ABSTRACT # 977

SB-277011, A SELECTIVE DOPAMINE D3 RECEPTOR ANTAGONIST, DELAYS EJACULATION IN ANESTHETIZED AND CONSCIOUS RATS

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ABSTRACT

Objectives: 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. We aimed at clarifying the role of DA D3 receptors in the control of the male sexual response.
Material and methods: The effects of a selective DA D3 receptors antagonist (SB-277011) 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 (7-OH-DPAT) to induce ejaculation and (ii) conscious rats using sexual incentive motivation and mating tests. Three doses of SB-277011 (1, 3, and 10 mg/kg; intraperitoneal) were investigated in male Wistar rats. Physiological markers of erection, emission and expulsion phases of ejaculation were measured in anesthetized rats. Behavioral parameters of sexual incentive motivation and mating tests were quantified in conscious males.
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. In conscious rats, 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 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 D3 receptors in the expulsion phase of ejaculation and provide preclinical evidence for the investigation of the therapeutic potential of D3 antagonism for treating premature ejaculation.

OBJECTIVE

➢ We aimed at clarifying the role of D3 receptors in the male sexual activity in anesthetized and conscious rats by using standardized experimental paradigms.

➢ For this purpose, we used (i) the 7-OH-DPAT-induced sexual responses in anesthetized rats to explore the effects of SB-277011 on emission and expulsion phases of ejaculation as well as on erection; and (ii) the 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

All animal experiments were carried out in accordance with the European Community Council Directive (86/609/EEC) on the use of laboratory animals.

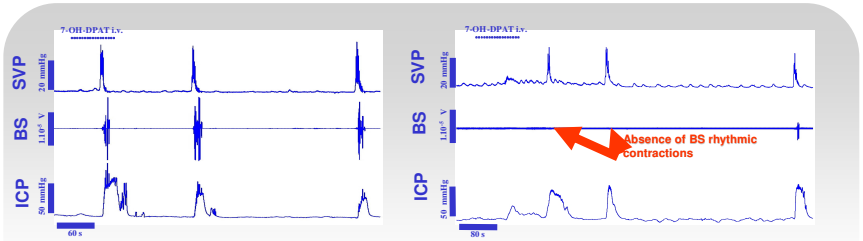
Anesthetized rat study

Adult sexually naïve male Wistar rats were anesthetized with isoflurane (1-1.2%) and the carotid artery catheterised for blood pressure measurement. Seminal vesicle pressure (SVP) was measured with a catheter, filled with mineral oil, inserted in one seminal vesicle through the apex. Intracavernous pressure (ICP) was measured with a catheter inserted into one corpus cavernosum. Electrical activity of the bulbospongiosus muscle (BS) was recorded by passing a Teflon insulated stainless–steel wire laterally throughout the muscle with two 1-2 mm pieces (separated by 1-2 mm) of insulation stripped off.
SB-277011 was delivered i.p. and 30 min after sexual responses were induced by i.v. 7-OH-DPAT.

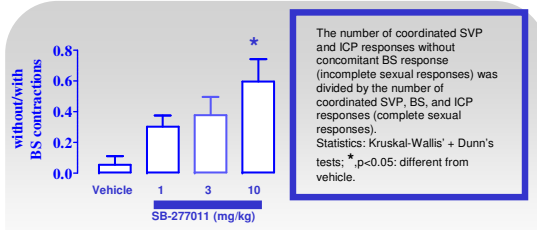
Behavioral study

Sexual incentive motivation test: Sexually experienced male Wistar rats placed, for 10 min, in testing arena with inaccessible male rat in one side and inaccessible receptive female in the opposite side.
Mating test: Sexually experienced male Wistar rats placed, for 30 min, in mating one-level chamber with accessible receptive female and free to copulate. Mating test was performed immediately after sexual incentive motivation test.
SB-277011 was delivered i.p. 30 min before the beginning of behavioral tests.

RESULTS



Sample of recording of seminal vesicle pressure (SVP), bulbospongiosus muscle EMG (BS), and intracavernous pressure (ICP) obtained in anesthetized rats after i.v. delivery of 7-OH-DPAT (1mg/kg). Left panel, i.p. pre-treatement with SB-277011 vehicle; right panel, i.p. pre-treatement with 10mg/kg SB-277011.



The number of coordinated SVP and ICP responses without concomitant BS response (incomplete sexual responses) was divided by the number of coordinated SVP, BS, and ICP responses (complete sexual responses).
Statistics: Kruskal-Wallis' + Dunn's tests; *,p<0.05: different from vehicle.

Effects of i.p. SB-277011 on the proportion of 7-OH-DPAT-induced coordinated sexual responses without BS contractions.

		SB-277011 i.p. (mg/kg)			
		Veh	1	3	10
Mean number	Ejaculation	1.4±0.2	1.0±0.1	0.6±0.2	0.4±0.2*
	SVP	3.0±0.4	3.1±0.4	3.0±0.4	2.5±0.5
	BS	3.0±0.5	2.1±0.3	1.9±0.4	1.4±0.5
	ICP	3.1±0.4	3.0±0.4	3.3±0.6	2.6±0.4
Latency (s)	Ejaculation	64±10	210±41†	279±69†	417±137‡
	SVP	45±4	72±12	60±9	69±13
	BS	60±10	225±39	246±62	322±108†
	ICP	49±4	72±12	62±9	71±11

Effects of SB-277011 on the number and latency of sexual responses induced by 7-OH-DPAT. Mean number and latency of ejaculation, SVP, BS, and ICP responses are expressed as mean±SEM (n=4-9).

Statistics: Kruskal-Wallis' + Dunn's tests, * p<0.05; One-way ANOVA + Student Newman Keuls' tests, † p<0.05, ‡ p<0.01.

SEXUAL INCENTIVE MOTIVATION TEST

	SB-277011 i.p. (mg/kg)			
	Veh	1	3	10
Time in social incentive zone	59.1±6.8	61.6±7.5	61.9±6.9	73.3±8.3
Time in sexual incentive zone	275.7±24.6	270.9±18.7	264.4±20.8	225.6±23.9
Nb visits social incentive zone	12.2±0.5	13.6±0.8	12.6±0.8	13.1±1.5
Nb visits sexual incentive zone	21.7±2.0	19.8±1.5	21.3±2.1	17.6±1.1

Effects of SB-277011 on sexual incentive motivation in male rats. Data are presented as mean ± SEM of 12 rats. Time spent in the different incentive zones are expressed in seconds.

MATING TEST

	SB-277011 i.p. (mg/kg)			
	Veh	1	3	10
ML (s)	4.8±1.2	7.9±3.9	4.8±1.0	12.8±8.1
IL (s)	15.1±4.2	13.4±4.1	11.7±3.4	20.1±9.1
Nb M+I	22.2±1.5	22.7±2.9	20.0±2.5	20.9±2.5
CE	0.53±0.04	0.61±0.05	0.62±0.04	0.64±0.04
EJL (s)	231.2±27.5	252.1±36.6	251.8±40.4	308.2±39.9*
PEI (s)	315.9±16.9	344.3±22.2	347.5±25.6	388.0±26.6†

Statistics: one-way ANOVA on original (CE) or log transformed data (all other behavioural parameters); followed by *post-hoc* Dunnett's test, * p=0.055, † p<0.05 as compared to vehicle.

Effects of SB-277011 on copulatory parameters in male rats. Mount latency (ML), intromission latency (IL), number of mounts and intromissions (M+I), copulatory efficiency (CE), ejaculation latency (EJL), and post-ejaculatory interval (PEI) are presented as mean ± SEM of 12 rats.

CONCLUSIONS

➢ In the 7-OH-DPAT model, selective antagonism of D3 receptors impairs ejaculation by specifically altering the expulsion phase of ejaculation with no effect on other aspects of sexual functions.

➢ In sexual incentive motivation test, selective antagonism of D3 receptors exerts no effect on male rat sexual motivation.

➢ In mating test, selective antagonism of D3 receptors increases ejaculation latency and post-ejaculatory interval with no effect on other aspects of male rat copulatory behavior.

➢ These results open new avenues for the development of pharmacological management of premature ejaculation.

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