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Chapter II

Metabotropic glutamate receptors – different therapeutic perspectives

Introduction

Glutamate receptors can be divided in two large groups: ionotropic and metabotropic receptors. To the ionotropic group there belong NMDA, AMPA and kainate receptors. Metabotropic glutamate receptors (mGluRs) do not form ion channels but, when activated, produce – via G proteins – a cascade of second messengers within a cell. So far 8 different types of metabotropic receptors have been cloned. They are divided into three groups according to their molecular structure, involved second messenger and the pharmacological profile.

In contrast to the ionotropic receptors, which are mainly localised on the postsynaptic membrane, the metabotropic ones are localised on both sides of the synapse. They can influence postsynaptically the impulse flow, or can lower or raise the glutamate levels via a receptor (autoreceptor) on the presynaptic side. It has been shown that group I postsynaptic receptors are activated only by excessive amounts of glutamate during synaptic hyperactivity, whereas activation of presynaptic receptors, which probably also belong to the group I, enhances the glutamate release. It is generally assumed that activation of group I mGlu receptors increases neuronal excitability, whereas activation of group II or group III mGlu receptors reduces synaptic excitation. Moreover, activation of presynaptic group II receptors (autoreceptors) inhibits glutamate release. Apart from a few exceptions, it is expected that excitotoxicity should be prevented by group I antagonists, whereas group II and III agonists are likely to be neuroprotective.

To date little is known about therapeutic perspectives for mGluRs ligands. The aim of this symposium is to present a few preclinical studies which show directions of future investigation to be carried out by pharmacologists.

Glutamate is a major stimulatory neurotransmitter which conveys impulses in approximately 90% of stimulatory synapses in the brain. No wonder that it is involved in many different functions of the central nervous system.

The first three papers of this chapter deal with: (1) putative anxiolytic activity of mGluRs ligands, (2) a search for antipsychotic action of mGluRs ligands, and (3) a prospective antiparkinsonian action of mGluRs ligands. Papers 4 and 5 are different, and are aimed to give an overview of behavioural (Dr Kronthaler) and electrophysiological (Dr Pisani) effects of mGluRs ligands.

The most interesting finding to be presented in these papers is that two effects, anxiolytic (Vogel's drinking conflict test) and antiparkisonian (haloperidol-induced muscle rigidity test) result from the agonistic action produced at the group II mGluRs and/or antagonistic action provided at the group I mGluRs. It seems that both these effects lead to a decreased tone of the glutamate synapse. The results presented in the second paper (Dr Ossowska) do not seem to confirm literature data suggesting an antipsychotic action (pre pulse-inhibition test and delayed alternation task) of group II mGluRs agonists. On the basis of electrophysiological effects (Dr Pisani) it is concluded that group I mGluRs located on medium spiny cells might account for the differential vulnerability to excitotoxic damage observed in striatal neuronal subtypes.

Stanisław Wolfarth