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AT ANTIPSYCHOTIC-LIKE EFFECTIVE DOSES, CARIPRAZINE DISPLAYS POTENT DOPAMINE D3 AND D2 RECEPTOR OCCUPANCY IN VIVO AND EFFICACY ACROSS ANIMAL MODELS

N. Adham[1], I. Gyerty·n[2], **I. Laszlovszky**[3], B. Kiss[4]

[1]Pharmacology, Forest Research Institute, Jersey City, USA ; [2]Behavioral Pharmacology, Gedeon Richter Plc, Budapest, Hungary ; [3]Medical Division, Gedeon Richter Plc, Budapest, Hungary ; [4]Pharmacological and Safety Research, Gedeon Richter Plc, Budapest, Hungary

Introduction: Schizophrenia is a multifactorial disease requiring treatment that manages a broad spectrum of symptoms. Cariprazine is a dopamine D_3 and D_2 receptor partial agonist antipsychotic candidate with preferential D_3 receptor binding.

Objective: Evaluate the pharmacological/behavioral profile of cariprazine in animal models.

Aims: To determine the activity and receptor occupancy of cariprazine in rat models at doses that confer antipsychotic-like efficacy.

Methods: Cariprazine was evaluated in rat paradigms that model symptoms of schizophrenia, mania, and depression. Occupancy of cariprazine, aripiprazole, and risperidone at D_3 and D_2 receptors was also compared.

Results: Cariprazine showed antipsychotic-like efficacy on conditioned avoidance response and amphetamine-induced motor activity tests (ED_{50}: 0.8 and 0.1 mg/kg) with potencies similar to risperidone (ED_{50}: 0.9 and 0.2 mg/kg) and greater than aripiprazole (ED_{50}: 18 and 3.9 mg/kg). While all 3 compounds displayed high *in vivo* occupancy of D_2 receptors, only cariprazine displayed potent *in vivo* occupancy of D_3 receptors at antipsychotic-like doses (ED_{50} [% inhibition]: cariprazine, 0.43 mg/kg [99.3]; aripiprazole, >30 mg/kg [26.4]; risperidone: ~2.3 mg/kg [53.4]). At or below antipsychotic-like doses, cariprazine demonstrated antimanic-like, antidepressant-like, anxiolytic-like, and procognitive effects in rats. As determined using D_3 receptor knockout mice, procognitive and antidepressant-like effects of cariprazine were shown to be mediated via the D_3 receptor.

Conclusion: At antipsychotic-like effective doses in rats, cariprazine demonstrated balanced and significant occupancy at both dopamine D_2 and D_3 receptors; other antipsychotics displayed relatively low D_3 receptor occupancy. Additionally, at antipsychotic-like doses cariprazine demonstrated efficacy in different rat models of mania, mood, anxiety, and cognition.

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