



# Chronic Stress Effects on Sexual Behavior in Male and Female Rats: Mediation by 5-HT<sub>2A</sub> Receptors

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Received 13 June 1997; Revised 15 April 1998; Accepted 30 April 1998

GORZALKA, B. B., L. A. HANSON AND L. A. BROTTO. *Chronic stress effects on sexual behavior in male and female rats: Mediation by 5-HT<sub>2A</sub> receptors.* PHARMACOL BIOCHEM BEHAV **61**(4) 405–412, 1998.—The effects of chronic psychosocial stress on sexual behavior and on the serotonergic type 2A (5-HT<sub>2A</sub>) receptor-mediated behavior “wet dog shakes” (WDS) were investigated in male and female rats. In Experiment 1, both bilaterally adrenalectomized and sham-adrenalectomized female rats were assigned to either a psychosocial stress condition or a control condition for 62 days. On the 63rd day, estrogen-primed females were compared on measures of sexual behavior and WDS. Immediately after the behavioral tests, the same rats were primed with a subthreshold level of progesterone. Three hours after the administration of progesterone, rats were again scored for sexual behavior and WDS. Psychosocial stress was found to facilitate sexual behavior and increase WDS in sham-adrenalectomized female rats providing they were primed with both estrogen and progesterone. In Experiment 2, intact male rats were assigned to either the psychosocial stress condition or the control condition for 30 days. On the 31st day, males were compared on measures of sexual behavior and WDS. No significant differences were revealed on the spontaneous expression of sexual behavior and WDS. Subsequently, males were retested following the administration of the 5-HT<sub>2A</sub> agonist, DOI. Psychosocial stress resulted in a significant decrease in male sexual behavior and a concurrent increase in WDS, following the administration of DOI. Taken together, these results suggest that chronic psychosocial stress facilitates female sexual behavior and inhibits male sexual behavior, and that the effects of stress on sexual behavior may be mediated by 5-HT<sub>2A</sub> receptor activity. © 1998 Elsevier Science Inc.

Wet dog shakes    Serotonin    Stress    Sexual behavior    5-HT<sub>2A</sub> receptor    Estrogen    Progesterone

STUDIES employing serotonin (5-HT) agonists and antagonists relatively selective for specific receptors have demonstrated the behavioral complexity of the serotonergic system. It is now known that specific 5-HT receptors can mediate diverse effects on the same behavior. For example, the expression of sexual behavior can be either inhibited or facilitated, depending on which 5-HT subtype is activated (22). It has also been demonstrated that specific 5-HT subtypes may mediate differential effects on female and male sexual behavior. 5-HT<sub>1A</sub> receptor activation facilitates sexual behavior in the male rat but inhibits in the female (33). Similarly, the 5-HT<sub>2A</sub> receptor has been shown to have different effects on the expression of sexual behavior, depending on the sex of the animal. In the female rat, administration of 5-HT<sub>2A</sub> agonists, such as (±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), have been shown to stimulate sexual behavior (27), while the 5-HT<sub>2A</sub> an-

tagonists pirenperone and ketanserin inhibit sexual receptivity (34,35). These findings support the suggestion that 5-HT<sub>2A</sub> activation in the female rat facilitates sexual behavior. By contrast, in the male rat, the agonist DOI inhibits sexual behavior (17), and this effect is readily blocked by 5-HT<sub>2A</sub> antagonists (50). Overall, the available data suggest that 5-HT<sub>2A</sub> receptor activation mediates a facilitation of female sexual behavior and an inhibition of male sexual behavior.

Prior to the discovery of multiple 5-HT receptors, the wet dog shake (WDS) behavior was identified and described in the rat. The frequency of WDS, a quivering shudder of the head, neck, and trunk, is correlated with increases in 5-HT activity (3). Once multiple 5-HT receptors were identified, it was revealed that the WDS is primarily mediated by 5-HT<sub>2A</sub> activity (55). The WDS can be induced pharmacologically with 5-HT<sub>2A</sub> agonists in rats and mice (19,55), and has since

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been used as a behavioral assay for quantifying 5-HT<sub>2A</sub> activity (51,55). Central administration of DOI produces a dose-dependent increase in WDS that is attenuated by the administration of the 5-HT<sub>2A</sub> antagonist, ritanserin (49). Although the 5-HT<sub>2A</sub> agonist DOI also has high affinity for 5-HT<sub>2C</sub> receptors (26), studies with antagonists varying in 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> activity indicate that the action of DOI on 5-HT<sub>2C</sub> receptors is not relevant to the display of DOI-induced WDS (46).

The spontaneously occurring WDS has been used as a non-invasive measure of 5-HT<sub>2A</sub> activity in the context of male sexual behavior (51). An inverse relationship exists between frequency of male copulatory activity and spontaneous WDS. Moreover, this inverse relationship is magnified by the administration of DOI. These results support the hypothesis that increased 5-HT<sub>2A</sub> activity mediates a facilitation in WDS behavior and an inhibition in sexual behavior in the male rat. To date, there have been no reports in the literature on the relationship between WDS and sexual behavior in the female rat. Given the facilitatory role of 5-HT<sub>2A</sub> activity in female sexual behavior, it is reasonable to expect that spontaneous WDS would be positively correlated with sexual receptivity, and that a 5-HT<sub>2A</sub> agonist would enhance both sexual behavior and WDS in the female. Spontaneous WDS will be used in the present study as a behavioral index of endogenous 5-HT<sub>2A</sub> activity during the concurrent display of sexual behavior.

Stress has been postulated to interact with the serotonergic system and affect sexual behavior in both the female and the male rat. Chronic psychosocial stress, which involves the manipulation of an animal's environmental and social conditions in a manner that triggers neuroendocrine changes, has been demonstrated to increase sexual receptivity and proceptivity in ovariectomized female rats primed with estrogen (54). Some chronic psychosocial stressors facilitate sexual receptivity in ovariectomized, but not ovariectomized-adrenalectomized, females, suggesting that adrenocortical secretions may be a mediating factor (23). In the male rat, chronic sequential exposure to a variety of mild stressors produce effects opposite to those in the female, with a significant decrease in sexual behavior [e.g., (5,8,43,45)]. However, the effects of acute stressors on male sexual behavior appear to be biphasic. Low levels of acute stress have been shown to facilitate male sexual behavior, while high levels of acute stress inhibit copulation (2,15,16).

Chronic stressors have been shown to activate the hypothalamic-pituitary-adrenocortical (HPA) axis. HPA axis activation is part of the body's physiological response to stress, and plasma corticosterone levels are commonly used as an indication of the degree to which an animal is stressed (38). It has been suggested that a state of chronic stress has been achieved when prolonged exposure to a stressor has induced both sustained corticosterone elevation and a behavioral disruption (40). During chronic stress, the HPA axis fails to return corticosterone levels to baseline, and these sustained corticosterone levels have morphological and behavioral effects such as damage to the hippocampus (38) and significant spatial learning impairments (7). The observation that chronic stress can inhibit or facilitate sexual behavior in the rat suggests that corticosterone might influence sexual behavior. Indeed, recent evidence from our laboratory indicates that chronic corticosterone administration inhibits male sexual behavior (20) and facilitates female sexual behavior (25).

Recently, the effects of stress and adrenal corticosterone secretion on 5-HT<sub>2A</sub> activity have been examined; however, results have not been consistent. Subordinate rats subjected to chronic social stress (32) and rats subjected to inescapable

shock (37) have significantly increased serum corticosterone levels and increased 5-HT<sub>2A</sub> receptors in the parietal cortex, and these changes in 5-HT<sub>2A</sub> receptor number are proportional to the extent of HPA axis activation and corticosterone secretion (32). Consistent with these findings, chronic administration of corticosterone significantly increases 5-HT<sub>2A</sub> receptor density in the neocortex of the rat forebrain as measured by radioligand binding using <sup>3</sup>H-ketanserin (28), and behaviorally by increased WDS (4,20,25). Moreover, corticosterone restores selective brain site decreases in 5-HT<sub>2A</sub> receptor density following adrenalectomy (31). These studies suggest that adrenal secretion of corticosterone may trigger 5-HT<sub>2A</sub> receptor upregulation. However, inconsistent with this are reports of either no change in 5-HT<sub>2A</sub>-mediated head twitches after corticosterone treatment (56), or no change in 5-HT<sub>2A</sub> binding after corticosterone removal by adrenalectomy (6). Although there is strong evidence that corticosterone is implicated in the regulation of 5-HT<sub>2A</sub> receptor activity, the conflicting findings render this suggestion equivocal.

Using concurrent WDS behavior as an *in vivo* measure of 5-HT<sub>2A</sub> activity, the present study was designed to investigate the interaction between stress and 5-HT<sub>2A</sub> activity, and their influence on sexual behavior in the female and male rat.

## METHOD

### *Subjects*

Female and male Wistar rats were obtained from stock originally acquired from Charles River Canada Inc., Montreal. All rats were screened for copulatory proficiency, and of these, 22 females and 34 males were selected to be used. Subjects were housed in groups of three or four in standard wire mesh cages on a reversed 12 D:12 L cycle with the lights off at 0900 h, and were maintained in a housing environment at 21°C. Purina Rat Chow and tap water were available *ad lib*. At the time of behavioral testing, females were 18 months (350–450 g), and males were approximately 7 months of age (600–700 g).

In addition, 12 sexually experienced male Long-Evans rats (Studs), and 24 ovariectomized female Wistar rats (Stims) were used for sexual testing of the female and male subjects, respectively. Of these Stims, five were used to sexually arouse Studs in preparation for sexual behavior testing of the female subjects. Long-Evans males were chosen as Studs because they are more proficient copulators than Wistar males independent of the strain of the female (44). Studs were 5 months and Stims were 10 months of age, and all were housed, four per cage, in identical conditions as the subjects.

### *Surgeries*

Female subjects and Stims were bilaterally ovariectomized at 3 months of age using standard surgical procedures while under a combination of 75 mg/kg ketamine hydrochloride and 7 mg/kg xylazine anesthesia. Eleven female subjects were randomly chosen to be adrenalectomized (ADX) via a bilateral lumbar incision at 12 months of age under a combination of the same anesthetics. For 3 days postoperatively, ADX females were maintained on 10% sucrose solution (*ad lib*) and 0.9% saline solution, and no solid food was made available. From the fourth day onward, they were provided with Purina Rat Chow and 0.9% saline solution *ad lib*. The remaining female subjects underwent sham surgery (SHAM) at the same time, with the surgical procedure identical to that employed in the ADX group, except that the adrenals were left intact. SHAM females were returned to a normal diet of Purina Rat

Chow and tap water (ad lib) immediately after surgery. Upon recovery from surgery, all females were returned to their standard home cages.

#### *Stress Apparatus*

*Female psychosocial stress.* A black wooden arena (118 × 118 × 30 cm) covered with San-i-cel, a strobe light, and white noise (100 ± 5 dB) emitted from a microcassette recorder mounted approximately 1 m above the wooden arena, were used to administer the chronic stress regime.

#### *Behavioral Testing Apparatus*

Sexual behavior and wet dog shake (WDS) testing for both females and males were conducted in clear Plexiglas chambers (30 × 30 × 45cm) covered with San-i-cel. A stopwatch was used to record the length of the testing periods, and all observations were recorded manually on standard scoring sheets.

#### *Hormone and Drug Administration*

Estradiol benzoate (EB) (0.8 µg) and 20 µg progesterone (P), both dissolved in 0.1 cc peanut oil (Sigma Chemical Co., St. Louis, MO), were used for experimental females. The hormonal doses were determined from a pilot study conducted on adrenalectomized females to arrive at doses that create a moderate level of receptivity and proceptivity. Stims were given 10 µg EB and 500 µg P, each dissolved in 0.1 cc peanut oil, prior to each testing session. DOI, obtained from Research Biochemicals International (Natick, MA), was dissolved freshly, just prior to Experiment 2B, in 0.9% saline (1 mg/cc).

### EXPERIMENT 1A

The first experiment was designed to determine whether chronic psychosocial stress administration had an effect on the display of sexual behavior in estrogen-treated, ovariectomized female rats. Potential adrenal involvement was determined by comparing adrenalectomized and sham-adrenalectomized animals. Finally, the possible role of 5-HT<sub>2A</sub> mediation was examined through concurrent measurement of spontaneous WDS.

#### *Stress Procedure*

Five ADX females and six SHAM females were randomly chosen and assigned to the chronic stress group (STRESS). The stress regimen followed a procedure previously described (54), which was shown to significantly increase sexual behavior and elevate serum corticosterone levels in the female rat. It consisted of 30 min/day of crowding in the black arena and simultaneous exposure to strobe lighting and white noise in a dark testing room. Immediately following stress exposure, all females were transferred back to their home cages until the next day's stress period. Stress was delivered during the middle third of the dark cycle, and was continued for 59 consecutive days. The remaining six ADX and five SHAM females formed the control group (NO STRESS), and were left untouched in their home cages while the STRESS females were removed daily.

#### *Behavioral Testing Procedure*

On day 58, all female subjects were injected with 0.8 µg EB subcutaneously (SC) and five Stims with 10 µg EB (SC). On day 60, Stims were given 500 µg P (SC) 4 h prior to testing. In addition, female subjects received 0.9% saline (1 cc/kg, SC) 30

min prior to testing. Females were tested in clear Plexiglas chambers, by a trained observer who was blind to the experimental condition of the subjects. Females were allowed 5 min to habituate to the testing environment before presentation of Stud. Studs were given brief access, in a separate Plexiglas chamber, to the fully receptive Stims, to become sexually aroused before exposure to the female subjects. Data collection was terminated once each female subject had received 10 mounts with pelvic thrusting from a sexually vigorous Stud. If a male did not mount, a new male was introduced to replace the first. Receptivity scores were determined by the lordosis quotient (LQ): the ratio of full female lordotic responses to male mounts with pelvic thrusting × 100%. Simultaneously, proceptivity scores and WDS were recorded during this interval. WDS behavior was scored by counting the frequency of WDS during the testing interval and dividing this number by the test duration to achieve a score of WDS/min. Proceptive behaviors included ear wiggles (vibrations of the external ears symmetrically around an erected position for 1–2 s), and darts and hops (rapid movements with an abrupt halt). The frequency of proceptive behaviors were derived by calculating a composite score of darts and hops, and ear wiggles per minute (21), yielding a score of solicitations/min. Sexual rejection was also assessed by assigning a subjective rejection score between 0 and 3 based on the female's overall defensive response (e.g., kicking, pushing, lying on back, defensive upright, etc.) to the mounting male with a 0 assigned to "no display of rejection," a 1 or 2 to "moderate displays of rejection," and a 3 assigned to "maximal rejection and defensive behavior." All testing was conducted during the middle third of the dark cycle, and results were subsequently analyzed using 2 × 2 analyses of variance (ANOVAs) on each variable, followed by Newman-Keuls comparisons ( $p < .05$ ) using the Kramer method for unequal  $ns$ .

#### *Results*

The effects of stress and surgery on sexual behavior and WDS are presented in Table 1. An examination of WDS results suggests no effect of stress or surgery but a possible interaction between the two. However, the WDS interaction effect failed to reach statistical significance,  $p > 0.05$ . Similarly, there were no statistically significant main effects on WDS. Although inspection of Table 1 suggests that the STRESS females displayed more rejection behavior, more lordosis behavior, and more solicitations than the NO-STRESS females, these effects did not reach statistical significance,  $p > 0.05$ . Furthermore, there was no effect of adrenalectomy on any measure of sexual behaviour, nor was there an interaction between stress and adrenalectomy,  $p > 0.05$ .

#### *Discussion*

These results fail to replicate the findings that chronic psychosocial stress increases both sexual receptivity and proceptivity and decreases sexual rejection (54). That study used subcutaneously implanted estrogen capsules and a high dose of progesterone (500 µg, SC) to induce sexual behavior, whereas the present study used a very low, acute dose of estrogen (0.8 µg, SC) and no progesterone. This suggests that if stress does effect the display of female sexual behavior and WDS, it is not apparent after the administration of acute estrogen alone. It may be that progesterone is required, that estrogen needs to be administered chronically, or both.

Although females show partial receptivity without progesterone, complete sexual responsiveness, including significant

TABLE 1  
SEXUAL BEHAVIOR MEASURES (MEAN  $\pm$  SEM) AND WDS (MEAN  $\pm$  SEM) FOR ESTROGEN-PRIMED FEMALES AS A FUNCTION OF STRESS AND ADRENALECTOMY (ADX)

	WDS	Solicitation	LQ	Rejection
No Stress				
Sham	0.00 $\pm$ 0.00	2.12 $\pm$ 2.12	26.67 $\pm$ 14.98	0.50 $\pm$ 0.34
ADX	0.15 $\pm$ 0.11	0.05 $\pm$ 0.03	14.00 $\pm$ 6.78	0.40 $\pm$ 0.24
Stress				
Sham	0.24 $\pm$ 0.18	3.82 $\pm$ 2.61	38.33 $\pm$ 14.47	0.83 $\pm$ 0.17
ADX	0.09 $\pm$ 0.05	1.02 $\pm$ 0.46	52.00 $\pm$ 21.77	1.40 $\pm$ 0.51

displays of proceptivity, may require the presence of both estrogen and progesterone (12,48). Similarly, the administration of both estrogen and progesterone may be necessary to reveal the effects of stress on sexual behavior.

It is surprising that adrenalectomy had no significant effect on the display of either receptive, proceptive, or rejection behaviors in the estrogen-treated rat. However, the literature regarding the effects of adrenalectomy on female sexual behavior remains controversial with reports of both facilitatory effects [e.g., (10,11,23)] or no effects [e.g., (9,21,48)].

#### EXPERIMENT 1B

The results of Experiment 1A indicate that there is no effect of stress or adrenalectomy on the display of sexual behavior and WDS in ovariectomized females treated acutely with a low dose of estrogen. However, it may be that the effects of stress or adrenalectomy on WDS or sexual behavior are progesterone dependent. Therefore, in the present experiment, WDS and sexual behavior were measured in ovariectomized rats treated with both estrogen and progesterone.

#### Procedure

Female subjects were each injected with 20  $\mu$ g P (SC) immediately following testing in Experiment 1A. After 2 h, each female was injected with 0.9% saline (0.1 cc/kg, SC) and was tested 30 min later for sexual behavior and WDS as described in Experiment 1A. Immediately following testing, females were returned to their home cages and the stress administration was terminated. Results were statistically analyzed as in Experiment 1A.

#### Results

All results for measures of sexual behavior and WDS are presented in Table 2.

*WDS.* Inspection of Table 2 suggests that chronic stress elevated WDS in nonadrenalectomized rats. A significant interaction was found between stress and surgery,  $F(1, 18) = 7.74$ ,  $p = 0.012$ . Subsequent Newman-Keuls tests showed that the STRESS/SHAM group had increased WDS relative to each of the other three groups, which did not differ significantly from each other.

*Proceptivity.* Inspection of the solicitation scores in Table 2 suggests that chronic stress elevated proceptivity in adrenalectomized rats. This was confirmed by a significant interaction between surgery and stress,  $F(1, 18) = 6.02$ ,  $p = 0.019$ . Subsequent Newman-Keuls tests revealed that the STRESS/SHAM females displayed significantly more proceptivity than each of the other three groups, which did not differ significantly from each other.

*Receptivity.* The pattern of results for receptivity were parallel to those for proceptivity. That is, the stressed, nonadrenalectomized animals showed the highest level of receptivity. However, the interaction between stress and surgery failed to reach statistical significance,  $p > 0.05$ . The main effect of stress on receptivity approached statistical significance,  $p < 0.1$ , with the STRESS females displaying higher receptivity scores than the control females. The main effect of surgery was not significant,  $p > 0.05$ .

*Rejection.* Although the main effects of stress and surgery were not significant,  $p > 0.05$ , the interaction between these factors approached significance,  $p < 0.1$ . Paralleling their elevated proceptivity and receptivity scores, the females in the STRESS/SHAM group were least likely to reject the males' sexual advances.

#### Discussion

These results suggest that stress significantly increases proceptivity and WDS in females treated with estrogen and progesterone, and this effect is prevented by adrenalectomy.

TABLE 2  
SEXUAL BEHAVIOR MEASURES (MEAN  $\pm$  SEM) AND WDS (MEAN  $\pm$  SEM) FOR ESTROGEN- AND PROGESTERONE-PRIMED FEMALES AS A FUNCTION OF STRESS AND ADRENALECTOMY (ADX)

	WDS	Solicitation	LQ	Rejection
No Stress				
Sham	0.00 $\pm$ 0.00	3.56 $\pm$ 1.36	41.67 $\pm$ 20.07	0.50 $\pm$ 0.34
ADX	0.03 $\pm$ 0.03	1.99 $\pm$ 0.69	62.00 $\pm$ 8.00	0.40 $\pm$ 0.24
Stress				
Sham	0.24 $\pm$ 0.09	17.26 $\pm$ 4.23	91.67 $\pm$ 5.43	0.00 $\pm$ 0.00
ADX	0.09 $\pm$ 0.00	3.32 $\pm$ 1.07	68.00 $\pm$ 18.55	1.00 $\pm$ 0.45

This replicates previous findings (54) of a facilitation in sexual behavior following chronic stress in females treated with estrogen and progesterone. The blocking of this effect by adrenalectomy indicates that the adrenals or adrenal secretions are necessary for the facilitation of stress-induced proceptivity. The significant interaction between stress and surgery on WDS, and the higher WDS scores of the STRESS/SHAM group, support the hypothesis of 5-HT<sub>2A</sub> involvement in female sexual behavior. Experiment 1B provides the first evidence of a relationship between female sexual behavior and spontaneous WDS.

It is surprising that the effect of stress on sexual behavior and WDS only became apparent after the administration of progesterone. Progesterone possesses anxiolytic properties (42), which could have potentially blocked the behavioral effects of stress. However, other evidence suggests that the effects of stress on serotonin levels are partially dependent on progesterone. Ovariectomized rats pretreated with progesterone and exposed to electric footshock had higher serotonin concentrations than control animals exposed to footshock (29); therefore, it may be that progesterone acts to enhance serotonergic activity at the 5-HT<sub>2A</sub> receptor.

#### EXPERIMENT 2A

It has been observed that, in the male rat, stress inhibits sexual behavior, whereas in the female rat it has the opposite effect. The results from Experiment 1 suggest that the facilitation in female rat sexual behavior seen in the STRESS/SHAM group is likely the result of an interaction between progesterone, the HPA axis and the 5-HT<sub>2A</sub> system. This is supported by the results of a significant increase in WDS in this group, thus reflecting an increase in 5-HT<sub>2A</sub> activity. It has also been noted that males show decreased sexual behavior and increased WDS in response to 5-HT<sub>2A</sub> activation [e.g., (51)]. If it were shown that chronic stress concurrently inhibits sexual behavior and increases WDS, this would strengthen the hypothesis of 5-HT<sub>2A</sub> involvement in the stress-induced inhibition of sexual behavior in males. The present study was designed to test this hypothesis.

#### Stress Procedure

A cage rotation scheme was used to administer stress to the male rats according to a procedure that has been described elsewhere, and was shown to significantly elevate plasma corticosterone levels and disrupt reproduction (47). This stress procedure for males differed from that employed for females in Experiment 1. The psychosocial stress procedure, which has been found to significantly increase glucocorticoids and sexual behavior in female rats (54), has yet to be tested for its effects on glucocorticoids and sexual behavior in male rats.

Animals in the STRESS group received random cage rotation into a new cage with unfamiliar cage mates each day. The number of rats per cage and all other housing conditions remained constant. In the NO-STRESS group, males were also moved into new cages; however, familiarity of cage mates was maintained by transferring all members from one cage together into the new cage. The stress procedure was carried out for 27 days during the middle third of the dark cycle.

#### Aggression Screening

Male subjects were tested for their relative aggression according to a procedure previously described by Taylor and

colleagues (47). This was performed prior to stress administration so that the possible confounding effect of aggressive behavior on corticosterone secretion could be eliminated. Only males displaying equivalent levels of aggression and dominance were selected for the study. Males were paired in a partial round-robin manner for three 5-min sessions over a 1-week period. Each male was allowed to habituate for 5 min in a testing chamber before being placed into a new chamber with one other male. Each was scored for typical offensive behaviors (e.g., lateral attack, chase, biting, piloerection, standing on top), and defensive behaviors (e.g., lying on back, flight, freezing, upright posture). Each rat was tested three times with a new male each time, and at least one of the three opponents was a cage mate. One rat was removed from the study due to illness, thus leaving 33 male subjects. Rats who displayed moderate, but equal, aggression were assigned either to the STRESS group ( $n = 17$ ), or the NO-STRESS group ( $n = 16$ ).

#### Behavioral Testing Procedure

Receptivity was induced in 24 Stims by injection of 10  $\mu$ g EB (SC) 48 h prior to testing and 500  $\mu$ g P (SC) 4 h prior to testing. Both hormones were dissolved in 0.1 cc of peanut oil. On day 28, each male was injected with 0.9% saline solution (1 cc/kg, IP) 30 min prior to testing. Males were then allowed 5 min to habituate to the Plexiglas testing chamber before presentation with a receptive Stim. Upon presentation, the frequency of mounts with pelvic thrusting (mounts), and mounts with pelvic thrusting and penile intromission (intromission) before ejaculation were recorded. In addition, the number of ejaculations, and the latency to mount (ML), intromit (IL), and ejaculate (EL) were recorded as well as the postejaculatory interval (PEI), or time interval between the first ejaculation and the subsequent intromission. WDS behavior was scored by counting the frequency of WDS during the testing interval and dividing this number by the test duration to achieve a score of WDS/min. Males were scored in adjacent testing chambers by a trained observer who was blind to the experimental condition of the subjects. Tests of sexual behavior and WDS were 30 min in duration, and Stims were rotated between adjacent chambers every 10 min to maintain sexual interest of the males. Tests were conducted during the middle third of the dark cycle, and the daily stress regimen was administered immediately following behavioral testing on day 28, and for an additional 6 days. Results were analyzed using an Independent samples *t*-test with a contrast-based error rate set at 0.05. Levene's Test for Equality of Variance was performed on each variable prior to performing *t*-test analyses. Rats that failed to reach ejaculation during the test interval were dropped from the data analyses of mounts and intromissions, and latency scores for animals failing to exhibit a behavior were set to the maximum (1800 s).

#### Results and Discussion

All results are expressed in Table 3 as means and standard errors. Independent samples *t*-tests performed between the STRESS and NO-STRESS groups showed no statistically significant differences on any measure of sexual behavior or WDS ( $p > 0.05$ ). However, on most measures the trend was in the hypothesized direction of stressed males showing impaired sexual performance and increased WDS.

The present results fail to replicate previous findings that chronic stress significantly decreases male sexual behavior (8,45). The reasons for this are not obvious. Furthermore, the

WDS results do not support the hypothesis that stress increases 5-HT<sub>2A</sub> activity in the male rat.

#### EXPERIMENT 2B

In the present experiment, pharmacological manipulation of 5-HT<sub>2A</sub> receptor activity was employed to enhance any potential effect of chronic stress on sexual behavior and WDS. Previous research has shown that the relationship between sexual behavior and WDS is magnified by the administration of a 5-HT<sub>2A</sub> agonist (51). Therefore, in the present experiment, the effects of chronic stress on sexual behavior and WDS were examined following DOI administration.

#### Procedure

Immediately following the behavioral test on day 28 of Experiment 2A, the daily stress regimen was administered and continued until day 34. To induce receptivity, Stims were injected with 10 µg EB (SC) on day 33, and with 500 µg P (SC) 4 h prior to testing on day 35. Thirty minutes prior to testing, males were injected (IP) with freshly prepared DOI (1 mg/cc) dissolved in 0.9% saline. Males were then allowed 5 min to habituate to the Plexiglas testing chamber before being presented with a receptive Stim. Subjects were scored for sexual behavior and WDS in an identical procedure to that of Experiment 2A. Testing was conducted for 30 min, and upon termination, STRESS males received their daily cage rotation, which was continued for an additional 2 days thereafter. Results were subsequently analyzed with an Independent samples *t*-test.

#### Results

Means and standard errors of all variables are shown in Table 4. Statistical analysis revealed that following chronic stress exposure, males displayed significantly fewer ejaculations,  $t(32) = 2.39, p = 0.023$ ; increased mount latency,  $t(32) = 2.39, p = 0.023$ ; and required more intromissions for ejaculation to occur,  $t(15) = 2.17, p = 0.05$ . Stressed males appeared to have a longer intromission latency although this effect did not reach statistical significance,  $p > 0.05$ . It is apparent from Table 4 that chronic stress increased the frequency of WDS that occurred concurrently during sexual behavior testing. This effect was statistically significant,  $t(32) = 2.56, p = 0.015$ .

#### Discussion

The inhibitory effects of chronic stress on sexual behavior are consistent with previous reports in the male rat (5,8,45).

The finding that some, but not all measures are affected, is also consistent with previous reports (5). Comparison of the results of Experiments 2A and 2B suggests that DOI inhibited sexual behavior and increased WDS, and that chronic stress enhanced both effects. This supports previous findings that chronically stressed male rats have increased 5-HT<sub>2A</sub> receptor activity (32).

#### GENERAL DISCUSSION

Taken together, the results from both Experiments 1 and 2 suggest that the stress-induced observed facilitation and inhibition of female and male rat sexual behavior, respectively, and the increased WDS in both females and males reflect increased 5-HT<sub>2A</sub> activity. Evidence that chronic corticosterone treatment significantly increases 5-HT<sub>2A</sub> receptor activity (4,25,28) support the present observation that increased WDS reflects increased 5-HT<sub>2A</sub> activity in response to stress-induced corticosterone secretion. The concurrent effect on sexual behavior may be induced by the same mechanism, with corticosterone secretion increasing 5-HT<sub>2A</sub> activity, which would exert effects on sexual behavior. The effects on sexual behavior can, in turn, be predicted by whether 5-HT<sub>2A</sub> activity is stimulatory, as in the female, or inhibitory, as in the male (22).

The results of Experiment 1B indicate that exposure to chronic stress significantly increases proceptivity and WDS in nonadrenalectomized females pretreated with both estrogen and progesterone. The significant increase in proceptivity, but not receptivity, in the STRESS/SHAM females after progesterone administration, may reflect the differential effects of estrogen and progesterone on these behaviors and the likely possibility that these hormones act on different neural circuits to influence aspects of sexual behavior (48,52).

Because adrenalectomy blocked the enhancing effect of stress on proceptivity, the adrenal response to psychosocial stress may be responsible for the enhancement. It has been suggested that adrenal corticosterone is responsible for the increase in stress-induced receptivity and proceptivity by competitively binding to progesterone receptors (54). Notwithstanding this possibility, the significant increase in WDS evident in the present study suggests an alternative mechanism. Adrenal corticosterone may instead be interacting with the 5-HT<sub>2A</sub> system. Support for this has been demonstrated by an increase in radioactively labeled 5-HT<sub>2A</sub> receptors and WDS after corticosterone administration (4,25,28). These physiological and behavioral changes occur in the absence of any changes in plasma 5-HT/5-HIAA levels, thus indicating that if corticosterone regulates or is otherwise involved in 5-HT<sub>2A</sub>

TABLE 3

MEASURES OF SPONTANEOUS SEXUAL BEHAVIOR (MEAN ± SEM) AND WDS (MEAN ± SEM) FOLLOWING STRESS IN THE MALE RAT

	No Stress	Stress
Ejaculations	1.71 ± 0.31	1.47 ± 0.31
Ejaculation latency	918.94 ± 158.16	1117.18 ± 140.86
Intromissions	7.62 ± 1.24	8.09 ± 1.05
Intromission latency	429.94 ± 161.21	672.94 ± 185.75
Mounts	17.77 ± 4.13	14.55 ± 1.67
Mount latency	348.65 ± 168.93	363.35 ± 144.12
Postejaculatory interval	778.94 ± 165.10	969.29 ± 174.32
WDS	1.23 ± 0.50	1.53 ± 0.51

TABLE 4

MEASURES OF SEXUAL BEHAVIOR (MEAN ± SEM) AND WDS (MEAN ± SEM) FOLLOWING STRESS IN THE DOI-TREATED MALE RAT

	No Stress	Stress
Ejaculations	1.00 ± 0.24	0.35 ± 0.12
Ejaculation latency	1178.12 ± 148.84	1498.76 ± 117.64
Intromissions	8.73 ± 0.74	11.61 ± 1.24
Intromission latency	821.88 ± 173.91	1299.59 ± 174.65
Mounts	16.54 ± 1.83	19.16 ± 3.44
Mount latency	566.76 ± 162.17	1168.94 ± 192.69
Postejaculatory interval	1188.12 ± 162.50	1411.24 ± 150.90
WDS	6.82 ± 1.04	11.25 ± 1.37

activity it does so independently of changes in circulating 5-HT levels. However, because 5-HT<sub>2A</sub> receptor activity in the female rat was not manipulated pharmacologically in Experiment 1, the possibility remains that the effects of stress on female sexual behavior and WDS were mediated by separate mechanisms. Further research is needed to confirm that stress alters female sexual behavior via a 5-HT<sub>2A</sub> receptor mechanism.

The adrenals are hyperactive during the stress response and usually result in the release of numerous adrenal hormones (38), some of which may have effects on sexual activity. For example, adrenal deoxycorticosterone, testosterone, progesterone, or estrogen secretion during stress may combine additively with exogenous estrogen to facilitate proceptivity. Testosterone has been shown to increase female sexual behavior, presumably after being aromatized (53), while deoxycorticosterone has been shown to facilitate sexual receptivity (24). It remains to be determined, however, whether testosterone or deoxycorticosterone have effects on 5-HT<sub>2A</sub> receptor activity.

Results from Experiments 2A suggest and 2B indicate that chronic stress decreases sexual behavior and increases WDS in the male rat, and these effects are likely mediated by increased 5-HT<sub>2A</sub> activity. The stress created by cage rotation did not affect the spontaneous expression of sexual behavior and WDS (Experiment 2A), but did result in physiological changes that become behaviorally apparent upon pharmacological manipulation (Experiment 2B). Presumably, one of these physiological changes was an increase in 5-HT<sub>2A</sub> density. It has also been suggested that the best indicator of chronic stress is both increased corticosterone levels and alterations in behavior, and that some stress paradigms are not sufficiently intense to elicit behavioral changes despite elevations in corticosterone levels (39). It is possible that WDS do not reflect receptor activity under stress. It is also possible that the current paradigm was not sufficiently intense to evoke behavioral changes in WDS and sexual behavior even though HPA axis arousal triggered an elevation in corticosterone levels and concurrent physiological changes. The significance of these behavioral changes after stimulation of the 5-HT<sub>2A</sub> receptor with DOI support this suggestion. Although physiological changes had occurred, the corresponding behavioral changes became apparent only after pharmacological manipulation.

It is possible that the GABA–benzodiazepine system is involved in some effects of stress on sexual behavior. Research

has demonstrated that the GABA–benzodiazepine and serotonergic systems are both involved in the regulation of anxiety and stress (30). Additionally, it has been shown that GABA agonists inhibit while antagonists facilitate male sexual behavior (14). Data suggest that GABA antagonists also facilitate female sexual behavior, and that this effect is dependent on adrenal secretions (13). The role of GABA in the effects of stress on sexual behavior in the present study needs to be further investigated.

Results from the present series of experiments may have human implications. It has been demonstrated in animal models that chronic stress results in biochemical and behavioral changes similar to the symptoms of human depression (8), and that this model responds appropriately to antidepressant and nonantidepressant drugs (41). There have been numerous observations of hyperactivity of the adrenal cortex and excess cortisol secretion in patients with depression (36) that resemble the adrenal hyperactivity and excess secretion of corticosterone in chronically stressed rats [e.g., (8,32)]. Central to the stress response is activation of the HPA axis (1), which has been implicated in the rat model of human depression (8). The HPA axis functions to return the body to homeostasis after a reaction to stress. However, in conditions of chronic exposure to a stressor, there is a failure for the HPA axis to end the stress response, and the result is excess cortisol levels that resemble those in depressed patients (36). Additionally, the behavioral and physiological changes that occur during the general adaptation response to stress parallel the symptoms of depression (18). Therefore, chronic stress and the resulting HPA axis disruption may act as a predisposing factor for depression. These parallels between human and rat HPA axis disruption allow the chronically stressed rat to provide for a reliable model of human depression.

Depression, which has been modeled in the rat using a learned-helplessness procedure, has been shown to induce 5-HT<sub>2A</sub> receptor hypersensitivity and to increase WDS (37). It is possible that the increase in 5-HT<sub>2A</sub>–mediated WDS and changes in sexual behavior observed after exposure to chronic stress reflect an upregulation of 5-HT<sub>2A</sub> receptors.

#### ACKNOWLEDGEMENTS

This work was supported by a grant to B. Gorzalka from the Natural Sciences and Engineering Research Council of Canada (NSERC) and a NSERC Predoctoral Fellowship to L. Hanson. The technical assistance of S. Au Young is gratefully acknowledged.

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