A_{2A} and A_{2B} Adenosine receptors affect HIF-1α signalling in activated primary microglial cells

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Microglia are central nervous system (CNS)-resident immune cells, that play a crucial role in neuroinflammation (Kettenmann et al., 2013). Hypoxia-inducible factor-1 (HIF-1), the main transcription factor of hypoxia-inducible genes, is also involved in the immune response, being regulated in normoxia by inflammatory mediators (de Lemos et al., 2013). Adenosine is an ubiquitous nucleoside that has an influence on many immune properties of microglia through interaction with four receptor subtypes (Fredholm, 2012). The aim of this study was to investigate whether adenosine may affect microglia functions by acting on HIF-1α modulation. Primary murine microglia were activated with lipopolysaccharide (LPS) with or without adenosine, adenosine receptor agonists and antagonists and HIF-1α accumulation and downstream genes regulation were determined. Adenosine increased LPS-induced HIF-1α accumulation leading to an increase of HIF-1α target genes involved in cell metabolism (Glucose transporter-1, GLUT-1) and pathogens killing (inducible nitric-oxide synthase, iNOS) but did not induce HIF-1α dependent genes related to angiogenesis (vascular endothelial growth factor, VEGF) and inflammation (tumor necrosis factor-α, TNF- α). The stimulatory effect of adenosine on HIF-1α and its target genes was essentially exerted by activation of A_{2A} through p44/42 and A_{2B} subtypes via p38 mitogen-activated protein kinases (MAPKs) and Akt phosphorylation. Furthermore the nucleoside raised VEGF and decreased TNF-α levels, by activating A_{2B} subtypes. In conclusion adenosine increases GLUT-1 and iNOS gene expression in a HIF-1α-dependent way, through A_{2A} and A_{2B} receptors, suggesting their role in the regulation of microglial cells function following injury. However, inhibition of TNF-α adds an important anti-inflammatory effect only for the A_{2B} subtype.

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