Acute effects of an inverse agonist selective for alpha5 GABA-A receptors on rat behavior in the forced swim test

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Introduction
It is recently recognized that drugs with antidepressant/mood-stabilizing effects profoundly alter GABAergic transmission. Data from experimental models demonstrate depression-like behavior in mouse models with specific changes in GABA_A receptors (1). This hypothesis is also supported by studies demonstrating changes in cortical GABA levels in patients suffering with depression (2).

Benzodiazepine (BZ) site ligands exert their effects through four distinct populations of GABA_A receptors, containing the alpha1, alpha2, alpha3 or alpha5 subunit in addition to the gamma2-subunit. The application of genetic studies pointed to the specific contribution of individual receptor subtypes to the spectrum of behavioral actions of BZ site ligands, which may exert positive, neutral or negative (agonists, antagonists and inverse agonists, respectively) modulatory influence on the basal GABA-ergic transmission.

The ligand PWZ-029 possesses in vitro binding selectivity and moderate inverse agonist functional selectivity at alpha5-containing GABA_A receptors. It has been shown that this ligand did not affect anxiety level or muscle tone, whereas at the dose of 5 mg/kg facilitated passive, but not active, avoidance learning in rats (3). The present study aimed to further investigate the behavioral profile of PWZ-029 in the forced swim test (FST) and also its impact on locomotor activity.

Materials and methods

Animals and drugs
Experiments were carried out on adult male Wistar rats. PWZ-029 was synthesized at the Department of Chemistry, University of Wisconsin - Milwaukee. Time of administration and doses of PWZ-029 were chosen based on previous studies (3). All drugs were suspended in a solvent containing 85% distilled water, 14% propylene glycol, and 1% Tween 80, and were administered intraperitoneally, in a volume of 1 ml/kg. The number of rats per treatment group was 7-8.

Forced swim test (FST)
FST was performed in a glass cylinder, 45 cm high, 20 cm diameter filled with water up to a height of 30 cm, with a temperature of 21-23 °C. Male Wistar rats were exposed to two swimming sessions (an initial 15-min pretest session, followed 24 h later by a 5-min test session).

The duration of immobility (seconds) was scored during the 5-min test session and the rat was considered immobile whenever it floated passively in the water and only made movements necessary to keep its head above the water line. The time of struggling (seconds) during the 5-min test session consists of explosive muscular movements against the apparatus wall, in an attempt to escape from the cylinder.

Measurement of locomotor activity
Twenty minutes after receiving the treatment or saline, single rats were placed in a clear Plexiglas chamber (40 x 25 x 35 cm). Activity under dim red light (20 lux) was recorded for a total of 30 min, without any habituation period, using ANY-maze Video Tracking System software (Stoelting Co., Wood Dale, IL, USA).

Results
In forced swim test, during the test session, ANOVA indicated statistically significant effects of PWZ-029 (F(3,20)=6.42, p<0.05). Dunnett’s analysis showed that PWZ-029 significantly decreased immobility time at the highest applied dose of 10 mg/kg, exerted acute antidepressant-like effects (Fig. 1). However, PWZ-029 did not induce significant differences in time of struggling behavior during the test (data not shown).

Conclusions
⇒ The ligand PWZ-029 possesses in vitro binding selectivity and moderate inverse agonist functional selectivity at alpha5-containing GABA_A receptors
⇒ The negative modulation at GABA_A receptors containing the alpha5 subunit might have triggered the acute antidepressant-like effects
⇒ The antidepressant-like effects are not confounded by hyperlocomotion, since PWZ-029 tended to decrease, not increase, locomotor activity
⇒ The overall effect of PWZ-029 may thus reflect better performance based on motivational enhancements
⇒ To the best of our knowledge, our study is one of the first reports the influence of a benzodiazepine inverse agonist on rat behavior in forced swim test.

References

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Conflict of interest statement
We declare that we have no conflict of interest.