Comparison of the Anticonflict Effect of Buspirone and Its Major Metabolite 1-(2-Pyrimidinyl)-Piperazine (1-PP) in Rats

Manabu Amano1, Arata Goto1, Atsuko Sakai1, Minako Achiha, née Hara1, Norimitsu Takahashi1, Chiaki Hara2 and Nobuya Ogawa2

1Pharmacology Laboratory, Preclinical Research Laboratories, Bristol-Myers Squibb K.K., 1 Futagoyama, Sakazaki, Kohta-cho Nakata-gun, Aichi 444-01, Japan
2Department of Pharmacology, Ehime University School of Medicine, Shizukawa, Shigenobu-cho, Onsen-gun, Ehime 791-02, Japan

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ABSTRACT—The anxiolytic effects of buspirone and its major metabolite, 1-(2-pyrimidinyl)-piperazine (1-PP) have been investigated with a conflict (shock-induced suppression of drinking) paradigm in rats. Buspirone (10 mg/kg, p.o.) showed an anticonflict activity with a bell-shaped dose-response relationship without any effect on spontaneous water consumption. Higher doses of buspirone reduced the punished response. Diazepam (20 and 40 mg/kg, p.o.) also showed an anticonflict activity in a dose-dependent manner, but animals with diazepam showed an increase in spontaneous water consumption at these doses. On the other hand, 1-PP (6.25–200 mg/kg, p.o.) showed a weak anticonflict activity with a significant effect at 25 mg/kg without any effect on spontaneous water consumption. In the 7-day treatment test, buspirone (5 and 10 mg/kg, p.o.), 1-PP (5 and 25 mg/kg, p.o.) and diazepam (10 and 40 mg/kg, p.o.) did not develop the tolerance to the anticonflict activity. Conversely, the anticonflict activity of diazepam was increased by the repeated treatment. Diazepam (10 mg/kg, p.o.) showed an anticonflict activity without any effect on spontaneous water consumption in this test. These results demonstrated that buspirone clearly exhibited an anticonflict effect similar to that of diazepam in a Vogel-type conflict test, and its real anxiolytic effect may not be always based on 1-PP, the main metabolite of buspirone.

Keywords: Anticonflict effect, Buspirone, 1-(2-Pyrimidinyl)-piperazine (1-PP), Diazepam, Vogel’s conflict test

Buspirone is a novel anxiolytic drug which has been shown to be active in animals and in man. Like the benzodiazepines, buspirone increased punished responses in many conflict tests in pigeons, rats and monkeys (1–4). Also clinically, buspirone has been reported to be effective, similar to diazepam, in relieving anxiety (5). In spite of possessing anxiolytic activity with efficacy similar to that of diazepam, buspirone had no sedative, muscle relaxing and anticonvulsant properties (6, 7).

Various mechanisms have been proposed for the anticonflict activity of buspirone. Unlike diazepam, buspirone does not interact directly with the benzodiazepine-GABA receptor complex (8) but involves an interaction with the 5-hydroxytryptamine1A (5-HT1A) receptor and participation of dopaminergic systems (9–11). However, these hypotheses have been questioned (12). For example, recent evidence suggests that the dopaminergic properties of buspirone are not shared by its active analogue, gepirone (13–15).

A major metabolite of buspirone, 1-(2-pyrimidinyl)-piperazine (1-PP) appears in significant concentrations in rat plasma and brain (16–20). This compound had been found to have an anticonflict activity in rats (17). 1-PP is also a metabolite of gepirone (18), and it may be that 1-PP, rather than the parent compound, may be responsible for the anxiolytic activity (19). In vitro studies suggested that 1-PP binds to α2-adrenoreceptors, but not to serotonin or dopamine receptor sites; in this respect, it is different from its parent compounds (20, 21). Some studies have indicated that α2-adrenoceptor blocking agents have an anticonflict effect. Gardner and Piper (22) reported that piperoxane and yohimbine, α2-adrenoceptor antagonists, have anticonflict effects, while clonidine, an α2-adrenoceptor agonist, had no effect. Recently, Gower and Tricklebank (23) found that an α2-adrenoceptor antagonist including 1-PP have the anticonflict effect.

On the basis of these findings, we investigated the anxiolytic effects of buspirone in comparison with 1-PP in an
anticonflict drinking test following a single administration and 7 daily administrations. We further determined their effects on spontaneous drinking behavior with the same apparatus as used in the conflict procedure.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (211–347 g, Charles River, Japan, Inc., Atsugi) were used. The animals were housed in groups of two per cage under a climate-controlled room (23±2°C and 55±15% relative humidity) with a 12-hr light-dark cycle (lights on 6:00–18:00) and provided food and tap water ad libitum. The rats were used for the experiments following adaptation to laboratory conditions for at least 7 days. Each rat was used only once.

Drugs and administration

Buspirone HCl and 1-(2-pyrimidinyl)-piperazine HCl (1-PP) (Fig. 1) (Bristol-Myers Squibb K.K., Tokyo) were dissolved in distilled water. Diazepam (Cercine tablet, Takeda, Osaka) was suspended in 0.5% carboxymethyl cellulose solution. Drugs were administered orally in a dosing volume of 5 ml/kg body weight. All control animals received an equivalent volume of the appropriate vehicle. Doses refer to the salts used.

Anticonflict activity

The experimental procedure was a modified version of that described by Vogel et al. (24). Rats were deprived of water for 24 hr prior to the first training session (unpunished session) consisting of a 3-min period. Each animal was then placed in a test box (30 x 30 x 28 cm). The test box, which was equipped with a grid floor of stainless steel and a drinking bottle containing water, was enclosed in a semi-sound-proof box. A water bottle was fitted on the middle portion of the outside wall of the test box so that the spout extended 2 cm into the box at the height of 6 cm above the floor. The rat was allowed to explore the drinking spout to drink water. The number of licks at the spout for 3 min was counted without any electric shocks. Only rats making more than 300 licks during an unpunished session were allowed to progress to a further 24-hr deprivation of water.

Twenty-four hours after the unpunished session (48 hr after access to water), the rat was again placed in the test box. The second session (pre-drug punished session) consisting of a 3-min period was started. When the rat completed 20 licks, the first electric shock (2.0 mA, 2 sec duration) was delivered from the grid to its pad. So, the rats received one foot shock every 20 licks. Only rats showing suppression of licking (less than 200 licks) by punishment during the pre-drug punished session were used in the following drug test. If the number of licks did not achieve the above criterion, the electric current of the individual foot shock was gradually increased, ranging from 2.0 to 3.5 mA (0.5 mA interval), until the number of licks decreased to under 200 licks.

Drugs were administered 30 min after the pre-drug punished session. Then the number of shocks taken in the 3-min post-drug punished session was measured at 30 min after the oral administration of buspirone, 1-PP or diazepam. In the repeated administration test, each drug was applied to animals once daily for 7 days, and the number of shocks taken in the 3-min post-drug punished session was measured. The animals showing immobility for more than 6 min were excluded in the post-drug punished session, because many animals usually took only a few minutes to find a drinking spout to begin to drink. Each animal was used only once in these studies.

Spontaneous water drinking test

To examine the influence of test drugs on the baseline of water consumption, the spontaneous water drinking test was performed with the same apparatus as used in the conflict procedure. Rats were deprived of water for 24 hr prior to the first training session consisting of a 3-min period. Only rats making more than 300 licks (15 drinking counts) during the 3-min training session progressed to a further 24 hr deprivation of water. Twenty-four hours after the training session (48 hr after access to water), the rat was again placed in the test box. Thirty minutes after the oral administration of buspirone, 1-PP or diazepam, the water consumption of each rat was measured for 3 min. In the same way, following 7 day-medication of buspirone, 1-PP or diazepam, the water consumption of each rat was measured.

Fig. 1. Chemical structures of buspirone and 1-(2-pyrimidinyl)-piperazine (1-PP).
Statistical analysis

The data were analyzed by the non-parametric type Dunnett's test for multiple comparisons with the vehicle-treated group. The criterion for statistical significance was P<0.05 in this evaluation (two-tailed).

RESULTS

Anticonflict activity

Single administration: Buspirone significantly increased the number of shocks at a dose of 10 mg/kg compared with saline, but the efficacy decreased at higher doses. The dose-response relationship was bell-shaped. Diazepam significantly and dose-dependently increased the number of punished licks at 20 and 40 mg/kg compared with the vehicle. The maximal effect of buspirone was observed at 10 mg/kg, and it was comparable to those of diazepam observed at 20–40 mg/kg. 1-PP (6.25–200 mg/kg), a metabolite of buspirone, also increased punished licks moderately. A significant increase was observed at the dose of 25 mg/kg (Fig. 2).

Repeated administration: Buspirone produced a significant increase in the number of shocks following repeated administration of 10 mg/kg for 7 days. There was no
marked difference between the single and repeated administration groups. Diazepam at 10 mg/kg exhibited a greater anti-conflict effect with the chronic administration than the single one (Fig. 3). 1-PP moderately increased the number of shocks following repeated administration of 25 mg/kg, similar to the single administration, but there was no significant change from the vehicle-administered animals.

**Spontaneous water drinking test**

*Single administration:* Buspirone did not affect the baseline of drinking at doses up to 20 mg/kg, but tended to decrease water intake at 40 mg/kg. 1-PP caused no significant increase in the number of licks at doses up to 200 mg/kg. In contrast to buspirone and 1-PP, diazepam significantly increased the number of licks at doses of 5 to 40 mg/kg (Fig. 4).

*Repeated administration:* Repeated administration of buspirone or 1-PP for 7 days did not change the baseline of drinking at doses of 5 and 10 mg/kg or 5 and 25 mg/kg, respectively, while diazepam significantly increased the number of licks at a dose of 40 mg/kg. There was a notable difference between the single and 7-day administrations with 10 mg/kg of diazepam (Fig. 5).

![Fig. 4. Effects of buspirone, 1-PP and diazepam on the spontaneous drinking behavior in rats. Each bar is the mean value ± S.E.M. of the number of animals shown in the column. One drinking count means 20 licks. * and ** indicate a significant difference from the corresponding control group, P < 0.05 and P < 0.01, respectively.](image1)

![Fig. 5. Effects of repeated administration of buspirone, 1-PP and diazepam on the spontaneous drinking behavior in rats. Each bar is the mean value ± S.E.M. of the number of animals shown in the column. One drinking count means 20 licks. ** indicates a significant difference from the corresponding control group, P < 0.01.](image2)
DISCUSSION

Buspirone is a non-benzodiazepine anxiolytic drug that is clinically as efficacious as diazepam (5, 25 - 27) yet lacks the pharmacological properties of the benzodiazepines which are ancillary to anxiolysis (6, 7, 28). It has been suggested that the ability of buspirone to act as an agonist on the central 5-HT\textsubscript{1A} receptor is important for its anxiolytic activity (10, 11). However, the precise mechanism of action of buspirone is unclear at this time.

It is well known that in Vogel’s conflict procedure, the anticonflict action predicts clinical anxiolytic activity (29), and there have been many reports showing that benzodiazepines with clinical anxiolytic activity were effective in this test. Buspirone has also been reported to increase rates of licking suppressed by punishment in rats, but again, the effects have often been weak and variable (3, 30 - 34). While buspirone is well absorbed, it is subjected to first-pass metabolism. Then, it is eliminated as hydroxylated metabolites, including 5-hydroxybuspirone and 1-PP (16 - 20). The concentration of the latter metabolite in the rat brain after oral administration of buspirone is 15 - 30 times higher than that of buspirone. This finding has led to the hypothesis that 1-PP may contribute to the pharmacological effects of buspirone (16, 17, 20, 35). In fact, some studies indicate that 1-PP has an anticonflict effect (22, 23). The metabolite is 20% as potent as buspirone following oral administration of equiactive doses of each in Vogel’s anticonflict paradigm (17).

On the basis of these findings, the present study was designed to confirm the anticonflict effect of buspirone or 1-PP in the shock-induced suppression of the drinking paradigm (the modified Vogels’ test). The doses of buspirone and 1-PP in this test were selected according to the reports of Gamman et al. (17) and Shimizu et al. (36).

The present study showed that buspirone as well as diazepam clearly exhibited an anticonflict effect in Vogel’s conflict test at 10 mg/kg and over 20 mg/kg, respectively. The relative potency of buspirone was about two times more than that of diazepam. Diazepam showed an anticonflict effect dose-dependently. In contrast, buspirone antagonized the punished suppression of drinking only at a dose of 10 mg/kg; further increasing the doses did not elicit any increase of drinking above the control levels. That is to say, the dose-response relationship of buspirone was bell-shaped. A possible explanation for the lack of effect at the higher doses may be that higher doses (20 and 40 mg/kg) of buspirone elicited the flattened body posture in our experiment, which is one of the 5-HT syndromes. Diazepam produced a significant increase in the number of licks at doses of 5 to 40 mg/kg in the spontaneous drinking test. This result suggests that the effects of diazepam on the primary drive might partly contribute to its anticonflict activity in this conflict model. On the other hand, buspirone failed to facilitate the water consumption. Conversely, this compound tended to decrease it at 40 mg/kg. This fact suggests that the anticonflict activity of buspirone may be primarily due to its anxiolytic effect without the promotion of primary drive. In contrast, all doses of 1-PP (25 - 200 mg/kg) had no significant effect on unpunished drinking, but produced a moderate increase in the mean number of shocks received in the punished drinking test. A significant difference was found at 25 mg/kg of 1-PP, when compared to those of the vehicle-treated animals. These results suggest that 1-PP may not contribute predominantly to the effect of buspirone.

It has been demonstrated that 1-PP preferentially binds to \( \alpha_2 \)-adrenoceptors and has an \( \alpha_2 \)-adrenoceptor blocking activity (23, 37). Using a similar paradigm, Gower and Tricklebank (23) had reported the anticonflict action of 1-PP as well as an \( \alpha_2 \)-adrenoceptor antagonist. In contrast, the \( \alpha_2 \)-adrenoceptor agonist clonidine blocked the anticonflict activity of buspirone. For these reasons, they suggested that the anticonflict effect of buspirone was involved in its \( \alpha_2 \)-adrenoceptor antagonist action. This discrepancy between the 5-HT\textsubscript{1A} receptor and \( \alpha_2 \)-receptor hypotheses might be due to differences in both experimental conditions or methods for the statistical analysis of data obtained.

The present study found that only 10 mg/kg buspirone produced a significant effect. The brain concentration of 1-PP at 30 min after oral administration of 10 mg/kg buspirone to rats was 7.6±1.4 (nmol/g±S.E.M.), while at the same time point after administration, even 2.5 mg/kg oral administration of 1-PP appeared as a higher concentration of 1-PP in the rat brain; the concentration was 17.3±1.7 (nmol/g±S.E.M.) (16). Because of this, it will be necessary to test the lower doses of 1-PP.

Furthermore, we assessed effects of 7-day treatments with buspirone and 1-PP on anticonflict activity and spontaneous water drinking. In addition, we also investigated the chronic effect of diazepam on these tests. With respect to the effect of buspirone on anticonflict activity and spontaneous water drinking, we found that the effective doses in both single and repetitive administration tests were equivalent. This result was different from that reported previously by Shefte et al. (38). They have suggested that the full anxiolytic efficacy of buspirone requires repeated administration (4 mg/kg/day for 4 weeks, followed by 8 mg/kg/day for 12 weeks, i.p.) in rats by conflict model utilizing the primary drive of thirst to motivate the subject’s behavior. In fact, in humans, it is recommended that buspirone be administered chronically for 2 - 4 weeks to be maximally effective (39). On the other hand, Wettstein (40) has reported that effects of buspirone on the schedule-controlled behavior of squirrel monkeys are un-
changed over a 12-day period of daily administrations. The studies on effect of chronic, 12-day treatment with buspirone on conflict behavior in rats are sorely lacking (40). Our results agree with those reported by Shimizu et al. (36) that the anticonflict activity of buspirone was not changed following consecutive treatments for 10 days in the Vogel's type test. The inconsistencies in the chronic effect of buspirone, which are found in these reports, may be based on a difference in drug treatment conditions; for example, administration route and/or administration schedule. Chronic treatment with 1-PP produced anticonflict activity and spontaneous drinking behavior similar to the single administration. In the single treatment, we found a moderate but significant increase in the number of licks at 25 mg/kg of 1-PP. However, we could not find a significant effect in the repeated administration test. This may suggest that 1-PP has a weak anticonflict activity which is near to the detectable limit of statistical significance, while chronic treatment with diazepam produced a stronger anticonflict effect than that of the single treatment in spite of the spontaneous water intake being the same as that of the control animals. It is generally accepted that tolerance to the anxiolytic activity of the benzodiazepines does not develop, but there is a development of side effects conversely. We also observed that tolerance to the anticonflict activity of diazepam did not develop. In our results, consecutively treated diazepam exhibited a greater anticonflict effect. This may indicate that tolerance to the side effects, which obstructed the anticonflict effect of diazepam, produced such a greater efficacy.

In conclusion, the present study demonstrated that buspirone clearly exhibited an anticonflict effect similar to diazepam in Vogel's conflict paradigm and its real anxiolytic effect may not be always based on 1-PP, one of the main metabolites of buspirone. However, the precise mechanism of action of buspirone remains unclear and further investigation will be needed.

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