



ELSEVIER

European Journal of Pharmacology 342 (1998) 163–165

ejp

Short communication

The antidepressant, nefazodone, attenuates corticosterone-induced increases in 5-HT_{2A} receptor-mediated behaviors in the female rat

Laura A. Hanson, Boris B. Gorzalka^{*}, Lori A. Brotto*Department of Psychology, The University of British Columbia, Vancouver, BC, Canada V6T 1Z4*

Received 8 December 1997; accepted 9 December 1997

Abstract

The effects of chronic corticosterone administration on sexual behavior and on wet-dog shakes, a 5-HT_{2A} mediated behavior, were investigated in the female rat. In addition, effects of the antidepressant nefazodone, a selective 5-HT_{2A} receptor antagonist, both alone and in combination with corticosterone were examined. Testing was conducted in ovariectomized animals primed with estrogen and progesterone. Corticosterone was found to significantly increase sexual receptivity, sexual proceptivity and wet dog shakes. While nefazodone alone had no significant effects, it completely attenuated the corticosterone-induced increases in both sexual behavior and wet dog shakes. This suggests that corticosterone influences sexual behavior and wet dog shakes via a 5-HT_{2A} receptor mechanism. © 1998 Elsevier Science B.V.

Keywords: Nefazodone; Corticosterone; 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{2A} receptor; Sexual behavior

1. Introduction

In the female rat, administration of 5-HT_{2A} receptor agonists stimulates sexual behavior while administration of 5-HT_{2A} receptor antagonists inhibits or reverses the effect (for review, see Gorzalka et al., 1990). Moreover, chronic stress elevates glucocorticoids and concurrently stimulates sexual behavior in the female (Williams et al., 1992). Since chronic corticosterone treatment has been shown to increase the density of brain 5-HT_{2A} receptors (Kuroda et al., 1992), it is reasonable to speculate that this treatment would increase sexual behavior and 5-HT_{2A} receptor antagonism would reverse this effect.

The frequency of wet dog shakes, a quivering shudder of the head, neck and trunk is correlated with increases in serotonergic activity (Bedard and Pycock, 1977) and has been successfully employed as a non-invasive measure of 5-HT_{2A} receptor activity in vivo (e.g. Yap and Taylor, 1983; Watson and Gorzalka, 1990). In addition, chronic administration of high doses of corticosterone (ranging from 20 mg/kg daily to 50 mg/kg twice daily) has been shown to produce plasma levels that resemble the level after a physical stressor (Hodges and Jones, 1963) and to

increase the frequency of wet dog shakes behavior (Berenzen et al., 1996).

Nefazodone, a potent antidepressant that affects serotonergic neurotransmission by both blocking reuptake and blocking 5-HT_{2A} receptors (Taylor et al., 1995), decreases the frequency of WDS in rats treated with a 5-HT_{2A} receptor agonist (Eison et al., 1990). Since corticosterone and nefazodone apparently exert opposite effects on 5-HT_{2A} receptor activity as seen by their effects on wet dog shakes in the rat, it appears reasonable that nefazodone would antagonize any increase in wet dog shakes induced by the chronic administration of corticosterone. In addition, if nefazodone and corticosterone both regulate 5-HT_{2A} receptor activity, nefazodone may attenuate any effects of corticosterone on female sexual behavior that are mediated by alterations in 5-HT_{2A} receptors. Therefore, the purpose of the present experiment is to investigate the chronic effects of nefazodone and corticosterone, singly and in combination, on female sexual behavior and wet dog shakes.

2. Materials and methods

2.1. Subjects

Thirty-six Long–Evans female rats and twenty Long–Evans male rats were bred from stock originally obtained

^{*} Corresponding author. Tel.: +1-604-8223095; fax: +1-604-8226923; e-mail: bgorzalka@neuron3.psych.ubc.ca

from Charles River, Montreal, Canada. Females (200–250 g) were bilaterally ovariectomized at 3 months of age using standard surgical procedures while anesthetized with 75 mg/kg ketamine HCl and 7 mg/kg xylazine (UBC Animal Care Center, Vancouver, Canada). Ovariectomized females were housed in groups of 3 or 4. At 3 months of age, Long–Evans males were screened for copulatory proficiency and those showing consistent, vigorous sexual activity were selected to elicit sexual behavior in the females. Males were housed in groups of 3 or 4 in the same colony room as the female subjects.

All rats were housed in standard triple wire mesh cages in a colony maintained at $21 \pm 1^\circ\text{C}$ and kept on a reversed 12 h dark/12 h light cycle with the lights off at 09.00 h. All rats were provided with free access to water and Purina rat chow.

2.2. Injection procedure

Corticosterone-21-acetate (Sigma Chemical Co., Chicago) was suspended in propylene glycol (10 mg/ml) while nefazodone (Pfizer, Groton, USA) was dissolved in saline (50 mg/ml) and both drugs were injected subcutaneously (s.c.) for 10 days (2 ml/kg). Saline and propylene glycol were also injected s.c. for 10 days (2 ml/kg). Female subjects were randomly assigned into four treatment groups: saline and propylene glycol, 100 mg/kg nefazodone and propylene glycol, saline and 20 mg/kg corticosterone and 100 mg/kg nefazodone and 20 mg/kg corticosterone. On the ninth day of injections, female subjects were injected s.c. with 0.8 μg estradiol benzoate (Sigma Chemical Co., Chicago). On day 11, females received 50 μg progesterone (Sigma Chemical Co., Chicago) s.c. Both estradiol benzoate and progesterone were dissolved in 0.1 ml peanut oil.

2.3. Behavioral testing procedure

3 h after progesterone administration, female subjects were tested for sexual behavior and for the frequency of wet dog shakes in Plexiglas chambers (30 \times 30 \times 45 cm in height) with contact bedding covering the floor.

After 5 min of habituation to the chambers, male rats were presented with the female subjects. Receptivity was

measured using the lordosis quotient the proportion of full lordoses exhibited in response to 10 mounts with pelvic thrusting by a male. Proceptivity was measured by the frequency per hour of ear wiggles (1–2 s vibrations of the external ears). The frequency of wet dog shakes and sexual rejection were also measured. Any defensive kick, push, run or roll onto the back was scored as one rejection response. The frequency of proceptivity, wet dog shakes and rejection were calculated by dividing the number of responses by the duration of the test. If a male did not attempt to mount the female within a five min time period, the female subject was transferred into a chamber with a different male. Data collection was terminated for each female after she had received 10 mounts with pelvic thrusting by a male, which on average took approximately 10–15 min.

All testing was conducted during the middle third of the dark cycle by a trained observer who was blind to the experimental condition of the subjects. Results were subsequently analyzed using a one-way analysis of variance followed by pairwise comparisons using the Newman–Keuls procedure. A statistical significance level of $P < 0.05$ was used for all tests.

3. Results

Receptivity, proceptivity and wet dog shakes results are presented in Table 1. There was a significant difference between groups in the display of sexual receptivity, $F(3, 32) = 3.03$, $P = 0.043$. Subsequent Newman–Keuls tests indicated greater receptivity in the corticosterone group than in any of the other three groups, which did not differ significantly from each other.

As shown in Table 1, a similar pattern was obtained for proceptivity. Again, there was a significant group difference, $F(3, 32) = 2.97$, $P = 0.045$. Newman–Keuls tests confirmed that animals in the corticosterone group displayed significantly more proceptivity than those in each of the other three groups, which did not differ from each other.

Table 1 suggests that corticosterone increased wet dog shakes and nefazodone completely attenuated the effect. This was confirmed statistically. There was a significant

Table 1

Effects of corticosterone (20 mg/kg) and nefazodone (100 mg/kg) on receptivity (lordosis quotient), proceptivity (frequency per hour) and wet dog shakes (per hour) in ovariectomized rats treated with estrogen and progesterone

	Receptivity	Proceptivity	Wet dog shakes
Saline–propylene glycol	48.3 \pm 16.8	14.4 \pm 11.4	18.5 \pm 6.0
Nefazodone–propylene glycol	51.0 \pm 15.4	19.2 \pm 9.6	21.0 \pm 7.8
Saline–corticosterone	89.0 \pm 8.0*	105.0 \pm 45.6*	78.5 \pm 20.4*
Nefazodone–corticosterone	43.0 \pm 10.4	13.2 \pm 9.0	11.7 \pm 3.6

Values represent means \pm S.E.M.

* Significantly different from all other groups, $P < 0.05$.

group difference, $F(3, 32) = 6.59$, $P = 0.0014$. The corticosterone-treated group exhibited higher WDS than each of the other three groups, which did not differ from each other.

There were no significant differences between groups in the frequency of sexual rejections ($P > 0.05$).

4. Discussion

The present results indicate that a corticosterone regimen which maintains levels at those produced by a physical stressor, increases receptivity, proceptivity, and wet dog shakes in the female rat. The increase in wet dog shakes seen in females in this study replicates previous findings in the male (Berendsen et al., 1996). To the best of our knowledge, this is the first report of an increase in sexual behavior following corticosterone treatment. In previous studies, acute or chronic administration of corticosterone failed to produce any effect on sexual behavior in ovariectomized, estrogen-treated rats (Gorzalka and Whalen, 1977; DeCatanzaro and Gorzalka, 1980). However, corticosterone doses in previous studies may have been insufficient to alter 5-HT_{2A} receptor mediated behavior. The present results also support a previous suggestion that stress-induced increases in sexual receptivity may be mediated by elevated glucocorticoids (Williams et al., 1992).

Although nefazodone alone has no effect on either sexual behavior or wet dog shakes, it does antagonize the corticosterone-induced increases in these behaviors. The wet dog shakes results are consistent with previous findings that nefazodone attenuated quipazine-induced increases in wet dog shakes (Eison et al., 1990). The present results may be explained by a 5-HT_{2A} receptor-mediated mechanism since nefazodone acts to decrease 5-HT_{2A} receptor activity (Taylor et al., 1995) and rats with chronically elevated corticosterone levels have significantly increased 5-HT_{2A} receptor density (Kuroda et al., 1992; McKittrick et al., 1995).

Whereas one action of nefazodone is to block 5-HT_{2A} receptors, it also inhibits the reuptake of serotonin thereby increasing activity at all postsynaptic 5-HT receptors, including the 5-HT_{1A} receptor. There is evidence to suggest that chronic administration of a corticosteroid can down-regulate 5-HT_{1A} receptors in rodents (Young et al., 1992). Since data indicate that decreased 5-HT_{1A} receptor activity results in a facilitation of female rat sexual behavior (Gorzalka et al., 1990), it is possible that the current effects on female sexual behavior may, in part, be mediated by alterations in 5-HT_{1A} receptor activity. However, it is unlikely that this would account for the present wet dog shakes results.

Therefore it is reasonable to suggest, as a preliminary hypothesis, that nefazodone attenuates any increases in 5-HT_{2A} receptor activity induced by chronic corticosterone

administration and thereby prevents the corticosterone-induced increases in receptivity, proceptivity and wet dog shakes in the female rat. Further investigations are needed to clarify the nature of the interaction between 5-HT_{2A} receptor-mediated behavior and corticosterone.

Acknowledgements

This research was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) grant to B.B.G.

References

- Bedard, P., Pycock, C.J., 1977. Wet-dog shake behaviour in the rat: A possible quantitative model of central 5-hydroxytryptamine activity. *Neuropharmacology* 16, 663–670.
- Berendsen, H.H.G., Kester, R.C.H., Peeters, B.W.M.M., Broekkamp, C.L.E., 1996. Modulation of 5-HT receptor subtype-mediated behaviours by corticosterone. *Eur. J. Pharmacol.* 308, 103–111.
- DeCatanzaro, D., Gorzalka, B.B., 1980. Effects of dexamethasone, corticosterone, and ACTH on lordosis in ovariectomized and adrenalectomized-ovariectomized rats. *Pharmacol. Biochem. Behav.* 12, 201–206.
- Eison, A.S., Eison, M.S., Torrente, D.P., Wright, R.N., Yocca, F.D., 1990. Nefazodone: Preclinical pharmacology of a new antidepressant. *Psychopharm. Bull.* 26, 311–315.
- Gorzalka, B.B., Whalen, R.E., 1977. The effects of progestins, mineral-corticoids, glucocorticoids, and steroid solubility on the induction of sexual receptivity in rats. *Horm. Behav.* 8, 94–99.
- Gorzalka, B.B., Mendelson, S.D., Watson, N.V., 1990. Serotonin receptor subtypes and sexual behavior. *Ann. N. Y. Acad. Sci.* 600, 435–446.
- Hodges, J.R., Jones, M.T., 1963. The effect of injected corticosterone on the release of adrenocorticotrophic hormone in rats exposed to acute stress. *J. Physiol.* 167, 30–37.
- Kuroda, Y., Mikuni, M., Ogawa, T., Takahashi, K., 1992. Effect of ACTH, adrenalectomy and the combination treatment on the density of 5-HT₂ receptor binding sites in neocortex of rat forebrain and 5-HT₂ receptor-mediated wet-dog shake behaviors. *Psychopharmacology* 108, 27–32.
- McKittrick, C.R., Blanchard, D.C., Blanchard, R.J., McEwen, B.S., Sakai, R.R., 1995. Serotonin receptor binding in a colony model of chronic social stress. *Biol. Psychiatry* 37, 383–393.
- Taylor, D.P., Carter, R.B., Eison, A.S., Mullins, U.L., Smith, H.L., Torrente, D.P., Wright, R.N., Yocca, F.D., 1995. Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. *J. Clin. Psychiatry* 56 (Suppl. 6), 3–11.
- Watson, N.V., Gorzalka, B.B., 1990. Relation of spontaneous wet dog shakes and copulatory behavior in male rats. *Pharmacol. Biochem. Behav.* 37, 825–829.
- Williams, G.W., McGinnis, M.Y., Lumia, A.R., 1992. The effects of olfactory bulbectomy and chronic psychosocial stress on serum glucocorticoids and sexual behavior in female rats. *Physiol. Behav.* 52, 755–760.
- Yap, C.Y., Taylor, D.A., 1983. Involvement of 5-HT₂ receptors in the wet-dog shake behaviour induced by 5-hydroxytryptophan in the rat. *Neuropharmacology* 22, 801–804.
- Young, A.H., MacDonald, L.M., StJohn, H., Dick, H., Goodwin, G.M., 1992. The effects of corticosterone on 5-HT function in rodents. *Neuropharmacology* 31, 433–438.