ADENOSINE A_{2A} RECEPTORS IN THE MODULATION OF NEUROTROPHIC EFFECTS IN PHYSIOLOGIC AND PATHOLOGIC CONDITIONS

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Brain-derived neurotrophic factor (BDNF), a member of neurotrophin family, is able to enhance synaptic transmission and to regulate neuronal proliferation and survival. Both BDNF and its tyrosine kinase receptors (TrkB) are highly expressed in the hippocampus, where an interaction with adenosine A_{2A} receptors (A_{2A}Rs) has been recently reported (1). To further investigate the role of A_{2A}Rs in the regulation of BDNF, we evaluated whether the levels and the functional effects of BDNF were changed in the hippocampus of A_{2A} receptor knock-out (KO) vs. wild-type (WT) mice. In electrophysiological experiments in hippocampal slices (450 um) from WT mice, application of BDNF (10ng/ml) increased the slope of excitatory post-synaptic field potentials (fEPSPs) recorded in the stratum pyramidale of CA1 region (113± 6.7%, $P<0.05$ *vs* basal, N=11). The co-application of the selective A_{2A} antagonist ZM 241385 (50 nM) abolished the BDNF-induced potentiation of fEPSP slope (99.43±1.05%, N=6). Conversely, in slices from A_{2A}R KO mice, BDNF was no longer able to increase the fEPSP slope and it even reduced it (88.83±3.29 $P<0.05$ *vs* basal and *vs* WT, N= 12). Western Blot (WB) experiments revealed that such a reduced functional ability of BDNF did not depend on a reduction in TrkB R protein. Conversely, enzyme immunoassay studies showed a significant reduction in hippocampal BDNF levels in A_{2A}R KO vs WT mice (-31%, $P<0.05$, N=6). Having found an even marked reduction in the striatum of A_{2A}R KO mice (-53%, $P<0.05$, N=6), and since both BDNF and A_{2A}Rs have been implicated in the pathogenesis of Huntington's disease (HD, an inherited striatal neurodegenerative disease), we then evaluated whether the pharmacological blockade of A_{2A}Rs could influence striatal levels of BDNF in experimental models of HD. Two models of HD were used: the quinolinic acid-induced lesion in rats and the transgenic R6/2 mice. In both QA-lesioned rats (N=5) and early symptomatic (8 weeks) HD mice (N=4), striatal levels of BDNF tended to increase, most probably reflecting a compensatory response. The A_{2A}R antagonist SCH 58261 (0.01 mg/kg i.p.) markedly reduced striatal BDNF levels in both cases (-49±8 and -37±6% in rats and mice, respectively, $P<0.05$ vs vehicle in both cases). These results indicate that the presence and the tonic activation of A_{2A}Rs are necessary to allow BDNF-induced potentiation of synaptic transmission and to sustain a normal BDNF tone. They also suggest that A_{2A}R blockade might negatively influence striatal neurodegenerative diseases by reducing BDNF levels.

(1) J. Neurosci. 2004, 24(12): 2905.