ORIGINAL RESEARCH—BASIC SCIENCE

Further Definition on the Multiple Partner Choice Arena: A Potential Animal Model for the Study of Premature Ejaculation

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ABSTRACT

Introduction. The multiple partner choice arena (MPCA) is an experimental setup in which male rats display a significant shortening of ejaculation latency, which is the main characteristic of premature ejaculation (PE) in men. Thus, the MPCA is a potential animal model for PE.

Aim. In this study, we further analyze whether the features of the MPCA satisfy the validity criteria for it to be considered an animal model as well as the possible participation of the serotoninergic system in the faster ejaculation exhibited by male rats in the MPCA.

Methods. In Experiment 1, male rats were tested in a standard arena to assess their sexual behavior, then were assessed 1 week later in the MPCA. Another group was first tested in the MPCA, then in a standard arena. In Experiment 2, male rats divided into two groups were treated daily with WAY-100635 (5-HT_{1A} antagonist) or vehicle for 15 days. In each group, half of the subjects were tested in a standard arena and half were tested in the MPCA on days 1, 8, and 15 of treatment.

Main Outcome Measures. Number of intromissions and intromission and ejaculation latencies were the main outcome measures.

Results. In Experiment 1, males tested in the MPCA ejaculated significantly faster, regardless of the order in which they were evaluated in both arenas. In Experiment 2, the administration of WAY-100635 increased intromission and ejaculation latencies, and the number of intromissions in the MPCA.

Conclusions. The results obtained in the MPCA support its use as an animal model for PE evaluation. **Olayo-Lortia J, Ferreira-Nuño A, Velázquez-Moctezuma J, and Morales-Otal A. Further definition on the multiple partner choice arena: A potential animal model for the study of premature ejaculation. J Sex Med 2014;11:2428–2438.**

Key Words. Animal Models; Premature Ejaculation; Validation Criteria; Sexual Behavior; Serotonin Receptors

Introduction

Premature ejaculation (PE) in male humans is a sexual dysfunction characterized by an ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration, the inability to delay ejaculation in all or nearly all vaginal penetrations, and the negative personal consequences including distress, frustration, and/or the avoidance of sexual intimacy [1,2]. Additionally, PE is a prevalent, yet often underdiagnosed, sexual disorder that affects men of all ages [3] with a global prevalence of 30% [4,5]. Because of the impact this disorder has on sexual health in males, PE has been studied clinically and in animal studies (the rat, for example) for over 20 years [1].

Neurochemically, the ejaculatory reflex involves a complex interplay between central serotonergic and dopaminergic neurons, with secondary

involvement of cholinergic, adrenergic, oxytocinergic, and gamma aminobutyric acid (GABAergic) neurons [2,6]. Although different neurotransmitters are involved in the neurobiology of ejaculation, dopamine and serotonin have emerged as essential neurochemical factors. For example, dopamine promotes seminal emission/ejaculation via D_2 receptors, whereas serotonin inhibits ejaculation via 5-HT_{2C} receptors. Moreover, serotonergic neurons are widely distributed in the brain and spinal cord and are predominantly found in the brainstem, raphe nuclei, and the reticular formation [2]. Although multiple serotonin (5-hydroxytryptamine [5-HT]) receptors have been characterized [7], stimulation of the 5-HT_{2C} receptor with 5-HT_{2C} agonists results in a delay of ejaculation in male rats, whereas stimulation of postsynaptic 5-HT_{1A} receptors results in a shortened ejaculation latency (EL) [8], leading to Waldinger's hypothesis that men with PE may have hyposensitivity of 5-HT_{2C} receptors and/or hypersensitivity of 5-HT_{1A} receptors [1,9–11].

On the other hand, animal models play an essential role in scientific research on behavior and physiological mechanisms, as well as in pathological research involving normal or abnormal behavioral control [12]. Most of the current knowledge of the anatomy and neurobiology of sexual behavior is based on studies that used animal models, among which the rat stands out [13,14].

Sexually experienced rats have been used as an animal model to understand the neurobiological mechanisms of sexual behavior, as well as different sexual disorders, including PE [13]. It has been suggested that to be validated, an animal model must satisfy certain previously established criteria [13,14]. In 1984, Willner proposed the following criteria that must be satisfied by animal models used to study neurobehavioral disorders: face validity, construct validity, and predictive validity [15]. Face validity refers to the extent to which the proposed animal model is capable of replicating the disorder being studied as it is exhibited in humans. The replication of symptoms corresponding to the disorder can be the starting point to develop an animal model and identify its potential to facilitate the study of certain neurobehavioral disorders such as PE [15,16]. Construct validity refers to the extent to which the animal model is consistent with a proposed theory on the disorder or physiological phenomenon being studied [15]. This validation criterion is often considered to be one of the most important to develop an animal model because it shows that the proposed model has a solid theoretical foundation [16]. Lastly, predictive validity refers to the extent to which the animal model is capable of responding to drugs designed to regulate the disorder or physiological phenomenon being studied [15].

On the other hand, research carried out on the etiology of PE and the development of therapeutic agents targeting this disorder have made it difficult to develop a standard animal model to study it. The animal model currently used to study PE consists of a standard arena (SA), which can be a rounded acrylic enclosure (50×40 cm) inside of which the sexual behavior of sexually experienced male rats is recorded for 30 minutes. Once the basal levels of sexual activity are recorded, drugs thought to delay ejaculation are administered to the male rats. If ejaculation is delayed, the dosage and duration of treatment necessary to do so is determined [13,14]. This animal model has been shown to satisfy the criteria of predictive validity proposed by Willner [15] as ejaculation in male rats has been delayed with drugs designed to regulate PE. Nevertheless, this model does not achieve face validity because even though the drugs delay ejaculation, male rats do not initially exhibit signs of PE. Lastly, it must be taken into account that animal models that are more suitable to studying PE will lead to the development of more effective therapeutic treatments [13,14].

Regarding the latter, Ahlenius et al. [8] showed that stimulation of the 5-HT_{2C} receptor delays ejaculation in male rats, while stimulation of the 5-HT_{1A} receptor significantly reduces EL. In 2005, de Jong et al. [17] showed that coadministration of WAY-100635, a selective 5-HT_{1A} receptor antagonist, and citalopram, a selective serotonin reuptake inhibitor (SSRI), completely inhibited ejaculation. The authors reported a complete ejaculatory inhibition after chronic administration. Other studies have also shown that different chronically administered SSRIs delay ejaculation in sexually experienced rats [17–21]. Dapoxetine and sertraline are the SSRIs with the greatest efficacy for increasing ejaculatory latency in male rats and humans [19–21].

Given this background, our research team recently developed a multiple partner choice arena (MPCA) to study the sexual behavior of rats [22]. This arena consists of four acrylic cylinders arranged in a circle, forming a central compartment from which a receptive female rat is able to choose one of four males (one in each cylinder) with which to copulate. In these conditions, we