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Anxiolytic-Like Effects of Perospirone, a Novel Serotonin-2 and Dopamine-2 Antagonist (SDA)-Type Antipsychotic Agent

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SAKAMOTO, H., K. MATSUMOTO, Y. OHNO AND M. NAKAMURA. *Anxiolytic-like effects of perospirone, a novel serotonin-2 and dopamin-2 antagonist (SDA)-type antipsychotic agent.* PHARMACOL BIOCHEM BEHAV **60**(4) 873–878, 1998.—We examined the anxiolytic potential of perospirone, a novel serotonin-2 and dopamine-2 antagonist (SDA)-type antipsychotic agent, and compared its effects with those of the standard anxiolytic diazepam and the conventional antipsychotic haloperidol by using conditioned defensive burying (CDB) and social interaction (SI) tests in rats. The tests were conducted 1 h after oral administration of the drug. Diazepam inhibited CDB specifically directed toward a probe previously associated with brief electric shock and increased the time spent in SI by pairs of naive rats in a brightly illuminated novel environment. Perospirone mimicked the effects of diazepam by dose dependently suppressing CDB and facilitating SI. In contrast, haloperidol failed to inhibit CDB or increase SI. Thses results suggested that, unlike the conventional antipsychotic haloperidol, perospirone exerts anxiolytic-like effects in animal models with different motivational and emotional states. A braoder efficacy of perospirone for the treatment of anxiety and related symptoms in schizophrenia is discussed. © 1998 Elsevier Science Inc.

Perospirone Haloperidol Diazepam Antipsychotic SDA Anxiolytic Social interaction Conditioned defensive burying Rats

THE symptoms of schizophrenia are heterogeneous. Despite some disagreement with respect to psychopathological definitions and subtyping of schizophrenia, it is generally agreed that there is a fundamental dichotomy in symptomatology, such as positive vs. negative or nondeficit vs. deficit symptoms (2,8,12,23). It has also been proposed that dysphoric emotional disturbances, consisting of anxiety, tension, and depression, are frequent accompanying symptoms in schizophrenia (1,34). There is some consensus that atypical antipsychotics with serotonin-2 and dopamine-2 antagonist (SDA) properties such as clozapine, risperidone, and olanzapine are superior to conventional antipsychotics in the treatment of negative symptoms (6,20,26,37). It has also been reported that clozapine and risperidone are significantly more effective than conventional antipsychotics or placebo, respectively, in ameliorating anxiety and/or depression in schizophrenic patients (5,40). These findings suggest that the SDA-type atypical antipsychotics possess broader clinical profiles, particularly with regard to the efficacy for the emotional or motivational axis of schizophrenic symptomatology.

Perospirone (*cis-N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl] cyclohexane-1,2-dicarboximide) is a newly developed SDA-type antipsychotic agent (17,21) with reduced potentials for the extrapyramidal side effects liability (17,30,32). An open-label study demonstrated that perospirone significantly improved anxiety and depression as well as the positive and negative symptoms in schizophrenic patients (28). These preliminary findings were confirmed by the recent multicenter, double-blind, randomized, comparative study with haloperidol (29). Based on these clinical observations, it appears that perospirone possesses a broader clinical spectrum than the conventional antipsychotics for the treatment of schizophrenia.

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In preclinical research using laboratory animals, it is difficult to evaluate the efficacy of antipsychotics for the treatment of negative or deficit symptoms because of the lack of valid animal models. In contrast, accumulating evidence suggests that the SDA-type antipsychotics including clozapine and risperidone may possess anxiolytic potentials in animals (7,25,41). With regard to the efficacy of perospirone, there is some evidence that indicates its putative anxiolytic and/or antidepressant potential in the conditioned contextual fear model (19). However, more detailed investigations are necessary to determine whether perospirone possesses anxiolytic efficacy in behavioral models involving different motivational and emotional states. Therefore, the present study was conducted to examine anxiolytic potentials of perospirone and compare its effects with the conventional antipsychotic haloperidol, using conditioned defensive burying (CDB) (31,38) and social interaction (SI) (14,15) protocols in rats.

METHOD

Subjects

The subjects were male Lister hooded rats (Nihon Dobutu, Japan), each weighing 180.5–317.5 g at the beginning of the experiments. The rats were group housed in a ventilated, temperature (23 ± 2°C)- and humidity (55 ± 10%)-controlled animal care room under a standard 12 L:12 D cycle (lights on at 0800 h, lights off at 2000 h), with free access to food and water. The housing conditions of the rats complied with the institutional guidelines of Sumitomo Pharmaceuticals Research Center.

Conditioned Defensive Burying Test

Apparatus. The CDB test chamber consisted of an open-top clear acrylic box (30 × 40 × 40 cm). Two identical polystyrene probes (length: 9 cm, diameter: 1 cm), serving as a shock probe or shock-control probe, were wrapped with exposed wires and attached on either side of the end wall at 7 cm above the floor. The shock probe was connected to a shock generator (BRS/LVE, Laurel, MD) that delivered a 5 mA, d.c., electric shock (ES). In each experiment, the floor of the chamber was covered with 3 cm of clean wood shavings as used in the home cages (Nihon Dobutu, Japan). The general activities of the rats were measured by an automated photocell-equipped activity monitor (SCANET, Toyo Sangyo, Japan).

Procedure. All experiments were conducted in a ventilated, sound-attenuated room maintained at 23 ± 2°C and 55 ± 10% relative humidity. The rats were randomly assigned to groups of 8 to 10 each. One hour after PO administration of diazepam (0, 0.5, 1, 1.5, or 2 mg/kg), perospirone (0, 0.03, 0.1, 0.3, or 1 mg/kg) or haloperidol (0, 0.03, 0.1, or 0.3 mg/kg), the rats were gently placed in the middle of the chamber and allowed to habituate for a few minutes. This habituation period was scheduled to ensure that each rat had an opportunity to familiarize itself with both probes and test environment.

Following the habituation period, brief ES was delivered whenever the animal touched the shock probe with some part of its body. The time spent in burying the shock and shock-control probes (i.e., time spent in spraying or pushing the bedding materials toward each probe with rapid movements of the snout or forepaw) was measured for 15 min starting from the moment that the rats received the ES. In the present study, a two-probe discrimination paradigm was employed in which species-specific defensive burying of an aversive stimulus (i.e., shock probe) and nonspecific burying of a nonaversive stimulus (shock-control probe) were concurrently examined (14,35). In this paradigm, suppression of burying behavior selectively directed toward the shock probe must be evident for the indication of intact discriminative learning (35) and reduced aversive motivation associated with anxiety and fear (14).

For the assessment of motility, groups of 8 to 12 rats were administered (PO) the test drug. One hour after drug administration, the activity of each rat, as defined by the sum of the amount of horizontal and vertical movements, was measured for 15 min (i.e., the same duration as CDB assessment).

Social Interaction Test

Apparatus. The SI test arena consisted of an open-top, gray PVC box (50 × 50 × 35 cm) with 16.6 × 16.6 cm areas marked on the floor. An extra PVC wall was provided to mask extraneous visual stimuli. The light intensity of the arena was set at approximately 1200 lx by additional light sources. An electric fan was used to maintain constant ambient temperature inside the arena. The SI behavior of the rats was recorded with a home video system (Sanyo, Japan) for analyses.

Procedure. All tests were performed in a ventilated, sound-attenuated room maintained at 23 ± 28C and 55 ± 10% relative humidity. The rats were randomly assigned to groups of 16 to 20 (8–10 pairs) each. Following 2 days of individual housing, the animals were orally (PO) administered with diazepam (0 or 5 mg/kg), perospirone (0, 0.1, 0.3, or 1 mg/kg), or haloperidol (0, 0.03, 0.1, or 0.3 mg/kg). One hour after drug administration, two naive rats from separate cages (i.e., rats that were not previously housed together) were placed in the SI test arena and their social behavior was recorded for 10 min.

Behavioral observation and quantification. Two researchers, one blind to the treatment condition, were assigned to watch the video tapes to assess SI behavior. The duration of the following activities was measured as active SI behavior: sniffing the partner, mutual grooming, crawling under and climbing over the partner, following and walking around the partner, and genital investigation of the partner. Aggressive behavior such as boxing, wrestling, biting and kicking, or passive SI behaviors including sitting and lying next to each other with bodies in contact but without interacting with each other, were not counted. The number of times the animals crossed over the lines marked on the floor (line crossing) and rearing when both front paws were lifted were also measured.

Drugs

Perospirone hydrochloride, haloperidol, and diazepam were synthesized in our laboratories (Sumitomo Pharmaceuticals Research Center, Osaka, Japan). All drugs were suspended in 0.5% methylcellulose and administered in a volume of 5 ml/kg of body weight. Vehicle groups received identical volumes of 0.5% methylcellulose.

Statistical Analyses

In the CDB test, an overall two-way (dose × probe type) ANOVA was performed on each drug followed by separate ANOVAs, if necessary. Post hoc multiple comparisons among the means were carried out by two-tailed Dunnett's tests. The general motor activity was analyzed by one-way ANOVA followed by two-tailed Dunnett's tests, when appropriate.

In the SI test, the measures of the SI duration by the two observers were averaged for each pair of rats, and these data

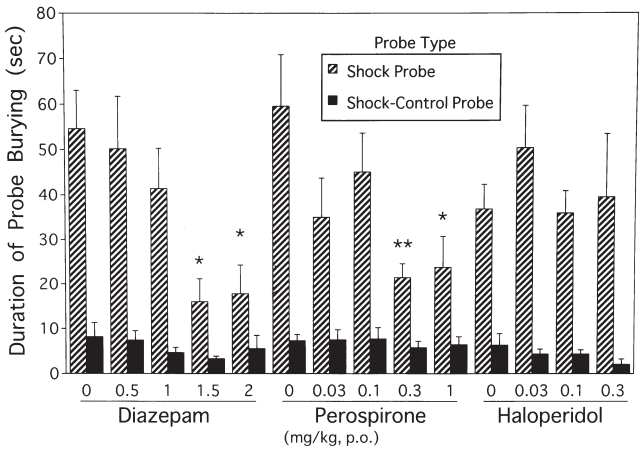

FIG. 1. Effects of diazepam, perospirone, and haloperidol on the duration of defensive burying directed toward the shock and shock-control probes in rats. The columns represent the measn ± SEM of each dose group (n = 8–12). *$p < 0.05$; **$p < 0.01$ vs. the vehicle/shock group, as determined by two-tailed Dunnett's test.

were analyzed by t-tests or overall one-way analysis of variance (ANOVA). As an index of overall motility in each rat, the sum of the frequency of line crossing and rearing were calculated and analyzed by one-way ANOVA. The significance level was set at $p < 0.05$ for all comparisons.

RESULTS

Conditioned Defensive Burying Test

As shown in Fig. 1, there was a significant dose-related differential response to the shock and shock-control probes in animals treated with the anxiolytic diazepam [dose × probe type interaction: $F(4, 90) = 3.316$, $p < 0.0139$]. The time spent in burying the shock probe was dose dependently decreased by diazepam, $F(4, 45) = 4.284$, $p < 0.0051$, whereas that of the shock-control probe was not affected. Diazepam did not depress the motility (Fig. 2). Thus, diazepam dose dependently inhibited CDB at doses that did not depress the general motor activity. Except at the highest 2 mg/kg dose, the differential response to the shock and shock-control probes was maintained at each dose [vehicle, $F(1, 22) = p < 0.0001$; 0. 5 mg/kg, $F(1, 18) = p < 0.0018$; 1 mg/kg, $F(1, 18) = p < 0.0007$; 1.5 mg/kg, $F(1, 14) = p < 0.0273$]. At 2 mg/kg, burying performance toward the shock and shock-control probes differed but did not reach statistical significance.

Perospirone mimicked the effects of diazepam (Fig. 1). There was a significant differential respone to the shock and shock-control probes at all doses tested, $F(4, 110) = 3.256$, $p < 0.0145$, with a significant dose-dependent decrease in shock probe burying, $F(4, 55) = 3.707$, $p < 0.0096$. The response to the shock-control probe was not affected. Unlike 2 mg/kg diazepam, a significant difference between burying of the shock and shock-control probes was preserved at all doses [vehicle, $F(1, 22) = p < 0.0001$; 0.03 mg/kg, $F(1, 22) = p < 0.0059$; 0.1 mg/kg, $F(1, 22) = p < 0.0004$; 0.3 mg/kg, $F(1, 22) = p < 0.0002$; 1 mg/kg, $F(1, 22) = p < 0.025$]. Perospirone did not produce any significant change in the general motor activity (Fig. 2). Therefore, similarly to diazepam, perospirone was effective in inhibiting CDB at doses that did not suppress general motor activity. In contrast, haloperidol failed to mimic the effects of diazepam (see Fig. 1). Although differential response toward aversive shock and nonaversive shock-control probes was evident [probe type effect: $F(1, 76) = 64.302$, $p < 0.0001$], there were no dose-related reductions in responses to the shock and shock-control probes. Haloperidol did not affect the motor activity (see Fig. 2).

Social Interaction Test

As illustrated in Fig. 3, the anxiolytic diazepam significantly increased the time spent in active SI at 5 mg/kg, $t(18) = 22.617$, $p < 0.0175$. Perospirone produced a significant dose-related change in the time spent in active SI, $F(3, 36) = 3.567$, $p < 0.0234$. Perospirone mimicked the effects of diazepam and significantly facilitated SI at 0.1 mg/kg ($p < 0.05$), relative to the vehicle condition. Haloperidol did not produce reliable increases in the SI time at any dose. Moreover, diazepam, perospirone, and haloperidol at the doses tested herein induced no overall changes in the motor activity (Fig. 4).

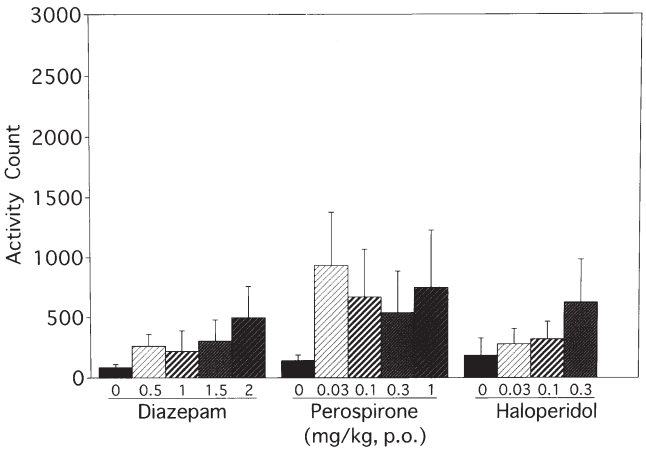

FIG. 2. Effects of diazepam, perosprione, and haloperidol on motility in rats. The motility is shown as the sum of horizonatl and vertical movement. The columns represent the means ± SEM of each dose of a given drug type (n = 8–12).

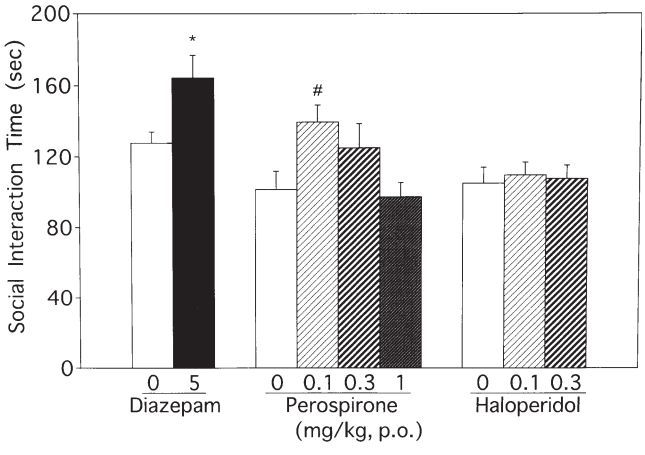

FIG. 3. Effects of diazepam, perospirone, and haloperidol on the duration of active social interaction by pairs of naive rats. The columns represent the means ± SEM of each group (9–10 pairs/group). *$p < 0.0175$ as determined by one-way ANOVA; #$p < 0.01$ vs. the vehicle group as determined by two-tailed Dunnett's tests.

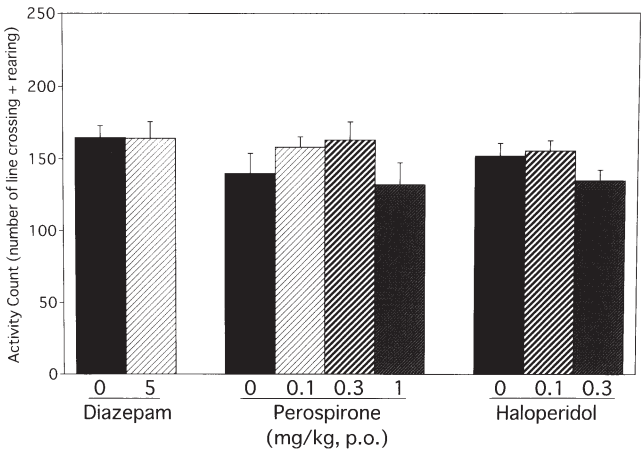

FIG. 4. Effects of diazepam, perospirone, and haloperidol on motility in the rat SI test. The motility is shown by the sum of line crossing and rearing. The columns represent the means ± SEM of each dose of a given drug type (9–10 pairs/group).

DISCUSSION

The principle findings of the present study were three fold: (a) the anxiolytic diazepam significantly inhibited CDB of the probe previously paired with the aversive stimulus (i.e., shock probe) and significantly prolonged the time spent in active SI between naive rats in the brightly illuminated, novel environment; (b) the SDA-type antipsychotic perospirone, but not the conventional antipsychotic haloperidol, mimicked the effects of diazepam by significantly inhibiting CDB at 0.3 and 1 mg/kg, and significantly facilitating SI at 0.1 mg/kg; and (c) in both the case of diazepam and perospirone, the inhibition of CDB and the facilitation of SI occurred at doses that did not stimulate or depress the overall motor activity, respectively. Consistent with the present finding, comparable doses of diazepam and other clinically effective anxiolytics with different mechanisms of action inhibited CDB (22,38). In the case of the SI test, orally administered 5 mg/kg diazepam, an identical dose used in our study, produced a significant increase in SI behavior without suppressing line crossing in Lister hooded rats in high-light, unfamiliar-partner setting, a similar experimental condition used in the present study (43). When injected intraperitoneally (IP), diazepam (3 or 10 mg/kg) also significantly facilitated SI (3,9,10,13). These studies suggest that active SI can be facilitated by relatively high doses of diazepam, regardless of routes of drug administration and lines of rats. Therefore, the CDB and SI protocols are valid behavioral models for detecting anxiolytic potentials of psychoactive drugs.

Using these models, it was found that the SDA-type antipsychotic perospirone mimicked the effects of diazepam, whereas the conventional antipsychotic haloperidol did not. In the CDB model, perospirone exerted response patterns similar to those observed with diazepam. Therefore, the time spent in burying the shock probe previously paired with aversive ES was significantly inhibited by perospirone in a dose-dependent manner. In contrast, burying of the shock-control probe was not affected. Further analyses revealed that perospirone significantly inhibited CDB specifically directed toward the ES-paired probe at 0.3 and 1 mg/kg. Haloperidol was ineffective in the CDB test. These findings suggest that the SDA-type antipsychotic perospirone, but not the conventional antipsychotic haloperidol, inhibits the species-specific defensive reactions by reducing ES-associated fear in rats. Consistent with the present evidence, perospirone was shown to effectively suppress the conditioned fear-motivated immobilization in rats (19).

In the SI test, perospirone produced significant and moderate increases in the time spent in active SI at 0.1 and 0.3 mg/kg, respectively. The degree of SI enhancement by 0.1 mg/kg (34%) was roughly comparable to that by 5 mg/kg diazepam (28.6%). It should be noted that perospirone did not augment the concurrent measure of general motor activity. The absence of motor effects can rule out the possibility that facilitated SI behavior was simply an artifact of motor stimulation. The present study further demonstrated that the conventional antipsychotic haloperidol failed to facilitate SI in rats at the doses that produced no changes in the overall motor activity. These findings suggest that, unlike the conventional antipsychotic haloperidol, perospirone possesses anxiolytic-like potential in procedures employing ethologically valid, unconditioned fear-motivated responses (24). In agreement with these findings, a previous study also demonstrated that the atypical antipsychotics risperidone, clozapine (11), and sertindole (33) facilitated SI by pairs of unfamiliar rats. Assuming that species-specific, spontaneous unconditioned responses (e.g., active SI) (3) and genetically prepared forms of defensive responses (e.g., CDB) (39) are mediated by different aversive and motivational states (18), these findings suggest the possibility that perospirone ameliorates the emotional states of fear and anxiety with diverse etiology.

The anxiolytic potentials of the SDA-type antipsychotics including clozapine, risperidone, and a series of recently introduced SDA-type antipsychotics, sertindole, olanzapine, quetiapine, and/or ziprasidone, have been demonstrated in animal models of fear and anxiety (4,7,25,27,33,41). The conventional antipsychotics were found mostly ineffective. Indeed, some clinical evidence is available indicating anxiolytic actions of clozapine and risperidone in schizophrenics (5,40), and of ziprasidone in nonschizophrenics (42). Based on these findings, it seems likely that the SDA-type antipsychotics generally possess the capacity to alleviate fear and anxiety under different conditions.

It is noteworthy that the open-label study revealed significant efficacy of perospirone in improving anxiety and depression in 167 schizophrenic patients previously treated with conventional antipsychotics (28). The recent multicenter, double-blind study with 145 Japanese schizophrenic patients confirmed these findings, and demonstrated significant superiority of perospirone to haloperidol with measurements of anxiety items and the anxiety-depression cluster of the BPRS (29). Perospirone was also shown to possess equivalent or superior efficacy to haloperidol for the treatment of the psychotic and the negative symptoms, respectively, of schizophrenia.

Evidence regarding neuronal mechanisms of perospirone's antianxiety actions is not yet available. However, it can be speculated that serotonin-2 blockade (17,21,36) may have some contributions. Indeed, perospirone mimicked the effects of the serotonin-2 blocker ritanserin by diminishing conditioned fear-motivated immobilization in rats (19). The serotonin-1A receptor antagonism (36) may also be responsible for the induction of anxiolytic actions. A series of preclinical studies have also demonstrated anxiolytic effects of serotonin-2 and serotonin-1A receptor antagonists under various experimental conditions, including the SI and CDB protocols that elicit fear and anxiety of different nature [see review (16)].

Further studies are required to elucidate the precise pharmacological mechanisms of the anxiolytic actions of perospirone.

In conclusion, the present study demonstrated that perospirone possesses anxiolytic effects in the SI and CDB models. In contrast to perospirone, the conventional antipsychotic haloperidol was ineffective in producing anxiolytic actions in both tests. These evidence supports the clinical findings that perospirone significantly alleviated anxiety in the patients with schizophrenia (28,29).

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