CONCLUSIONS
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- Agonist stimulation of adenosine A₁ and A₂A receptors (A₁R and A₂AR) induces neurite outgrowth in SH-SY5Y neuroblastoma cells as an early step of differentiation. Two different signaling pathways, MAPK and PKC are involved in this process. Furthermore, activation of both receptors accelerates the process of differentiation of neuronal precursor cells.

- A₂AR form homodimers. These homodimers, but not monomers, are the functional species at the cell surface. Although its agonist activation leads to the formation of receptor clusters, it does not affect the degree of dimerization.

- In addition to homodimerization, A₂AR and dopamine D₂ receptors (D₂R) are able to form heterodimers. This heteromerization has been demonstrated in SH-SY5Y neuroblastoma cells stably transfected with the D₂R. Stimulation of A₂AR and/or D₂R induces co-aggregation and co-internalization of both receptors in SH-SY5Y cells as well as in primary cultures of striatal neurons.

- A₂A/D₂ heterodimers have been detected in living cells where the stimulation of both receptors doesn’t modify neither the number nor the distance within the heteromer. Heterodimers between A₂AR and D₂R might be responsible, at least in part, for the strong functional antagonistic interactions between adenosine A₂A receptors and dopamine D₂ receptors.

- The helix 5 and/or helix 6 and the N-terminal portion of the third intracellular loop of the D₂R and helix 4 and the C-terminal tail of the A₂AR are important domains for the interaction in the A₂A/D₂ heteromer as deduced from molecular modeling as well as from experimental approaches. Furthermore, the involvement of epitope-epitope electrostatic interactions in the heteromerizations has also been identified.

- There are strong structural differences in A₂A homodimers and A₂A/D₂ heterodimers formation since the C-terminal tail of A₂AR does not participate in homodimerization but is involved in the formation of heteromers.