EFFECT OF THE SELECTIVE ANTAGONISM OF ADENOSINE A_{2A} RECEPTOR ON MOTOR BEHAVIOR AND NEURONAL NITRIC OXIDE SYNTASE EXPRESSION IN THE STRIATUM OF HUNTINGTON TRANSGENIC MICE

Cipriani Sara[1], Melani Alessia[1], Gianfriddo Marco[2], Vannucchi Maria G[3], Pedata Felicita[1]

[1]Department of Preclinical and Clinical Pharmacology M.A. Mancini, University of Florence, Italy,
[2] Siena Biotech S.p.A., 53100 Siena, Italy,
[3]Department of Anatomy, Istology and Forensic Medicine, University of Florence, Italy

Huntington disease (HD) is an autosomal, dominantly inherited neurodegenerative disorder characterized by progressive motor and cognitive disturbances caused by an expansion in CAG repeats in the IT15 gene which encodes the huntingtin protein. A pathogenetic role for excitotoxic cell death mediated by increased glutamatergic excitoxicity in the striatum has been proposed. Drugs able to modulate striatal levels of glutamate are thus candidates to protect striatal neurons from neurodegeneration. Extracellular concentration of adenosine increases in the striatum of HD transgenic R6/2 mice in symptomatic phase (10-11 week) and the selective antagonist of adenosine A_{2A} receptors, SCH 58261, directly administered in the striatum, significantly reduces glutamate outflow (1).
In this work we investigated the effect of SCH 58261 chronically administered (0.01 mg/Kg i.p. twice a day for two weeks) on body weight and motor deficit of HD (R6/2) mice (n=7-8) at 9-10 weeks of age At this age, HD mice display a clear clasping behaviour and impairment in the rotarod and inclined plane tests. SCH 58261 did not modify the body weight and did not affect rotarod test. The drug tended to improve the inclined plane test although it incremented clasping behaviour in comparison to vehicle-treated mice (n=6-8).
Double immunostaining studies by antibodies against the c-fos early gene protein and against neurons showed that c-fos protein was not changed in the brain of transgenic mice (n=5) in comparison to wild type mice (n=5) at 10 week of age, but it was clearly incremented in the piriform cortex in 14 week old mice (n=2). The increase in c-fos expression indicates late cell activation limited to the cortex.
Immunostaining studies by antibodies against neuronal nitric oxide syntase (nNOS) and neurons showed that nNOS protein expression was decreased in the striatum of HD mice at 10 weeks of age (n=6) in comparison to wild-type mice (n=5). On the contrary, nNOS expression in 14 week old transgenic mice (n=2) is comparable to that of wild-type mice (n=3). Increased expression of nNOS is likely related to neuronal and animal survival. SCH 58261, subchronically administered (0.01 mg/kg i.p. twice a day), significantly increased nNOS expression in the striatum (n= 3) in comparison to vehicle-treated mice (n=2).
Results are relevant to the putative therapeutic utility of adenosine A_{2A} receptor ligands in HD.
(The work was supported by a grant of Fondazione Monte dei Paschi di Siena, Italy).

1. Gianfriddo M., Melani A., Giovannini M.G. and Pedata F. **(**2004) Neurobiol.Dis. 17: 77-88.