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TOPIC PAPER

Marcel D. Waldinger · Berend Olivier

Animal models of premature and retarded ejaculation

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Abstract Most of our current understanding of the neurobiology of sexual behavior and ejaculatory function has been derived from animal studies using rats with normal sexual behaviour. However, none of these proposed models adequately represents human ejaculatory disorders. Based on the "ejaculation distribution theory", which postulates that the intravaginal ejaculation latency time in men is represented by a biological continuum, we have developed an animal model for the research of premature and delayed ejaculation. In this model, a large number of male Wistar rats are investigated during 4–6 weekly sexual behavioural tests. Based on the number of ejaculations during 30 min tests, rapid and sluggish ejaculating rats are distinguished, each representing approximately 10% at both ends of a Gaussian distribution. Together with other parameters, such as ejaculation latency time, these rats at either side of the spectrum resemble men with premature and delayed ejaculation, respectively. Comparable to the human situation, in a normal population of rats, endophenotypes exist with regard to basal sexual (ejaculatory) performance.

M. D. Waldinger (✉)
Department of Psychiatry and Neurosexology,
Leyenburg Haga Hospital, Leyweg 275,
2545 CH The Hague, The Netherlands
E-mail: md@waldinger.demon.nl
Tel.: +31-70-3612086
Fax: +31-70-3614902

M. D. Waldinger · B. Olivier
Department of Psychopharmacology,
Utrecht Institute for Pharmaceutical Sciences
and Rudolf Magnus Institute for Neurosciences,
Utrecht University, Utrecht,
The Netherlands

B. Olivier
Department of Psychiatry,
Yale University School of Medicine,
New Haven, Connecticut, USA

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Introduction

Pharmacological research into human ejaculatory disorders is limited to clinical studies with registered drugs affecting the ejaculation process. However, for a deeper insight into the effects of medication on underlying pharmacological processes, animal research seems a prerequisite. Animal pharmacological research has provided the most important contribution to our current knowledge and understanding of the neuropharmacology and neuroanatomy of sexual behaviour. Although we have gained much understanding, particularly of the serotonergic contribution to ejaculatory behaviour, an animal model for ejaculatory disorders has, thus far, not been available.

Recent data obtained in our laboratory suggest that a worthwhile approach to studying ejaculatory disturbances may be to focus on individual variability in ejaculatory behavior. In this paper, we describe various animal models of sexual behavior as well as our current approach to studying individual variability in ejaculatory behaviour.

Sexual side effects of SSRIs

Shortly after the introduction of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression, anxiety disorders and obsessive compulsive behaviour, it appeared that this group of antidepressants had sexual side effects [1]. They mainly delayed ejaculation in men and orgasm in women, and to a lesser extent exerted a negative effect on erectile function and sexual arousal in patients with psychiatric disorders. The ejaculation-delaying effects of some SSRIs were soon used therapeutically to treat premature ejaculation [2–5].

Major negative effects of SSRIs on erectile function and sexual arousal in men with premature ejaculation have been reported less frequently.

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 [6, 7]. In these studies, the copulatory behaviour of laboratory rats was investigated. 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 copulatory behaviour is characterized by a series of mounts, either with or without vaginal intromission, that eventually lead to ejaculation after approximately 10–15 intromissions and a duration of around 10 min. The consummatory aspects of sexual behaviour, including intromission latency, ejaculation latency, mount frequency and intromission frequency may all affect ejaculatory behavior. Over the last decades, numerous pharmacological studies have shown that various neurotransmitters and/or neuropeptides in the CNS may be involved in male rat ejaculatory behavior.

Moreover, the neuroanatomical pathways of male rat ejaculatory behavior are becoming increasingly well understood, both at the supraspinal [8, 9], and spinal cord levels [10, 11].

Most of our current understanding of the anatomy and neurobiology of sexual behavior is based on animal studies using sexually experienced rats that 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 the results obtained in rats that display normal sexual behavior to dysfunctions such as premature and retarded or even (an)ejaculation.

Acute and chronic animal models

Animal studies have been performed to investigate whether there is a difference in the degree to which various SSRIs influence sexual behaviour. One can distinguish an acute [12, 13] and a chronic animal model [14–17]. In our own group, we initially used an acute model. Sexually experienced and naive rats were tested 60 min after the oral administration of clomipramine, fluvoxamine, fluoxetine, sertraline or paroxetine. No major inhibitory effects of clomipramine and the SSRIs on male rat sexual behaviour at non-sedative doses were found [12]. It was therefore concluded that masculine sexual behaviour in rats, using an acute model paradigm, does not constitute a suitable model to investigate the differential mechanisms of sexual inhibition of SSRIs [12]. Using a chronic model, in which the sexual behaviour of the rats was tested after 7 and 14 days of daily oral SSRI (paroxetine, fluvoxamine, placebo) treatment, we found significant effects of paroxetine, but only mildly ejaculation delaying effects of fluvoxamine [17]. Both the acute and chronic models resemble the effects of SSRIs in men. Acute (on-demand) treatment of SSRIs has no relevant effect on ejaculation after 1–5 h [18], while chronic (daily) SSRI treatment results in clinically very relevant ejaculation delaying effects [5].

Pharmacological model for premature ejaculation

Numerous studies have indicated that a variety of selective pharmacological compounds, neurotransmitters and neuropeptides may facilitate sexual behaviour [19, 20]. The most interesting are those studies in which male rat sexual behavior is potently facilitated and in which the behavior 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, such as 8-OH-DPAT [21, 22], FG-5893 [23] and flesinoxan [20, 24] potently decrease ejaculation latencies and intromission and mount frequencies, although the mechanism of action of these effects is still unclear. Beside selective 5-HT_{1A} receptor agonists, a selective dopamine D_2 receptor agonist SND-919 [25] has also been shown to decrease ejaculation latencies in rats, although its effects were much less pronounced than those of 5-HT_{1A} receptor agonists.

Not only pharmacological manipulation can facilitate ejaculatory behavior, but, interestingly, also 'tactile' stimulation such as shock and tail-pinching [26, 27]. Presumably such facilitatory effects are mediated by activation of the brain's dopaminergic system [28].

Animal models for premature and delayed ejaculation

Both the acute and chronic drug-administration models, like the 5-HT_{1A} receptor and dopamine D_2 receptor agonist model in normal rats, are not adequate for research on genuine premature and delayed ejaculation, as the rats in these models, whether sexually experienced or naive, usually have a normal or average ejaculation latency by nature. It is this feature of the ejaculation latency time that is so characteristically disturbed by nature in men with premature and delayed ejaculation.

Therefore, the investigation of animals that do not display normal sexual behavior may help us understand the underlying neurobiological mechanisms and provide further insights into the etiology of ejaculatory dysfunctions.

In 1998, Waldinger et al. [29] postulated the "ejaculation distribution theory" (EDT) according to which the intravaginal ejaculation latency time (IELT) [2], defined as the time between intravaginal penetration and intravaginal ejaculation, is postulated to follow a continuum in the general population (see also this issue [30]). Waldinger et al. postulated that early ejaculation belongs to normal biological variability of IELT in men. In other words, EDT states that any random sample of men includes a small subgroup of early ejaculators, another subgroup with delayed or even absence of ejaculation, while the majority of men have a "normal" or "average" ejaculation time. Recently, a stopwatch study on 491 unselected men from five different countries (The Netherlands, UK, Spain, Turkey and USA) confirmed the existence of such an IELT continuum in men. The shape of the IELT distribution was positively skewed, with a median IELT of 5.4 minutes (range 33 s–44 min) [31]. Using the 0.5 and 2.5 percentiles as cut-off 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% of those studied [32].

In order to investigate whether the postulated IELT continuum exists in an unselected population of animals, and particularly with the aim of developing a rat model for ejaculatory disorders, we investigated the existence of such a biological continuum in large samples of male rats.

Biological variability in the ejaculation latency time in animals

Lifelong premature ejaculation may be characterized by a triad of symptoms: ejaculation after few penile thrusts, a short IELT, and occurrence of an early ejaculation during (nearly) every coitus. On the other hand, lifelong delayed ejaculation may be characterized by the following three symptoms: ejaculation after a large number of penile thrusts, a long duration of the IELT, and occurrence at (nearly) every coitus.

We investigated whether a biological continuum in the ejaculation latency time with the above mentioned triad of symptoms exists in male rats [33, 34]. Therefore, we investigated the presence of 'rapidly' and 'sluggishly' ejaculating rats in large populations of Wistar rats. With regard to the variability in male rat sexual behavior, during a standardized mating paradigm of 30 min (see for methods [12]), ejaculation frequencies in several experiments showed a Gaussian distribution with approximately 10% of the rats displaying hyposexual behavior and 10% displaying hypersexual behavior after at least four to six successive weekly sexual tests of 30 min. Based on this biological continuum in ejaculation frequencies, we further investigated whether the naturally hyper- and hyposexual 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 for a variety of other parameters of sexual behavior, resembling clinical symptoms in men suffering from premature and retarded (an)ejaculation. 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 achieve an ejaculation. In contrast, the rapid ejaculators ejaculated after only little vagino-penile sexual arousal. The differences in mounting behavior may suggest differences in penile sensitivity between the groups, as has been shown in men suffering from premature ejaculation [35]. Intromission frequencies and mount latencies, the latter often regarded as a putative index of sexual motivation [36], did not differ between sluggish, normal and rapid ejaculators, suggesting no differences in the appetitive or sexual motivation components of sexual behavior.

When the sexually inactive (retarded ejaculation) group was subsequently tested with a prosexual dose of 8-OH-DPAT, all animals were able to ejaculate, indicating that physical abnormalities did not underlie the lack of sexual activity. When retested under no-treatment conditions 1 week after 8-OH-DPAT treatment, the rats were back to their original phenotype, i.e. sexually inactive. One could argue that aversive sexual experience during the first sexual tests might cause definitive changes in the later sexual level of performance, but treating naive rats with 8-OH-DPAT before the first sexual test and inducing a higher than normal sexual performance did not change the final distribution in approximately 10% sluggish, 10% rapid and 80% normal ejaculators.

Conclusions

Most of our current understanding of the neurobiology and neuroanatomy of sexual behavior and ejaculatory function has been derived from preclinical studies using rats with normal sexual behaviour. However, none of these models adequately represents human ejaculatory disorders. With reference to the ejaculation distribution theory, which postulates that the IELT in men is represented by a biological continuum from early ejaculation toward failure of ejaculation, we have developed an animal model for the research of premature and delayed

ejaculation. This model consists of a standardized mating paradigm of 30 min, in which a large number of male Wistar rats are investigated during 4–6 weekly sexual behavioural tests. At the final test, rats are distinguished according to their ejaculation frequencies. It appears that both ejaculation frequencies and ejaculation latencies are distributed according to a continuum represented by a Gaussian distribution with approximately 10% of the rats being rapid ejaculators and 10% sluggish ejaculators. The distinction between rapid and sluggish ejaculators forms a stable pattern throughout the weekly experiments.

This strongly suggests that in a normal population of rats, as in humans, endophenotypes may exist for 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. The next step is to further identify the underlying mechanisms that could contribute to the observed differences in copulatory behavior. We are currently performing pharmacological, molecular and endocrinological studies to clarify this.

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