Corticosterone Regulation of 5-HT$_{2A}$ Receptor-Mediated Behaviors: Attenuation by Melatonin

BORIS B. GORZALKA, LORI A. BROTTO AND JANIE J. HONG

Department of Psychology, The University of British Columbia, Vancouver, British Columbia, Canada, V6T 1Z4

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GORZALKA, B. B., L. A. BROTTO AND J. J. HONG. Corticosterone regulation of 5-HT$_{2A}$ receptor-mediated behaviors: Attenuation by melatonin. PHYSIOL BEHAV 67(3) 439–442, 1999.—The effects of chronic corticosterone treatment on consummatory measures of sexual behavior and on wet-dog shakes (WDS), a serotonergic type 2A (5-HT$_{2A}$) receptor-mediated behavior, were explored in the male rat. In addition, the effects of acute melatonin treatment, both alone and in combination with corticosterone, were investigated. Chronic injections of corticosterone resulted in an overall decrease in consummatory measures of sexual behavior, and an increase in WDS. Furthermore, although an acute injection of melatonin alone had no effect on any recorded behavior, it attenuated the effects of corticosterone on sexual behavior and WDS. The data suggest that in the context of 5-HT$_{2A}$ receptor-mediated behaviors, melatonin has possible implications as a 5-HT$_{2A}$ antagonist. © 1999 Elsevier Science Inc.

IN the male rat, serotonergic type 2A (5-HT$_{2A}$) receptor activity has been reliably found to modulate an inhibition of sexual behavior (15). Furthermore, the frequently employed behavior known as “wet-dog shakes” (WDS) has been found to be largely mediated by 5-HT$_{2A}$ activity, with activation of the 5-HT$_{2A}$ receptor producing a robust facilitation of WDS in the rat (29). WDS, which consist of a rotational shudder of the upper body (2), resemble the purposeful movement, as seen in dogs, and have reliably been used as a behavioral assay of 5-HT$_{2A}$ receptor activity (29). A strong, inverse correlation exists between male sexual behavior and WDS, such that activation of the 5-HT$_{2A}$ receptor produces an increase in WDS, and a concomitant decrease in sexual behavior (27). As a result, spontaneously occurring WDS have been frequently employed as a noninvasive index of 5-HT$_{2A}$ activity during sexual behavior.

Unique to the 5-HT$_{2A}$ receptor is its “nonclassical” mechanism of regulation (24). The receptor’s relative resistance to upregulation in response to serotonergic manipulation has triggered an interest in nonserotonergic methods of its regulation. For example, the adrenal hormone, corticosterone, has been explored in this context, and has been found to exert some regulatory effects on the 5-HT$_{2A}$ receptor. Chronic corticosterone treatment has been demonstrated to significantly increase the density of central 5-HT$_{2A}$ receptors (9,21,26), and to significantly facilitate 5-HT$_{2A}$ receptor-mediated behaviors (3,13,18).

The hormone, melatonin, has also been explored in the context of 5-HT$_{2A}$ receptor regulation. Eison et al. (8) demonstrated a dose-dependent attenuation by melatonin of the increase in WDS induced by a 5-HT$_{2A}$ receptor agonist. Moreover, radioligand binding techniques demonstrated that melatonin reduced the concentration-dependent 5-HT$_{2A}$-mediated phosphoinositide (PI) hydrolysis response to 5-HT$_{2A}$ agonists without altering central 5-HT$_{2A}$ receptor density (8). Furthermore, investigations that demonstrate a similarity in the behavioral effects of melatonin to 5-HT$_{2A}$ antagonists (10) are consistent with melatonin’s putative 5-HT$_{2A}$ antagonism.

Given the apparently opposing effects of corticosterone and melatonin on 5-HT$_{2A}$ receptor activity, it seems reasonable to predict that concurrent administration of melatonin would attenuate the behavioral effects of corticosterone treatment. Furthermore, because drugs that antagonize 5-HT$_{2A}$ receptor activity, including ritanserin, pirenperone, ketanserin,
and nefazodone, exert no effects on sexual behavior (28) and WDS (18), it is expected that neither should melatonin, a putative 5-HT<sub>2A</sub> antagonist, exert effects on these measures when administered alone. The aim of the present study is to investigate the effects of corticosterone, both alone and in combination with melatonin, on sexual behavior and WDS, and to explore the possibility of 5-HT<sub>2A</sub> antagonism as a result of melatonin treatment.

MATERIALS AND METHODS

Subjects

Eighty Long–Evans male rats (Charles River Canada Inc., Quebec), were obtained at 5 weeks of age. Prior to testing, males were screened for copulatory proficiency, and those displaying consistently vigorous sexual activity were selected for the study. The screening procedure resulted in 68 males being employed in the study. At the time of testing, males were 4.5 months of age and 475 g on average. In addition, 18 sexually experienced female rats were used to elicit sexual behavior in the males. Females were previously bilaterally ovariectomized at 3 months of age using standard surgical procedures while anesthetized with ketamine HCl (50 mg/kg) and xylazine (7 mg/kg) obtained from the UBC Animal Care Centre, Vancouver, Canada.

All rats were housed in same-sex groups of three or four, in standard wire mesh cages, and were allowed free access to Purina Rat Chow and water. Colony conditions were maintained at 21 ± 1°C, and animals were kept on a reverse 12/12-h light cycle (lights off at 0900 h).

Injection Procedure

Corticosterone-21-acetate (Sigma Chemical Co., Chicago, IL) was suspended in propylene glycol (20 mg/mL) and melatonin (Sigma Chemical Co.) was dissolved in a solution of 20% dimethyl sulfoxide (DMSO) and saline (6 mg/mL). Corticosterone or the vehicle, propylene glycol, was injected subcutaneously for 14 days (1 mL/kg). On the 15th day, animals received an intraperitoneal injection of either melatonin (1 mL/kg), or the vehicle, DMSO, 45 min prior to testing. In addition, 18 sexually experienced female rats were used to elicit sexual behavior in the males. Females were previously bilaterally ovariectomized at 3 months of age using standard surgical procedures while anesthetized with ketamine HCl (50 mg/kg) and xylazine (7 mg/kg) obtained from the UBC Animal Care Centre, Vancouver, Canada.

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Behavioral Testing Procedure

Females were injected subcutaneously with 10 μg estradiol benzoate (Sigma Chemical Co.) 2 days before testing, and 500 μg progesterone (Sigma Chemical Co.), 4 h before testing. Hormones were dissolved in 0.1 mL peanut oil. Males were tested in Plexiglas chambers (30 × 30 × 45 cm in height) covered with contact bedding.

Males were given 5 min to habituate to the chambers before being presented with a receptive female. Measures of sexual behavior included: mount, intromission, and ejaculation frequencies and latencies, and the postejaculatory interejaculation interval.

DISCUSSION

The present results support previous findings of a corticosterone-induced inhibition of sexual behavior in the male rat (13) and facilitation of WDS (3,18). The chronic corticosterone regimen employed in these studies results in plasma corticosterone levels that are similar to those produced after a chronic stressor (22), and various stressors have been found to inhibit sexual behavior and facilitate WDS in the male rat (4,14). Although acute melatonin treatment alone exerted no effect on male sexual activity, it completely reversed the corticosterone-induced inhibition of ejaculatory behavior. These are the first reported data to suggest that melatonin may protect against the debilitating effects of chronic stress on male sexual behavior.

The observed behavioral responses to chronic corticosterone treatment are consistent with a 5-HT<sub>2A</sub> receptor-medi-
For example, pretreatment with the antidepressant, mianserin, (29) therefore, the present observation of increased WDS attributable to activity at 5-HT receptors other than the 5-HT receptor (25). Melatonin has been implicated as a mood enhancer, and as possessing some possible therapeutic benefits to individuals with depression (17). As a preliminary hypothesis, melatonin may play a role in mood elevation by acting as an antagonist at the 5-HT receptor upregulation independent of changes in 5-HT levels (21). The previous suggestion that hormones of the HPA axis may play a major role in the regulation of 5-HT receptor density (4) may also be extended to include melatonin (8).

A melatonin–corticosterone interaction has been widely investigated, and melatonin has been suggested to exert anti- glucocorticoid effects (1). Melatonin has been implicated as protecting against the detrimental effects of elevated glucocorticoids on the hypothalamic–pituitary–adrenal axis (19,20). In addition, Chuang and Lin (6) have reported that the thermal stress-induced increases in locomotor activity are effectively attenuated by acute melatonin treatment. However, melatonin has no effect on corticosterone-induced thymus regression (16). Therefore, it remains possible that antiglucocorticoid effects of melatonin may not become apparent behaviorally until pharmacological doses are administered, and that at physiological levels, there may be little or no coupling between these hormones. These antiglucocorticoid effects of melatonin may be mediated, in part, by a 5-HT receptor antagonist.

Elevated circulating glucocorticoids are one physiological response to stress in humans, and stress has been identified as one of the predisposing factors for major depression (12). Postmortem studies on the brains of depressed suicide victims have found an increase in 5-HT receptor density (23), and the therapeutic onset of most antidepressants occurs with the concurrent downregulation of the 5-HT receptor (25). Melatonin has been implicated as a mood enhancer, and as possessing some possible therapeutic benefits to individuals with depression (17). As a preliminary hypothesis, melatonin may play a role in mood elevation by acting as an antagonist at the 5-HT receptor.

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