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Effect of delequamine (RS15385) on female sexual behaviour in the rat

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Abstract

The role of α_2-adrenoceptors in mediating the noradrenergic control of female sexual behaviour was investigated employing a selective α_2-adrenoceptor antagonist, delequamine (RS15385). The drug was given in graded doses of 0.01–30 mg/kg p.o. to ovariectomised plus adrenalectomised rats primed with either 2 μg oestradiol benzoate which yielded mainly non-receptive animals or 5 μg oestradiol benzoate followed 48 h later by 0.5 mg progesterone, which stimulated a high level of receptivity. Doses between 0.1 and 30 mg/kg significantly increased lordotic activity (receptivity) with an ED_{50} of 0.32 mg/kg, but had no effect on ear-wiggling or hopping-and-darting (proceptivity). Delequamine had no inhibitory effect in animals displaying high levels of receptivity. Thus we have shown a selective α_2-adrenoceptor antagonist, given orally, can stimulate female receptivity in a dose-dependent manner. Bilateral administration into the ventromedial nucleus, but not medial preoptic area, of delequamine (10 μg/side/rat) stimulated receptivity and it is suggested that the α_2-adrenoceptor may exert its effect by enhancing endogenous noradrenaline release at its active sites.

Keywords: Delequamine; RS15385; α_2-Adrenoceptor; Lordosis; Sexual behavior, female; (Rat)

1. Introduction

The ascending noradrenergic system is essential for normal reproductive behaviour in the female rat (Hansen et al., 1980; Davis et al., 1991). It is hypothesised that it conveys somatosensory information from the vagina necessary for initiating lordosis, acting finally within the hypothalamus to first suppress a dopaminergic system and then enhance passive immobile receptive behaviour (Hansen et al., 1980; Caggiula et al., 1978).

Several reports indicate that noradrenaline may be the mediator of the stimulatory effect on sexual receptivity of a number of hormones, including the gonadal steroids (Vathy and Etgen, 1989; Etgen and Karkanias, 1994; Blaustein et al., 1994; Montemayor et al., 1990), gonadotrophin-releasing hormone (Mora and Diaz-Veliz, 1986; Gonzalez-Mariscal and Beyer, 1989), α-melanocyte stimulating hormone (α-MSH) (Gonzalez et al., 1993) and oxytocin (Vincent and Etgen, 1993; Etgen and Karkanias, 1994). Although there is some conflict over the site(s) of noradrenergic activity (Davis et al., 1991) direct injections of noradrenaline into the ventromedial nucleus stimulate sexual receptivity (Foreman and Moss, 1978; Gonzalez et al., 1993), while administration into the preoptic area is inhibitory (Caldwell and Clemens, 1986). The receptors mediating these two effects have not been clearly elucidated as yet, although it seems likely that the stimulatory action is exerted by α_1-adrenoceptors and/or β-adrenoceptors (Foreman and Moss, 1978; Fernandez-Guasti et al., 1985; Kow et al., 1992; Gonzalez et al., 1993). The inhibitory effect of noradrenaline in the preoptic area is mimicked by clonidine and reversed by yohimbine indicating an α_2-adrenergic effect (Caldwell and Clemens, 1986) although yohimbine alone in the preoptic area has some inhibitory activity itself (37% of the group) and a more selective α_2-adrenoceptor antagonist, idaxozan was ineffective when implanted into either the preoptic area or ventromedial nucleus (Etgen, 1990).

However in this latter report, the effect of the two antagonists were only assessed in fully receptive animals and so any putative stimulatory effects could not be seen. The hypothalamus is rich in α_2-adrenoceptors (Brünig et al., 1987), some of which are probably sited presynapti-

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cally, exerting an inhibitory effect on noradrenaline release. Karkanias and Etgen (1993) have shown that oestradiol facilitates noradrenaline transmission by attenuating α_2-adrenoceptor activity, and suggest that this, in turn, increases sexual activity (Etgen and Karkanias, 1994). The mechanisms of action is not yet understood, since oestradiol does not down-regulate α_2-adrenoceptors (Etgen and Karkanias, 1990), but the authors comment that there may have been selective down-regulation of presynaptic α_2-adrenoceptors or an action at an intra-cellular site (Etgen and Karkanias, 1994).

Delequamine (RS-15385-197) is a highly potent and selective α_2-adrenoceptor antagonist (Clark et al., 1990; Brown et al., 1993; Redfern et al., 1992) with a greater than 1000-fold selectivity for α_2-adrenoceptors versus other receptors compared to yohimbine, rauwolescine and idazoxan (Clark et al., 1990). It is 4000–10 000-fold more selective for α_2- than α_1-adrenoceptors, although it cannot distinguish between α_{2A}- and α_{2B}-adrenoceptors or pre- and postsynaptic α_2-adrenoceptors. It has no appreciable affinity for 5-HT receptors and it is also devoid of any partial agonist activity (MacKinnon et al., 1992; Brown et al., 1993). It seems worthwhile, therefore, using this selective α_2-adrenoceptor antagonist to elucidate the role of α_2-adrenoceptors in mediating the noradrenergic control of female sexual behaviour. In these experiments, the drug has been given orally, as it is known to be active by this route and to pass the blood brain barrier (Brown et al., 1993). Pilot studies on the effect of administration of delequamine into specific hypothalamic sites were also carried out.

2. Materials and methods

Fifty Wistar female rats bred at St. George's Hospital were maintained on normal chow and 0.9% saline instead of water and placed 5 per cage in a reversed-lighting room (lights off 7 a.m. to 7 p.m.). The rats were ovariectomised and adrenalectomised under halothane/N_2O gas and left for three weeks. Long-term adrenalectomy causes degeneration of the hippocampal dentate granule cells, which affects learning and memory (Armstrong et al., 1993; Sloviter et al., 1995). This can be prevented by addition of corticosterone to the drinking water but unfortunately this hormone affects sexual behaviour (Wilson, 1993). In spite of the inevitable brain damage, we felt it was important in these experiments to ablate all sources of endogenous steroids. In this way, any possibility was removed that the drug treatment might induce sexual activity by acting peripherally to stimulate ovarian and/or adrenal steroids. Many drugs are known to stimulate adrenal progesterone production, which in an oestrogen primed rat would contribute to enhance sexual activity (see Hunter et al., 1985).

Forty eight hours before the experiment 25 rats were primed with 2 μg/rat oestradiol benzoate subcutaneously in 0.1 ml of corn oil (2 μg oestradiol benzoate is a low dose which has little effect on receptivity). Forty eight hours later, the animals were tested for sexual behaviour, and the non-receptive ones randomized and divided into two groups of 10 rats, (i.e. of the original 25 animals a few were always receptive and not used for this experiment). The rats were then treated orally with either 1 ml/kg saline, or delequamine (RS 15385) in saline at 1 ml/kg, at doses of 0.01, 0.3, 0.1, 1, 3 10 or 30 mg/kg; one dose was tested per experiment and the concentrations were applied in a random order. Thirty minutes after treatment the animals were tested for sexual activity again (see description below: *2.1. Test for sexual activity*).

The rats were left for 2 weeks, and then the injection of oestradiol benzoate was repeated and the experiment was carried out with the two groups receiving the reverse treatment, so that finally the saline and drug treatment groups consisted of 20 rats each at each dose. Each animal served as its own control by comparing pre- and post-treatment activity, and also because each rat received saline and the drug in either the first or second test. They also had a parallel control group on the day, as half the animals received saline in each test.

Two weeks later the animals were tested again, repeating the procedure as above, administering another dose of delequamine, until all the doses were completed with a 4 week interval between them. Once four doses of delequamine had been tested the 25 rats were discarded and the remaining 3 doses were tested on a fresh batch of 25 animals. In this way, each rat used in this experiment was tested 6/8 times over 12/16 weeks, this being a reasonable schedule in order to avoid developing sensitivity towards the steroid priming.

One group of 20 animals were treated with 5 μg oestradiol benzoate s.c./rat, followed 48 h later by 0.5 mg s.c./rat progesterone which induced full sexual receptivity in nearly all the rats. They were tested for sexual behaviour 4 h after the progesterone and only receptive animals were then used. Half the rats received saline and the other half 10 mg/kg p.o. Delequamine, and were tested for sexual activity 30 min later. Two weeks later the procedure was repeated with the treatments reversed.

In a final experiment permanent implants were placed into the medial preoptic area or ventromedial nucleus of ovariectomised rats anaesthetized with saffan (3 ml/kg i.p.; Glaxo Intervet). The cannulae (made at St. George's Hospital Medical School workshop) consisted of a Maranyl nylon disc (diameter 10 mm and depth 3 mm) in which were embedded 2 steel tubes (gauge 21; 0.8 mm diameter), the tops flush with the surface of the disc and the lower ends protruding 8.0 mm below. The centre of the 2 lumens of the tubes were exactly 1 mm apart. In order to keep the cannulae patent a bent stylet of stainless steel was placed, each end, into the 2 lumens and only removed before injection. The cannulae were sited according to co-ordinates obtained from the Rat Atlas (Paxinos and Watson, 1982).

Fig. 1. Coronal section of rat brain at the level of the ventromedial nucleus (VMN) showing the site of the bilateral implant at its lowest point.

They were placed 0.8 mm behind Bregma for the medial preoptic area and 2.3 mm behind Bregma for the ventromedial nucleus. Each inlet tube was 0.5 mm lateral to the midline. The cannulae were kept in place with acrylic dental cement (Simplex Rapide; Howmedia Int.) and prior to adding the cement 3 small screws were placed in the skull to aid 'grip'. In order to inject either 0.5 μl saline or 10 μg delequamine in 0.5 μl saline, a 30 gauge needle, 1.6 mm (ventromedial nucleus) or 1.8 mm (preoptic area), longer than the cannulae inlets, was placed in turn into each inlet for 1 min. The needle was attached via a fine polythene tube to a 10 μl Hamilton syringe in a delivery pump (Microjet; BioInvent HB; Lindingo, Sweden) and set at 0.5 μl/min. At the end of the experiment the placement of the cannulae was assessed histologically on 60 μm frozen sections of the brains stained with toluidine blue. Only results from the correctly placed cannulae were included in this report, see Fig. 1. In these experiments ovariectomised rats primed with 2 μg oestradiol benzoate and showing no receptivity were employed. Half the groups received saline and the other half delequamine and two weeks later the experiment was repeated with the treatments reversed.

2.1. Test for sexual activity

The tests took place at least 3 h into the dark period under red illumination. One vigorous male was placed in each of 4 observation arenas at least 5 min before introduction of the female. Each female was placed with one or

Table 1
The effect of delequamine given orally on lordotic activity (lordosis quotient ± S.E.M.)

	0.01 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Saline ($n = 20$) Pre-injection	1.0 ± 1.0	0.0 ± 0.0	0.0 ± 0.0	1.0 ± 1.0	5.0 ± 2.2	1.0 ± 1.1	1.5 ± 0.2
30 min post-injection	1.5 ± 1.5	0.0 ± 0.0	0.0 ± 0.0	5.0 ± 2.6	9.0 ± 4.5	11.0 ± 5.3	3.5 ± 1.9
	(20%)	(0%)	(0%)	(25%)	(30%)	(30%)	(15%)
Delequamine ($n = 20$) Pre-injection	1.5 ± 1.0	1.5 ± 1.5	1.0 ± 0.7	1.5 ± 1.0	5.5 ± 2.2	1.5 ± 1.5	1.0 ± 0.7
30 min post-injection	7.0 ± 5.9	15.3 ± 6.0 [a,c]	36.2 ± 9.3 [b,d]	37.0 ± 7.5 [a,d]	65.0 ± 8.2 [b,d]	51.7 ± 6.4 [b,d]	53.3 ± 9.7 [b,d]
	(15%)	(35%)	(65%)	(70%)	(85%)	(95%)	(70%)

[a] $P < 0.001$; [b] $P < 0.0001$ vs. saline; [c] $P < 0.05$; [d] $P < 0.0001$ vs. pre-injection same group. Figures in parentheses: percentage of animals showing lordosis. The mean LQ has been calculated from results of the whole group (i.e. active plus inactive rats).

more of the males until she had been subjected to 10 mounts. The number of lordotic responses to the mounts was noted. The results were expressed as lordosis quotient (LQ), which is the percentage lordotic responses to mounts (LQ = No of lordoses/No. of mounts × 100). The number of times the female exhibited soliciting behaviour was also recorded (hopping-and-darting and ear-wiggling). After the test the drug or vehicle was administered and 30 min later the test was repeated.

Sexual activity was also noted in groups of rats bearing permanent cannulae either in the ventromedial nucleus ($n = 7$) or the medial preoptic area ($n = 8$). The rats were tested just before bilateral administration of delequamine or saline and then at 15, 30, 45, 60, 90 and 120 min intervals post-injection.

2.2. Statistics

One-way analysis of variance (ANOVA) followed by Gabriel's test was used to compare the results of the different doses of delequamine and the saline groups. Student's *t*-test was used to compared treated vs. vehicle group at each dose used and a paired *t*-test was used to compare pre- vs. post-test for each group.

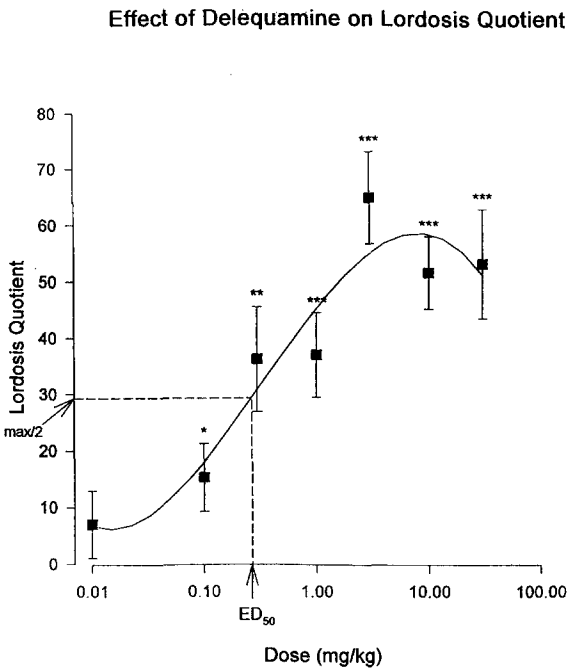

Fig. 2. Log of the doses of Delequamine (RS15385) (at 0.01, 0.1, 0.3, 1, 3, 10 and 30 mg/kg, p.o) against the LQ response of non-receptive female rats (** $P < 0.001$, *** $P < 0.0001$ vs. saline, Student's *t*-test). The dose that produces a response that is 50% of the maximum (0.32 mg/kg) (effective dose 50%; ED_{50}) has been calculated.

3. Results

3.1. Effects of delequamine on non-receptive female rats

Table 1 shows means and standard errors of the LQ at all the doses studied, as well as percentages of rats showing lordosis.

Fig. 2 shows graphically the effect of all the doses given p.o. on the LQ. The ED_{50} (0.32 mg/kg) is calculated as the dose of the drug that produces a response that is 50% of the maximum.

Proceptivity measures (ear-wiggling and hopping-and-darting) were absent both before and after all treatments.

Receptivity, as measured by the lordosis quotient, was significantly increased after the administration of delequamine (ANOVA $P < 0.0001$) in non-receptive rats. When each dose was compared to the correspondent vehicle, and to the correspondent pretest, the doses of 0.1, 0.3, 1, 3, 10 and 30 mg/kg resulted in a significant increase of LQ (see significances in Table 1 and Fig. 2). The dose of 0.01 mg/kg was ineffective.

No differences were seen in the saline-treated groups between tests before and after administration, although there was a marginal significance ($P = 0.0507$) between the LQ at the pretest and the test in the saline group correspondent to 10 mg/kg of the drug, in the non-receptive animals.

3.2. Effects of delequamine on receptive female rats

Delequamine did not show any inhibitory effect on sexual activity in rats made highly receptive following treatment with oestradiol benzoate plus progesterone (saline ($n = 10$): pretest LQ = 100 ± 0%, post-test LQ = 100 ± 0%; delequamine ($n = 10$): pretest LQ = 99 ± 1%, post-test LQ = 100 ± 0%).

Table 2
The effect of delequamine on lordotic activity after intra-hypothalamic administration lordosis quotient ± S.E.M. after treatment

Site of injection	Bilateral treatment	No.	0 min	15 min	30 min	45 min	60 min	90 min	120 min
POA	Saline (0.5 μl)	8	0	0	0	0	0	0	0
	Delequamine (10 μg)	8	0	0	0	0	0	0	0
VMN	Saline (0.5 μl)	7	0	0	0	0	0	0	0
	Delequamine (10 μg)	7	0	0	12.9 ± 12.9	24.3 ± 16.0 [a]	60.0 ± 16.1 [b]	77.1 ± 13.9 [b]	72.8 ± 13.9 [b]
				(0/7)	(1/7)	(2/7)	(5/7)	(6/7)	(6/7)

[a] $P < 0.05$; [b] $P < 0.001$ vs. saline or pre-injection same group. No. of rats showing lordosis in parentheses. The mean LQ has been calculated from results of the whole group (i.e. active and inactive rats).

3.3. Effects of delequamine after intra-hypothalamic administration in non-receptive rats

Bilateral injection of 10 μg/side delequamine into the medial preoptic area of non-receptive ovariectomised rats primed with 2 μg oestradiol benzoate, had no effect on sexual activity at any time up to 120 min post-administration. However, when the antagonist was injected into the ventromedial nucleus, there was a marked increase in receptivity in 6 out of 7 rats with maximum effects (between 70 and 100% LQ) seen either from 60 or 90 min (see Table 2).

4. Discussion

There is some evidence that an α_2-adrenergic system is inhibitory to male sexual behaviour since α_2-adrenoceptor agonists i.e. clonidine (Clark et al., 1985) and guanabenz (Benelli et al., 1993) inhibit, while α_2-adrenoceptor antagonists, i.e. yohimbine (Clark et al., 1985; Clark, 1989) and efaroxan (Benelli et al., 1993) enhance male sexual activity. The evidence for a role of an α_2-adrenergic system in the control of female sexual behaviour is less clear, since as described in the Introduction, although yohimbine reverses the inhibitory effect of noradrenaline in the preoptic area on female receptivity, the effect of the α_2-adrenoceptor antagonists, yohimbine and idazoxan were not tested on the relevant model (Caldwell and Clemens, 1986; Etgen, 1990).

In this report, we have tested the effect of a potent and selective α_2-adrenoceptor antagonist, delequamine (RS-15385) on female sexual behaviour in ovariectomised rats primed with a low dose of oestradiol benzoate so that most of them displayed a low level of receptivity. In these rats, delequamine given orally, over a range of 0.1–30 mg/kg, stimulated lordotic activity in a dose-dependent manner with an ED_{50} of 0.32 mg/kg. Soliciting behaviour was not noted at any of the doses used, indicating that while stereotypic receptivity was facilitated, proceptive behaviour was not. This is similar to the effect of the endogenous noradrenergic system (see Wilson, 1993).

Previous reports have shown that systemic administration of certain agents such as α-MSH (Thody and Wilson, 1988), dopaminergic drugs (Grierson et al., 1988) and serotonergic drugs (Hunter et al., 1985) exert a dual effect on female sexual behaviour being stimulatory in non-receptive and inhibitory in receptive animals. When delequamine was given orally at 10 mg/kg to highly receptive animals, previously primed with oestradiol plus progesterone, it had no effect on either proceptive or receptive behaviour. This indicates that delequamine lacked this duality, although it is always possible that it was unable to overcome a supermaximal effect of the steroids.

The likely mechanism of action of delequamine on female sexual behaviour is that it is acting to raise endogenous hypothalamic noradrenaline levels by blocking autoregulatory presynaptic α_2-adrenoceptors. Delequamine has been shown to enhance cortical noradrenaline release in vivo and release from hypothalamic slices in vitro (Redfern et al., 1992). Recently Etgen and Karkanias (1994) have suggested oestradiol acts in a similar manner to an α_2-adrenoceptor blocking agent to enhance endogenous noradrenaline release and thence receptivity. Alternatively delequamine may be antagonising a putative inhibitory noradrenergic system within the preoptic area (Caldwell and Clemens, 1986). This action of noradrenaline has only been reported once and so further investigation of this possibility is required. To this end, we have carried out a small experiment applying delequamine centrally into either the medial preoptic area where it was found to be ineffective or the ventromedial nucleus where it mimicked the effect of noradrenaline applied to the ventromedial nucleus and stimulated receptive behaviour (Gonzalez et al., 1993). This suggests that the α_2-adrenoceptor antagonist is acting on presynaptic receptors enhancing the release of endogenous noradrenaline. Our findings do not support the existence of an inhibitory α_2-adrenoceptor receptor system in the preoptic area.

In conclusion, we have shown that a highly selective α_2-adrenoceptor antagonist, given orally, can stimulate female lordotic activity in a dose-dependent manner and it is likely that delequamine (RS15385) is exerting its effect by increasing NA release at its active sites.

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