

ABSTRACT Facilitation of proceptivity/sexual motivation in female rats by a serotonin 2A/2C (5-HT_{2A/2C}) receptors agonist

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ABSTRACT

Facilitation of proceptivity/sexual motivation in female rats by a serotonin 2A/2C (5-HT_{2A/2C}) receptors agonist.

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Introduction and Objective: In women, genital arousal (potency) is separated from psychological arousal (libido, motivation). Similarly and respectively, in female rat, proceptivity (lordosis, hops, dart, solicitation), 5-HT_{2A/2C} receptor-agonists have been reported to increase lordosis in normal and ovariectomized rats supplemented with estradiol benzoate (EB) and progesterone (P). Nevertheless, few information is available regarding the effect of 5-HT_{2A/2C} agonists on proceptivity/sexual motivation. We investigated the effects of DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) (5-HT_{2A/2C} receptors agonist) on proceptivity behavior in ovariectomized rats with a submaximal hormonal supplementation.

Methods: Ovariectomized Long-Evans rats were injected subcutaneously (s.c.) with EB and P (10 and 250 µg in 0.1 ml of paraffin oil, respectively). Mating test was performed with sexually experienced males. Female rat was placed 5 min alone in the arena for habituation. For baseline determination, they were tested for 10 min with a male. Following this test, DOI (0.5 or 1 mg/kg) or saline were s.c. injected and 10 min later, female was placed again with the male and sexual behavior was scored for 30 min. Data were analyzed for three 10 min periods.

Results: Compared to vehicle, DOI 1 mg/kg showed a significant increase in the number of darts, hops and ear wiggles. DOI 0.5 mg/kg increased hops and darts. Lordosis was not affected by DOI.

Conclusions: This study confirms the involvement of 5-HT_{2A/2C} receptors in the control of female sexual activity. DOI (0.5 and 1 mg/kg) facilitated sexual proceptivity behavior in ovariectomized rats with a submaximal hormonal treatment. 5-HT_{2A/2C} receptors agonist in combination with hormonal replacement therapy could represent a treatment option for postmenopausal women complaining about hypoactive sexual desire.

	Darts and Hops /mounts			Ear wiggles/mounts		
	Saline (n=7)	DOI 0.5 mg/kg (n=7)	DOI 1 mg/kg (n=8)	Saline (n=7)	DOI 0.5 mg/kg (n=7)	DOI 1 mg/kg (n=8)
Baseline	0.76±0.16	0.72±0.18	1.26±0.30	1.19±0.17	0.99±0.11	1.13±0.22
1 st 10 min period post treatment	0.58±0.16	0.92±0.20	2.54±0.50 ***	1.07±0.15	1.31±0.17	2.36±0.46 *
2 nd 10 min period post treatment	0.86±0.21	1.37±0.25	1.55±0.31	1.31±0.34	1.40±0.14	1.43±0.27
3 rd 10 min period post treatment	0.54±0.14	1.54±0.30 **	1.61±0.48	0.98±0.10	1.47±0.18	1.74±0.51
2 way ANOVA vs. saline	ns	§§	§§§	ns	ns	§

Results expressed as mean ± SEM
 2 way ANOVA †p<0.05 ‡p<0.01 §§p<0.001
 Bonferroni test used for post-hoc comparisons in function of time *p<0.05 **p<0.01 ***p<0.001

BACKGROUND

> In Europe, 10 to 40 % of women aged between 14 and 60 years report low sexual desire (see review by Agmo et al., 2004).

> In women, desire has been described as "conscious impulse toward something" or "sexual urge or appetite", which are signs of motivation. According to these definitions, desire in women is equivalent to what is called sexual motivation in animals (Agmo et al., 2004).

> Estrous female rats display hopping, darting and ear wiggle and solicitation for provoking males to initiate mounting. These female sexual behaviors, which represent anticipatory and motivational aspects have been collectively termed proceptivity by behavioral scientists (Beach, 1976)

> Sexual receptivity has been defined in terms of the display of a characteristic spinal reflex, the lordosis response (Hardy and DeBold, 1971), which represents the consummatory aspect of sexual behavior (Beach, 1976).

> DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride) is a 5-HT_{2A/2C} receptors agonist.

> DOI increased lordosis in low sexually receptive females (Wolf et al., 1998; 1999) or could protect against the lordosis-inhibiting effects of 5-HT and of 5-HT_{1A} agonists (Maswood et al., 1996).

> The administration of DOI to non ovariectomized female rats primed with estradiol benzoate (EB) and progesterone (P), increased sexual motivation in paced mating behavior, by decreasing return latencies following ejaculation and inter-intrusion intervals (Nedergaard et al., 2004).

OBJECTIVES

> To investigate the effects of DOI on proceptive (darts and hops and ear wiggles) and receptive (lordosis) behaviors in ovariectomized female rats with a submaximal hormonal supplementation.

METHODS

> Female Long Evans rats (250-275 g) were bilaterally ovariectomized (OVX) under isoflurane anesthesia.

> OVX rats were injected subcutaneously (s.c.) with a submaximal hormonal priming with estradiol benzoate (EB 10 µg at 48 h before the test) and progesterone (P 250 µg at 4-5 h before testing) in a volume of 0.1 ml/rat (Pfaus and Pfaff, 1992).

> Proceptive and receptive behaviors were evaluated in a rectangular chamber (60 L X30 W X35 H cm) during dark phase of light/dark cycle. After a 5-min habituation period for the female to the chambers, a sexually active male (previously habituated to the chamber) was placed with the female for a 30-min mating test.



Lordosis displayed by the female during male ejaculation.

> For each mount, lordosis, darts and hops and ear wiggles by the female was noted.

> The lordosis quotient (LQ) was defined as the total number of lordosis responses (L)/total number of mounts (M) multiplied by 100 (L/Mx100).

> Sexual proceptivity was quantified as the darts and hops per mount (D&H/M) ratio (Pfaus et al., 1999) and ear wiggles per mount (EW/M) ratio.

> For baseline determination, females were tested for 10 min with a sexually active male (pre inj). Females (n=8) were then treated (saline, DOI 0.5 and 1 mg/kg s.c. injected), and placed 10 min after treatment delivery with a male for a 30 min behavioral test. Some females received only two different treatments.

> Data analysis was performed with two way ANOVA followed, whenever p<0.05, by Bonferroni test post-hoc comparisons.

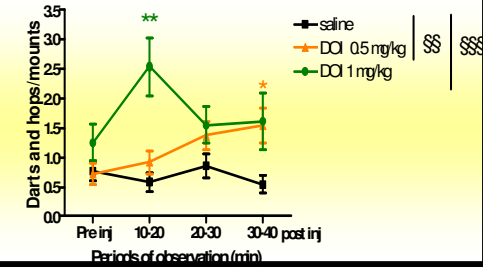
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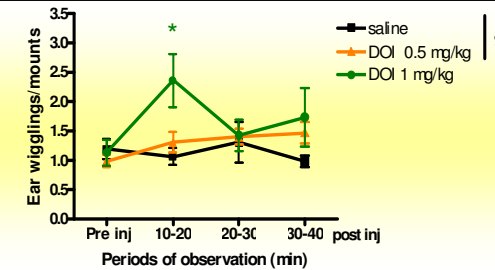
RESULTS

➡ Darts and hops/mounts were significantly increased 10-20 min after injection of DOI 1 mg/kg, as compared to saline.

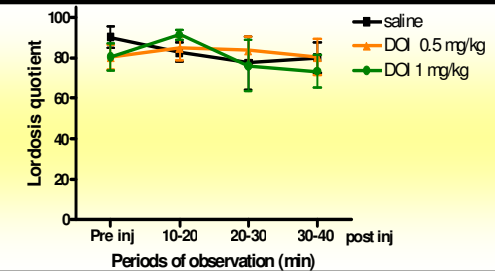
➡ Darts and hops/mounts were significantly increased 30-40 min after injection of DOI 0.5 mg/kg, as compared to saline.



➡ Ear wiggles/mounts were significantly increased 10-20 min after injection of DOI 1 mg/kg, as compared to saline.



➡ No effect of DOI (0.5 and 1 mg/kg) on lordosis, as compared to saline.



Results are expressed as mean±SEM 2 way ANOVA vs saline †p<0.05 ‡p<0.01 §§p<0.001 Bonferroni test used for post-hoc comparisons vs saline in function of periods of observation *p<0.05, **p<0.01.

SUMMARY OF RESULTS

> Our data demonstrated that DOI at 0.5 and 1 mg/kg increased sexual proceptive behavior investigated with the display of hops and darts per mount that is the most common soliciting behavior in ovariectomized female rats (Erskine, 1989) receiving a submaximal hormonal supplementation. Ear wiggles were also increased with DOI (1 mg/kg).

> Lordosis was not modified by DOI treatment whatever the dose.

CONCLUSION

> DOI facilitated sexual motivation in females which received a submaximal hormonal supplementation, without modifying the lordosis response.

> 5-HT_{2A/2C} receptors agonist combined with hormonal replacement therapy may represent an interesting target for the treatment of postmenopausal women complaining about hypoactive sexual desire.