Influence of new high affinity serotonin transporter ligands on cellular cAMP levels

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The 5-HT_{1A} receptors are inhibitory and their activation attenuates both the rate of firing of raphe 5-HT neurons and, consequently, the 5-HT synthesis and release from axon terminals [Blier et al., Ann NY Acad Sci, 1998; Fornal et al., J Pharmacol Exp Ther, 1996]. 5-HT_{1A} receptors are negatively coupled to adenylate cyclase and cellular cAMP level via G_s protein. Their agonists (e.g. 8-OH-DPAT) evoke decrease in rectal body temperature in mice (hypothermia) the effect being supposed to be connected to the activation of presynaptic 5-HT_{1A} receptors. It has also been found that the hypothermia may be caused by some serotonin reuptake inhibitors (e.g. fluoxetine) [Li et al., Eur J Pharmacol, 2009].

In the present paper we examined the influence of new serotonin transporter (SERT) inhibitors on the cellular cAMP levels. For that purpose several new high affinity SERT ligands were synthesized. Simultaneously CHO-K1 cell lines with stable over-expression of the HTRA1 gene were prepared. On those lines the influence of new high affinity SERT ligands on the cAMP level have been examined. Some of the ligands, devoid of substantial 5-HT_{1A} receptor affinity (but active in hypothermia test in mice [Nowak, Chilmonczyk, unpublished results]) diminished cellular cAMP levels in the obtained CHO cells with the over-expression of HTRA1 gene.

Acknowledgment:
This study was supported by a grant PNRF-103-AI-1/07 through the Norwegian Financial Mechanism.

Evidence for antidepressant- and anxiolytic-like properties of ketamine in animal models

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Clinical reports indicate a high degree of comorbidity of depression and anxiety, with symptomatology reflecting affective, somatic and cognitive dysregulation associated with both disorders. The frequent presence of anxiety symptoms in depressive patients suggests that the pathophysiology of anxiety and depression may have a common neurochemical mechanism. A large number of experimental data indicate that the N-methyl-D-aspartate (NMDA) receptors may be involved in the mechanism of action of antidepressant and anxiolytic drugs and, by implication, in the pathogenesis of depression and anxiety. A number of different classes of NMDA receptor antagonists, acting at various sites on the NMDA receptor complex, can mimic clinically effective agents in animal models predictive of antidepressant and anxiolytic action, and therefore, these receptors are suggested to play an important role in the neurobiology and treatment of these mood disorders. Ketamine, a dissociative anesthetic agent, is a non-competitive NMDA antagonist, which shows antidepressant and anxiolytic effects in animal studies and appears to have similar activity in clinically depressed patients.

The present study was design to evaluate an antidepressant-like activity of ketamine in a well-validated animal model of depression, the chronic mild stress