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Meeting abstract

Mapping the binding sites for accessory proteins on the A_{2A} adenosine receptor

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Among the four receptors for the purine nucleoside adenosine the A_{2A} receptor subtype is the only one with an extended cytoplasmic domain and this is due to a remarkably long carboxyl terminal tail (C-tail). We have previously identified from an adult human brain cDNA library potential interaction partners which bind to the receptor C-tail and suggest that they impinge on receptor biology. (i) ARNO, the activator of the small GTP-binding protein ARF6, was shown to propagate sustained receptor signalling to ERK (extracellular signal regulated kinase); (ii) the ubiquitin-splitting protease USP4 controls receptor turnover; (iii) SAP (synapse-associated protein) 102 may form an anchor localizing the receptor in nerve cells. While ARNO binds to the membrane proximal portion, USP4 and SAP102 recognize more distal segments of the C-tail. In the case of SAP102 the recognition sequence could be narrowed down to a stretch of five amino acid residues (DVELL) which is conserved between species. A receptor where the DVELL sequence was changed to RVRAA has been characterized upon stable transfection of HEK293 cells (which express SAP102). Surface expression, radioligand binding and receptor-dependent stimulation of the effector adenylyl cyclase were similar to the wild type. In contrast, the agonist-dependent activation of ERK was attenuated in cells stably expressing the mutant receptor. Hence, SAP102 may be necessary to establish a signalling complex including ERK and the receptor as has been previously observed for the NMDA receptor in nerve cells.