Effect of the adenosine A\textsubscript{2A} receptor agonist CGS21680, and iron chelator VK-28, on the \textit{de novo} synthesis of kynurenine pathway metabolites in Huntington’s disease mice.

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The kynurenine pathway (KP) of tryptophan degradation is hypothesized to play an important role in Huntington’s disease, a neurodegenerative disorder caused by an abnormal polyglutamine expansion in the huntingtin protein. The brain levels of two KP metabolites, the excitotoxin quinolinic acid (QUIN) and its precursor, the free radical generator 3-hydroxykynurenine (3-HK), are elevated in patients during early stages of the disease, but the mechanism by which kynurenine pathway up-regulation occurs in Huntington disease is still unknown.

In the present study, we evaluated the possible effect of two potential therapeutic agents, the adenosine A\textsubscript{2A} receptor agonist CGS21680 and the iron chelator VK-28, on the \textit{de novo} synthesis of kynurenine metabolites after intrastriatal injection of \textsuperscript{3}H-kynurenine. We administered the drugs systemically in wild-type and R6/2 transgenic mice at 10-11 weeks of age. Then (after 2 h for CGS21680 and 1 h for VK-28) we injected tritiated kynurenine into the striatum (2.5 µCi). For the detection of kynurenine pathway metabolites, tissues homogenates were analyzed by HPLC.

After acute administration of CGS21680, there were significant differences in \textsuperscript{3}H-3-HK levels of treated animals, but no changes in QUIN levels. In contrast, VK-28 had no significant effect on the production of tritiated KP metabolites in treated animals compared to controls. These data suggested that there was no specific interaction between these drugs and the KP.