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A2A receptors and methamphetamine toxicity: a role of adenosine as an endogenous neurotoxin

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Adenosine A2A 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, it is worth to mention that A2A antagonists prevent neuronal death and dyskinesia in Parkinsonism. Moreover the neuroprotective effects observed after blockade of adenosine A2A receptors in several models of neurotoxicity suggests a toxic effect for endogenous adenosine

In the light of these evidences, in the present study, by using in vitro models of DA neurons, we investigated: (i) whether A2A antagonists protect DA containing neurons against methamphetamine (METH); (ii) whether activation of A2A receptors produce neurodegeneration. This was done either using A2A agonist receptor NECA or the endogenous compound adenosine; (iii) whether specific cell mechanisms are involved in these phenomena.

We found that A2A antagonists protect DA cells against METH neurotoxicity. Moreover, we found that NECA and adenosine both produced a toxic effects.

In the light of the key role of autophagy in modulating the survival of DA neurons we found that A2A antagonists increase, while A2A agonists decrease, autophagy. These results suggest that neuroprotection induced by A2A antagonists may be mediated by enhancement of autophagy. As expected we found that pretreatment with a non-adenosine related inducer of autophagy produced the same protective effects obtained with A2A antagonists.

Our data indicate for the first time, that A2A antagonists are protective in DA neurons against METH. Such an effect appear to be mediated by the enhancement of autophagy.

On the other hand we found that activation of A2A receptor produces neurotoxicity.

Interestingly these effects was reproduced by administering endogenous adenosine. This suggests that adenosine may produce neurodegeneration by inhibiting the autophagy pathway.

Keywords: Adenosine receptors A2A, methamphetamine, autophagy, neurodegeneration, dopamine