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Antipanic Drug Treatments: Failure to Exhibit Anxiolytic-Like Effects on Defensive Burying Behavior

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BEARDSLEE, S. L., E. PAPADAKIS, D. J. FONTANA AND R. L. COMMISSARIS. *Antipanic drug treatments: Failure to exhibit anxiolytic-like effects on defensive burying behavior.* PHARMACOL BIOCHEM BEHAV **35**(2) 451–455, 1990.—Although the Defensive Burying paradigm has been used as a behavioral "model" for the study of anxiety and/or antianxiety agents, the effects of chronic treatment with antidepressant agents (i.e., "antipanic" agents) have not been examined in this paradigm. The present study examined the effects of two antianxiety treatments on this behavior: 1) acute treatment (30-minute pretreatment) with the benzodiazepine anxiolytic chlordiazepoxide and 2) chronic treatment (twice daily for 7–12 weeks) with the antipanic agents imipramine (IMI), desipramine (DMI) or pargyline (PARG). Prior to testing, female Sprague-Dawley rats were placed in a 40 × 30 × 40 cm Plexiglas® chamber containing clay bedding material (5 cm deep) for 30-minute periods on each of four consecutive days. On the fifth day, a wire-wrapped prod was placed at one end of the chamber. Rats were placed in the chamber individually and a 3 mA shock was delivered upon contact with the prod. Defensive Burying behavior (i.e., the moving of bedding material toward or over the prod) was recorded for 15 minutes postshock. In a dose-dependent manner, acute treatment with chlordiazepoxide reduced the frequency of occurrence of burying behavior, increased the latency to initiation of burying, and decreased the duration of burying. In contrast, chronic treatment with IMI, DMI, or PARG failed to exhibit anxiolytic-like effects on any measure of Defensive Burying. These data suggest that the Defensive Burying paradigm may not be an "animal model" for the study of panic disorder and potential antipanic agents.

Defensive burying Chlordiazepoxide Anxiety Panic disorder Conflict behavior Antipanic Imipramine Desipramine Pargyline

THE results of recent studies by Treit and others (2, 27–32) suggest that the Defensive Burying paradigm may serve as a behavioral "model" for the study of anxiety and/or antianxiety agents. The basis for this hypothesis stems from their findings with numerous traditional and novel anxiolytics: diazepam, chlordiazepoxide, pentobarbital and buspirone each significantly decreased the frequency of occurrence and also the duration of burying behavior (2, 27–29, 31, 32).

Panic disorder is a serious anxiety disorder characterized by unexpected and recurrent panic attacks often leading to agoraphobia and restricted lifestyles. As such, panic disorder is classified as an anxiety neurosis different from generalized anxiety disorder (7). The results of pharmacological studies also support this distinction between generalized anxiety disorder and panic disorder. In the 1960s, Klein and co-workers reported that the frequency of occurrence and the intensity of spontaneous panic attacks could be reduced by chronic treatment with tricyclic antidepressants (TCAs), a treatment which did not affect background anxiety (16–18). Conversely, traditional benzodiazepine therapy ameliorates generalized anxiety but has little effect on panic attacks (20,23). The antipanic efficacy of TCAs and monoamine oxidase inhibitors (MAOIs) has since been demonstrated by several investigators (14, 15, 19, 22, 24, 25, 33, 34).

Several "animal models" for anxiety have been shown not to be affected by chronic antidepressant treatment (4, 9, 10). However, it has been demonstrated that chronic treatment with antidepressant agents produces time-dependent anticonflict (i.e., "antipanic") effects in the Conditioned Suppression of Drinking (CSD) and Novelty-Suppressed Feeding (NSF) conflict paradigms (3, 8, 11–13). Although acute treatment with imipramine has been reported to decrease Defensive Burying (5,6), studies examining the effects of chronic antidepressant treatment on Defensive Burying behavior have not been conducted. The objective of the present study, therefore, was to examine Defensive Burying

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behavior in rats chronically treated with the antidepressants imipramine (IMI), desipramine (DMI) or pargyline (PARG). The effects of acute treatment with the traditional anxiolytic agent chlordiazepoxide were also determined.

METHOD

Subjects

The subjects were female Sprague-Dawley rats (225–250 grams) from Charles River (Cambridge, MA), housed in groups of 4 or 5 in climate-controlled rooms (lights on 0700–1900 hours), with food and water continuously available throughout the experiment. Subjects were tested for Defensive Burying behavior only once.

Apparatus

The test apparatus, similar to that described by Treit (29) and Beardslee *et al.* (1), was a 40 × 30 × 40 cm Plexiglas® chamber. The floor of the chamber was covered with clay bedding material (5 cm deep). In the center of one wall of the chamber, 2 cm above the level of the bedding material, was a small hole (diameter = 0.5 cm) through which a wire-wrapped prod could be inserted.

Procedure

Habituation and testing sessions were conducted between 1000 and 1500 hours using the procedure described by Beardslee *et al.* (1).

Habituation sessions. Animals were placed in groups of four into the chamber for 30-minute sessions on each of four consecutive days. The wire-wrapped prod was not in place during these sessions.

Testing sessions. On the fifth day, prior to testing, the wire-wrapped prod was inserted through the wall to protrude 6 cm into the chamber. Animals were placed in the chamber individually in Defensive Burying testing sessions. Upon contact with the wire-wrapped prod (usually with the paw or mouth), the animal received a 3 mA shock for the duration of contact with the prod (less than 1 second). Animals which did not make contact with the electrified prod within 15 minutes (less than 5 percent) were removed from the chamber. Only animals which received shock were included in the analyses.

The animals were observed for 15 minutes after shock administration by one of two trained and blinded observers. Three parameters were monitored in this period: 1) the presence or absence of burying behavior (directing bedding material toward the prod), 2) the latency from prod contact to the initiation of burying behavior and 3) the duration of burying behavior.

Drug administration—Acute chlordiazepoxide effects in naive rats. Thirty minutes prior to Defensive Burying testing, the subjects received 0, 3.5, 5, or 7.1 mg/kg chlordiazepoxide, IP. Clordiazepoxide was dissolved in saline and administered in a volume of 1 ml/kg. These doses were selected because pilot studies had indicated they exert an effect on Defensive Burying behavior without producing sedation, as measured in locomotor activity studies (Commissaris *et al.*, unpublished).

Drug administration—Chronic antidepressant effects. The effects of chronic treatment with IMI (2.5 mg/kg, b.i.d.), DMI (5 mg/kg, b.i.d.) or PARG (15 mg/kg, b.i.d.) were determined in separate experiments, with each experiment having its own control (chronic saline). Subjects in the chronic treatment studies received IMI, DMI, PARG or saline treatment (IP, twice daily at 0800 and 2000 hr) for 7 (IMI), 8 (DMI) or 12 (PARG) weeks prior to the week of Defensive Burying. On the week of testing, the morning injections were withheld until 30 minutes after the habituation or test session. Thus, Defensive Burying behavior in these chronically treated subjects was evaluated 14–18 hours after their last injection. These chronic dosing regimens and this injection-test interval were chosen because they have been shown to result in significant anticonflict effects in the CSD conflict paradigm (8, 11–13). IMI, DMI and PARG were dissolved in saline and administered in a volume of 1 ml/kg body weight. Subjects which received chronic DMI and chronic PARG treatments had previously been tested in the CSD conflict paradigm [DMI: see (8); PARG: see (13)] through weeks 5 (DMI) and 8 (PARG) of chronic treatment; subjects in the chronic IMI study had no prior experience in the CSD conflict paradigm.

Drug administration—Acute chlordiazepoxide effects in CSD-experienced subjects. Because subjects in two of the chronic antidepressant treatment studies described above had been tested for several weeks in the CSD conflict paradigm prior to the burying experiment, the effects of acute treatment with saline or 7.1 mg/kg chlordiazepoxide were determined in a group of subjects which had received twice daily saline injections and had been tested in the CSD conflict paradigm for eight weeks. CSD testing was suspended for the week of habituation and Defensive Burying in these subjects.

Statistical analyses. In each experiment, the percent of shocked animals exhibiting burying behavior in the two conditions (drug versus vehicle) was evaluated by chi-square analysis for proportions. The effects of various doses of chlordiazepoxide on the latency to initiation and the duration of burying behavior were evaluated using one-way ANOVA, followed by post hoc comparisons using the least significant differences (lsd) test. Data on the latency to initiate burying and the duration of burying in the chronic treatment studies were evaluated using *t*-tests for unpaired values. In all comparisons, $p<0.05$ was used as the criterion for statistical significance (26).

TABLE 1

THE FREQUENCY OF OCCURRENCE OF DEFENSIVE BURYING BEHAVIOR IN NAIVE AND CONFLICT-EXPERIENCED SPRAGUE-DAWLEY RATS TREATED WITH 0.0 (SALINE), 3.5, 5 or 7.1 mg/kg CHLORDIAZEPOXIDE (CDP)

	Chlordiazepoxide Dose (mg/kg)			
	0.0 (SAL)	3.5	5.0	7.1
Naive	100% (9/9)	90% (9/10)	47% (7/15)*	33% (4/12)*
Conflict-Experienced[a]	100% (8/8)	—	—	36% (4/11)*

[a]Eight weeks of CSD conflict testing prior to Defensive Burying. See text for further details.

*$p<0.05$, CDP-treated significantly different from saline-treated subjects, chi-square for proportions.

RESULTS

Well over 95% of the animals in the present study made contact with the shock probe shortly (less than 15 seconds) after initiation of the test session. Table 1 depicts the effects of acute treatment with the anxiolytic chlordiazepoxide on the frequency of occurrence of Defensive Burying behavior. As has been reported by Treit and others for various anxiolytic agents (2, 5, 6, 27–31), both 5.0 and 7.1 mg/kg chlordiazepoxide significantly reduced the frequency of occurrence of Defensive Burying behavior (Table 1).

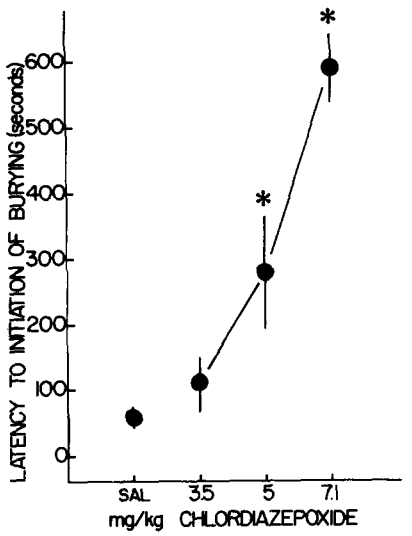

FIG. 1. The effects of chlordiazepoxide treatment on the latency to initiation of Defensive Burying. Each value represents the mean ± SEM obtained from 4–9 subjects. *$p<0.05$, the indicated dose significantly different from saline controls, post hoc lsd test following one-way ANOVA.

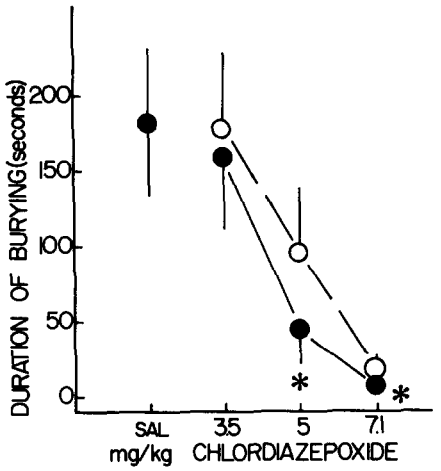

FIG. 2. The effects of acute chlordiazepoxide treatment on the duration of Defensive Burying behavior. Open symbols: data derived from only those animals which exhibited Defensive Burying. Filled symbols: data including those animals which failed to exhibit Defensive Burying (duration = 0 seconds). Each value represents the mean ± SEM obtained from 4–9 (open symbols) or 9–15 (filled symbols) subjects. *$p<0.05$, the indicated dose significantly different from saline controls, post hoc lsd test following one-way ANOVA.

Table 1 also illustrates that the ability of 7.1 mg/kg chlordiazepoxide to reduce the frequency of Defensive Burying is not affected by previous experience in the CSD conflict paradigm.

Chlordiazepoxide treatment increased the latency to initiation of Defensive Burying in a dose-dependent manner, $F(3,25) = 16.24$, $p>0.05$, with doses of 5 and 7.1 mg/kg found to be significantly different from saline (Fig. 1). Figure 2 illustrates that acute chlordiazepoxide treatment also decreased the duration of Defensive Burying in a dose-related manner. When only the animals which exhibited Defensive Burying were included in the analysis (Fig. 2; open symbols), this effect was not statistically significant, $F(3,25) = 1.79$, n.s., because of the variability and relatively small sample sizes at the higher doses of chlordiazepoxide (only 11 out of 27 rats exhibited burying at the 5 and 7.1 mg/kg doses). However, when animals which did not exhibit burying (duration = 0 seconds) were included in the analysis (Fig. 2; filled symbols), a significant effect was observed, $F(3,41) = 7.12$, $p>0.05$. Post hoc lsd comparisons revealed significant effects of 5 and 7.1 mg/kg chlordiazepoxide on this measure of Defensive Burying. Thus, on all three measures of Defensive Burying behavior, chlordiazepoxide exerted significant and dose-related anxiolytic effects.

Table 2 and Figure 3 illustrate the effects of chronic administration of IMI, DMI, or PARG on Defensive Burying behavior. As can be seen in Table 2, chronic treatment with these agents did not significantly reduce the frequency of occurrence of burying behavior in any experiment. Moreover, no chronic treatment significantly affected the time to initiation of Defensive Burying [IMI: $t(11) = 1.12$, n.s.; DMI: $t(4) = 0.82$, n.s.; PARG: no data on initiation]. In the animals which displayed Defensive Burying behavior, chronic treatment with IMI or PARG also failed to affect the duration of burying [IMI: $t(11) = 0.58$, n.s.; PARG: $t(8) = 1.15$, n.s.], while chronic DMI treatment significantly *increased* the duration of burying behavior, $t(4) = 2.86$, $p<0.05$. When data from animals which did not exhibit burying were included in the analyses (duration = 0 seconds), there was still no evidence for an effect of these chronic treatments to decrease Defensive Burying (data not shown). Thus, on all measures of Defensive Burying behavior, chronic IMI, DMI or PARG treatments failed to exert significant anxiolytic-like effects.

DISCUSSION

There exists considerable pharmacological support for the Defensive Burying paradigm as a "model" for anxiety, with Treit and others reporting that numerous benzodiazepines and other antianxiety agents decrease the duration and frequency of burying behavior (2, 5, 6, 27–32). Although Craft *et al.* (5,6) have questioned the specificity of this procedure for anxiolytics, a recent report by Treit and Fundytus (29) suggests that these discrepancies relate to procedural differences used in the Treit *et al.* versus Craft *et al.* studies. Using the procedure described by Treit and co-workers (30), we observed that, in a dose-related manner, acute chlordiazepoxide treatment decreased the percent of animals exhibiting Defensive Burying and decreased the duration of Defensive Burying behavior. These data are consistent with the hypothesis that the Defensive Burying procedure is an effective

TABLE 2

THE FREQUENCY OF OCCURRENCE OF DEFENSIVE BURYING BEHAVIOR IN RATS CHRONICALLY TREATED WITH SALINE (SAL), IMIPRAMINE (IMI; 2.5 mg/kg, TWICE DAILY FOR 7 WEEKS), DESIPRAMINE (DMI; 5 mg/kg, TWICE DAILY FOR 8 WEEKS) OR PARGYLINE (PARG; 15 mg/kg, TWICE DAILY FOR 12 WEEKS)

	Treatment	
	Saline	Drug
Imipramine Study	75% (6/8)	88% (7/8)
Desipramine Study	60% (3/5)	60% (3/5)
Pargyline Study	63% (5/8)	63% (5/8)

No significant saline versus drug differences were found.

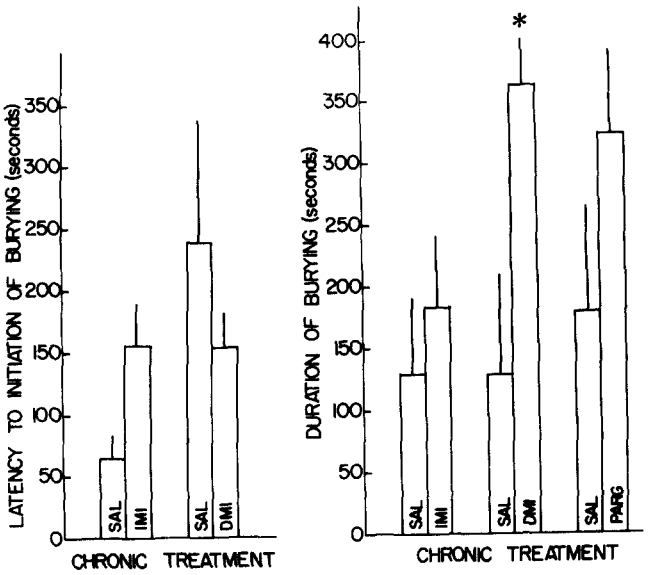

FIG. 3. The effects of chronic treatment with IMI, DMI or PARG on the latency to initiation (left panel) and the duration (right panel) of Defensive Burying. Each value represents the mean ± SEM obtained from 3–7 subjects. Only subjects which exhibited burying were included in the analyses. (See text for details of chronic IMI, DMI and PARG treatments.) *$p<0.05$, duration of Defensive Burying in DMI-treated subjects significantly greater than that of saline-treated controls, *t*-test for unpaired values.

"animal model" for the study of generalized anxiety disorder and traditional antianxiety agents [see review by Treit (27)]. The effect of chlordiazepoxide to decrease the frequency of occurrence of Defensive Burying was not affected by repeated exposure in the CSD conflict paradigm.

Previous studies on Defensive Burying have focussed on the percent of animals exhibiting this behavior and on the duration of the behavior. The present results suggest that the anxiolytic effects of chlordiazepoxide might also be reflected as an increase in the latency to initiation of Defensive Burying. In fact, this measure might be a more powerful indicator of the anxiolytic activity than the duration of Defensive Burying, since the effect of chlordiazepoxide on the duration of burying was not statistically significant unless those animals which exhibited no burying were included in the analysis. Recently, drug-induced increases in the number of contacts with the electrified prod have been used as a measure of the anxiolytic effects of various agents (21,29). Unfortunately, we did not measure the number of electrified prod contacts in the present experiments.

The primary purpose of the present study was to examine Defensive Burying behavior in rats chronically treated with the antidepressants IMI, DMI and PARG. Chronic treatment with traditional antidepressants is effective in reducing the frequency and severity of panic attacks in patients suffering from panic disorder (14–20, 22–25, 33, 34). Moreover, chronic treatment with these antipanic agents has been shown to exhibit time-dependent anticonflict effects in the Conditioned Suppression of Drinking (CSD) paradigm (8, 11–13) and also the Novelty-Suppressed Feeding (NSF) task (3). It has also been reported that acute treatment with imipramine or yohimbine decreases Defensive Burying (5, 6, 32). Thus, it was anticipated that chronic treatment with these agents would exhibit anxiolytic effects in the Defensive Burying paradigm. However, our study revealed no antianxiety effects on any measure of burying behavior following chronic IMI, DMI or PARG treatments. In this regard the Defensive Burying paradigm resembles several other "animal models" for anxiety which have been shown to be unaffected by chronic antidepressant treatment [see (4, 9, 10)].

In summary, chlordiazepoxide administration exerted dose-dependent "antianxiety" effects in the Defensive Burying paradigm—it decreased the percent of animals exhibiting burying, increased the latency to initiation of burying behavior, and decreased the duration of burying. This finding is consistent with its utility as an "animal model" for generalized anxiety and the study of traditional antianxiety agents. In contrast, chronic treatment with antipanic agents (IMI, DMI or PARG) exhibited no anxiolytic effects on any measure of Defensive Burying behavior. Thus, although the Defensive Burying paradigm appears to be a sensitive and effective model behavior for the study of some types of anxiety and antianxiety treatments, the present findings suggest that the Defensive Burying paradigm may not be a good "animal model" for the study of panic disorder and/or potential antipanic agents.

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