

Differences in Sexual Behaviour in Male and Female Rodents: Role of Serotonin

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Abstract Serotonin plays an important role in both male and female sexual behaviour. In general, reduction of 5-HT function facilitates, whereas enhancement inhibits sexual behaviour. Most fundamental research on the involvement of 5-HT in sex has been performed in rats. Selective serotonin reuptake inhibitors (SSRIs)

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have comparable effects on male and female sexual behaviour in rats; they inhibit it but only after chronic administration. Activation of the 5-HT_{1A} receptor facilitates sexual behaviour in male rats but inhibits sexual behaviour in female rats, suggesting a differential role for 5-HT_{1A} receptors in male and female rats. Research on sexual behaviour in rats with null mutations in the serotonin transporter (SERT) indicated also a differential role for 5-HT_{1A} receptors in male and female sexual behaviour. Evidence exists that different pools of 5-HT_{1A} receptors have differential roles in various parts of the cascade of sexual events occurring during sexual interactions. Roles for other 5-HT receptors are less well defined although 5-HT_{1B}, 5-HT_{2A/B} and 5-HT₇ receptors seem to be involved. Identification of putative differential or comparable roles in female and male sexual activities requires more research.

Keywords 5-HT · 5-HT_{1A} receptor · 5-HTT · 8-OH-DPAT · Gender · Hypersexual behaviour · Hyposexual behaviour · Paroxetine · Premature ejaculation · Retarded ejaculation · Serotonin · Serotonin receptor knockout rat · Serotonin transporter · SERT polymorphism · Sexual behaviour · SSRI · WAY100635

1 Introduction

Sexual behaviour in rodents (and we strictly focus on the rat) happens when animals reach adulthood and engage in behaviours that result in the joining of a male and female, ending in copulation, with the intent to reproduce. The female rat's sexual behaviour is dependent on the reproductive cycle, whereas the male's sexual behaviour is not. The female's sexual behaviour is strongly dependent on peripheral gonadal steroids that have both peripheral and central nervous system (CNS) effects. Steroids act on the brain to induce sexual receptivity and all associated behaviours (proceptive, receptive and pacing behaviours). Quite some work has been performed to delineate the neural circuitry and neurochemistry of female behaviour, especially from lordosis, a behaviour that is evoked by external stimuli, normally, a male rat. Lordosis behaviour is only observed when the female is hormonally (or naturally) primed (oestradiol + progesterone) and the circuitry involves sensory, brain, spinal cord and motoric activation. In the CNS, the ventromedial nucleus of the hypothalamus (VMH), the preoptic area (POA), the midbrain central gray (MCG) and two areas in the spinal cord (cervical and lumbar) are the key structures. All structures contain oestrogen receptors that seem essential for the final integrative performance of full sexual behaviour. Many neurotransmitter systems in the CNS regulate or modulate (aspects of) sexual behaviour, including serotonin. There is strong evidence that the serotonergic modulation of sexual behaviours mainly occurs at the level of the VMH and POA.

In male rodents (rat), testosterone (T) acts during development to promote genital development and organization of the CNS neural circuitry. In adulthood, the neural circuitry along with the appropriate sensory and motoric systems controls the male's sexual motivation and performance. Male rat's sexual behaviour includes penile erection, sexual motivation and mating behaviour. All can be

studied while observing the mating behaviour of a male rat in direct interaction with a receptive female. In such an interaction, the male approaches the female, sniffs her and starts mounting (the female displays lordosis). The male displays a series of mounts and intromissions that end in ejaculation. After an ejaculation, the male displays for some time sexual quiescence followed by the next series of mounts and intromissions, leading again to ejaculation, and so on. In the male rat, the testicular secretion of T occurs throughout the year, although pulsatile patterning occurs over the day. Seasonal variations in behavioural responsiveness to T of male rats have not been found, making the male (and female) rat ideal experimental animals to study the neural mechanisms of, and neurotransmitter involvement in, sexual behaviour.

The neural systems involved in male sexual behaviour seem to involve many structures that are also involved in female sexual behaviour, although clear differences are also notable. The POA and the bed nucleus of the stria terminalis (BNST) are core structures via which T acts to activate male sexual behaviour. In particular, the POA seems an integrative structure in coordinating the actions of T on both motivational and consummatory aspects of male sexual behaviour. Several neurochemical systems, including peptidergic, dopaminergic and serotonergic systems, play a role in mediating sexual behaviour.

2 Serotonin and Sexual Behaviour

The focus of this chapter is the role of serotonin in male and female sexual behaviour in the rat. There is hardly any research performed on gender differences in the development and adult functioning of the 5-HT system in the brain and spinal cord. Seeing the overlap, but also the divergence of the various neural structures and hormonal receptor systems in the male and female rat CNS, it may be difficult to predict the effects of psychopharmacological treatment with serotonergic ligands on male and female sexual behaviour.

Serotonergic psychopharmacology in humans is rather limited; only the selective serotonin reuptake inhibitors (SSRI) are selective serotonergic drugs extensively used in patients, whereas most other drugs with some serotonergic profile exert inherently other mechanisms like dopamine D₂ receptor antagonism (olanzapine, risperidone, buspirone). In the latter case, it is often impossible to purely deduct the specific contribution of the serotonergic component on the putative effects on sexual behaviour or sexual dysfunctions induced. SSRIs are widely used to treat depression both in human males and females and are notoriously implicated (Zemishlany and Weizman 2008) in inducing sexual disturbances (Kennedy and Rizvi 2009; Balon 2006). However, a complicating factor is that major depression per se is often (if not always) associated with sexual disturbances (e.g. in libido, motivation, erection: Kendurkar and Kaur 2008; Kennedy and Rizvi 2009). SSRIs enhance serotonergic neurotransmission which is generally believed to inhibit sexual behaviour, both in males and females (Zemishlany and Weizman 2008; Williams et al. 2006; Kennedy and Rizvi 2009; Kendurkar and Kaur 2008). This is confirmed by various studies showing that SSRI antidepressants induce

sexual disturbances, in addition to already present dysfunctions due to the underlying depression, in both males and females (Cyranowski et al. 2004; Regitz-Zagrosek et al. 2008). No studies in humans have looked into the brain mechanisms underlying the SSRI-induced sexual dysfunction and putative gender differences. While it is still assumed that high extracellular 5-HT levels (e.g. after SSRI treatment) are needed to promote antidepressant activity, the disadvantage is the directly associated decrease in sexual behaviours. The emerging pattern seems to indicate that SSRIs, which enhance serotonergic neurotransmission in the brain, have similar inhibitory effects in human males and females. In line with the latter notion is the finding (Sugden et al. 2009) that gene expression for 5 serotonergic genes (including 5-HTT) did not differ between genders in postmortem human brains.

3 Serotonin, Serotonergic Receptors and Male Sexual Behaviour

3.1 Introduction

The importance of 5-HT in male sexual behaviour has been demonstrated by numerous studies showing that, for instance, lesions of the brainstem raphe nuclei (Albinsson et al. 1996) and 5-HT depletion (Tagliamonte et al. 1969) facilitate sexual behaviour. On the other hand, administration of 5-hydroxytryptophan, the direct precursor of 5-HT, 5-HT itself and 5-HT releasers such as MDMA and fenfluramine, inhibits sexual behaviour (Ahlenius et al. 1980; Dornan et al. 1991; Foreman et al. 1992; Gonzales et al. 1982). Altogether these findings suggest that a decrease in 5-HT neurotransmission may be involved in facilitation, whereas an increase in 5-HT neurotransmission may result in inhibition of male sexual behaviour.

3.2 SSRIs and Male Sexual Behaviour

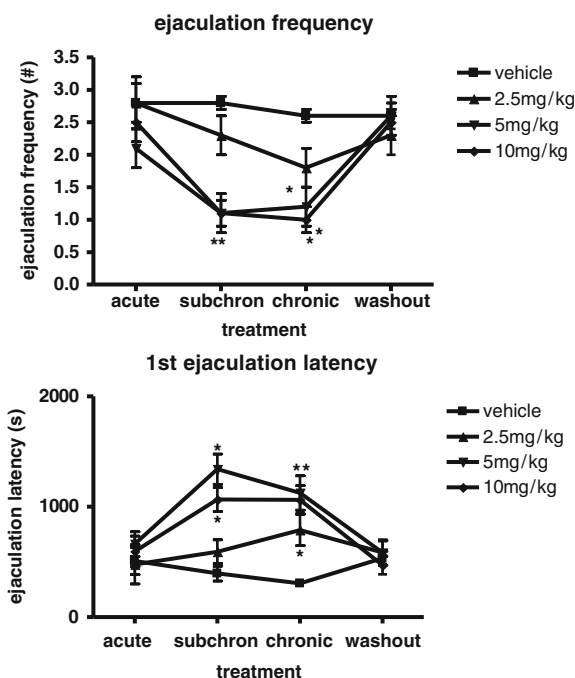
The frequently reported sexual effects of SSRIs in men demonstrate an important role of 5-HT in human ejaculatory behaviour. In several human studies we and others have demonstrated that SSRIs including paroxetine, sertraline and fluoxetine are able to delay ejaculation in premature ejaculation (for review, see Waldinger 2002; De Jong et al. 2006). Moreover, these studies show that SSRIs exert only a minimal ejaculation delay in the first week that is often not clinically relevant. A clinically relevant ejaculation delay occurs gradually after 2–3 weeks of daily treatment. Interestingly, despite the putative similar underlying mechanism of action of SSRIs – briefly, preventing the reuptake of 5-HT, thereby elevating 5-HT levels – not all SSRIs delay ejaculation to the same extent. In humans, the tricyclic antidepressant, clomipramine and the SSRI, paroxetine have stronger ejaculation-delaying effects after 4–6 weeks of daily treatment than other SSRIs (Waldinger et al. 1998, 2001a, b).

3.3 Acute and Chronic SSRI Administration in Male Rats

Analogous to the human situation, in male rats a distinction can be made between the effects of acute and chronic SSRI administration on ejaculation. Acute administration of various SSRIs, such as citalopram, paroxetine, sertraline, fluoxetine and fluvoxamine, did not or marginally delay ejaculation (Mos et al. 1999; Ahlenius and Larsson 1999; Matuszcyk et al. 1998). On the other hand, chronic administration of fluoxetine (Matuszcyk et al. 1998; Cantor et al. 1999; Frank et al. 2000) and paroxetine (Waldinger et al. 2001a, b) delayed ejaculation in male rats. Nonetheless, as in humans, not all SSRIs potentially delay ejaculation after chronic administration in male rats: fluvoxamine slightly affected some aspects of copulatory behaviour, but did not affect ejaculation (Waldinger et al. 2001a, b; De Jong et al. 2005a). It is unclear why the various SSRIs differ in their ability to delay ejaculation after chronic administration. The delay in onset of the therapeutic effect of SSRIs in depression and anxiety disorders has been related to adaptive changes of serotonergic autoreceptors (Haddjeri et al. 1998; Le Poul et al. 2000), and it is conceivable that the ejaculation-delaying effects of various SSRIs are due to differential adaptive changes of 5-HT receptors.

An example of the effects of an SSRI antidepressant (paroxetine) in male rat sexual behaviour is shown in Fig. 1. The effect is clearly seen in the number of ejaculations per 30-min test in sexually trained animals. Acutely (Day 1: 30 min after injection) paroxetine does not inhibit sexual behaviour whereas after 7 (sub-chronic; 5 and 10 mg/kg) or 14 days treatment (chronic; 2.5, 5.0 and 10.0 mg/kg)

Fig. 1 The mean number of ejaculations \pm SEM of male rat groups treated with vehicle or different doses of the SSRI paroxetine (2.5, 5.0 and 10.0 mg/kg IP) is given after acute (30 min pre-treatment), sub-chronic (7 days; once daily) and chronic (14 days; once daily) treatment. One week after cessation of treatment (washout), sexual behaviour was again measured but now without any treatment. Sexual behaviour tests were run on days 1, 7, 14 and 21 and consisted of a 30-min test in which a male rat had free access to a female that was hormonally brought into oestrus (method: Chan et al. 2010). * $p < 0.05$ compared to vehicle

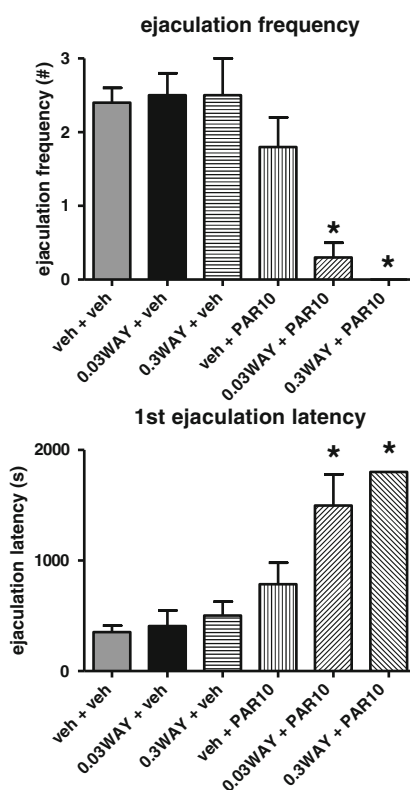


paroxetine strongly (and dose dependently) reduces sexual behaviour. The effect is reversible as animals return to their pre-testing level 1 week after cessation of treatment. A similar picture emerges for the first ejaculation latency that is not affected acutely, but is dose-dependently enhanced after 7 days and 14 days of treatment, and returns to baseline 1 week after cessation of treatment.

Ahlenius and Larsson (1999) have studied the mechanism of SSRI-induced delay of ejaculation in more detail and showed that acute treatment with citalopram did not affect ejaculatory behaviour. Co-administration of the 5-HT_{1A} receptor antagonist WAY-100635 with citalopram strongly delayed ejaculation latencies, suggesting 5-HT_{1A} receptor involvement in the effect of citalopram on ejaculation. De Jong et al. (2005a, b) also showed that citalopram, acutely or chronically, while not inhibiting sexual behaviour itself, when combined with a sexually inactive dose of WAY100635 completely abolished sexual behaviour.

We studied this phenomenon further and confirmed earlier findings (Looney et al. 2005) that a dose as low as 0.01 mg/kg of WAY100635 facilitated the behaviourally inactive acute 10 mg/kg paroxetine dose and led to strong inhibition of male sexual behaviour (Fig. 2). The data suggest that the inhibitory action of SSRIs after (sub) chronic treatment are related to changes at certain 5-HT_{1A} receptors after long-term treatment.

Fig. 2 Sexually trained male rats were acutely injected with saline or 10 mg/kg paroxetine (IP; 30 min before testing) immediately followed by an injection of either saline or a dose (0.03 and 0.3 mg/kg IP) of the 5-HT_{1A} receptor antagonist WAY100635. During an ensuing sexual behaviour test of 30 min, the sexual behaviour of the male was scored. In the figure, the mean number of ejaculations \pm SEM is given. *PAR* paroxetine, *WAY* WAY100635, *VEH* vehicle. * $p < 0.05$ compared to vehicle



Subsequently, it was found that the ejaculation-delaying effects of the combination of citalopram and WAY100635 could be fully blocked by a selective 5-HT_{1B} receptor antagonist, suggesting a role for this receptor subtype in the delay of ejaculation (Hillegaart and Ahlenius 1998). Interestingly, a previous study from the same laboratory also suggested a role of the 5-HT_{1B} receptor in the delay of ejaculation. In this study, it was shown that the 5-HT_{1B} receptor agonist anpirtoline dose-dependently delayed ejaculation in rats (Hillegaart and Ahlenius 1998).

3.4 SERT-KO Rats and Male Sexual Behaviour

In humans, the SERT plays a prominent role in the homeostasis of serotonergic neurotransmission. Polymorphisms in the promoter region of the SERT influence the activity of SERT, and the two length alleles (S and L allele) have functional consequences for the function of the 5-HT system (Murphy and Lesch et al. 2008). L and S (LL > LS > SS) generate allele-dependent 5-HT activity with associated functional consequences (Lesch et al. 2008). Rats do not possess such promoter length polymorphisms but genetic knockout of the SERT gene might generate rat models of the S-allele versions of the human SERT. Therefore, SERT^{-/-} and SERT^{+/-} can be compared to wild-type (SERT^{+/+}) male rats and their sexual behaviour studied (Chan et al. 2011). It was expected, in analogy to treatment with chronic SSRI treatment, that SERT^{-/-} and SERT^{+/-} rats would display a lowered sexual behaviour compared to SERT^{+/+} rats.

All rats (30 per genotype) were trained up to seven times (once weekly a test of 30 min) and gene knockout rats indeed showed lower sexual performance than wild-type rats. On average the mean number of ejaculations at week 7 was 1.6 for SERT^{+/+}, 1.1 for SERT^{+/-} and 0.7 for SERT^{-/-} rats (Fig. 3), a significant decrease

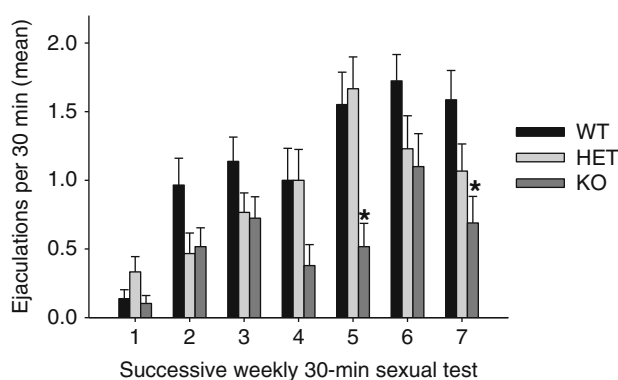


Fig. 3 Development of sexual behaviour (mean number of ejaculations/test) in male wild-type (SERT^{+/+}, WT), heterozygous (SERT^{+/-}, HET) and homozygous (SERT^{-/-}, KO) rats tested weekly over 7 weeks in a sexual behaviour test of 30 min with an oestrus female. **p* < 0.05 compared to WT animals

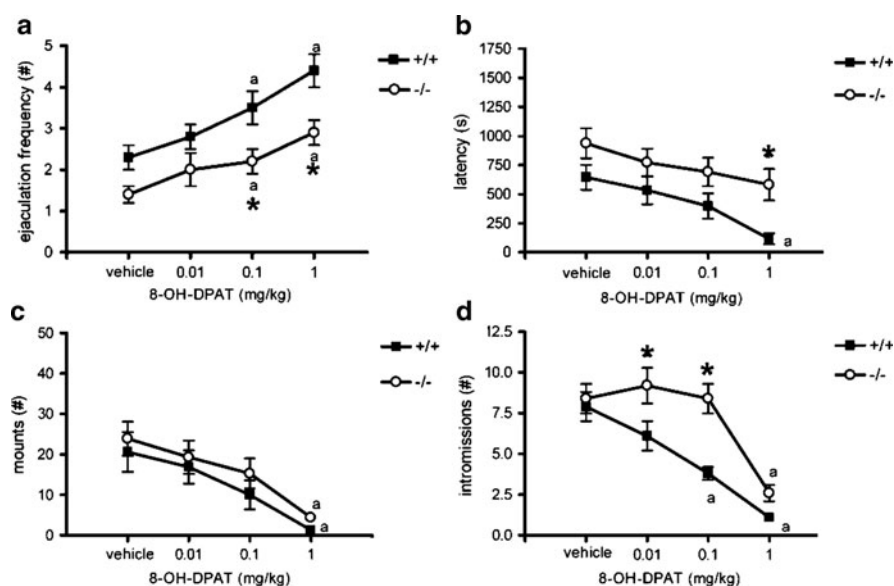


Fig. 4 Effects of the 5-HT_{1A} receptor agonist 8-OH-DPAT (s.c.) on ejaculation frequency over a 30-min test (a), latency to first ejaculation (b), first ejaculatory series mounts (c) and first ejaculatory series intromissions (d) of $SERT^{+/+}$ (+/+) and $SERT^{-/-}$ (-/-) animals. * p < 0.05 compared to wild type (+/+); a: p < 0.05 compared to vehicle treatment

for the homozygote gene knockout. The heterozygote KO was not different from the wild type.

Next, the 5-HT_{1A/7} receptor agonist +/-8-OH-DPAT was tested. 5-HT_{1A} stimulation has pro-sexual activities in rats which also occur in the three genotypes. Although the basal level of sexual behaviour (number of ejaculations, ejaculation latency, post-ejaculatory latency) in the $SERT^{-/-}$ is lower than in the other two genotypes (Fig. 4), the stimulant effect of 8-OH-DPAT in all three genotypes is similar, indicating that 5-HT_{1A} receptors mediating this effect have not changed [(de)sensitized].

The 5-HT_{1A} receptor antagonist WAY100635 had no effects in the WT and heterozygote rats but had a dose-dependent inhibitory effect in the $SERT$ -KO (Fig. 5), suggesting that a different pool of 5-HT_{1A} receptors is involved in its action and that these receptors appear sensitized in the $SERT$ -KO. Remarkably, the heterozygous $SERT^{+/-}$ rats did in no way differ from the WT rats. Heterozygous $SERT$ -KO rats have intermediate enhanced extracellular 5-HT levels compared to WT and $SERT$ -KO ($SERT^{-/-}$ > $SERT^{+/-}$ > $SERT^{+/+}$). Apparently, like the effective dose of SSRIs that need to occupy at least 80% of the SERTs before antidepressant efficacy is observed (Kugaya et al. 2003), the $SERT^{+/-}$ still has sufficient SERT capacity (50%) left to show undisturbed sexual behaviour.

To summarize, the sexual side effects of SSRIs are still not fully understood. Nevertheless, some recent findings and genetic evidence suggest that adaptive changes in the 5-HT system and probably its interactions with neuroendocrine systems (De Jong et al. 2007) may be responsible for their sexual effects.

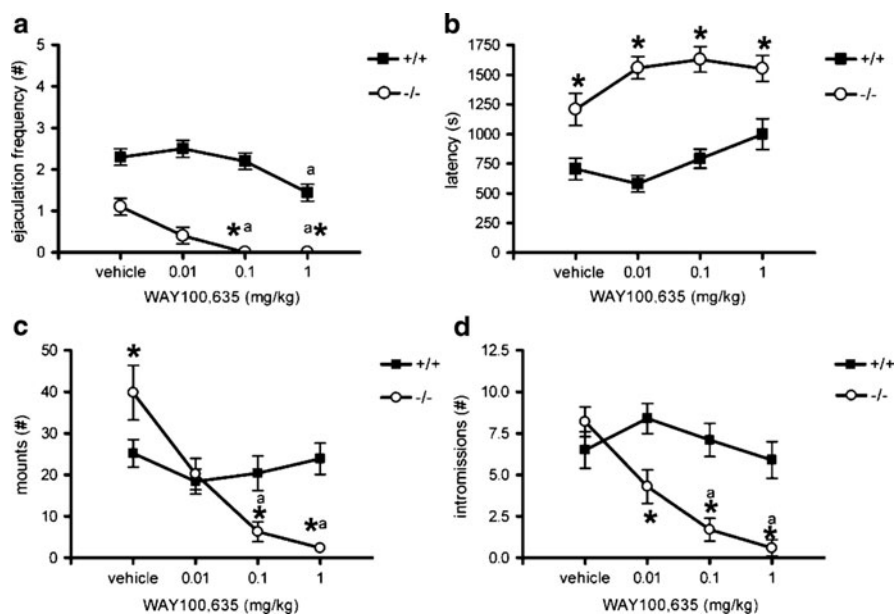


Fig. 5 Effects of WAY100635 (IP) on ejaculation frequency over 30-min test (a), latency to first ejaculation (b), first ejaculatory series mounts (c) and first ejaculatory series intromissions (d) of wild-type (+/+) and serotonin transporter knockout (-/-) animals. * $p < 0.05$ compared to wild type (+/+); a: $p < 0.05$ compared to vehicle treatment

3.5 Serotonin Receptor Agonists and Antagonists and Ejaculation in Male Rats

As described above, activation of 5-HT_{1B} receptors has been associated with delaying ejaculation in male rats. 5-HT₂ receptors are also implicated in modulation of sexual activity, e.g. shown by the 5-HT_{2A/2C} receptor agonist DOI-induced inhibition of sexual behaviour (Klint and Larsson 1995). On the other hand, several other studies have shown that 5-HT_{2A/2C} receptor agonists generally inhibit sexual behaviour by decreasing the number of animals that initiated copulation, but do not affect ejaculation latencies in animals that do initiate copulation (Ahlenius and Larsson 1998; Klint et al. 1992; Watson and Gorzalka 1991). Thus, it appears that 5-HT₂ receptors in general inhibit sexual behaviour, but their precise role in the regulation of ejaculation is not entirely clear.

A facilitatory role on ejaculation has been ascribed to activation of 5-HT_{1A} receptors, and various selective agonists for this receptor, such as 8-OH-DPAT (Ahlenius and Larsson 1990), FG-5893 (Andersson and Larsson 1994) and flesinoxan (Haensel and Slob 1997; Mos et al. 1991), potentially facilitate sexual behaviour and decrease ejaculation latencies. Nevertheless, the underlying mechanisms of the facilitatory effects of 5-HT_{1A} receptor agonists are still unclear. A possibility for the mechanism of action may be activation of presynaptic 5-HT_{1A} receptors that

Table 1 Mean number of ejaculations, mounts and intromissions and ejaculation latency (in seconds) for sexually naïve male rats during a 15-min test with a sexually active, oestrus female

Drug (route)	Dose (mg/kg)	EF	MF	IF	EL (s)
8-OH-DPAT (SC)	0	0.1	10.5	8.3	869
	0.1	1.5 ^a	6.5 ^a	7.6	351 ^a
	0.2	1.9 ^a	3.5 ^a	5.1	187 ^a
	0.4	1.7 ^a	1.1 ^a	1.1 ^a	238 ^a
Flesinoxan (IP)	0	0.3	13.9	12.2	854
	0.1	1.0 ^a	7.9	13.4	636 ^a
	0.3	1.3 ^a	5.5 ^a	9.8	459 ^a
	1.0	1.8 ^a	3.3 ^a	8.2	281 ^a
Buspirone (IP)	0	0.3	10.3	9.9	860
	3.0	1.2 ^a	7.0	11.3	502 ^a
	10.0	0.1	0.3 ^a	1.8 ^a	849
Ipsapirone (IP)	3.0	0.9 ^(a)	7.9	11.3	502 ^a
	10.0	1.5 ^a	10.9	12.2	636 ^a

All data are depicted as means

EF ejaculation frequency, *MF* mount frequency, *IF* intromission frequency, *EL* ejaculation latency

^aSignificantly different ($p < 0.05$) from the corresponding vehicle (0 mg/kg) dose

will lead to an inhibition of 5-HT neuronal firing and consequently results in facilitation of sexual behaviour as described above. Alternatively, activation of postsynaptic 5-HT_{1A} receptors may result in facilitation of sexual behaviour. Evidence for a postsynaptic mechanism of action is provided by studies demonstrating that injection of 8-OH-DPAT directly into the medial preoptic area potentially facilitated sexual behaviour and lowered ejaculatory threshold (Matuszewich et al. 1999). Administration of 5-HT_{1A} receptor antagonists does not lead to any change in sexual behaviour (Ahlenius and Larsson 1999; De Jong et al. 2005a; Sura et al. 2001). Moreover, the effects of 5-HT_{1A} receptor agonists can be antagonized by 5-HT_{1A} receptor antagonists. When 5-HT_{1A} receptor antagonists are combined with SSRIs (after acute or chronic administration), the inhibitory action of SSRIs is facilitated indicating a role for the 5-HT_{1A} receptor in the inhibitory action of SSRIs in male sexual behaviour (De Jong et al. 2005a, b; Table 1)

3.6 Animal Models of Premature and Retarded Ejaculation

Most of our current understanding of the anatomy and neurobiology of sexual behaviour is based on animal studies using rats that are sexually experienced and display normal sexual behaviour. Interestingly, the comparable ejaculation-delaying effects of SSRIs in humans and rats suggest high translational validity with regard to the regulation of ejaculation. Nevertheless, face validity is low when one tries to extend results obtained in rats that display normal sexual behaviour to dysfunction such as premature and retarded or even (an)-ejaculation. Over the last decades, several groups have studied rats that display hyposexual behaviour and are referred to, by different investigators, as sexually inactive, sluggish, impotent or

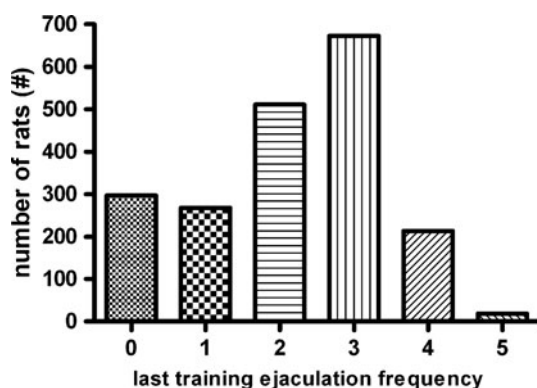


Fig. 6 More than 1,900 male rats were tested over a period of 5 years and trained weekly for 4 weeks in a sex test of 30 min against a female rat brought into behavioural oestrus. The graph represents the number of animals that displayed: 0, 1, 2, 3, 4 or 5 ejaculations during the last training test. Animals with 0 or 1 ejaculations/test were depicted as “slow” or “sluggish”; animals with two to three ejaculations/test as “normal” and animals with more than three ejaculations/test as “fast”

non-copulating rats. Recent findings suggest the presence of neurobiological differences associated with the hyposexual behaviour that these rats display. On the other hand, hypersexual behaviour can also be provoked pharmacologically. However, there are only few studies that have studied rats that are hypersexual by nature. Thus, investigating animals that do not display normal sexual behaviour may help understanding of the underlying neurobiological mechanisms and hopefully will provide further insight in the aetiology of ejaculatory dysfunction.

In our laboratory, we have found (Pattij et al. 2005; Olivier et al. 2005) that male outbred Wistar rats display sexual “endophenotypes”. In subsequent cohorts of 100–120 male rats, we consistently found rats that display a very low (0–1), normal (2–3) or high (4–5) number of ejaculations in 30-min tests with a receptive female even after four to eight training tests. The behaviour of these males seems very stable, and we suggest the low performing animals as putative model for delayed ejaculation in humans and the high performing rats as model for premature ejaculation (Pattij et al. 2005; Olivier et al. 2006). Figure 6 shows the distribution of these “endophenotypic” sexual phenotypes in 1,982 male rats we tested thus far.

These various endophenotypes are now the subject of pharmacological studies.

3.7 Studies with Rats Displaying Hyposexual Behaviour

It was already demonstrated in early experiments in the 1940s that rats reared in isolation are either not capable to achieve ejaculation or remain sexually inactive, after repeated exposure to a receptive female (Beach 1942). In contrast, rats that were reared in groups with either same-sex or hetero-sex cage mates did not show these clear deficits in copulatory behaviour. Importantly, in most but not all of the

isolation-reared males, sexual performance gradually improved with experience. These early findings suggest that experience and learning play an important role in rat copulatory performance, but apparently do not exclusively determine the ability to successfully copulate until ejaculation. In early studies focussing on rats displaying different levels of sexual performance, in our laboratory we have tried to create hyposexual behaviour in male rats by manipulating the level of sexual experience (Mos et al. 1990). To this end, we have studied the sexual behaviour of 278 sexually naïve male Wistar rats in 15-min tests with an oestrus female. From those 278 males, 23 showed no sexual activity at all, i.e. no intromissions and maximally one mount was scored during the test. From the remaining 255 rats, 211 displayed sexual activity, but failed to ejaculate during the test. The average ejaculation latency of the 44 ejaculating males was 620 ± 28 s. If sexually naïve male rats were treated with 5-HT_{1A} receptor agonists, these males performed quite well (Table 1). In particular, the two full 5-HT_{1A} receptor agonists (\pm)-8-OH-DPAT and flesinoxan enhanced sexual behaviour to the level of sexually experienced male rats. The partial 5-HT_{1A} receptor agonists buspirone and ipsapirone also facilitated sexual activity. These findings indicate that naïve male rats are able to perform sexual activities reminiscent of sexually “experienced” rats in a very short time interval. Apparently, sexually naïve rats may be influenced by certain factors that can be overcome by treatment with psychoactive drugs, at least 5-HT_{1A} receptor agonists and (not shown here) α_2 -adrenoceptor antagonists like yohimbine and idazoxan (Mos et al. 1990, 1991).

These pharmacological studies strongly suggest that neurobiological mechanisms underlie the differences observed in basal sexual behaviour.

3.8 Studies with Rats Displaying Hypersexual Behaviour

In contrast to studies focussing on rats that are hyposexual by nature, reports of rats that are hypersexual by nature are scarce. Nevertheless, numerous studies have indicated that a variety of selective pharmacological compounds, neurotransmitters and neuropeptides may facilitate sexual behaviour (Bitran and Hull 1987; Argiolas 1999). Most interesting are those studies in which male rat sexual behaviour is potentially facilitated and in which the behaviour shares some of the characteristics of human premature ejaculation. Indeed, some of the clinical symptoms of premature ejaculation can be evoked pharmacologically in male rats. For instance, various selective 5-HT_{1A} receptor agonists have been shown to potently decrease ejaculation latencies and intromission and mount frequencies. Apart from selective 5-HT_{1A} receptor agonists, a selective dopamine D₂ receptor agonist SND-919 (Ferrari and Giuliani 1994) has also been shown to decrease ejaculation latencies in rats, although its effects were much less pronounced compared to the effects of 5-HT_{1A} receptor agonists.

Not only can pharmacological manipulations facilitate ejaculatory behaviour, but “tactile” stimulation, such as shock and tail-pinching (Barfield and Sachs 1968; Wang and Hull 1980), also facilitate ejaculatory behaviour. Presumably these

facilitatory effects are mediated by activation of the brain dopaminergic system (Leyton and Stewart 1996).

3.9 Conclusion: Serotonin and Male Sexual Behaviour

Research in humans and rats has indicated that modulating 5-HT levels in the CNS changes ejaculatory thresholds and associated sexual behaviour. Activation of 5-HT_{1A} receptors and blockade of 5-HT_{2C} receptors facilitates sexual behaviour, whereas activation of 5-HT_{1B} and 5-HT_{2A} receptors inhibits it. SSRIs, which facilitate serotonin neurotransmission, inhibit sexual behaviour but only after chronic administration or genetic inactivation of the SERT gene. There is a paucity of data on the putative role of other 5-HT receptors in the modulation of male sexual behaviour.

4 Serotonin, Serotonergic Receptors and Female Sexual Behaviour

4.1 Introduction

The pharmacology of sexual behaviour in females is rather restricted compared to males. The majority of work has focused on one aspect of it: the lordosis reflex. Female sexual behaviour consists of attractivity, proceptivity and receptivity. Attractivity reflects behaviour, smell and sounds by the female that attract the male and most often leads to proceptive behaviour of the female, including solicitation, hopping and darting. Receptivity is reflected in the lordosis reflex required for successful copulation. Beach (1948) introduced the lordosis quotient (LQ = lordosis to mount ratio X 100) reflecting the lordotic response of the female to a mounting male. The LQ is the most frequently used parameter when studying effects of hormones and drugs on female sexual behaviour (cf. Uphouse 2000; Uphouse and Guptarak 2010). The lordosis reflex (arching of the back, elevation of the rump, dorsoflexion of the tail and extension of the neck) is a very stereotyped posture in response to a mounting male (Pfaff 1999). The tactile stimulation stimulates cutaneous receptors in the flank, rump, tail base and perineum, which feed their information to the brain where primarily areas in the hypothalamus (notably the VMH) are crucial in the control of lordosis. Oestrogen (Er_α) receptor activation is required to induce the lordosis reflex, and there is a minimum amount of circulating oestrogen needed to reach a certain lordosis threshold. Moreover, a latent period (minimally 16 h) is needed for receptivity development. Normally, both oestrogen and progesterone are used to optimally organize the libido reflex, but progesterone is not needed if the oestrogen dose is extra high. Adding progesterone reduces the amount of oestrogen needed to induce lordosis behaviour.

Pharmacological studies often use submaximal oestrogen (or progesterone) doses in ovariectomized females which produce submaximal lordosis quotients and generate a model that can be pharmacologically manipulated. Early studies showed that reduction of monoamine levels in the brain (e.g. by pCPA or reserpine) activated lordosis in suboptimally oestrogen-primed ovariectomized rats, while activation of 5-HT function inhibits it (for review, see Uphouse 2000; Uphouse and Guptarak 2010). With the emerging availability of selective 5-HT receptor ligands more specific studies could be performed, but still serotonergic psychopharmacology has been mainly restricted to 5-HT_{1A} and 5-HT₂ receptors.

Activation of 5-HT_{1A} receptors leads to inhibition of the lordosis reflex in hormonally suboptimally and optimally primed female rats (Ahlenius et al. 1986; Mendelson and Gorzalka 1986). Work from Uphouse's group (Uphouse 2000) has found that the underlying mechanism of this inhibition is mediated via postsynaptic 5-HT_{1A} receptors in the hypothalamus, specifically, although not exclusively, in the VMH. Blocking of these 5-HT_{1A} receptors, however, did not lead to facilitation of the lordosis reflex which also does not happen after systemic administration of 5-HT_{1A} receptor antagonists (Uphouse 2000), a finding we confirmed in our laboratory (see SERT-KO data later).

The role of 5-HT_{1B} receptors in lordosis is somewhat disputed (Uphouse and Guptarak 2010). Notwithstanding the limited evidence and lack of selective agonists, data suggest that activation of presynaptic 5-HT_{1B} receptors facilitates lordosis (Mendelson 1992), whereas blockade of 5-HT_{1B} receptors inhibits it (Uphouse et al. 2009).

Activation of 5-HT_{2A/2C} receptors (e.g. by DOI) facilitates lordosis in suboptimally primed rats (Mendelson and Gorzalka 1990), whereas 5-HT_{2A/2C} receptor antagonists inhibit it (Hunter et al. 1985; Mendelson and Gorzalka 1985). These effects seem also to be mediated in the hypothalamus probably in close interaction with those mediated by 5-HT_{1A} receptors (Uphouse 2000; Uphouse and Guptarak 2010).

5-HT₃ receptors do not play an important role in female sexual behaviour; the few studies reported (for overview, see Uphouse and Guptarak 2010) do not point to central 5-HT₃ receptors as a primary target. Similarly, an inhibitory role in lordosis of 5-HT₇ receptors has been suggested (Siddiqui et al. 2007), but these data are much linked to 5-HT_{1A} receptor modulation and research involving selective 5-HT₇ receptor agonists is required.

As SSRIs are reported to induce a high incidence of sexual disturbance in human females (Balon 2006; Montgomery et al. 2002), it is relatively surprising that only a few studies have been performed in rats. Acute treatment with SSRIs reduces lordosis in hormonally primed ovariectomized rats (Frye et al. 2003; Sarkar et al. 2008). Because sexual side effects of SSRIs in humans are particularly disturbing after chronic administration, animal studies using chronic SSRIs are particularly relevant. Matuszcyk et al. (1998) found that chronic fluoxetine reduced sexual behaviour in female rats. This and other studies (Maswood et al. 2008; Uphouse and Guptarak 2010) are complicated by the fact that natural cycling females were used and fluoxetine affected the cycle, at least in a large number of the animals. A better strategy would be to chronically treat

ovariectomized female rats with an SSRI, prime them with a dose of oestrogen and progesterone to induce lordosis and to test the effects of the SSRI in this model. Sarkar et al. (2008) found, using this paradigm, that fluoxetine acutely reduced lordosis but this effect was attenuated after sub-chronic fluoxetine administration, suggesting that some tolerance for the sexual inhibitory effect of the SSRI had occurred.

4.2 SERT-KO Rats and Female Sexual Behaviour

An alternative way to study the role of the SERT in female sexual behaviour is using genetically modified animals, in this case the SERT-KO rat made by ENU mutagenesis (Smits et al. 2006). Female Wistar intact rats were tested in a paced mating design where sexually experienced males were restricted to one side of a cage, whereas the female (brought into behavioural oestrus by a high dose of oestradiol) could spend time on both sides of a divider which allowed passage of the female (but not the male) through a couple of openings in the divider. Figure 7 shows that mutant SERT genotypes (SERT^{+/-} and SERT^{-/-}) were not different from wild types (SERT^{+/+}) in any aspect of proceptive or receptive behaviour over three consecutive tests of 30 min. This indicates that permanent absence of the serotonin transporter has no influence on female sexual behaviour under normal conditions. Treatment with a 5-HT_{1A} receptor agonist (+/-8-OH-DPAT) dose-dependently reduced proceptive behaviours (b) in all three genotypes, but in the

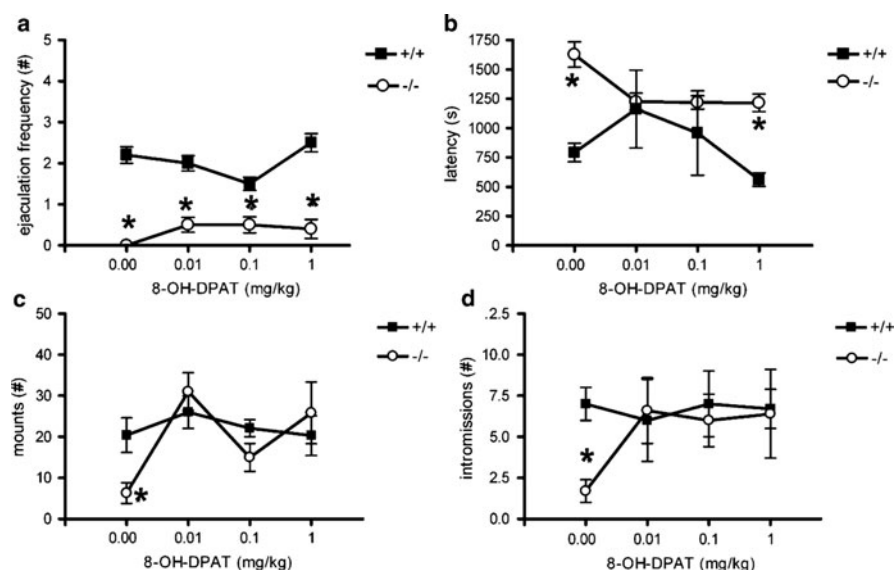


Fig. 7 Effects of three doses of 8-OH-DPAT (0.01, 0.1 and 1 mg/kg, SC) and one dose of WAY100635 (0.1 mg/kg, IP) on ejaculation frequency over 30-min test (a), latency to first ejaculation (b), first ejaculatory series mounts (c) and first ejaculatory series intrusions (d) of SERT^{+/+} (+/+) and SERT^{-/-} (-/-) animals. **p* < 0.05 compared to wild type (+/+)

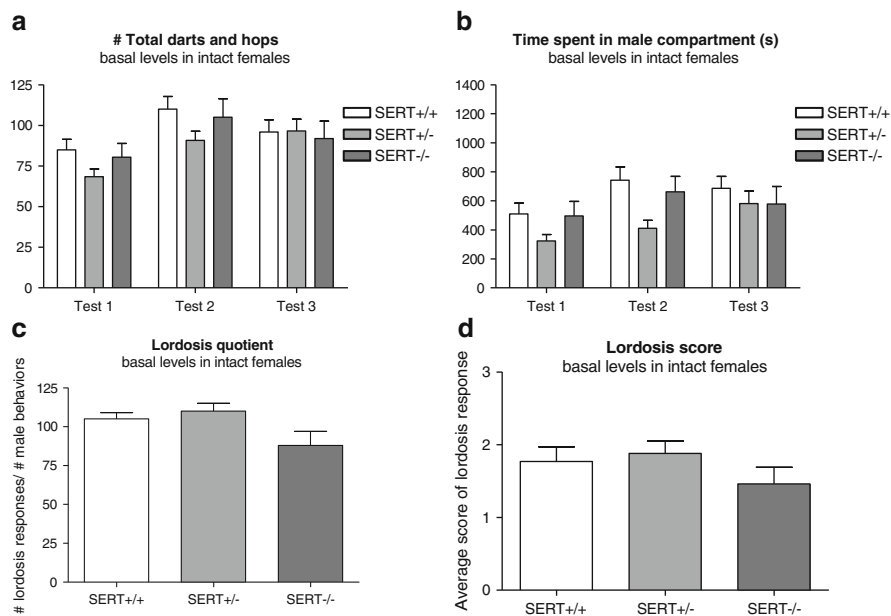


Fig. 8 In a paced mating situation (Snoeren et al. 2010) female wild-type (SERT^{+/+}), heterozygous (SERT^{+/-}) and homozygous (SERT^{-/-}) rats were brought into behavioural oestrus by hormonal priming and tested against a sexually experienced male rat. Females could pace the behaviour and stay in- or outside the male compartment. The number of proceptive [hopping and darting (a)] and receptive behaviours [Lordosis quotient and Lordosis score (c and d)] and the time spent in the male compartment (b) were measured

SERT-KO the dose–response curve clearly shifted to the right, indicative of a desensitized 5-HT_{1A} receptor (Fig. 8). However, time spent with the male was not affected (a), showing that the decreased proceptive behaviour was not caused by a diminished interaction with the male. Treatment with a 5-HT_{1A} receptor antagonist (WAY100635) did not affect any behaviour alone [(c) and (d)], whereas a selected dose of WAY100635 (0.1 mg/kg IP) was able to antagonize the 8-OH-DPAT-induced reduction in proceptive behaviour (f). Apparently, normal female sexual behaviour is not dependent on the functional status of 5-HT_{1A} receptors, but when challenged 5-HT_{1A} receptors appear desensitized in homozygous, but not heterozygous SERT-KO rats (Fig. 9).

5 Conclusions

The neurotransmitter serotonin clearly plays a role in male and female sexual behaviour (Table 2). Lowering serotonergic function seems to facilitate and enhancing it to inhibit sexual behaviour. The availability of blockers of the

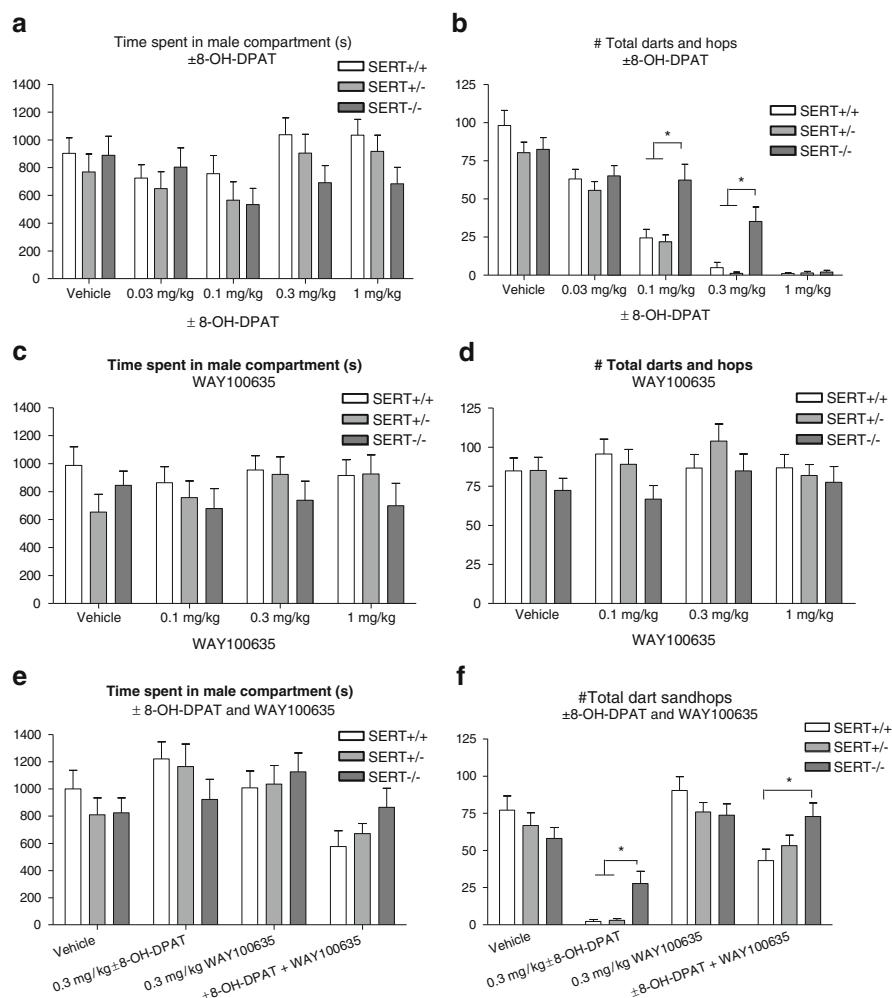


Fig. 9 Female wild-type (SERT^{+/+}), heterozygous serotonin transporter knockout (SERT^{+/-}) and homozygous serotonin transporter knockout (SERT^{-/-}) rats brought into behavioural oestrus were treated with the 5-HT_{1A} receptor agonist \pm 8-OH-DPAT (**a**); the 5-HT_{1A} receptor antagonist WAY100635 (**b**) or a combination of selected doses of 8-OH-DPAT (0.3 mg/kg) and WAY100635 (0.3 mg/kg) (**c**). The *left part* of each figure shows the time spent by the female in the male compartment; the *right part* the number of proceptive behaviours (hopping and darting) performed by the female during the test. The test was performed using a paced mating design in which the male and female were separated by a perforated wall that could be crossed by the female but not by the male. The female decides whether she wants to spend time with the male and receive mounts, intromissions and ejaculations. * $p < 0.05$ compared to wild type

Table 2 Summary of the effects of various serotonergic ligands on male and female sexual behaviour in rats after acute or chronic treatment

Target/ligand	Treatment	Male sexual behaviour	Female sexual behaviour
SERT/SSRI	Acute	=	=
SERT/SSRI	Chronic	↓	nd
5-HT _{1A} R agonist	Acute	↑	↓
5-HT _{1A} R agonist	Chronic	↑	nd
5-HT _{1A} R antagonist	Acute	=	=
5-HT _{1A} R antagonist	Chronic	nd	nd
5-HT _{1B} R agonist	Acute	↓	↑
5-HT _{1B} R agonist	Chronic	nd	nd
5-HT _{1B} R antagonist	Acute	=	↓
5-HT _{1B} R antagonist	Chronic	nd	nd
5-HT _{2A/C} R agonist	Acute	↓	↑
5-HT _{2A/C} R agonist	Chronic	nd	nd
5-HT _{2A/C} R antagonist	Acute	↓	↓
5-HT _{2A/C} R antagonist	Chronic	nd	nd
5-HT ₇ R agonist	Acute	nd	↓
5-HT ₇ R agonist	Chronic	=	nd
5-HT ₇ R antagonist	Acute	=	=
5-HT ₇ R antagonist	Chronic	=	nd

= not affected, nd not determined, ↑ enhanced, ↓ lowered, R receptor, SSRI selective serotonin reuptake inhibitor, SERT serotonin transporter

serotonin transporter and ligands for various serotonergic receptors has led to studies on male and female rat sexual behaviour that shed light on the contributions of individual receptors/transporter in male and female sexual function. SSRIs, blocking the SERT, generally lead to inhibition (after chronic treatment) of male and female sexual behaviour in agreement with the theory that enhancement of serotonergic function inhibits sexual behaviour. 5-HT_{1A} receptor activation facilitates male ejaculatory behaviour but inhibits female lordosis behaviour, suggesting an opposing role for this receptor in males and females. Clear-cut roles for other serotonergic receptors are less developed and need considerable research efforts.

Genetic manipulation of the SERT in rats indicated a differential influence of the absence of the SERT in male and female sexual behaviour; KO males, but not females, had lower baseline sexual activities. 5-HT_{1A} receptors were not desensitized in male KO, but were desensitized in females, indicating a differential role of various 5-HT_{1A} receptor pools in male and female sexual behaviour.

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