A_1 AND P_2Y_1 PURINERGIC RECEPTORS: LOCALIZATION AND FUNCTIONAL CROSS-TALK IN HYPPOCAMPUS

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Adenosine and ATP, via their specific P_1 and P_2 receptors, modulate a variety of cellular and tissue functions playing a neuroprotective and/or neurodegenerative role in brain damage. Although, in general, adenosine inhibits excitability and ATP functions as an excitatory transmitter in the central nervous system, recent data suggest the existence of a heterodimerization and a functional interaction between P_1 and P_2 receptors in the brain. (1). In the present work we investigated the localization/co-localization of A_1 adenosine receptors (ARs) and P_2Y_1 receptors and their functional interaction at the membrane level in rat hippocampus, which is considered as a damage sensitive brain area. After this step, we focused on the study of the A_1-P_2Y_1 receptor functional cross-talk in human astroglial cells.
By immunogold-electron microscopy we demonstrated that the two receptors are highly express and co-localized at the synaptic membranes and surrounding astroglial membranes of glutamatergic synapses. Moreover, a functional interaction of these receptors at membrane G protein level was determined: in particular we showed P_2Y_1 receptor stimulation impaired A_1 AR-G protein coupling, whereas the stimulation of A_1 ARs increased P_2Y_1 functional responses . Since A_1 and P_2Y_1 receptors mainly interact at level of astrocytes, the studies were then focused on human astroglial cells (ADF). Immunoprecipitation experiments demonstrated these receptors dimerized to form an heteromeric complex. P_2Y_1 receptor agonist, MeSADP, was able to modulate pharmacological profile of agonists/antagonists to A_1 ARs without directly interact with A_1 AR binding sites. Moreover, functional studies showed the P_2Y_1 receptor activation induced an impairment of A_1R/G-protein coupling and a decrease of A_1AR-inhibition of adenylate cyclase activity, suggesting a heterologus A_1AR desensitisation induced by the P_2Y_1R. These results suggested ATP and adenosine interact at level of glia in regulating purine-mediated signalling. This may be particularly important during pathological conditions, when large amount of these mediators are released.

1) Yoshioda K and Nakata H, 2004. *J Pharmacol Sci*, 94: 88-94.