The activation of μ-opioid receptor potentiates the LPS-induced activation of NF-kB promoting an inflammatory phenotype in cultured microglia

S. Gessi[1], P.A. Borea[1], S. Bencivenni[1], K. Varani[1], S. Merighi[1]

[1]Dept. of Medical Sciences, Pharmacology Unit, School of Medicine, University of Ferrara, Italy

Morphine activates PKCε and Akt pathway upstream of ERK1/2 to mediate μ-opioid receptor-induced proinflammatory phenotype in microglial cells (Merighi et al., 2013). In the present study, we examined whether activation of μ-opioid receptor affects the activation of NF-kB to induce proinflammatory signalling and whether PKCepsilon, Akt and ERK1/2 kinases are mediators of this event. Activation of PKCε by morphine increased the DNA-binding activity of NF-kB. PKCε mRNA depletion or inhibition diminished NF-κB translocation to the nucleus with subsequent impairment of NF-kB activation in response to morphine in LPS-activated microglia. PKCε-induced activation of NF-kB was abolished by inhibition of ERK1/2 and Akt pathways. The blockade of μ-opioid receptor decreased the activation of IkappaB (IkB) kinase, reducing the IkB degradation, thereby decreasing p65 NF-kB nuclear translocation. Finally, the NF-κB inhibitors Bay 11-7082 and MG 132 abolished the proinflammatory action of morphine in microglia through the reduction of NO, TNF-α, IL-1ß and IL-6 production. The identification of PKCε as a crucial upstream regulator of NF-κB signalling in microglia argues for a central role of this kinase in the control of pathways involved in neuroinflammation development and progression. Thus, targeting the morphine-PKCε-NF-κB pathway may provide novel means for the treatment of neuroinflammation or other diseases where this pathway may prove to be relevant.

Merighi et al. (2013) *Biochem Pharmacol* 86: 487-496.