

OC.5-OREXIN-A PREVENTS LPS-INDUCED NEUROINFLAMMATION AT THE LEVEL OF THE GUT-BRAIN AXIS

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Gut-brain axis, the bidirectional communication system between the central and the enteric nervous systems, is regulated also by the gut microbiota. In states of dysbiosis, the intestinal epithelial barrier (IEB) permeability is increased as consequence of disruption of the epithelial tight junction protein network, thus promoting endotoxemia, i.e. bacterial lipopolysaccharides (LPSs) translocation and systemic circulation of pro-inflammatory cytokines. Orexin-A (OX-A), a neuropeptide implicated in many physiological functions, is produced mainly in the lateral hypothalamic area but also in the myenteric plexus, where the OX-A receptor-1 (OX-1R) is located on the plasma membrane of enteric neurons. Several lines of evidence suggest a role of OX-A on the microglia activation. Here, we sought to investigate if OX-A is able to prevent the increase of IEB permeability induced by LPS and of consequent activation of microglia. In a co-culture system with intestinal epithelial Caco-2 cells in the apical side and murine primary culture of microglia in the basolateral side, we demonstrated that treatment with OX-A on Caco-2 cells preserve the expression of occludin, the main component of protein forming the tight junction network, and activation of microglia induced by LPS. These protective effects are reversed by OX-1R antagonist (SB334867). These data were confirmed by in vivo studies, showing that the i.p. injection of OX-A coupled with LPS prevented the increase of IEB permeability and microglia activation in an OX1R-dependent manner, since SB334867 treatment inhibits the OX-A beneficial effects. In conclusion, our results suggest the role of OX-A as an epithelial barrier protective factor that may prevent LPS translocation to the CNS and, consequently, neuroinflammation.

