A_1 and A_3 adenosine receptors inhibit LPS-induced Hypoxia-inducible factor-1 accumulation in hypoxic murine astrocytes

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Adenosine (Ado) exerts neuroprotective and anti-inflammatory functions by acting through four receptor subtypes A_1, A_{2A}, A_{2B} and A_3. Astrocytes are one of its target in the central nervous system. Hypoxia-inducible factor-1 (HIF-1), a master regulator of oxygen homeostasis, is induced after hypoxia, ischemia and inflammation and plays an important role in brain injury. HIF-1 is expressed by astrocytes, however the regulatory role played by ado on HIF-1α modulation induced by hypoxic and inflammatory conditions has not been investigated.

Primary murine astrocytes were activated with lipopolysaccharide (LPS) with or without ado, ado receptor agonists, antagonists and receptor silencing, before exposure to hypoxia. HIF-1α accumulation and downstream genes regulation were determined.

In murine astrocytes ado inhibited LPS-increased HIF-1α accumulation under hypoxia, through activation of A_1 and A_3 ado receptors. In cells incubated with the blocker of p44/42 MAPK, LPS-induced HIF-1α accumulation and ado-mediated inhibition were significantly decreased, suggesting the involvement of p44/42 MAPK in both these effects. A series of angiogenesis and metabolism related genes were modulated by hypoxia in an HIF-1 dependent way, but not additionally increased by LPS and not modified by ado. Instead, genes involved in inflammation, like inducible nitric-oxide synthase (iNOS) and A_{2B} ado receptors, were strongly stimulated by LPS in concert with hypoxia and were inhibited by ado, through A_1 and A_3 receptor subtypes.

In conclusion Ado A_1 and A_3 receptors reduce the LPS-mediated HIF-1α accumulation in murine astrocytes, resulting in a downregulation of genes involved in inflammation like iNOS and A_{2B} ado receptors.