A2B adenosine receptors stimulate IL-6 production in primary murine microglia through p38 MAPK kinase pathway

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The hallmark of neuroinflammation is the activation of microglia, the immunocompetent cells of the CNS, releasing a number of proinflammatory mediators implicated in the pathogenesis of neuronal diseases (Kettenman et al., 2013). Adenosine is an ubiquitous autacoid regulating several microglia functions through four receptor subtypes named A1, A2A, A2B and A3 (ARs), that represent good targets to suppress inflammation occurring in CNS (Borea et al., 2016). Here we investigated the potential role of ARs in the modulation of IL-6 secretion and cell proliferation in primary microglial cells. The A2BAR agonist 2-[[6-Amino-3,5-dicyano-4-[4-(cyclo-propylmethoxy)phenyl]-2-pyridinyl]thio]-acetamide (BAY60-6583) stimulated IL-6 increase under normoxia and hypoxia, in a dose- and time-dependent way. In cells incubated with the blockers of phospholipase C (PLC), protein kinase C epsilon (PKC-ε) and PKC delta (PKC-) the IL-6 increase due to A2BAR activation was strongly reduced, whilst it was not affected by the inhibitor of adenylyl cyclase (AC). Investigation of cellular signalling involved in the A2BAR effect revealed that only the inhibitor of p38 mitogen activated protein kinase (MAPK) was able to block the agonist's effect on IL-6 secretion, whilst inhibitors of pERK1/2, JNK1/2 MAPKs and Akt were not. Stimulation of p38 by BAY60-6583 was A2BAR-dependent, through a pathway affecting PLC, PKC-ε and PKC- but not AC, in both normoxia and hypoxia. Finally, BAY60-6583 increased microglial cell proliferation involving A2BAR, PLC, PKC-ε, PKC- and p38 signalling.

In conclusion, A2BARs activation increased IL-6 secretion and cell proliferation in murine primary microglial cells, through PLC, PKC-ε, PKC- and p38 pathways, thus suggesting their involvement in microglial activation and neuroinflammation (Merighi et al., 2017).

Kettenman et al. (2013). Neuron 77: 10-18.

Borea et al. (2016). Trends Pharmacol. Sci. 37: 419-34.

Merighi et al. (2017). Pharmacol. Res. 117: 9-19.