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Adenosine A_2A antagonists: neuroprotection and autophagy induction by a new compound

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Adenosine receptors A_2A are a class of purinergic receptors largely expressed in dopamine (DA)-rich areas of the central nervous system. In particular, they are abundant within basal ganglia, where they modulate the activity of various neurotransmitters, including DA.Despite the lack of knowledge on their fine physiological mechanisms, tt is worth to mention that A_2A antagonists prevent neuronal death and dyskenisia in Parkinsonism.

A new compound, ATBI-10, bind with high selectivity to A_2A receptors with antagonist activity. In the present study, by profiting of such an highly selective compound we investigated: (i) whether such a novel compound protect DA containing neurons against the parkikinsonian neurotoxin 1-methyl-4-phenylpirydinium and the dyskinetogenic compound methamphetamine. (ii) The cellular mechanisms which are involved in these phenomena as a consequence of A2A receptor modulation. We carried out an *in vitro* study using two models of DA neurons PC12 and SH-SY5Y. We found that ATBI-10 at doses of 16 and 32 nM protects against DA neurotoxicity in all models, being mostly effective against MA toxicity (complete prevention). In light of the key role of autophagy in modulating the survival of DA neurons we investigated the association between A2A receptors and the the autophagic pathway. We found that antagonism at A2A receptors produces an increased autophagy (increased LC3-II levels). This effects appear to be shared by all A2A antagonists.

Our data indicate that A_2A antagonists are neuroprotective against a vatriety of insults to DA neurons and such an effect appear to be mediated by the enhancement of autophagy. We are now evaluating *in vitro* and *in vivo* whether endogenous adenosine might produce neurodegeneration by activating A2A receptors. These results indicate novel therapeutic effects of A2A antagonists and provide evidence on their mechanism of action.