ADENOSINE RECEPTORS IN NEUROPROTECTION

Ana M. Sebastião

Institute of Pharmacology and Neurosciences, Faculty of Medicine and
Institute of Molecular Medicine, University of Lisbon, Lisboa, Portugal. anaseb@fm.ul.pt

Adenosine is quite well established as an efficient local chemical regulatory signal to address communication between cells. It is released by most cells in particular under stress conditions. Two high affinity G-protein coupled receptors, inhibitory A1 and excitatory A2A, are responsible for most of the adenosine actions in the nervous system. Through A1 receptors, adenosine inhibits glutamate release (but not GABA release), inhibits excitatory synaptic transmission, and inhibits NMDA receptor activation. These actions are crucial to facilitate recovery of synaptic transmission after hypoxic insults (Sebastião et al., 2001 – J Neurosci, 21:8564-8571).

Adenosine A2A receptors facilitate glutamate release and through this mechanism they can exacerbate excitotoxicity processes. However, a particularly relevant action of adenosine A2A receptors in what concerns their putative neuroprotective role is the ability to trigger or facilitate synaptic actions of neurotrophic factors. Thus, the facilitatory actions of Brain Derived Neurotrophic Factor (BDNF) upon synaptic transmission in the CA1 area of the hippocampus (Diogenes et al., 2004 - J Neurosci. 24:2905-13) and in motor nerve endings (Pousinha et al., 2006 - Neurosci Lett. 404:143) are prevented by blockade of adenosine A2A receptors. Modulation of hippocampal synaptic transmission by BDNF changes according with age and this could be related to opposite changes induced by age in the density of TrkB and of adenosine A_{2A} receptors (Diógenes et al., Hippocampus, in the press). The cross talk between neurotrophic factors and adenosine is extended to Glial Derived Neurotrophic Factor (GDNF) since its ability to facilitate dopamine release from striatal nerve terminals also requires co-activation of adenosine A2A receptors (Gomes et al., Brain Res. 1113:129).

A_{2A} receptor antagonists are have been proposed as neuroprotective drugs in some neurodegenerative diseases, such as in Parkinson's disease due their ability to prevent A2A receptor-mediated inhibition of dopamine D2 receptor function in the stratum (e.g. Ferré et al., 2003, Curr. Med. Chem. 3:1-26). On the other hand, neurotrophic factors have a high therapeutic potential in neurodegenerative diseases. Our findings on the prevention synaptic actions of neurotrophic factors by A_{2A} receptor antagonism point towards the need of further studies on the consequences of long-term therapy with A_{2A} receptor blockers in neurodegenerative diseases where neurotrophic factors may play a beneficial role. One issue that should be explored in the future is the optimal time window for combined beneficial effects for neurotrophic factors and A_{2A} receptor agonists/antagonists. If, in the late stages of neurodegenerative diseases, A_{2A} receptor antagonists can be advantageous, in the early stages, where an enhancement of neurotrophic factors should be highly desirable, A_{2A} receptor antagonists should be avoided in order to allow neurotrophic influences.

In conclusion, adenosine A2A receptors are key molecules in what concerns modulation of the neuromodulatory actions of neurotrophic factors in the nervous system, reinforcing the idea that A2A receptors are involved in the fine tuning of neuronal activity and suggesting that A2A receptors may have trophic actions in the nervous system.

Work supported by FCT (Portugal) and EU. BDNF is a gift by Regeneron