ABSTRACT

508

Increase in proceptivity/sexual motivation by melanotan-II (MT-II) in female rats

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ABSTRACT

Introduction &objectives

In women, sexual arousal is separated into two categories: genital (potency) and psychological (libido, motivation) arousal. This distinction is similar in female rat, where respectively receptivity (lordosis) is distinguished from proceptivity (darts, hops, ear wigglings, solicitation). There are some arguments to support the role of melanocortin receptors (MCR) in the control of female sexual behavior, including receptivity and proceptivity. MT-II is a cyclic peptide analogue of alpha-melano stimulating hormone with an agonist activity at four of the five known MCR: MC1R, MC3R, MC4R and MC5R. A potent initiator effect of MT-II on penile erection in men with erectile dysfunction has been reported. We investigated the effects of MT-II on proceptive behavior in female rats.

Material & Methods

Ovariectomized Long-Evans rats were injected subcutaneously (s.c.) with EB and P (10 and 500 µg in 0.1 ml of paraffin oil, respectively). Paced mating test was performed with sexually experienced males in unilevel chambers during 30 min. Females received 4 preliminary tests of sexual behavior in the unilevel chambers. MT-II (1 and 3 mg/kg) and saline were i.v. delivered in a random order 5 min before each behavioral test.

Results

Compared to vehicle, MT-II (1 and 3 mg/kg) showed a significant increase in the number of darts, hops and ear wigglings. Solicitation and lordosis were not affected by MT-II.

	Darts and Hops			Ear wigglings		
	Saline (n=7)	MT-II 1 mg/kg (n=7)	MT-II 3 mg/kg (n=7)	Saline (n=7)	MT-II 1 mg/kg (n=7)	MT-II 3 mg/kg (n=7)
30 min test	23.29±2.63	38.57±2.20 *	44.43±6.30 **	25.29±2.27	40.71±2.38 *	40.00±5.91 *

Results are expressed as mean±SEM 1 way ANOVA with repeated measures followed by Bonferroni test used for post-hoc comparisons vs saline *p<0.05 and **p<0.01

Conclusions

In these experiments, MT-II (1 and 3 mg/kg) facilitates sexual proceptive behaviors in ovariectomized rats supplemented with hormones. This study provides preliminary evidence that melanocortin receptors agonists may be useful in the treatment of women with hyposexual desire.

BACKGROUND

➢Female as well as male sexual behavior can be separated into arousal (libido, motivation) and performance (potency, execution of sexual reflexes) categories (Davidson 1980; Clark 1993).

➢In women, genital arousal (potency) is separable from psychological arousal (libido, motivation) (Roger et al., 1985; Laan et al., 1995).

➢This distinction is similar in female rats (Pfeifle and Edwards 1983; Clark, 1993) where sexual activies are divided into proceptivity, which represents anticipatory and motivational aspects and receptivity, which represents reflexive activity during copulation (Beach, 1976).

➢Melanotan-II (MT-II) is a cyclic synthetic peptide analog of α-MSH with an agonist activity at 4 of the 5 known melanocortin receptors: MC1R, MC3R, MC4R, MC5R.

➢Increase in lordotic activity has been reported after bilateral administration of α-MSH and γ-MSH in the medial preoptic area of ovariectomized rats primed with estradiol (Nocetto et al., 2004).

➢PT-141, a peptide analog of alpha-melanocyte-stimulating hormone that binds to central melanocortin receptors, selectively stimulated solicitational behaviors in the female rat (Pfaus et al., 2004).

OBJECTIVES

➢To investigate the effects of MT-II on proceptive (darts and hops, ear wigglings and solicitations) and receptive (lordosis) behaviors in ovariectomized female rats with a 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 estradiol benzoate (EB 10 µg at 48 h before the test) and progesterone (P 500 µg at 4-5 h before testing) in a volume of 0.1 ml/rat (Pfaus et al., 2004).

➢Proceptive and receptive behaviors were evaluated in unilevel chambers (60 L X 40 W X 40 H cm) divided by a transparent Plexiglas wall during dark phase of light/dark cycle. Three regular spaced openings in the separation wall allowed the female free passage between the halves. Females received four preliminary tests of paced mating in the unilevel chambers.

➢For each mount lordosis reflex, darts and hops and ear wigglings displayed by the female were noted. Solicitations (headwise orientation to the male followed by an abrupt runaway, regardless of whether the female remained in the side of the male or not) were also scored.

Paced mating in the unilevel chambers

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

➢Females were injected i.v. with the treatments (saline, MT-II 1 and 3 mg/kg). Five min after treatment delivery, females were placed alone in the unilevel chambers for a 5 min period of habituation. Then, a sexually active male (previously habituated to the chambers) was placed with the female for a 30-min paced mating test. Because of its size, male was not able to follow the female through the openings.

➢All females (n=7) received the three treatments in a random order and behaviors were visually identified and manually scored by a blinded trained observer.

➢Data analysis was performed with one way ANOVA with repeated measures followed, whenever p<0.05, by Bonferroni post-hoc test.

References

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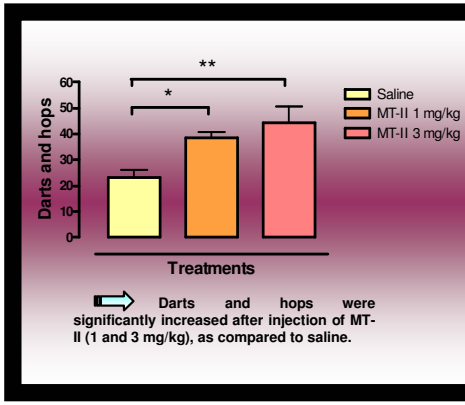
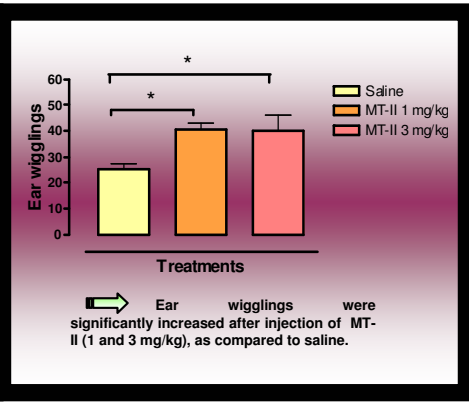
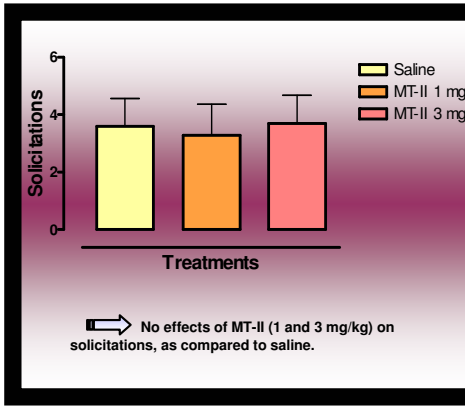
RESULTS



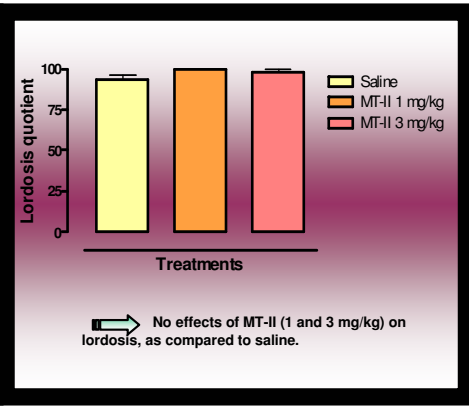
➢ Darts and hops were significantly increased after injection of MT-II (1 and 3 mg/kg), as compared to saline.



➢ Ear wigglings were significantly increased after injection of MT-II (1 and 3 mg/kg), as compared to saline.



➢ No effects of MT-II (1 and 3 mg/kg) on solicitations, as compared to saline.



➢ No effects of MT-II (1 and 3 mg/kg) on lordosis, as compared to saline.

Results are expressed as mean±SEM. 1 way ANOVA with repeated measures followed by Bonferroni test post-hoc comparisons vs saline *p<0.05, **p<0.01

SUMMARY OF RESULTS

➢Our data demonstrated that MT-II at 1 and 3 mg/kg increased female rat sexual proceptive behavior in darts and hops that is the most common soliciting behavior displayed by females (Erskine, 1989). Ear wigglings were also increased with MT-II (1 and 3 mg/kg).

➢Solicitations and lordosis were not modified by MT-II treatment.

CONCLUSION

➢MT-II (1 and 3 mg/kg) increased sexual motivation in ovariectomized Long Evans females primed with EB and P, without modifying the lordosis response.

➢Melanocortin receptors agonist may represent an interesting target for the treatment of women with hypoactive sexual desire.