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BRIEF COMMUNICATION

Anticonflict Effects of Acute and Chronic Treatments With Buspirone and Gepirone in Rats

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YAMASHITA, S., R. OISHI AND Y. GOMITA. *Anticonflict effects of acute and chronic treatments with buspirone and gepirone in rats.* PHARMACOL BIOCHEM BEHAV **50**(3) 477–479, 1995.—The anticonflict activities of buspirone and gepirone were examined in the Vogel's water licking test in rats. Acute treatment with buspirone induced a significant increase in water licking response, but gepirone showed slightly more marked effect than buspirone. The anticonflict activities of these compounds were potentiated by chronic administration. Especially, gepirone exhibited a dramatically remarkable anticonflict effect. These results suggest that gepirone has a great possibility of promising drug for anxiety.

Buspirone Gepirone Anticonflict Chronic treatment Rat

VARIOUS novel nonbenzodiazepine compounds, which have direct actions on serotonergic systems, have been shown to possess an anxiolytic activity (4,19). One of these compounds, buspirone, is currently used as an alternative to benzodiazepines for the management of anxiety (7,10,12). Gepirone, analogue of buspirone, has also been shown to possess a potent anxiolytic activity in clinical trials (2,8). Effects of buspirone (5,9,14,21) and gepirone (1,3,18) on conflict behavior in animals have been extensively investigated. However, in most experiments only acute anticonflict effect has been examined. In the present study, we examined the effects of acute and chronic treatments with buspirone and gepirone on conflict behavior in rats.

METHODS

Animals

Male Wistar strain rats supplied by Charles River Lab. (Atsugi, Japan) were kept in groups of 4–5 animals each in plastic walled cages (33 × 28 × 17 cm) in a room with a 12 L : 12 D cycle (light on from 0700–1900) at 22 ± 1°C and approximately 60% relative humidity. Animals were allowed free access to food and water until the experiment.

Conflict Test

A drinking conflict procedure described by Vogel et al. (20) was used. The apparatus (Neuroscience Inc., Tokyo, Japan) consisted of a plastic box (25 × 30.5 × 27.5 cm), equipped with grid floor made of stainless steel bar. Through a hole in the wall the rat had access to a stainless steel drinking tube connected with a shock device. During the training period (for 1 day), water-deprived rats were placed in the apparatus for 3 min without stimuli.

For the conflict test, the rats deprived of water for 48 h were placed in the apparatus and allowed to drink water for 5 s without stimuli, then the shock circuit of 0.5 mA was delivered for 1 s. The impulses were released every tenth drink. The number of drinks during 3 min test-period was recorded.

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Drugs

Buspirone hydrochloride and gepirone hydrochloride (gifts from Bristol-Myers Research Institute, Tokyo, Japan) were dissolved in saline. Drugs were given IP 30 min before the experiment in a volume of 1 ml/kg. In the second experiment, drugs were repeatedly administered at the same time (1800) once a day for 7 days, and the conflict test was performed 30 min after the final injection.

Statistical Analysis

Data were analyzed by the Kruskal-Wallis test followed by the Mann-Whitney *U*-test.

RESULTS

Figure 1 shows the effects of acute treatments with buspirone and gepirone on conflict behavior. The baseline number (±SE) of licks without stimuli was 372.5 ± 29.8 during 3 min. The number (±SE) of licks with stimuli after saline administration was 88.9 ± 20.5, and was considered as 100%. Buspirone at 5 and 10 mg/kg significantly increased the number of licks to twice the control. Gepirone at 1-10 mg/kg also increased the number of licks to 2-3 times the control. As shown in Fig. 2, when administered repeatedly for 7 days, these compounds showed marked anticonflict effects. The baseline number (±SE) of licks without stimuli was 351.1 ± 50.8. The number (±SE) of licks with stimuli after saline administration for 7 days was 45.6 ± 9.6, and was considered as 100%. Buspirone at 5 and 10 mg/kg increased the number of licking to 2.4 and 3 times the control, respectively. On the other hand, gepirone at 5 and 10 mg/kg increased to 5.9 and 4.1 times the control, respectively.

DISCUSSION

Although the anticonflict effect of acute treatment with buspirone has been examined in several conflict models, the results are inconsistent among studies. Several investigators have shown only a weak or no anticonflict effect following acute treatment with buspirone in water licking (21) and conditioned water licking tests (9) in rats or lever pressing test in monkeys (6). But, positive results have also been reported in lever pressing test in monkeys (5), Barrett-Witkin test in pigeons (22), and water licking tests (16,17). On the other hand, gepirone administered acutely has been reported to exhibit marked effects on conflict behavior in water licking test in rats (3,16). As a characteristic of long-term administration of buspirone, it is raised that patients treated for a long period have shown no tolerance to anxiolytic effects, no heightened sensitivity (13), and withdrawal syndrome or rebound phenomena (11).

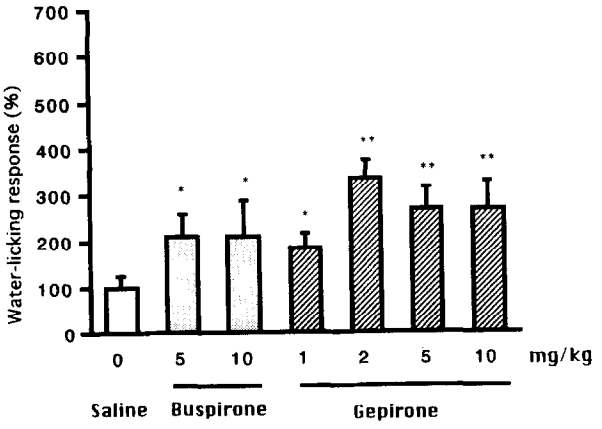

FIG. 1. Anticonflict effects of single administration of buspirone and gepirone in rats. The test was performed 30 min after intraperitoneal injection. Each value represents the mean ± SE of 3-5 animals. The water licking response is expressed as the percent of the control. $*p < 0.05$, $**p < 0.01$; significant difference from the saline group.

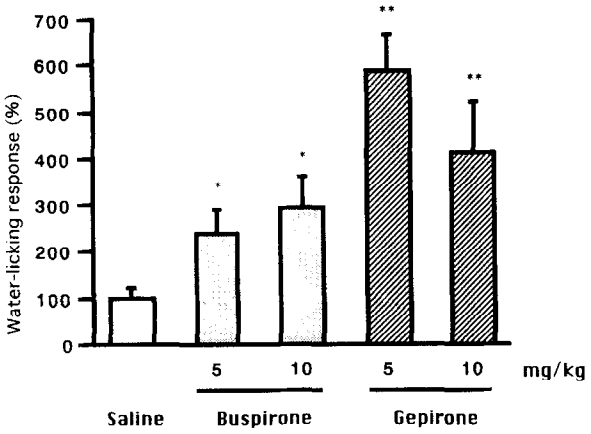

FIG. 2. Anticonflict effects of repeated administration of buspirone and gepirone in rats. The drugs were repeatedly and intraperitoneally (IP) administered once a day for 7 days. The test was performed 30 min after final IP injection. Each value represents the mean ± SE of 3-9 animals. The water licking response is expressed as the percent of the control. $*p < 0.05$, $**p < 0.01$; significant difference from the saline group.

In the present experiment, clear anticonflict effects of both acute buspirone and gepirone treatments were shown, although gepirone showed a more marked effect. This is consistent with the results of Seymour et al. (16), who reported that the gepirone's effect is about twofold larger than the buspirone's effect. Inconsistent results on the effect of buspirone might be due to its comparatively weak anticonflict activity. Both buspirone and gepirone showed more marked anticonflict activities by chronic treatment. This suggests that anticonflict effects of these compounds become more marked by repeated administration. Although a similar result was reported by chronic treatment with buspirone (15), extremely marked effect of chronic treatment with gepirone is the first observation.

On the other hand, it is well known that 5-HT mechanism is involved in both pain-sensitivity and the regulation of ingestive behavior. Since buspirone and gepirone are 5-HT_{1A} agonist, these points have to be considered for studying the anticonflict effect on water licking test with these compounds. But, it is reported that pain sensitivity and drinking motivation with buspirone or gepirone treatments have no changed stimulus threshold of flinch, jump responses by shock in a stepwise manner and free drinking volume (18). In the present experiment, we could not also observed a marked behavioral changes on pain sensitivity and drinking after administration

of these drugs. Therefore, it may be somewhat unnecessary to consider the influence of these drugs on the pain sensitivity and the drinking motivation.

In conclusion, these results suggest that gepirone may be useful as a new antianxiety drug.

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