

Dopaminergic stabilizers for the treatment of schizophrenia

Rat studies focusing on negative symptoms and mechanisms of action

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Karl Isaksson, Medicinaregatan 16, Göteborg, onsdagen den 12 december 2007, kl. 09.00

av

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Avhandlingen baseras på följande arbeten:

- I **Rung JP**, Carlsson A, Rydén Markinhuhta K, Carlsson ML (2005) (+)-MK-801 induced social withdrawal in rats; a model for negative symptoms of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*, 29(5): 827-832.
- II **Rung JP**, Carlsson A, Rydén Markinhuhta K, Carlsson ML (2005) The dopaminergic stabilizers (-)-OSU6162 and ACR16 reverse (+)-MK-801-induced social withdrawal in rats. *Prog Neuropsychopharmacol Biol Psychiatry*, 29(5): 833-839.
- III **Rung JP**, Rung E, Helgeson L, Johansson AM, Svensson K, Carlsson A, Carlsson ML (2007) Effects of (-)-OSU6162 and ACR16 on motor activity in rats, indicating a unique mechanism of dopaminergic stabilization (*submitted*).
- IV **Rung JP**, Rung E, Johansson AM, Svensson K, Carlsson A, Carlsson ML (2007) The dopaminergic stabilizers (-)-OSU6162 and ACR16 stimulate prolactin release in rats (*manuscript*).

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Schizophrenia is a severe mental disorder manifested by positive, negative and cognitive symptoms. Current antipsychotic drugs have poor effects on negative and cognitive symptoms, thus necessitating the development of new antipsychotic treatments.

Dopaminergic stabilizers constitute a novel concept for the treatment of schizophrenia. These drugs are claimed to normalize dopaminergic transmission in case of either excessive or deficient signalling. Possibly, such drugs are particularly useful for treating conditions involving both increased and decreased dopaminergic tone, as may be the case in schizophrenia. The present thesis focuses on the dopaminergic stabilizers (-)-OSU6162 and ACR16.

The main objectives of this thesis were to 1) test the effects of (-)-OSU6162 and ACR16 in a rat model for negative symptoms, 2) explore their stabilizer properties and 3) shed light on the mechanisms of action of these drugs. (-)-OSU6162 and ACR16 were found to reverse social withdrawal in rats, induced by the NMDA receptor antagonist (+)-MK-801. These results suggest that these drugs may be effective against negative symptoms of schizophrenia. (-)-OSU6162 and ACR16 both had baseline dependent effects on motor activity in drug naïve rats, inhibiting behaviour in rats with a high motor activity level and stimulating behaviour in rats with a low activity level. These effects may be interpreted as support for dopaminergic stabilization.

Based on the effects on prolactin secretion observed in the present work and results from studies performed in other laboratories, it appears that (-)-OSU6162, and probably also ACR16, have negligible intrinsic activities at the D2 receptor. Thus, the behavioural inhibition caused by these drugs is probably a result of D2 receptor blockade. The present results suggest that (-)-OSU6162 and ACR16 act via at least two D2-receptor associated targets with opposing actions on dopaminergic transmission. A recent in vitro study suggests that (-)-OSU6162, apart from blocking the orthosteric site, also facilitates receptor activation by binding to an allosteric site at the D2 receptor. This finding provides a candidate for the activating target for (-)-OSU6162 and ACR16.

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