CONCLUSIONS

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- Agonist stimulation of adenosine A_1 and A_{2A} receptors (A_1R and $A_{2A}R$) 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.

- $A_{2A}R$ 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 de degree of dimerization.

- In addition to homodimerization, $A_{2A}R$ and dopamine D_2 receptors (D_2R) are able to form heterodimers. This heteromerization has been demonstrated in SH-SY5Y neuroblastoma cells stably transfected with the D_2R. Stimulation of $A_{2A}R$ and/or D_2R induces co-agregation and co-internalization of both receptors in SH-SY5Y cells as well as in primary cultures of striatal neurons.

- A_{2A}/D_2 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 $A_{2A}R$ and D_2R might be responsible, at least in part, for the strong functional antagonistic interactions between adenosine A_{2A} receptors and dopamine D_2 receptors.

- The helix 5 and/or helix 6 and the N-terminal portion of the third intracellular loop of the D_2R and helix 4 and the C-terminal tail of the $A_{2A}R$ are important domains for the interaction in the A_{2A}/D_2 heteromer as deduced from molecular modelling 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 A_{2A} homodimers and A_{2A}/D_2 heterodimers formation since the C-terminal tail of $A_{2A}R$ does not participate in homodimerization but is involved in the formation of heteromers.