METABOTROPIC GLUTAMATE RECEPTOR LIGANDS: NEW TARGET FOR DRUG RESEARCH

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L-Glutamic acid (L-Glu) is the main excitatory neurotransmitter in the mammalian central nervous system involved in several physiological and pathological conditions. L-Glu exerts its action *via* the activation of ionotropic glutamate (iGlu) receptors and metabotropic glutamate (mGlu) receptors. mGlu receptors modulate glutamatergic excitations by presynaptic, postsynaptic, and glial mechanism. Eight subtypes of mGlu receptors ($mGlu_{1-8}$) are categorized into three groups according to their agonist pharmacology, sequence similarity and signal transduction pathways. Group I mGlu receptors consist of $mGlu_1$ and $mGlu_5$, both of which are positively coupled to phospholipase C and are activated by 3,5-DHPG. Group II mGlu receptors include the $mGlu_2$ and $mGlu_3$ subtypes, which are negatively coupled to adenylyl cyclase and are preferentially activated by DCG-IV. Group III mGlu receptors consist of $mGlu_{4/6/7/8}$ and are also negatively coupled to adenylyl cyclase but are preferentially activated by L-AP4. Pharmacological studies with group-selective agonists suggest that, in general, group I receptors reside postsynaptically and, upon activation, increase the excitability of neurons, while group II and group III agonists reside, at least in part, presynaptically and function to suppress glutamatergic neuronal excitations. Within the last few years, new potent and selective agonists and antagonists as well as radioligands acting on these receptors have been developed. A number of compounds active also after systemic administration were found. In the addition to competitive agonists and antagonists, non-amino acid molecules have recently been identified that non-competitively blocking mGlu receptors activation. Dysfunctional glutamate neurotransmission has been associated with a variety of pathophysiological states and diseases including epilepsy, stroke, ischemia, trauma, pain, anxiety, psychosis, Parkinson's disease, drug withdrawal and diminished cognitive functioning. The potential therapeutic use of mGlu receptor ligands is discussed as new type anxiolytic, analgesic and antiepileptic drugs as well as molecules that will suppress the withdrawal effects or could be used in the therapy of schizophrenic patients.

This study was supported by grant No. 4 P05F 007 17 from the State Committee for Scientific Research, Warszawa, Poland

FROM THE MODELS OF LIGAND-RECEPTOR INTERACTIONS TO THE TREATMENT OF DISEASES: SEROTONIN LIGANDS AND MENTAL DISORDERS

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The role of serotonin (5-HT) system in the modulation of diverse functions of the central nervous system is well documented. At least 14 distinct 5-HT receptors have been cloned and with the exception of $5\text{-}HT_3$, others belong to the superfamily of G-protein-coupled-receptors (GPCRs). A majori-

ty of them seems to be involved in the etiology of severe mental disorders, which exact pathomechanism, highly complex and of heterogeneous nature, is still incompletely understood. Moreover, very little is known about the complex ligand-receptor interactions primarily because no direct structural information is currently available regarding any details of the receptor or the ligand receptor-complexes. In the absence of those data different molecular modeling approaches are used to explain 3-D molecular structure of 5-HT receptors (or any other GPCR) as well as the entire process of ligand-receptor interactions.

A number of models of 5-HT receptors (i.e. pharmacophoric, based on CoMFA method and direct 3-D receptor protein structures) have been constructed but none of them can be regarded universal. First, because they were developed on the basis of a very limited number of compounds and/or second, because a majority of ligands used were flexible. The last problem can be tackled by using an active ligand with restricted conformational freedom as a template.

Recently, several conformationally constrained compounds from the arylpiperazine group (the biggest and thoroughly studied class of 5-HT_{1A} receptor ligands) have been examined and bioactive conformation of postsynaptic 5-HT_{1A} receptor antagonists has been hypothesized. Comparative, systematic structure-activity relationship studies on the basis of conformationally constrained compounds within different subtypes of 5-HT receptors may lead to the qualitative change in our knowledge about selective/nonselective ligand design, receptor structure and ligand-receptor complex formation. Since psychiatric disorders cannot be attributed to dysfunction of only one receptor type, new drugs with desired multireceptor profile are needed.

PERSPECTIVES IN MOLECULAR PHARMACOLOGY. GENE THERAPY

Organizer: *Ryszard Przewłocki*

GENE THERAPY OF CANCER

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Identification of numerous tumour antigens (TA) in several malignancies which occasionally induce spontaneous tumour regressions, better understanding of antitumour immune responses and gene engineering technologies prompted development of genetically modified tumour vaccines (GMTV). Cellular vaccines are based on autologous or allogeneic tumour cells genetically engineered to secrete different cytokines, co-stimulatory molecules or allogeneic HLA molecules in order to provide a strong stimulatory signal together with the presented TA. Another promising approach that is targeted on