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REVIEW

Psychopharmacology of male rat sexual behavior: modeling human sexual dysfunctions?

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Most of our current understanding of the neurobiology, neuroanatomy and psychopharmacology of sexual behavior and ejaculatory function has been derived from preclinical studies in the rat. When a large population of male rats is tested on sexual activity during a number of successive tests, over time individual rats display a very stable sexual behavior that is either slow, normal or fast as characterized by the number of ejaculations performed. These sexual endophenotypes are postulated as rat counterparts of premature (fast rats) or retarded ejaculation (slow rats). Psychopharmacology in these endophenotypes helps to delineate the underlying mechanisms and pathology. This is illustrated by the effects of serotonergic antidepressants and serotonergic compounds on sexual and ejaculatory behavior of rats. These preclinical studies and models contribute to a better understanding of the neurobiology of ejaculation and boost the development of novel drug targets to treat ejaculatory disorders such as premature and retarded ejaculation.
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Introduction

Many drugs have influence on male and female sexual performance and/or behavior. Regarding the extremely complex mechanisms involving the regulation of sexual behavior in humans, but almost as complex in other mammals, it is not surprising that such, often disturbing effects occur. On the other hand, there is an increasing use of drugs promoting different aspects of sexual performance or behavior, including PDE-5 inhibitors for erectile dysfunction, antidepressants (selective serotonin reuptake inhibitors – SSRIs) for premature ejaculation and androgens for female libido.[1]

Research into the mechanisms involved in all aspects of sexual behavior, including physiological, neurological, pharmacological, neuroanatomical, endocrinological and pathological mechanisms is strongly increasing, and shares the emerging pharmaceutical market aiming at 'sexual health' products.

In this context, is it extremely important to have access to preclinical animal models that have face, predictive and construct validity towards human sexual disorders and dysfunctions.

The present paper starts with a short description of the serotonergic system, serotonergic receptors and ejaculatory behavior, focusing on the role played by the serotonin transporter and SSRIs in sexual dysfunctions. Also, the effects of other serotonergic ligands in sexual activities are discussed. The main emphasis of the present paper is on the development of novel rat paradigms modeling premature, normal and retarded ejaculation in human males. Effects of a selected number of psychoactive drugs will be described in these three different models. Finally, a discussion on the relevance and therapeutic use of the findings and their interpretation is performed.

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Animal sexual behavior

Increasing understanding of the neurobiology of normal and 'pathological' sexual functioning has

been derived from animal studies in which specific brain areas have been manipulated or animals have been challenged pharmacologically.[2,3] Most of the current theoretical models of animal sexual functioning – and underlying neurobiology – have been based on copulatory behavior of laboratory rats. Typically, in these experiments, male rats are exposed to a receptive female and allowed to copulate for a certain period of time, or until ejaculation has occurred. Male rat sexual behavior is characterized by a series of mounts, either with or without vaginal intromission that eventually will lead to ejaculation after a number of intromissions and certain duration of around 5–10 min. A distinction can be made between appetitive and consummatory aspects of copulatory behavior, where latency until the first mount putatively reflects some of the appetitive aspects and sexual motivation.[4] Consummatory aspects of sexual behavior include intromission latencies, ejaculation latencies, mount frequencies and intromission frequencies and may all affect ejaculatory behavior. With regard to male rat ejaculatory behavior, over the last decades numerous pharmacological studies have shown that various neurotransmitters and/or neuropeptides may be involved.

Moreover, the neuroanatomical pathways of male rat ejaculatory behavior are increasingly well understood, both at the supraspinal[5,6] and spinal cord level.[7,8] Nonetheless, little is known with regard to the putative underlying neurobiology of ejaculatory dysfunctions, such as premature and retarded ejaculation or an-ejaculation.

Serotonin, serotonergic receptors and ejaculatory behavior

Over the last decades, an extensive body of research has indicated that central neurotransmitters such as dopamine and serotonin and their receptors play an important role in the regulation of ejaculation. As excellent reviews exists concerning the role of central dopamine and central serotonin in sexual behavior,[9–14] here we only briefly review the most important findings with regard to the role of serotonin in the regulation of ejaculation and sexual activities in human ejaculation.[9,10,15]

The serotonergic neurotransmitter system is equipped with one endogenous ligand, 5-hydroxytryptamine (5-HT, serotonin) and has at least 14 structurally, functionally and pharmacologically distinct 5-HT receptor subtypes. These receptor subtypes can be assigned to one of seven families, namely 5-HT_{1-7} and each receptor subtype appears to have a distinct and limited distribution in the central nervous system.[16] Nonetheless, whether all these different receptor families and/or subtypes have their own distinct functions is unclear although very likely. Importantly, in addition to their postsynaptical distribution throughout the central nervous system, 5-HT_1 receptors are also located presynaptically as autoreceptors, where they regulate the activity of 5-HT neurons in the dorsal raphé nucleus.[17] Moreover, serotonergic transporter molecules (5-HTT) are present on serotonergic neurons (both somatodendritically and presynaptically) where they facilitate the re-uptake of 5-HT after cell firing-induced 5-HT release. SSRI inhibit this transporter and cause enhanced serotonin levels in the synaptic cleft leading to enhanced serotonergic neurotransmission. The importance of 5-HT in sexual behavior has been demonstrated by numerous studies showing that, for instance, lesions of the brainstem raphé nuclei[18] and 5-HT depletion[19] facilitate sexual behavior. On the other hand, administration of 5-hydroxytryptophan the direct precursor of 5-HT, 5-HT itself and 5-HT releasers such as MDMA (ecstacy) and fenfluramine have been shown to inhibit sexual behavior in male rats.[20–23] 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 sexual behavior. Moreover, these findings fit with the idea that spinal genitourinary circuits are under inhibitory control of supraspinal brainstem structures presumably mediated by 5-HT.[24–26]

Effects of SSRIs on ejaculation in humans

The frequently reported sexual side effects of SSRIs in men suggest an important role of 5-HT in human ejaculatory behavior.[27] As described previously, in several human studies, we and others have demonstrated that various SSRIs such as paroxetine, sertraline and fluoxetine are able to delay ejaculation in men with premature ejaculation.[28,29] Moreover, *daily* treatment SSRI studies in men with premature ejaculation with an intravaginal ejaculation latency time (IELT)[30] of less than 1 min, suggest that SSRIs exert a clinically not relevant ejaculation delay in the first week of treatment.[28,31,32] Although several studies have suggested that SSRIs may have faster onset of action than that is normally observed for antidepressant activity (4–6 weeks), we found that clinically relevant ejaculation delays occurs gradually after 2–3 weeks of daily treatment.[28,31,32] Several authors claim, however, that some SSRIs may have acute effects and can be used for on-demand treatment.[33–35] Their studies, however, suffer from methodological insufficiencies impairing a generalization of the study results. In contrast, in a recent double-blind stopwatch study in men with lifelong premature ejaculation, it was found that on-demand treatment with 20 mg paroxetine exerted a fold-increase IELT of only 1.41 (95% CI: 1.22–1.63) at a drug coitus interval time of approximately 5 h.[36] The calculated 1.4-fold increase means that on-demand treatment with 20 mg paroxetine in

men with an IELT of less than 1 min would induce only approximately 40% ejaculation delay. Patients and their partners considered the resulting degree of ejaculation delay as clinically not relevant. In contrast to SSRIs, the tricyclic antidepressant clomipramine (25 mg) taken at least 4–6 h before intercourse, may result in clinical relevant ejaculation delay.[36]

The serotonin enhancing effects of SSRIs are already present after acute treatment, and are further enhanced after chronic treatment. The relatively slow onset of action of SSRIs in the treatment of premature ejaculation, that is however clearly faster than in depression, indicates that chronic elevated activation of certain serotonergic receptors is needed for the effect on ejaculation. Apparently, this effect on ejaculation is not similar to the antidepressant activity of the SSRIs. The more so because, 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, for instance, of all the various SSRIs, paroxetine appears to have the strongest ejaculation delaying effects after 4–6 weeks of daily treatment whereas fluvoxamine and citalopram hardly show a clinically relevant inhibition.[28,29,32]

Acute and chronic SSRI administration

Analogous to the human situation, also in male rats, a distinction can be made between the effects of acute and chronic SSRI administration on ejaculation. Acute administration of various SSRIs, including citalopram, clomipramine, paroxetine, sertraline, fluoxetine and fluvoxamine did not have any delaying effects on ejaculations as shown earlier.[37–39] On the other hand, chronic administration of fluoxetine[39–41]and paroxetine[42] did have delaying effects on ejaculation in male rats. Nonetheless, as in humans not all SSRIs potently delay ejaculation after chronic administration in male rats. For instance, fluvoxamine slightly affected some aspects of copulatory behavior, but did not affect ejaculation even after chronic administration.[42] Furthermore, preliminary results obtained in our laboratory suggest that also chronic citalopram does not delay ejaculation in rats that are sexually active, although it completely abolished sexual behavior in some rats (unpublished observations).

Until now it is still 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.[43,44] Therefore, it is conceivable that also the ejaculation-delaying effects of various SSRIs are due to adaptive changes of, for instance, 5-HT receptor subtypes.

Ahlenius and Larsson[38] have studied the mechanism of SSRI-induced delay of ejaculation in more detail and showed that acute treatment with citalopram did not affect ejaculatory behavior. Nonetheless, when the 5-HT_{1A} receptor antagonist WAY-100635 was coadministered with citalopram, ejaculation latencies were strongly delayed, suggesting the involvement of 5-HT_{1A} receptors in effects of citalopram on ejaculation. De Jong *et al.*[45] also showed that doses of citalopram, acutely or chronically, that did not inhibit sexual behavior on itself, when combined with one sexually inactive dose of WAY-100635, completely abolished sexual behavior. Subsequently, Ahlenius and co-workers[46] showed that the ejaculation delaying effects of the combination of citalopram and WAY-100635 could be fully blocked by a selective 5-HT_{1B} receptor antagonist, suggesting a role for this receptor subtype in the delay of ejaculation. 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.[46] Several other explanations for the differential effects of SSRIs on ejaculation have been postulated, including, next to the inhibition of the serotonin transporters, other mechanisms of action in the various molecules. However, most if not all of these competing mechanisms in SSRIs, are only activated at higher doses of the SSRI than used in the treatment of premature ejaculation. We postulate here that the inhibitory effects of some SSRIs (paroxetine, sertraline, fluoxetine, clomipramine) on ejaculation are mediated via activation of particular serotonergic receptors, probably in specific brain or spinal cord areas. The noneffective SSRIs (citalopram, fluvoxamine) apparently do not (or not enough) activate these particular 5-HT receptors. It is feasible that the inhibiting SSRIs particularly activate 5-HT_{2C} receptors and not, or hardly 5-HT_{1A} receptors, whereas the reverse would hold for the noninhibitory SSRIs.

Interestingly, the adaptive changes in 5-HT receptors after chronic SSRI administration have been shown to affect neuroendocrine systems as well. One of these systems is the oxytocinergic system, which is generally known to facilitate sexual behavior.[47] Chronic fluoxetine[48] and paroxetine[49] administration have been shown to reduce G-protein levels in the hypothalamus. As a consequence, neuroendocrine responses, including oxytocin release, to 5-HT_{1A} receptor agonists were blunted in animals chronically treated with SSRIs compared to controls. It may be possible that the blunted oxytocin responses due to adaptive changes of G-proteins are responsible for the sexual side effects of SSRIs. Evidence supporting this comes from a recent study where it was shown that the sexual side effects of fluoxetine in rats could be completely reversed by coadministration of oxytocin.[49]

To summarize, until now the sexual side effects of SSRIs are not fully understood. Nevertheless, some

recent findings suggest that adaptive changes in the 5-HT system and its interactions with neuroendocrine systems may be responsible for their sexual side effects. For the development of novel therapeutic interventions to treat premature ejaculation, it is important to identify where in the central nervous system and in which – if any – 5-HT receptor subtypes these adaptive changes have occurred.

Effects of various serotonin receptor agonists and antagonists on ejaculation in male rats

As described above, activation of 5-HT_{1B} receptors has been associated with delaying ejaculation in male rats. Other 5-HT receptor subtypes implicated in the inhibition of ejaculation are 5-HT_2 receptors. For instance, in a standard mating paradigm, the nonselective 5-$HT_{2A/2C}$ receptor agonist DOI inhibited sexual behavior including ejaculation.[50] On the other hand, several other studies have shown that 5-$HT_{2A/2C}$ receptor agonists generally inhibit sexual behavior by decreasing the number of animals that initiated copulation, but do not affect ejaculation latencies in animals that do initiate copulation.[51–53] Thus, it appears that 5-HT_2 receptors in general inhibit sexual behavior, but their precise role in the regulation of ejaculation is not entirely clear.

In contrast to 5-HT_2 receptors, a facilitatory role on ejaculation has been ascribed to activation of the 5-HT_{1A} receptor and various selective agonists for this receptor, such as 8-OH-DPAT,[54] FG-5893[55] and flesinoxan[56,57] have been shown to potently facilitate sexual behavior 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 will lead to an inhibition of 5-HT neuronal firing and consequently results in facilitation of sexual behavior as described above. Alternatively, activation of postsynaptic 5-HT_{1A} receptors may result in facilitation of sexual behavior. Evidence for a postsynaptic mechanism of action is provided by studies demonstrating that injection of 8-OH-DPAT directly into the medial preoptic area potently facilitated sexual behavior and lowered ejaculatory threshold.[58]

Animal models of premature and retarded ejaculation

Most of our current understanding of the anatomy and neurobiology of sexual behavior is based on animal studies using rats that are sexually experienced and display normal sexual behavior. Interestingly, the comparable ejaculation-delaying effects of SSRIs in humans and rats suggest high predictive 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 behavior to dysfunctions such as premature and retarded or even (an)-ejaculation. Over the last decades, several groups have studied rats that display hypo-sexual behavior and are referred to, by different investigators, as sexually inactive, sluggish, impotent and noncopulating rats. Recent findings suggest the presence of neurobiological differences associated with the hypo-sexual behavior that these rats display. On the other hand, hypersexual behavior 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 behavior may help understanding of the underlying neurobiological mechanisms and hopefully provides further insights in the etiology of ejaculatory dysfunctions.

Studies with rats displaying hypo-sexual behavior

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.[59] 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 behavior. 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 hypo-sexual behavior in male rats by manipulating the level of sexual experience.[60] To this end, we studied the sexual behavior of 278 sexually naïve male Wistar rats in tests of 15 min with an estrus female. From those 278 males, 23 showed no sexual activity at all, that is, 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 enhances sexual behavior to the level of sexually experienced male rats. The partial 5-HT_{1A} receptor agonists buspirone and ipsapirone also facilitated sexual activity although buspirone at a higher dose was sedative. 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

Table 1 Mean number of ejaculations, mounts and intromissions and ejaculation latency (in s) for sexually naïve male rats during a 15-min test with a sexually active, estrus 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*	6.5*	7.6	351*
	0.2	1.9*	3.5*	5.1	187*
	0.4	1.7*	1.1*	1.1*	238*
Flesinoxan (ip)	0	0.3	13.9	12.2	854
	0.1	1.0*	7.9	13.4	636*
	0.3	1.3*	5.5*	9.8	459*
	1.0	1.8*	3.3*	8.2	281*
Buspirone (ip)	0	0.3	10.3	9.9	860
	3.0	1.2*	7.0	11.3	502*
	10.0	0.1	0.3*	1.8*	849
Ipsapirone (ip)	3.0	0.9*	7.9	11.3	502*
	10.0	1.5*	10.9	12.2	636*

All data are depicted as means.
Drugs are injected subcutaneously (sc) or intraperitoneally (ip) 15 min (8-OH-DPAT or 30-min (other drugs) before the test.
EF, ejaculation frequency; MF, mount frequency; IF, intromission frequency; EL, ejaculation latency.
*Significantly different ($P<0.05$) from the corresponding vehicle (0 mg/kg) dose.

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.[57,60]

Mos *et al*.[60] also showed that males treated with 5-HT_{1A} receptor agonists (flesinoxan, gepirone) were more attractive to females than vehicle treated males using a tethered two-choice paradigm, whereas α_2-adrenoceptor antagonist treated males were equally or even less attractive than vehicle-treated males for estrus females under such tethered conditions. It has already been shown earlier that hypo-sexual behavior in sexually inactive rats can be reversed by the opioid receptor antagonist naloxone.[61] Following these findings, numerous other studies have shown that also other pharmacological compounds and certain neuropeptides were able to improve copulatory behavior in sexually inactive rats. Again, the 5-HT_{1A} receptor agonist 8-OH-DPAT potently increased sexual activity in rats that were sexually inactive.[62] Similarly, the erectogenic drug sildenafil[63,64] and low doses of the hormone melatonin[65] were able to reverse the hyposexual behavior of sexually inactive rats. These pharmacological studies strongly suggest that neurobiological mechanisms underlie the differences observed in basal sexual behavior. Indeed, in recent years, neurobiological differences have been found between rats that are sexually inactive and rats that display normal sexual behavior.

The neurotransmitter oxytocin appears to play a facilitatory role in ejaculation;[47] however, until now its precise role has not fully been understood. Oxytocin-producing neurons in the brain are primarily located in the paraventricular nucleus of the hypothalamus and projections from these hypothalamic areas have been shown to reach into the lumbosacral portion of the spinal cord.[66] In a study by Arletti *et al*.,[67] it was shown that the expression of oxytocin mRNA was reduced in the paraventricular nucleus of the hypothalamus of sexually inactive rats strongly suggesting a functional role of oxytocin in the expression and execution of copulatory behavior. It would therefore be interesting to measure levels of oxytocin in, for instance, men suffering from retarded or an-ejaculation to determine whether oxytocin levels in these men are decreased.

There is general agreement that brain opioids are involved in the inhibition of copulatory behavior.[47,68] In line with this view, recent findings indicate that in the hypothalamus of sexually inactive rats levels of the endogenous opioid octapeptide are elevated[69] and mRNA expression of pro-enkephalin and pro-dynorphin is increased.[67] Whether these findings are related to the observed differences in behavior remain to be proven in subsequent experiments, although the findings fit the idea that opioid peptides inhibit sexual behavior.

Beside these findings – to our knowledge – there have been no other reports on neurobiological differences between rats displaying hypo-sexual and normal sexual behavior. In summary, the recent findings obtained in hypo-sexual rats have identified some neurobiological targets that may be responsible for the expression of the hypo-sexual behavior. Of course, more studies are necessary to validate and extend these findings; however, it would already be worthwhile to study these targets in men suffering from retarded ejaculation and an-ejaculation.

Studies with rats displaying hyper-sexual behavior

In contrast to studies focussing on rats that are hypo-sexual by nature, reports of rats that are hyper-sexual by nature are scarce. Nevertheless, numerous studies have indicated that a variety of selective pharmacological compounds, neurotransmitters and neuropeptides may facilitate sexual behavior.[11,47] Most interesting are those studies in which male rat sexual behavior is potently facilitated and in which it shares 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, such as 8-OH-DPAT,[54,60] FG-5893[55] and flesinoxan[56,60] potently decrease ejaculation latencies and intromission and mount frequencies, although the mechanism of action of these effects is still unclear

as discussed above. Beside selective 5-HT_{1A} receptor agonists, a selective dopamine D_2 receptor agonist SND-919[70] also decreased ejaculation latencies in rats, although its effects were far less pronounced compared to 5-HT_{1A} receptor agonists.

Besides pharmacological manipulations, 'tactile' stimulation, such as shock and tail-pinching[71,72] also facilitates ejaculatory behavior. Presumably, these facilitatory effects are mediated by activation of the brain dopaminergic system.[73]

Although the experiments described here are certainly not directly comparable to human ejaculatory disorders, the results do provide further support and insight into which neural mechanisms are involved in the facilitation of copulatory behavior. It would therefore be highly interesting to examine these mechanisms in men suffering from premature ejaculation.

Variability in ejaculatory behavior: a putative model for premature, normal and retarded ejaculation?

In 1998 Waldinger and Olivier[9] hypothesized that premature ejaculation is not a psychological disorder but part of a biological variation of the IELT in men with a possible genetic component as depicted in Figure 1. According to this hypothesis there are men who throughout their live always have an early ejaculation, men who always have retarded or even no ejaculation, and men who ejaculate in a range that can be characterized as having an average or 'normal' ejaculation time.

Based on this hypothesis, we investigated whether such a biological variation does exist in male rats. Therefore, we investigated the presence of 'rapidly' and 'sluggishly' ejaculating rats in large populations of Wistar rats, an out-bred laboratory rat strain used standard in our lab in the study of sexual behavior. With regard to the variability in male rat sexual behavior, it appears that during a 'standardized' mating paradigm of 30-min (see Methods[37]), ejaculation frequencies in several experiments are distributed following a Gaussian distribution as depicted in Figure 2, with approximately 10% of the rats displaying 'hypo-sexual' and 10% displaying 'hyper-sexual' behavior after at least four successive weekly sexual tests of 30-min. Based on this biological continuum in ejaculation frequencies we further investigated whether the by nature 'hyper-' and 'hypo-sexual' rats could be used as a model for human premature and delayed (an)-ejaculation, respectively.

To this end, we matched rats on either side of the Gaussian distribution into groups of 'sluggish' ejaculators (defined as 0–1 ejaculation within 30 min) and 'rapid' ejaculators (4–5 ejaculations within 30 min). Interesting differences were found between these groups of rats on a variety of other parameters of sexual behavior, resembling clinical symptoms of men suffering from premature and

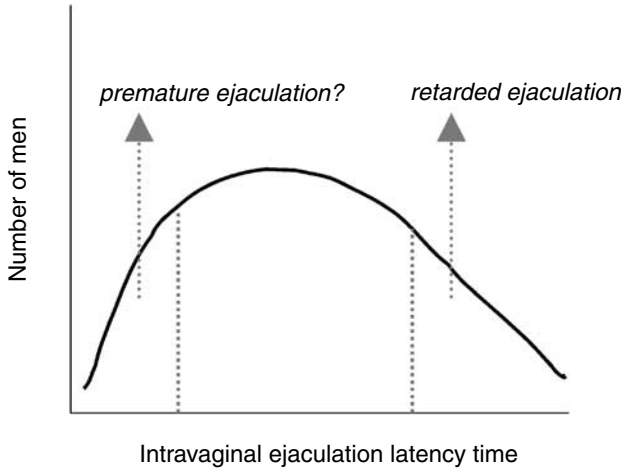

Figure 1 Hypothetical distribution of intravaginal ejaculation latency times in men, with on either side of the 'Gaussian' distribution men suffering from premature ejaculation (left) and retarded or an-ejaculation (right).

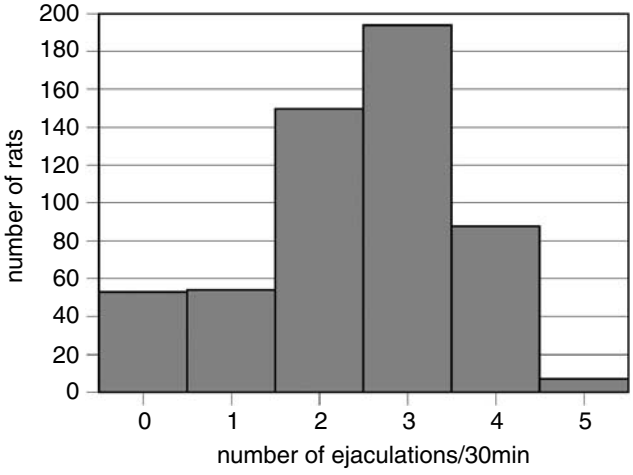

Figure 2 Histogram displaying number of ejaculations during a 30-min mating test in a pooled population of male Wistar rats (total $N = 546$, obtained from six experiments). The data were collected during the fourth mating test, representing stable copulatory behavior. Male rats on either side of the Gaussian distribution were matched into 'sluggish' (0–1 ejaculation) and 'rapid' ejaculators (4–5 ejaculations) and compared to 'normal' ejaculators (2–3 ejaculations).

retarded (an)-ejaculation. As displayed in Table 2, in addition to differences in ejaculation frequencies, significant differences were found between 'sluggish' and 'rapid' ejaculators in their latencies to achieve ejaculation. Compared to 'normal' ejaculators, ejaculation latency was shortest in 'rapid' and longest in 'sluggish' ejaculators. Also, the number of mounts the animals displayed prior to ejaculation varied between groups. Sluggish ejaculators, although the majority did not achieve ejaculation, displayed the highest number of mounts, whereas 'rapid' ejaculators displayed the lowest number of

mounts prior to ejaculation. In other words, the high number of mounts may suggest that these rats needed more vagino-penile sexual stimulation to get an ejaculation. In contrast, the rapid ejaculators ejaculated already after little vagino-penile sexual arousal. The differences in mounting behavior may suggest differences in penile sensitivity between groups as has been shown in men suffering from premature ejaculation.[74] Intromission frequencies and mount latencies, the latter often regarded as a putative index of sexual motivation[4] did not differ between 'sluggish', 'normal' and 'rapid' ejaculators, suggesting no differences in appetitive components of sexual behavior. We consider these different sexual phenotypes as endophenotypes, because they emerge in every population of rats and are very stable over time. More research is of course needed to prove whether these sexual endophenotypes have particular genetic genotypes (polymorphisms) and are strictly under genetic control or dependent on environmental conditions and/or genotypic/environmental interactions.

When the sexually inactive (retarded ejaculation) group was subsequently tested with a prosexual (0.8 mg/kg ip) dose of (±)-8-OH-DPAT, all animals were able to ejaculate, indicating that physical

Table 2 Copulatory behavior of a population of 100 male Wistar rats after matching into 'sluggish', 'normal' and 'rapid' ejaculators

Behavior	*Sluggish*	*Normal*	*Rapid*
MF	42±4.0	23±4.0*	8.2±1.8*,**
IF	5.6±1.4	7.6±0.9	7.5±1.0
EF	0.2±0.1	1.9±0.3*	3.7±0.2*,**
EL	1697±80	717±133*	247±45*,**
ML	47.6±30.6	6.5±0.8	13.6±7.7

Data depict mean±s.e.m.
All behaviors were calculated during the sixth sexual behavior test for the first ejaculatory series, except for ejaculation frequency which was calculated for the entire 30-min period; $n=12$ per group.
MF, mount frequency; IF, intromission frequency; EF, ejaculation frequency; EL, ejaculation latency (s); ML, mount latency (s); *significantly different ($P<0.05$) compared to 'sluggish' ejaculators and **significantly different from 'normal' ejaculators.

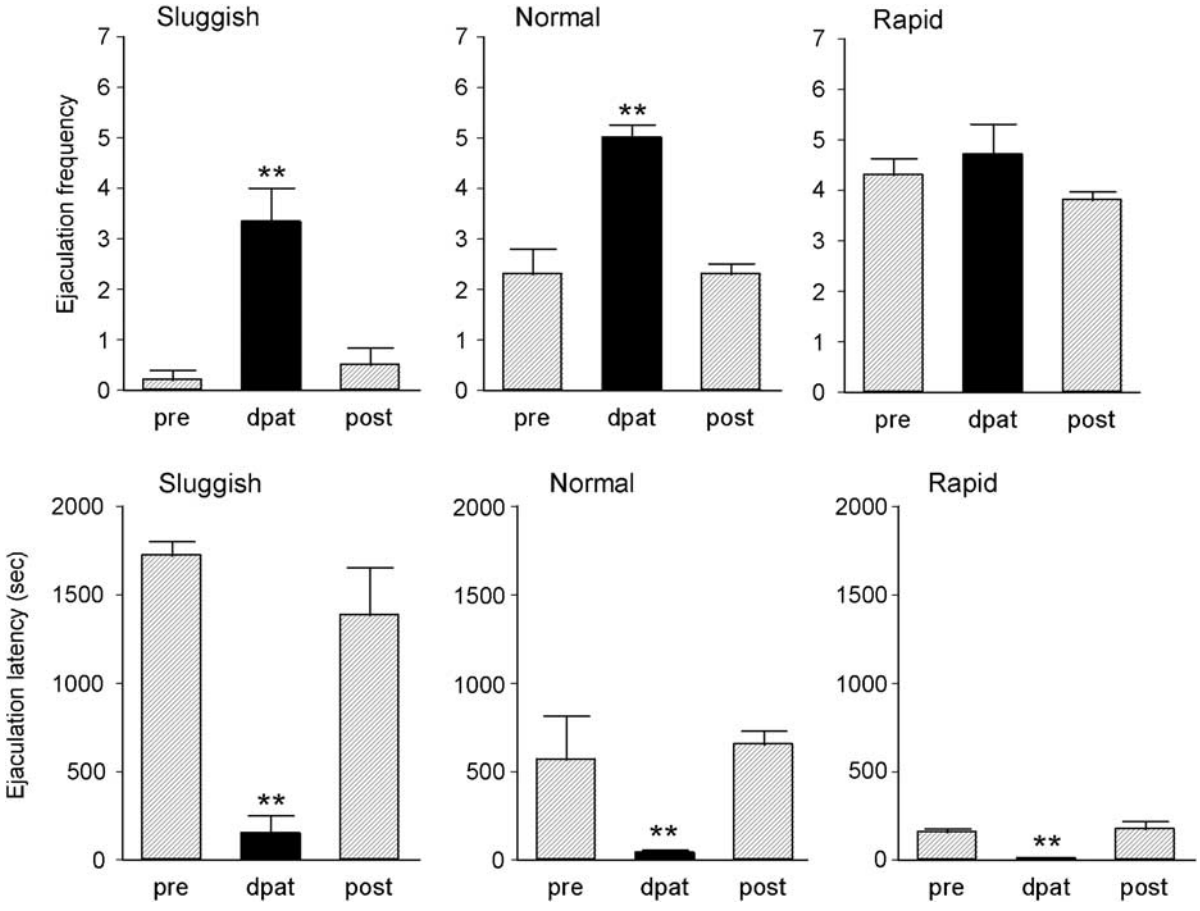

Figure 3 Relapse into 'original' ejaculatory behavior after facilitatory effects of 8-OH-DPAT (0.8 mg/kg, sc). Top: mean (±s.e.m.) number of ejaculations during baseline training (pre) and 1 week following (post) test with 8-OH-DPAT (dpat) in sluggish, normal and rapid ejaculators. Bottom: mean (±s.e.m.) ejaculation latencies during baseline training (pre) and 1 week following (post) test with 8-OH-DPAT (dpat) in sluggish, normal and rapid ejaculators. **Indicates $P<0.05$ compared to pre and post.

abnormalities do not underlie the lack of sexual activity (Figure 3). When retested under no-treatment conditions 1 week after the 8-OH-DPAT treatment, rats were back to their original endophenotypic behavior, that is, sexually inactive. One could argue that aversive sexual experience during the first sexual tests might cause definitive changes in later sexual level of performance, but treating sexually naïve rats with 8-OH-DPAT before the first sexual test, which led to higher than normal sexual performance, did not change the final distribution (after four successive tests) in approx. 10% sluggish, 10% rapid and 80% normal ejaculators. This strongly suggests that in a normal population rats, like in the human population, endophenotypes may exist with regard to basal sexual (ejaculatory) performance. Therefore, the behavioral differences found in sluggish and rapid ejaculators in rats strongly suggest commonalities with human premature and retarded ejaculation, namely differences in tactile stimulation (number of mounts needed to achieve ejaculation) and ejaculation latency.

Although normal and rapid ejaculating rats have higher basal levels of sexual activity (Figure 3), they are still sensitive to the prosexual activity of 8-OH-DPAT. Even in the rapid ejaculators, the ejaculation latency is further decreased. This illustrates that presumably 5-HT_{1A} receptors play a role in sexual behavior of all three endophenotypes, although it is unlikely that the basal differences in sexual behavior are due to adaptive changes in this receptor.

We presently are pursuing pharmacological studies on these various sexual endophenotypes. It is expected that various neural mechanisms involved in sexual behavior are regulated at different levels in the different endophenotypes and that pharmacological treatment may show differential sensitivity towards different pharmacological challenges.

The next step is to further identify the underlying mechanisms that could have contributed to the observed differences in copulatory behavior. We are currently performing molecular and endocrinological studies to clarify this.

It should be noted that ejaculatory dysfunctions in men are complex and may arise from a combination of neurobiological, physiological and psychological factors. Recently, a stopwatch study in 491 non-selected men from five different countries (The Netherlands, United Kingdom, Spain, Turkey and USA) demonstrated the existence of an IELT continuum in men. The shape of the IELT distribution was positively skewed, with a median IELT of 5.4 min (range, 33 s to 44 min).[75] Using the 0.5 and 2.5 percentiles as cutoff points for dysfunction definition, the study demonstrated a prevalence of IELTs less than 0.9 min in 0.5% and less than 1.3 min in 2.5%.[76]

Psychopharmacological studies have shown that premature ejaculation is probably highly neurobiological determined. In addition, there is hardly any well-controlled evidence-based research confirming the psychological basis of and successful psychological treatment of these ejaculatory disorders. Still, a certain influence of psychological factors ca not be fully excluded *a priori*. The present findings of a natural occurrence of rapid, average (normal) and delayed ejaculation latencies in rats may be used as a model of human ejaculatory dysfunctions. The approach seems worthwhile, because as described earlier, several differences in neurobiology have been shown in rats that are hypo-sexual compared to controls. Also, in other fields of neuroscience, variability in certain behaviors has been focus of research to further elucidate the neurobiological determinants of, for instance, addiction (low grooming versus high grooming rats),[77] schizophrenia (apomorphine susceptible versus unsusceptible rats),[78] aggression (short attack latency versus long attack latency mice)[79] and anxiety and depression (8-OH-DPAT sensitive versus insensitive rats).[80]

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