BEHAVIOURAL STUDIES OF NEW AND SELECTIVE MGLUR7 NEGATIVE ALLOSTERIC MODULATORS

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By mediating modulatory response to glutamate signaling, metabotropic glutamate receptors (mGluRs) play a crucial role in many physiological operations of central nervous system such as learning and memory, sensory perception, development of synaptic plasticity, motor control, respiration and regulation of cardiovascular function. As a result, targeting mGluRs in development of new ligands that induce a receptor response may lead to discovery of new drugs and therefore therapies for a number of neuropsychiatric and neurodegenerative disorders such as anxiety, depression, schizophrenia, cognitive disorders, epilepsy and movement disorders, addiction, pain perception, Parkinson's, Alzheimer's diseases, fragile X syndrome and more (for reviews see 1-2). From historical point of view the interest in mGluRs ligand discovery concentrated mostly on group I and II leading several potential drug candidates into clinical trials [3]. Group III of mGluRs remained the least recognized until a great progress has been made within last decade.Belonging to the group III mGlu7 receptors located on presynaptic terminals are highly expressed in brain regions involved in reward, cognition and emotion, such as the dorsal striatum, nucleus accumbency, hippocampus, amygdala, ventral pallidum, olfactory bulb, locus coeruleus, and ventral tegmental area [4].Both PAMs and NAMs of mGlu7 receptor were reported recently in the literature [3]. Among them only ADX71743 was characterized as a nanomolar potent mGluR7 NAM inactive against other subtypes of mGlu receptor family [5]. In vivo efficacy of ADX71743 was evaluated in rodent models of anxiety, depression and psychosis. ADX71743 showed anxiolytic-like effect in the marble burying and elevated plus maze test in mice, antipsychotic-like effect in the amphetamine-induced hyperactivity, DOI-induced head twitches and conditioned avoidance response test in rodents and failed to show antidepressant-like profile in the mice forced swim test.Herein we report results of behavioural studies of most potent and selective representatives of a new discovered group of mGluR7 NAMs. Ligands were tested in mice models of anxiety, depression and psychosis showing anxiolytic and antipsychotic-like profile.

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