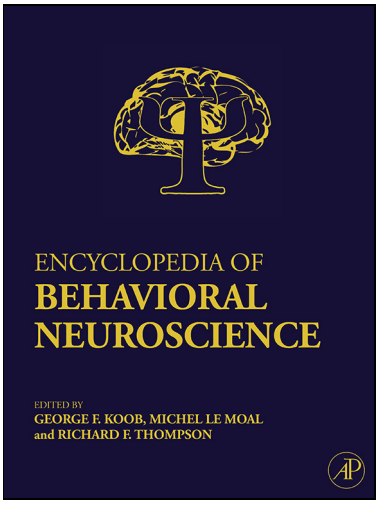

Hull EM (2010) Male Sexual Behavior. In: Koob G.F., Le Moal M. and Thompson R.F. (eds.) *Encyclopedia of Behavioral Neuroscience*, volume 2, pp. 154–162 Oxford: Academic Press.

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Male Sexual Behavior

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Glossary

Corpora cavernosa – A pair of sponge-like tubes along the length of the penis that contain most of the blood during erection; they merge at the head of the penis.
Corpus spongiosum – A sponge-like tube along the bottom of the penis that contains the urethra and enlarges at the distal end to form the glans penis.
Postejaculatory interval – The time after an ejaculation until the next vaginal intromission.
Spinal nucleus of the bulbocavernosus (SNB) – A nucleus in the lumbosacral spinal cord that exerts somatomotor control of genital reflexes through the pudendal nerve, which splits into motor and sensory branches, both of which also carry sympathetic efferents.
Urethrogenital reflex – A model of ejaculation and orgasm elicited in anesthetized, spinally transected male rats by distending the urethra with saline and then releasing the pressure; it is characterized by clonic contractions of the perineal muscles, rhythmic firing of the cavernous nerve, erection, and ejaculation.
Vomeronasal organ – A pair of tunnels along the sides of the nasal cavity that contain receptors for species-specific chemosensory stimuli; it is the first processing stage of the accessory olfactory system.

Patterns of Male Sexual Behavior

Description of Behavioral Elements

Most male mammals mount females dorsally from the rear. The female may assume a reflexive dorsoflexion of the spine, called lordosis. The male then begins pelvic thrusts, which may or may not result in vaginal insertion. During a nonintromissive mount, the male dismounts slowly. Intromission is characterized by a deeper thrust, followed by a springing dismount and genital grooming. Most, but not all, male mammals ejaculate after multiple intromissions. Ejaculation in rodents includes a deeper, longer thrust during which semen is ejected. The male dismounts and begins genital grooming. Male canids begin to ejaculate soon after penile insertion; a swelling at the base of the penis results in a lock of the male to the female. Male ungulates ejaculate immediately upon intromitting. In humans, rhythmic contractions of skeletal and striated perineal muscles accompany ejaculation and are associated with orgasm.

Ejaculation is followed by sexual quiescence, the postejaculatory interval (PEI). In rats, this lasts 5–10 min and is accompanied by 22 kHz ultrasonic vocalizations during the first 75%, called the absolute refractory period, because the male will not copulate in response to any stimulus. During the remaining PEI, the relative refractory period, the male may resume mating in response to nonspecific arousal or a novel female partner. After the PEI, male rats copulate until they reach satiety, often after seven to nine ejaculations. Copulation to satiety increases dopamine (DA) metabolites in the medial preoptic area (MPOA) and nucleus accumbens (NAcc) and enkephalins in the hypothalamus. Androgen receptor density decreases in the MPOA, NAcc, and ventromedial hypothalamic nucleus (VMH).

Sexual Experience

Sexual experience decreases latencies to copulate and to ejaculate. It also may decrease the disruptive effects of a novel environment, various lesions, and castration. Experienced rats have higher levels of nitric oxide synthase (NOS) in the MPOA, greater androgen secretion, and more cells in the MPOA and NAcc activated by ejaculation.

Puberty and Aging

Male rats begin mounting between 40 and 50 days of age, intromitting between 44 and 75 days, and may show the behavioral pattern of ejaculation between 48 and 75 days.

Encyclopedia of Behavioral Neuroscience, 2010, Vol. 2, 154-162

Prepubertal castration prevents copulation, while exogenous testosterone (T) or estrogen (E) can hasten its onset. However, exogenous hormones cannot hasten copulation in male Syrian hamsters. In male rats, T levels start to rise about day 40, with a surge occurring around day 50. However, the T surge occurs after the onset of copulatory behaviors and *ex copula* reflexes. Copulation in male hamsters begins after the increase in T begins, but before the T surge; the lack of pubertal T impairs T-induced mating in adulthood.

Aging in humans, monkeys, and rodents decreases the probability of mating and increases latencies to mount, intromit, and ejaculate. In male rats and humans T levels decline, but exogenous T may only partially restore sexual ability. A decline in estrogen receptors (ER), but not androgen receptors (AR), may mediate the ejaculatory deficit of old male rats. Behavioral deficits in middle-aged rats (18–19 months) may be associated with decreased DA and norepinephrine (NE), and increased serotonin (5-HT), in the NAcc and MPOA.

Sexual Reflexes

Observations during Copulation

In many species, the penis is visible during copulation; however, erections in rodents are very brief and hidden from view. Erection, intromission, and ejaculation are usually inferred from characteristic behaviors, and the female's vagina can be examined for the presence of sperm. Penile pressure and electrical activity in the striated perineal muscles can be measured during copulation; however, these techniques are technically difficult. Therefore, *ex copula* measures of sexual reflexes are often used. However, *in copula* and *ex copula* erections may differ in their hormonal, physiological, and neurochemical regulation.

Ex-Copula Sexual Reflexes

Male rodents occasionally have erections without any obvious sexual stimulus; such erections may be increased by certain drugs or the presence of an inaccessible receptive female. They consist of extension of the engorged glans from the penile sheath and are often accompanied by genital grooming. Reflexive erections can be elicited by manual stimulation in many species. However, such stimulation in rats inhibits erection. Genital reflexes can be elicited in rats or mice by restraining them on their backs and retracting the penile sheath. Pressure around the base of the penis elicits erections and anteroflexions (flips); seminal emission may also occur. The urethrogenital reflex in anesthetized, spinally transected male rats is a model for both erection and ejaculation. The urethra is distended with saline; when the pressure is released, clonic contractions of the perineal muscles occur, with rhythmic firing of the cavernous nerve, erection, and ejaculation. A similar pattern is observed in human climax and rats' ejaculation.

Mechanisms of Erection

Erection of the vascular penes of humans, monkeys, dogs, cats, and rodents results primarily from vascular relaxation, coordinated with striated muscle contraction, whereas the fibroelastic penes of ungulates, such as sheep and goats, are extruded by the penile muscles. Most of the penile shaft comprises the paired corpora cavernosa; the corpus spongiosum surrounds the urethra and enlarges into the glans at the end of the penis. The corpora cavernosa are enclosed by a tough capsule, so when they fill with blood, pressure against the venous outflow traps blood in the penis. Contraction of perineal striated muscles enhances the erection.

Three major pathways control penile erection: the pelvic nerves (mostly parasympathetic, proerectile), the hypogastric nerves (sympathetic, antierectile), and the pudendal nerves (somatosensory and motor). The pelvic nerve exits the lumbosacral spinal cord and travels to the penile corpora and vasculature through the pelvic plexus and cavernous nerve. It also carries some sympathetic axons. The spinal nucleus of the bulbocavernosus (SNB) exerts somatomotor control through the pudendal nerve, which splits into motor and sensory branches, both of which also carry sympathetic efferents. Stimulation of the striated perineal muscles increases rigidity of an erection, but does not result in erection if the penis is flaccid. Sympathetic, primarily antierectile influence arises from two sources. The lumbar splanchnic nerves synapse in the hypogastric plexus, from which hypogastric nerves travel via the cavernous nerve to the penis. Axons from the paravertebral sympathetic chain travel via the pelvic nerve to the pelvic plexus, then through the cavernous nerve to the penis. Tonic sympathetic input keeps the penis flaccid. However, the sympathetic system contributes to erection, perhaps by constricting nonpenile vessels, thereby diverting blood to the penis.

Cellular Mediators of Erection

The main mediator of erection is nitric oxide (NO), a soluble gas produced by nitric oxide synthase (NOS), that acts as both a second messenger and a neurotransmitter. Parasympathetic nerves contain neuronal NOS (nNOS), and the endothelium contains endothelial NOS (eNOS). NO from parasympathetic nerves diffuses into smooth muscle cells and activates guanylyl cyclase, which produces cGMP, which then activates protein kinase G, and to some extent protein kinase A. These enzymes phosphorylate proteins that sequester Ca^{2+}, leaving less in

the cytoplasm and relaxing the smooth muscle. Phosphodiesterase 5 (PDE_5) terminates cGMP activity. Sildenafil citrate (Viagra), tadalafil (Cialis), and vardenafil (Levitra) treat erectile dysfunction by inhibiting PDE_5. The initial increase in blood flow induces shear stress in endothelial tissue, which activates eNOS and prolongs the erection. Erection can also be elicited by vasoactive intestinal peptide, calcitonin gene-related peptide, and prostaglandin E_1.

Ejaculation

Ejaculation depends on coordinated autonomic and somatic responses. Seminal emission includes autonomic activation of the prostate, and ejection involves rhythmic contraction of perineal and pelvic floor striated muscles. Friction on penile skin and intravaginal pressure stimulate seminal drain into the posterior urethra, and chemical and mechanical stimulation of the urethra by the semen triggers expulsion. A central pattern generator in the lumbosacral cord includes a group of galanin-containing neurons that integrate and relay genital sensory and motor signals related to ejaculation. Serotonin (5-HT) from the nucleus paragigantocellularis (nPGi) in the medulla tonically inhibits ejaculation, though intraspinal 5-HT may act through $5\text{-}HT_{1A}$ and $5\text{-}HT_{2C}$ receptors to elicit ejaculation. Dopamine (DA), norepinephrine (NE), acetylcholine (ACh), and oxytocin may also stimulate ejaculation.

Role of Gonadal Steroids

Testosterone (T) and its Metabolites

Male sexual behavior is heavily dependent on T and its metabolites estradiol (E_2) and dihydrotestosterone (DHT). Although steroids are essential for mating in most rodents, they play a more modulatory role in humans. T exerts organizational effects during sex differentiation and activational effects in adulthood. T has primarily slow, genomically mediated effects, although it can also have faster effects through membrane receptors. T levels are higher than necessary to activate sexual behavior; higher levels are needed for sperm production in the testes.

Castration and T Restoration

Plasma levels of T become immeasurable by 24 h after castration, though male rats may continue to copulate for days or weeks. However, intromission latency increases within days, and the number of intromissions before ejaculation actually decreases; thus, T may increase intromissions preceding ejaculation, thereby increasing sperm in the ejaculate and triggering a progestational state in the female. Half to two-thirds of men who were castrated as treatment for sexual offenses lost sexual interest rapidly, while others reported gradual decreases. Long-term castrated rats require 5–10 days of T to restore mating; 5–7 weeks are required for hamsters. However, in rats, T affected MPOA firing within minutes, and rats and mice started mounting in 35 and 60 min, respectively. Thus, steroids activate brain areas within minutes but require slower genomic effects to restore copulation fully. Compared to copulation, e*x copula* reflexes are lost more quickly after castration and restored more rapidly after T replacement. In spinally transected rats, reflexive erections were decreased 24 h after castration and restored by 24 h of T replacement. Spinally intact males required an additional day of T, probably to reduce supraspinal inhibition.

Role of T Metabolites

T is primarily a prohormone, being converted in target organs to either E_2 or DHT. There are at least two E receptors, ERα and ERβ. Both T and DHT bind to the AR, but DHT binds with greater affinity. Some target cells produce both E_2 and DHT and have both ERs and ARs. The relative importance of estrogenic and androgenic stimulation is species specific. In castrated rats and mice, E_2 can reinstate most aspects of copulation. DHT, which cannot be aromatized to E_2, cannot. However, E is usually insufficient to fully maintain or restore copulation. Thus, stimulation of both ER and AR is necessary to fully restore mating. In addition, DHT is both necessary and sufficient to maintain and restore *ex copula* reflexes in rats. Gonadally intact males that lack ERα (ERα knockout mice, ERαKO) or aromatase (ArKO) have almost no ejaculations. However, treatment with T and a dopamine agonist in ERαKO mice restored copulation. Aromatization is not required in other species, including rabbits, guinea pigs, hamsters, deer mice, and monkeys. However, males normally produce both classes of hormone, which together promote all aspects of mating. Men with erectile dysfunction have relatively normal T levels. However, T or DHT treatment of hypogonadal men or aging men with moderate decreases in T can improve erectile function.

Systemically and Intraventricularly Injected Drugs

Dopamine (DA)

In the late 1960s, the DA precursor L-Dopa was found to increase libido and sexual potency in Parkinsonian patients. In rats, mice, and men, systemically administered DA agonists facilitate, and DA antagonists impair, copulation and sexual motivation. There are two families of DA receptors: the D_1-like family activate adenylyl cyclase

and comprise the D_1 and D_5 subtypes; the D_2-like family consists of D_2, D_3, and D_4 subtypes that inhibit adenylyl cyclase. D_1-like agonists increase sexual motivation in rats and mice and facilitate sexual behavior across taxa, including whiptail lizards, geckos, quail, and starlings. The effects of DA agonists are dose dependent; low doses facilitate, and high doses inhibit copulation, perhaps by inducing stereotypic behavior. There are contradictory effects of D_1- and D_2-like agonists on *ex copula* reflexes, due perhaps to lack of selectivity of the agonists.

Norepinephrine (NE)

NE can either facilitate or inhibit male sexual behavior, depending on the dose and receptor subtype activated. Sympathetic axons to the penis promote detumescence. However, increased NE activity, either by blockade of α_2 autoreceptors or stimulation of α_1 adrenoceptors, can increase sexual arousal. The influence of β adrenoceptors is not clear.

Serotonin (5-HT)

5-HT generally inhibits male sexual behavior. Selective serotonin reuptake inhibitors (SSRIs) increase 5-HT in the synapse and impair sexual function in humans and rats. However, 5-HT_{1A} receptor stimulation markedly facilitates male rat ejaculation. 5-HT's inhibitory actions may be mediated by 5-HT_{1B} and 5-HT_2 receptors in rats. In mice, in contrast to rats, both the 5-HT_{1B} and the 5-HT_{1A} subtypes inhibit mating. Stimulation of 5-HT_{2C} receptors can increase erections and inhibit ejaculation in monkeys and facilitate erection in rats.

The fact that the facilitative effects of 5-HT_{1A} agonists on ejaculation are opposite to those of 5-HT itself and that somatodendritic autoreceptors are the 5-HT_{1A} subtype, suggest that 5-HT_{1A} agonists act at those autoreceptors to reduce 5-HT release. However, facilitative effects of 5-HT_{1A} agonists are obtained after infusion into the sites where only postsynaptic receptors are found. Therefore, postsynaptic receptors may mediate the facilitative effects.

Glutamate

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). Low doses of kainic acid, an agonist at α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate glutamate receptors, enhance copulatory behavior in sexually sluggish male rats, but not in good copulators. Systemic injection of an *N*-methyl-D-aspartate (NMDA) antagonist impairs mating in experienced and naïve male rats and blocks the improvement due to noncopulatory exposures to estrous females.

Nitric Oxide (NO)

NO facilitates erection (parasympathetic) but inhibits ejaculation (sympathetic). Neuronal nitric oxide synthase knock-out (nNOS KO) mice have normal penile function due to a compensatory increase in endothelial NOS (eNOS) and ejaculate with fewer mounts and intromissions. Intraperitoneal injection of NO's precursor, L-arginine, enhances copulation in naïve and experienced rats, whereas intracerebroventricular (icv) injection of a NOS inhibitor impairs mating in naïve rats.

Endocannabinoids

Endocannabinoids are retrograde neuromodulators. The cannabinoid CB1 receptor is located almost exclusively at axon terminals, where it inhibits neurotransmitter release. Delta-9-tetrahydrocannabinol (THC) and other endogenous and exogenous CB1 agonists impair copulation in mice and rats, while a CB1 antagonist accelerates ejaculation.

Endogenous Opioids

There are three major classes of endogenous opioid peptides: endorphins, enkephalins, and dynorphins. Exogenous opiates, such as morphine and heroin, impair sexuality in male addicts and in various other species. Furthermore, sexually inactive male rats have increased basal concentrations of several endogenous opioids in the hypothalamus. Endogenous opioids act on μ, δ, and κ receptors, with μ and δ receptors mediating most of the inhibitory effects. Opioid antagonists facilitate sexual behavior in sexually inactive or naïve rats, reverse sexual satiation, decrease ejaculatory threshold, and increase the percentage of ejaculating animals.

However, opioids may also have facilitative effects, depending on dose, brain site, time of the day, and sexual-activity level of the animals. Opioid peptides are apparently released during mating, since physiological mechanisms of analgesia and reward are activated during sexual behavior, and naloxone blocks both. Systemic morphine inhibits reflexive erections and seminal emission; naloxone antagonizes those effects, but a low dose, administered alone, also inhibits erection, suggesting that some opioid activity can facilitate reflexes.

Oxytocin (OT)

OT is released from the posterior pituitary and in numerous brain and spinal sites. Systemic or icv injections of OT facilitate copulation in male rats, and icv injections of an OT antagonist impair or abolish copulation. Systemic OT can reverse the inhibitory effects of chronic fluoxetine, an SSRI. Furthermore, OT in cerebrospinal fluid markedly increases after copulation.

Gonadotropin-Releasing Hormone (GnRH)

GnRH stimulates the anterior pituitary to release gonadotropins. GnRH is released naturally when male rodents encounter female vaginal fluid. It facilitates motivation or copulation in several rodent species and exogenous GnRH restores fertility and sexual activity in hypogonadal men. However, adverse effects of GnRH can result from continuous high doses, which inhibit LH release and gonadal function; endogenous GnRH is released in a pulsatile fashion.

Orexin/Hypocretin

Orexin/hypocretin (orx/hcrt) is produced in neurons of the perifornical lateral hypothalamus that project to monoaminergic nuclei in the midbrain and brainstem and to basal forebrain areas, including the medial preoptic area (MPOA). Orx/hcrt regulates feeding and wakefulness and also enhances male sexual behavior. Orx/hcrt expression is decreased after castration and restored by E_2, and systemic administration of an orx/hcrt antagonist impairs copulation.

Other Neurotransmitters

GABA is the main inhibitory neurotransmitter in the mammalian brain. Systemic administration of GABAergic drugs inhibits male rat sexual behavior, and cerebrospinal fluid levels of GABA increase dramatically during the postejaculatory interval (PEI). Prolactin (PRL), secreted by the anterior pituitary, promotes lactation but has numerous other functions. Hyperprolactinemic patients often have erectile problems and low sexual desire. Plasma PRL levels increase markedly after ejaculation in men and may contribute to postejaculatory refractoriness. Chronically elevated PRL impairs male rat sexual behavior, but short-term PRL has no effect or facilitates copulation. Early studies using high doses of acetylcholine agonists and antagonists produced contradictory results. However, lower doses of nicotine and muscarinic agonists have produced facilitative effects.

Brain Areas and Circuitry

See **Table 1** for a summary of neurotransmitter effects in specific brain areas.

Sensory Inputs

Olfactory bulbs

Volatile odors are transduced by receptors in the nasal mucosa, whose axons project through the cribriform plate to the main olfactory bulb (MOB). Both nonvolatile and volatile species-specific cues are detected in the vomeronasal organ (VNO), located at the base of the nasal cavity and projecting to the accessory olfactory bulb (AOB). Vomeronasal cues are important in rodents, but the VNO and AOB are regressed in humans. Olfactory bulbectomy abolishes mating by male Syrian hamsters, though the relative importance of the main and accessory systems is not clear. Male rats are less dependent on chemosensory

Table 1 Brain areas and neurotransmitter effects on male sexual behavior

	MeA	*MPOA*	*PVN*	*Mesolimbic Tract*	*LH*	*nPGi*	*Spinal Cord*
Dopamine		↑ cop. D1 ↑ erec. D2 ↑ ejac.	↑ erec., ejac	↑ cop.			↑ erec., ejac.
Norepinephrine							↑ erec., ejac.
Serotonin	1A ↑ cop.	1A ↑ cop. 1B ↓ cop.	1A ↑ cop.		↓ cop.	↓ cop.	1A, 2C ↑ cop
Acetylcholine		↑ cop.					↑ erec., ejac.
Oxytocin		↑ cop.	↑ erec., ejac.				↑ erec., ejac.
Glutamate		↑ cop.	↑ erec., ejac.				
GABA		↓ cop.					↓ erec., ejac.
Opioids		Lo dose ↑ Hi dose ↓ cop.	↓ erec.	↑ DA			
Nitric oxide		↑ cop.	↑ erec., ejac.				
hypocretin/orexin		↑ cop.			↑ cop.		
Galanin/Cholecystokinin/ Neurokinin							↑ ejac.

MeA, medial amygdala; MPOA, medial preoptic area, PVN, paraventricular nucleus, LH, lateral hypothalamus; nPGi, nucleus paragigantocellularis; GABA, gamma amino butyric acid; cop., copulation; erec., erection; ejac., ejaculation

stimuli, though bilateral bulbectomy severely compromises mating in some males. In rats and mice, the main olfactory system is more critical than the vomeronasal system. Odor cues result in neurons immunoreactive for the immediate early gene product c-Fos (Fos-ir) in the MOB and AOB of male hamsters, rats, and mice, whether they can mate or not; however, only experienced copulators show Fos-ir in all downstream structures of the VNO.

Amygdala

The amygdala is a collection of nuclei that contribute to learning, motivation, and fear (central nucleus and basolateral division) and chemosensory processing and social behaviors (corticomedial division). The medial amygdala is larger in males than in females, and the corticomedial region is critical for integration of chemosensory, genitosensory, and hormonal stimuli. Corticomedial lesions impair copulation, with the severity dependent on the specific location and species. The posterodorsal medial amygdala (MeApd) is one site at which serotonin 5-HT_{1A} agonists facilitate copulation. A subregion of the MeApd is linked to sexual satiety. Fos-ir in the MeA, but not the MPOA, of male rats correlates with the length of the PEI, suggesting that some neurons there contribute to postejaculatory quiescence. T or E, but not DHT, implants in the MeA of castrated rats and hamsters delay the loss of, or partially restore, sexual behavior. However, DHT implants in male rats treated with subthreshold systemic E can restore mating. Thus, both ARs and ERs in MeA contribute to mating.

A major output of the MeA is to the MPOA. Unilateral lesions of the MPOA impair, but do not abolish copulation in male rats or gerbils; however, contralateral lesions of the MeA and MPOA severely disrupt mating. Chemical stimulation of the MeA increases MPOA DA release similar to that during copulation, and microinjection of a DA agonist into the MPOA restores copulation abolished by large lesions of the MeA. Small radiofrequency MeA lesions do not affect basal MPOA DA but do eliminate the DA response to a female and also impair copulation. Thus, MeA activity increases MPOA DA in anticipation of and during mating. The MeA of rats contains no dopaminergic neurons, but MeA efferents may directly or indirectly activate MPOA DA cell bodies or terminals.

Bed nucleus of the stria terminalis (BST)

Axons from the MeA either travel directly to the MPOA or synapse in the BST, which then relays information to the MPOA and other sites. However, the BST does more than simply relay input. The posteromedial BST has abundant steroid receptors and is important for male sexual behavior. Males also have more BST neurons that contain arginine vasopressin, galanin, and the aromatase enzyme, which converts testosterone to estradiol. In male rats, hamsters, and gerbils, copulation, or to a lesser extent, exposure to female odors, elicits Fos-ir in the BST. However, mating decreases Fos-ir in male macaques.

Central tegmental field and subparafascicular nucleus of the thalamus (CTF/SPF)

The midbrain tegmentum, MPOA, MeA, and anterior hypothalamus are reciprocally connected. Subregions of the tegmentum have been called the central tegmental field (CTF) or dorsolateral tegmentum (DLT). The CTF/DLT is dorsal to the lateral half of the substantia nigra and may include the adjacent subparafascicular nucleus (SPF) and several other nuclei. Bilateral lesions of the CTF in rats impair mating but not sexual motivation. The medial parvocellular division of the SPF (SPFp) relays somatosensory input from the genitals to the MPOA and MeA. In male rats, the SPFp receives projections from lumbar spinothalamic neurons that are essential for ejaculation. Fos-ir is increased in the CTF or SPFp only after ejaculation in rats, gerbils, hamsters, and musk shrews. In men, ejaculation stimulates blood flow in the SPFp. In addition, electrical stimulation of the CTF facilitates mating in rats. SPFp neurons contain ARs, and many AR-ir neurons that project to the MPOA express ejaculation-induced Fos-ir. Thus, the SPFp and CTF convey ejaculation-related somatosensory input to higher brain areas.

Major Integrative Sites

Medial preoptic area (MPOA)

The MPOA is a critical integrative site for male sexual behavior. It receives indirect input from all sensory modalities and sends reciprocal connections to modify processing of that input. Steroid receptors in the MPOA and its afferents bias input to favor sexually relevant stimuli. Efferents to hypothalamic, midbrain, and brainstem nuclei regulate somatomotor or autonomic patterns and motivational states. A medial periventricular zone regulates neuroendocrine function, and a medial zone, including the medial preoptic nucleus (MPN) and posterodorsal preoptic nucleus (PdPN), controls male sexual behavior and maternal behavior. Large MPOA lesions abolish copulation in numerous species. More severe deficits occur with more caudal lesions that include part of the anterior hypothalamus. MPOA lesions also diminish, but do not eliminate sexual motivation. Stimulation of the MPOA facilitates sexual behavior in numerous species, but does not reverse sexual satiety. Repeated electrical stimulation of the MPOA in noncopulating male rats can lead to mating on subsequent stimulation-free tests. In anesthetized rats, MPOA stimulation increases intracavernous pressure and can elicit the urethrogenital reflex, even without urethral stimulation. Axons from the MPOA do not project directly to the lumbosacral cord, but

stimulate downstream sites that then control the reflexes. However, the MPOA is not necessary for genital reflexes.

Steroid implants in the MPOA facilitate sexual behavior in castrated rats, ferrets, birds, and lizards, but do not completely restore mating. Aromatization of T in the MPOA is important for T's facilitative effects. T implants in castrated quail facilitated copulation correlated with induction of aromatase immunoreactivity (ARO-ir) in the preoptic area. Sexual preference in rams is also related to aromatization in the MPOA. Rams that prefer to mate with other males have lower levels of serum T and E and decreased MPOA aromatase activity, compared with those that prefer to mate with females. In contrast to E, DHT in the MPOA of castrated male rats is relatively ineffective, unless accompanied by subthreshold systemic E or DHT. However, an antiandrogen in the anterior MPOA impairs copulation, but not partner preference; in the posterior MPOA it impairs motivation, but not performance.

Neurons of the periventricular DA system, along the third ventricle, project laterally into the MPOA and anterior hypothalamus. MPOA microinjections of classic D_1/D_2 agonists and antagonists facilitate and inhibit, respectively, copulation, *ex copula* reflexes, and sexual motivation. A DA agonist in the MPOA can restore copulation in males with large amygdala lesions. D_1-like agonists facilitate parasympathetically mediated erections and the early phase of copulation, and D_2-like drugs produce dose-dependent effects. Low doses disinhibit reflexes (decrease latencies), but high doses of D_2-like agonists, or of D_1 antagonists, shift autonomic balance toward sympathetically mediated ejaculation. It is not clear whether these dose-dependent effects are mediated by different receptor subtypes or populations of neurons with different levels of tonic inhibition.

Large doses of serotonin (5-HT) microinjected into the MPOA inhibit copulation, in part through 5-HT_{1B} receptors. However, reverse-dialysis of a 5-HT_{1A} agonist into the MPOA facilitates mating and increases both DA and 5-HT levels. Some of these facilitative effects are mediated by increased extracellular DA, stimulating D_2-like receptors. There are numerous GABAergic neurons in the MPOA of male rats, and some mating-activated neurons in male gerbils contain GABA. Enhancing MPOA GABAergic transmission impairs copulation in rats and blocking either GABA synthesis or $GABA_A$ receptors enhances mating. However, a $GABA_A$ antagonist did not reverse sexual satiation. Microinjection of low doses of a μ or a κ opioid agonist into the MPOA can facilitate copulation, and a μ antagonist prevents induction of sexual reinforcement. However, high doses of μ agonists impair copulation. Microinjection of NE facilitates sexual behavior, and decreasing NE levels by stimulating autoreceptors impairs copulation.

Reverse-dialysis of the NO precursor L-arginine into the MPOA facilitates copulation, and a NOS inhibitor impairs it, but increases the number of *ex copula* seminal emissions. NO also mediates the facilitative effects of repeated exposures to an inaccessible estrous female. Castration in both rats and hamsters decreases NOS-ir in the MPN; there is also less NOS-ir in ERαKO mice. nNOS is co-localized with both ERα and AR in the MPOA of rats, mice, and hamsters. Reverse-dialysis of an NO donor into the MPOA of castrated rats maintained on systemic DHT (to maintain genital and sensory structures) fully restored copulation in half the animals. NO's effects are at least partially mediated by cGMP.

Glutamate microinjections into the MPOA of anesthetized male rats elicit erectile responses and also the urethrogenital reflex without genital stimulation. Conversely, an NMDA antagonist inhibits mating in male rats. Nearly all neurons in the MPOA that show mating-induced Fos-ir contain NMDA receptors, and an NMDA antagonist decreases mating-induced Fos-ir. Thus, glutamate in the MPOA facilitates mating, at least in part through NMDA receptors.

Orx/hcrt, acetylcholine, and prostaglandin E_2 in the MPOA also exert facilitative effects. Some MPOA neurons increase their firing rates only before male rats or monkeys copulate; others increase only during mating. DA levels in male rats rise in the presence of an inaccessible female and increase further during mating; the DA response shows both anatomical and behavioral specificity. Both basal and female-stimulated DA levels are hormone dependent, with E mediating most, but not all, of the facilitative effects of T on DA levels and behavior. Tissue (stored) DA levels are actually higher in castrates than in intact males, suggesting that castration impairs DA release, but not synthesis. Release is controlled by NO, and T and E positively regulate MPOA NOS-ir. MeA lesions block the DA response to a female but do not affect basal levels; those males show suboptimal mating ability. Similarly, olfactory bulbectomy in hamsters impairs both copulation and MPOA DA release.

Copulation increases Fos-ir in the MPOA of male rats, gerbils, hamsters, and mice. At least some of the Fos-ir is in AR-containing neurons. Previous sexual experience enhances Fos-ir to sexual stimuli in rats and hamsters. Efferents from the MPOA project to other areas of the hypothalamus, midbrain motivation and somatomotor regions, and midbrain and brainstem areas that project to the spinal cord. These connections are mostly reciprocal, allowing downstream sites to influence their own input. Output to the nPGi may disinhibit genital reflexes, while other efferents may activate autonomic areas that regulate erection and ejaculation.

Mesocorticolimbic and Nigrostriatal DA Tracts

DA cell bodies in the VTA send axons to the NAc and mPFC; this mesocorticolimbic tract is critical for motivated behaviors. DA is released in the NAc both before and during copulation. Sexual behavior activates both DA and non-DA neurons in the VTA, apparently mediated by endogenous opioids, which inhibit GABAergic interneurons, thereby releasing DA cells from tonic inhibition. The mPFC sends largely glutamatergic axons back to VTA, providing positive feedback. mPFC axons also contact the NAc, MPOA, BST and subparafascicular nucleus (SPF). Lesions of the mPFC, VTA, and NAc impair sexual arousal. Stimulation of the dorsal VTA facilitates, but ventral stimulation inhibits, copulation. Mating induces Fos-ir in the NAc and VTA, and sexual experience enhances Fos-ir in response to estrous females. Decreasing DA activity, by blocking NAc DA receptors or stimulating VTA autoreceptors, slows motor behavior and may decrease sexual motivation.

The nigrostriatal DA tract originates in the substantia nigra (SN) and projects to the dorsal striatum. DA is released only after copulation begins, suggesting greater importance for motor activation than motivation. Bilateral SN lesions slow copulation and decrease ejaculations.

Paraventricular nucleus of the hypothalamus (PVN)

The PVN integrates endocrine and autonomic functions. Parvocellular neurons project to several brain areas and the spinal cord, and magnocellular neurons release OT and vasopressin from the posterior pituitary. Axons projecting to the spinal cord release several transmitters, including OT, vasopressin, and DA. Input to parvocellular PVN includes DA from periventricular neurons and NE and 5-HT from the brainstem. The PVN is important for noncontact erections and seminal emission, but is less critical for reflexive erections and copulation.

Microinjection of DA (especially D_4) agonists, OT, NO donors, or NMDA elicits drug-induced erections, increases reflexive erections and seminal emissions, and increases intracavernous pressure in anesthetized rats. Both noncontact erections and copulation are accompanied by increases in DA and NO. Intra-PVN morphine inhibits both noncontact erections and the NO increase. Sexually competent male rats have more OT mRNA and less opioid mRNA in the PVN than do impotent males, and NOS and OT are co-localized. The PVN projects to the hippocampus, lumbosacral spinal cord, and other areas, including the nPGi, where terminals form close appositions to serotonergic neurons that inhibit genital reflexes.

Lateral hypothalamus (LH)

The LH contributes to autonomic, endocrine, and emotional responses. Electrical stimulation induces copulation in male rats, and lesions impair mating. 5-HT in the anterior LH (aLH) delays and slows copulation and decreases basal and female-elicited DA release in the NAc. 5-HT levels are increased during the PEI. The aLH contains orx/hcrt neurons, which contribute to arousal and reward and are activated by copulation. 5-HT in the aLH may inhibit copulation by inhibiting orx/hcrt neurons, which would eliminate their facilitation of VTA DA cell firing.

Ventromedial hypothalamus (VMH)

The VMH, known primarily for its role in female lordosis, may also influence males. It has numerous ERs and ARs and receives genital and chemosensory input. Mating induces Fos-ir in the VMH of rats and gerbils, but not in musk shrews, hamsters, mice, ferrets, or macaques.

Major Motor Outputs

Midbrain periaqueductal gray (PAG)

PAG lesions blocked elicitation of the urethrogenital reflex by MPOA electrical stimulation. There are numerous ERs and ARs in the PAG, and afferents from the MPOA end near ER- and AR-ir neurons, some of which project to the nPGi. Thus, hormones can affect control of the nPGi by the MPOA through the PAG.

Nucleus paragigantocellularis of the medulla (nPGi)

Much of the supraspinal inhibition of genital reflexes arises from the nPGi. Lesions facilitate copulation and reflexive erections and allow the urethrogenital reflex to be elicited without spinal transection. They also increase the number of ejaculations preceding satiety. Electrical stimulation activates sympathetic fibers in the pudendal nerve. Most nPGi axons to the lumbosacral cord contain 5-HT, which suppresses the urethrogenital reflex.

Spinal cord

Erection is elicited by inhibiting the thoracolumbar sympathetic antierectile pathway and stimulating the proerectile parasympathetic sacral and pudendal pathways. A central pattern generator for ejaculation in the lumbosacral cord includes neurons that contain galanin, cholecystokinin, and neurokinin receptors. Stimulation of these neurons elicits seminal emission followed by expulsion. Although 5-HT is primarily inhibitory, 5-HT_{1A} and 5-HT_{2C} agonists facilitate the urethrogenital reflex. Cerebrospinal fluid levels of GABA, and to a lesser extent glutamate and aspartate, increase markedly after ejaculation. GABA may inhibit, and glutamate, DA, NE, and ACh facilitate, sexual reflexes at the spinal level.

Sexual Behavior in the Context of Mammalian Social Behavior

Brain areas that control male sexual behavior influence other social behaviors as well, including female sexual behavior, maternal behavior, aggression, and territorial marking. Most of those areas, except the midbrain, contain abundant steroid receptors, and all influence more than one behavior. Perinatal, adolescent, and adult hormones can provide a bias toward sexually dimorphic responses to social stimuli. It is not clear whether the same neurons within a structure contribute to more than one behavior, or whether neurons specific for one behavior lie among those specific for other behaviors. However, there are common themes underlying the various social behaviors and the neural mechanisms that control them.

See also: Animal Models of Sexual Function; Hormonal Contributions to Arousal and Motivation; Mating Behavior; Sexual Motivation.

Further Reading

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