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Atypical Anxiolytic Profile of Buspirone and a Related Drug, SM-3997, in a Modified Forced Swim Test Employing Straw Suspension

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NISHIMURA, H., M. TANAKA, A. TSUDA AND Y. GONDOH. *Atypical anxiolytic profile of buspirone and a related drug, SM-3997, in a modified forced swim test employing straw suspension.* PHARMACOL BIOCHEM BEHAV 46(3) 647–651, 1993.—Previous reports have shown that immobility time increases in the presence of suspended straws in association with an inhibition of straw-climbing behavior after acute administration of a prototypical anxiolytic benzodiazepine (BZD) such as diazepam. In this modified forced swim (MFS) test employing straw suspension, the effects of two new non-BZD compounds were tested and compared with those of diazepam (0.5, 1, and 5 mg/kg, IP) used in a previous MFS test. After a 5-min test of forced swimming, four straws were suspended just above the surface of the water and subsequently the straw-climbing trials were counted for 5 min as an index of escape behaviors induced by negative emotionality (stress and/or anxiety). Rats were injected IP with either saline, buspirone HCl (0.5, 1, and 5 mg/kg), or a related compound, SM-3997 (5, 10, and 20 mg/kg), 30 min before testing. At lower doses, both buspirone (0.5, 1 mg/kg) and SM-3997 (5, 10 mg/kg) reduced the duration of immobility, as opposed to that of diazepam. Conversely, buspirone at the highest dose of 5 mg/kg significantly prolonged the duration of immobility, and SM-3997 at 20 mg/kg also prolonged its duration, indicating a biphasic effect. All doses of buspirone and SM-3997 inhibited straw-climbing counts, in the same manner as diazepam. These results suggest that buspirone may possess relatively weak and/or atypical anxiolytic effects at lower doses, whereas at 5 mg/kg this compound may have an anxiolytic effect. In addition, SM-3997 may be a less potent anxiolytic drug than buspirone in the MFS test following a single-injection protocol.

Modified forced swim test Straw suspension Immobility Straw-climbing behavior Buspirone SM-3997 Anxiolytic effect

AS an animal model of stress, the straw suspension method in a modified forced swim (MFS) test has been validated behaviorally and pharmacologically (17–19). This animal test titrates the natural tendency of rats to climb up to the straws, against the inescapable aversive situation of water in the swimming cylinder. In addition, this MFS test (following a single-injection protocol) suggested that three subclasses of anxiety-related compounds could be distinguished. For example, anxiogenics, such as β-carboline-3-carboxylic acid ethyl ester (β-CCE) and yohimbine enhanced straw-climbing at doses that either did or did not reduce immobility time; a weak anxiogenic, such as flumazenil (Ro 15-1788), enhanced straw-climbing at doses without affecting immobility behavior; and an anxiolytic, the classical benzodiazepine (BZD) such as diazepam, inhibited straw-climbing at doses lower than or equal to those that prolonged immobility time (17,18,20). Within this experimental paradigm, three possible behavioral measurements can be utilized as indices of "acute swim stress" (including anxiety): the duration of immobility with and/or without straw suspension, and the incidence of straw-climbing attempts (17,18).

Buspirone is a non-BZD compound that possesses anticonflict activity in animals (4,7,10,13,15,30) and potent anxiolytic activity in humans (5,11,23), whereas in vivo, this compound enhances BZD binding (21,26). This drug also shows high affinity for 5-hydroxytryptamine (5-HT)$_{1A}$ receptors (2,4,8,30) and α-adrenoceptors (9,24), including an involvement with dopaminergic systems (6,14,15,27,29) in the central nervous system, and exhibits clinical potency equal to diazepam for the treatment of anxiety without typical side effects observed with BZD derivatives (e.g., muscle relaxation, ataxia, and/or sleepiness, etc.) (5,6,16). SM-3997 [(3aα,4β,7β,7aα)-hexahydro-2-(4-(4-(2-pyrimidinyl)-1-piperazinyl)-butyl)-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione dihydrogen citrate] was developed recently, and it also functions as a 5-HT$_{1A}$ agonist and possesses anticonflict activity in rats. This compound can be considered

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as an anxiolytic drug candidate (25,28), but does not directly interact with the BZD/GABA/chloride ionophore complex, thus indicating that it is a non-BZD drug.

The present study examined whether these non-BZD compounds have the same anxiolytic profile as that of the prototypical BZD agonist (e.g. diazepam), and attempted to clarify the differences between BZD and non-BZD drugs from the point of view of behavioral pharmacology. The test for evaluating these drugs for anxiolytic potential was performed by using an MFS test employing straw suspension (17–19).

METHOD

Subjects

Male Sprague–Dawley rats (140–170 g) were housed four per cage. Rats had free access to food and water and were kept under constant temperature (25 ± 1°C) and humidity (50 ± 10%) conditions in a room illuminated for 12 h per day (lights on 0700 h).

Drugs

The drugs used were buspirone HCl (a gift from Bristol-Myers Squibb Co., Ltd.) and SM-3997 (a gift from Sumitomo Pharmaceuticals Co., Ltd.). All drugs were dissolved in 0.9% saline and injected IP at a fixed volume of 0.2 ml/100 g body weight.

Apparatus

The apparatus used was a vertical glass cylinder (height: 40 cm; diameter: 18 cm) equipped with four pieces of straw (length: 24 cm; diameter: 0.4 cm) that were suspended from above. The cores of these straws were filled with cotton rope. These straws were painted black from the surface of the water to a height of 10 cm, as described earlier (18,19). The apparatus was filled to a height of 15 cm with water maintained at 25°C.

Behavioral Procedure

Individual experimental rats were forced to swim in the apparatus without straw suspension (pretest session). After 15 min in the water, they were removed and allowed to dry for 15 min at 32°C before being returned to their home cages. Twenty-four hours later, they were randomly divided into seven groups (n = 6–7 per group). One dose of buspirone, SM-3997, or saline was injected IP 30 min before the rats were replaced into the apparatus without the straw suspension. The total duration of immobility for 5 min (non-straw-suspending period) was measured by an observer equipped with a quartz stopwatch. Immediately after this 5-min observation period, four pieces of straw were suspended and the total duration of immobility in the following 5-min period with the straw suspension (straw-suspending period) was again measured (17,18). These straws were oriented perpendicular to the surface of the water, as illustrated in the previous report [see (18) for details]. Straw-climbing behavior was defined as escape-directed movements from the water such that the rat grasped at the straw with both forelimbs and attempted to lift its body up the straw. A straw-climbing attempt was counted when the rat climbed up a straw and reached a height of 10 cm and then slid down again to the water, as previously reported (18).

Statistical Evaluation

The results are expressed as the mean ± SEM and were analyzed statistically by one- or two-way analysis of variance (ANOVA) and post hoc Tukey test for multiple comparisons.

RESULTS

Non-Straw-Suspending Period

As shown in Fig. 1A, in the first 5-min period of the forced swim test without straw suspension, buspirone caused a biphasic effect on the duration of immobility, $F(3, 40) = 31.05$, $p < 0.01$. Post hoc analysis showed that the drug at 0.5 and 1 mg/kg significantly reduced immobility time compared with the respective saline control, although buspirone at 5 mg/kg

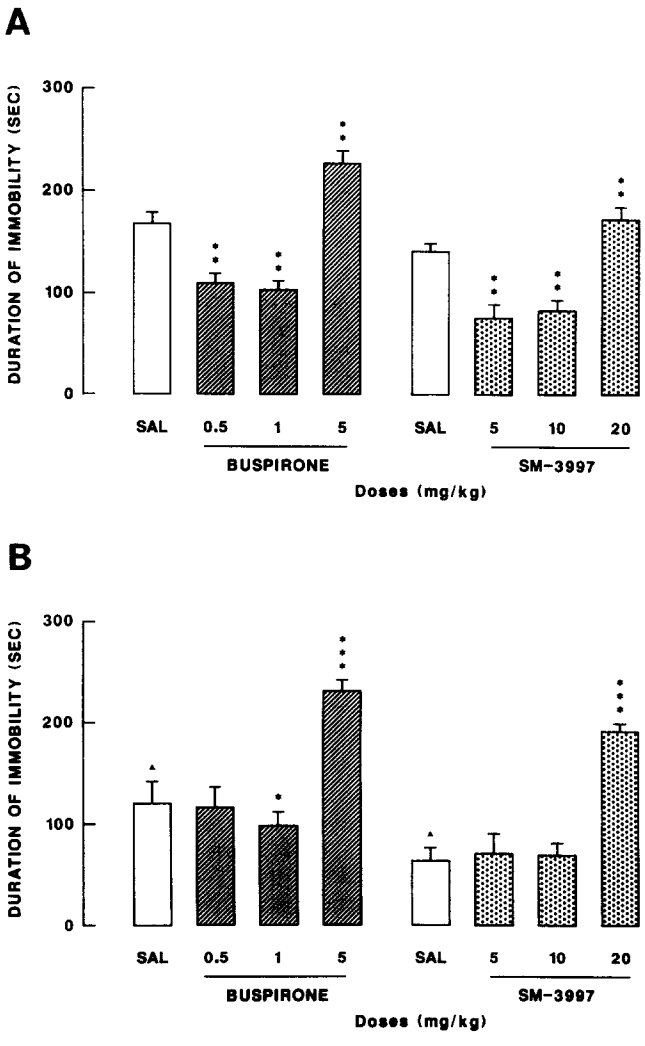

FIG. 1. Biphasic effects of buspirone and SM-3997 on the duration of immobility during (A) a 5-min test session without straw suspension and (B) a 5- to 10-min test session with straw suspension in forced swimming rats. Each value indicates the mean ± SEM of six or seven rats. All drugs were administered IP. Statistical significance: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. the respective saline (SAL) control group; $\blacktriangle p < 0.001$ vs. the respective non-straw-suspending SAL control group.

significantly prolonged immobility time. SM-3997 also caused a biphasic effect on the duration of immobility, $F(3, 48) = 29.34, p < 0.01$. Post hoc analysis showed that at 5 and 10 mg/kg of SM-3997 there was a significant reduction in immobility compared with the respective saline control, although SM-3997 at 20 mg/kg significantly prolonged immobility time.

Straw-Suspending Period

As shown in Fig. 1B, in the second 5-min period of the forced swim test with straw suspension, the duration of immobility in both saline groups was shorter when compared with that seen in the non-straw-suspending period (each $p < 0.001$). Buspirone caused a biphasic effect on the duration of immobility with straw suspension compared to the respective saline control group, $F(3, 40) = 31.05, p < 0.01$. Post hoc analysis showed that buspirone at 1 mg/kg reduced immobility time, although this drug at 5 mg/kg significantly prolonged immobility time. SM-3997 also prolonged immobility time with straw suspension, $F(3, 40) = 29.34, p < 0.01$. Post hoc analysis showed that there was a significant prolongation in immobility only at a dose of 20 mg/kg. As shown in Fig. 2, buspirone and SM-3997 caused a significant inhibition of straw-climbing counts in a dose-dependent manner [for buspirone: $F(3, 20) = 3.43, p < 0.05$; for SM-3997: $F(3, 24) = 4.19, p < 0.05$ compared with the respective saline control]. Post hoc analysis of these data showed that at all doses there was a significant inhibition of straw-climbing counts.

DISCUSSION

Previous research has shown that immobility time increases in the presence of suspended straws in association with an inhibition of straw-climbing behavior after acute IP administration of the typical anxiolytic benzodiazepine (BZD) diazepam at doses of 0.5, 1, and 5 mg/kg (i.e., immobility: +108%, +285%, and +346% of controls; straw-climbing: −89.3%, −94.3%, and −100% of controls, respectively) [see (18)]. Thus, this finding was interpreted as an anxiolytic effect in conjunction with a sedative effect of diazepam. The present study extends these findings by examining the effects of 5-HT$_{1A}$ drugs such as buspirone in the MFS test employing straw suspension.

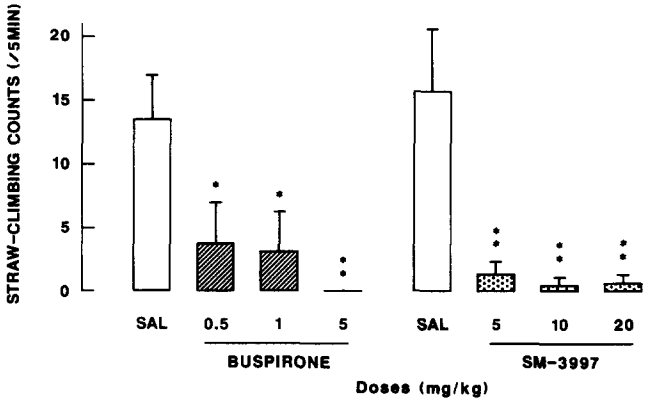

FIG. 2. Inhibitory effects of buspirone and SM-3997 on straw-climbing counts during a 5- to 10-min test session with straw suspension in forced swimming rats. Each value indicates the mean ± SEM of six or seven rats. All drugs were administered IP. Statistical significance: $*p < 0.05$, $**p < 0.01$ vs. the respective saline (SAL) control group.

Most notable from the present results are the biphasic effects on immobility duration seen between low and high doses of both buspirone and its analog SM-3997, indicating an atypical profile (i.e., only at lower doses tested in this study), when compared to that of diazepam. A recent study also reported that biphasic effects of low vs. high doses of buspirone, particularly in relation to stress-induced gastric ulcer formation in rats, were found (15,26,27). Moreover, the effect of anxiolytics on exploratory behavior was biphasic, with a facilitatory effect occurring at low doses and an inhibitory effect occurring at high doses (32). However, there have been some controversial effects of buspirone in the forced swim test; immobility time is reduced (33), prolonged, or unchanged (3,22). Differences in test conditions (e.g., water depth, temperature, etc.), treatment schedules of drug injection (acute vs. subchronic; IP vs. SC), and doses tested were offered as possible explanations of the different results. It was known that, like buspirone, SM-3997 (25) was also metabolized to 1-(2-pyrimidinyl)piperazine (1,9), which has been reported to have high affinity for α_2-adrenoceptors (24,26), specifically, an antagonist of such adrenoceptors, suggesting that the net effect of these drugs might depend on the relative proportion of this common metabolite and its parent drugs. While both buspirone and SM-3997 have high affinity for 5-HT$_{1A}$ receptors, another selective 5-HT$_{1A}$ agonist, 8-OH-DPAT, at low doses (0.25, 0.5 mg/kg, SC) has been known to reduce the duration of immobility in the forced swim test (3). Thus, such reductions in immobility at low doses may be at least partly due to actions on 5-HT$_{1A}$ receptors. In humans, it has been reported that buspirone preserves arousal in a manner different from that of the BZDs such as diazepam (5,6), and that buspirone produces less sedation than diazepam in anxious patients (23). Recent findings indicate that the ability of 5-HT$_{1A}$ drugs such as tandospirone (SM-3997) to reduce immobility time in the forced swim test is not due to an increase in motor activity, since subchronic administration of this compound at 5 and 10 mg/kg produced a significant decrease in locomotor activity (33). Thus, the possibility that the reducing effects of both drugs tested at relatively low doses on immobility duration involve overt behavioral disinhibition (15) and/or arousal (e.g., lack of sedation) cannot be ruled out. Moreover, it seems likely that the observed drug effects occurred as a result of evoking a shift in baseline behavior toward an increased level of stress. Nevertheless, it should be noted that straw-climbing behavior was subsequently inhibited at such doses (see Fig. 2), like the anxiolytic BZD diazepam. It is interesting that this BZD-like effect was not observed until the second 5-min period with the straw suspension, i.e., 30–35 min after injection. Perhaps it may be somewhat slower in onset of the BZD-like behavioral effect of buspirone than diazepam in this MFS test.

With the reported activity of buspirone as an antidepressant drug in man, the study extended over 4 weeks (i.e., chronic treatment with buspirone). Moreover, buspirone is known to relieve anxiety and associated depression, with a mean therapeutic dose of about 25 mg daily (approximately equivalent to 0.5 mg/kg) [see (11)]. In animal experiments, it has been reported that buspirone, when administered three times in 24 h, may have an antidepressant-like activity in the forced swimming-induced behavioral despair test (33). In addition, it should be noted that the rats were tested in a greater depth of water (e.g., 24 cm), and a high dose of buspirone (20 mg/kg, SC) was effective in reducing immobility time. Unlike the original "behavioral despair" test following subchronic treatment, it is more difficult to assume that buspirone is

active regarding the possible antidepressant interpretation of the present data, since only a single acute dose of buspirone was examined in this MFS test in rats. To more fully detect an antidepressant/anxiolytic action of buspirone, it would be necessary to further investigate the behavioral action of chronic (but not acute) treatment with this drug by looking at the behavior of depressed and/or anxious animals.

In contrast, the highest doses (5 mg/kg of buspirone and 20 mg/kg of SM-3997) significantly prolonged the duration of immobility in a manner similar to that induced by diazepam at 5 mg/kg (18), indicative of BZD-like activity. However, caution is required in interpreting the effects of 5-HT_{1A} drugs at higher doses on behavior as representing an anxioselective action, since there is a possibility that very high doses of these drugs (higher than used in this study) could induce a 5-HT behavioral syndrome (data not shown).

In the control rats seen in the second 5-min period with straw suspension (i.e., straw suspension test), results presented in Fig. 1 show that climbing behavior occurred frequently and the duration of immobility was reduced compared with that seen in the nonsuspending situation. In this test, buspirone at 5 mg/kg prolonged immobility duration (+96% of controls), although reduction in this behavior was observed only at 1 mg/kg. SM-3997 also prolonged immobility duration, but only at 20 mg/kg. Furthermore, the effect of buspirone on ataxia has been examined using other experimental paradigms; however, this drug (5 mg/kg, IP) did not produce significant ataxia, as measured by the latency to fall off the inclined plane (data not shown). The present results indicate that buspirone (5 mg/kg) and SM-3997 (20 mg/kg) have the same profile of action as diazepam at doses from 0.5 to 5 mg/kg, suggesting that these effects might be due to a behaviorally anxiolytic-like range of 5-HT_{1A} drug doses.

Like diazepam, both buspirone and SM-3997 at all doses inhibited straw-climbing counts. It was reported that, unlike diazepam, buspirone did not share the muscle relaxant properties of diazepam, as evidenced by its relative lack of potency to induce muscle weakness in the rats' hanging bar test (29), and that SM-3997 also had no effects on muscle relaxation (25). Therefore, these findings suggest that much of the inhibitory effects of these drugs on straw-climbing behavior may not be due simply to muscle relaxation, but to other central drug effects. In particular, straw-climbing counts were completely inhibited with only a dose of 5 mg/kg of buspirone (−100% of controls), which also prolonged the duration of immobility in the forced swim test. This effect caused by buspirone is in the same direction as that of a relatively high (5 mg/kg, IP), sedative/anxiolytic dose of diazepam used in a previous MFS test (18). In addition, this finding is supported by previous experiments demonstrating that buspirone at high doses from 1 to 10 mg/kg (SC) may have been exerting a sedative effect in the two-compartment exploratory test in rodents (12,15). In light of these data, it would seem then that a trend toward mild sedation (including anxiolysis) was seen at a higher dose of buspirone (5 mg/kg, IP).

At present, it is difficult to fully detect an anxiolytic action of buspirone in animal tests following a single-injection protocol, since there is a lag time of 1–2 weeks for the onset of the anxiolytic effect of buspirone in clinical trials (30). However, the animal tests sensitive to the acute action of anxiolytic drugs have indicated that the anxiolytic profile of buspirone at 0.5 mg/kg is observed in the social interaction test (7), and at doses ranging from 0.1 to 1 mg/kg in the conditioned defensive burying test (31). It should be pointed out that the 1-mg/kg dose of buspirone IP used in the present study was similar to effective doses found in the conflict test (e.g., 1–5 mg/kg, PO) (14), and both buspirone and SM-3997 possess anticonflict activity in rats (4,25). It is also noteworthy that buspirone is equipotent to diazepam, particularly in the treatment of anxiety-neurosis patients (11). These data suggest that the inhibitory effects on straw-climbing behavior in this MFS test may depend upon anxiolytic effects, particularly when given at higher doses (i.e., at doses that significantly prolonged immobility time). Moreover, it can be seen that although it has been possible to detect some anxiolytic action of 5-HT_{1A} drugs tested (i.e., at lower doses that reduced immobility time) only in the straw suspension test, the effects are relatively weak, since we interpreted reduced immobility in this MFS test as reflecting a relatively higher level of stress (18). In total, the behavioral effects of SM-3997 resembled those of buspirone, although buspirone was approximately 4 to 10 times more potent than SM-3997 in the MFS test employing straw suspension.

Taken together, it appears that a compound that results in an atypical behavioral profile, which includes inhibition of straw-climbing behavior at doses that reduce immobility time, will be weaker as an anxiolytic than a compound that inhibits straw-climbing at doses that significantly prolong immobility duration. In view of this pharmacological profile, we suggest that non-BZD drugs such as buspirone and SM-3997, which have a biphasic effect on immobility duration, might be expected to have relatively weaker anxiolytic effects than the BZD diazepam.

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