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Chapter V

Neuro- and psychotropic effects of drugs active at metabotropic glutamate receptors – Therapeutic perspectives – Introduction

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The aim of the present symposium is to check the status of the present knowledge and recent experiments dealing with drugs active at glutamate receptors of the metabotropic type, which may be useful in the therapy of some neurologic and psychiatric disorders such as, e.g., pain, anxiety and antidepressant therapy and – last but not least – degenerative diseases, mainly Parkinsons's disease.

It is well known that glutamate is the main stimulating transmitter in the brain, and that glutamate and γ-aminobutyric acid (GABA) neurons represent more than 90% of all the neurons in the brain. Therefore no wonder that many physiological functions depend upon glutamate receptors and that they are involved in such a number of brain disorders. Glutamate is a common transmitter of 3 ionotropic receptors, i.e. NMDA, AMPA and kainic acid receptors, and of 8 metabotropic receptors (mGluRs).

The aim of the first paper of the symposium (Conn J., Atlanta, Ga, USA) is to discuss the physiological role and regulation of metabotropic glutamate receptors in the basal ganglia, however mainly of these which may be effective in the treatment of Parkinson's disease. The role of presynaptic mGluR4 and mGluR7 receptors (group III), located on striatal terminals in the globus pallidus, as well as of those of group I (mGluR1 and mGluR5), found on subthalamic and nigral neurons, is discussed. Also the anti-parkinsonian-like effect of group II agonists which inhibit the haloperidol catalepsy in rats is considered.

The second paper (Ossowska et al., Kraków, Poland) deals mainly with parkinsonian-like muscle rigidity which is measured as resistance of a hind foot and as electromyogram of its muscles being increased previously by haloperidol. Reduction of the haloperidol-induced muscle rigidity by various agonists and antagonists belonging to mGluRs of group I and II was observed. The obtained results suggest that either blockade of striatal group I mGluRs or stimulation of group II mGluRs in the striatum may be effective in the amelioration of parkinsonian syptoms.

The successive paper (Golembiowska et al., Kraków, Poland) presents the effect of blockade of mGluR 5 (MPEP), as well as of stimulation of mGluR 2/3 (LY379268) on spontaneous and veratridine-stimulated dopamine release in rat striatum using an in vivo microdialysis. The antiparkinsonian-like effect of the blockade of mGlu 5 receptors seem to be mediated by sites located outside the striatum. Moreover, a potential neuroprotective activity of the blockade of mGluRs 5 in a model of the methamphetamine neurotoxicity is suggested.

An interesting paper by Kuhn and coworkers (Basel, Switzerland) seems to open a new avenue in the exploration of metabotropic glutamate receptors. It has been designed to search an entirely new binding site within the mGlu receptors, particularly within the mGluR 5 one. This binding site is unrelated to the glutamate binding site located in the large extracellular N-terminal domain which can be blocked by the majority of amino acid-like competitive antagonists of mGluRs.

The novel, subtype-selective mGluR 5 receptor antagonists, synthetized by NOVARTIS, are structurally unrelated to competitive mGlu receptor ligands; moreover, they seem to act as inverse agonists

of the above mentioned novel allosteric binding site in the seven-transmembrane domain. They seem to be important for the treatment of pain, anxiety and depressive disorders, as well as for the therapy of Parkinson's disease.

The last paper (Pilc et al., Kraków, Poland) deals mainly with two antagonists of group I of mGluRs, i.e. MPEP (a noncompetitive, systemically active mGluR5 antagonist) and with AIDA (a competitive mGluR1 antagonist). They were checked in three tests, designed to discover antidepressive action of drugs: a despair test in rats, a tail suspension test in mice, both measuring the immobility time decreased by antidepressive drugs, and a deficit test in passive avoidance learning in bulbectomized rats. Moreover, the level of expression of mGluR5 in the hippocampus, increased by imipramine or MPEP or by a prolonged electroconvusive shock treatment was tested. The results suggest that the mGluRs belonging to the group I might play a role in the therapy of depression.