Delay of Ejaculation Induced by SB-277011, a Selective Dopamine D3 Receptor Antagonist, in the Rat

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DOI: 10.1111/j.1743-6109.2008.01173.x

ABSTRACT

Introduction. Dopamine (DA) plays a key role in different aspects of the male sexual response, including sexual motivation and arousal, penile erection, and ejaculation. The modalities of action of DA are however unclear, although the various DA receptors may differentially mediate the activity of DA in different aspects of the male sexual response.

Aim. To clarify the role of DA D_3 receptors in the control of the male sexual response.

Methods. The effects of a highly selective DA D_3 receptors antagonist (SB-277011; intraperitoneal) were tested in experimental paradigms exploring several aspects of the male sexual response in (i) anesthetized rats using 7-hydroxy-N,N-di-n-propylaminotetralin to induce ejaculation and (ii) conscious rats using sexual incentive motivation and mating tests.

Main Outcome Measures. Physiological markers of erection and emission and expulsion phases of ejaculation were measured in anesthetized rats. Behavioral parameters of sexual incentive motivation and mating tests were quantified.

Results. In anesthetized rats, we found that SB-277011 specifically and dose-dependently inhibited the expulsion phase of ejaculation without impairing either emission phase or erection, and this resulted in delayed ejaculation. Administration of SB-277011 had no effect on the spontaneous preference that males displayed for sexually receptive females as shown in sexual incentive motivation test. Delayed ejaculation was confirmed when male rats were administered with the highest dose of SB-277011 (10 mg/kg) in mating test, where males were free to copulate with estrous females. In addition, the refractory period following ejaculation was lengthened in rats treated with SB-277011.

Conclusion. As a whole, the present data demonstrate the specific and primary role of D_3 receptors in the expulsion phase of ejaculation and provide preclinical evidence for the investigation of the therapeutic potential of D_3 antagonism for treating premature ejaculation. **Clément P, Pozzato C, Heidbreder C, Alexandre L, Giuliano F, and Melotto S. Delay of ejaculation induced by SB-277011, a selective dopamine D3 receptor antagonist, in the rat. J Sex Med 2009;6:980–988.**

Key Words. 7-OH-DPAT; Bulbospongiosus Muscle; Mating; Seminal Vesicle; Sexual Incentive

Introduction

The male sexual response encompasses appetitive and consummatory behaviors. The former includes sexual desire, excitement, and arousal, whereas the latter consists of genital stimulation leading to ejaculation and related orgasm. Over the last decades, an extensive body of research has indicated that dopamine (DA) plays an important role in the central regulation of the male sexual response [1,2]. The involvement of D_2 and/or D_3 receptors in male rat sexual motivation is well established. The D_2/D_3 antagonist haloperidol reduces the interest of a male rat toward an estrous female and sexually conditioned stimulus [3,4]. D_2-like receptors, which include D_2, D_3, and

D_4 subtypes, mediate the proerectile activity of DA agonists [5]. Induction of erection by a selective D_4 agonist was recently reported in conscious rats [6], although the participation of D_2 and D_3 receptors cannot be ruled out. Moreover, conflicting results exist on the proerectile activity of D_1 brain receptors [7]. The respective contributions of the different DA receptors remain to be clarified, but it is evident that they depend on the degree and site of stimulation, as well as the context in which erections are induced. In rats, stimulation of D_2-like receptors was shown to facilitate ejaculation [8–10] and can even trigger ejaculation in anesthetized rats [11]. In an effort to better characterize the role of D_3 receptors in male sexual behavior, the effects of the preferential D_3 receptor agonist 7-hydroxy-N,N-di-n-propylaminotetralin (7-OH-DPAT) were studied. When injected systemically, this compound facilitates ejaculation without affecting sexual arousal [12,13]. In addition, 7-OH-DPAT induces ejaculation in anesthetized rats when delivered i.c.v. or into the medial preoptic area of the hypothalamus, and this effect is reversed by D_3 but not D_2 preferential antagonists [14,15]. Altogether, these findings suggest that D_3 receptors may play a major role in the brain control of the different aspects of the male sexual response. However, the ligands used to date were not highly selective for the various DA receptor subtypes, and this prevented the drawing of a clear picture of the respective contribution of D_2, D_3, and D_4 receptors. Improving our understanding of this issue may open new avenues for the development of pharmacological treatment of human sexual dysfunctions, and, more particularly, premature ejaculation which is a major concern [16] still requiring an effective therapeutic solution [17].

Aims

We aimed to clarify the role of D_3 receptors in the male sexual activity by testing the selective D_3 antagonist SB-277011 [18] in anesthetized and conscious rats using standardized experimental paradigms. The 7-OH-DPAT-induced sexual responses in anesthetized rats were used to explore the effects of SB-277011 on emission and expulsion phases of ejaculation as well as on erection. Behavioral study included sexual incentive motivation and mating tests for the exploration of SB-277011 effects on, respectively, motivational and copulatory aspects of male rat sexual behavior.

Methods

Animals

All in vivo procedures were carried out in accordance with the European Community Council Directive (86/609/EEC) on the use of laboratory animals and conformed to GlaxoSmithKline ethical standards. All efforts were undertaken to minimize the number of animals used and their suffering. All animals were housed under standard laboratory conditions (22 ± 1°C), on a 12-hour light/dark cycle, and with food and water available ad libitum.

Sexually naive male Han Wistar rats (Charles River, L'Arbresle, France) weighing 300–360 g and housed at groups of four were used in anesthetized rats study. In behavioral study, male (300–325 g upon arrival) and female (ovariectomized, 225–250 g upon arrival) rats Han Wistar were purchased from Charles River and housed in pairs.

Anesthetized Rat Study

Surgical Preparation

Rats were anesthetized with isoflurane (2.8% during surgery; 1–1.2% during test). Their temperature was maintained at 37°C using homeothermic blanket. The jugular vein was catheterized with polyethylene tubing filled with heparinized saline (50 IU/mL) to allow i.v. administration of 7-OH-DPAT. The carotid artery was catheterized with polyethylene tubing filled with heparinized saline (50 IU/mL) to record blood pressure via a pressure transducer (EM750, Elcomatic, Glasgow, UK).

The right seminal vesicle was exposed via coeliotomy and seminal vesicle pressure (SVP) was measured with a polyethylene catheter (0.5 mm), filled with mineral oil, inserted in the seminal vesicle through the apex and connected to a pressure transducer.

The bulbospongiosus muscle (BS) was exposed via a perineal incision. Electromyogram of BS (BS EMG) was recorded by passing a Teflon insulated stainless steel wire laterally throughout the muscles with two 1–2 mm pieces (separated by 1–2 mm) of insulation stripped off. Electrical signal from the BS was amplified (DP-301, Warner Instrument Corp., Phymep, Paris, France; gain, 1,000; Low pass, 1 KHz; High pass, 10 Hz) before being digitized.

For intracavernous pressure (ICP) monitoring, the penis was denuded of skin and a 25-gauge needle connected to a catheter was inserted into one corpus cavernosum. A pressure transducer permitted the recording of ICP variations.