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The Effects of Acute Administration of Gepirone in Rats Trained on Conflict Schedules Having Different Degrees of Predictability

N. L. COSTELLO,[1] J. N. CARLSON, S. D. GLICK AND M. BRYDA

Department of Pharmacology and Toxicology, Albany Medical College, Albany, NY 12208

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COSTELLO, N. L., J. N. CARLSON, S. D. GLICK AND M. BRYDA. *The effects of acute administration of gepirone in rats trained on conflict schedules having different degrees of predictability.* PHARMACOL BIOCHEM BEHAV **40**(4) 795–800, 1991.—The anticonflict activity of gepirone, a putative anxiolytic and antidepressant, was examined on three schedules which conditioned the suppression of licking. The novel schedules differed in the degree to which they predicted (signalled) the presentation of a conflict-inducing electric shock. Three doses of gepirone (1.25, 2.5, and 5 mg/kg SC) were evaluated on a predictable, a moderately predictable, and an unpredictable schedule of shock presentation. Gepirone induced a nondose-dependent increase from baseline in punished licking on the predictable schedule on the last two days of a five-day test period. The lowest dose (1.25 mg/kg) of gepirone induced a significant increase in punished licking on the moderately predictable schedule on the last two days of testing. The highest dose (5 mg/kg) induced initial decreases in overall responding on this schedule. However, responding returned to baseline over the course of the four days of testing. When administered to rats trained on an unpredictable schedule of shock presentation, all doses of gepirone induced an initial decrease from baseline. The lowest dose group returned to baseline control response levels over the next four days, whereas the suppressive effects of the higher doses persisted. The initial decrease in responding observed on all schedules may be due to the effects of gepirone on motor functioning. However, the 2.5-mg/kg dose induced a proconflict or anxiogenic effect on the last test day (decreased punished responding alone) on the unpredictable schedule, while inducing an anticonflict effect on the predictable one. The unpredictable schedule is sensitive to detecting decreases as well as increases in punished responding and as such may be a unique conflict model for evaluating novel anxiolytics. The results indicate that the pharmacological effects of gepirone vary depending on the schedule of shock presentation as well as the dose and frequency of administration.

Anticonflict Gepirone Predictability Conditioned suppression of drinking

CONFLICT procedures are commonly used to screen drugs for potential anxiolytic activity. These procedures are based upon the punishment, typically by the means of a brief electric shock, of behavior which is usually rewarded. Anxiolytic drugs release behavior that has been suppressed by such punishment (25,61). The release of the behavior that is suppressed in these models is often predictive of anxiolytic potential in humans (25, 37, 59, 61, 64). These procedures are primarily used to screen traditional anxiolytic drugs such as those of the benzodiazepine and barbiturate classes.

Research that focuses upon the investigation of serotonin's role in the mechanisms of anxiety has found renewed interest. Various novel compounds which have direct effects upon serotonergic systems also possess anxiolytic activity (19, 24, 56). One such compound, buspirone, is an effective antianxiety agent and is currently used as an alternative to benzodiazepine treatment for the management of anxiety (17, 28, 50, 52). Another novel putative anxiolytic agent, gepirone, has been observed to possess potent anxiolytic activity in both preclinical (16,64) and clinical trials (12, 30, 64) and has also exhibited some potential as an antidepressant (11,33). These two compounds are structurally unrelated to and lack the side effects of the benzodiazepines (51, 57, 58). Drugs from this class are partial agonists at the serotonergic receptor subtype 5HT-1A (4, 22, 26, 65). They exhibit high affinity for this subtype at pre- (dorsal raphé) and postsynaptic (hippocampal) neuronal sites (5, 22, 65). Gepirone's anxiolytic profile in animal models has not been extensively investigated. Orally administered gepirone has been shown to possess anticonflict activity (16), and subcutaneous administration of the drug blocked the fear-potentiated startle response (34). In contrast, buspirone's activity has been extensively studied using a wide range of animal tests, yet has yielded inconsistent results (13, 21, 43, 45, 48). The most notable inconsistencies are observed in conflict studies which yield an irregular pattern, owing perhaps to differences in the type of conflict method used, the range of doses, the species of animal used, and the route of administration chosen (6, 8, 16, 29, 39, 48).

It has been suggested that the animal models by which anxi-

[1]Requests for reprints should be addressed to Nancy L. Costello, Ph.D., 300 Crittenden Blvd., Box PSYCH (Department of Psychiatry), Division of Behavioral and Psychosocial Medicine, University of Rochester Medical Center, Rochester, NY 14642.

olytic activity is measured may have become "tailored" to detecting the properties of drugs from the benzodiazepine class (1). In addition, it was proposed that the activity of buspirone may be dependent upon the predictability of the stress used in a particular animal model (1,10). Buspirone has anticonflict activity in the conditioned suppression of drinking (CSD) conflict procedure (39,53). Parallel data on gepirone's activity in this particular conflict model are not yet available. We have developed two novel forms of the CSD type of conflict methodology in order to determine if the manipulation of the predictability (signalling) of the stressor, electric shock, will affect the sensitivity of a conflict model to the anxiolytic potential of gepirone. It was thought that by varying the signalling of the shock onset, we might induce a state of conflict which was very different from the one induced in the traditional CSD procedure. Studies have shown that differences in serotonergic activity develop under predictable and unpredictable forms of shock (2). The purpose of the development of these three schedules was to determine if serotonergic agents, when tested under these three different conflict conditions, might exhibit differences in their ability to induce anticonflict behavior. Previous studies had shown that diazepam, the prototypical benzodiazepine, had anxiolytic activity in each of these schedules, while buspirone at low and high doses exhibited both anticonflict and proconflict activity, respectively, on the schedule with the least amount of predictability (10). The present study evaluated the effects of three doses of gepirone upon three conflict schedules, each having different levels of the predictability of lick-suppressing electric shock.

METHOD

Subjects

Female Long-Evans rats (Blue Spruce Farms, Altamont NY), weighing 225–249 grams at the start of the experiment, were housed three to four per cage and maintained on a twelve-hour light/dark cycle. Animals had ad lib access to food, while water was restricted throughout each of the experiments.

Behavioral Apparatus

Training and testing was conducted in identical Plexiglas cylinders, which measured 30 centimeters diameter × 30 centimeters high. Floors consisted of aluminum grid bars spaced 1.75 centimeters apart. The top of each cylinder was equipped with both a light and a tone. Through one part of the cylinder, a metal drinking tube protruded and was connected to a drinkometer and to a shock source delivered through normally open and normally closed relay contacts, respectively. This area of the chamber was lined on the inside with metal so that the Plexiglas could not serve as an insulator from the shock. The shock source was a Lehigh Valley Electronics solid-state shocker. The entire system was housed in a sound-attenuated chamber and was connected to an Apple IIe computer via a Med Associates Interface.

Procedure

Training. Initially, all animals were placed in the chambers and allowed free access to a five percent sucrose solution which was used as the reinforcer throughout training and testing. Rats were then trained to one of three schedules of shock-induced suppression of licking. Shocks of 0.35 mA lasting 1 s were delivered according to the particular schedule of shock presentation to which the subject had been randomly assigned. Shock was delivered only when the rat made contact with the drinking tube and completed an electrical circuit. The schedules are described as follows:

Predictable schedule (CSD-like). This procedure was based upon the conditioned suppression of drinking (CSD) paradigm as previously described (36,53). A random-interval schedule of twenty-one seconds was used in which seven-second periods of tone and light were presented. During the first two seconds of tone and light, licks were recorded but not shocked. Shock was delivered for every contact made with the drinking tube during the last five seconds of the tone and light period. This schedule was considered to produce a situation that is highly predictive of conflict periods in that the tone/light combination predicts shock one-hundred percent of the time.

Moderately predictable schedule (MOD). This procedure was developed in order to reduce the predictability of the shock presentation. Twenty-four nonshock and twenty-four shock (signalled with tone and light) periods were presented alternately during a ten-minute period. Each of the two five-minute blocks was divided into twelve nonshock (150 seconds) and twelve shock components (150 seconds). The length of each individual component was randomly assigned and was either 5, 10, 15, or 20 s in length. All shock components were accompanied by the presentation of a tone and light which remained on throughout the duration of that component. Shocks were presented on a random-ratio schedule of four (RR4), so that on average, only every fourth lick made by the subject was shocked. This was done in order to make the shock presentation less predictable than that found in the traditional CSD, such that the tone/light combination occasionally predicts shock.

Unpredictable schedule (UNP). This method was developed to substantially diminish the predictability of the presentation of shock. The schedule of nonshock and shock presentation was exactly the same as that of the Moderately Predictable (MOD) schedule, with the exception that the tone and light no longer signalled the shock component. This was done to develop a situation in which there would be very little in terms of cues that would allow the animal to discriminate between nonshock and shock periods. Most of the cues, with the exception of the shock itself, are associated with both components of this schedule. However, some degree of predictability still exists with this schedule since a shock tends to "predict" the possibility that a second shock is forthcoming.

All rats were trained and tested during ten-minute sessions until stable baselines were obtained consistently for a one- to two-week period. Stability criteria were determined by no change which was greater than ten percent from day to day. The response acquired during both shock and nonshock components is stable for each of the three schedules. For each of four consecutive days, all subjects were injected subcutaneously behind the neck with saline vehicle fifteen minutes prior to a ten-minute testing session. The injection volume was 1 mg/kg. The average number of licks on the last three days of testing served as the animal's baseline for each respective component (nonshock or shock component). Subjects were matched on the basis of licking on the shock component and assigned to one of three dose groups (1.25, 2.5, and 5 mg/kg SC). For the next five days, subjects were injected subcutaneously with their appropriate dose of gepirone fifteen minutes prior to a ten-minute test session. On the subsequent sixth day of testing, subjects were once again injected with saline vehicle fifteen minutes prior to testing.

Drugs

Gepirone (Bristol Myers) was dissolved in 0.9 percent normal saline. Injections of gepirone were made subcutaneously

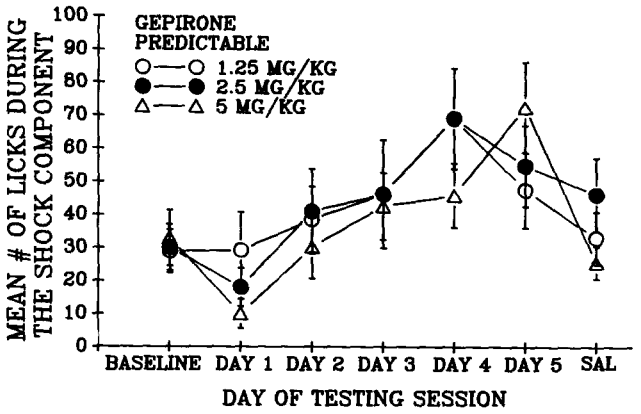

FIG. 1. Data represent the mean (±S.E.M.) number of licks made during the shock component on the CSD-like predictable schedule. Data were collapsed across three dose groups, 1.25, 2.5, and 5 mg/kg (n's = 9). Significant increases in shock component licking were observed on days 4 and 5 of drug testing (Newman-Keuls multiple comparisons $p<0.05$). Drug administered 15′ prior to the session.

(SC) in the back of the neck fifteen minutes prior to testing. The injection volume was 1.0 mg/kg, and the vehicle was 0.9 percent normal saline.

RESULTS

Conditioned Suppression of Drinking Predictable Schedule

Figure 1 represents the mean number of shock component licks made by each group on the saline baseline day and on each of five consecutive drug testing days. Split-plot ANOVA with dose group and test day as variables revealed a significant main effect of day of testing, $F(5,115)=10.27$, $p<0.001$. Repeated-measures factorial ANOVA and Newman-Keuls tests for multiple comparisons were performed on data collapsed across dose groups. Results revealed that gepirone had an anticonflict effect in that it significantly increased from baseline the number of licks made during the shock component on the last two days of testing (days 4 and 5), without affecting responding on the nonshock component.

Similar analyses were conducted on licking during the nonshock component. Main effects of dose group, $F(2,23)=6.698$, $p<0.005$, test day, $F(5,115)=16.948$, $p<0.001$, and a significant interaction, $F(10,115)=2.37$, $p<0.01$, were observed. Further analysis revealed that the 2.5-mg/kg dose of gepirone decreased the number of nonshock licks made on the first three days of drug testing, but not on the last two days, where the drug exhibited anticonflict activity. However, the 5-mg/kg dose did significantly decrease from saline baseline nonshock licking on each of the days of testing with the drug. The lowest dose of the drug, 1.25 mg/kg, did not affect licking on the nonshock component on any of the days tested.

A sixth day of testing in which saline was administered was added to the analysis. Split-plot ANOVA revealed a main effect of test day, $F(6,138)=8.563$, $p<0.001$, and repeated-measures ANOVA collapsed on dose with Newman-Keuls multiple comparisons revealed that there was a significant decrease in shock component licks from the last two days of testing and no difference from baseline. This indicates that subjects' responding returned to baseline when the vehicle was administered on the last day of testing.

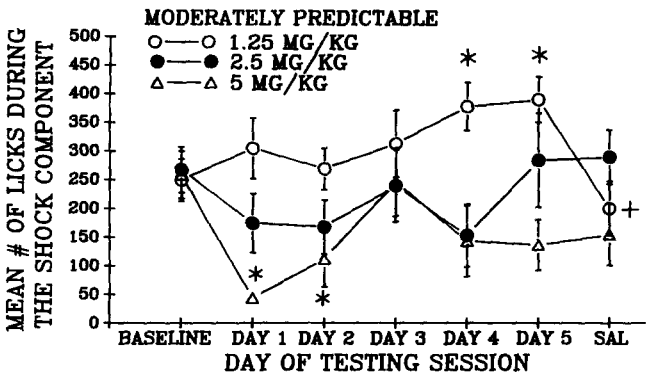

FIG. 2. The effects of three doses of gepirone (1.25, 2.5, and 5 mg/kg, n = 9) upon the MOD predictable schedule are illustrated. Mean (± S.E.M.) number of shock component licks on baseline and 5 days of drug testing and on a sixth day with saline administration (SAL). Gepirone at a dose of 1.25 mg/kg induced an anticonflict effect on days 4 and 5 of testing. Higher doses of the drug either had no effect (2.5) or initially decreased overall licking. Asterisks (*) indicate significant differences from saline baseline, $p<0.05$. Crosses (+) represent significant differences from days 4 and 5, $p<0.05$. Drug administered 15′ prior to the session.

Moderately Predictable Schedule

The effects of gepirone on punished behavior in rats trained on a moderately predictable schedule (MOD) are illustrated in Fig. 2. The results of a split-plot ANOVA revealed main effects of dose group, $F(2,24)=4.88$, $p<0.01$, and of test day, $F(5,120)=3.73$, $p<0.003$, and a significant dose group by test day interaction, $F(10,120)=2.63$, $p<0.006$. Further analysis revealed that the highest dose of gepirone (5 mg/kg) decreased the number of shock component licks on the first and second days of drug testing, but licking returned to baseline levels on days 3 through 5. The 1.25-mg/kg dose had anticonflict effects in that it induced a significant increase in shock component licking by the last two days of testing (days 4 and 5).

Student *t*-tests for paired values were performed to determine if changes in licking were induced during the nonshock component on the days where increases or decreases in shock component licking were observed. Results showed that 5 mg/kg of gepirone also induced a decrease in responding on this component on the first two days of drug testing. In contrast, nonshock component licking was not changed on the last two days of testing for the 1.25-mg/kg dose. This indicates that the effect of 1.25 mg/kg of gepirone on licking is specific for the shock component of this schedule and is therefore a pure anticonflict effect. When drug vehicle (saline) was administered on a sixth day of testing, there was a return to baseline of licking on the shock component for the 1.25-mg/kg dose group.

Unpredictable Schedule

Split-plot ANOVA revealed a main effect of test day, $F(5,125)=12.469$, $p<0.001$, and a significant interaction, $F(10,125)=2.12$, $p<0.03$ (see Fig. 3). Newman-Keuls multiple-comparison tests showed that all doses of the drug induced an initial decrease in licking on the shock component on day one, with the 1.25-mg/kg dose group returning to baseline levels on the other drug test days. With the exception of the third day for 5 mg/kg, the 2.5- and 5-mg/kg doses of gepirone continued to

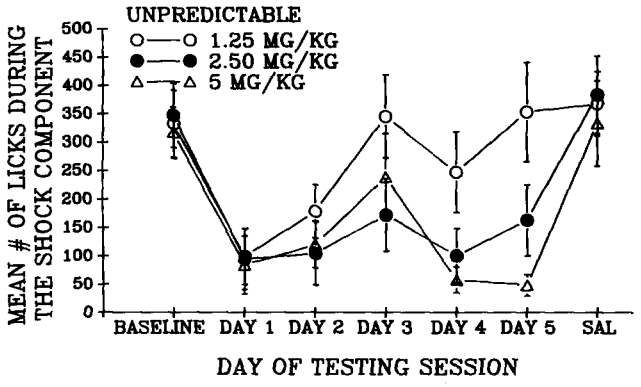

FIG. 3. Data represent the mean (±S.E.M.) number of licks made during the shock component at baseline and after administration of one of three doses of gepirone (n=9 to 10) on the UNP schedule. Higher doses of gepirone (2.5 and 5) induced a significant decrease in shock component licking for each of the five days of testing. Asterisks represent significant differences from baseline, $p<0.05$. Crosses (+) represent significant differences from days 1–5, $p<0.05$. Drug administered 15′ prior to the session.

suppress shock component licking on each of the subsequent days of testing.

Post hoc comparisons on nonshock licking using paired *t*-tests revealed that gepirone also significantly decreased responding on the nonshock component ($p<0.05$). However, on the last day of testing, there were no significant differences from baseline in nonshock licking for the 2.5-mg/kg group. This indicates that this drug induces "proconflict effect" (decreased punished responding alone) at this dose. When saline vehicle was administered on day six of testing the subjects licking, in the higher dose groups, returned to baseline levels.

It should be noted that environmental cues become associated with both the nonshock and shock components of the unpredictable schedule and are thus all part of the same stimulus complex. Thus it is not surprising to observe that gepirone affects licking on both components, even though licking is suppressed to a larger degree on the shock component relative to the nonshock component at baseline. The proconflict effect may be more readily observed at doses of the drug between 1.25 and 2.5 mg/kg, which may differentially affect punished responding while sparing unpunished responding.

DISCUSSION

Anxiety manifested in humans is characterized by a wide range of symptoms (14,23). Preclinical screening of potential anxiolytic drugs requires the use of animal models. Recently, a great deal of controversy has developed about the reliability of these models as screening procedures for novel drugs such as gepirone and buspirone. Many questions have been raised in response to the fact that these drugs are clinically active anxiolytics, yet are inactive in some of the typical screening tests (1,8). It has been suggested that the models in current use have become "tailored" to detecting the anxiolytic properties of the benzodiazepines (1,3). It has been further suggested that drugs like buspirone may be more effective in anxiety associated with unpredictable stressors, which may be analogous to depressive anxiety (1,18).

The present study used three conflict techniques to evaluate the ability of punisher predictability to affect the anticonflict profile of the buspirone analogue, gepirone (formerly MJ-13805). Gepirone is a partial agonist at the serotonergic receptor subtype 5HT-1A (5, 22, 26, 65). The drug has been shown to have anticonflict activity in other conflict models, and this activity is probably associated with the drug's effect upon serotonergic systems (16,64). Three schedules of shock presentation were designed to vary the signalling (prediction) of conflict-inducing electric shock. Theoretically, a predictable type of stressor should have less impact on the subject since it is always associated with cues that signal the absence of the stressor (54). Studies have shown that predictable and unpredictable uncontrollable shock can differentially influence brain norepinephrine and serotonin systems as well as the responsiveness of other physiological systems such as the immune system (2, 44, 60). We have developed these novel schedules to test whether different levels of conflict can be induced with different levels of stressor predictability, and whether this potential difference will influence the anticonflict activity of drugs tested under these conditions. Recent studies conducted in this laboratory indicated that buspirone induced biphasic effects on punished responding on a schedule designed to diminish the salience of the cues predictive of conflict-inducing shock [i.e., an unpredictable schedule of shock presentation (UNP)] (10). A low dose of buspirone induced anticonflict effects (increased punished responding) while a high dose of the drug induced proconflict effects (decreased punished responding). The drug was without activity on the two other schedules with varying degrees of predictability (CSD-like and MOD).

The results of the current study indicate that gepirone also exhibits anticonflict activity which is dependent upon the predictability of the conflict-inducing shock. Gepirone induced an increase in punished responding (anticonflict) on the CSD-like predictable schedule. This effect was observed on the last two days of five days of drug testing. This suggests that gepirone requires repeated administration in order to exert its anticonflict properties. This finding is substantiated by clinical and experimental findings that suggest that drugs from this class require chronic administration to be effective (27, 30, 32, 53, 64). Studies have shown that with chronic treatment, gepirone decreases brain 5HT-2 receptors while agumenting postsynaptic (hippocampal) 5HT-1A receptors (4,15) and that these changes may be correlated with clinical efficacy (5, 64, 65). The lowest dose (1.25 mg/kg) of gepirone also increased the number of licks made during the shock component on the MOD schedule. Again, this effect was only observed on the last two days of testing. The highest dose (5 mg/kg) of gepirone decreased licking on both components of this schedule on the first two days of testing. The 2.5-mg/kg dose had no effect on this schedule. All doses of gepirone decreased responding on the first day of drug testing on the UNP schedule. While subjects in the low-dose group recovered to control baseline levels of responding, the higher doses of the drug continued to suppress responding on each of the days of testing. On the fifth day, no effects on unpunished licking were observed, thus indicating that a proconflict effect was induced with the 2.5-mg/kg dose on the UNP schedule.

Since the literature on gepirone is scarce at this time, comparisons must be made to other 5HT-1A agonists such as buspirone, ipsapirone, and 8-OH-DPAT. A decrease in the number of licks on the shock component may be considered to be a proconflict effect. Previous studies conducted in this laboratory indicated that buspirone induced anticonflict and proconflict effects on the UNP schedule. Similarly, 2.5 mg/kg of gepirone induces a proconflict effect (decreases in shock licking alone) on the last day of testing on the UNP schedule. However, since the stimulus complex is extremely similar for the shock and nonshock components, it is possible that some of the response-decreasing

effects observed on the nonshock component of the UNP schedule may also reflect proconflict activity. This may be particularly true on the last few days of testing when tolerance to other response-decreasing effects should have developed. In contrast to buspirone, gepirone had anticonflict effects on the CSD-like and MOD schedules, and not on the UNP schedule. It may be that the range of doses of gepirone chosen did not parallel the range of doses chosen in the buspirone study. Differences in the potency of these drugs to induce anticonflict or proconflict effects may be related to their relative affinity for different receptors, and to the location of those receptors in the brain. In contrast to buspirone, gepirone lacks activity at dopamine receptors and has somewhat lower affinity for 5HT-1A sites (41,42). It should be considered that gepirone, buspirone, and ipsapirone are not be pure agonists at the 5HT-1A site, since they have been reported to antagonize the behavioral effects of the potent selective 5HT-1A agonist 8-OH-DPAT (49). One concern of these findings may be related to the fact that we used female rats as our subjects. Some studies have suggested that the anxiolytic efficacy of some antianxiety drugs can vary depending upon the time the drug is administered during the estrous cycle. However, it has been shown that the anxiolytic effects of buspirone and other serotonergic agents do not vary according to the time of administration relative to the estrous cycle (20). If the estrous cycle were interfering with our results, we would have expected to have observed diminished or enhanced effects of gepirone across each of the schedules examined over the course of the five days of testing. In addition, other studies have used female rats and determined that buspirone possessed anticonflict activity, which is similar to our current findings with gepirone (39)

Proconflict and anxiogenic effects of 5HT-1A agonists have been observed elsewhere. A recent study reported that orally administered buspirone decreased punished licks and was thus considered to be inactive (6). Increasing doses of buspirone had a dual effect upon performance in a Vogel conflict task (62). This study observed that low doses of orally administered buspirone induced anticonflict effects, whereas higher doses resulted in a reduction in the number of animals approaching the drinking spout. Gepirone, buspirone, ipsapirone, L-5-HTP, and 8-OH-DPAT have been reported to possess anxiogenic activity in other models of anxiety such as the elevated plus maze, the Montgomery conflict test, and the Vogel conflict test (31, 47, 55). High doses of buspirone have recently been reported to decrease rates of punished responding in squirrel monkeys (63). There are some recent clinical findings that suggest that these drugs may have some unpleasant side effects which, in some cases, may be interpreted as anxiogenic (7, 9, 38, 40). Some of these unpleasant effects, particularly those associated with panic attacks, may be related to hypersensitivity of serotonergic receptors (35,46).

Exposure to different types of predictable stress may influence the reactivity of serotonergic system to different degrees (2,60). Differences in the sensitivity of subpopulations of serotonin receptors could result from such conflict-inducing treatments. This may account for the detection of inconsistent results with drugs that act via the serotonin systems. The present study shows that gepirone's pharmacological profile interacts with the predictability of the punisher to produce varying degrees of anticonflict and potentially proconflict effects.

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