ROLE OF ADENOSINE A2B RECEPTORS IN THE MODULATION OF ENTERIC GLIAL CELL ACTIVITY IN A MODEL OF OBESITY

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Introduction: Enteric glial cells (EGCs) appears to be critically involved in the onset of enteric neuropathy and the maintenance of an inflammatory condition under pathological conditions, such as obesity. The adenosine pathway exerts a pivotal role in bowel dysmotility associated with obesity, mainly via adenosine A_{2B} receptors (A_{2B}Rs). However, data regarding the contribution of this receptor subtype to the modulation of EGC activity, and thereby its involvement in the pathogenesis of bowel motor dysfunctions occurring in patients with obesity, are lacking. The aim of the present study was to investigate the role of A_{2B}Rs in the modulation of EGC activity in an experimental model of obesity.

Methods: To mimic the *in vivo* features of a high-fat diet (HFD) exposure, cultured rat EGCs were incubated with palmitate (PA, 400 mM) and/or lipopolysaccharide (LPS, component of Gram-negative bacteria, 10 mg/ml), in the absence or in the presence of BAY60-6583(selective A_{2B}R agonist, 0.05mM) or MRS1754(A_{2B}R antagonist, 0.25mM). The expression of toll-like receptor (TLR)-4, inducible nitric oxide synthase (iNOS) and phospho/c-Jun N-terminal kinase (JNK) was assessed by western blot. The release of interleukin-1β (IL-1β), glial cell-derived neurotrophic factor (GDNF) and substance P (SP) into the culture medium of EGCs was determined by ELISA.

Results: In cultured EGCs, co-incubation with PA and LPS increased TLR-4expression, JNK phosphorylation as well as IL-1β, GDNF and SP release, as compared with control cells. Under the above conditions, there was a trend to increase in iNOS expression, which, however, did not achieve the level of statistical significance. Treatment with BAY60-6583, in the presence of PA and LPS, determined a significant reduction of TLR-4expression as well as a decrease in IL-1β, GDNF and SP release. Moreover, the pharmacological activation of A_{2B}Rs reduced iNOS expression and the level of JNK phosphorylation. Such effects were significantly antagonized under incubation of ECGs with MRS1754.

Discussion and conclusions: In vitro incubation of EGCs with PA and LPS, aimed at mimicking an *in vivo* exposure to a HFD, elicited an increased release of both IL-1β and SP, suggesting an involvement of these cells in supporting the enteric inflammation and the abnormal tachykininergic responses associated with obesity. The pharmacological stimulation of A_{2B}Rs on EGCs, beside reducing IL-1β release, counteracted also the increase in SP release, highlighting a potential modulatory action of A_{2B}Rs on SP release from EGCs through the activation of GDNF pathway. Overall, these results indicate the A_{2B}R as a putative target for the pharmacological modulation of EGC dysfunctions associated with obesity.