Brilaroxazine (RP5063), a novel serotonin-dopamine stabilizer, displays antipsychotic efficacy in rodents

Laxminarayan Bhat, Kouacou Adiey, Seema R. Bhat, and Prabhu Mohapatra

Reviva Pharmaceuticals Holdings, Inc., Cupertino, California, USA (19925 Stevens Creek Blvd., Ste 100, Cupertino, CA 95014)

INTRODUCTION

Schizophrenia, a complex, chronic, and debilitating psychiatric syndrome, afflicts ~1% of the world’s population. It is characterized by positive, negative, and disorganized symptoms, cognitive impairment, and immune system abnormalities.1 This condition’s pathophysiology involves a disturbance of dopaminergic and serotonergic systems, which are involved in neurotransmission and autoregulatory actions.2 Substantial unmet medical needs remain.3

Brilaroxazine (RP5063)-i.p. with high affinity for 5-HT2A,5-HT2C, and dopamine D1 receptors and moderate affinity for D2 receptors are multifaceted antidepressant drug candidates that target serotonergic and dopaminergic functions.4 Brilaroxazine provides unique evidence of brilaroxazine’s effects on pro-inflammatory cytokines and 5-HT2A receptors, and is found in psychiatric disorders.5

METHODS

Apomorphine-induced Deficit in Prepulse Inhibition (PPI)s,6 involved 5 groups of 15 Wistar rats (body weight 240-300 g) at 24-29 g): brilaroxazine (1, 3, and 10 mg/kg i.p.), haloperidol (0.5 mg/kg i.p.), and vehicle (0.2% HPMC in physiologic saline).

Animals received treatments (p.o.) 15 minutes before apomorphine injection (1 mg/kg, s.c.). After placement of each animal adjacent to a wire grid wall, evaluation of its behavior occurred every ten minutes using a five-point scale at each time point (10, 20, and 30 minutes). The field contained an imaginary center 24 cm from the center of the grid and a 14 cm black plastic wall. The distance measured (cm) was defined as 0 = normal behavior; 1 = excitation/sniffing; 2 = occasional climbing (2 paws); 3 = occasional climbing (4 paws); and 4 = permanent climbing (4 paws). The total score (5-point scale) was defined as 0 = normal behavior; 1 = excitation/sniffing; 2 = occasional climbing (2 paws); 3 = occasional climbing (4 paws); and 4 = permanent climbing (4 paws). The total score was defined as 0 = normal behavior; 1 = excitation/sniffing; 2 = occasional climbing (2 paws); 3 = occasional climbing (4 paws); and 4 = permanent climbing (4 paws).

RESULTS

Figure 1: Effects of brilaroxazine at 3 mg/kg (B3), 10 mg/kg (B10), and 30 mg/kg (B30) on spontaneous locomotion (n=9-10/group). **p<0.01; ***p<0.001 versus dizocilpine + control. One-way ANOVA followed by the Newman-Keuls multiple comparison test.

FIGURE 2

Figure 2: Illustrates the results for the focal PPI evaluation. Brilaroxazine at 10 and 30 mg/kg on 30 minutes before the test (i.e., minutes before apomorphine induction) attenuated the apomorphine-induced PPI deficit in all the examined animals. The 10 mg/kg dose increased PPI at an intensity of 0.7 dB compared with apomorphine controls (p<0.05).

DISCUSSION

Brilaroxazine demonstrated significant antipsychotic effects on pharmacological-induced behaviors associated with dopamine and schizophrenics drugs.2 Compared with the baseline all dose groups (1, 3, and 10 mg/kg) were numerically superior, and the 30 mg dose was statistically superior (p<0.01) in improving the primary endpoint, the PPI test total score. The median scores of improvement in PPI test total score over baseline in the 15- and 30-mg groups were 25% and 22%, respectively. Both were superior to placebo for improving PPI total scores for positive symptoms, negative symptoms, and social functioning, and Clinical Global Impression-Improvement scores.

ACKNOWLEDGMENTS

Grants supporting these studies were awarded to Porsolt & Partners Pharmacology.

REFERENCES