

Adenosine A_{2A} Antagonists and Huntington's disease

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SUMMARY

Huntington's Disease (HD) is a neurodegenerative disorder caused by expansion of a CAG repeat in the gene encoding for Huntingtin (Htt) and resulting in progressive degeneration of the striatal GABAergic/enkephalin neurons. These neurons express both the A_{2A} and D2 receptors which stimulate and inhibit adenylyl cyclase, respectively. In this study we analyzed the possibility of an involvement of the A_{2A} receptor and its signalling components in the pathogenesis of HD. We report here that striatal cells expressing mutant Htt exhibit increased binding affinities for the selective A_{2A} receptor ligand 3H-ZM 241385. Furthermore, despite identical basal adenylyl cyclase activity in all cells, forskolin, a direct activator of this enzyme, significantly over-stimulated cAMP production in mutant Htt cells with respect to parental or wild type Htt-expressing cells. Remarkably, coupling of the A_{2A} receptor to adenylyl cyclase was also aberrantly increased. Nevertheless, in all clones, stimulation of cAMP production by 10⁻⁷ M NECA was fully counteracted by selective A_{2A} receptor antagonists as ZM 241385, SCH 58261, CGS 15943 and caffeine. Altogether, these data suggest that expression of mutant Htt induces an amplification of adenylyl cyclase-transduced signals and an aberrant coupling of the A_{2A} receptor to this transduction system. Given the involvement of adenylyl cyclase in key physiological functions including cell growth and cell survival, we speculate that these changes may alter the susceptibility of striatal neurons to cell death and may contribute to the development of HD.