1 Male Sexual Behavior

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Chapter Outline

Glossary

g9000 **anteroflexion** Elevation of the penis elicited by pressure around the base of the penis.

g9005 **noncontact erection** Erection in response to the sight or smell of an estrous female.

g9010 **reflexive erection** Erection elicited in rats and mice by pressure around the base of the penis.

g9015 **urethrogenital reflex** Synchronized perineal muscle contractions elicited by distension of the urethra, followed by release of the distension; a model of orgasm.

s0005 # 1.1 Patterns of Male Sexual Behavior

s0010 ## 1.1.1 Description of Behavioral Elements

p0005 Male sexual behavior comprises a complex pattern of genital and somatomotor responses, elicited, directed, and maintained by external and internal signals. It includes copulation as well as precopulatory behaviors that allow the male to detect and locate a mate, assess her potential mating appropriateness, and stimulate a receptive response.

s0015 ### *1.1.1.1 Precopulatory behaviors*

p0010 Precopulatory behavior may consist simply of anogenital investigation or may include highly elaborate behavioral patterns, depending on the species. Male and female rodents show an initial period of mutual anogenital investigation; they also emit ultrasonic vocalizations of 50 kHz, which are mutually arousing (Geyer and Barfield, 1978; Pomerantz and Clemens, 1981). Males engage in urine marking (Meisel and Sachs, 1994). Receptive females will solicit mating from the male by characteristic proceptive behaviors, and the male will pursue and mount her.

s0020 ### *1.1.1.2 Copulatory behavior*

p0015 Male rodents exhibit a highly stereotyped copulatory pattern, shaped by three distinct behavioral motor patterns: mount, intromission, and ejaculation.

s0025 #### 1.1.1.2(i) Mounts

p0020 Almost all male mammals mount females dorsally and from the rear, posing his forelegs over the female's back and with his hindfeet on the ground. The female may assume a lordosis posture, a reflexive dorsiflexion of the spine, accompanied by deflection of the tail to the side. The male then begins anteroposterior pelvic thrusts (19–23 Hz) (Beyer et al., 1981) that induce or intensify the female's receptive posture. During a nonintromissive mount, the male does not achieve penile insertion and dismounts the female slowly.

s0030 #### 1.1.1.2(ii) Intromissions

p0025 Intromission, the defining event of copulation, refers to intravaginal penile insertion. The male mounts the female, performs pelvic thrusting, and suddenly displays a deeper thrust, with a mean duration of 200–300 ms (Beyer et al., 1981), that coincides with vaginal penetration, followed by an abrupt backward dismount and grooming of his genitalia.

s0035 #### 1.1.1.2(iii) Ejaculation

p0030 Most mammals achieve the ejaculatory threshold after multiple intromissions. Ejaculation in rats starts with an intromission but includes a deeper, longer thrust (750–2000 ms) (Beyer et al., 1981) that coincides with seminal ejection. The male then raises his forelegs and dismounts slowly, then typically grooms himself. Mice show essentially the same ejaculatory pattern, except that during ejaculation, they may freeze before dismounting. Male canids begin ejaculating soon after penile insertion and develop a swelling at the base of the penis, which results in a lock of the male to the female (Beach, 1969). Male ungulates also ejaculate immediately upon intromitting (Lott, 1981). Rhythmic contractions of skeletal and striated perineal muscles usually accompany ejaculation and are associated with orgasm in humans.

s0040 #### 1.1.1.2(iv) Postejaculatory behavior

p0035 The most patent effect of ejaculation is a period of sexual quiescence: the postejaculatory interval (PEI). In rats, refractoriness lasts 5–8 min after a first ejaculation and increases with each successive ejaculation. During the initial 75% of the PEI, the male emits 22 kHz ultrasonic vocalizations and will not copulate in response to any stimulus; for that reason, it is called the absolute refractory period (Barfield and Geyer, 1975). The remaining 25% of the PEI, the relative refractory period, is no longer accompanied by vocalizations, and its duration can be reduced if the male is subjected to nonspecific arousing stimuli, like a mild electrical shock (Barfield and Sachs, 1968) or a novel female partner (Zucker and Wade, 1968). After the PEI, male rats resume pursuance and mounting of the female. Mice resume sexual activity after 1–24 h, depending on the mouse strain, while hamsters have much shorter PEIs, from a few seconds to 1.5 min (reviewed in Burns-Cusato et al. (2004), Hull and Dominguez (2007), and Meisel and Sachs (1994)). During successive ejaculatory series, the duration of the PEI increases and the number of pre-ejaculatory intromissions decreases (Rodríguez-Manzo and Fernández-Guasti, 1994).

1.1.2 Sexual Satiety s0045

p0040 When allowed to copulate without restriction, male rats will show approximately seven ejaculations before reaching sexual satiety, which may last up to 3 days (Rodríguez-Manzo and Fernández-Guasti, 1994). Twenty-four hours after reaching satiety, male rats may show a complete absence of sexual activity or may execute one ejaculatory series without recovery (Rodríguez-Manzo and Fernández-Guasti, 1994). Sexual satiety has also been described in hamsters (Beach and Rabedeau, 1959), mice (Dewsbury, 1983), and rhesus monkeys (Bielert and Goy, 1973).

p0045 Copulation to satiety in rats increases dopamine (DA) metabolite levels in the medial preoptic area (mPOA), which remain elevated during the first 48-h period of sexual inhibition (Mas et al., 1995a), while nucleus accumbens (NAc) DA levels increase during copulation to exhaustion (Fiorino et al., 1997). The hypothalamic content of enkephalins is also increased in sexually satiated rats for at least 48 h after sexual exhaustion (Rodríguez-Manzo et al., 2002a). Androgen receptor density is reduced in the mPOA, NAc, and ventromedial hypothalamic nucleus (VMH), but not in the bed nucleus of the stria terminalis (BNST), of satiated rats (Fernández-Guasti et al., 2003). Fos-immunoreactivity (Fos-ir, a marker of neural activation) was increased in regions of the BNST, mPOA, and medial amygdala (MeA) following sexual satiety in male hamsters (Parfitt and Newman, 1998), while in rats the relevant brain structures were the MeA and septum (Phillips-Farfán and Fernández-Guasti, 2007). A contribution of the nucleus paragigantocellularis (nPGi) in satiety can be inferred from the fact that nPGi lesions increased the latency to, and the number of, ejaculations that preceded sexual satiation (Yells et al., 1992).

p0050 Sexual satiety is regulated by norepinephrine (NE) (Fernández-Guasti and Rodríguez-Manzo, 1997; Rodríguez-Manzo and Fernández-Guasti, 1994, 1995b), serotonin (5-HT) (Arnone et al., 1995; Fernández-Guasti and Rodríguez-Manzo, 1997; Rodríguez-Manzo and Fernández-Guasti, 1994), endogenous opioids (Miller and Baum, 1987; Pfaus and Gorzalka, 1987; Rodríguez-Manzo and Fernández-Guasti, 1995a), and DA (Mas et al., 1995b; Rodríguez-Manzo, 1999b), but not gamma-aminobutyric acid (GABA) (Rodríguez-Manzo et al., 2000). Most of the drugs that reverse satiety appear to do so via the NE system (Rodríguez-Manzo and Fernández-Guasti, 1995b), coupled in turn to the DA system, which would be a final pathway for the reversal (Rodríguez-Manzo, 1999b). However, changing the stimulus female after reaching satiety (the so-called Coolidge effect (Fisher, 1962)) interferes with the establishment of the sexual inhibition characteristic of sexual exhaustion, 24 h after satiety; neurotoxic lesions of NE neurons did not interfere with this effect (Rodríguez-Manzo, 1999a).

p0055 In addition to the inhibition of copulation, other responses are also modified by sexual exhaustion. Thus, sexually satiated rats show a general increase in sensitivity to drug actions, including those of yohimbine, 8-hydroxy-2-(di-*n* propylamino) tetralin (8-OH-DPAT), naloxone, and desipramine (Martínez-Mota et al., 2005; Rodríguez-Manzo and Fernández-Guasti, 1994, 1995a). Modifications in the neural control of copulation appear to occur after sexual satiation in rats. Hence, prior to sexual exhaustion electrical stimulation of the mPOA (Rodríguez-Manzo et al., 2000), the dorsal region of the ventral tegmental area (VTA) (Rodríguez-Manzo and Pellicer, 2007), or the NAc (Rodríguez-Manzo and Pellicer, 2003) markedly facilitated sexual behavior, but after sexual satiety the same animals no longer responded to this stimulation. Also, the anxiolytic-like properties of ejaculation, seen in nonexhausted rats, disappeared in the population of sexually satiated males that can ejaculate 24 h after satiation (Rodríguez-Manzo et al., 1999). Thus, copulation to satiation promotes long-lasting changes in male rats' physiology.

s0050 1.1.3 Motivation and Performance

p0060 The motivation to engage in sexual activity may be distinguished from the actual performance of such activity. This distinction is similar to the classic differentiation between appetitive and consummatory behavior (reviewed in Ball and Balthazart (2008), Pfaus (1996), and Sachs (2008)). Appetive behaviors are more variable and bring an individual into close contact with a goal; they are thought to be evidence for an underlying motivational state. Consummatory behaviors are more stereotoyped, species-specific behaviors. Sachs (2008) argues that the terms appetitive and consummatory have fallen from common use in the ethological literature that spawned their introduction. Another problem is that the categories are fuzzy and overlapping; anogenital sniffing of a female may be considered appetitive, although it usually merges seamlessly into mounting, which then occasions intromitting, ejaculation, and postejaculatory behaviors. Each behavior may be considered an appetitive precursor to the next. Nevertheless, it seems clear that certain behaviors, in either the natural environment or the lab, reflect a motivational state that energizes the approach to a goal, which may be a series of overlapping consummatory behaviors. In addition, unlike appetitive, the term motivation has not faded from use; a recent PubMed search resulted in 1330 articles on sexual motivation. We shall consider sexual motivation to comprise factors comparable to an engine that may drive several goal-directed behaviors, while other, hormone-sensitized, stimulus-driven factors steer behavior down specific paths. However, manipulations designed to affect motivation may result in changes that are confounded with effects on sensory or motor processes or the ability to learn new associations.

p0065 Several tests of sexual motivation meet at least some of these criteria. Place preference tests assess whether previous sexual experience in one compartment results in greater time spent in that compartment, even without a stimulus female. Advantages of this test are that little motor ability is required to express a preference, and any drugs administered during conditioning would be metabolized before the test day. However, it does require the male to associate the external stimuli with the positive stimuli of copulation. A similar procedure uses naive males that spend time near either an estrous or nonestrous female (Ågmo, 2003; Amstislavskaya and Popova, 2004). Motor ability to approach the two females is equivalent; however, drugs administered before the test may affect sensory processing. Another test is the obstruction apparatus, which requires a male to cross a barrier or an electrified grid to gain access to a female. This procedure again confounds motivation with motor ability. An additional test utilizes a bilevel apparatus in which a male and female are allowed to copulate; later, the male is placed into the apparatus alone, and the number of times he changes levels,

presumably in search of a female, is used as the measure of motivation (Mendelson and Pfaus, 1989). This test also confounds motivation and motor ability. Yet another test is lever pressing for a secondary reinforcer that was previously paired with copulation (Everitt, 1990). As with the previous tests, this confounds motivation with motor ability and the ability to associate secondary stimuli with copulation. The X-maze or cross-maze records the percentage of trials on which a male chooses a compartment containing an estrous female, with which he can copulate, compared to compartments that are empty or contain other goal objects (Hull et al., 1991; Warner et al., 1991). Motor ability is measured as the speed of running to all goal boxes and the number of trials on which the male does not leave the central start area. This dissociates motor ability from motivation, scored as the percent of trials on which he chooses the female, out of all trials on which he leaves the start area. Copulatory measures can also be assessed. However, drugs administered on the test day may affect sensory processes or memory of cues that mark the female's goal box. A similar test uses a runway and goal compartment, in which a male can enter a female's chamber through a one-way door, copulate, and then leave through a second one-way door leading to the original start box (Beck et al., 2002). Motivation is measured as time in the female's compartment, while run latency, run duration, and the number of copulatory behaviors reflect both motivation and motor ability. As with the X-maze, drugs on the test day may influence sensory processes. Therefore, there are no pure tests of motivation that are free of potential confounds. It would be desirable to have additional tests of sensory and motor abilities, as well as the ability to remember conditioned cues, in order to differentiate these factors from sexual motivation. In the absence of such tests, reports of effects on sexual motivation should include a caveat that effects on measures of motivation may be influenced by changes in sensory, motor, or learning ability.

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1.1.4 Sexual Experience

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Experience plays an important role in the full development and efficiency of sexual behavior. Thus, sexual learning reduces the time to initiate sexual contact and to achieve ejaculation, as well as the amount of stimulation required to ejaculate (Pfeiffer and Johnston, 1994). Sexual experience also improves copulatory ability (Domjan, 1992; Pfaus et al., 2001; Woodson, 2002), sharpens the olfactory interest of male rodents in female sexually related chemosignals (Hayashi and Kimura, 1974; Lydell and Doty, 1972; Pfeiffer and Johnston, 1994; Swaney et al., 2007), and increases male fertility (Domjan et al., 1998; Rastogi et al., 1981). Some of the learning-induced changes in male sexual ability can be interpreted as experience-dependent increases in sexual motivation, since males engage in sexual behavior more rapidly, ejaculate more often, and display shorter PEIs. Furthermore, sexual experience diminishes or eliminates the disruptive effect of a novel environment, seen in sexually naive males (Pfaus and Wilkins, 1995). Increased investigation of female chemosignals has also been suggested to result from the increased sexual interest exhibited by sexually experienced male mice (Swaney et al., 2007), although a recent study in hamsters revealed that, in this species, sexual experience did not affect male preference for a receptive female (Ballard and Wood, 2007). Interestingly, sexually experienced male cats (Rosenblatt and Aronson, 1958), mice (Manning and Thompson, 1976), and hamsters (Constantini et al., 2007), but not rats (Bloch and Davidson, 1968), are less susceptible to the disruptive effects of castration. Sexual experience also attenuates the negative effects of several brain lesions on sexual performance, such as bilateral olfactory bulbectomy in rats (Bermant and Taylor, 1969), ablation of the vomeronasal organ (VNO) in hamsters (Meredith, 1986) and rats (Saito and Moltz, 1986), but not those resulting from zinc sulfate-lesions of the main olfactory epithelium in mice (Keller et al., 2006). The effects of lesions in the medial posterior BNST (Claro et al., 1995) or the sexually dimorphic nucleus of the mPOA (Arendash and Gorski, 1983; de Jonge et al., 1989) on copulation were also greater in sexually naive than in sexually experienced male rats. Enhanced neuronal responses as a result of sexual experience have also been reported. Thus, ejaculation activated more cells, determined by the number of Fos-ir neurons, within the mPOA (Lumley and Hull, 1999) and the NAc (Lopez and Ettenberg, 2002a), of sexually experienced male rats, compared with sexually naive animals. By contrast, in male Japanese quail, sexual experience decreased the expression of another immediate early gene, *egr-1*, in brain areas involved in male sexual behavior, compared to that exhibited by first-time copulators (Can et al., 2007). Sexually experienced rats also had higher levels of nitric oxide synthase (NOS) in the mPOA (Dominguez et al., 2006), as well as a greater androgen secretion (Edinger and Frye, 2007), than sexually naive males. Finally, sexual experience increased precontact ultrasonic vocalizations (50 kHz) (Bialy et al., 2000)

and decreased anxiety-like behavior of male rats (Edinger and Frye, 2007).

s0060 ### 1.1.5 Sexual Behavior during Puberty and Aging

s0065 #### *1.1.5.1 Puberty*

p0075 The development of copulatory behavior has been studied in male rats mainly by testing prepubertal animals with young estrous females (Sachs and Meisel, 1979). The data from such studies established that mounting behavior appears between 40 and 50 days of age; intromission, between 44 and 75 days; and the behavioral pattern of ejaculation, between 48 and 75 days (reviewed in Meisel and Sachs (1994)). The development of copulatory behavior in rats clearly depends on gonadal hormones, since prepubertal castration prevents its appearance (Larsson, 1967), while exogenous testosterone (T) or estrogen (E) hastens its onset (Södersten et al., 1977). By contrast, in male Syrian hamsters adult-typical reproductive behavior cannot be activated by gonadal steroids prior to puberty (Sisk et al., 2003). In male rats, reflexive erections appeared at 40 days of age, penile flips at 44 days, and penile cups at 48 days (Sachs and Meisel, 1979).

p0080 In male rats, T levels begin to rise by about day 40, with the so-called pubertal T surge occurring around day 50. However, the T surge occurs after the onset of mount, intromission, and ejaculatory behaviors and the appearance of sexual reflexes (Sachs and Meisel, 1979). Male hamsters begin to copulate after the increase in pubertal T begins, but before the T surge (Romeo et al., 2002). In this species, the lack of pubertal T impaired T-induced mating in adulthood, produced in hamsters that were castrated after puberty (Schulz et al., 2004). Thus, the effects of pubertal hormones on the adolescent brain are important for the maturation of adult social behaviors like copulation (Schulz and Sisk, 2006), and perturbations during this period may result in important physiological and behavioral alterations in adulthood (Romeo, 2005). Indeed, chronic consumption of ethanol beginning at puberty impaired sexual behavior and fertility in adult male rats (Oliva et al., 2006), and consumption of anabolic androgenic steroids (AASs), alone or combined, during puberty increased or decreased sexual and aggressive behaviors in adulthood, depending on the drug or drug combination used (Wesson and McGinnis, 2006).

p0085 Neural changes have been associated with pubertal maturation of sexual behavior. Pubertal maturation of the brain includes remodeling of synaptic connections. Accordingly, at the onset of puberty in male rats, dendritic arborization of the sexually dimorphic spinal nucleus of the bulbocavernosus increases, followed by a decrease during puberty (Goldstein and Sengelaub, 1994). In male hamsters the number of dendrites and spines in the posterodorsal MeA decreases during puberty, which coincides with sexual behavior maturation (Zehr et al., 2006).

1.1.5.2 Aging

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p0090 Aging is associated with changes in male sexual function in humans, monkeys, and rodents. The probability of initiating copulation decreases, and once initiated, the latencies to mount (ML), intromit (IL), and ejaculate (EL) increase in old male rodents and monkeys (Meisel and Sachs, 1994). A relationship between these deficits and lower T levels has not been clearly established. In male rats, the decline in sexual behavior is accompanied by a decrease in circulating T (Chambers et al., 1991; Smith et al., 1992), but exogenous T only partially restores copulatory behaviors (Chambers et al., 1991). Maintenance of T levels by long-term replacement prevented the decline in intromission frequency (IF) in old rats, but did not prevent the age-related loss of ejaculatory response (Hsu et al., 1986). By contrast, the decrease in sexual activity of old male rhesus monkeys is not accompanied by a decline in gonadal hormones or changes in the diurnal pattern of androgen plasma levels, and exogenous T does not increase their sexual activity; however, in old long-term castrated monkeys, T increased sexual behavior (Phoenix and Chambers, 1986). In men, the decline in T levels during aging has been correlated with sexual impairment, as in young men with hypogonadism; however, it is not clear whether T treatment improves sexual performance (Moncada, 2006). A direct relationship between low T levels and decreased libido in aging men has also been difficult to establish (Travison et al., 2006). However, a role for sexual motivation in male rats' age-related sexual behavior decline has been inferred from the fact that treatment with yohimbine, a drug that stimulates sexual arousal (Viitamaa et al., 2006), improved copulatory behavior of old rats and increased mounting in old males with penile anesthesia to levels of untreated young animals (Smith and Davidson, 1990).

p0095 A decline in E receptors (Roselli et al., 1993), but not in androgen receptors (ARs) (Chambers et al., 1991), might underlie the ejaculatory deficit of old male rats, since it was found that old intact rats had

fewer nuclear E receptors (ERn) in the amygdala than did young animals, with no difference in circulating E levels. Castration reduced ERn in young and old males, but exogenous T restored copulation and ERn in the amygdala only in young males; T in old males restored copulation and ERn only to precastration levels, not to that of young males (Roselli et al., 1993). The authors suggested that an inability of T to increase ERn in the amygdala might play a role in the sexual deficits characteristic of old males.

p0100 In men, there was an age-related loss of motoneurons in the lumbar spinal cord controlling penile reflexes (Cruz-Sánchez et al., 1998). In a recent study in rats, no age-related decrease in motoneuron number in the spinal nuclei involved in rats' sexual reflexes was found, but an age-related atrophy of these motoneurons and the muscles they innervate was detected (Fargo et al., 2007). Exogenous T reversed the decreases in penile muscle weight and motoneurons' soma size and dendritic length, suggesting that T might play a role in maintaining neuronal connectivity.

p0105 Various levels of sexual performance are observed in middle-aged rats (18–19 months), with some able to ejaculate, others showing only mounts and intromissions, and some failing to exhibit any sexual activity. Incomplete sexual behavior has been associated with decreased DA and NE, and increased 5-HT, in the NAc (Tsai et al., 2006) and with decreased DA in the mPOA and arcuate nucleus, as well as decreased NE in the mPOA (Chen et al., 2007). Aged males showing complete copulatory behavior had monoamine levels similar to those of young sexually active rats. These data suggest that changes in monoamine contents in diverse brain regions could play a role in the sexual behavior decline of aged male rats.

s0075 1.2 Sexual Reflexes

s0080 1.2.1 Observations during Copulation

p0110 Although the penis can be observed during copulation in many species, erections in rodents are usually very brief and obscured from view. Characteristic behaviors are generally used to infer the presence of erection, intromission, and ejaculation. The female's vagina can be examined for the presence of sperm after a suspected ejaculation, and direct observation of the penis can be made with a slanted mirror placed under the floor of a clear cage. Electrodes have been implanted in the striated perineal muscles to detect electrical activity during copulation (Holmes et al., 1991), and penile pressure has also been measured (Giuliano et al., 1994). However, these techniques are technically difficult. Therefore, *ex copula* measures of sexual reflexes have been developed. However, *in copula* and *ex copula* erections may differ in their physiological, neurochemical, and hormonal regulation (Sachs, 2000). Furthermore, experimental manipulations may affect sexual reflexes without altering the behavioral pattern. For example, male rats with a neurochemical lesion of the NE system repeatedly exhibited the behavioral pattern of ejaculation without seminal ejection, evidenced by the absence of a seminal plug in the female's vagina, in response to the α_2-adrenoceptor antagonist yohimbine (Rodríguez-Manzo and Fernández-Guasti, 1995b). Thus, we must be cautious in extrapolating from *ex copula* tests to copulation or vice versa.

1.2.2 *Ex Copula* Sexual Reflexes s0085

1.2.2.1 Spontaneous or drug-induced erections s0090

Occasionally, male rodents have erections in their home cage or a neutral test arena without any obvious sexual stimulus. Such erections can be increased by administering certain drugs. These spontaneous or drug-induced erections usually consist of extension of the engorged glans from beneath the penile sheath and are often accompanied by genital grooming. The obvious advantage of this model is its simplicity. However, drug-induced erections can be modified by previous copulation (Sachs et al., 1994). p0115

1.2.2.2 Noncontact erections s0095

Male rodents often have erections in the presence of an inaccessible receptive female or even the volatile odors of an estrous female (Kondo et al., 1999; Sachs, 1997). Such erections are similar to spontaneous or drug-induced erections and are considered to be a model of psychogenic erection in men. They are elicited by central, rather than peripheral, stimuli. However, the primary stimuli to elicit such erections in rodents are olfactory, whereas the primary cues for psychogenic erections in men are visual and auditory, suggesting that the central pathways controlling these erections may differ across species. As with spontaneous and drug-induced erections, the primary advantage of this model is its simplicity. However, there is evidence that different brain areas may regulate noncontact versus *in copula* erections (Liu et al., 1997b). Also, noncontact erections may p0120

be elicited only in pigmented rats and not in albinos (Sachs, 1996).

s0100 #### 1.2.2.3 Reflexive erections, anteroflexions, and seminal emissions

p0125 Reflexive erections, also referred to as touch-based erections, can be elicited by manual stimulation of the penis in numerous species. However, tactile stimulation of the rat penis actually inhibits erection (Hart, 1968). To overcome this difficulty, genital reflexes can be elicited by restraining male rats (Hart, 1968) or mice (Sachs, 1980) on their backs and retracting the penile sheath. Pressure around the base of the penis elicits erections (engorgement of the glans due to vasodilatation in the corpus spongiosum) and anteroflexions (flips, elevations of the penis caused by engorgement of the corpora cavernosa and contraction of the ischiocavernosus muscles). Three gradations of glans erections have been noted: (1) elongation and rising of the body of the penis; (2) engorgement and flaring of the glans; and (3) intense flaring of the glans into a cup. The cup deposits the ejaculate around the female's cervix, where it coagulates and forms a copulatory plug. This plug prevents the semen from seeping out of the vagina; without it, pregnancy rarely occurs (Sachs, 1982). *Ex copula* seminal emission may also occur. Reflexive and *in copula* erections both are mediated by parasympathetic vasodilation and striated penile muscle contractions (Hart, 1968; Holmes et al., 1991). However, as with noncontact erections, there are differences in the neural mechanisms of erection in the two contexts (Sachs, 1983).

s0105 #### 1.2.2.4 The urethrogenital reflex

p0130 A model for both erection and ejaculation has been developed in anesthetized, acutely spinalized male rats (McKenna et al., 1991). The urethra is first distended with saline, and then the pressure is released, resulting in clonic contractions of the perineal muscles, rhythmic firing of the cavernous nerve, erection, and ejaculation. The simultaneous firing in all the perineal muscles is similar to bursts observed in human climax (Gerstenberg et al., 1993) and, in rats, during ejaculation (Holmes et al., 1991; Miura et al., 2001). Synchronized activity in both the pelvic (parasympathetic) and hypogastric (sympathetic) nerves drives the bursts in the cavernous nerve, which are synchronized with somatic muscle contractions. This reflex is usually evoked only after spinal transection or lesions of certain brain nuclei, suggesting tonic descending inhibition (however, see Section 1.5.2.1).

1.2.3 Erection

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1.2.3.1 Anatomy of the penis and mechanisms of erection

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An erect penis is necessary to deliver sperm into the female's reproductive tract. Some mammalian penes are highly vascular, while others are more fibroelastic. The vascular penes of humans, monkeys, dogs, cats, and rodents become engorged as a result of vascular relaxation, coordinated with striated muscle contraction. The fibroelastic penes of ungulates, such as sheep and goats, rely very little on engorgement, but are extruded by the action of penile muscles. There is considerable variability across species in the relative importance of these two factors.

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The basic anatomical structure of the penis is common across mammalian species. Most of the shaft of the penis is occupied by the paired corpora cavernosa, while the corpus spongiosum surrounds the urethra and enlarges into the glans at the end of the penis. The two corpora cavernosa are fused in most species, including humans, so that a drug injected anywhere in the structure can diffuse throughout. Similarly, intracavernous pressure can be monitored from any site. The corpora cavernosa consist of large cavernous sinuses, or trabeculae, that receive blood from the helicine arteries, which in turn are supplied by the cavernosal artery (reviewed in Hull et al. (2002), (2006)). Because the corpora cavernosa are enclosed by a tough capsule (the tunica albuginea), when they fill with blood, the pressure against the venous outflow traps blood in the penis, which enlarges and becomes rigid. The proximal ends of the corpora cavernosa taper into crura (legs) that are attached to the ischium (hip bone) and are surrounded by the ischiocavernosus muscle. The proximal end of the corpus spongiosum enlarges into the urethral bulb and is surrounded by the bulbospongiosus muscle. Contraction of the ischiocavernosus muscle further increases cavernosal pressure, and contraction of the bulbospongiosus muscle increases pressure in the glans (Gerstenberg et al., 1993). The relative contribution of vascular and muscular factors varies across species, with the rat relying more on the striated penile muscles, and humans, less so (Gerstenberg et al., 1993; Schmidt and Schmidt, 1993).

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Reflexive erections in the rat are correlated with steady subsystolic increases in pressure in the corpora cavernosa (Bernabé et al., 1999) and corpus spongiosum (Schmidt et al., 1995). These increases are interrupted by ~1-s peaks of suprasystolic pressure,

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elicited by bursts of firing in the ischiocavernosus and bulbospongiosus muscles. The bursts occur during glans erections, anteroflexions, and cups. Cups were eliminated by excision (Sachs, 1982) or denervation (Monaghan and Breedlove, 1992) of the bulbospongiosus muscle, and anteroflexions were blocked by excision of the ischiocavernosus muscle (Sachs, 1982). Pelvic and cavernous nerve stimulation produced plateau increases in penile pressure, and pudendal nerve stimulation elicited suprasystolic increases (Giuliano et al., 1995; Lue et al., 1984). Thus, erections require coordination of parasympathetically controlled blood flow to the penis and pudendal stimulation of the perineal striated muscles.

s0120 #### 1.2.3.2 Neural innervation

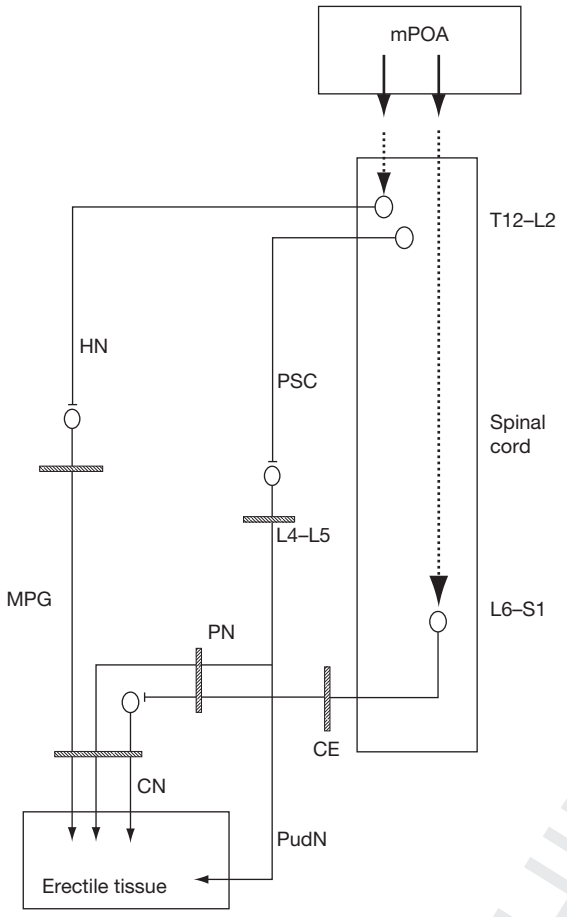
p0150 Three major pathways control penile erection: the pelvic nerves (primarily parasympathetic and proerectile), the hypogastric nerves (sympathetic and antierectile), and the pudendal nerves (somatosensory and motor). The major proerectile innervation is via the pelvic nerve (Lue et al., 1995; Tai et al., 1998), which originates in the lumbosacral spinal cord and travels via the pelvic plexus (pelvic ganglion) and cavernous nerve to the corpora and vasculature of the penis. In addition to parasympathetic fibers, it carries some sympathetic postganglionic axons (Dail et al., 1986). Somatomotor control is exerted by neurons in the spinal nucleus of the bulbocavernosus (SNB) and dorsolateral nuclei of the lumbosacral spinal cord (Schrøder, 1980). Their axons travel in the pudendal nerve, which splits into motor and sensory branches, both of which also carry sympathetic efferents (McKenna and Nadelhaft, 1986). Stimulation of the ischiocavernosus and bulbospongiosus muscles while the penis is flaccid does not result in erection. But if the penis is erect, striated muscle contraction dramatically increases its rigidity and intracavernosal pressure increases to suprasystolic levels (Schmidt and Schmidt, 1993).

p0155 The third major pathway conveys primarily antierectile sympathetic influence (Diederichs et al., 1991; Giuliano et al., 1995). Preganglionic axons travel via the lumbar splanchnic nerves or the paravertebral sympathetic chain of ganglia (Jänig and McLachlan, 1987) and synapse on neurons in the hypogastric plexus or paravertebral sympathetic chain ganglia, respectively. Postganglionic fibers travel via two major routes. First, the hypogastric nerve relays to the pelvic plexus, and then via the cavernous nerve to the penis. Second, axons from the paravertebral sympathetic chain travel via the pelvic nerve to the pelvic plexus, and then through the cavernous nerve to the penis, providing most of the noradrenergic input to the penis (Giuliano and Rampin, 2000). Tonic sympathetic input maintains the penis in a relaxed, nonerect state, and injection of noradrenergic antagonists into the corpora cavernosa can elicit erections in men (Brindley, 1986).

p0160 Although the main influence of the sympathetic input is antierectile, a proerectile effect has been observed in anesthetized rats (Giuliano et al., 1997) (**Figure 1**). Electrical stimulation of the mPOA, a critical brain area for male sexual behavior, increased cavernosal pressure. This increase was abolished by bilateral section of the pelvic or cavernous nerves, indicating that the major proerectile effect of mPOA stimulation is via the parasympathetic system. However, bilateral section of the paravertebral sympathetic chain at the level of L4–L5 also significantly decreased the effect of mPOA stimulation, as did lesioning of sympathetic fibers by the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA). Bilateral section of the hypogastric nerves produced a nonsignificant decrease in the penile response. The authors suggested that the sympathetic system may produce vasoconstriction in nonpenile areas, thereby diverting blood to the penis and enhancing erection. Thus, the mPOA is able to elicit erection by a coordinated activation of both the parasympathetic and sympathetic systems.

s0125 #### 1.2.3.3 Cellular mediators of erection

p0165 Penile erection results from relaxation of both arterial smooth muscle, which increases blood flow into the penis, and trabecular smooth muscle, which opens sinusoids in the erectile tissue. Trabecular smooth muscle cells are linked by gap junctions, allowing current to spread electrotonically and second messengers to pass from cell to cell. Therefore, autonomic input can influence the whole network by innervating relatively few cells (Christ et al., 1999). Tonic flaccidity is maintained largely by NE from sympathetic nerves, acting on postsynaptic α_1- and, to a lesser extent, α_2-adrenergic receptors (reviewed in Traish et al. (2000)). Drugs that block these receptors can elicit erection or induce priapism (prolonged erection) (Abber et al., 1987). Stimulation of α_1- and α_2-adrenergic receptors results in activation of phospholipase C and resultant increases in intracellular Ca^{2+}, which ultimately leads to contraction of arterioles and trabeculae, producing detumescence (Andersson and Stief, 1997; Christ, 1995; Traish et al., 2000). However, soon after the initial contraction, Ca^{2+} levels return to near basal levels,



f0005 **Figure 1** Diagrammatic representation of peripheral autonomic pathways potentially involved in erectile response elicited by medial preoptic area (mPOA) stimulation. Sites of neural lesions are represented by hatched bars. No direct projections from mPOA to spinal autonomic nuclei have been reported. CE, cauda equina; CN, cavernous nerve; HN, hypogastric nerve; L4–L5, 4th and 5th lumbar levels of the paravertebral sympathetic chain; L6–S1, 6th lumbar and 1st sacral level of the spinal cord; MPG, major pelvic ganglion; PN, pelvic nerve; PSC, paravertebral sympathetic chain; PudN, pudendal nerve; T12–L2, 12th thoracic to 2nd lumbar level of the spinal cord. Reproduced from Giuliano F, Bernabé J, Brown K, Droupy S, Benoit G, and Rampin O (1997) Erectile response to hypothalamic stimulation in rats: Role of peripheral nerves. *American Journal of Physiology* 273: R1990–R1997, used with permission from The American Physiological Society.

while the contractile tone remains. This continuing contraction is due to Ca^{2+} sensitization, mediated by the guanosine triphosphate (GTP)-binding protein Ras homolog gene family, member A (RhoA) and its major effector, Rho-kinase (reviewed in Jin and Burnett (2006) and Somlyo and Somlyo (2000)). A Rho-kinase antagonist (Y-27632) inhibited contraction of human or rabbit cavernosal tissue strips that had been elicited by an α-receptor agonist or electrical stimulation *in vitro* (Rees et al., 2001). Y-27632 also stimulated erection in rats (Dai et al., 2004; Rajasekaran et al., 2005). Castration increased RhoA and Rho-kinase protein levels, but intracavernosal injection of Y-27632 increased cavernosal pressure in the castrates, as well as in intact and T-replaced rats (Wingard et al., 2003). Therefore, one factor in the loss of erectile ability after castration may be the upregulation of the RhoA/Rho-kinase pathway. Furthermore, inhibition of this pathway could provide a potential treatment for erectile dysfunction. However, the decrease in blood pressure that would be caused with systemic administration would require that these inhibitors be applied locally or else target tissue-specific isoforms of RhoA regulatory proteins (Jin and Burnett, 2006).

p0170 The main mediator of erection is nitric oxide (NO) (reviewed in Bivalacqua et al. (2000)), a short-lived gaseous messenger produced by NOS. Neuronal NOS (nNOS, or NOS I) is present in parasympathetic nonadrenergic noncholinergic (NANC) nerves that innervate the erectile tissue. Endothelial NOS (eNOS, or NOS III) is in the endothelium of erectile tissue. The initial stimulus for erection is NO produced by nNOS in the parasympathetic nerves. It diffuses into the smooth muscle cells and activates soluble guanylyl cyclase, which produces cyclic guanosine monophosphate (cGMP), which then activates protein kinase G (PKG), and to a lesser extent protein kinase A (PKA). These enzymes phosphorylate regulatory proteins in the cell, which ultimately result in more Ca^{2+} being sequestered and less available in the cytoplasm, which relaxes the smooth muscles and produces erection (reviewed in Ignarro et al. (1999)). The activity of cGMP is terminated by phosphodiesterase 5 (PDE_5). Several drugs used to treat erectile dysfunction, including sildenafil citrate (Viagra), tadalafil (Cialis), and vardenafil (Levitra), act by inhibiting PDE_5 and thereby prolonging the effects of cGMP.

p0175 Although the initial stimulus for erection is NO from the parasympathetic nerves, a longer-lasting mediator of erection is NO from eNOS in the endothelium of blood vessels and sinusoidal spaces. The initial increase in blood flow induces shear stress in those tissues, which activates several enzymes, resulting in phosphorylation of eNOS at Ser 1177 and sustained production of NO (reviewed in Musicki and Burnett (2006)). Phosphorylation at other sites by other enzymes may increase or decrease eNOS activity.

In addition to its direct effects on vasodilation, NO also inhibits the antierectile RhoA/Rho-kinase pathway (Mills et al., 2002). Conversely, the RhoA/Rho-kinase pathway may inhibit phosphorylation of eNOS at Ser 1177 and thereby inhibit erection (Ming et al., 2002). It may also suppress eNOS gene expression and enzyme activity (Bivalacqua et al., 2004). Therefore, there is an inverse functional relationship between the proerectile NO/cGMP/PKG pathway and the antierectile RhoA/Rho-kinase pathway.

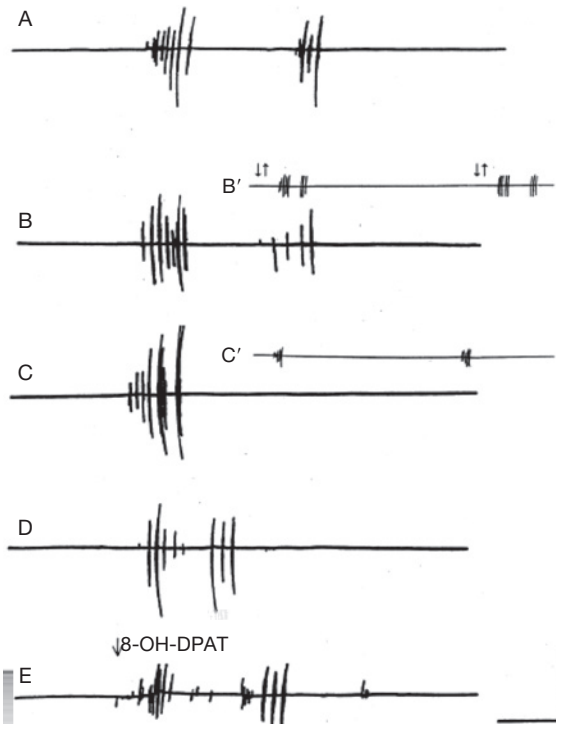
p0180 Erection can also be stimulated by activation of adenylyl cyclase by vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and prostaglandin E_1 (PGE_1) (reviewed in Bivalacqua et al. (2000)). The resultant activation of PKA sequesters intracellular Ca^{2+}. PGE_1 also increases production of NO, and repeated treatments increase both nNOS and eNOS in the penis, resulting in greater erectile response to nerve stimulation (Escrig et al., 1999).

s0130 1.2.4 Ejaculation

p0185 Ejaculation is the expulsion of the semen from the urethra. This process consists of two stages: an emissive phase and an ejective phase (Mitsuya et al., 1976; Newman et al., 1982). The emissive phase involves an autonomic component that elicits synchronized activation of visceral accessory structures such as the prostate and the tunica albuginea (Exintaris et al., 2006; Shafik et al., 2005), while the ejective phase involves rhythmic contraction of perineal and pelvic floor striated muscles and the maintenance of penile rigidity. During the emissive phase, the bladder neck sphincters close, and the seminal vesicles, prostate, vas deferens, and coagulant glands contract. Both parasympathetic and sympathetic mechanisms promote deposition of seminal secretions into the prostatic urethra. The expulsive phase consists of the forceful ejection of semen from the urethral meatus, caused by the rhythmic and coordinated contraction of all genital muscles surrounding the genital tract (Carro-Juárez and Rodríguez-Manzo, 2000; Gerstenberg et al., 1993; Kollberg et al., 1972; Shafik, 1997). Thus, successful ejaculation depends on coordinated responses involving autonomic and somatic events. In copulating animals, ejaculation requires the pelvic thrusting pattern that results in vaginal penetration and seminal deposition, and the genital motor pattern of forceful seminal ejection (Moralí et al., 2003). Although these patterns can be separately studied (Moralí et al., 2003), only the genital motor pattern of ejaculation can be observed in experimental models with lesions where penile rigidity, penile movements, and ejaculatory expulsions are not disturbed (Carro-Juárez and Rodríguez-Manzo, 2000; Carro-Juárez et al., 2003; McKenna et al., 1991).

p0190 The stimulus that initiates ejaculation is at present unknown; however, it has been proposed that genital sensory stimulation that comprises friction of penile skin and intravaginal pressure, acting against the penis during penetration, commences seminal drain into the posterior portion of the urethra, and when the ejaculatory threshold is reached, due to the concomitant chemical and mechanical stimulation of the urethra (by continuous seminal deposition), ejaculation takes place (de Jong et al., 2006; Sachs and Barfield, 1976). Individual differences in the ejaculatory threshold have been demonstrated, and males have been classified into praecox, intermediate, and retarded ejaculators (Pattij et al., 2005). The physiological control of the ejaculatory threshold remains one of the biggest riddles in the neurobiology of ejaculatory function. Tonic descending inhibition from the nPGi prevents untimely release of the reflex (see Sections 1.5.3.3 and 1.5.3.5), and supraspinal excitatory influences originate in the mPOA and PVN (see Sections 1.5.2.1 and 1.5.2.4 for details).

p0195 The neural commands for ejaculation are organized at the spinal level. Recent studies have demonstrated that a central pattern generator, located in the lumbosacral cord, is involved in the control of ejaculation (**Figure 2**) (Borgdorff et al., 2008; Carro-Juárez and Rodríguez-Manzo, 2000; Carro-Juárez et al., 2003; Truitt and Coolen, 2002). A group of galanin-containing neurons in this portion of the cord is part of this ejaculation generator (Truitt and Coolen, 2002). This pattern generator is positioned to relay and integrate all genital sensory and motor signals related to ejaculation, and its activation is able to turn on and off all somatic and autonomic events associated with ejaculation, including penile erection and movements of the penis driving seminal ejection (Borgdorff et al., 2008; Carro-Juárez and Rodríguez-Manzo, 2000, 2003, 2005b, 2006; Carro-Juárez et al., 2003). The spinal pattern generator for ejaculation (SGE) can modulate genitosensory-induced excitatory and/or inhibitory mechanisms regulating the facilitation or inhibition of the ejaculatory response at a spinal level (see Carro-Juárez and Rodríguez-Manzo (2008) for an extensive review). Thus, repeated activation of ejaculation-related afferent signals modifies the activity of the SGE, inducing a short-lasting inhibition that



f0010 **Figure 2** Summary figure showing the evidence that the ejaculatory motor pattern follows the general principles of rhythmic motor patterns produced by a central pattern generator, CPG: (1) a rhythmic muscular response, the genital motor pattern, is registered during the ejaculatory event (A); (2) this ejaculatory motor response has similar EMG characteristics in intact and in spinal urethane-anesthetized male rats ((A) and (B), respectively); (3) deafferentation does not disrupt the expression of the ejaculatory motor train (C); (4) a change in the stimulation interval does not alter the intrinsic pacing of the ejaculatory-like response (D); and (5) fictive ejaculation can be pharmacologically induced (E). Calibration bar 50 mV, 5 s. Tracing inserts (B′ and C′) illustrate two consecutive ejaculatory motor responses obtained in a 4-min period in a spinal rat with intact afferents and in a deafferented spinal rat. Adapted from Carro-Juárez M, Cruz SL, and Rodríguez-Manzo G (2003) Evidence for the involvement of a spinal pattern generator in the control of the genital motor pattern of ejaculation. *Brain Research* 975: 222–228, with permission from Elsevier.

could be related to the ejaculation delay phenomenon attained by the pause squeeze method as well as long-lasting inhibitory states (Carro-Juárez and Rodríguez-Manzo, 2005b) with characteristics similar to those observed in sexually exhausted animals after repeated ejaculation (Carro-Juárez and Rodríguez-Manzo, 2000, 2005b). Thus, the SGE can be modulated through the activation of spinal sensory feedback mechanisms (Carro-Juárez and Rodríguez-Manzo, 2000, 2001, 2005b).

Spinal circuits in the lumbosacral spinal cord are p0200 modulated by supraspinal structures, since the SGE can be activated only after lesion of the nPGi or spinal cord transection (Marson and McKenna, 1990). Although the nPGi is thought to exert a 5-HT-mediated tonic inhibition on ejaculation (Marson and McKenna, 1992), recent data suggest an intraspinal 5-HT excitatory mechanism, via activation of 5-HT_{1A} (Carro-Juárez and Rodríguez-Manzo, 2001; Carro-Juárez et al., 2003) and 5-HT_{2C} receptors (Stafford et al., 2006b), in addition to the descending inhibitory influence. A stimulating role for DA has also been postulated (Peeters and Giuliano, 2008; Stafford et al., 2006a), since activation of DA receptors by apomorphine induces ejaculation-like responses in anesthetized rats (Stafford and Coote, 2006). The spinal NE system also facilitates ejaculation. Ejaculatory autonomic and somatic rhythmic patterns, including the expulsion of urethral contents and penile erections, are obtained after increasing NE tone by systemic yohimbine (Carro-Juárez and Rodríguez-Manzo, 2003, 2006). Stimulation of α_1- (Carro-Juárez and Rodríguez-Manzo, 2006) or α_2-adrenoceptors (Carro-Juárez and Rodríguez-Manzo, 2003) also activates the SGE. Moreover, inhibited ejaculation due to repeated genital mechanical stimulation may be overcome by blockade of α_2-adrenoceptors with yohimbine (Carro-Juárez and Rodríguez-Manzo, 2003). Cholinergic stimulation of the SGE, mediated by the M_2-, M_3-, and M_4-muscarinic receptor subtypes, has also been suggested (Gómez et al., 2005). Finally, systemic injection of oxytocin (OT) in male rats elicits ejaculatory sequences similar to those obtained by genitosensory stimulation in adult (Carro-Juárez and Rodríguez-Manzo, 2005b) or neonatal rats (Carro-Juárez and Rodríguez-Manzo, 2005a; see Section 1.6.2).

1.3 Role of Gonadal Steroids in the Control of Male Sexual Behavior s0135

1.3.1 Testosterone and Its Metabolites s0140

Male sexual behavior depends heavily on T and its p0205 metabolites. T is secreted by the Leydig cells of the testes and is carried in the blood to its nontesticular targets. In all mammals studied, sexual behavior by adult males is promoted by circulating T and/or its metabolites, estradiol (E_2) and dihydrotestosterone (DHT). A pubertal increase in T is essential for the increased sexual activity of maturing males; after castration, sexual drive and activity usually decline.

However, there is interspecies variation in the importance of gonadal steroids for sexual activity. Testicular steroids are essential for mating in most rodents, but they play a more modulatory role in humans (Heim and Hursch, 1979).

p0210 The stimulatory effects of T in adulthood are referred to as activational effects, to distinguish them from the organizational effects of T during sex differentiation. In adult males T has primarily slow, genomically mediated permissive effects that prepare the male to respond to a receptive female. T is usually present in higher quantities than necessary to activate sexual behavior, and small fluctuations in T levels do not usually affect behavior (reviewed in Ågmo and Ellingsen (2003)). The higher levels are required to stimulate sperm production in the testes.

s0145 #### 1.3.1.1 Time course of changes in copulation following castration and testosterone restoration

p0215 Levels of T in plasma decline to unmeasurable levels within 24 h after castration (Krey and McGinnis, 1990), but male rats may continue to copulate for days or weeks, although the latency to intromit begins to increase within days. The number of intromissions required to elicit ejaculation actually decreases for some days after castration. Therefore, one function of T may be to increase the number of intromissions preceding ejaculation, which would increase the number of sperm in the ejaculate, facilitate sperm transport, and trigger a progestational state in the female (Toner et al., 1987). There is disagreement about the effects of castration on sexual desire and copulation in men. Kinsey et al. (1948) used anecdotal reports to conclude that castration may not seriously impair sexual function in most men. However, more detailed prospective studies of men who had been castrated as treatment for sexual offences found that one-half to two-thirds of the men reported a rapid loss of sexual interest (Heim and Hursch, 1979). The remaining men reported gradual decreases in interest, with 10% still able to copulate 20 years later. Men who were older at the time of castration were most affected.

p0220 Five to ten days of exposure to T are required to reinstate copulation in long-term castrated rats (McGinnis et al., 1989; Putnam et al., 2001), and 5–7 weeks are required for hamsters (Ballard and Wood, 2007). However, in rats T increased firing in the mPOA in response to female odors within minutes (Pfaff and Pfaffman, 1969). Castrated rats started mounting within 35 min after E administration (Cross and Roselli, 1999), and T stimulated mounting within 60 min in castrated mice (James and Nyby, 2002). Therefore, steroids activate certain brain areas within minutes but require longer-term genomic effects to restore copulation fully.

s0150 #### 1.3.1.2 Role of testosterone metabolites in maintaining and restoring copulation

p0225 T is the principal hormone produced by the testes and present in systemic circulation. However, T is primarily a prohormone, being converted in target organs either to E_2 by aromatase or to DHT by 5α-reductase. There are at least two E receptors, ERα and ERβ. Although both T and DHT bind to the AR, DHT does so with approximately fivefold greater affinity (Wilbert et al., 1983). DHT cannot be aromatized to E_2, and therefore is considered to have only androgenic action. Some target cells may produce both E_2 and DHT and have both ERs and ARs.

p0230 The relative importance of estrogenic and androgenic stimulation for male sexual behavior is complex and species-specific. In castrated male rats, E_2 is sufficient to reinstate most aspects of copulation (Cooke et al., 2003). Similarly, synthetic androgens that can be aromatized to E_2, but not 5α-reduced to DHT, were able to restore copulation in castrated rats (Moralí et al., 1993) or mice (Ogawa et al., 1996). In contrast, neither DHT nor the nonaromatizable androgen methyltrienolone (R1881) (reviewed in Hull et al. (2006)) restored or maintained copulation after castration. Aromatase inhibitors (Bonsall et al., 1992; Roselli et al., 2003; Vagell and McGinnis, 1997) and ER antagonists (Beyer et al., 1976) inhibited the ability of T to restore copulation in castrated rats. These results support the aromatization hypothesis, which states that aromatization of T to E is critical for maintaining or restoring copulation in male rats.

p0235 However, another ER antagonist (RU 58668) inhibited scent marking and 50-kHz vocalizations, but did not diminish T's ability to restore copulation in rats, although an AR antagonist (hydroxyflutamide) did inhibit restoration of copulation as well as scent marking and vocalizations (Vagell and McGinnis, 1998). This suggests that ARs do play a role, at least in some experimental conditions, in restoring copulation in male rats. In support of this hypothesis, E is usually insufficient to fully maintain or restore sexual behavior after castration (Kaplan and McGinnis, 1989; Putnam et al., 2003, 2005), and antiandrogens reduce T's ability to restore copulation (Vagell and McGinnis, 1998). Therefore, aromatization of T to E is not sufficient to

restore or maintain copulatory behavior; stimulation of both ERs and ARs may be necessary for full restoration of mating behavior (see Hull et al. (2006) for a more extensive review).

p0240 Studies of genetically altered mice that lack ERα or ERβ have provided new insights into the roles of estrogens and androgens in male sexual activity. Gonadally intact males that lacked the ERα (ERα knockout (KO) mice, or ERαKO) mounted, but had fewer intromissions than wild-type males, and almost no ejaculations (Ogawa et al., 1997, 1998). These males actually have higher levels of T than wild-type mice, because of decreased ER-mediated negative feedback (Wersinger et al., 1997). Castrated ERαKO males with replacement of normal levels of T (Wersinger et al., 1997) or higher than normal levels of DHT (Ogawa et al., 1998) showed increased mounting, but few or no ejaculations. However, treatment with T and a DA agonist restored copulation to ejaculation (Wersinger and Rissman, 2000). Deficits were also reported in aromatase KO (ArKO) mice (Bakker et al., 2002a; Matsumoto et al., 2003). In contrast, βERKO males mated normally (Ogawa et al., 1999), although the pubertal onset of ejaculation was delayed (Temple et al., 2003). These results support the hypothesis that ERα and aromatase, perhaps together with androgens, are important for male mouse sexual behavior.

p0245 Aromatization of T to E is not required in numerous other species, including rabbits, guinea pigs, hamsters, deer mice, monkeys, and mice (see Hull et al. (2006)). However, a recent study suggested that E does contribute to the ability of male macaques to copulate to ejaculation, whereas androgens are important for sexual motivation (Barrett et al., 2006). In castrated hamsters the aromatizable androgens androstenedione (A) and T restored all sexual behaviors; E promoted anogenital investigation and some mounting, but not ejaculation; and DHT was ineffective (Arteaga-Silva et al., 2005). In that study, the combination of E plus DHT was less effective than A or T, suggesting that aromatization, perhaps local, may be a factor. Although the relative importance of E and A varies across species, males are normally exposed to both classes of hormone, which together promote appetitive and consummatory aspects of mating.

s0155 ### 1.3.1.3 Effects of castration and hormone replacement on ex copula penile responses

s0160 #### 1.3.1.3(i) Animal studies

p0250 *Ex copula* reflexes are more sensitive than is copulation to the presence or absence of gonadal steroids. Reflexes are lost more rapidly after castration and restored more rapidly after T replacement. In spinally transected animals, reflexive erections were diminished 24 h after castration (Hart et al., 1983). In spinally intact males, castration decreased the number of cups by day 4, the earliest time tested, decreased anteroflexions by 7 days, and glans erections by 11 days (Meisel et al., 1984). Reflexive erections were increased within 6 h of T replacement in spinally transected males, with maximal stimulation by 24 h (Hart et al., 1983). In spinally intact males, increases were observed at 24 h after T replacement, with maximal increases at 48 h (Gray et al., 1980). The longer intervals required in spinally intact males may reflect the time required to reduce supraspinal inhibition, so that the already primed spinal effectors can act. Noncontact erections are also lost more rapidly after castration (3 days) and restored more rapidly after T replacement (3 days) (Manzo et al., 1999). Lower levels of T than are present in gonadally intact males are effective in restoration (Davidson et al., 1978); so, as with copulation, plasma T in adult males is higher than needed to activate penile reflexes.

p0255 Although copulation in male rats is more dependent on E, reflexes rely more heavily on androgenic stimulation. DHT is both necessary and sufficient for maintaining and restoring reflexive (Gray et al., 1980; Meisel et al., 1984) or NO-mediated (Lugg et al., 1995, see below) erections in male rats. The DHT regimens that maintained or restored *ex copula* reflexes were ineffective in activating mounting (Gray et al., 1980; Meisel et al., 1984). Noncontact erections were also maintained by DHT, but not E (Cooke et al., 2003; Manzo et al., 1999). However, *in copula* erections can be maintained by E. The E-treated castrates achieved vaginal insertion on as high a percentage of intromissions as did control males (O'Hanlon et al., 1981). E was also as effective as T in maintaining the duration, frequency, and amplitude of EMG bursts in the bulbospongiosus muscles during intromissions (Holmes and Sachs, 1992). Sachs (1983) proposed that E can activate a behavioral cascade, organized in the brain, that can activate reflexes during copulation, but cannot disinhibit those reflexes *ex copula.*

1.3.1.3(ii) Studies on human males

s0165

p0260 T levels in men with erectile dysfunction are not significantly lower than those in normally functioning men (Becker et al., 2001; Rhoden et al., 2002). However, in aging men with moderate decreases in T levels, exogenous T improved erectile function and

nocturnal penile tumescence (Cavallini et al., 2004; Schultheiss et al., 2000). Furthermore, T treatment of hypogonadal men increased the number of erections in diary reports (O'Carroll et al., 1985; Salmimies et al., 1982). Exogenous T in hypogonadal men (which resulted in normal levels) or in eugonadal men (which produced supraphysiological levels) did increase sexual arousal in response to sexual audiotapes (Alexander et al., 1997). T and DHT were equally effective in stimulating sexual activity in agonadal men, and administration of either an ER antagonist or an aromatase inhibitor did not inhibit sexual function. Thus, androgenic stimulation in men appears to facilitate sexual interest and ability (reviewed in Traish and Guay (2006)).

s0170

1.3.2 Steroid Action on Steriod Hormone Receptors

p0265

ARs and ERs, distributed widely but selectively throughout the brain, are thought to mediate most hormonal effects on sexual behavior. These receptors are concentrated in areas that are important for male sexual behavior, including the mPOA (see Simerly

1.4 Effects of Systemically and Intraventricularly Injected Drugs

1.4.1 Dopamine

DA has long been known to facilitate male sexual function. L-Dopa, the precursor of DA, administered to parkinsonian patients increases libido and sexual potency (Barbeau, 1969; Bowers et al., 1971), and the nonspecific DA agonist apomorphine has been used to treat sexual dysfunction (Dula et al., 2000; Giuliano and Allard, 2002; Lal et al., 1987).

In rats, systemically administered DA agonists facilitate male sexual behavior (reviewed in Bitran and Hull (1987), Giuliano and Allard (2001), Hull et al. (2006), Melis and Argiolas (1995), and Olivier et al. (2007)), induce sexually sluggish males to copulate (Tagliamonte et al., 1974), elicit copulation in sexually exhausted males (Mas et al., 1995b; Rodríguez-Manzo, 1999b), and partially restore copulation in castrates (Malmnäs, 1976; Scaletta and Hull, 1990). In mice lacking the ERα, which usually show little sexual behavior, apomorphine induces normal copulation (Wersinger and Rissman, 2000). It also elicits penile erections and genital grooming in mice (Rampin et al., 2003).

Systemically administered DA antagonists impair sexual behavior in both sexually experienced (Ahlenius and Larsson, 1990; Pfaus and Phillips, 1989) and naive rats (Ågmo and Picker, 1990). The negative effects of DA antagonists range from increased IL and EL to failure to copulate (reviewed in Bitran and Hull (1987), Giuliano and Allard (2001), and Melis and Argiolas (1995)). Haloperidol, a nonspecific DA antagonist, inhibits measures of sexual motivation as well as copulation itself (Lopez and Ettenberg, 2000, 2001, 2002b). In human males, DA antagonists reduce sexual desire, arousal, and orgasm (Baldwin and Mayers, 2003).

DA receptors are classified into two families: the D_1-like family includes receptors positively coupled to adenylyl cyclase and comprises the D_1- and D_5-receptor subtypes, while the D_2-like family consists of D_2-, D_3-, and D_4-receptor subtypes, which are negatively coupled to adenylyl cyclase (Missale et al., 1998). At the supraspinal level, DA has a facilitative effect on ejaculation, mediated especially in the mPOA and PVN by D_2-like receptors (reviewed in Hull et al. (2004)). Systemic activation of D_2-like receptors with either D_3-(7-OH-DPAT) or D_2/D_3-receptor agonists (SND 919 and BHT 920) facilitated ejaculation by decreasing both IF and EL in sexually experienced rats, but not in sexually inactive ones (Ferrari and Giuliani, 1995, 1996a; Giuliani and Ferrari, 1996). In anesthetized rats, ICV and intra-mPOA injection of a D_3 agonist induced bulbospongiosus rhythmic contractions and ejaculation – effects blocked by a D_2/D_3 (raclopride) and a preferential D_3 antagonist (nafadotride) (Clement et al., 2007; Kitrey et al., 2007). Thus, supraspinal command of ejaculation appears to be mediated by D_2-like receptors, probably of the D_3 subtype, in the mPOA. D_1-like receptor agonists increased sexual motivation in rats (Beck et al., 2002) and facilitated copulation in DA-deficient mice (Szczypka et al., 1998). D_1-like receptor facilitation of male sexual behavior appears to be conserved across phyla, since it has been detected in lizards (Woolley et al., 2001), geckos (Woolley et al., 2004), Japanese quail (Balthazart et al., 1997), and European starlings (Schroeder and Riters, 2006).

The effects of DA agonists are dose-dependent, with low doses facilitating, and high doses inhibiting, copulation, the latter effect possibly due to the induction of stereotypic behavior (Foreman and Hall, 1987; Szczypka et al., 1998). Contradictory effects of D_1- and D_2-like receptor agonists on *ex copula* genital reflexes have been reported. A D_2-selective agonist was reported to elicit erections, while a D_1-receptor agonist inhibited them (Zarrindast et al., 1992). However, the D_2/D_3 receptor agonist quinelorane decreased the number of reflexive erections in restrained rats (Bitran et al., 1989b), but promoted penile erection in rhesus monkeys in the presence of sexually receptive females, which they could see, hear, and smell, but could not contact (Pomerantz, 1991). Other D_2/D_3-selective receptor agonists elicited erections in rats in a neutral arena (Ferrari et al., 2002). However, a D_2/D_3 antagonist (eticlopride) actually increased erections elicited by a presumed-selective D_2 agonist or cocaine in rats (Ferrari and Giuliani, 1996b). Cocaine would have increased extracellular DA, which would have stimulated both D_1 and D_2 receptors. It is possible that the presumed-selective D_2 agonist actually stimulated some D_1 receptors, as did cocaine, and that inhibition of D_2 receptors disinhibited the D_1-like effect.

1.4.2 Norepinephrine

NE has both facilitative and inhibitory effects on male sexual behavior. Inhibition of NE synthesis impaired copulation, increasing ML, IL, EL, and

PEI (McIntosh and Barfield, 1984). However, lesions of the NE system have rendered inconsistent results. Electrolytic lesion of the locus ceruleus (LC), which contains the majority of NE cell bodies in the brain (Kuhar et al., 1999), inhibited copulation (McIntosh and Barfield, 1984); but similar lesions of the dorsal NE bundle, which connects the LC with the cerebral cortex and hippocampus (Kuhar et al., 1999), decreased the PEI and increased the ejaculations in a 1-h test (Clark, 1975, 1980). Central NE depletion by the neurotoxin DSP-4 increased the PEI (Hansen et al., 1982); but in another study it had no effect on copulation (Fernández-Guasti and Rodríguez-Manzo, 1997), neither did the lesion of the dorsal NE bundle with the neurotoxin 6-OHDA (Clark, 1980). DSP-4 induced lesion did not interfere with the Coolidge effect, although it reduced the number of ejaculations prior to satiation and in the ensuing Coolidge effect copulatory period (Rodríguez-Manzo, 1999a).

p0315 NE exerts its effects by stimulating α- and β-adrenoceptors. α-Adrenoceptors have been shown to modulate sexual arousal (Viitamaa et al., 2006), since α_2-adrenoceptor antagonists like yohimbine, idazoxan, and imiloxan, which enhance NE transmission by blocking autoreceptors, increased mounting rates in rats with genital anesthetization, augmented copulatory behavior in sexually sluggish and castrated males (Smith et al., 1987; Tallentire et al., 1996), increased the percentage of sexually naive rats that copulated to ejaculation (Benelli et al., 1993; Tallentire et al., 1996), and decreased IL, EL, and PEI in sexually experienced males (reviewed in Meisel and Sachs (1994)). Conversely, α_2-adrenoceptor agonists (clonidine and guanabenz) dose-dependently suppressed ejaculation or increased ML, IL, and PEI in sexually vigorous male rats and decreased the number of inexperienced males achieving ejaculation (Benelli et al., 1993). Blockade of α_1-adrenoceptors with prazosin increased IL, EL, and PEI, while the α_1-adrenoceptor agonist methoxamine had the opposite effect (reviewed in Meisel and Sachs (1994)).

p0320 The influence of β-adrenoceptors on copulation is not clear. β-Adrenoceptor antagonists, used for the treatment of cardiovascular diseases (Borchard, 1998), cause sexual dysfunction in men (Düsing, 2005). In rats, s.c. and ICV injection of the β_1/β_2-blockers propanolol and pindolol profoundly inhibited sexual behavior, almost abolishing ejaculation (Smith et al., 1990, 1996a). In sexually vigorous male rats, the β_2-adrenoceptor agonist clenbuterol reduced mount frequency (MF) and IF and increased the PEI, but in sexually sluggish animals it improved copulatory behavior by increasing the percent of males achieving ejaculation and reducing ML, IL, EL, and PEI (Benelli et al., 1990). Chronic oral administration of propanolol to male rabbits impaired sexual behavior, affecting performance more than arousal aspects (Grotthus et al., 2007).

p0325 The NE system regulates male sexual functions through ascending pathways to the brain and descending pathways to the spinal cord (Giuliano and Rampin, 2000), and adrenoceptors are found in the brain and spinal cord of animals and humans (Roudet et al., 1994; Smith et al., 1995; Wada et al., 1996). The activity of spinal preganglionic neurons is modulated by NE, and postganglionic sympathetic nerve terminals release NE in the penis, promoting penile detumescence (Giuliano and Rampin, 2004). In contrast to the effects on copulation, both agonists and antagonists at α_2-adrenoceptors inhibit reflexive erections as well as seminal emission in rats. However, the effects of the α_2-receptor antagonist yohimbine appear to be dose-dependent, with low doses facilitating, and higher doses inhibiting, the erectile response (reviewed in Meisel and Sachs (1994)). A similar effect is seen on seminal emission in dogs (Yonezawa et al., 1991). Activation of α_1-adrenoceptors inhibits reflexive erection in dogs but stimulates seminal emission in rats. There is also evidence that the β-adrenergic antagonist propanolol has a negative impact on rat reflexive erectile and ejaculatory reflexes (Smith et al., 1995). Together, these data suggest that increased NE activity, either by blockade of α_2-autoreceptors or by stimulation of α_1-adrenoceptors increases sexual arousal. β-Adrenoceptors facilitate copulation, but NE inhibits reflexive erections, probably at the penis.

1.4.3 Serotonin

s0195

p0330 5-HT is generally inhibitory to male sexual behavior (reviewed in Bitran and Hull (1987) and Hull et al. (2004)). A common side effect of selective serotonin reuptake inhibitor (SSRI) antidepressants, which increase extracellular 5-HT, is to impair male sexual function in humans and rats (Mos et al., 1999; Rosen et al., 1999). Contrary to the general inhibitory role of 5-HT in copulation, stimulation of the 5-HT_{1A} receptor subtype markedly facilitates male rat ejaculation (Ahlenius et al., 1981). Fourteen 5-HT receptor subtypes, belonging to one of seven receptor families, have been identified (Hoyer et al., 2002); however, only a few of them have been related to male sexual

function. The inhibitory actions of 5-HT appear to be mediated by 5-HT_{1B} receptors in rats and mice (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998; Rodríguez-Manzo et al., 2002b) and by the 5-HT_2 receptor in rats (Foreman et al., 1989; Klint and Larsson, 1995), while the 5-HT_{1A} receptor mediates the facilitative actions of this neurotransmitter in rats (Ahlenius et al., 1981). Thus, systemic and intrabrain injection of 5-HT_{1B} agonists inhibit male rat sexual behavior (Fernández-Guasti et al., 1989, 1992) and co-administration of subeffective doses of 5-HT_{1B} agonists and the 5-HT precursor 5-hydroxytrytophan (5-HTP) synergize to inhibit copulation (Fernández-Guasti and Rodríguez-Manzo, 1992). 5-HT_{1B} receptor antagonists completely block the inhibitory actions of 5-HTP on copulation, while antagonists to other subtypes do not (Ahlenius and Larsson, 1998). In 5-HT_{1B} receptor KO mice (KO_{1B}), males become interested earlier in sexual behavior and are less sensitive to the inhibitory actions of 5-HTP than the corresponding wild-type strain. However, KO_{1B} mice require more stimulation to achieve ejaculation than wild-type males. Pharmacological manipulation in these animals revealed that in mice, in contrast to rats, both the 5-HT_{1B} and the 5-HT_{1A} receptor subtypes contribute to the inhibitory actions of 5-HT (Rodríguez-Manzo et al., 2002b). The inhibitory role ascribed to the 5-HT_2 receptor subtype in male rat sexual behavior is mainly derived from results showing that systemic, intraraphe, and intralateral hypothalamus (LH) administration of 5-HT_2 receptor agonists dose-dependently decreased its expression (Foreman et al., 1989; Riolo et al., 1999; Watson and Gorzalka, 1991, 1992), while a 5-HT_2 antagonist facilitated copulation (Gonzalez et al., 1994). Stimulation of 5-HT_{2C} receptors has increased erections and inhibited ejaculation in monkeys (Pomerantz et al., 1993), and facilitated erection in anesthetized (Steers and De Groat, 1989) and conscious rats (Millan et al., 1997).

p0335 Brain sites where microinjection of 5-HT has been reported to impair male rat sexual behavior are the mPOA (Verma et al., 1989) and the NAc (Fernández-Guasti et al., 1992). However, accumulation of 5-HT in the mPOA induced by SSRI local injection did not affect sexual behavior, although SSRI injection into the anterior LH did inhibit copulation (Lorrain et al., 1997; see Section 1.5.2.5). Besides, a tonic inhibitory influence on sexual reflexes exerted by brainstem 5-HT descending pathways to the spinal cord has been described (Marson and McKenna, 1992, 1994b; Marson et al., 1992).

p0340 The facilitative effects on ejaculation resulting from stimulation of the 5-HT_{1A} receptor subtype were characterized with the 5-HT_{1A} receptor agonist 8-OH-DPAT, which dramatically decreased the IF and EL of sexually competent male rats, to the point that some rats ejaculated on their first intromission (Ahlenius et al., 1981, 1989; Coolen et al., 1997a; Schnur et al., 1989). Similar facilitation has been reported in sexually satiated rats (Rodríguez-Manzo and Fernández-Guasti, 1994). Other 5-HT_{1A} agonists such as flesinoxan (Haensel and Slob, 1997), buspirone (Mathes et al., 1990), or ipsapirone (Fernández-Guasti et al., 1989) induced a behavioral profile similar to that of 8-OH-DPAT, although animals did not ejaculate on their first intromission. That 5-HT_{1A} receptor stimulation yields opposite effects to those produced by 5-HT itself, together with the fact that somatodendritic autoreceptors in 5-HT neurons belong to the 5-HT_{1A} receptor subtype, led to the postulation that 8-OH-DPAT acted as an agonist at somatodendritic receptors to reduce 5-HT release (Ahlenius et al., 1981). However, lesion of raphe nuclei did not alter the 8-OH-DPAT facilitative actions on copulation, suggesting that they were exerted at postsynaptic sites (Fernández-Guasti and Escalante, 1991). In addition, facilitative effects of 8-OH-DPAT were obtained after its infusion into the mPOA and the NAc, but not into the dorsal raphe, where somatodendritic receptors are found (Fernández-Guasti et al., 1992; Matuszewich et al., 1999). The anterior LH (Riolo et al., 1999) and the posterodorsal MeA (de Castilhos et al., 2006) are two additional brain areas where injection of 8-OH-DPAT facilitates ejaculation.

p0345 8-OH-DPAT's facilitative effects on copulation require normal T levels and sexual experience (Rowland and Houtsmuller, 1998). Both NE and DA systems are involved in 8-OH-DPAT's facilitative effects, since neurotoxic lesions of the central NE system blocked or attenuated them in sexually exhausted and nonexhausted rats, respectively (Fernández-Guasti and Rodríguez-Manzo, 1997; Rodríguez-Manzo and Fernández-Guasti, 1995b). Besides, the D_2 antagonist raclopride, but not the 5-HT_{1A} antagonist p-MPPI, decreased 8-OH-DPAT's facilitative effects in the mPOA (Matuszewich et al., 1999). Intrathecal administration of 8-OH-DPAT at the level of the lumbosacral spinal cord also reduced the IF and EL (Lee et al., 1990).

p0350 Chronic SSRI treatment is frequently associated with delayed ejaculation. Acutely, SSRIs inhibit 5-HT reuptake, elevating extracellular 5-HT levels (Malagie et al., 2000); however, after chronic

administration they cause desensitization of 5-HT_{1A} receptors (Le Poul et al., 1995). Apparently, this desensitization plays a role, not only in SSRI's antidepressant properties (Artigas et al., 1996), but also in the chronic treatment-induced delayed ejaculation (De Jong et al., 2005). Stimulation of spinal 5-HT_{1A} receptors inhibits rat penile erection (Pomerantz et al., 1993; Rehman et al., 1999). In summary, 5-HT exerts a general inhibitory influence on male sexual behavior that is mediated by 5-HT_{1B} and 5-HT_2 receptor subtypes. However, stimulation of the 5-HT_{1A} receptor subtype has a marked facilitative effect on male rat ejaculation.

s0200 **1.4.4 Acetylcholine**

p0355 There is little information on selective effects of ACh on copulation in males. Early studies reported suppression of male sexual behavior by high doses of nicotine and of physostigmine, an acetylcholinesterase inhibitor, as well as by antagonists like atropine and scopolamine. However, a relatively low dose of nicotine increased EF and reduced IF, EL, and PEI (for review, see Bitran and Hull (1987)), and the muscarinic agonist oxotremorine reduced IF and EL (Ahlenius and Larsson, 1985). Later, physostigmine-induced increases in ACh level and stimulation of muscarinic receptors with pilocarpine increased EF and promoted erections (Maeda et al., 1990; Zarrindast et al., 1994) (see Sections 1.5.2.1 and 1.5.3.5).

s0205 **1.4.5 Gamma-Aminobutyric Acid**

p0360 GABA is the main inhibitory neurotransmitter in the mammalian brain (Paul, 1995). Systemic administration of GABAergic drugs inhibited male rat sexual behavior (Ågmo and Paredes, 1985; Paredes et al., 1997). There are reports of inhibitory effects of GABAergic drugs in the mPOA, PVN, and spinal cord (see Sections 1.5.2.1, 1.5.2.4, and 1.5.3.5). In addition, cerebrospinal fluid (CSF) concentrations of GABA increased dramatically during the PEI (Qureshi and Södersten, 1986).

s0210 **1.4.6 Glutamate**

p0365 Excitatory amino acids appear to facilitate copulation and penile erection. Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). Intraperitoneal injection of low doses of kainic acid, an agonist of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors, enhanced copulatory behavior in sexually sluggish male rats, but did not affect good copulators (Drago and Bus, 1997). Systemic injection of the *N*-methyl-D-aspartic acid (NMDA) antagonist MK-801 impaired sexual behavior in sexually experienced and sexually naive male rats (Powell et al., 2003), an effect also obtained in the mPOA (Dominguez et al., 2007). Repeated exposure of sexually naive animals to inaccessible estrous females improves copulatory behavior, and this improvement was blocked by MK-801 (Powell et al., 2003). There is considerable evidence for glutamatergic facilitation of both copulation and genital reflexes following microinjections into the mPOA, PVN, and spinal cord (see Sections 1.5.2.1, 1.5.2.4, and 1.5.3.5). Thus, glutamate appears to be a major facilitator of copulation at both brain and spinal levels.

1.4.7 Nitric Oxide s0215

NO is a soluble gas that acts both as a second messenger and as a neurotransmitter that has been implicated in male sexual functions that include penile erection (Andersson, 2001) and brain control of sexual behavior (Bialy et al., 1996). NO is produced by the action of NOS, which converts L-arginine into citrulline. Systemically administered NOS inhibitors impair copulation, decreasing the proportion of sexually naive (Benelli et al., 1995) and experienced (Bialy et al., 1996; Hull et al., 1994) male rats that ejaculate, while augmenting MF and decreasing IF. NOS inhibitors also decrease the number of noncontact erections (Melis et al., 1998), as well as reflexive erections, and also increase seminal emission (Hull et al., 1994). These effects are consistent with a facilitative role of NO in parasympathetic function and an inhibitory one in sympathetic activity. An NOS inhibitor did not affect sexual motivation, evaluated in a female choice maze (Hull et al., 1994), although another report found a diminution evaluated by precoital activity and the percentage of rats mounting (Ratnasooriya et al., 2000). nNOS KO mice have normal penile function, due to a compensatory increase in eNOS (Burnett et al., 1996) and achieve ejaculation with fewer mounts and intromissions (Kriegsfeld et al., 1999). Intraperitoneal injection of L-arginine increased the percentage of sexually naive rats that copulated and improved sexual performance in experienced males, whereas ICV injection of the NOS inhibitor N (G)-nitro-L-arginine methyl ester (L-NAME) impaired copulatory parameters only in sexually naive rats (Benelli et al., 1995). NO may control both copulation and gential reflexes via

actions in the mPOA, PVN, and spinal cord (see Sections 1.5.2.1, 1.5.2.4, and 1.5.3.5). In rodents the expression of NOS in regions implicated in the control of male sexual behavior is under the control of gonadal hormones (Panzica et al., 2006). NO also plays a crucial role in the initiation and maintenance of increased intracavernous pressure and penile erection by acting on smooth muscle cells (Toda et al., 2005).

s0220

1.4.8 Endocannabinoids

p0370 Endocannabinoids are neuromodulators in the CNS. The main endocannabinoids are small molecules derived from arachidonic acid: anandamide and 2-arachidonoylglycerol. Its neuronal receptor, the cannabinoid CB1 receptor, is located almost exclusively at axon terminals, where its stimulation inhibits neurotransmitter release (Freund et al., 2003). It has been found on glutamatergic terminals in hypothalamic nuclei related to reproductive function (Melis et al., 2006). Delta-9-tetrahydrocannabinol (THC), a cannabinoid CB1 receptor agonist, impairs copulation in mice (Shrenker and Barke, 1985) and rats (Murphy et al., 1994). Acute and subchronic treatment with the CB1 agonist HU 210 impaired copulation in sexually active male rats in a dose-dependent manner (Ferrari et al., 2000). Anandamide, the endogenous ligand for CB1 receptors, impairs male sexual behavior similarly to high doses of exogenous agonists (Martínez-González et al., 2004). A CB1 antagonist accelerated ejaculation, with male rats requiring fewer intromissions and less time to achieve ejaculation, while inhibition of anandamide reuptake with AM404 significantly increased IL (Gorzalka et al., 2008). CB1 receptor antagonism in the PVN of male rats has also been reported to induce penile erection (Melis et al., 2004a; Succu et al., 2006b). It has been hypothesized that CB1 receptor antagonists act at GABAergic and glutamatergic neurons to increase oxytocinergic transmission which in turn would promote penile erection and facilitate ejaculation (Castelli et al., 2007; Gorzalka et al., 2008). Together, the available data, although scarce, suggest that the endocannabinoid system has an inhibitory influence on copulatory responses that include erection and ejaculation.

s0225

1.4.9 Endogenous Opioids

p0375 Exogenous opiates such as morphine and heroin are known to have negative effects on the sexuality of male addicts, reducing sexual interest, impairing genital responses, and blocking ejaculation and orgasm (Pfaus and Gorzalka, 1987). Endogenous opioids belong to one of three major classes: endorphins, enkephalins, or dynorphins (Mains and Eipper, 1999). These peptides are generated by enzymatic processing from three precursor molecules, pro-opioimelanocortin (POMC), pro-enkephalin, and pro-dynorphin (Akil et al., 1984). An inhibitory role of endogenous opioid peptides in the control of male sexual behavior is commonly accepted, based on animal studies showing that acute and chronically administered morphine, heroin, and methadone inhibit copulatory behavior in males of various species (Pfaus and Gorzalka, 1987). Similar results have been obtained after injection of opioid peptides such as β-endorphin, morphicepin, and a Met-enkephalin analog into the mPOA (Hughes et al., 1987; Matuszewich and Dornan, 1992; Pellegrini-Quarantotti et al., 1978). When infused into the amygdala, they retard sexual performance (McGregor and Herbert, 1992b). Moreover, it has been reported that sexually inactive male rats have a constitutively increased basal concentration of the endogenous opioid octapeptide Met-Arg6-Gly7-Leu8 in the hypothalamus (Rodríguez-Manzo et al., 2002a), as well as increased expression of pro-enkephalin (the precursor of the endogenous octapeptide) and pro-dynorphin mRNAs in the PVN (Arletti et al., 1997), compared with sexually active animals.

p0380 Endogenous opioids exert their effects by acting on μ, δ, and κ receptor subtypes. The inhibitory actions of these peptides on copulation appear to be mainly mediated by μ and δ receptors, although involvement of κ opioid receptors has also been found. Systemic injection of the κ opioid receptor agonist U-50,488H inhibited several sexual parameters, which were differentially prevented by intra-VTA, intra-NAc, or intra-mPOA injections of the κ receptor antagonist nor-binaltorphimine (Leyton and Stewart, 1992). The inhibitory role of endogenous opioids in copulation is also suggested by studies showing that opioid receptor antagonists (e.g., naloxone and naltrexone) facilitate sexual behavior in sexually inactive rats (Gessa et al., 1979), facilitate the display of mounts and intromissions in sexually naive rats (Pfaus and Wilkins, 1995), reverse the sexual inhibition of sexually satiated rats (Rodríguez-Manzo and Fernández-Guasti, 1995a), decrease the ejaculatory threshold in sexually competent intact rats, and increase the percentage of ejaculating animals (Myers and Baum, 1979).

p0385 However, there are inconsistent effects of opioid agonists and antagonists on rodent male sexual

behavior. Although a large body of evidence points to the inhibitory nature of opioid agonist actions, there are also data suggesting facilitative effects of these peptides. Thus, increasing enkephalin levels by ICV administration of an enkephalinase inhibitor decreased IF and EL (Ågmo et al., 1994) and intra-VTA injection of morphine and dynorphin facilitated male sexual behavior and increased DA transmission in the NAc (Mitchell and Stewart, 1990). Opioid facilitation may result from disinhibition of mesolimbic DA neurons by acting at μ receptors on VTA GABAergic neurons that exert a tonic inhibitory influence on DA transmission (Balfour et al., 2004). On the other hand, opioid antagonists also have had inhibitory effects, increasing the duration of the PEI (McConnell et al., 1981; Sachs et al., 1981). Thus, a complex picture of potentially excitatory and inhibitory effects of endogenous opioids on male sexual behavior emerges. This complexity appears to be related to several factors, including dose-based, biphasic effects of agonists and antagonists, the brain site where they were administered, the time of the day when rats were tested, and the sexual activity level of the animals. Thus, the inhibitory effect of β-endorphin is dose dependent (Argiolas, 1999) and is believed to occur mainly through actions at the mPOA and the amygdala. In the former it disrupts copulatory behavior, while in the latter it disrupts precopulatory exploration (Bancroft, 1999). Systemically administered opioid receptor antagonists enhance sexual performance under certain testing conditions; for example, low doses of naloxone facilitated behavior when tested nocturnally, but not during the light phase (Van Ree et al., 2000). As to sexual activity level, naloxone in the mPOA facilitates sexual performance in poor copulators, but impairs it in average copulators (Van Ree et al., 2000), and low doses of both naloxone and naltrexone induce copulation in sexually satiated rats, while higher doses lose this ability (Rodríguez-Manzo and Fernández-Guasti, 1995a).

p0390 Evidence suggests that opioid peptides are released during sexual activity, since the physiological mechanisms of analgesia and reward are concurrently activated during sexual behavior (Szechtman et al., 1981), and both phenomena are blocked by naloxone (Ågmo and Berenfeld, 1990; Forsberg et al., 1987). In addition, increases in Met-enkephalin and the opioid octapeptide Met-Arg(6)-Gly(7)-Leu(8) were detected in the hypothalamus of rats that ejaculated once or copulated to satiation 24 or 48 h earlier (Rodríguez-Manzo et al., 2002a). Furthermore, the content of opioid octapeptide was higher in the hypothalamus of sexually inactive males, compared to sexually active males (Rodríguez-Manzo et al., 2002a). Mating-induced μ-opioid receptor internalization, a marker for ligand-induced receptor activation, was detected in the mPOA (Coolen et al., 2004b) and VTA (Balfour et al., 2004) of rats after one ejaculation.

p0395 Systemic morphine dose-dependently reduced the proportion of animals showing reflexive erections and virtually eliminated seminal emission; naloxone antagonized the effects of morphine, but the lowest dose, administered alone, also inhibited erectile response, suggesting that some opioid activity can facilitate sexual reflexes (Gomez-Marrero et al., 1988). Stimulation of CNS μ-opioid receptors prevents penile erection (reviewed in Andersson (2001)), and opioid mechanisms in the spinal cord appear to raise ejaculation threshold, since intrathecal morphine increased the IF before ejaculation (Wiesenfeld-Hallin and Södersten, 1984).

1.4.10 Oxytocin

s0230

p0400 OT is expressed in neurons of the magnocellular PVN and supraoptic nucleus (SON), both of which project to the posterior pituitary, and in parvocellular PVN neurons that project to several brain areas and the lumbosacral spinal cord, where erectile and ejaculatory reflexes are controlled. Either ICV or systemic injections of OT facilitated copulation in male rats (reduced EL and PEI); conversely, ICV injections of an OT antagonist impaired or abolished copulation in sexually experienced rats (reviewed in Argiolas and Melis (2005)). Facilitative effects were also seen in older (~20 months) rats that were sexually sluggish; OT treatment reduced MLs, ILs, ELs, and PEIs and increased the number of animals able to resume copulation after the first ejaculation (Arletti et al., 1990). Systemic OT also reversed the inhibitory effects of chronic fluoxetine, an SSRI, on the ability of male rats to ejaculate (Cantor et al., 1999). There was also a marked increase in OT in CSF after copulation (Hughes et al., 1987; see Section 1.5.2.4).

1.4.11 Prolactin

s0235

p0405 Prolactin (PRL) is secreted by the anterior pituitary into the general circulation. This peptide has a well-established role in lactation; however, PRL has been reported to have more than 300 functions across vertebrates, a majority of which relate to reproduction (Bancroft, 2005). Hyperprolactinemic patients have

low sexual desire often associated with erectile problems (Corona et al., 2007). Plasma PRL levels increase markedly following ejaculation and orgasm in men (Bancroft, 2005). This postorgasmic PRL increase may act as a feedback control of the refractory period following orgasm (Krüger et al., 2003). In line with this hypothesis, there is a case report of a multiorgasmic healthy man that showed no PRL response to three consecutive orgasms (Haake et al., 2002). Animal experiments confirm that chronic exposure to elevated PRL impairs male rat sexual response, increasing IL and EL and reducing reflexive erections; short-term PRL increase had either no effect or facilitated copulation (Melis and Argiolas, 1995).

s0240 #### 1.4.12 Gonadotropin-Releasing Hormone

p0410 Gonadotropin-releasing hormone (GnRH) is a peptide hormone, produced by the mediobasal hypothalamus, lamina terminalis, and the mPOA, that acts on the anterior pituitary where it stimulates gonadotropin release. Earlier studies found that GnRH, administered systemically or ICV, facilitated male sexual behavior in castrated rats maintained with low doses of T, but not in intact animals (Moss et al., 1975). By contrast, Myers and Baum (1980) found a facilitative effect of GnRH only in gonadally intact rats and not in castrates replaced with T. A facilitative action of GnRH on sexual motivation was also established in a mounting test in rats with penile anesthesia, after its ICV infusion (Dorsa and Smith, 1980). GnRH is released naturally when male rodents (mice and hamsters) encounter female vaginal fluid chemosignals (Westberry and Meredith, 2003), and GnRH-containing neurons are activated in male rats by estrous female odors (Kippin et al., 2003). In sexually naive hamsters, GnRH infused ICV restored mating behavior impaired by removal of VNOs (Meredith and Fernandez-Fewell, 1994). Systemic GnRH facilitates sexual behavior in hyperprolactinemic male rats treated with T (Dennison et al., 1996), and exogenous GnRH restores fertility and sexual activity in men with hypogonadism associated with low levels of circulating T (Mortimer et al., 1974).

p0415 However, adverse effects of GnRH treatment have also been reported. Thus, GnRH in old rhesus monkeys increased the PEI (Phoenix and Chambers, 1990). Chronic administration of a synthetic GnRH analog [(6-D-(2-napthyl)-alanine)GnRH] initially increased IL in intact rats, and eliminated sexual behavior 6–8 weeks later, along with a decrease in T (Dorsa et al., 1981). The inhibitory effects probably resulted from the continuous high doses of GnRH, which inhibit LH release and gonadal function, whereas endogenous GnRH is released in a pulsatile fashion. Studies in hypogonadal mice bearing a deletion of the GnRH encoding gene suggest that this peptide is not essential for male sexual behavior (Gibson et al., 1997).

s0245 #### 1.4.13 Orexin/Hypocretin

p0420 The orexin/hypocretin (orx/hcrt) peptides (orexin A and B/hypocretin 1 and 2) are produced in cells of the perifornical lateral hypothalamus that project widely to monoamergic nuclei in the midbrain and brainstem and to a number of basal forebrain areas, including the mPOA. These peptides are primarily known for their ability to regulate feeding and wakefulness; however, they can also enhance male sexual behavior. Their expression is hormonally regulated, being decreased after castration and restored by E_2; a slight increase by DHT was not statistically significant (Muschamp et al., 2007). Both copulation and estrous female odors increased Fos expression in orx/hcrt neurons, implying their activation during copulation; in addition, systemic administration of an orx/hcrt antagonist (SB334867) delayed the onset of copulation and decreased the number of ejaculations per 30-min test (Muschamp et al., 2007; please see Hull et al. (2006), for discussion of effects of other neuropeptides).

s0250 ## 1.5 Brain Areas and Circuitry Implicated in the Control of Masculine Sexual Behavior

s0255 ### 1.5.1 Sensory Inputs

s0260 #### *1.5.1.1 Olfactory bulbs*

p0425 Chemosensory signals are transduced in the olfactory mucosa and VNO and are transmitted to the olfactory bulbs. The importance of chemosensory cues varies across species, but these cues are especially important in rodents and other nocturnal species. The olfactory system includes the anatomically and functionally distinct main and accessory olfactory systems. Volatile odors, processed by the main olfactory system, 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 chemosensory cues, or pheromones, are detected in the VNO, located at the base of the nasal cavity and projecting to the accessory olfactory bulb (AOB). While vomeronasal cues are important in rodents and other macrosmotic animals, the VNO and AOB are regressed in humans and may be nonfunctional.

s0265 p0430

1.5.1.1(i) Effects of lesions

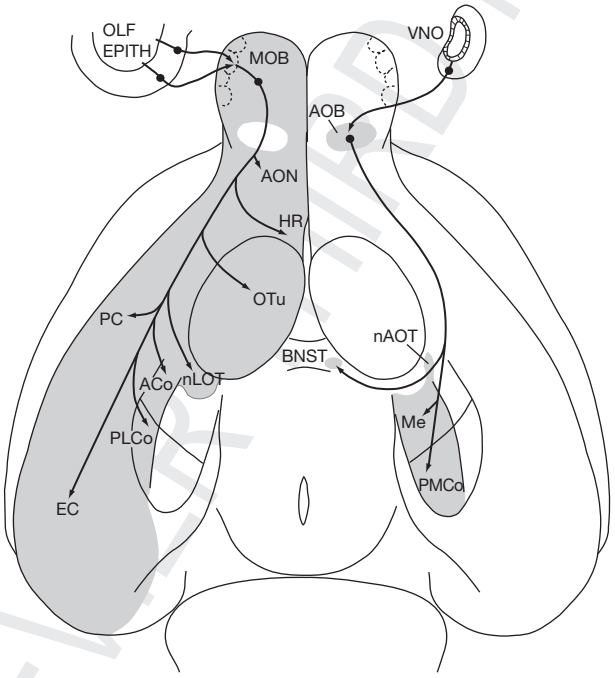
s0275 ### *1.5.1.2 Amygdala*

s0280 #### *1.5.1.2(i) Anatomy*

p0455 There is controversy about whether the amygdala should be regarded as a single entity or a collection of nuclei that contribute to learning, motivation, and fear (central nucleus and basolateral division) or to chemosensory processing and social behaviors (corticomedial division) (Swanson and Petrovich, 1998). Clearly, the corticomedial region is very important for male rodent sexual behavior, serving as an integration site for chemosensory, somatosensory, and hormonal stimuli and projecting to the mPOA and other central regulatory areas. The AOB projects via the lateral olfactory tract to the medial and posteromedial nuclei, while the MOB projects diffusely to the anterior and posterolateral cortical nuclei and to the ventral allocortex (**Figure 3**). The MeA also receives somatosensory input from the genitals, relayed via the subparafascicular nucleus, which also projects directly to the mPOA. In addition, there are abundant ERs and ARs in the MeA, especially the posterior subnucleus, and in the mPOA and other hypothalamic nuclei. The volume and soma size of the posterodorsal quadrant of the MeA (MeApd) are larger in male than in female rats (Cooke et al., 1999; Hines et al., 1992), and are maintained by stimulation of both ARs and ERs (Cooke et al., 2003). Males also have more neurons and glial cells in that area; although the number of glia is influenced by circulating androgens, neuron number appears to be organized before adulthood (Morris et al., 2008).

1.5.1.2(ii) Effects of lesions s0285

p0460 Lesions of the central nucleus and basolateral division have little effect on copulation, although they do impair conditioned responses during fear and



f0015 **Figure 3** Diagram of the ventral surface of the hamster brain. Shaded areas indicate brain regions that receive efferent projections of the olfactory system, via the main olfactory bulb (left), and of the vomeronasal system, via the accessory olfactory bulb (right). ACo, anterior cortical nucleus of the amygdala; AOB, accessory olfactory bulb; AON, anterior olfactory nucleus; BNST, bed nucleus of the stria terminalis; EC, entorhinal cortex; HR, hippocampal rudiment; MeA, medial nucleus of the amygdala, anterior division; MeP, medial nucleus of the amygdala, posterior division; MOB, main olfactory bulb; nAOT, nucleus of the accessory olfactory tract; nLOT, nucleus of the lateral olfactory tract; OLF EPITH, olfactory epithelium; OTu, olfactory tubercle; PC, piriform cortex; PLCo, posterolateral cortical nucleus of the amygdala; PMCo, posteromedial cortical nucleus of the amygdala; VNO, vomeronasal organ. Reprinted from Wood RI and Newman SW (1995b) Hormonal influence on neurons of the mating behavior pathway in male hamsters. In: Micevych PE and Hammer RP, Jr. (eds.) *Neurobiological Effects of Sex Steroid Hormones*, ch. 1, pp. 3–39. New York: Cambridge University Press, with the permission of Cambridge University Press.

reinforcement (reviewed in Everitt (1990)). In contrast, corticomedial lesions do impair copulation, with the severity dependent on the specific location and the species. Anterior MeA lesions abolish copulation in male hamsters, while more posterior lesions impair, but do not eliminate, mating (Lehman et al., 1980). A more recent study reported that lesions of the MeApd in male hamsters decreased attraction to female odors, but anterior MeA lesions led to prolonged investigation of both male and female odors (Maras and Petrulis, 2006). The authors suggested that the MeApd may increase arousal toward relevant social stimuli, whereas the anterior MeA may filter stimuli and direct the arousal toward appropriate social cues. In rats (de Jonge et al., 1992; Dominguez et al., 2001; Kondo, 1992; McGregor and Herbert, 1992a) and gerbils (Heeb and Yahr, 2000), MeA lesions delay and slow copulation and increase the intromissions required to elicit ejaculation.

p0465 Radiofrequency lesions of the posterior MeA of male rats eliminated noncontact erections and decreased preference for an estrous female, but did not affect copulation (Kondo and Sachs, 2002; Kondo et al., 1998). A subregion of the MeApd has been linked to sexual satiety. Lesions of the MeApd in male hamsters delayed sexual satiety (Parfitt et al., 1996; see Section 1.5.1.3).

s0290 ***1.5.1.2(iii) Activation of c-fos or other immediate-early genes***

p0470 Chemosensory stimuli can induce Fos-ir in the corticomedial amygdala in rats (Bressler and Baum, 1996; Coolen et al, 1997b; Kelliher et al., 1999), hamsters (Fernandez-Fewell and Meredith, 1994; Fiber et al., 1993; Kollack and Newman, 1992), and gerbils (Heeb and Yahr, 1996). Increasing amounts of sexual behavior elicited increasing amounts of Fos-ir in nuclei of the amygdala of rats (Baum and Everitt, 1992; Coolen et al., 1996; Veening and Coolen, 1998), with the largest number of Fos-ir cells in the MeA, especially the posterior subnucleus, and fewer in the anterior and posteromedial cortical nuclei (Kollack and Newman, 1992). Mating also elicited Fos-ir in amygdaloid nuclei of hamsters (Kollack-Walker and Newman, 1992, 1997), gerbils (Heeb and Yahr, 1996), prairie voles (Wang et al., 1997), and musk shrews (Gill et al., 1998). In gerbils the medial part of the MeApd was activated (Fos-ir) by sex-related odors, whereas the lateral portion was activated only after ejaculation (Heeb and Yahr, 1996). Similarly, in hamsters Fos-ir in the MeApd was correlated with the onset of satiety (Parfitt and Newman, 1998). Fos-ir in the MeA, but not in the mPOA, of male rats was correlated with the length of the PEI (Lumley and Hull, 1999), suggesting that some neurons in that area may contribute to postejaculatory quiescence. In rats (Gréco et al., 1998b) and hamsters (Wood and Newman, 1993), AR-containing cells in the posterior MeA are activated by mating, though castration did not reduce mating-induced Fos-ir in the MeA of rats (Baum and Wersinger, 1993) or odor-induced Fos-ir in the MeA of hamsters (Swann, 1997). Similarly, mice lacking the gene for aromatase had similar response to odors as in wild-type mice (Aste et al., 2003).

1.5.1.2(iv) Effects of hormone implants s0295

In castrated male rats, bilateral T implants in the p0475 MeA delayed the loss of mating and of noncontact erections (Berendsen and Broekkamp, 1987), and E implants stimulated mounting, but not ejaculation (Huddleston et al., 2003). Similarly, in castrated hamsters either T (Wood, 1996) or E (Coolen and Wood, 1999; Wood and Coolen, 1997), but not DHT (Wood, 1996), implants in the MeA restored copulation. However, DHT implants were successful in male rats treated with subthreshold systemic injections of E (Baum et al., 1982). Either an ER antagonist in male hamsters (Wood and Williams, 2001), or an aromatase (Huddleston et al., 2006) or AR (McGinnis et al., 1996) antagonist in male rats impaired, but did not block, copulation, suggesting that both androgenic and estrogenic stimulation contributes to mating in male rats and hamsters. Furthermore, MeA implants of E_2 conjugated to bovine serum albumin (which prevents E_2 from crossing the membrane) was ineffective in maintaining mating behavior (Huddleston et al., 2006), suggesting an intracellular mechanism of action. Because both hormonal and chemosensory stimuli are critical for mating in male hamsters, and are processed in the MeA, their interactions were probed. Unilateral olfactory bulbectomy, either ipsi- or contralateral to a T implant in the posterior MeA of castrated hamsters, rendered the implant ineffective (Wood and Coolen, 1997), suggesting that bilateral chemosensory input is essential for T in this nucleus to stimulate sexual behavior. However, with similar T implants in both the mPOA and BNST, only ipsilateral bulbectomy blocked the facilitation by T (Wood and Newman, 1995c). Thus, communication between groups of neurons that process hormonal and chemosensory stimuli is critical for male hamster sexual behavior.

s0300 #### 1.5.1.2(v) Microinjections of drugs

p0480 Microinjection of the 5-HT_{1A} agonist 8-OH-DPAT into the MeApd speeded the onset of copulation and decreased the PEI in male rats (de Castilhos et al., 2006). Therefore, the MeApd is one site at which 5-HT_{1A} agonists facilitate copulation. Angiotensin microinjections into the MeA impaired copulation in male rats; however, it is not clear whether increased thirst may have interfered with sexual behavior (Breigeiron et al., 2002).

s0305 #### 1.5.1.2(vi) Amygdaloid efferents

p0485 A major output of the MeA is to the mPOA. Unilateral lesions of the mPOA impaired, but did not abolish copulation in male rats; however, contralateral lesions of the MeA and mPOA severely disrupted sexual behavior (Kondo and Arai, 1995). Similar results were reported for gerbils (Heeb and Yahr, 2000). Chemical stimulation of the MeA increased DA release in the mPOA (Dominguez and Hull, 2001), and microinjection of the DA agonist apomorphine into the mPOA restored copulation that had been abolished by large excitotoxic lesions of the MeA (Dominguez et al., 2001). Basal extracellular DA in the mPOA was not affected by small radiofrequency MeA lesions, but the DA release in response to a female and during copulation was eliminated by the lesions, which also impaired, but did not abolish, copulation (Dominguez et al., 2001). Indeed, chemical stimulation of the MeA elicited DA release in the mPOA of a magnitude similar to that observed during copulation (Dominguez and Hull, 2001). Thus, it appears that one result of MeA activity is to increase DA in the mPOA in anticipation of, and during, mating. There are no dopaminergic neurons in the MeA of rats; therefore, efferents from the MeA may activate, either directly or indirectly, dopaminergic cell bodies or terminals in the mPOA and thereby facilitate mating.

s0310 ### 1.5.1.3 Bed nucleus of the stria terminalis

s0315 #### 1.5.1.3(i) Anatomy

p0490 Output from the MeA travels either directly to the mPOA or to synapses in the BNST, which then relays the information to the mPOA and other sites. The posteromedial division of the BNST is especially relevant to the control of male sexual behavior (Alheid et al., 1995). As with the posterior MeA, the posteromedial BNST has abundant steroid hormone receptors (Li et al., 1993; Simerly et al., 1990; Wood and Newman, 1993).

1.5.1.3(ii) Effects of lesions

s0320

p0495 In male rats and hamsters the more dorsal part of the BNST appears to contribute more to preparation for mating than to copulation *per se* (reviewed in Hull et al. (2006)). In rats, lesions decreased the number of noncontact erections and slowed the rate of copulation, but did not affect the intromission ratio, suggesting that *in copula* erections were unaffected; in contrast, lesions of the mPOA had little effect on noncontact erections but severely impaired copulation (Liu et al., 1997b). Finn and Yahr (2005) suggested that previous studies that showed little effect on copulation targeted the dorsal part of the BNST. In contrast, they made excitotoxic lesions of the ventral BNST (vBNST), which projects to the retrorubral field (A8) of the midbrain and other downstream sites. vBNST lesions in rats resulted in severe copulatory deficits, although damage to the adjacent posterodorsal preoptic nucleus may have contributed to the impairment (Finn and Yahr, 2005). The authors suggested that the vBNST in rats may be the counterpart to the gerbil sexually dimorphic area (SDA) of the preoptic area, which is critical for male gerbil sexual behavior. In gerbils, contralateral lesions of the caudal medial BNST and the SDA severely impaired copulation, but contralateral lesions of the MeA and SDA produced less of a deficit, suggesting that the caudal medial BNST does more than simply transmit information from the MeA to the SDA (Sayag et al., 1994).

1.5.1.3(iii) Activation of c-fos or other immediate-early genes

s0325

p0500 In male rats, hamsters, and gerbils, copulation or, to a lesser extent, exposure to female odors elicits Fos-ir in the BNST, especially in the posterior and medial subdivisions (Coolen et al., 1996; Fernandez-Fewell and Meredith, 1994; Heeb and Yahr, 1996; Kelliher et al., 1999; Kollack-Walker and Newman, 1995). In contrast, mating decreased Fos-ir in male macaques (Michael et al., 1999), and female odors did not affect Fos-ir in male ferrets (Kelliher et al., 1998).

1.5.1.3(vi) Hormonal effects

s0330

p0505 There are abundant steroid receptors in the posteromedial BNST, extending from the stria terminalis to the MPN (Li et al., 1993; Simerly, 1995; Simerly et al., 1990; Wood and Newman, 1993). Castration decreased, and T restored, immunoreactivity to cholecystokinin (CCK) in the encapsulated portion of the BNST

(Simerly and Swanson, 1987). Similar effects were seen in sexually dimorphic areas of the MeA and MPN.

s0335 #### 1.5.1.4 Central tegmental field/ subparafascicular nucleus of the thalamus

s0340 ##### 1.5.1.4(i) Anatomy

p0510 There are reciprocal connections between the midbrain tegmentum and the mPOA, MeA, and anterior hypothalamus (Coolen et al., 1998, 2003; Gréco et al., 1999, 1998b; Murphy et al., 1999a; Simerly, 1995; Simerly and Swanson, 1988). Subregions of the tegmentum have been referred to as the central tegmental field (CTF; e.g., Baum and Everitt, 1992; Gréco et al., 1999; Simerly and Swanson, 1986) or dorsolateral tegmentum (DLT; e.g., Edwards and Einhorn, 1986; Giordano et al., 1998; Maillard and Edwards, 1991). The CTF/DLT is dorsal to the lateral half of the substantia nigra and includes the subparafascicular nucleus (SPFp), part of the zona incerta, the peripeduncular nucleus, the mesencephalic reticular nucleus, and the anterior pretectal nucleus. The medial parvocellular division of the SPFp relays somatosensory input from the genitals to the mPOA and MeA. It is considered to be part of an ejaculation circuit.

s0345 ##### 1.5.1.4(ii) Effects of lesions

p0515 Bilateral neurotoxic lesions of the CTF decreased the percentages of male rats that could mount, intromit, and ejaculate (Romero-Carbente et al., 2007). Partner preference and sexual incentive motivation were not affected. Even misplaced lesions in adjacent areas impaired behavior, suggesting that the effects were not specific to the CTF. In tests 3 weeks after the lesion, copulation had returned to normal. Earlier studies reported more severe deficits (Brackett and Edwards, 1984; Giordano et al., 1998), and contralateral lesions of the mPOA and CTF impaired both copulation and pursuit and sniffing of the female (Edwards and Einhorn, 1986). Combined ipsilateral lesions of the CTF and MeA abolished mating-induced Fos-ir in the mPOA, whereas single lesions of each did not (Baum and Everitt, 1992). Bilateral SPFp lesions in gerbils did not affect copulation, suggesting that the Fos-ir elicited in that nucleus following ejaculation resulted from sensory input, rather than motor control of ejaculation (Heeb and Yahr, 2000). However, in male rats the SPFp has been shown to receive projections from lumbar spinothalamic neurons (Coolen et al., 2003), which are essential for ejaculation (Truitt and Coolen, 2002) and express ejaculation-related Fos-ir (Truitt et al., 2003).

1.5.1.4(iii) Activation of c-fos or other immediate-early genes

s0350

p0520 Fos-ir was selectively increased in either the CTF or SPFp after ejaculation in rats (Baum and Everitt, 1992; Coolen et al., 1997b, 1996; Wersinger et al., 1993), gerbils (Heeb and Yahr, 1996), hamsters (Kollack-Walker and Newman, 1997), and musk shrews (Gill et al., 1998). Fos-ir was not increased after chemosensory investigation, mounts, or intromissions. In men, ejaculation stimulated blood flow in the SPFp, as measured with positron emission tomography (PET) (Holstege et al., 2003). Also, electrical stimulation of the CTF facilitated mating in rats (Shimura and Shimokochi, 1991).

1.5.1.4(iv) Presence of steroid receptors

s0355

p0525 SPFp neurons contain ARs (Gréco et al., 1996), and many AR-ir neurons that project to the mPOA express ejaculation-induced Fos-ir (Gréco et al., 1998b).

1.5.1.4(v) Connections

s0360

p0530 The medial SPFp contains many galanin-ir fibers, and neurons containing mating-induced Fos-ir in the medial SPFp are surrounded by galanin-ir fibers (Veening and Coolen, 1998). Neurons in laminae 7 and 10 of the lumbosacral spinal cord project to the medial SPFp (Coolen et al., 2003; Gréco et al., 1999; Truitt et al., 2003), which also connects reciprocally with forebrain nuclei that control copulation (Coolen et al., 2003). Therefore, galanin may convey ejaculation-related somatosensory input through the SPFp to higher brain areas.

1.5.2 Major Integrative Sites

s0365

1.5.2.1 Medial preoptic area

s0370

1.5.2.1(i) Anatomy

s0375

p0535 The mPOA is a critical integrative site for male sexual behavior in all vertebrate species tested. This is remarkable, in that a wide range of sensory stimuli elicit mating, and diverse motor patterns comprise the species-specific behaviors. Every sensory modality sends indirect input to the mPOA, and reciprocal connections allow the mPOA to modify the processing of sensory input (Simerly and Swanson, 1986). Furthermore, steroid receptors in the mPOA and its major afferents can bias input to favor sexually relevant stimuli. Efferents from the mPOA to hypothalamic, midbrain, and brainstem nuclei regulate somatomotor or autonomic patterns and motivational

states (reviewed in Simerly and Swanson (1988) and Yahr (1995)).

p0540 The mPOA comprises heavily interconnected subnuclei with various functions, connections (Maragos et al., 1989; Simerly et al., 1986), and neurotransmitter content (Simerly et al., 1986). A medial periventricular zone regulates neuroendocrine function, and a medial zone, including MPN and posterodorsal preoptic nucleus (PdPN), controls male sexual behavior and maternal behavior. The mPOA is essential for copulation and contributes to sexual motivation.

s0380 ***1.5.2.1(ii) Effects of lesions***

p0545 Large lesions of the mPOA abolish copulation in numerous species ranging from monkeys to fish (reviewed in Hull et al. (2006)). Similar effects are obtained with electrolytic lesions, which destroy both cell bodies and axons passing through, and axon-sparing neurotoxic lesions; thus, neurons in the mPOA are critical for activating copulation. Generally, more severe deficits were found with more caudal lesions that included portions of the anterior hypothalamus. Smaller lesions have produced less severe deficits. In gerbils, small lesions of the posterodorsal preoptic nucleus, which is activated selectively by ejaculation (Heeb and Yahr, 1996), decreased mounting and delayed ejaculation (Heeb and Yahr, 2000). Unilateral lesions of the medial SDA in gerbils together with lesions of the contralateral lateral SDA impaired copulation as effectively as bilateral lesions of each (Yahr and Gregory, 1993).

p0550 Large mPOA lesions disrupt the initiation of copulation as well as its performance, suggesting that it contributes to sexual motivation. However, male rats, cats, dogs, and monkeys showed interest in sexual behavior even after mPOA lesions abolished their ability to copulate (reviewed in Everitt (1990) and Hull et al. (2006)). Similarly, noncontact erections were not affected by lesions that abolished copulation (Liu et al., 1997b). This apparent dissociation of copulatory performance and sexual motivation following mPOA lesions led Everitt to suggest that the mPOA controls only copulatory performance and not sexual motivation (Everitt, 1990).

p0555 However, mPOA lesions have decreased sexual motivation in several contexts, including female partner preference in rats (Edwards et al., 1996; Paredes et al., 1998) and ferrets (Kindon et al., 1996; Paredes and Baum, 1995), pursuit of a female by male rats (Paredes et al., 1993), or precopulatory behaviors in marmosets (Lloyd and Dixson, 1988). Similarly, inactivation of the mPOA with lidocaine impaired both copulation and sexual incentive motivation (Hurtazo et al., 2008). Thus, mPOA lesions do not eliminate sexual motivation, but they clearly diminish it. The evolutionary conservation of mPOA influence on both sexual performance and motivation is seen in studies of Japanese quail and starlings, in which small mPOA lesions decreased time spent in front of a window through which the male could see a female (Balthazart et al., 1998) or reduced singing and gathering of nesting materials (Riters and Ball, 1999).

s0385 ***1.5.2.1(iii) Effects of electrical or chemical stimulation***

p0560 Because mPOA lesions impair male sexual behavior, it was expected that stimulation would facilitate it, and, indeed numerous early studies of rats, guinea pigs, and opossums showed such facilitative effects (reviewed in Hull et al. (2006)). Decreases in mounts and intromissions preceding ejaculation and shortened ejaculation latency and PEIs were reported. A more recent study found facilitation of copulation following electrical stimulation of the mPOA of male rats; however, such stimulation did not restore copulation 24 h after they had copulated to sexual satiety (Rodríguez-Manzo et al., 2000). Furthermore, combining electrical stimulation with subthreshold doses of the DA agonist apomorphine or the α_2-adrenoceptor antagonist yohimbine was also ineffective. Higher doses of both drugs had previously restored sexual behavior in satiated males (Rodríguez-Manzo, 1999b). Therefore, sexual satiety and postejaculatory quiescence may be based on different neural mechanisms.

p0565 Repeated electrical stimulation of the mPOA in previously noncopulating male rats resulted in kindling (increased after discharges leading to a seizure) and to the ability of most males to copulate on subsequent stimulation-free tests (Paredes et al., 1990). Males that could initially copulate without stimulation were not further facilitated. In another study, kindling-like stimulation that did not produce a seizure nevertheless facilitated copulation for at least 8 months in previously noncopulating rats (Portillo et al., 2003). Even in T-treated female rats, mPOA kindling resulted in male-like sexual behavior (Dominguez-Salazar et al., 2003).

p0570 Either electrical or glutamatergic stimulation of the mPOA of anesthetized rats increased intracavernous pressure (Giuliano et al., 1996; Sato et al., 2001) and elicited the UG reflex, even without urethral stimulation (Marson and McKenna, 1994b). The effects of

mPOA stimulation on intracavernous pressure were enhanced by intrathecal injection of an NO donor, a cGMP analog, and sildenafil, and were inhibited by the NOS inhibitor L-NAME (Sato et al., 2001). Axons from the mPOA do not project directly to the lumbosacral spinal cord, where erection and ejaculatory reflexes are controlled; thus, efferents from the mPOA must stimulate downstream sites that then regulate the reflexes. However, the mPOA is not necessary for genital reflexes, since mPOA lesions have minimal effect on noncontact erections (Liu et al., 1997b), reflexive erections (Szechtman et al., 1978), or spontaneous seminal emission (Ågmo et al., 1977).

s0390 ***1.5.2.1(iv) Effects of direct application of steroids or steroid antagonists***

p0575 Numerous studies have shown facilitative effects of steroid implants in the mPOA of castrated rats, ferrets, birds, and lizards (reviewed in Hull et al. (2006)). However, these implants have not resulted in complete copulatory behavior, as other central and peripheral targets also require hormonal priming. Aromatization of T to E in the mPOA is important for T's facilitative effects. The aromatase inhibitor fadrozole, microinjected into the mPOA of gonadally intact male rats inhibited copulation; only the mPOA contained numerous unoccupied ERs as a result of the inhibitor, suggesting that the inhibitor had not spread to other sites (Clancy et al., 1995). Conversely, implantation of E into the mPOA of intact males treated systemically with fadrozole increased MF,

fully restored copulatory ability of males whose large excitotoxic lesions of the amygdala had severely impaired their ability to copulate (Dominguez et al., 2001).

p0595 D_1- and D_2-like receptors in the mPOA appear to have different roles in the regulation of copulation. Stimulation of D_1-like receptors has facilitated copulation and reflexive erections, whereas stimulation of D_2-like receptors has produced dose-dependent effects (reviewed in Dominguez and Hull (2005) and Hull et al. (2006)). A low dose of the D_3/D_2 agonist quinelorane decreased the latency to the first *ex copula* reflex without affecting the numbers of reflexes, suggesting a disinhibition of reflexes; however, a high dose of quinelorane, or of the D_1 antagonist SCH-23390, decreased erections but increased sympathetically mediated seminal emissions (Bazzett et al., 1991). The D_1 agonist dihydroxyphenyltetrahydrothienopyridine (THP) increased reflexive erections and facilitated copulation but inhibited *ex copula* seminal emissions (Hull et al., 1995; Markowski et al., 1994). Experiments using low and high doses of apomorphine with D_1- and D_2-like antagonists also support the suggestion that stimulation of D_1-like receptors promotes erections, while intense stimulation of D_2-like receptors facilitates ejaculation (Hull et al., 1992). Similarly, in tests of copulation the D_1-like agonist increased copulatory efficiency (Markowski et al., 1994), and the D_1-like antagonist increased intromission latency but decreased the threshold for ejaculation (Hull et al., 1989). The antagonist also decreased sexual motivation (choice of the female in an X-maze) (Moses et al., 1995). Similarly to the D_1-like antagonist, a high dose of the D_3/D_2 agonist quinelorane delayed the start of copulation, but decreased ejaculation threshold (Hull et al., 1989; Moses et al., 1995). It is not clear whether the dose-dependent effects of quinelorane are mediated by different subtypes of D_2-like receptors or by different populations of neurons that are under different levels of tonic inhibition. However, the data consistently support the hypothesis that stimulation of D_1-like receptors increases parasympathetically mediated erections and the early phase of copulation, whereas stimulation of D_2-like receptors shifts the autonomic balance to favor sympathetically mediated ejaculation. This hypothesis has been recently supported by a review that included unpublished data showing that the preferential D_3 agonist 7-OH-DPAT, microinjected into the mPOA, elicited ejaculation-related events in anesthetized male rats (Peeters and Giuliano, 2008).

1.5.2.1(vii) Serotonin s0405

p0600 Microinjection of large doses of 5-HT into the mPOA inhibited copulation (Fernández-Guasti et al., 1992; Verma et al., 1989) and a 5-HT_{1B} agonist delayed ejaculation (Fernández-Guasti et al., 1992). As with systemic injections of 5-HT_{1A} agonists, reverse-dialysis of 8-OH-DPAT into the mPOA facilitated copulation (Matuszewich et al., 1999) and increased both DA and 5-HT levels (Lorrain et al., 1998). The D_2 antagonist raclopride partially blocked the effects of 8-OH-DPAT, but the 5-HT_{1A} antagonist did not, suggesting that elevation of extracellular DA levels resulted in stimulation of D_2 receptors in the mPOA, which mediated much of the facilitation (Matuszewich et al., 1999). Microinjection of an SSRI (alaproclate) into the mPOA did not significantly affect behavior, although it did inhibit copulation when microinjected into the anterior LH (Lorrain et al., 1997).

1.5.2.1(viii) Gamma-aminobutyric acid s0410

p0605 High concentrations of GABA have been reported in the mPOA of male rat brains (Andersson, 2001) as well as in mating-activated neurons of this brain area and of the MeA in male gerbils (Simmons and Yahr, 2003). Enhancement of GABAergic transmission in the mPOA by blocking GABA degradation or stimulating $GABA_A$ receptors with muscimol reduced the proportion of copulating rats (Fernández-Guasti et al., 1986a). Inhibition of GABA synthesis or blockade of $GABA_A$ receptors within the mPOA had a potent stimulatory effect on male rat sexual behavior, expressed by a marked reduction of the PEI (Fernández-Guasti et al., 1986a) and the virtual elimination of the ultrasonic vocalizations that accompany the absolute refractory period (Fernández-Guasti et al., 1986b). However, bicuculline did not restore copulation in satiated male rats, suggesting that sexual satiety is regulated by mechanisms different from those that control the PEI (Rodríguez-Manzo et al., 2000).

1.5.2.1(ix) Opioids s0415

p0610 The lowest dose of the μ agonist morphine and of the κ agonist dynorphin (1–13), microinjected into the mPOA, facilitated copulation, but the highest dose of morphine led to failure to resume mating after the second ejaculation (Band and Hull, 1990). The μ agonist morphiceptin increased the latency to copulate, but did not affect copulatory performance, motivation, or locomotion (Matuszewich et al., 1995). However, β-endorphin delayed the start of mating

and inhibited its performance (Holmes et al., 1997; van Furth et al., 1995). In support of facilitative effects of low levels of opioids in the mPOA, the antagonist naloxone in the mPOA prevented the induction of sexual reinforcement (Ågmo and Paredes, 1988).

s0420 ***1.5.2.1(x) Norepinephrine***

p0615 Microinjection of NE into the mPOA facilitated both sexual arousal and copulation, whereas the α-adrenergic antagonist phenoxybenzamine and the β-adrenergic antagonist propranolol inhibited mating (Mallick et al., 1996). Stimulating autoreceptors with the α_2

1988a,b) and prostaglandin E_2 (Clemens and Gladue, 1977) in the mPOA (reviewed in Hull et al. (2006)).

s0440 ***1.5.2.1(xiv) Electrophysiological recordings***

p0635 Some neurons in the mPOA increased their firing rates only before male rats began to mate, and others increased their firing only during copulation (Shimura et al., 1994). mPOA neurons in monkeys also responded differentially during lever pressing to gain access to a female and during copulation; activity decreased markedly after ejaculation (Oomura et al., 1988). In mPOA slices from male quail, bath applications of DA inhibited 52–80% of cells, but excited 10–25% (Cornil et al., 2002). The inhibitory and excitatory effects were mediated by α_2- and α_1-adrenoreceptors, respectively. Therefore, in the quail mPOA DA affects neural activity via crosstalk with NE receptors. In voltage-clamp recordings from dissociated neurons from the mPOA of male rats, with presynaptic nerve endings intact, 5-HT inhibited both GABAergic miniature inhibitory postsynaptic currents (mIPSCs) and glutamatergic miniature excitatory postsynaptic currents (mEPSCs) (Lee et al., 2008). The inhibition of mIPSCs was mediated by 5-HT_{1A} receptors, whereas the inhibition of mEPSCs was mediated by 5-HT_{1B} receptors. The authors suggest that stimulation of adenylyl cyclase, and the consequent activation of PKA, increase mIPSCs and mEPSCs and counteract the effects of 5-HT. Therefore, even though 5-HT did not increase in the mPOA at the time of ejaculation (Lorrain et al., 1997), and an SSRI microinjected into the mPOA did not significantly impair behavior (Lorrain et al., 1997), 5-HT may influence sexual behavior by reducing the effects of GABAergic and glutamatergic transmission.

s0445 ***1.5.2.1(xv) Chemical changes detected by microdialysis or from tissue punches***

p0640 There is a close relationship between extracellular DA levels in the mPOA and male rat sexual behavior. DA levels rose when an inaccessible female was introduced and remained high or increased further during copulation (Hull et al., 1995; Sato et al., 1995). The recent presence of T was permissive for both copulation and DA release, with two-thirds of 1-week castrates able to copulate and to show a DA response to the female, while no 2-week castrate could copulate or show a DA response (Hull et al., 1995). There was both anatomical and behavioral specificity for the DA response (Hull et al., 1995, 1993). The fact that DA increased before copulation began suggests that the increase was not caused by copulation, but was likely associated with sexual motivation. Not only is the DA response to the female lost after castration, but basal extracellular levels are also lower than in gonadally intact males; however, intracellular levels were actually higher than in intact males (Du et al., 1998). Therefore, synthesis and storage of DA in the mPOA was at least as great in castrates as in intact males; the deficiency in castrates was in their ability to release their abundant stores. Restoration of T for 2, 5, or 10 days resulted in increasing sexual behavior and DA response to the female (Putnam et al., 2001). No 2-day T-treated castrate could copulate or show a DA response; eight of nine 5-day T-treated castrates copulated and showed a DA response, with five of the eight able to ejaculate. All of the 10-day T-treated castrates copulated and all showed the DA response. There were numerous correlations between DA levels and copulatory measures. Therefore, both the loss of copulation following castration and its restoration by T are closely associated with the female-elicited DA response in the mPOA. E and DHT were differentially effective in restoring basal and female-stimulated DA release in long-term castrates (Putnam et al., 2003). E_2 resulted in high basal DA levels but no increase in response to a female; E_2-treated castrates intromitted, but did not show an ejaculation pattern. DHT was no more effective than the oil vehicle in restoring copulation and basal and female-stimulated DA levels. However, the combination of E_2 and DHT fully restored both basal and female-stimulated DA levels, as well as copulation. In contrast to the positive correlations between extracellular DA and behavior, tissue (stored) DA levels were negatively correlated with mating, suggesting that tissue DA levels are high because it cannot be released (Putnam et al., 2005). A similar relation between apparent DA release and ability to copulate was reported in male hamsters (Schulz et al., 2003). Adult males had an increase in the major metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in punches from the mPOA in response to vaginal secretions from female hamsters. The increase in DOPAC is taken as evidence that DA was released, transported back into the axon terminal, and metabolized. Juveniles showed no such increase and were also unable to copulate.

p0645 DA release in the mPOA is regulated by NO. Both basal (Lorrain and Hull, 1993) and copulation-induced (Lorrain et al., 1996) extracellular DA levels were dependent on NOS activity. As noted above, T and E positively regulate NOS-ir in the mPOA.

Thus, gonadal steroids may maintain DA levels in the mPOA by upregulating NOS.

p0650 A major stimulus for the DA response to a female is input from the MeA. Small radiofrequency lesions of the MeA impaired copulation and abolished the mPOA DA response to the female but did not affect basal DA levels in the mPOA (Dominguez et al., 2001). Thus, as with E_2 restoration of copulation in castrates (Putnam et al., 2003), basal DA levels in the mPOA were sufficient for suboptimal mating ability, but an additional increase in response to a female is required for optimal copulation. As noted above, microinjections of apomorphine into the mPOA completely restored copulation in males with large excitotoxic lesions of the amygdala (Dominguez et al., 2001), providing additional evidence that a major way in which the MeA facilitates sexual behavior is by increasing extracellular DA in the mPOA in response to a female. In agreement with a facilitative effect of DA, chronic systemic administration of an extract of ginkgo biloba increased tissue DA levels in the mPOA and arcuate nucleus, decreased serum prolactin, and facilitated copulation (Yeh et al., 2008). Similarly, tissue levels of DA in the mPOA and arcuate were higher in middle-aged rats that could copulate to ejaculation, compared to middle-aged males that could not copulate or that could mount and intromit, but not ejaculate (Chen et al., 2007). Tissue levels of NE were not different among the groups.

p0655 Chemosensory stimuli processed by the olfactory bulbs provide the major signal relayed by the amygdala to the mPOA of rodents. In male hamsters with sham bulbectomies, or with unilateral bulbectomy contralateral to the mPOA microdialysis probe, presentation of an estrous female increased DA levels, and animals copulated to ejaculation (Triemstra et al., 2005). Males with ipsilateral bulbectomy also copulated to ejaculation, but there was no female-stimulated DA response. Bilateral bulbectomy abolished both copulation and the DA response to the female. Therefore, chemosensory stimuli are essential for the mPOA DA response in male hamsters.

p0660 The 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) was increased in the POA of male rats following ejaculation (Fumero et al., 1994; Mas et al., 1995a), and 5-HT was increased in POA tissue punches after ejaculation (Mas et al., 1987). The authors suggested that increased 5-HT may have contributed to the PEI. However, a more recent microdialysis study that measured 5-HT itself found that 5-HT in the mPOA and the more lateral POA remained constant during copulation, ejaculation, and the PEI (Lorrain et al., 1997). However, 5-HT did increase in the anterior LH in the sample during which the male ejaculated. The 5-HIAA increase in the earlier studies may have diffused from the anterior LH to the adjacent POA. Thus, it seems unlikely that 5-HT in the POA contributes significantly to the PEI.

1.5.2.1(xvi) Activation of c-fos or other measures of neural activity s0450

p0665 Copulation increases Fos expression in the mPOA of male rats (Baum and Everitt, 1992; Robertson et al., 1991; Veening and Coolen, 1998), gerbils (Heeb and Yahr, 1996), hamsters (Fernandez-Fewell and Meredith, 1994; Kollack-Walker and Newman, 1992, 1995), and mice (Halem et al., 1999). Sexual experience may enhance future responsiveness to sexual stimuli; there were more Fos-ir neurons in the MPN of sexually experienced male rats after one ejaculation than in previously naive males, even though the naive males required more intromissions to trigger the ejaculation (Lumley and Hull, 1999). Similarly, chemosensory cues in sexually experienced male hamsters stimulated greater Fos expression than in sexually naive males (Fewell and Meredith, 2002). Copulation increases Fos-ir in AR-containing neurons in the mPOA of male rats (Gréco, 1998a), but not in aromatase-containing neurons in male quail (Foidart et al., 1999). Copulation-induced Fos-ir in the mPOA can be elicited by input from either the MeA or the CTF (Baum and Everitt, 1992), and Fos-ir neurons in the mPOA project to the PAG, among other sites (Struthers, 2001). Sexual behavior was also associated with an increase in 2-deoxyglucose

response to odor cues (Kiyatkin and Mitchum, 2003). Fos was also elicited in the mPOA of male hamsters by electrical stimulation of the VNO (Meredith and Fewell, 2001). However, there have also been negative reports of Fos induction in rats (Baum and Everitt, 1992; Coolen et al., 1997b), mice (Halem et al., 1999), hamsters (Fernandez-Fewell and Meredith, 1994), and ferrets (Kelliher et al., 1998). Ejaculation selectively activated the MPN of hamsters (Kollack-Walker and Newman, 1997) and rats (Coolen et al., 1997b), and the PdPN of gerbils (Heeb and Yahr, 1996).

p0675 The neurochemical identity of Fos-ir neurons has been addressed. In gerbils half of the Fos-ir neurons in the medial SDA and PdPN were GABAergic; almost one-fourth of the neurons in the medial SDA were glutamatergic, but there were no glutamatergic cells in the PdPN (Simmons and Yahr, 2003). In rats, galanin-containing cells are selectively activated by ejaculation (Bakker et al., 2002b). Ejaculation-induced Fos-ir in the mPOA of male rats was decreased by administration of a D_1 antagonist (Lumley and Hull, 1999), suggesting that stimulation of D_1 receptors mediated at least some of the copulation-induced Fos-ir.

s0455 ***1.5.2.1(xvii) Effects of intracerebral grafts***

p0680 Injection of fetal mPOA neurons into the mPOA of aging male rats improved their ability to copulate between 21 and 45 days after implantation; the benefits lasted until the end of the experiment, 4.5 months later (Hung et al., 1997). Serum T was also increased. Implants from other brain areas were ineffective.

s0460 ***1.5.2.1(xviii) Activation of neurotransmitter receptors***

p0685 Endocytosis of μ-opioid receptors occurred within 30 min after copulation and lasted for at least 6 h (Coolen et al., 2004b). The opioid antagonist naloxone prevented receptor internalization. Microinjection of a μ agonist elicited similar internalization, and mating elicited Fos-ir in μ-receptor-containing neurons. However, naloxone did not prevent the mating-induced Fos expression in μ-receptor-containing neurons, suggesting that the mating-induced Fos response did not result from stimulation of μ receptors.

s0465 ***1.5.2.1(xix) Summary of medial preoptic area functional roles***

p0690 The mPOA receives indirect sensory input from all senses and has reciprocal connections with the sources of afferent input, allowing hormone-concentrating neurons to bias the processing of sexually relevant input. mPOA efferents to other hypothalamic, midbrain, and brainstem nuclei regulate somatomotor patterns and genital reflexes and contribute to sexual motivation.

1.5.2.2 Mesocorticolimbic dopamine tract

s0470

1.5.2.2(i) Anatomy

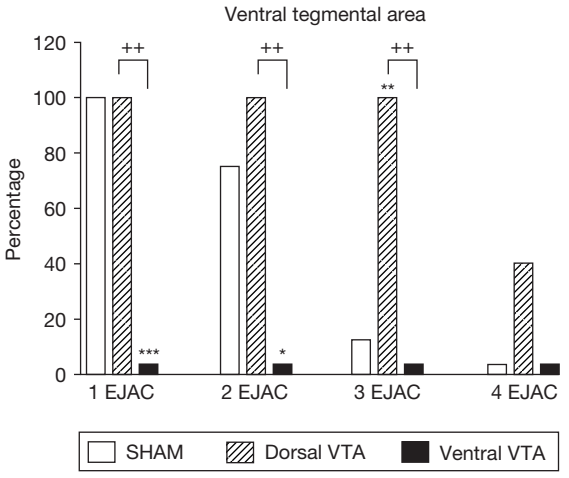
s0475

p0695 The mesocorticolimbic circuit comprises DA cell bodies in the VTA ascending to the NAc and the medial prefrontal cortex (mPFC) and plays a central role in motivated behaviors (Alcaro et al., 2007). Electrical stimulation studies have implicated this system in positive rewarding states (Wise and Rompre, 1989) and appetitive motivated behaviors (Berridge and Robinson, 1998). Sexual behavior, and especially ejaculation, is a rewarding and reinforcing behavior (Balfour et al., 2006) that activates the mesocorticolimbic circuit. Hence, DA efflux is increased in the NAc in response to the presence of an estrous female behind a barrier, as well as during copulation (Damsma et al., 1992; Fiorino et al., 1997; Pfaus et al., 1990). In the VTA, sexual behavior activates both DA and non-DA neurons. VTA activation appears to be mediated by endogenous opioids released during sexual activity, which inhibit VTA GABAergic interneurons, thereby releasing DA cells from tonic inhibition (Balfour et al., 2004). The mPFC receives DA inputs from the VTA and sends projections back to this structure (Tzschentke, 2000). Projections from the mPFC to the VTA are largely glutamatergic; thus it is possible that mPFC inputs contribute to excitation of VTA neurons via glutamate release during copulation (Balfour et al., 2006). Efferent projections from the mPFC also contact other brain areas involved in sexual behavior and motivation, including the NAc shell and core, the mPOA, BNST, and SPF.

1.5.2.2(ii) Effects of lesions or electrical stimulation

s0480

p0700 Lesion of the mPFC disrupted male rat sexual behavior, particularly its initiation (Ågmo et al., 1995). VTA lesion increased the duration of the PEI (Brackett et al., 1986), while NAc lesions impaired both copulation and noncontact erections, suggesting that the NAc plays an excitatory role in the regulation of sexual arousal (Kippin et al., 2004). Electrical stimulation of the VTA facilitated copulation (Markowski and Hull, 1995); however, the facilitative effect is restricted to its dorsal portion and stimulation of its



f0020 **Figure 4** Percentage of sexually experienced male rats achieving 1–4 successive ejaculations within a 30-min period, when electrically stimulated in two different anatomical locations of the ventral tegmental area (dorsal or ventral regions). Fisher exact probability test. Asterisks denote comparisons with control sham-operated rats; crosses denote comparisons between dorsally and ventrally stimulated animals; $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, and $++P < 0.01$. Reproduced from Rodríguez-Manzo G and Pellicer F (2007) Electrical stimulation of the ventral tegmental area exerts opposite effects on male rat sexual behavior expression depending on the stimulated sub region. *Behavioural Brain Research* 179: 310–313, with permission from Elsevier.

ventral portion inhibited mating (Rodríguez-Manzo and Pellicer, 2007) (**Figure 4**).

s0485 ***1.5.2.2(iii) Activation of c-fos or receptors***

p0705 Fos expression is induced in the NAc and VTA of male rats in response to mating (Balfour et al., 2004). Female odors and conditioned nonsexual odors paired with mating stimulated Fos expression in NAc (Kippin et al., 2003). Moreover, sexual experience enhanced estrous female-induced NAc Fos-ir (Lopez and Ettenberg, 2002a). mPFC is also activated during sexual behavior and sends projections to sex-activated neurons in the VTA, as determined by Fos-ir (Balfour et al., 2006). In the VTA, mating to ejaculation induced μ-opioid receptor internalization, an indicator for ligand-induced receptor activation (Balfour et al., 2004).

s0490 ***1.5.2.2(iv) Microinjections of drugs***

p0710 Microinjection of D_1- and D_2-like receptor antagonists into the NAc decreased sexual motivation (Pfaus and Phillips, 1991). Apomorphine, a nonselective DA agonist, microinjected into the VTA, delayed the onset of copulation and slowed its rate, presumably by stimulating autoreceptors and thereby decreasing dopaminergic activity (Hull et al., 1990). Conversely, the nonselective DA antagonist *cis*-flupenthixol reduced IL for those rats that copulated, presumably by blocking autoreceptors, but also decreased the proportion of copulating rats, perhaps due to depolarization block. These effects appeared to be due to motoric slowing, not a decrease in specifically sexual motivation or genital reflexes (Hull et al., 1991). Infusion of 5-HT into the NAc impairs copulation in rats, while a facilitative effect was obtained after 8-OH-DPAT (Fernández-Guasti et al., 1992). Intra-VTA microinjection of morphine and dynorphin facilitated male sexual behavior and increased DA transmission in the NAc (Mitchell and Stewart, 1990), both effects probably resulting from μ-opioid receptor-mediated release from GABAergic tonic inhibition (Balfour et al., 2004).

s0495 ***1.5.2.3 Nigrostriatal dopamine tract***

p0715 The nigrostriatal pathway originates in the zona compacta of the substantia nigra and sends its projections to the caudate nuclei and putamen of the striatum. The nigrostriatal DA system has been implicated in the control of procedural aspects of movement and motivated behaviors, as it reaches dorsal areas of the basal ganglia (Alcaro et al., 2007). DA is released in the dorsal striatum only after the male begins to copulate, suggesting that this release reflects motor activation rather than motivational aspects of copulation (Damsma et al., 1992). Bilateral lesions of the substantia nigra slowed the rate of copulation and decreased ejaculatory capacity (Brackett et al., 1986). Copulation did not induce Fos-ir in the dorsal striatum, in contrast to mesocorticolimbic areas like the NAc, VTA, and mPFC (Coolen et al., 1996). Apomorphine injected into the striatum did not affect copulation in male rats (Hull et al, 1986), and bilateral haloperidol infusions only increased EF (Pfaus and Phillips, 1991).

s0500 ***1.5.2.4 Paraventricular nucleus of the hypothalamus***

s0505 ***1.5.2.4(i) Anatomy***

p0720 The PVN is an important integrative site for endocrine and autonomic functions. It comprises a parvocellular division, which projects to several brain areas and the spinal cord, and a magnocellular division, which releases OT and vasopressin from the posterior

pituitary (reviewed in Swanson and Sawchenko (1980)). Axons that project to the spinal cord release OT, vasopressin, somatostatin, DA, and other, undetermined transmitters. Periventricular DA neurons and brainstem NE and 5-HT nuclei provide input to the parvocellular PVN. The PVN is important for noncontact erections and seminal emission, but is less critical for reflexive erections and copulation. DA, glutamate, NO, and hexarelin analog peptides stimulate OTergic neurons that project to several brain areas and the spinal cord (reviewed in Argiolas and Melis (2005)). GABA and opioid peptides inhibit those neurons.

s0510 ***1.5.2.4(ii) Effects of electrolytic or cell body lesions***

p0725 Excitotoxic lesions of the parvocellular PVN decreased noncontact erections without affecting copulation (Liu et al., 1997a). Similar lesions decreased the volume of semen ejaculated and decreased the OT-ir innervation of the lumbosacral spinal cord, but again did not affect mating (Ackerman et al., 1997). Larger lesions of both the parvo- and magnocellular divisions inhibited both reflexive and noncontact erections and led to some impairment of mating (Liu et al., 1997a). However, electrolytic lesions actually speeded the first reflexive erection (Monaghan et al., 1993). Thus, the PVN contributes to both noncontact and reflexive erections and seminal emission, but does not consistently affect copulation or reflexive erections. Lateral parvocellular PVN lesions destroyed neurophysin-ir axons to the sexually dimorphic SNB (Wagner and Clemens, 1993). Neurophysin is a marker for OT and vasopressin; thus, the PVN is the source of OT projections to the SNB that promote erection, seminal emission, and ejaculation.

s0515 ***1.5.2.4(iii) Effects of direct applications of drugs affecting specific transmitters***

s0520 p0730 **1.5.2.4(iii)(a) Dopamine and oxytocin** Microinjections of mixed and selective D_2-like agonists or of OT elicited drug-induced erections and increased reflexive erections and seminal emissions (reviewed in Argiolas and Melis (2005)). The mixed DA agonist apomorphine also increased intracavernous pressure in anesthetized rats (Allard et al., 2002). The D_2-like receptor has more recently been hypothesized to be the D_4 receptor, which apparently opens N-type calcium channels; the calcium then activates NOS in the OT neurons (see Melis et al. (2005) and references therein). The noncontact erections elicited by DA agonists were inhibited by an OT antagonist administered ICV, but not into the PVN, suggesting that DA excites neurons that release OT elsewhere (Melis et al., 1999a). OT released in the PVN itself apparently acts via OT receptors on OT neurons by increasing calcium influx, thereby stimulating NOS, which acts intracellularly to stimulate OT neurons (reviewed in Argiolas and Melis (2005)). PVN apomorphine acts via OT projections to the VTA to increase DA release in the NAc and elicit erections (Melis et al., 2007).

s0525 p0735 **1.5.2.4(iii)(b) Nitric oxide** Microinjection of NO donors or a high dose of the NO precursor L-arginine into the PVN elicited erections, whereas the NOS inhibitor L-NAME decreased noncontact erections and impaired mating (Melis et al., 1998). Reverse-dialysis of another NOS inhibitor, L-NMMA, decreased reflexive erections, and L-arginine increased erections; however, neither drug affected copulation (Sato et al., 1999). Those authors reported that similar administration of L-NMMA into the mPOA did impair copulation. Thus, NO-related drugs have consistently affected noncontact and reflexive erections, but have had inconsistent effects on mating.

s0530 p0740 **1.5.2.4(iii)(c) Amino acids** Microinjections of the glutamate agonist NMDA elicited erections, an effect blocked by an NMDA antagonist and an NOS inhibitor in the PVN (Melis et al., 1997) and also by an OT antagonist injected ICV, but not into the PVN (Melis et al., 2000b). The NMDA antagonist impaired both noncontact erections and copulation when administered alone (Melis et al., 2005). NMDA in the PVN also increased intracavernosal pressure in awake and anesthetized male rats (Chen and Chang, 2003; Zahran et al., 2000). Conversely, a $GABA_A$, but not a $GABA_B$, agonist in the PVN inhibited erections elicited by apomorphine, OT, or NMDA (Melis et al., 2000a).

s0535 p0745 **1.5.2.4(iii)(d) Other transmitters** Morphine microinjections before introduction of an estrous female prevented both noncontact erections and the rise in NO that occurred in control rats (Melis et al., 1999b). Hexarelin analog peptides, which were originally known for their ability to induce growth hormone release, activate specific receptors on OT neurons in the PVN to admit calcium and thereby stimulate NOS in the OT neurons and elicit erections (reviewed in Argiolas and Melis (2005)). A cannabinoid CB1 antagonist, microinjected into

the PVN, elicited erections, an effect reduced by CB1 agonists, an NMDA antagonist, and an NOS inhibitor in the PVN, and by an ICV OT antagonist (Melis et al., 2004b). The CB1 receptors in the PVN are mostly on GABAergic terminals, which in turn impinge on both OT and glutamatergic neurons (Castelli et al., 2007). The authors note that one would expect inhibition of the inhibitory CB1 receptors to increase GABA release; however, they suggest that stimulation of CB1 receptors may inhibit GABA reuptake in the PVN; therefore, blocking CB1 receptors would increase GABA reuptake and disinhibit glutamatergic and OT neurons. Thus, the mechanism of CB1 antagonists' effects is not clear. Pro-VGF-derived peptides are cleavage products of VFG, the product of the *vgf* gene, which is selectively induced by nerve growth factor (see references in Argiolas and Melis (2005)). They may activate OT neurons in the PVN and thereby facilitate erections; their effects are inhibited by both NOS and OT antagonists (reviewed in Argiolas and Melis (2005)).

s0540 p0750 **1.5.2.4(iii)(e) Chemical changes detected by microdialysis** DA and excitatory amino acid levels increased during noncontact erections and, to a greater extent, copulation (Melis et al., 2003, 2004b). Both noncontact erections and copulation were also accompanied by an increase in NO, inferred from increases in NO_2 and NO_3 (Melis et al., 1998). In the same study, L-NAME in the PVN inhibited both the increase in NO_2 and noncontact erections; however, PVN injections of hemoglobin, an NO scavenger, blocked the increase in NO_2, but not noncontact erections, suggesting that NO works only intracellularly in the PVN. Morphine microinjections into the PVN inhibited the copulation-induced increase in NO and copulation (Melis et al., 1999b). Reverse-dialysis of L-arginine increased both reflexive erections and the NO increase, and L-NMMA inhibited both (Sato et al., 1999). Apomorphine or a D_2 agonist, but not a D_1 agonist, increased NO production and erections (Melis et al., 1996), as did NMDA (Melis et al., 1997). Omega conotoxin, an inhibitor of N-type calcium channels, prevented the elicitation of erections and NO production by apomorphine and OT; NO donors overcame the need for calcium channel activation (Succu et al., 1998). Microinjection of a CB1 antagonist increased extracellular glutamate (Succu et al., 2006b) and NO production (Melis et al., 2006), whereas microinjection of morphine decreased both erections elicited by a CB1 antagonist and the increases in glutamate and NO production (Succu et al., 2006b).

s0545 p0755 **1.5.2.4(iii)(f) Immunocytochemistry** Thirty percent of lateral parvocellular neurons in the PVN contain ER-ir, and almost half of them project to the lumbar spinal cord (Wagner et al., 1993). Therefore, some hormone effects on the SNB may be indirect, via steroid-sensitive afferents.

p0760 Ejaculation induced greater Fos expression in the parvocellular and magnocellular PVN than did intromission, especially in the caudal lateral parvocellular PVN, with one-third of the Fos-ir neurons containing OT (Witt and Insel, 1994). Neurons in that area project to the brainstem and lumbar spinal cord. Furthermore, female odor elicited Fos-ir in OT-containing neurons in the parvocellular PVN of sexually experienced, but not naive male rats; direct exposure to an anesthetized estrous female elicited Fos-ir in both groups, compared to nonexposed controls (Nishitani et al., 2004). However, in gerbils neither mating nor exposure to a previous mating arena elicited Fos-ir in the PVN (Heeb and Yahr, 1996). Sexually competent male rats had more OT mRNA and less mRNA for proenkephalin and prodynorphin in the PVN than did impotent males (Arletti et al., 1997). Furthermore, NOS and OT were co-localized (Yamada et al., 1996).

p0765 In addition to projections to the hippocampus, lumbosacral spinal cord, and other brain areas, there is a direct projection to the nPGi, where terminals form close appositions to serotonergic neurons that project to the lumbosacral cord and inhibit genital reflexes (Bancila et al., 2002).

1.5.2.5 Lateral hypothalamus s0550

1.5.2.5(i) Anatomy s0555

p0770 The LH is reciprocally connected with brain regions that process emotional information. It may control the autonomic nervous system via connections to the nucleus of the solitary tract and parabrachial nucleus, endocrine secretion via those to the PVN, and emotional responses via connections to periaqueductal gray (PAG) and midbrain extrapyramidal area. Activation of this system leads to both motor arousal and emotional/cognitive arousal (Ikemoto, 2007).

1.5.2.5(ii) Effects of electrical stimulation and lesions s0560

p0775 LH electrical stimulation has rewarding effects and has induced stimulation-bound copulation in male rats (Huston, 1971), while males with lesions in the anterior LH intromitted repeatedly, but few copulated to ejaculation (Kippin et al., 2004). During

exposure to an inaccessible receptive female, anterior LH-lesioned males had increased noncontact erections. Thus, the anterior LH may inhibit sexual arousal but facilitate ejaculation.

s0565 #### 1.5.2.5(iii) Microinjections, microdialysis, and Fos-ir

p0780 Microinjection of an SSRI into the anterior LH delayed the onset of copulation and increased the EL (Lorrain et al., 1997), while reverse-dialysis of 5-HT decreased basal and female-elicited DA release in the NAc (Lorrain et al., 1999). In addition, anterior LH 5-HT levels were increased at the time of ejaculation, coincident with the copulatory refractory period (Lorrain et al., 1997). The LH contains orx/hcrt neurons, which appear to play a critical role in arousal and reward (Harris and Aston-Jones, 2006) and are activated following copulation (Muschamp et al., 2007). It has been proposed that 5-HT in the anterior LH might inhibit male sexual behavior by inhibiting orx/hcrt neurons, which would eliminate their facilitative influence on VTA DA cell firing (Muschamp et al., 2007).

s0570 ### 1.5.2.6 Ventromedial hypothalamus

s0575 #### 1.5.2.6(i) Anatomy

p0785 Although the VMH is primarily known for its role in female receptive behavior, it may also influence male sexual behavior. It has numerous ERs and ARs (Simerly et al., 1990; Wood et al., 1992) and receives both genitosensory (Coolen et al., 2003) and chemosensory (Canteras et al., 1995; Coolen and Wood, 1998; Gomez and Newman, 1992) information.

s0580 #### 1.5.2.6(ii) Effects of lesions and hormonal manipulations

p0790 Electrolytic microlesions in the dorsomedial VMH impaired the ability of T implants to restore ultrasonic vocalizations and scent marking, but had relatively little effect on mating (Harding and McGinnis, 2005). T implants in VMH failed to restore copulation or ultrasonic vocalizations in rats (Harding and McGinnis, 2003) or mice (Nyby et al., 1992), but did restore partner preference in rats (Harding and McGinnis, 2003) and increased urine marking in mice (Nyby et al., 1992). Hydroxyflutamide (AR antagonist) in the VMH of castrated, T-replaced rats inhibited both sexual motivation (Harding and McGinnis, 2004) and mating (Harding and McGinnis, 2004; McGinnis et al., 1996). Thus, ARs in the VMH may contribute to male sexual behavior.

1.5.2.6(iii) Expression of c-fos

s0585 p0795 Copulation induced Fos-ir in the VMH of both rats (Coolen et al., 1996) and gerbils (Heeb and Yahr, 1996). Chemosensory signals induced Fos-ir in gerbils (Heeb and Yahr, 1996), but not in rats (Bressler and Baum, 1996). Pelvic nerve transection did not affect ejaculation-induced Fos-ir in rats, suggesting that other sensory inputs, such as the pudendal nerve or chemosensory input, contribute to mating-induced Fos-ir (Wersinger et al., 1993). Copulation did not increase Fos-ir in the VMH of musk shrews (Gill et al., 1998), hamsters (Kollack-Walker and Newman, 1997), mice (Halem et al., 1999), or ferrets (Kelliher et al., 1998; Lambert et al., 1992), and actually decreased Fos-ir in macaques (Michael et al., 1999).

1.5.3 Major Motor Outputs

s0590

1.5.3.1 Ventral premammillary nucleus

s0595 p0800 The mPOA, VMH, and MeApd provide input to the ventral premammillary nucleus (Canteras et al., 1992), which contains ARs in rats (Simerly et al., 1990; Yokosuka and Hayashi, 1996; Yokosuka et al., 1997) and hamsters (Wood and Newman, 1995a). Mating increased Fos-ir in AR-containing neurons in rats (Gréco et al., 1998b). Fos-ir was elicited in male mice by female-soiled bedding (Yokosuka et al., 1999).

1.5.3.2 Midbrain PAG

s0600 p0805 PAG lesions blocked elicitation of the UG reflex by mPOA electrical stimulation (Marson, 2004), but unilateral lesions of ventrolateral PAG and contralateral SDA of gerbils did not affect copulation (Finn and Yahr, 1994). There are numerous ERs and ARs in the caudal two-thirds of the PAG (Murphy et al., 1999b), with afferents from the mPOA in close apposition to ER- and AR-ir neurons, some of which project to nPGi (Murphy and Hoffman, 2001). Thus, hormones can modulate transmission from the mPOA to the nPGi, via the PAG. The PAG of monkeys projects to a premotor area of the medulla, the nucleus retroambiguous (Vanderhorst et al., 2000).

1.5.3.3 Nucleus paragigantocellularis of the medulla

s0605

1.5.3.3(i) Effects of lesions

s0610 p0810 Spinal nuclei that control genital reflexes are under tonic inhibitory control; spinal transection increases the number or intensity of erections or UG reflexes

(reviewed in Hull et al. (2006)). Much of that inhibition is from the nPGi. More sexually naive male rats ejaculated on their first exposure to an estrous female after bilateral nPGi lesions, compared to controls, and they copulated more efficiently (Yells et al., 1992). Similar lesions decreased the latency and increased the numbers of reflexive erections (Holmes et al., 2002; Marson et al., 1992) and allowed the UG reflex to be elicited without spinal transection (Marson and McKenna, 1990).

s0615 #### 1.5.3.3(ii) Effects of electrical stimulation

p0815 Electrical stimulation of the nPGi elicited field potentials in the lumbosacral spinal cord near the SNB (Tanaka and Arnold, 1993). nPGi stimulation specifically activated sympathetic fibers in the pudendal nerve (Johnson and Hubscher, 2000), and activation of pudendal neurons by electrical stimulation of the dorsal nerve of the penis was inhibited by stimulation of nPGi (Johnson and Hubscher, 1998).

s0620 #### 1.5.3.3(iii) Immunocytochemistry

p0820 The nPGi receives input from the BNST, PVN, posterior hypothalamus, mPOA, and several other areas (Normandin and Murphy, 2008). Afferent neurons contained AR or ER, and those from the PVN and mPOA were Fos-ir after copulation. nPGi neurons project directly to pudendal motoneurons in the dorsomedial and dorsolateral nuclei, sympathetic and parasympathetic preganglionic neurons, and interneuronal regions of the medial gray lumbosacral spinal cord (Hermann et al., 2003; Marson et al., 1992). Most nPGi neurons that project to the lumbosacral spinal cord contain 5-HT (Marson and McKenna, 1992) and receive a projection from the PVN (Bancila et al., 2002). A serotonergic neurotoxin decreased descending inhibition of the UG reflex, and 5-HT applied to the spinal cord suppressed the reflex in spinally transected rats (Marson and McKenna, 1994a).

s0625 ### 1.5.3.4 Other brain areas

p0825 Several additional brain areas have been implicated in the regulation of male sexual behavior, although there is little information about their specific contributions. These include the lateral septum (Kondo et al., 1993), hippocampus (Chen et al., 1992), and caudal zona incerta (Edwards and Isaacs, 1991; Maillard and Edwards, 1991). In men, stroke damage in the basal ganglia and cerebellum impaired desire and ejaculation, respectively (Jung et al., 2008), whereas erotic images elicited activity in several cortical areas, including the inferior temporal cortex, right insula, right inferior frontal cortex, and left anterior cingulate cortex (Stoleru et al., 1999).

s0630 #### 1.5.3.5 Spinal cord

p0830 The spinal cord contains the autonomic and somatic nuclei controlling erection and ejaculation. The sympathetic and parasympathetic tones involved in the control of these reflexes are under the influence of sensory stimuli from the genitalia and are integrated at the spinal cord level, where supraspinal information also converges. The spinal cord contains thoracolumbar sympathetic, sacral parasympathetic, and sacral pudendal motoneurons anatomically linked with the penis. Erection is likely to occur when the spinal cord reduces the activity of the thoracolumbar sympathetic antierectile pathway with a concomitant increase in the activity of the proerectile parasympathetic sacral and pudendal pathways (for review, see Giuliano and Rampin (2004)). The neural commands controlling ejaculation are also organized at the spinal level, and a central pattern generator, located at the lumbosacral cord level, is involved in the relay and integration of the genital sensory and motor signals related to ejaculation (Carro-Juárez and Rodríguez-Manzo, 2008; Carro-Juárez et al., 2003). A group of lumbar spinothalamic (LSt) neurons, located in lamina VII and X of L3 and L4 segments in this portion of the cord, which express galanin, CCK, and neurokinin receptors, form part of this ejaculation generator (Truitt and Coolen, 2002). Microstimulation of these neurons elicits seminal emission (contraction of seminal vesicle and vas deferens) followed by expulsion (bulbospongiosus muscle contraction); injection of the $GABA_A$ agonist muscimol into the area after the electrical stimulation stopped the expulsion in midstream (Borgdorff et al., 2008).

p0835 Spinal cord transection releases sexual reflexes, indicating that supraspinal centers exert a descending inhibitory influence (McKenna et al., 1991), probably mediated by 5-HT (Marson and McKenna, 1994a). Intrathecal administration of 5-HT abolished the UG reflex (Marson and McKenna, 1992); however, $5\text{-}HT_{1A}$ (Carro-Juárez and Rodríguez-Manzo, 2001, Carro-Juárez et al., 2003) and $5\text{-}HT_{2C}$ receptor stimulation (Stafford et al., 2006b) facilitated the UG reflex, suggesting that 5-HT exerts a dual influence on male sexual behavior at the spinal level.

p0840 CSF levels of GABA, glutamate, and aspartate markedly increased after ejaculation, with the increase in GABA concentrations almost fivefold that of

excitatory amino acids (Qureshi and Södersten, 1986). Lumbosacral injection of the $GABA_B$ agonist baclofen inhibited *ex copula* reflexive penile erection (Bitran et al., 1989a), while that of a competitive NMDA or AMPA-kainate receptor antagonist depressed both dorsal penile nerve (DPN)-stimulated erection in anesthetized rats and reflexive erection in conscious animals (Rampin et al., 2004). Thus, GABA may inhibit, and glutamate facilitate, sexual reflexes at the spinal level. The DA agonist apomorphine, injected intrathecally at the lumbosacral level of conscious rats, impaired reflexive erection, but evoked erection in normal and spinal animals (Andersson, 2001) and induced ejaculation-like responses in anesthetized rats (Stafford and Coote, 2006).

p0845 Reflexive erections are inhibited by both α_1- and α_2-adrenoceptor agonists. α_2 Antagonists have dose-dependent effects, with low doses facilitating, and higher doses inhibiting, reflexive erections in rats (reviewed in Meisel and Sachs (1994)) and seminal emission in dogs (Yonezawa et al., 1991). The spinal NE system facilitates ejaculation, since increasing NE tone by systemic yohimbine, as well as stimulation of α_1- or α_2-adrenoceptors (Carro-Juárez and Rodríguez-Manzo, 2003, 2006) all activate the SGE. The ACh agonist muscarine, intrathecally administered, facilitated ejaculation, while the antagonist homatropine decreased the percentage of copulating rats and increased the EL in those ejaculating (Durán et al., 2000). Intrathecal injection of an NOS inhibitor abolished, and an NO donor enhanced, apomorphine-evoked bursting activity in the vas deferens nerve that is associated with ejaculatory responses (Brack et al., 2007).

p0850 These data show that the effects of neurotransmitters in the spinal cord may vary from those exerted in the brain or peripheral nervous system. Thus, opposite results may be obtained with the same drug on a given sexual reflex, depending on the animal model used (i.e., *in copula* vs. *ex copula* responses), conscious versus anaesthetized rats, spinally intact versus spinally transected animals. To integrate this knowledge to understand the spinal cord-mediated sexual functioning of an intact copulating animal is one of today's challenges.

s0635 1.6 Circuitry and Anatomical Interconnections

p0855 Organisms in natural settings weigh, prioritize, and integrate multiple internal and external signals in order to choose and perform various motivated behaviors, including mating. Here, we summarize several functional circuits that analyze and integrate sensory and hormonal stimuli and execute behavioral outcomes.

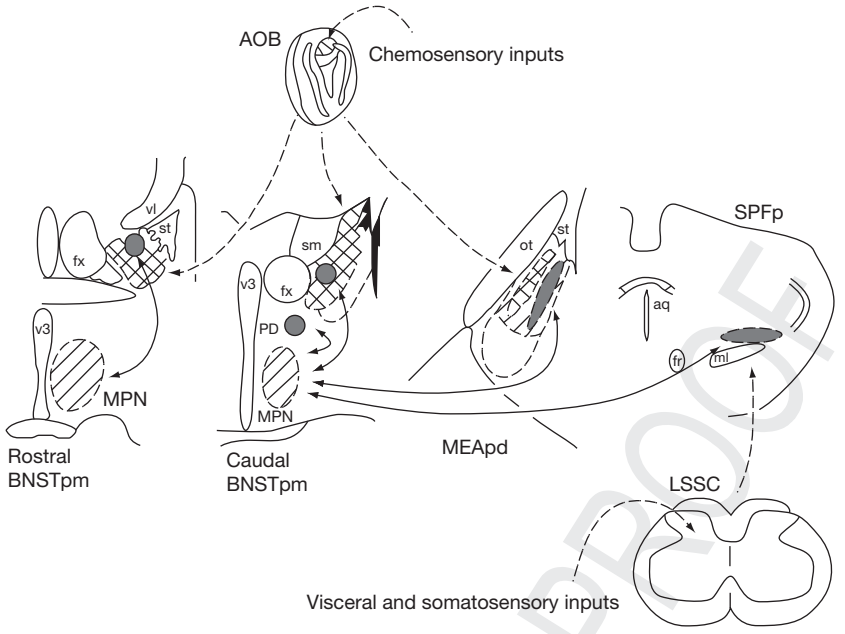
1.6.1 Sensory Inputs s0640

p0860 Rodents depend heavily on chemosensory signals for mating. The MeA, BNST, and mPOA are critical nodes in this circuit, and each contains numerous steroid receptors (Rasia-Filho et al., 1991; Wood and Newman, 1995b). T or E, but not DHT, in the MeA or mPOA enhance mating (Wood, 1996) and responsiveness to odor cues (Sipos and Nyby, 1998; Wood and Newman, 1995b). Hormones may permit or enhance release of transmitters, promote the production or placement of postsynaptic receptors, and increase growth and branching of neurons.

p0865 The major source of afferent input from the penis is the DNP (a branch of the pudendal nerve), which carries signals from the penile skin, prepuce, and glans; input from deeper structures is carried by the cavernous nerve (Steers, 2000). Afferents end mostly in medial portions of the dorsal horn and the medial central gray matter of the lumbosacral cord (reviewed in Hull et al. (2002, 2006)). Electrical stimulation of the DNP elicited responses in the nPGi, PVN, mPOA, and cortex (Hubscher and Johnson, 1996; Yanagimoto et al., 1996). Mating elicits Fos-ir in the CTF of rats (Baum and Everitt, 1992) and SPFp of rats (Coolen et al., 1996, 1997a,b), gerbils (Heeb and Yahr, 1996), and hamsters (Kollack-Walker and Newman, 1997); these areas all project to the mPOA. Axons from the L3 and L4 spinal segments terminate adjacent to SPFp neurons that project to the mPOA or BNSTpm (Wells and Coolen, 2001). Electrical stimulation of the DNP in men elicited activity in the midline of somatosensory cortex (Gerstenberg et al., 1991; Guerit and Opsomer, 1991).

1.6.2 An Ejaculation-Related Circuit s0645

p0870 Ejaculation, but not intromissions without ejaculation, elicited small areas of Fos-ir in MeApd, BNSTpm, PdPN, and SPFp of rats (Coolen et al., 1996, 1997a,b, 1998), hamsters (Fernandez-Fewell and Meredith, 1994; Kollack-Walker and Newman, 1997; Parfitt and Newman, 1998), and gerbils (Heeb and Yahr, 1996, 2001; Simmons and Yahr, 2002, 2003) (**Figure 5**). Neurons in each of these areas have



f0025 **Figure 5** Schematic overview of Fos immunoreactivity in MPN, BNSTpm, posterodorsal preoptic nucleus (PD), MEApd, SPFp, and accessory olfactory bulbs (AOB). Areas where Fos is induced following chemosensory cues or chemosensory investigation are illustrated by diagonal stripes from upper left to lower right. Areas where Fos is induced only following ejaculation are illustrated in gray. Areas where Fos is induced following all consummatory elements of sexual behavior are illustrated by diagonal stripes from lower left to upper right. LSSC, lumbosacral spinal cord; v3, third ventricle; fx, fornix; vl; lateral ventricle; st, stria terminalis; s, stria medularis; ot, optic tract; aq, aqueduct; fr, fasciculus retroflexus; ml, medial lemniscus. Reproduced from Coolen LM, Allard J, Truitt WA, and McKenna KE (2004a) Central regulation of ejaculation. *Physiology and Behavior* 83: 203–215, with permission from Elsevier.

reciprocal connections with the mPOA (Coolen et al., 1998; Gréco et al., 1998a; Heeb and Yahr, 2001). The MeApd and SPFp of rats and gerbils contribute to activation of the mPOA, as unilateral lesions decreased mating-induced Fos-ir there (Baum and Everitt, 1992; Heeb and Yahr, 2000). It is not clear whether the Fos-ir neurons received sensory input or activated motor patterns of ejaculation.

p0875 In gerbils, PdPN or MeApd lesions decreased mounting and delayed ejaculation; thus, these areas contribute to mating, but are not essential for ejaculation (Heeb and Yahr, 2000). However, lesions that included the SPFp and zona incerta of rats almost eliminated ejaculation (Maillard and Edwards, 1991). The BNSTpm and MePD contribute to sexual satiety of hamsters, as Fos-ir increased only after multiple ejaculations (Parfitt and Newman, 1998), and small lesions increased the number of ejaculations before satiety (Parfitt et al., 1996). LH lesions in rats disrupt ejaculation, but not intromissions or mounts (Kippin et al., 2004). 5-HT is released at the time of ejaculation and may promote the quiescence of the PEI (Lorrain et al., 1997). In men, PET showed increases in regional cerebral blood flow during ejaculation in the meso-diencephalic region, which includes the SPFp, as well as the cerebellum, lateral putamen, claustrum, and several cortical regions (Holstege et al., 2003). No increases were seen in the mPOA or BNST, in agreement with a study in male macaques (Michael et al., 1999).

1.6.3 Efferents from the mPOA s0650

Efferents from the mPOA target the periventricular p0880 and medial zones of the hypothalamus; the lateral hypothalamus; midbrain motivation/somatomotor regions, including the VTA and pedunculopontine nucleus; midbrain and brainstem areas that project to the spinal cord, including the PAG, certain raphe nuclei, and nPGi; the BNST; and part of the septal area (Simerly and Swanson, 1988; reviewed in Hull et al. (2006)). These connections are mostly reciprocal, allowing downstream sites to influence the input that they receive. They provide multiple ways to influence autonomic, motivational, and somatomotor patterns. Output to the nPGi, either directly or via

the PAG, may disinhibit erections and the UG reflex. However, it seems unlikely that mere disinhibition could elicit the reflexes that can be evoked by mPOA stimulation (Giuliano et al., 1996, 1997; Marson and McKenna, 1994b). Such excitatory inputs may include parasympathetic efferents, via the pelvic and cavernous nerves, and sympathetic outflow, via the paravertebral sympathetic chain and possibly the hypogastric nerve (Giuliano et al., 1997). A number of projection sites contain abundant steroid hormone receptors, allowing hormones to bias sexually relevant cues and responses.

s0655

1.6.4 Sexual Behavior in the Context of Mammalian Social Behavior

p0885

The brain areas that regulate male sexual behavior also influence other social behaviors. Newman (1999) suggested that these brain areas form a reciprocally interconnected circuit that serves all mammalian social behaviors. Most of the areas, except the midbrain, are richly endowed with steroid receptors, and all influence more than one behavior. Therefore, 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 mingle with those for other behaviors. However, there may be common themes that underlie the various social behaviors and the neural mechanisms that control them.

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Non-Print Items

Abstract:
Male sexual behavior comprises a complex pattern of genital and somatomotor responses. Hormones act via receptors in brain, spinal, and peripheral sites to bias sensory inputs and motor outputs to favor sexual responsiveness. Copulation includes mounts, intromissions, and ejaculations, followed by sexual quiescence. After 6–12 ejaculations, male rats become sexually satiated. Neural controls include chemosensory inputs via the main and accessory olfactory systems to the medial amygdala, which transmits information directly and indirectly to the medial preoptic area (mPOA), which integrates sensory and hormonal information and elicits genital reflexes and copulatory patterns and contributes to sexual motivation. Genital sensory input arrives via the central tegmental field/dorsolateral tegmentum (including the subparafasicular nucleus) directly or indirectly into the mPOA. Output from the mPOA is via the paraventricular nucleus and midbrain and brainstem sites. The mesocorticolimbic dopamine pathway contributes motivational fervor, and neural programs for erection and ejaculation reside in the lumbosacral spinal cord. Dopamine facilitates male sexual behavior, whereas serotonin (5HT) is largely inhibitory, although stimulation of 5-HT_{1A} receptors facilitates ejaculation. Norepinephrine has both stimulatory and inhibitory effects on copulation, via α_1- and α_2-adrenoceptors, respectively. Endogenous opioids play a complex modulatory role in all aspects of copulation. The brain areas that regulate male sexual behavior also influence other social behaviors.

Keywords: Bed nucleus of stria terminalis; Dihydrotestosterone; Dopamine; Ejaculation; Estradiol; *Ex copula* reflexes; Intromission; Medial amygdala; Medial preoptic area; Mesocorticolimbic dopamine tract; Mount; Norepinephrine; Nucleus paragigantocellularis; Opioids; Paraventricular nucleus; Postejaculatory interval; Serotonin; Sexual motivation; Sexual satiety; Spinal cord; Testosterone

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Elaine M. Hull has been professor in the Department of Psychology and the Program in Neuroscience at Florida State University, in Tallahassee, Florida, since 2004. She was previously professor of psychology at the University at Buffalo, State University of New York, for many years. She earned a PhD in psychology from Indiana University. She is author or co-author of 84 peer-reviewed articles and 11 chapters. For 25 years she has studied the roles of neurotransmitters in the medial preoptic area, mesocorticolimbic tract, and lateral hypothalamus in the control of male rat sexual behavior, as well as the influence of hormones on those neurotransmitters and behavior.

Gabriela Rodríguez-Manzo is professor in the Department of Pharmacobiology at the Center of Research and Advanced Studies (Cinvestav) in Mexico City, since 1997. She has done masters in science in psychobiology and PhD in pharmacology. She is author of 33 peer-reviewed journal articles and four book chapters and is a member of the Mexican National Researcher System since 1996. Her line of research has always been the study of rodent sexual behavior, with an early interest in female sexual behavior moving later to the study of male sexual behavior. At present she studies the neuropharmacology of male rat sexual behavior inhibition, using sexual satiety as a model, but is also interested in the brain functioning changes that result from copulation to satiety. The study of the spinal control of ejaculation is also a matter of her research interest.