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MR/Har and MNRA/Har Maudsley Rat Strains: Differential Response to Chlordiazepoxide in a Conflict Task

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COMMISSARIS, R. L., T. C. McCLOSKEY, G. M. HARRINGTON AND H. J. ALTMAN. *MR/Har and MNRA/Har Maudsley rat strains: Differential response to chlordiazepoxide in a conflict task.* PHARMACOL BIOCHEM BEHAV **32**(3) 801–805, 1989.—The Maudsley Reactive (MR/Har) and Non-Reactive (MNRA/Har) rat strains, selectively bred for differences in open field defecation, have also been shown to differ in their baseline behavior in the Conditioned Suppression of Drinking (CSD) procedure, a second "model" behavior for the study of anxiety and/or emotionality in rats. The present studies were designed to compare the responsiveness of these two strains to the typical antianxiety agent chlordiazepoxide in the CSD paradigm. In daily 10-minute sessions, water-deprived rats were trained to drink from a tube that was occasionally electrified (0.5 mA), electrification being signaled by a tone. Consistent with previous reports, after several weeks of CSD testing, MNRA/Har rats accepted significantly more shocks than did MR/Har rats during control (nondrug) sessions. In both strains, the number of shocks accepted was inversely related to the intensity of the shock used (0.25–1.0 mA), with MNRA/Har rats accepting significantly more shocks than MR/Har rats at all intensities examined. The effects of various doses (1.25–28.4 mg/kg, IP) of chlordiazepoxide were determined in subjects of the MNRA/Har strain at the original training intensity (0.5 mA), while a lower intensity (0.25 mA) was utilized in MR/Har rats. Although punished responding in control (i.e., nondrug) CSD sessions did not differ under these conditions, MNRA/Har rats were found to be more responsive to the anticonflict effects of chlordiazepoxide than rats of the MR/Har strain. This strain difference in anticonflict efficacy of chlordiazepoxide was quite dramatic, with MNRA/Har rats accepting twice as many shocks as MR/Har rats following maximally effective doses of chlordiazepoxide. Low doses of chlordiazepoxide increased water intake slightly, while higher doses decreased water intake. Surprisingly, the chlordiazepoxide-induced depression of water intake was greater in rats of the MR/Har strain. Thus, these Maudsley Reactive and Non-Reactive rat strains, bred originally for their differences in open field behavior, also differ markedly in their responsiveness to chlordiazepoxide in the CSD paradigm. These findings further support the hypothesis that the MR/Har and MNRA/Har rat strains may represent a genetically-based "animal model" for the study of emotionality and/or anxiety.

MR/Har and MNRA/Har Maudsley rat strains Conditioned Suppression of Drinking (CSD) Conflict behavior Anxiety Chlordiazepoxide Benzodiazepines Rate-dependency

THE Maudsley Reactive and Non-Reactive rats were selectively bred by Broadhurst for differences in open field defecation rates (4,5). Reactive (MR/Har) and Non-Reactive (MNRA/Har) Maudsley rats were maintained by Dr. Gordon Harrington (Har) at the University of Northern Iowa from 1965 (17) to 1986 and are presently maintained at the Lafayette Clinic (Detroit, MI). Animals of the MR/Har strain exhibit high levels of open field defecation, while animals of the MNRA/Har strain exhibit low levels of open field defecation. The number of open field defecations has been interpreted as an indicator of "emotionality." These strains have since been used in a variety of studies which continue to support the original contention that these strains differ in their response to novel or stressful stimuli (1, 2, 6, 7, 11, 18).

Although there exist numerous reports on neurochemical (2, 3, 20, 26, 28) and also receptor binding (23, 25, 29) differences between Maudsley Reactive and Non-Reactive rat strains, there are presently few reports on the responsiveness of these animals to antianxiety agents such as the benzodiazepines and barbiturates (8,16). This is particularly surprising considering the extensive use of these agents in the treatment of anxiety.

One animal procedure which has been used in the study of anxiety and/or antianxiety agents is the Conditioned Suppression

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of Drinking [CSD; (7, 9, 10, 12, 19, 22)], a modification of the Geller-Seifter conditioned conflict test (13–15) and the Vogel Acute Conflict test (30). We have recently reported that MR/Har and MNRA/Har rats differ in their control (nondrug) CSD behavior, with MNRA/Har rats accepting significantly more shocks than their MR/Har counterparts (7). We have also shown that MNRA/Har rats exhibit a greater anticonflict response to the benzodiazepine diazepam than do MR/Har rats (8). Although very interesting, it is possible that the phenomenon of "rate dependency" may have affected the difference observed, since these diazepam effects were observed in animals with different "baselines" for punished responding in the CSD.

The purpose of the present study, therefore, was to extend our previous findings regarding baseline CSD differences in the Maudsley strains and to further characterize their responsiveness to benzodiazepines. To this end, we examined the current intensity versus response functions for CSD behavior in MR/Har and MNRA/Har rats and, subsequent to that, determined the effects of the benzodiazepine chlordiazepoxide in these strains at comparable levels of baseline (i.e., nondrug) punished responding.

METHOD

Animals

Female MR/Har (F74) and MNRA/Har (F79) rats from the Harrington/Lafayette Clinic colony at Wayne State University were housed in pairs in a climate-controlled room with a 12-hour light:12-hour dark cycle (lights on 0700–1900 hours). Initially, food and water were available ad lib. Following a two-week accommodation period and continuing throughout the period of behavioral assessment, all animals were placed on the water restriction schedule described below under the Procedure section. Food continued to be available ad lib.

Open Field Testing

Reactivity in a novel environment was assessed in a 1 m × 1 m × 40 cm Plexiglas® chamber. The chamber was illuminated by a light (25 watts, 3.5 foot-candles) positioned directly over the center of the chamber. Extraneous noise was masked using a white noise generator and a ceiling-mounted speaker (40 dB in the center of the chamber). Animals were tested singly in 5-minute sessions between 1000 and 1300 hours. At the end of each session, the total number of fecal boli emitted was counted and recorded, and the test chamber was thoroughly cleaned.

Conditioned Suppression of Drinking (CSD) Testing

Apparatus. Conditioned suppression testing was conducted in an apparatus described previously (7,22). The testing chamber was a rectangular box with Plexiglas® sides and a metal floor and top. Protruding from one wall was a metal drinking tube, to which a calibrated (0.5 ml units) length of polyethylene tubing was attached for measuring the volume of water consumed. Programming for the test session was controlled by solid state modular programming equipment (Coulbourn Instruments, Co., Lehigh Valley, PA).

Procedure. For the first few sessions, water-restricted subjects were placed in the experimental chamber and allowed to consume fluid freely without the shock contingency. After one week of nonshock sessions, the tone/shock contingency was initiated. The 7-second tone periods were presented at regular (22 second ISI) intervals to the subjects. During the latter 5 seconds of these tone periods, contact between the floor and the metal drinking tube completed a circuit which resulted in the delivery of a shock to the rat. The shock intensity used in initial CSD sessions was 0.5 mA; shocks were delivered by a Coulbourn Instruments Shocker (Model No. E13-02).

Initially, the shock inhibited fluid consumption in the test chamber. After several days, however, all subjects learned to consume stable volumes of water during the silent periods and made relatively few and very brief contacts with the tube during the tone. Subjects were tested singly in 10-minute sessions at the same time of day (1300–1500 hr) Tuesday through Friday, and were allowed free access to water from Friday p.m. until Monday a.m. This schedule of 4-day/week testing was maintained throughout the remainder of the study.

Current intensity versus response determinations. In one experiment, the effects of various shock intensities on punished and unpunished responding in MR/Har and MNRA/Har rats were examined. In this study, subjects (n = 6/strain) were trained at the original 0.5 mA intensity for 27 weeks. Over the course of the next 10 weeks, the subjects were tested as previously, except that the shock intensity was varied each week in a counter-balanced design (1.0, 0.35, 0.71, 0.25, 0.5, 0.5, 0.25, 0.71, 0.35, 1.0 mA).

Drug testing. In a different group of MR/Har and MNRA/Har subjects (n = 9/strain), the effects of chlordiazepoxide on CSD behavior were determined. Again, initial CSD training was accomplished using the 0.5 mA shock intensity. As expected, punished responding did not differ between rat strains in the early weeks of CSD testing (MR/Har: 11.5 ± 0.5; MNRA/Har: 12.2 ± 1.0 shocks/session, n.s.; data from Weeks 1–3). After over 20 weeks of CSD testing at this intensity, however, MNRA/Har rats accepted significantly more shocks in control CSD sessions than did MR/Har rats [MR/Har: 18.9 ± 1.9; MNRA/Har: 27.7 ± 2.7 shocks/session, $t(16) = 2.67$, $p < 0.05$; data from Weeks 21–23]. The shock intensity of the MR/Har rats was then reduced to 0.25 mA, which increased punished responding in this strain to slightly greater than that observed in the MNRA/Har strain (28.3 ± 2.9 shocks/session; data from Weeks 25–35). Drug tests were initiated two weeks after this shock intensity adjustment in the MR/Har strain.

Drug tests were conducted on Thursdays and Fridays and used a standard "cross-over" procedure described by McCloskey *et al.* (22). On the Thursday drug tests, half the subjects received the chlordiazepoxide dose under examination and half received saline. These treatments were reversed on the Friday drug test. Thus, each animal served as its own control for the effects of a given drug dose. All rats received all doses of chlordiazepoxide in a randomized manner over the course of the experiment.

Drugs

Chlordiazepoxide HCl was obtained through NIDA and was administered IP 30 minutes prior to CSD testing in distilled water in a volume of 1 ml/kg body weight.

Statistical Analyses

Strain differences in open field defecation were evaluated using unpaired *t*-tests. Strain differences in the time course for baseline CSD performance were assessed using one-way ANOVA with repeated measures (repeated measure = weeks of baseline CSD sessions). Current intensity functions in MR/Har and MNRA/Har rats were evaluated by 2×5 factorial ANOVA with repeated measures (MAIN EFFECTS: Rat Strains, Current Intensities). The effects of single doses of chlordiazepoxide on CSD performance were compared to drug vehicle using *t*-tests for paired values.

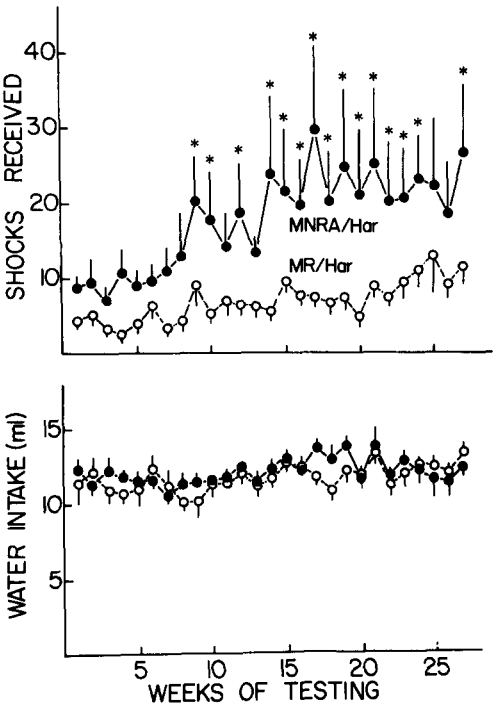

FIG. 1. Conditioned Suppression of Drinking (CSD) behavior of female MR/Har and MNRA/Har rats. Plotted are the number of shocks received (top panel) and volumes of water consumed (bottom panel) by MR/Har and MNRA/Har rats over 27 weeks of CSD testing. Each symbol and vertical line represents the mean ± SEM obtained from 6 subjects. *$p<0.05$, MR/Har versus MNRA/Har at that test week, least significant difference (lsd) test following one-way ANOVA with repeated measures.

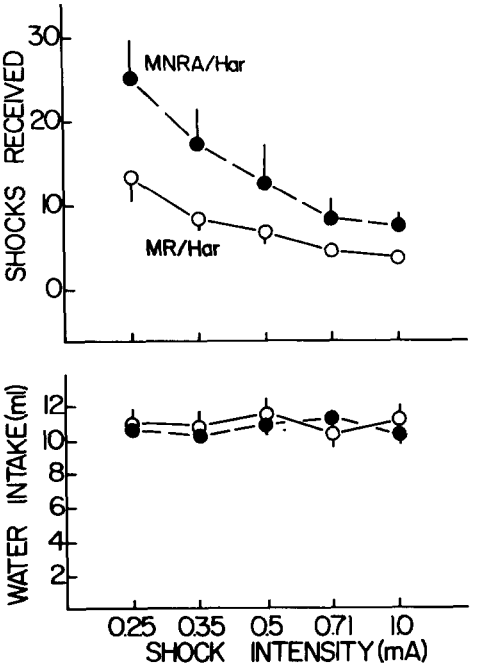

FIG. 2. Intensity versus response function for CSD behavior in female rats of the MR/Har and MNRA/Har strains. Plotted are the number of shocks received (top panel) and the volume of water consumed (bottom panel) in MR/Har (open symbols) and MNRA/Har (filled symbols) rats as a function of shock intensity. Each symbol and vertical line represents the mean ± SEM from 6 subjects.

Dose-response curves for the effects of chlordiazepoxide on CSD behavior in MR/Har and MNRA/Har rats were compared using a 2 × 7 factorial ANOVA with repeated measures (MAIN EFFECTS: Rat Strains, Chlordiazepoxide Doses) applied across the 3.5–28.4 mg/kg dose range. Post hoc comparisons of MR/Har and MNRA/Har rats at individual drug doses were made using the least significant differences (lsd) test. In all statistical comparisons, $p<0.05$ was used as the criterion for statistical significance (27).

RESULTS

As expected, there were significant strain differences in open field defecation [MR/Har: 2.2 ± 0.4; MNRA/Har: 0 ± 0 defecations; $t(10)=5.50$, $p<0.05$]. Thus, the Maudsely rats continue to exhibit strain differences on the behavior for which they were selectively bred.

The top panel of Fig. 1 depicts punished responding in these Maudsley rat strains over the course of 27 weeks of baseline (i.e., nondrug) CSD testing. As in a previous study examining the behavior of these Maudsley rats [Commissaris *et al.* (7)], significant differences between the MNRA/Har and MR/Har strains were not observed in the early weeks of CSD testing, but developed gradually over the course of many weeks of testing. Statistically, this is supported by the significant Rat Strain × Test Week Interaction, $F(26,260)=3.18$, $p<0.05$. Overall, a significant MAIN EFFECT for Rat Strains was also observed, $F(1,10)=6.76$, $p<0.05$, as was a significant MAIN EFFECT for Test Weeks, $F(26,260)=9.16$, $p<0.05$. Post hoc lsd comparisons revealed that MNRA/Har rats accepted significantly more shocks than their MR/Har counterparts at Test Weeks 9, 10, 12, 14–24 and 27.

The bottom panel of Fig. 1 illustrates water intake of MR/Har and MNRA/Har rats over the course of 27 weeks of baseline CSD sessions. On this measure, there were no significant MAIN EFFECTS for either Rat Strains, $F(1,10)<1.0$, n.s., or Test Weeks, $F(26,260)<1.0$, n.s., nor was there a Rat Strain × Test Weeks Interaction, $F(26,260)<1.0$, n.s. It should be noted that in both MR/Har and MNRA/Har rats, the number of punished licks was insignificant when compared to the number of unpunished licks (2500–3000/session); thus, water intake is an accurate reflection of unpunished responding in both strains.

The top panel of Fig. 2 illustrates punished responding as a function of shock intensity used in MNRA/Har and MR/Har rats. As can be seen, increasing the current intensity significantly increases response suppression; this is supported by a significant MAIN EFFECT for Current Intensity, $F(4,40)=6.44$, $p<0.05$. It can also be seen that MNRA/Har rats accepted significantly more shocks than did their MR/Har counterparts at all intensities examined, as evidenced by the significant MAIN EFFECT for Rat Strains, $F(1,10)=4.73$, $p<0.05$. Finally, there was also a significant interaction of Rat Strain × Current Intensity, $F(4,40)=14.79$, $p<0.05$, with the MR/Har versus MNRA/Har difference increasing with decreasing shock intensities.

The lower panel of Fig. 2 illustrates water intake as a function of shock intensity used in MNRA/Har and MR/Har rats. There was no significant MAIN EFFECT for Rat Strain on this measure, $F(1,10)<1.0$, n.s., nor was there a significant MAIN EFFECT for Current Intensity, $F(4,40)<1.0$, n.s. Finally, there was no Rat Strain × Current Intensity Interaction on Water Intake, $F(4,40)<1.0$,

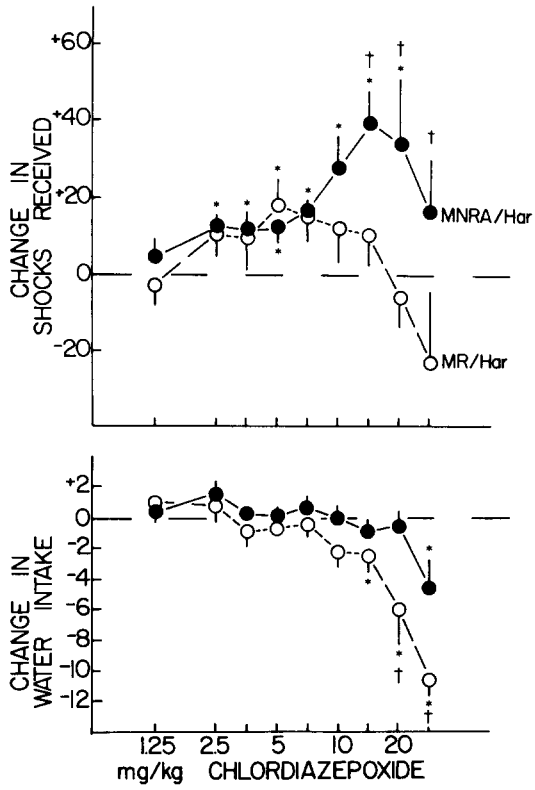

FIG. 3. Chlordiazepoxide effects on CSD behavior in female MR/Har and MNRA/Har rats. Plotted are the change scores (drug-saline) for the number of shocks received (top panel) and the volume of water consumed (bottom panel) by MR/Har (open symbols) and MNRA/Har (filled symbols) rats following administration of various doses of chlordiazepoxide. Each symbol and vertical line represents the mean ± SEM obtained from 9 subjects. *$p<0.05$, chlordiazepoxide dose significantly different from vehicle treatment, paired t-test. †$p<0.05$, MR/Har versus MNRA/Har at that chlordiazepoxide dose, least significant difference (lsd) test following one-way ANOVA with repeated measures.

n.s. Thus, changes in current intensity did not affect unpunished responding in the CSD.

Figure 3 illustrates the effects of various doses of chlordiazepoxide on CSD performance of these MR/Har and MNRA/Har rats. As can be seen, chlordiazepoxide produced an increase in punished responding in both strains. Although the dose-dependent nature of this effect was apparent in both strains, the magnitude was obtunded in the MR/Har strain. Factorial ANOVA revealed a significant MAIN EFFECT for Chlordiazepoxide Dose, $F(6,96) = 2.15$, $p<0.05$. More important, ANOVA also revealed a significant MAIN EFFECT for Rat Strains in the response to chlordiazepoxide, $F(1,16) = 5.53$, $p<0.05$. The Chlordiazepoxide Dose × Rat Strain Interaction was also statistically significant, $F(6,96) = 2.74$, $p<0.05$. Post hoc lsd comparisons of these rat strains at various chlordiazepoxide doses revealed a significantly greater chlordiazepoxide effect in rats of the MNRA/Har strain relative to the MR/Har strain at the 14.2, 20 and 28.4 mg/kg doses.

The lower half of Fig. 3 illustrates the effects of chlordiazepoxide on unpunished responding (water intake) in the CSD paradigm for these MR/Har and MNRA/Har rats. There was a significant MAIN EFFECT for Chlordiazepoxide Dose on the change in water intake, $F(6,96) = 14.80$, $p<0.05$. There was also a significant MAIN EFFECT for Rat Strains on this measure, $F(1,16) = 12.95$, $p<0.05$, with the MR/Har rats exhibiting a greater depression of water intake than MNRA/Har rats. Finally, there was a significant Rat Strain × Chlordiazepoxide Dose Interaction, $F(6,96) = 2.27$, $p<0.05$, for this measure. Post hoc lsd comparisons revealed that the MR/Har rats exhibited a significantly greater reduction in water intake than the MNRA/Har rats at the 20 and 28.4 mg/kg doses.

DISCUSSION

In the CSD, an "animal model" for anxiety, there was a prominent difference between the MR/Har and MNRA/Har rats, with the MNRA/Har rats accepting significantly more shocks than the MR/Har rats. This MNRA/Har versus MR/Har difference developed somewhat gradually over the course of repeated weeks of testing and is consistent with a previous report from our laboratory (7). Once developed, this difference in control CSD performance of MNRA/Har versus MR/Har rats was observed across a wide range of shock intensities. There was no strain difference in water intake in these CSD sessions at any shock intensity examined.

The MNRA/Har rats responded to chlordiazepoxide administration with a robust and dose-dependent increase in punished responding. This is similar to the effects of benzodiazepines and barbiturates on CSD behavior of non-Maudsley (e.g., outbred Sprague-Dawley) rats (9, 10, 12, 19, 22). In contrast, the MR/Har rats exhibited a much less dramatic increase in punished responding following chlordiazepoxide administration.

This greater anticonflict efficacy of chlordiazepoxide in rats of the MNRA/Har strain relative to MR/Har rats is consistent with previous reports on the effects of diazepam (8) and amobarbital (16) in Maudsley Reactive and Non-Reactive rats. The demonstration that this effect is observed even after strain differences in baseline CSD behavior have been "normalized" by changes in shock intensities suggests that the phenomenon of "rate dependency" probably cannot account for the differences previously observed with diazepam (8).

The basis of this MNRA/Har versus MR/Har strain difference in the anticonflict response to benzodiazepines is as yet unexplained. The greater responsiveness of the MNRA/Har rats relative to the MR/Har rats might be related to benzodiazepine binding differences in these strains. Indeed, Robertson *et al.* (25) reported that a British Maudsley Non-Reactive strain exhibits a significantly greater number of benzodiazepine binding sites than did Maudsley Reactive rats. Recently, however, Tamborska *et al.* (29) have reported that there are no significant differences in benzodiazepine binding sites for rats of the MR/N and MNR/N strains (maintained at the NIH breeding facilities). Future studies are planned to characterize benzodiazepine receptors in the MR/Har and MNRA/Har lines.

There was also a prominent strain difference for the effects of chlordiazepoxide on water intake, with higher doses (20, 28.4 mg/kg) decreasing water intake much more dramatically in rats of the MR/Har strain relative to the MNRA/Har strain. The mechanism for this difference is unknown at the present time, although an explanation based on differences in adenosine receptor function in these strains might be considered. Reporting on animals from the NIH colony, Marangos *et al.* (23) have recently demonstrated that the Maudsley Reactive (MR/N) rats have significantly more adenosine receptors (^{3}H-cyclohexyladenosine binding sites) in the cerebellum than do Non-Reactive (MNR/N) rats. In non-Maudsley (i.e., Sprague-Dawley) rats, we have found that the adenosinergic agonists do not exhibit significant anticonflict effects, but do produce decreases in water intake (21). Since benzodiazepines effectively block adenosine uptake [see review by Phillis (24)], the greater depression of water intake in the MR/Har relative to MNRA/Har rats following chlordiazepoxide administration may

relate to increased adenosine receptor activation in MR/Har rats. Again, however, adenosine receptor number and affinity have yet to be determined in MR/Har and MNRA/Har rats.

In summary, the MR/Har and MNRA/Har rat strains, bred originally for their differences in open field behavior, also differ markedly in their performance in the CSD paradigm. These strain differences include not only baseline behavior in the CSD, but also altered responsiveness to benzodiazepines as well. These findings further support the hypothesis that the Maudsley MR/Har and MNRA/Har strains may represent a genetically-based "animal model" for the study of emotionality and/or anxiety.

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