ADENOSINE/DOPAMINE RECEPTOR INTERACTION: IMPLICATION IN ANTIPSYCHOTIC THERAPY

Cuboni S, Trincavelli ML, Montali M, Ciampi O, Lucacchini A, Martini C.

Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, Italy

Antipsychotic drugs, potent dopamine receptor antagonists, are commonly used for treatment of psychotic and affective illness. As known in literature, A_{2A} adenosine receptors (ARs) colocalize with D_2 dopamine receptors (DRs) in the basal ganglia and modulate D_2 DR-mediated dopaminergic activities with antagonistic effects. These data suggest a possible involvement of adenosine system in the pathogenesis of psychiatric and neurological disorders characterized by dopamine system dysfunction. However the interaction between A_{2A} AR and D_2 DR could be of mutually antagonism or synergism in dependence of cell model system and the relative receptor abundance expression. So, in the present work we purposed to investigate the functional interaction between adenosine and dopamine receptors in two cell systems expressing A_{2A}AR and different levels of D_2DR.
In PC12 cells, which natively express A_{2A} AR and D_2 DR at low levels, we demonstrated these receptors dimerized to form an heteromeric complex in basal condition. Cell pre-treatment with typical antipsychotics, haloperidol, induced a significant up-regulation of A_{2A} AR binding sites. Moreover, haloperiodol was able to impair A_{2A}AR-G protein coupling also causing a drop in receptor functional responsiveness, as demonstrated by GTPγS binding experiments and cAMP assay. These results indicate that typical neuroleptics induce A_{2A} AR desensitisation suggesting a synergic A_{2A} AR/D_2 DR interaction in PC12 cells. On the contrary, the atypical drug, clozapine, did not induce any significant effect on A_{2A} functioning confirming the different regulatory effects of typical respect to atypical drugs.
Therefore, we interested in investigating A_{2A} AR/D_2 DR interaction in CHO ce lls stable transfected with human cDNA expressing A_{2A} and D_2 receptors at high levels. By immunoblotting and radioligand binding assay we demonstrated A_{2A} AR and D_2 DR expression in transfected CHO cells. Preliminary results demonstrated that in physiological conditions (medium containing 10% serum) cell pre-incubation with haloperidol (1μM) for different times (1-24 hours) was not able to modulate A_{2A} AR expression and functioning. On the contrary, in conditions of serum starvation (1% serum), a shift towards A_{2A} AR high affinity sites was detected with a reduction in agonist Kd value. These data suggested a role of dopaminergic system in the control of A_{2A} AR. Moreover, functional experiments are in progress to better clarify whether this cross-talk is antagonistic and/or synergic in dependence of receptor levels.