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Conflict behavior and the effects of 8-OHDPAT treatment in rats selectively bred for differential 5-HT_{1A}-induced hypothermia

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Abstract

The high DPAT sensitivity (HDS) and low DPAT sensitivity (LDS) rat lines are the result of selective breeding for differences in the hypothermic response to acute treatment with the 5-HT_{1A} receptor agonist 8-hydroxydipropylaminotetralin (8-OHDPAT). The HDS rats exhibit a much greater hypothermic response than do the LDS rats. The present study examined conflict anxiety-like behavior and the effects of acute challenges with 8-OHDPAT and phenobarbital (PhB) on conflict behavior in HDS and LDS rats. Water-restricted (24-h deprivation) HDS and LDS rats were trained to drink from a tube that was occasionally electrified. The 5-s bouts of drinking tube electrification occurred on a fixed interval (FI) 30-s schedule and were signaled by the presence of a tone. Under this schedule, responding is suppressed approximately 10-fold during the tone-on periods compared to the no-tone periods. After two weeks of training in this repeated measures drink suppression conflict paradigm, the effects of acute challenges with 8-OHDPAT (30–500 μg/kg, SC, +10 min) or PhB (20 mg/kg, IP, +10 min) were determined. In control (i.e., non-drug) conflict test sessions, rats of the HDS line accepted significantly fewer shocks than did rats of the LDS line. Acute treatment with 8-OHDPAT resulted in a modest increase in punished responding (maximum increase: +30–40 shocks/session) in both lines at doses of 60 and 125 μg/kg. Higher doses produced significant general behavioral disruption and substantial reductions in water intake (unpunished responding) in both HDS and LDS rats. Neither the increase in shocks received nor the decrease in water intake produced by these 8-OHDPAT challenges differed between HDS and LDS rats. In both lines, acute PhB treatment resulted in a more dramatic increase in punished responding than did 8-OHDPAT (+55–65 shocks/session) and an increase in water intake. The effects of PhB also did not differ between HDS and LDS rats. These data suggest that the HDS and LDS rats exhibit differences in baseline anxiety-like behavior in the conflict task, but do not differ in their response to acute challenges with PhB or 8-OHDPAT.

Keywords: Anxiety; Barbiturates; HDS rats; 5-HT_{1A} receptors; Anxiolytics; Conflict behavior; LDS rats; 5-Hydroxytryptamine (5-HT); 8-OHDPAT; Serotonin

1. Introduction

5-Hydroxytryptamine (5-HT) neurotransmission, particularly that mediated via 5-HT_{1A} receptors, has been implicated in the etiology of anxiety, depression and other psychiatric disorders [9,27,36]. Early studies using the 5-HT_{1A} agonist 8-hydroxydipropylaminotetralin (8-OHDPAT) as a pharmacological probe suggested that 5-HT_{1A} receptors are important for anxiety-like behaviors [3,12,28,30]. The introduction and use of the 5-HT_{1A} partial agonist buspirone and its chemical relative gepirone in the management of anxiety has implicated 5-HT_{1A} receptors in anxiety states [27]. More recent work by Parks et al. [35] demonstrating an increase in anxiety-like behavior in 5-HT_{1A} knock-out mice has further supported this contention.

Another function that is influenced by 5-HT_{1A} receptors is the regulation of core body temperature. Indeed, one of

Abbreviations: PhB, Phenobarbital; 8-OHDPAT, 8-Hydroxydipropylaminotetralin; IP, intraperitoneal; ANOVA, analysis of variance; ANCOVA, analysis of covariance; FI, fixed interval; 5-HT, 5-Hydroxytryptamine; CSD, conditioned suppression of drinking; SNK, Student Newman Keuls; SC, sub-cutaneous.

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the more pronounced effects of treatment with 8-OHDPAT in the rat is a reduction in body temperature (e.g., Gudelsky et al. [20]). It has been suggested that the 5-HT_{1A} receptors mediating hypothermia might be related to those involved in depression and anxiety [31]. The recent creation of two lines of rats with differential sensitivity to 8-OHDPAT-induced hypothermia [33,34] has made it possible to explore the relationship between 5-HT_{1A} receptors and depression and anxiety. Rats of the HDS (high DPAT sensitivity) line are more sensitive to the hypothermic effects of 8-OHDPAT (0.5 mg/kg, IP) than are rats of the LDS (low DPAT sensitivity) line [31,33,34]. Rats of the HDS line also exhibit increased immobility in the forced swim test [33] and heightened anxiety in some tests [14,19,33] compared to rats of the LDS line. The HDS rats also have increased 5-HT_{1A} receptor binding in limbic cortical brain, but not in the raphe nuclei or the hippocampus [25].

Initial reports on the anxiety-like behavior of HDS and LDS rats revealed differences that were dependent upon task and handling. The HDS rats exhibit greater anxiety-like behavior in the social interaction task [14,19] but not in the elevated plus maze task [19,33]. Although there were no significant differences in non-handled rats, following handling, the HDS rats exhibited greater anxiety-like behavior in the elevated plus maze when compared to the LDS rats [14]. To date, there are no reports on the anxiety-like behavior of the HDS and LDS rats in shock-based conflict paradigms such as the Geller–Seifter [18] or Vogel [41] conflict tasks.

The conditioned suppression of drinking (CSD) conflict paradigm is a repeated measures shock-based conflict paradigm that incorporates elements of the Geller–Seifter and Vogel conflict tasks. This procedure has been extensively used as a pre-clinical screening test for potential anxiolytics [15,29,37]. The CSD paradigm also has been used in studies investigating possible neuroanatomical and neurochemical substrates of anxiety [26,39]. Finally, the CSD paradigm also has been used to investigate the difference in anxiety-like behavior exhibited by the Maudsley reactive and non-reactive rats, another pair of inbred rats that differ in anxiety-like and also depression-like behavior [4–7,32,39].

The present studies were designed to evaluate the HDS and LDS rats in the CSD conflict paradigm. Both baseline (i.e., non-drug) anxiety-like behavior and the effects of acute challenges with 8-OHDPAT were determined. In addition, the effects of an acute challenge with the reference standard anti-anxiety agent, phenobarbital (PhB), were determined.

2. General methods

2.1. Animals

Naïve male HDS (n = 13) and LDS (n = 13) rats from the 16th and 17th generations were obtained from the colony maintained at the Skipper Bowles Center for Alcohol Studies at the University of North Carolina. The HDS and LDS rats range in pigmentation from brown to albino, but the majority of subjects in both lines have dark eyes and a coat that consists of white and brown patches (i.e., hooded). All of the rats used in the present study exhibited this pigmentation feature (i.e., animals with albino or solid brown coat pigmentation were excluded). The rats weighed 200–225 g at the time of arrival at WSU. The animals were quarantined for 4 weeks prior to the initiation of the present studies. In addition, prior to these studies, the animals were repeatedly tested in a spontaneous locomotor activity apparatus and were extensively handled. These locomotor activity tests were conducted one to two times each week for a period of approximately 2 months. The subjects received acute treatments with various doses of 8-OHDPAT (30, 125, 500 μg/kg, SC) or a single dose of amphetamine (1 mg/kg, IP) in conjunction with these locomotor tests. A period of 4 weeks without behavioral testing or any drug treatments immediately preceded the start of the present studies. Throughout the present studies, the animals were housed individually in the AAALAC approved animal facility maintained by the WSU Department of Lab Animal Research (DLAR). In the animal quarters, the lights were on from 0700 to 1900 h, the temperature was 21–23°C and the relative humidity was 40–50%. During the present study, all animals were maintained on a restricted water schedule (see below). Food continued to be available in the home cage. All procedures involving experimental animals were reviewed and approved by the WSU Animal Investigation Committee and followed all applicable NIH and USDA guidelines.

2.2. Apparatus

Conditioned suppression conflict testing was conducted in an apparatus similar to that described by Fontana et al. [16,17]. The testing chamber was a rectangular box with Plexiglas® sides and a metal floor and top. Recessed into one wall was a metal drinking tube; A calibrated (1.0 ml units) length of polyethylene tubing was attached to the metal tube and was used for measuring the volume of water consumed. Programming for the test sessions was controlled by solid state modular programming equipment (Coulbourn Instruments, Lehigh Valley, PA).

2.3. Conflict testing — general procedure

The CSD conflict task combines elements of the Vogel acute conflict task [41] (shock-mediated punishment of a consummatory response) and the Geller–Seifter conditioned conflict task [18] (repeated test design utilizing signaled punishment and non-punishment components). Daily test sessions were 10 min in duration. For the first few sessions, water-restricted (24 h deprivation) subjects were placed in the experimental chamber and were allowed to consume water freely without the shock contingency.

After 1 week (four sessions) of non-shock sessions, the tone/shock contingency was initiated. The 7-s tone-on periods were presented at regular (23-s ISI) intervals to the subjects. During the latter 5 s of these tone-on periods, contact between the floor and the metal drinking tube completed a circuit that resulted in the delivery of a shock (0.40 mA) to the rat. The duration of the shocks received was equal to the duration of the tube contact (less than 200 ms). Shocks were delivered by a Two-Pole Small Animal Shocker (Coulbourn Instruments, Model #E13-02).

In all experiments, subjects were tested individually in 10-min sessions at the same time of day. Conflict testing was conducted 4 days/week (Tuesday–Friday) and free access to water was provided in the home cage on non-test days (Friday night until Monday morning). All subjects achieved stable control values (day-to-day coefficients of variation of approximately 30% for individual rats) for punished and unpunished responding by the end of the second week of conflict sessions with the alternating tone-on:no-tone periods. Baseline (i.e., non-drug) conflict testing was continued for 2 additional weeks before drug treatments were initiated.

2.4. Acute drug challenges

Drug and vehicle challenges were conducted on Thursdays over the course of 7 test weeks. The treatments administered were 20 mg/kg PhB, a range of doses of 8-OHDPAT (30, 60, 125, 250, 500 μg/kg) and vehicle (distilled water). The results of pilot studies in Sprague–Dawley rats had revealed that the 30–500 μg/kg dose range included a no-effect dose (30 μg/kg) as well as a dose that dramatically interfered with the performance in the conflict task (500 μg/kg). A review of the literature revealed that the effects of 8-OHDPAT at these doses were reversed and/or prevented by treatment with the 5-HT_{1A} antagonist compound WAY100635 [2,8,21,24,40]. Thus, the effects were the result of 5-HT_{1A} receptor activation. All treatments were administered 10 min prior to the start of the conflict session. PhB was administered IP; 8-OHDPAT and vehicle were administered SC. The order of doses and treatments administered each week was counterbalanced across the various subjects and test weeks.

2.5. Drugs

PhB sodium was purchased from Sigma (St. Louis, MO); 8-OHDPAT HCl was purchased from Research Biochemicals (Natick, MA). Both drugs were dissolved in distilled water; doses refer to the salts. All treatments were administered in a volume of 1 ml/kg body weight.

2.6. Statistical analyses

The dependent variables in these experiments were the number of shocks received (punished responding) and the volume of water consumed (unpunished responding); the effects of the various treatments on these two variables were analyzed separately. The average value for these measures on Wednesdays and Fridays (drug treatments were administered on Thursdays) served as the measure of non-drug baseline values. These baseline values for punished and unpunished responding were compared using two-way analysis of variance (ANOVA) with repeated measures; main effects were rat lines and test weeks. Paired *t*-tests were used to evaluate the 'net' effects ("net" effect = acute drug [i.e., Thursday] − Wednesday/Friday average) of pre-test challenges with vehicle, individual doses of 8-OHDPAT or PhB in HDS or LDS rats. Dose–response curves for the effects of 8-OHDPAT in HDS and LDS rats were analyzed using 2 × 5 factorial ANOVAs with repeated measures; main effects were rat line and 8-OHDPAT dose. In addition, because baseline behavior can be correlated with the magnitude of the effect attributable to a particular treatment, data on the effects of PhB and 8-OHDPAT challenges were also evaluated using analysis of covariance (ANCOVA). In these ANCOVA analyses, baseline (i.e., Wednesday/Friday average) values for shocks received or water intake were used as the covariate. Post hoc comparisons were made using the Student–Newman–Keuls (SNK) test. In all statistical comparisons, $p < 0.05$ was used as the criterion for statistical significance [38].

3. Results

3.1. Baseline (i.e., non-drug) conflict behavior in HDS and LDS rats

Initially, fluid consumption in the test chamber was dramatically reduced by the shock. After several sessions, however, all subjects learned to consume relatively stable volumes of water during the silent periods and made relatively few and very brief contacts with the tube during the tone-on periods. Table 1 illustrates baseline conflict behavior in the HDS and LDS rats. As can be seen, HDS rats accepted significantly fewer shocks per session than did LDS rats ($F[1,26] = 11.23$, $p < 0.05$). This HDS versus

Table 1
Baseline (i.e., non-drug) conflict behavior in HDS and LDS rats

	HDS line	LDS line
Shocks received (punished responding)	38 ± 5[a,b]	49 ± 8[a]
Water intake (ml) (unpunished responding)	10.5 ± 0.8[c]	11.0 ± 0.8[c]

[a] Values represent the mean ± SEM number of shocks accepted on multiple Wednesday and Friday conflict sessions; values were obtained from 13 subjects.

[b] Values for the HDS rats are significantly different from those of the LDS rats, repeated measures ANOVA.

[c] Values represent the mean ± SEM volume of water consumed (ml) on multiple Wednesday and Friday (i.e., non-drug) conflict sessions; values were obtained from 13 subjects.

LDS line difference did not differ across the various weeks of conflict testing, as evidenced by the fact that both the main effect for test weeks ($F[6,135] < 1.0$, n.s.) and the rat line × test weeks interaction ($F[6,135] < 1.0$, n.s.) were not statistically significant. There was a tendency for LDS rats to weigh less than HDS rats (overall mean ± SEM values; HDS: 418 ± 12 g; LDS: 390 ± 14 g), but this difference was not statistically significant ($F[1,24] = 2.01$, n.s.). There was a tendency for a negative correlation between body weight and baseline shocks received, but this was not statistically significant ($r = -0.12$, n.s.).

Table 1 also illustrates water intake (unpunished responding) during control (i.e., non-drug) test sessions in the HDS and LDS rats. Although LDS rats did consume slightly more water per session when compared to HDS rats, this difference was not statistically significant ($F[1,26] = 2.30$, n.s.). In addition, neither the main effect for test weeks ($F[6,134] = 1.23$, n.s) nor the rat line × test

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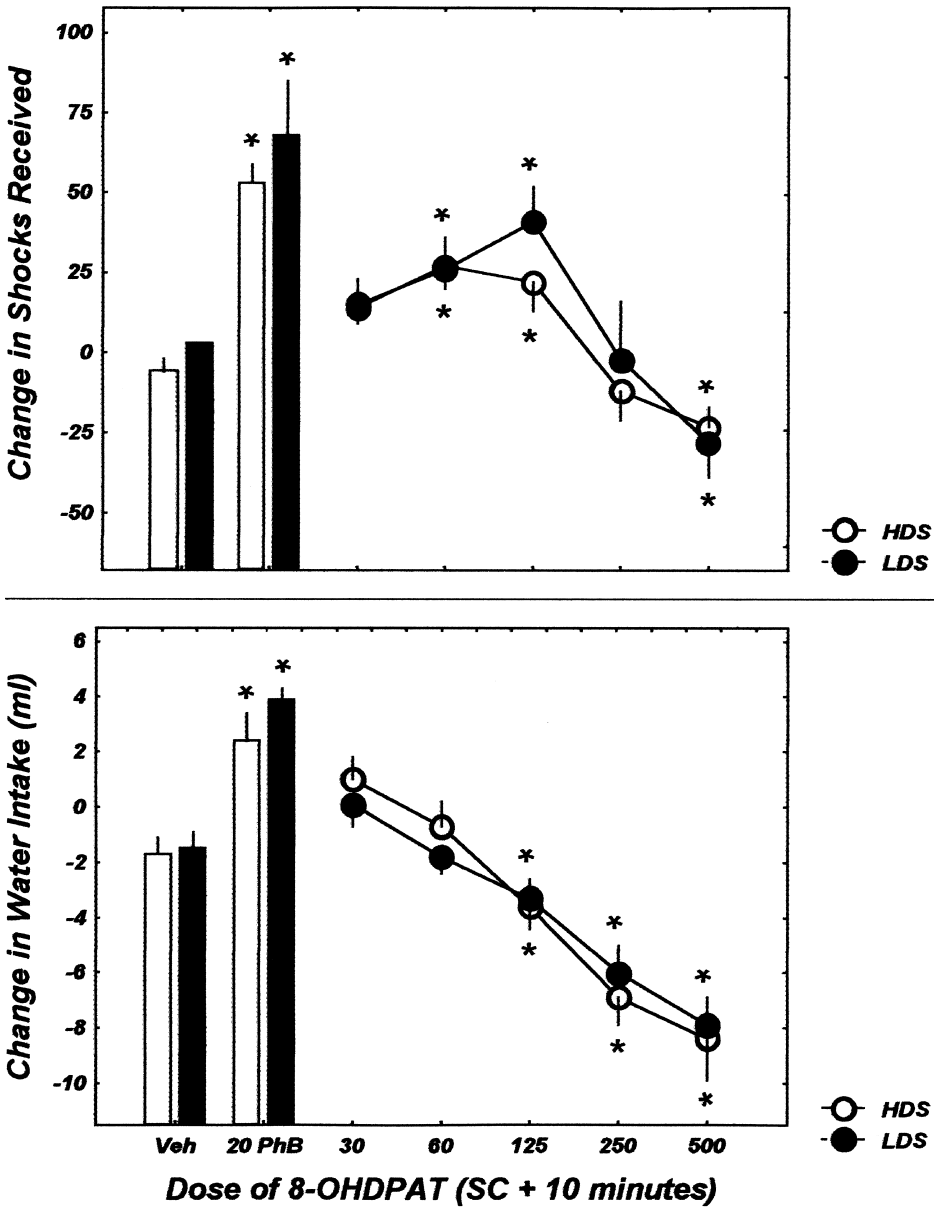

Fig. 1. The effects of acute PhB or 8-OHDPAT treatment on conflict behavior in HDS and LDS rats. The change in shocks received (upper panel) and change in water intake (lower panel) produced by vehicle (distilled water), 20 mg/kg PhB or various doses of 8-OHDPAT (administered IP, 10 min prior to testing) are plotted for HDS (open circles) and LDS (filled circles) rats. Each symbol represents the mean ± SEM from 13 subjects.

* $p < 0.05$: PhB or 8-OHDPAT treatment is significantly different from Wednesday/Friday baseline values, t-test for paired values. There was no significant difference between HDS and LDS rat on any measure (see text for further details).

weeks interaction ($F[6,134] < 1.0$, n.s.) were statistically significant. In contrast to the findings with punished responding, there was a significant negative correlation between body weight and water intake ($r = -0.32$, $p < 0.05$). However, ANCOVA analysis of baseline water intake in the HDS versus LDS rats (using body weights as the covariate) failed to reveal a significant HDS versus LDS rat line difference in water intake ($F[1,23] < 1.0$, n.s.). Moreover, there was no significant HDS versus LDS line difference in water intake when the data were expressed and analyzed as milliliters consumed per kilogram body weight (mean ± SEM values; HDS: 28 ± 3 ml/kg; LDS: 30 ± 4 ml/kg; $F[1,24] = 1.41$, n.s.). Thus, there was no HDS versus LDS line difference in unpunished responding as measured by water intake. It should be noted, for both HDS and LDS rats, the number of tube contacts during the shock component (35–50/session) was relatively insignificant compared to the number of tube contacts during the unpunished component (2000–2500/session). Thus, the volume of water consumed accurately reflects unpunished responding. Finally, it should be noted that for both HDS and LDS rats, responding during the tone-on periods was suppressed approximately 10-fold by the shock (35–50 punished licks/100 total seconds versus 2000–2500 unpunished licks/460 total seconds).

3.2. Effects of acute PhB and 8-OHDPAT treatments

The upper panel of Fig. 1 illustrates the effects of acute treatment with vehicle, 20 mg/kg PhB and various doses of 8-OHDPAT on the change in shocks received in these HDS and LDS rats. As can be seen, vehicle treatment did not dramatically affect shocks received in either line. Acute administration of PhB significantly increased shocks received. Analysis by either ANOVA ($F[1,24] < 1.0$, n.s.) or ANCOVA ($F[1,23]$,1.0, n.s.) revealed that this effect did not differ in HDS versus LDS rats. Acute treatment with 8-OHDPAT significantly increased shocks received at the 60- and 125-μg/kg doses and significantly decreased shocks received at the highest dose examined (500 μg/kg). In both HDS and LDS rats, the magnitude of the increase in shocks received was less than the effect of the 20-mg/kg PhB challenge. Finally, although there was a tendency for a greater anti-conflict effect in the LDS rats, this effect was not statistically significant. Statistically, there was a significant main effect for 8-OHDPAT dose (ANOVA: $F[4,96] = 10.65$, $p < 0.05$; ANCOVA: $F[4,95] = 12.90$, $p < 0.05$). The main effect for rat line was not significant (ANOVA: $F[1,96] < 1.0$, n.s.; ANCOVA: $F[1,95] = 2.80$, n.s.), nor was the rat line × 8-OHDPAT dose interaction (ANOVA: $F[4,96] = 1.10$, n.s., ANCOVA: $F[4,95] < 1.0$, n.s.). Thus, 8-OHDPAT treatment resulted in a modest, but dose-dependent anti-conflict effect in both HDS and LDS rats, although the maximum magnitude of the anti-conflict effect in both lines was less than that produced by the PhB challenge.

The lower panel of Fig. 1 illustrates the effects of acute treatment with vehicle, 20 mg/kg PhB and various doses of 8-OHDPAT on water intake (unpunished responding) in these HDS and LDS rats. As can be seen, vehicle treatment did not dramatically affect water intake in either line. Acute administration of PhB significantly increased water intake; this effect did not differ in HDS versus LDS rats (ANOVA: $F[1,25] < 1.0$, n.s.; ANCOVA: $F[1,24] < 1.0$, n.s.). In both HDS and LDS rats, acute treatment with 8-OHDPAT decreased water intake in a dose-dependent manner, with all doses greater than 60 μg/kg exerting statistically significant effects. The effect of 8-OHDPAT to decrease water intake did not differ in HDS versus LDS rats. Statistically, there was a significant main effect for 8-OHDPAT dose (ANOVA: $F[4,96] = 29.03$, $p < 0.05$; ANCOVA: $F[4,95] = 32.07$, $p < 0.05$); neither the main effect for rat line (ANOVA: $F[1,96] < 1.0$, n.s.; ANCOVA: $F[1,95] < 1.0$, n.s.) nor the rat line × 8-OHDPAT dose interaction (ANOVA: $F[4,96] < 1.0$, n.s.; ANCOVA: $F[4,95] < 1$, n.s.) were statistically significant.

4. Discussion

The HDS and LDS rats exhibited a significant difference in baseline conflict behavior, with the HDS rats accepting significantly fewer shocks when compared to the LDS rats. The greater anxiety-like behavior of the HDS rats in the present study is consistent with reports demonstrating that the HDS rats exhibited greater anxiety-like behavior in the social interaction task [14,19] and, for extensively handled animals, the elevated plus maze [14]. The subjects in the present study were extensively handled prior to even the first CSD conflict test session. Moreover, because the CSD conflict paradigm is a repeated measures task, animals are not behaviorally naïve for most of their behavioral testing. Thus, an evaluation of the influence of handling on CSD conflict behavior in the HDS and LDS rats was not possible in the present study.

The increased anxiety-like behavior of the HDS rats could be the result of increased 5-HT_{1A} neurotransmission in cortical regions of these rats relative to LDS rats. Cortical regions, particularly the frontal cortex, have been implicated in anxiety and depression [10,11]. Knapp et al. [25] have reported increased 5-HT_{1A} receptors in cortical regions in HDS rats. If 5-HT neuron discharge rates were the same and if the rates of pre-synaptic release of 5-HT are comparable in the two lines, the increased number of 5-HT_{1A} receptors in cortical regions might therefore result in greater 5-HT_{1A} neurotransmission effects and increased anxiety-like behavior. Unfortunately, there is currently no information available regarding the activity of 5-HT neurons or the dynamics of pre-synaptic release of 5-HT in HDS versus LDS rats.

Acute treatment with a mid-range dose of PhB (20 mg/kg) resulted in a significant increase in punished respond-

ing and also a significant increase in water intake. These effects are consistent with previous reports on the effects of PhB in this conflict task [17,29]. Moreover, the effects of PhB did not differ in HDS versus LDS rats. Thus, it appears that the HDS and LDS rats exhibit relatively typical responses to acute challenges with typical anxiolytics, even though they exhibit differences in basal anxiety-like conflict behavior.

Acute treatment with 8-OHDPAT resulted in a modest increase in punished responding and a dramatic and dose-dependent decrease in water intake in both HDS and LDS rats. For both lines, the magnitude of the 8-OHDPAT-induced anti-conflict effect was lower than that produced by acute PhB treatment. Moreover, there was no HDS versus LDS difference in anti-conflict effect (increase in shocks received) for 8-OHDPAT treatment, nor was there an HDS versus LDS line difference with respect to the 8-OHDPAT-induced decrease in water intake. Thus, although there was a significant difference in baseline anxiety-like behavior in these HDS and LDS rats, there were no differences in either the anti-conflict effect of 8-OHDPAT or its capacity to reduce water intake (unpunished responding).

The lack of an HDS versus LDS difference in the effects of 8-OHDPAT to increase shocks received or to reduce water intake is in direct contrast to the dramatic HDS versus LDS difference in the hypothermic response to 8-OHDPAT treatment [33,34]. Thus, the present data suggest that both the increase in punished responding and the decrease in unpunished responding are not mediated by those 5-HT_{1A} receptors that are responsible for mediating the hypothermic effects of 8-OHDPAT. The anti-conflict effects of 8-OHDPAT may be mediated by 5-HT_{1A} autoreceptors in the raphe nuclei. Because there are no differences in raphe 5-HT_{1A} receptors in the HDS and LDS rats [25], the lack of difference in the anxiolytic effects of 8-OHDPAT would be expected. The brain regions mediating the 8-OHDPAT-induced reduction in water intake are not known.

The present finding of no HDS versus LDS line difference in the anti-conflict effects of 8-OHDPAT would appear to be inconsistent with the report by Gonzalez et al. [19] demonstrating that 8-OHDPAT administered into the hippocampus produced an anxiogenic effect, and that only in LDS rats. The difference between the present studies and those by Gonzalez et al. [19] likely relates to the site of drug action. Administration of 8-OHDPAT into post-synaptic 5-HT_{1A} regions typically results in anxiogenic-like effects [1,13,22,23] as reported by Gonzalez et al. [19] (at least in LDS rats). In contrast, administration into the raphe nuclei typically results in anxiolytic-like effects [1,13,22,23]. This would suggest that the anti-conflict effects of systemically administered 8-OHDPAT are mediated largely by actions at somatodendritic 5-HT_{1A} autoreceptors located on dorsal raphe nucleus (DRN) neurons, and perhaps median raphe nucleus (MRN) neurons, as suggested above. Future studies examining the behavioral effects of local administration of 8-OHDPAT into the MRN, DRN and various post-synaptic sites in HDS and LDS rats would be of great assistance in clarifying the apparently opposing roles of the pre- and post-synaptic 5-HT_{1A} receptors in anxiety-related behavior.

In summary, the HDS and LDS rats exhibited a significant difference in baseline conflict behavior, with the HDS rats exhibiting greater anxiety-like behavior compared to LDS rats. In contrast, there was no HDS versus LDS difference in the anxiolytic-like effects of acute 8-OHDPAT or PhB treatment. These data are consistent with the hypothesis that different 5-HT_{1A} receptor systems are involved in baseline levels of anxiety-like behavior versus 8-OHDPAT-mediated changes in anxiety-like behavior.

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