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Short communication

Ketanserin attenuates the behavioural effects of corticosterone: implications for 5-HT_{2A} receptor regulation

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Abstract

The effects of chronic corticosterone treatment on sexual behaviour and wet-dog shakes were investigated in both female and male rats. The serotonergic type 2A (5-HT_{2A}) receptor antagonist ketanserin was administered to test the hypothesis that the behavioural effects of corticosterone were mediated by increased 5-HT_{2A} receptor activity. Rats were randomly assigned to one of four chronic treatment groups: control, ketanserin alone, corticosterone alone, or ketanserin and corticosterone. Ketanserin attenuated the corticosterone-induced changes in both sexual behaviour and wet-dog shakes. Ketanserin alone had no effect on these behaviours. Results suggest that increased 5-HT_{2A} receptor activity mediates the effects of corticosterone on sexual behaviour and wet-dog shakes.

Keywords: Corticosterone; Ketanserin; Sexual behaviour; Wet-dog shake; 5-HT_{2A} receptor

1. Introduction

Research on the central serotonergic (5-HT) system has been facilitated by the increasing availability of selective 5-HT receptor agonists and antagonists. These agents have helped to establish the existence and distinct functional properties of different 5-HT receptor subtypes. The current classification system separates these receptors into families, within which several functional subtypes may exist. For example, the 5-HT_2 family consists of the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptor subtypes (Hoyer and Martin, 1996).

It has been shown that the stimulation of different receptor types can mediate different (often opposing) effects on behaviour. For example, in the male rat, stimulation of the 5-HT_{1A} receptor induces an increase in sexual behaviour (Ahlenius and Larsson, 1991), whereas stimulation of the 5-HT_{2A} receptor exerts an inhibitory influence on sexual behaviour (Gorzalka et al., 1990).

The behavioural effects of receptor stimulation can also be dependent on the sex of the animal. Administration of the selective 5-$HT_{2A/2C}$ receptor agonist (±) 1-(2,5 dimethyl-4-iodophenyl)-2-aminopropane (DOI) induces an increase in both proceptive and receptive sexual behaviours in the female rat (James et al., 1989). In contrast, 5-HT_{2A} receptor stimulation causes a decrease in male rat sexual behaviour. Selective 5-HT_{2A} receptor agonists induce a dose-dependent decrease in ejaculation frequency and copulatory proficiency and an increase in ejaculation latency and postejaculatory interval (Foreman et al., 1989; Watson and Gorzalka, 1990, 1991). The behavioural effects of 5-HT_{2A} receptor agonists on both male and female rat sexual behaviour are effectively blocked by selective 5-HT_{2A} receptor antagonists (Mendelson and Gorzalka, 1985; Wilson and Hunter, 1985; Watson and Gorzalka, 1991). In sum, the results suggest that 5-HT_{2A} receptor activation induces opposing effects on male and female rat sexual behaviour, namely, an increase in female sexual behaviour and a decrease in male sexual behaviour.

Unique to the 5-HT_{2A} receptor is its influence on a behavioural stereotypy, wet-dog shakes. Wet-dog shakes, which can be identified as a reflexive shudder of the head, neck and trunk, has been shown to increase in frequency with increases in 5-HT_{2A} receptor activity in both female and male rats (Hanson and Gorzalka, 1999; Watson and Gorzalka, 1990). Wet-dog shakes can be both pharmacologically induced with 5-HT_{2A} receptor agonists (Goodwin et al., 1984; Gorzalka and Hanson, 1998; Pranzatelli, 1990) and inhibited with 5-HT_{2A} receptor antagonists

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(Lucki et al., 1987; Pranzatelli, 1990). It has also been shown that upon 5-HT_{2A} receptor activation, the observed increase in female rat sexual behaviour and decrease in male rat sexual behaviour is often accompanied by a concomitant increase in wet-dog shakes (e.g., Hanson and Gorzalka, 1999; Watson and Gorzalka, 1990). The relationship between these two behaviours has been used as a noninvasive behavioural assay of 5-HT_{2A} receptor activity (Eison et al., 1995; Gorzalka and Hanson, 1998; Hanson et al., 1998; Kuroda et al., 1992; Watson and Gorzalka, 1990; Yap and Taylor, 1983).

Recent studies have implicated the adrenal hormone corticosterone in playing a fundamental role in the regulation of 5-HT_{2A} receptor density (Kuroda et al., 1992; McKittrick et al., 1995). It has been demonstrated that chronic administration of corticosterone (at levels that mimic those seen during times of stress) can induce an increase in 5-HT_{2A} receptor density in the rat brain (Fernandes et al., 1997; Kuroda et al., 1992). Recent behavioural studies have demonstrated that a chronic corticosterone regimen induces an increase in wet-dog shakes (Berendsen et al., 1996) with a concurrent decrease in male rat sexual behaviour (Gorzalka and Hanson, 1998) and increase in female rat sexual behaviour (Hanson and Gorzalka, 1999). Moreover, administration of the drug nefazodone, which antagonizes 5-HT_{2A} receptors, attenuates the effects of corticosterone on female rat sexual behaviour and wet-dog shakes (Hanson et al., 1998). These results are consistent with corticosterone increasing 5-HT_{2A} receptor activity.

Ketanserin is a potent and relatively selective 5-HT_{2A} receptor antagonist (Brogden and Sorkin, 1990). Chronic administration of this antagonist has been shown to induce a downregulation of 5-HT_{2A} receptors (Eison and Mullins, 1996). The following experiments were designed to test whether the effects of corticosterone on sexual behaviour and wet-dog shakes are mediated by an upregulation in 5-HT_{2A} receptors. In order to test this hypothesis, ketanserin and corticosterone were administered both chronically and concurrently.

2. Materials and methods

2.1. Experiment 1

2.1.1. Animals

Thirty-six Long-Evans female rats (Charles River Canada, Montreal) were used. Procedures were consistent with the standards of the Canadian Council on Animal Care. Subjects were housed in groups of three or four in standard, triple wire mesh cages, with Purina Rat chow and tap water available ad libitum. The colony was maintained at a temperature of 21 °C and on a reverse 12-h dark/light cycle (lights off at 0900 h). All females were bilaterally ovariectomized at 3 months of age using standard surgical procedures while under a combination of 75 mg/kg ketamine hydrochloride (intraperitoneal) and 7 mg/kg xylazine (intraperitoneal) anaesthesia. At the time of behavioural testing, females were approximately 6 months of age and weighed between 300 and 350 g.

2.1.2. Apparatus

Cubical Plexiglas ($30 \times 30 \times 30$ cm) and cylindrical glass (30 cm diameter $\times$ 45 cm height) chambers were used to conduct all behavioural tests. Injections were performed using 26 gauge and 1/2-in. stainless steel needles.

2.1.3. Drugs

Doses of estradiol benzoate and progesterone (Sigma, St. Louis, MO, USA) were dissolved in 0.1 ml peanut oil.

Corticosterone-21 acetate (Sigma) was dissolved in propylene glycol (20 mg/ml).

Ketanserin tartrate (Research Biochemicals, Natick, MA, USA) was stored at 5 °C in dark conditions and was freshly dissolved in 0.9% saline at a concentration of 1 mg/ml.

2.1.4. Procedure

All behavioural testing occurred during the middle third of the dark cycle and was performed by trained observers who remained blind to the experimental condition of the subjects. Female subjects were randomly assigned to four treatment groups: saline and propylene glycol, 1 mg/kg ketanserin and 20 mg/kg corticosterone, saline and 20 mg/kg corticosterone and 1 mg/kg ketanserin and propylene glycol. This dose of corticosterone has been shown to increase 5-HT_{2A} receptor density (Kuroda et al., 1992). Injections were given once daily for a period of 10 days. Ketanserin and saline injections were given intraperitoneally while corticosterone and propylene glycol injections were administered subcutaneously. On Day 9, all subjects were injected with 0.8 μg estradiol benzoate and on Day 11, 50 μg progesterone (4 h prior to behavioural testing). Behavioural testing occurred 24 h after the last ketanserin or corticosterone injection.

2.1.5. Behavioural testing

Test sessions began with the presentation of the female to a sexually experienced male in individual testing chambers. Proceptive, receptive, rejection and wet-dog shake behaviours were simultaneously scored and recorded. Sexual receptivity was assessed by the lordosis quotient, which is defined as the proportion of full lordotic responses by a subject in response to 10 mounts (with pelvic thrusting) by a male. Full lordosis was defined as a significant downward arching of the back, an upward stretch of the neck and head and a deviation of the tail. If a male failed to mount the female after a period of 5 min, the female was removed and placed with a different male in another testing chamber. Proceptive behaviours included ear wiggles (vibrations of the external ears symmetrically around

an erected position for 1–2 s) and darts (rapid movements followed by an abrupt halt). Rejection behaviours included kicking, boxing, vocalizations and rolling onto the backside. The frequency of rejection, proceptive and wet-dog shake behaviours were tallied throughout the session. The length of each testing session was timed to calculate the frequency of rejection behaviours and wet-dog shakes per min. Data for each of the proceptive behaviours, namely ear wiggles and darts, were combined to form a composite proceptivity score of solicitations per min (Gorzalka and Moe, 1994).

2.1.6. Statistics

Results were subsequently analyzed using two-way analyses of variance, with a significance criterion of 0.05. Effect sizes using Cohen's *d* were calculated for all significant effects.

2.2. Experiment 2

2.2.1. Animals

Thirty-six Long-Evans male rats (Charles River Canada) were used for this experiment. Males were housed in the same conditions as the females in Experiment 1. Males were exposed to receptive females on at least four occasions prior to testing and were screened for copulatory proficiency. Copulatory proficiency was determined by a criterion of two ejaculations within a 30-min screening session with fully receptive females on at least two separate occasions. Males (400–450 g) were approximately 6 months of age at the time of testing. Ovariectomized Long–Evans female rats previously exposed to males on at least three separate occasions while in hormone-induced behavioural estrus were used as stimuli for the sexual behaviour testing of the males.

2.2.2. Apparatus

The same apparatus was used as Experiment 1.

2.2.3. Drugs

(±) 1-(2,5 dimethyl-4-iodophenyl)-2-aminopropane (DOI) (Research Biochemicals International) was dissolved in 0.9% saline (1 mg/ml). All other drugs used are listed in Experiment 1.

2.2.4. Procedure

Sexual receptivity was induced in stimulus females with injections of 10 μg of estradiol benzoate (subcutaneous, 48 h prior to testing) and 500 μg progesterone (subcutaneous, 4 h before testing). Males were randomly assigned to four treatment groups: saline and propylene glycol, 1 mg/kg ketanserin and 20 mg/kg corticosterone, saline and 20 mg/kg corticosterone and 1 mg/kg ketanserin and propylene glycol. Injections were administered once daily for a period of 10 days. Ketanserin and saline injections were given intraperitoneally while corticosterone and propylene glycol injections were administered subcutaneously. Behavioural testing occurred 24 h after the last ketanserin or corticosterone injection. In order to prevent a ceiling effect and to ensure that either an inhibition or facilitation could be seen, DOI (0.25 mg/kg) was administered to all subjects 30 min prior to behavioural testing.

2.2.5. Behavioural testing

Behavioural testing occurred in the middle third of the dark cycle. The following sexual behaviour parameters were scored: frequency of mounts with pelvic thrusting prior to ejaculation, frequency of penile intromissions prior to ejaculation, frequency of ejaculations, ejaculation latency (i.e., the period between the first intromission and the first ejaculation) and the postejaculatory interval (i.e., the period between ejaculation and the first intromission of the next copulatory bout). Copulatory efficiency was calculated by determining an animal's intromission frequency and dividing it by the total number of mounts and intromissions prior to the first ejaculation. A high score on this measure indicates that more copulatory attempts resulted in intromissions rather than mounts; this measure is relatively independent of motivational changes (Parrott, 1975). Wet-dog shakes were scored by measuring total wet-dog shakes within the testing interval and dividing this number by the test duration of 30 min, thus, achieving a frequency score of wet-dog shakes per minute. Stimulus females were rotated between males every 10 min to maintain sexual interest. Male rats that failed to ejaculate during the test session were dropped from the data analyses of copulatory efficiency, mount frequency and intromission frequency, while all latency scores were set to the maximum of 1800 s. Rats that did not intromit after the first ejaculation were dropped from the postejaculatory interval analysis.

2.2.6. Statistics

Results were subsequently analyzed using two-way analyses of variance, with a significance criterion of 0.05. Effect sizes were calculated using Cohen's *d* for all significant effects.

3. Results

3.1. Experiment 1

Data are presented in Table 1 as means ± S.E. A significant interaction between corticosterone and ketanserin was found for wet-dog shakes [$F(1,32) = 11.69$, $P = 0.002$]. Corticosterone significantly facilitated wet-dog shakes ($d = 1.5$) and this effect was attenuated by ketanserin treatment. Ketanserin alone had no effect on wet-dog shakes.

Table 1
WDS and sexual behaviour measures as a function of corticosterone and ketanserin treatment in female rats

	WDS/min[a]	Lordosis quotient[a]	Solicitations/min[a]	Rejections/min
No corticosterone				
Ketanserin	0.08 ± 0.04	48 ± 7	0.47 ± 0.12	0.17 ± 0.06
Saline	0.10 ± 0.03	36 ± 8	0.48 ± 0.11	0.23 ± 0.07
Corticosterone				
Ketanserin	0.09 ± 0.05	53 ± 7	0.27 ± 0.06	0.30 ± 0.09
Saline	0.86 ± 0.21	82 ± 6	1.33 ± 0.24	0.27 ± 0.08

Data are presented as mean scores ± S.E.
[a] Significant interaction between corticosterone and ketanserin.

Similarly, significant interactions between corticosterone and ketanserin were found for both receptivity [$F(1,32) = 8.26$, $P = 0.007$] and proceptivity [$F(1,32) = 11.96$, $P = 0.001$]. Corticosterone significantly increased both receptivity ($d = 1.9$) and proceptivity ($d = 1.3$). Ketanserin effectively blocked the effects of corticosterone and did not have any effects on receptive and proceptive behaviours when administered alone. Neither corticosterone nor ketanserin treatment had a significant effect on rejection behaviour.

3.2. Experiment 2

Data are presented in Table 2 as means ± S.E. A significant interaction between corticosterone and ketanserin was found for wet-dog shakes [$F(1,32) = 27.76$, $P < 0.0001$]. Corticosterone significantly facilitated wet-dog shakes ($d = 1.9$) and this effect was attenuated by ketanserin treatment. Ketanserin treatment alone had no effect on wet-dog shakes.

Only one of the nine animals in the group treated with corticosterone alone achieved ejaculation. In each of the three other groups, seven of the nine animals achieved ejaculation at least once. A significant interaction was observed between ketanserin and corticosterone for ejaculation [$F(1,32) = 6.68$, $P = 0.04$]. Corticosterone significantly decreased ejaculatory behaviour ($d = 1.3$) and ketanserin effectively attenuated this inhibition. Ketanserin treatment alone did not have an effect on the frequency of ejaculations, though it did decrease the latency to ejaculation [$F(1,32) = 6.55$, $P = 0.015$, $d = 0.31$]. Corticosterone and ketanserin treatment alone did not significantly affect any other measure of sexual behaviour ($P > 0.10$).

4. Discussion

The results of both Experiments 1 and 2 demonstrate an attenuation of corticosterone's behavioural effects by ketanserin. In Experiment 1, corticosterone significantly increased both proceptive and receptive behaviours in the female rat. Ketanserin effectively attenuated this sexual facilitation. In Experiment 2, ketanserin significantly blocked the corticosterone-induced decrease in ejaculation frequency. Corticosterone facilitated wet-dog shakes, which was blocked by ketanserin in both experiments.

The observed effects of a chronic corticosterone regimen on rat sexual behaviour and wet-dog shakes replicate previous findings. Chronic administration of corticosterone at doses of 20 and 50 mg/kg induces an increase in wet-dog shakes with a concomitant decrease in male rat sexual behaviour and increase in female rat sexual behaviour (Gorzalka and Hanson, 1998; Hanson and Gorzalka, 1999). These results are reminiscent of those found in studies using selective 5-HT_{2A} receptor agonists (Foreman et al., 1989; James et al., 1989; Watson and Gorzalka, 1991). Moreover, it has been shown that chronic corticosterone treatment increases 5-HT_{2A} receptor activity by increasing 5-HT_{2A} receptor density in the rat brain (Kuroda et al., 1992).

The results of the present study offer a link between findings on the behavioural effects of corticosterone and the effects of corticosterone on 5-HT_{2A} receptor density. Chronic administration of ketanserin, a selective 5-HT_{2A} receptor antagonist, results in the downregulation of 5-HT_{2A} receptors (Eison and Mullins, 1996). Thus, chronic ketanserin treatment should counteract a corticosterone-induced increase in 5-HT_{2A} receptor activity. The observed attenuation of corticosterone-induced changes in rat sexual behaviour and wet-dog shakes by ketanserin supports the

Table 2
WDS and sexual behaviour measures as a function of corticosterone and ketanserin treatment in male rats

	WDS/min[a]	Ejaculation frequency[a]	Ejaculation latency (s)	Postejaculatory interval (s)	Copulatory efficiency
No corticosterone					
Ketanserin	0.42 ± 0.11	0.80 ± 0.21	1192 ± 167	554.5 ± 40.9	0.30 ± 0.06
Saline	0.28 ± 0.06	1.10 ± 0.31	1363 ± 177	573.7 ± 77.3	0.29 ± 0.05
Corticosterone					
Ketanserin	0.08 ± 0.03	1.01 ± 0.24	1168 ± 180	538.8 ± 69.0	0.34 ± 0.06
Saline	0.76 ± 0.09	0.12 ± 0.11	1774 ± 9	–	0.15 ± 0.00

Data are presented as mean scores ± S.E.
[a] Significant interaction between corticosterone and ketanserin.

hypothesis that the behavioural influence of corticosterone is mediated by increases in 5-HT_{2A} receptor activity.

Although much weaker than its affinity for 5-HT_{2A} receptors, ketanserin has an affinity for alpha(1)-adrenoceptors, at which it has antagonist properties. Moreover, glucocorticoids have been shown to increase the expression of hypothalamic alpha(1)-adrenoceptor mRNAs in vitro (Feuvrier et al., 1999). However, it is unlikely that this would account for the present results as activity at alpha(1)-adrenoceptors facilitates both male (Clark et al., 1987) and female sexual behaviour (Chu and Etgen, 1999) whereas activity at 5-HT_{2A} receptors has opposite effects on male and female sexual behaviour.

A relationship between 5-HT_{2A} receptor activity and corticosterone has been reported for other behaviours. For example, it has been demonstrated that 5-HT_{2A} receptor agonists induce hypophagia in rats (Price et al., 1998) but only so in nonadrenalectomized animals (Yamada et al., 1996). The results suggest that the effects of 5-HT_{2A} receptors on feeding may be dependent on the presence of corticosterone.

The links between 5-HT_{2A} receptor activity, wet-dog shakes and sexual behaviour has led to the use of these behaviours as a noninvasive measure of 5-HT_{2A} receptor activity (e.g., Eison et al., 1995; Gorzalka and Hanson, 1998; Hanson et al., 1998). The current findings suggest the use of these behaviours as a possible indirect measure of corticosterone-induced 5-HT_{2A} receptor density changes. Studies implementing chronic corticosterone treatments may be able to deduce through noninvasive means the relative degree of change in 5-HT_{2A} receptor density through changes in wet-dog shakes and rat sexual behaviour.

As both 5-HT_{2A} receptors and cortisol abnormalities have been implicated in human depression (Arora and Meltzer, 1989; Lopez et al., 1997; Mann et al., 1989; Murphy, 1991), the demonstration of a neuroendocrine link between corticosteroids and 5-HT_{2A} receptors may lead to a better understanding of the etiology of affective disorders and potential therapeutic strategies.

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