Role of A_{2A} adenosine receptors in multiple sclerosis patients

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Adenosine has been shown to affect various physiological and pathological processes acting with four cell surface G protein-coupled receptors named as A_1, A_{2A}, A_{2B} and A_3 adenosine receptors (ARs) (Borea et al., 2015). An altered expression of A_{2A}ARs has been found in different inflammation-related pathologies suggesting the central role of this receptor in the pathogenesis of inflammatory diseases (Varani et al., 2009). Several studies have compared AR expression in human tissues and peripheral blood cells from normal and pathological conditions showing a positive association (Varani et al., 2003; 2006; 2011). A high correlation between A_{2A}AR density or functionality and Unified Parkinson's Disease Rating Scale (UPDRS) the most widely used clinical scale for Parkinson's disease that gives a comprehensive coverage of motor symptoms of the disease was found (Varani et al., 2010). In amyotrophic lateral sclerosis (ALS) the density of A_{2A}ARs was significantly increased and a protective role in ALS patients probably based on the well-known anti-inflammatory role of A_{2A}AR activation was reported (Vincenzi et al., 2013). In the present research the expression and the functionality of A_{2A}ARs in multiple sclerosis (MS) have been investigated by using different experimental approaches. A significant up-regulation of A_{2A}ARs in lymphocytes from MS patients in comparison with healthy subjects was described. The significance of the A_{2A}AR over-expression as a compensatory mechanism to limit inflammation was explored evaluating the anti-inflammatory effects of a well-known A_{2A}AR agonist. In human lymphocytes, the A_{2A} stimulation inhibited the release of different pro-inflammatory cytokines such as IL-1β, IL-6, IL-17 and INF-γ. The activation of the A_{2A}ARs mediates the reduction of the transcription factor NF-kB and of TNF-α levels. The MMP-3 and MMP-9 plasma levels were significantly increased in MS patients. One of the key features of MS is the transmigration of lymphocytes from the blood to the central nervous system an event mainly mediated by the adhesion molecule VLA-4 that is significantly upregulated in this disease. Interestingly, the A_{2A} activation was able to reduce VLA-4 expression in lymphocytes from MS patients. These data highlighted the pivotal role of A_{2A}ARs in relevant neurodegenerative disorders indicating a possible protective effect of this receptor that could represent a starting point for the study of alternative therapeutics based on A_{2A}AR modulation.

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