Anna Sławińska
Zakład Neurobiologii IF PAN

Potencjał terapeutyczny Lu AF21934, pozytywnego allosterycznego modulatora dla receptorów metabotropowych typu mGlu4

promotor: **Prof. Andrzej Pilc**
promotor pomocniczy: **Dr Joanna Wierońska**

Recenzenci: **prof. Halina Car**
prof. Ewa Poleszak

Glutamate is the most common and main excitatory neurotransmitter in the brain. It is estimated that approximately 60% of the cells are glutamatergic neurons, and glutamatergic receptors are expressed by almost all neurons and glial cells in the brain. These receptors are divided into ionotropic and metabotropic receptors. It has been shown that receptors for glutamate have great therapeutic potential in animal studies. The group of metabotropic receptors is of special interest. They are divided into three groups; in this paper the least so far studied the third group of these receptors were investigated. Those receptors are mainly located presynaptically in the central part of the synapse, strongly related to the regulation of glutamate release. They inhibit the activity of adenylyl cyclase and therefore after their activation, the inhibition of neurotransmitter release occurs.
Regarding ligands of the third group of metabotropic receptors, it has been demonstrated that this group is a promising grip point for action of psychotropic drugs. The first selective allosteric modulators of third group receptors was AMN082, activating receptor mGlu7 and showing anxiolytic and antidepressant like action, and PHCCC, activating mGlu4 receptors.
In the present study the role of mGlu4 receptors in the brain, mainly in terms of their therapeutic potential, has been investigated. Two newly synthesized positive allosteric modulators for mGlu4, Lu AF21934 and Lu AF32615 have been used. The main aim of the experiments was to check psychotropic activity of the compounds in animal behavioral models of anxiety, such as SIH, four-plate test or marble burying test, in model of depression- tail suspension test and in models of

positive, negative and cognitive symptoms of schizophrenia, such as amphetamine / MK-801 induced hyperactivity in mice, DOI-induced head twitches, social interaction, delayed alternation test.

Lu AF21934 the positive allosteric modulator of mGlu4 receptor showed strong anxiolytic like action in stress induced hyperthermia test in mice after subcutaneous administration. The anti-hyperthermic effect of Lu AF21934 (5 mg/kg) in the SIH test was inhibited by the benzodiazepine receptor antagonist flumazenil (10 mg/kg) and was not serotonin dependent, as it persisted in serotonin-deficient mice and upon blockade of either 5-HT1A receptors by WAY100635, or 5-HT2A/2C receptors by ritanserin. The potential anxiolytic like effect has been shown also in 4-plate test and marble burying test.

Further tests were performed to examine the potential antidepressant activity of Lu AF21934 in the tail suspension test in mice. Lu AF21934 did not significantly influence the immobility time of the animals.

To evaluate the antipsychotic properties of positive allosteric modulators of mGlu4 the following tests were used: hyperactivity induced by MK-801 or amphetamine, DOI-induced head twitch test, social interaction test and spatial delayed alternation test. Both Lu AF21934 and Lu AF32615 showed effect in all of these tests, Lu AF21934 showed U-shaped effect, and Lu AF32615 acted dose-dependently.

Lu AF21934 specificity was examined in a number of biochemical tests, which demonstrated that the compound has no affinity for other receptors or transporters. In the present study it was confirmed by using an inactive isomer Lu AF 21935 and mice with the deleted gene encoding mGlu4 receptor. In all experiments, isomer, showed no activity in a wide range of doses, whereas the compound Lu AF21934 was inactive in DOI-induced head twitches test in the mGlu4 - / - mice.