Abstract

Microglial activation is the most important component of neuroinflammation. It appears that opioids may affect microglial M1/M2 polarization in different ways depending on the type of receptor employed. In addition to opioid receptors, Toll-like receptor 4 (TLR4) of the innate immune system can also be activated by some opioid ligands and thus elicit specific cellular responses. Although opioid receptors (ORs) are known to regulate neurotransmission in various peptidergic neurons, their potential role in modulation of microglial function remains largely unknown. In this study, we investigated the effects of OR agonists, namely DAMGO, DADLE, and U-50488, on polarization and metabolic modulation of C8-B4 microglial cells. Our findings have revealed that opioids effectively suppress lipopolysaccharide (LPS)-triggered M1 polarization and promote the M2 polarization state. This was evidenced by decreased phagocytic activity, decreased production of nitric oxide (NO), diminished expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-86, and IL-12 beta p40, along with an increased migration rate and elevated expression of anti-inflammatory markers such as IL-4, IL-10, IL-13 arginase 1, and CD206 in microglia compared to cells influenced by LPS. Furthermore, we have demonstrated that opioids exert their influence on microglial polarization via the TLR4/TREM2/NF-κB signaling pathway. There is increasing evidence for a role of metabolic reprogramming in regulating microglial behavior. Nevertheless, the potential role of opioids in modulating mitochondrial function and energy metabolism in microglia has not been explored. Our findings that opioid ligands exert cytoprotective effects via the mechanism affecting LPS-induced ROS production, NADPH synthesis, and glucose uptake contribute to a better understanding of the link between the modulatory effects of opioids, metabolic states, and inflammatory responses in microglia. Interestingly, opioids elevated the level of reduced glutathione, increased ATP content, and enhanced mitochondrial respiration in microglial cells exposed to LPS. These beneficial effects were associated with the upregulation of the Nrf2/HO-1 pathway. These results indicate that activation of opioid signaling can regulate anti-inflammatory and antioxidant effects by preserving mitochondrial function while eliminating ROS in microglia. Inhibition of inflammatory stimuli may therefore be part of the future development of therapeutic approaches to promote proper microglial function, which is crucial for the prevention and treatment of neurodegenerative diseases.