Involvement of EPAC and TPL2 in IL-1β production in microglial cells following activation of β-adrenergic receptors

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Endogenous noradrenaline (NA) has multiple bioactive functions and, in the central nervous system (CNS), has been implicated in modulating neuroinflammation via β-adrenergic receptors (β-ARs). Microglia, resident macrophages in the CNS, have a central role in the brain immune system and have been reported to be activated by NA. However, intracellular signaling mechanisms of the AR-mediated proinflammatory responses of microglia are not fully understood. Using a rapid and stable *in vitro* reporter assay system to evaluate IL-1β production in microglial BV2 cells, we found that NA and the β-AR agonist isoproterenol upregulated the IL-1β reporter activity. This effect was suppressed by β-AR antagonists. We further examined the involvement of EPAC (exchange protein directly activated by cAMP) and TPL2 (tumor progression locus 2, MAP3K8) and found that inhibitors for EPAC and TPL2 reduced AR agonist-induced-IL-1β reporter activity. These inhibitors also suppressed NA-induced endogenous *Il1b* mRNA and IL-1β protein. Our results suggest that EPAC and TPL2 are involved in β-AR-mediated IL-1β production in microglial cells, and extend our understanding of its intracellular signaling mechanism.