghosh and others 1994). Several studies employed this approach and demonstrated mating-induced increases in the number of Fos-positive cells in the MPOA of rats (Baum and Everitt 1992; Bressler and Baum 1996; Robertson and others 1991; Veening and Coolen 1998), hamsters (Kollack-Walker and Newman 1997), gerbils (Heeb and Yahr 1996), quail (Taziaux and others 2006), and musk shrews (Gill and others 1998). Chemosensory cues, such as the dirty bedding or distal cues of an estrous female, also increased the number of Fos-positive cells in the MPOA of rats; however, the effects were less dramatic than those observed with two ejaculations (Kelliher and others 1999). Consistent with the notion that subregions of the MPOA differently influence behavior is that number of Fos-positive cells increased only in the posterodorsal preoptic region after ejaculation in rats (Coolen and others 1996), hamsters (Kollack-Walker and Newman 1997), gerbils (Heeb and Yahr 1996), and quail (Taziaux and others 2006). Although beyond the scope of this article, for a more detailed discussion of the idea that subregions of the MPOA differently influence appetitive versus consummatory aspects of sexual behavior, see a recent publication by Balthazart and Ball (2007).

Quantification of IEG, electrophysiological recordings, and central stimulation of the MPOA all suggest that mating increases neural activity in the MPOA. Several studies have attempted to discern the mechanisms responsible for this increase. To this end, reports have implicated a role for various neurotransmitters, including catecholamines, indolamines, GABA, acetylcholine, nitric oxide, and peptides (Dominguez and Hull 2005; Hull and others 2007; Hull and others 2006). Thus, although the studies reviewed in this article point to a key role of glutamate in the regulation of mating, it is not to say that only glutamate is involved. For example, hormones are another major factor in the regulation of sexual behavior (Hull and others 1999, 2002; McEwen and others 1979). This is evidenced by observations that gonadectomies or hypogonadal conditions impair sexual activity in several species, including rats (Beach and Holz-Tucker 1949; Davidson 1966; Stone 1939) and humans (Davidson and others 1979, 1982). Conversely, hormone replacement restores sexual function in hypogonadal conditions or after gonadectomy (Beach 1944; Beach and Holz-Tucker 1949;

Davidson 1966; Davidson and others 1979; Fisher 1956; Stone 1939). Not surprisingly, the MPOA appears to be partly responsible for integrating endocrine signals that facilitate sexual behavior. This is evidenced by studies showing that testosterone implants restored copulation in castrates and that mating activated androgen-sensitive neurons in the MPOA (Wood 1997; Wood and Newman 1993, 1995). Despite this obvious need for hormonal stimulation, it is unlikely that hormones alone are responsible for activation of the MPOA during mating. This is true partly because intracranial stimulation, without hormonal manipulations, induces sexual activity, as described above; these findings point to nonhumoral factors acting in the MPOA to facilitate behavior. Thus a more likely scenario is one in which hormones facilitate behavior by mediating responses of fast-acting neurotransmitters like glutamate.

Why Glutamate?

An enduring speculation has been that glutamate increases in the MPOA with mating and consequently facilitates the expression of behavior. Certainly the immunohistochemical data posits as much, in showing that mating increases Fos. This is because *c-fos* induction is largely dependent on Ca^{2+} influx via either the *N*-methyl-D-aspartate (NMDA) receptor–Ca^{2+} ionophore complex after glutamate binds to it or through voltage-sensitive Ca^{2+} channels (Ghosh and others 1994). Therefore, at least some Fos observed with mating is a result of glutamatergic activity. Similarly telling are studies using microinjections of glutamate directly into the MPOA. These showed that microinjections increased erections (Giuliano and others 1996) and the urethrogenital reflex (Marson and McKenna 1994) in rats. Conversely, administering dizocilpine (MK-801), an antagonist to the NMDA glutamate receptor, into the MPOA inhibited 50-kHz ultrasonic vocalizations that were evoked in anticipation of a receptive female (Brudzynski and Pniak 2002). This suggests that glutamate in the MPOA plays a role in both appetitive and consummatory aspects of behavior, perhaps, again, depending on the location of its release. Despite the evidence implicating glutamate in the activation of the MPOA, it was still not clear whether this was indeed the case.

Glutamate, the Medial Preoptic Area, and Male Sexual Behavior

To answer this question, in vivo microdialysis experiments were conducted in rats. The experiments were designed to determine whether levels of glutamate in the MPOA change with mating. Microdialysis samples were collected from the MPOA of freely moving, sexually experienced, adult rats during interactions with sexually receptive females. The samples were analyzed using high-performance liquid chromatography (HPLC). Results showed that glutamate release increases with mating. Specifically, levels increased ~300% of baseline in samples collected when animals ejaculated; levels then dropped precipitously in samples collected during the period following ejaculation (Dominguez, Gil, and others 2006; Fig. 2*A* and *B*). The decrease in glutamate following ejaculation was highly correlated with the length of time spent in quiescence, $r = 0.76$

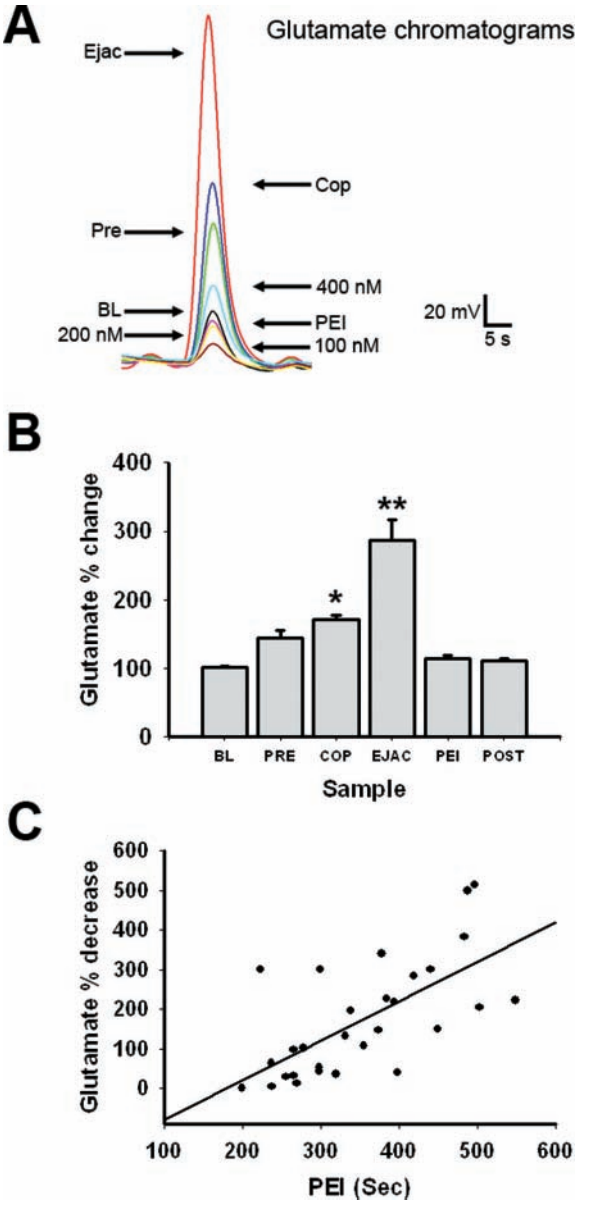

Figure 2. Levels of extracellular glutamate in the medial preoptic area of male rats change during mating. (**A, B**) Levels of glutamate were higher in samples collected during copulation (COP) and ejaculations (EJAC), when compared with samples collected with baseline (BL), precopulation (PRE), postejaculation (PEI), and postmating (after removal of the female). Levels dropped significantly after EJAC, during PEI. (**C**) The magnitude of this decrease correlated with the time spent in sexual quiescence of PEI. The figure is from Dominguez, Gil, and others (2006), with permission.

(Dominguez, Gil, and others 2006; Fig. 2*C*). This suggested that a larger decrease in glutamate is associated with a longer postejaculation interval (PEI). In a subsequent experiment, a cocktail of glutamate uptake inhibitors were reverse-dialyzed into the MPOA, while concurrently collecting glutamate and recording behavior. This cocktail prolonged the synaptic life of endogenously released glutamate, while also facilitating the expression of sexual behavior (Dominguez, Gil, and others

2006). Namely, males receiving the inhibitors displayed more ejaculations, required less time to reach ejaculations, and experienced shorter PEI (Dominguez, Gil, and others 2006), which suggests a biphasic relationship between sexual activity and glutamate in the MPOA. Specifically, levels increased during mating and then dropped after ejaculation. The upward swing represents increased release; perhaps coming from neurons in sensory-relevant regions, whereas the downward swing represents decreased release coupled with rapid uptake of glutamate and increased inhibitory input. This is, of course, only a hypothetical explanation of factors influencing the biphasic changes of glutamate in the MPOA.

Notwithstanding the hypothetical nature of this model, it is possible to speculate on what influences this pattern. For example, increase central serotonin is known to inhibit copulation in males (Hull and others 2004). We know that ejaculation-related serotonin released in the lateral hypothalamus (LH) inhibits dopamine (DA) activity in the nucleus accumbens (Lorrain and others 1999). Perhaps similar mechanisms also influence ejaculation-related glutamate in the MPOA. This conclusion is reasonable, especially because the MPOA is a recipient of input from the LH (Simerly and Swanson 1986). To conclude that decreases in glutamate are influenced by rapid uptake mechanisms is also reasonable, perhaps even necessary. This is because there is no known enzyme that metabolizes glutamate extracellularly (Danbolt 2001). Consequently, the only mechanism for removing glutamate is via high-affinity transporters present in glia and neurons. Without rapid removal, glutamate would accumulate and neurotoxicity and pathological conditions would quickly develop (Choi 1988; Danbolt 2001).

Regarding the upward swing of glutamate preceding ejaculation, this likely reflects increased glutamatergic input from regions integrating sex-relevant sensory information; the medial amygdala (MeA) and bed nucleus of the stria terminalis (BNST) are likely sources. This is evidenced by several reports: 1) sex-relevant chemosensory stimulation and the act of copulation increases activity in the MeA and BNST (Pfaus and Heeb 1997); 2) producing lesions in these regions inhibits mating and mating-induced Fos in the MPOA (Baum and Everitt 1992); 3) a quarter of cells activated by mating in the MeA of gerbils contained glutamate (Simmons and Yahr 2003); 4) stimulation of the MeA increased DA release in the MPOA (Dominguez and Hull 2001), which was also observed in response to exogenous glutamate (Dominguez and others 2004); and finally 5) at least some input coming from the MeA/BNST is glutamatergic (Kocsis and others 2003). This suggests that the MeA/BNST continuum influences glutamate release in the MPOA. It is important to note that there are several other possible sources of glutamate into the MPOA, other than the MeA/BNST, inasmuch as most terminals containing vesicular glutamate transporters did not colocalize with anterograde tract tracers coming from these regions (Dominguez and others 2003). The nature and influence of these other sources is still being determined.

Once released, glutamate changes postsynaptic activity by acting on several receptor subtypes. They are divided into two groups, the metabotropic and ionotropic receptors. Metabotropic receptors are seven transmembrane domain G protein–coupled receptors that mediate slower transmission. Ionotropic receptors are cation-specific channels that mediate faster transmission. Ionotropic receptors are subdivided into α-amino-3-hydroxy-5-methylsoxazole-4-propionate (AMPA), kainate, and NMDA receptors. Evidence presented to this point indicates that glutamate in the MPOA facilitates the expression of sexual behavior; however, it is not clear which receptors receive the signal responsible for this behavioral response. In the following section particular attention is given to the NMDA receptor; however, this is not to exclude possible influences by other non-NMDA glutamate receptors.

The NMDA receptor is particularly vital to brain function and plays a key role in glutamate transmission (Forrest and others 1994). Activation of this receptor results in a Na^+ and Ca^{2+} influx, which depolarizes the cell and initiates signal transduction cascades altering synaptic strength and connectivity (Dingledine and others 1999; Ozawa and others 1998). Once activated, receptor function is enhanced by phosphorylation via protein kinases, including protein kinase A (PKA), protein kinase C (PKC), or calmodulin kinase II (CAMKII). Phosphorylation increases current through the receptor and potentiates its response to later stimulation (Chen and Huang 1992; Dingledine and others 1999; Tingley and others 1997; Zheng and others 1998). As for male sexual behavior, earlier studies showed that systemic administration of MK-801 impaired copulation in male rats (Powell and others 2003), suggesting that NMDA receptors play some role in sexual behavior.

To determine whether NMDA receptors in the MPOA were activated with mating, several histological experiments were performed. These included colocalization of mating-induced Fos with NMDA receptors. Results showed that nearly 100% of cells containing Fos also contained the NR1 subunit of the NMDA receptor (Fig. 3*A*; Dominguez and others 2007). Focus was placed on the NR1 subunit because functional NMDA receptors require expression of this subunit (Dingledine and others 1999; Ozawa and others 1998). Nearly 100% colocalization is a strong indication that cells containing NR1 were activated; however, it does not directly demonstrate activation. This question can be answered more clearly by measuring mating-induced phosphorylation of NMDA receptors in the MPOA, using phosphorylation as a marker of activation. Western immunoblotting and immunohistochemical analyses, using an antibody specific to phosphorylated NR1, revealed that mating phosphorylates the receptor. Tissue collected from the MPOA yielded more dense protein bands for phosphorylated NR1 and a higher number of cells containing phosphorylated protein in mated animals versus controls (Dominguez and others 2007). The time course for mating-induced phosphorylation was also determined. Immunostaining of phosphorylated NR1 was performed in the MPOA of rats that were killed following 5 minutes of mating without display of ejaculation, or 0, 5, 10, 30, or 60 minutes following one ejaculation; a control group did not mate. Results revealed higher numbers of cells containing phosphorylated NMDA receptors in all mated groups compared with controls (Dominguez and others 2007). Finally, unilateral microinjections of MK-801 before rats mated decreased mating-induced Fos and phosphorylation of NR1 in the side receiving the drug, compared with the contralateral side (Dominguez and others 2007). These results strongly indicate that mating-induced glutamate activates

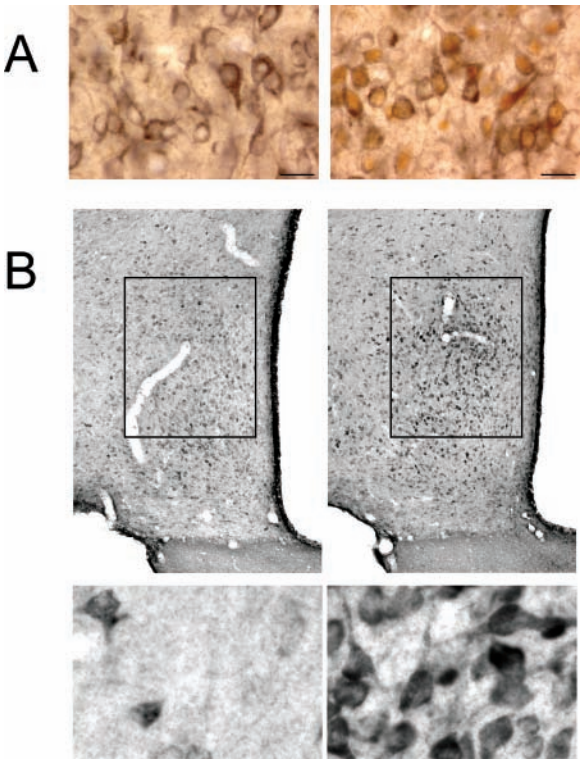

Figure 3. Mating activates *N*-methyl-D-aspartate (NMDA) receptors in the medial preoptic area of male rats. (A) Nearly all cells containing mating-induced Fos also contained NMDA receptors. (B) Mating also increased phosphorylation of NMDA receptors, suggesting activation. The figure is from Dominguez and others (2007), with permission.

NMDA receptors in the MPOA. However, it does not speak to the importance of glutamate for the expression of sexual behavior. This was answered with bilateral microinjections of MK-801 directly into the MPOA. Animals receiving MK-801 displayed fewer ejaculations, required more time to reach an ejaculation, and required more time to reinitiate mating after an ejaculation (Dominguez and others 2007). Together, these data offer behavioral, anatomical, and neurochemical evidence implicating glutamate in the MPOA as an important factor in mating, particularly, although not exclusively, via NMDA receptors.

Glutamate may also facilitate the expression of sexual behavior by mediating release of other neurotransmitters, for example, DA. Several studies point to a facilitative influence of DA in the MPOA on mating (Dominguez and Hull 2005). Evidence in support of this idea includes microinjections of DA agonists into the MPOA, which facilitate copulation (Hull and others 1986; Markowski and others 1994; Pehek, Thompson, and others 1988; Scaletta and Hull 1990), whereas antagonists impaired copulation, genital reflexes, and sexual motivation (Pehek, Warner, and others 1988; Warner and others 1991). Moreover, the presence of a sexually exciting stimulus or copulation itself increased DA release in the MPOA of male rats (Dominguez and others 2001; Hull and others 1995). Interestingly, reverse dialysis of glutamate into the MPOA increased levels of extracellular DA, indicating that DA release in the MPOA is responsive to changes in glutamate (Dominguez and others 2004). Moreover, evidence indicates that glutamate-mediated release of DA in the MPOA occurs via actions of nitric oxide (NO). Specifically, a NO synthase (NOS) antagonist blocked glutamate-evoked DA release (Dominguez and others 2004). These findings are relevant to the topic at hand because increased glutamate also stimulates production of NO. Glutamate acts via NMDA receptors to open Ca^{2+} channels, which leads to a Ca^{2+} influx. This influx activates calcium calmodulin, which activates NOS. Thus, activation of NMDA receptors may enhance dopaminergic action directly through depolarization and indirectly via NO. Of course, this is a unidirectional explanation of possible underlying mechanisms involved in this interaction. Conversely, it is also possible that DA mediates glutamate's action. Synergistic interactions between glutamate and dopamine are a topic of great interest and the idiosyncrasies of this relationship throughout the CNS are still being investigated (Carlsson and others 2004; de Bartolomeis and others 2005; Lange and others 1997; Meltzer and others 1997; Morelli 1997; Schmidt 1998; Sesack and others 2003). Likewise, the influences of these interactions on sexual behavior are also still being investigated.

Possible Role for Glutamate in Androgen-Mediated Facilitation of Male Sexual Behavior

Regarding sources of glutamate into the MPOA, injections of [^{3}H]D-aspartate revealed that putative sources include the lateral septum, BNST, MeA, the MPOA itself, and paraventricular, suprachiasmatic, ventromedial, arcuate, ventral premammillary, supramammilary, and thalamic paraventricular nuclei (Kocsis and others 2003). It is noteworthy that this list includes regions activated by sexually relevant stimuli and regions that are sensitive to stimulation by androgens, particularly the MeA and BNST. The idea that the MeA/BNST continuum is a possible source of glutamate to the MPOA is in agreement with observations that some anterogradely labeled axons from the MeA and many from the BNST were immunoreactive for the vesicular glutamate transporter, an indicator of glutamatergic terminals (Dominguez and others 2003). An appreciation of the relationship between the amygdala and hypothalamus and the role of these connections in mediating the release of glutamate in the MPOA should prove beneficial when trying to understand mechanisms via which androgens work in the CNS to facilitate sexual behavior. For instance, circulating testosterone reduces the refractory period of neurons in the MeA/BNST continuum, particularly those that project to the MPOA (Kendrick and Drewett 1979). Therefore, it is conceivable that testosterone facilitates sexual behavior, in part, by increasing the firing rate of glutamate-producing neurons projecting into the MPOA. A hypothetical model that integrates these findings is as follows: The presence of sexually exciting stimuli or the act of copulation itself activates glutamate-containing neurons in the MeA/ BNST. These neurons release glutamate thereby stimulating the MPOA at least in part via NMDA receptors. Testosterone facilitates sexual behavior by priming glutamate-containing neurons in this network. Such a model takes into account sexually relevant chemosensory stimulation and neuroendocrine mediation of mating-induced activity in the

MeA, BNST, and MPOA. Conversely, studies also show that glutamate directly mediates neuroendocrine activity (Mahesh and Brann 2005). An effect of glutamate on aromatase, the enzyme that converts testosterone to estradiol, is an example of such an interaction. Increased levels of glutamate influence Ca^{2+}-dependent phosphorylation of aromatase; this phosphorylation quickly suppresses enzymatic activity (Balthazart and others 2001, 2003). Consequently, changes in levels of glutamate during mating may impact rapid hormone action in the MPOA by acting on aromatase; this influences the expression of sexual behavior in the order of minutes (Balthazart and others 2006; Balthazart and Ball 2006; Cornil and others 2006). When combining these studies, it becomes apparent that a comprehensive model of glutamate-hormone interaction should reflect bidirectional influences, in which hormones mediate glutamate activity, as proposed by the model presented here, and where glutamate also mediates endocrine function to stimulate behavior.

Possible Implications

The idea that glutamate in the MPOA is important for male sexual behavior holds implications for behavioral changes occurring with sexual experience and for sexual dysfunctions. Compared with naïve animals, sexually experienced animals display increased sexual efficiency. Experienced male rats, for instance, require fewer mounts and intromissions to achieve ejaculations and less time to mount, intromit, and ejaculate (Bialy and others 2000; Dewsbury 1969; Larsson 1978); they also take less time to resume copulation after ejaculating (Larsson 1959). The physiological changes that accompany this experience-induced enhancement of sexual behavior are not fully understood. It is well established that glutamate, in part via activation of NMDA receptors, plays a major role in various types of neural plasticity, including long-term potentiation (Malenka and Nicoll 1999; Martin and others 2000), the acquisition of bird song (Nordeen 1997), fear conditioning (LeDoux 2000), the fear-potentiated startle response (Miserendino and others 1990), and memory of a novel environment (Carey and others 1998). Activation of NMDA receptors may also play a role in mediating changes that occur with sexual experience. Blocking experience-induced behavioral enhancements with systemic administration of MK-801 (Powell and others 2003) supports this conclusion. However, the location in the brain where NMDA receptors exert this effect is not known. Again, it would be falsely exalting to suggest that only the MPOA mediates changes in behavior occurring with sexual experience. However, when coupling the data described here with the understanding that glutamate is involved in plasticity and potentiation, then it is reasonable to conclude that preoptic glutamate plays some role in mediating experience-induced changes in sexual behavior. Perhaps sexual experience produces neural changes that facilitate activation of the MPOA that then enhance integration of sensory and endocrine signals in the presence of sex-relevant stimuli. In fact, changes of this magnitude have been observed when quantifying IEG products in the MPOA of experienced versus naïve males. This is true in rats (Lumley and Hull 1999) and Japanese quail (Can and others 2007). Similarly, sexual experience increased levels of NOS in the MPOA of male rats, as evidenced by both immunohistochemical and Western immunoblotting assays (Dominguez, Brann, and others 2006). It is interesting to note that behavioral changes occurring with enhanced glutamatergic activity in the MPOA are similar to those observed in sexually experienced males. Male rats receiving glutamate uptake inhibitors required less time and stimulation to reach an ejaculation and also required less time to reinitiate mating (Dominguez, Gil, and others 2006); this is similar to the behavioral changes observed in sexually experienced males. Experiments are currently being performed that elucidate the neural changes that allow for changes in behavior with experience.

A common side effect of therapeutic drugs such as antidepressants (Giuliano 2007; Segraves 2007; Woodrum and Brown 1998) and anticonvulsants (Hamed and others 2006; Montouris and Morris 2005; Smaldone and others 2004) is impaired sexual function. Several studies using infrahuman animal models examined these impairments (Cantor and others 1999; Sukoff Rizzo and others 2008) and showed that the overt effects of antidepressants in the rodent parallel those reported in humans. A role for preoptic glutamate in the regulation of sexual behavior may hold implications for selective serotonin reuptake inhibitors (SSRIs)-induced impairments. Recent studies support this conclusion. Serotonin reversed-dialyzed into the MPOA via a microdialysis probe, while concurrently measuring glutamate and sexual activity, resulted in attenuated glutamatergic response and impaired sexual behavior (Dominguez and others 2005). These findings suggest that one mechanism via which SSRIs impair sexual behavior is serotonin-mediated inhibition of glutamate in the MPOA. Experiments are currently being performed to investigate the relationship between central glutamate and sexual dysfunctions resulting from antidepressants (Dominguez and others 2005) and also anticonvulsants (Westerman and others 2007).

This summarizes several studies indicating an excitatory role for preoptic glutamate in the regulation of male sexual behavior. It is apparent that changes in preoptic glutamate influence sexual activity. These changes are likely mediated by sensory and endocrine stimulation and they hold implications for different aspects of sexual function and dysfunction.

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