Abstract

Zolpidem, a non-benzodiazepine hypnotic, is primarily used to treat insomnia. In a previous study, pior treatment with non-benzodiazepine receptor agonists was associated with inflammation. The present study aimed to clarify the association between the effects of zolpidem and inflammation in mice treated with lipopolysaccharide (LPS), a known model of inflammation. We assessed the zolpidem-induced loss of righting reflex (LORR) duration 24 h after LPS treatment in mice. Additionally, the expressions of γ-aminobutyric acid $(GABA)_A$ receptor subunit and K^+-Cl^- cotransporter isoform 2 (KCC2) mRNA in the hippocampus and frontal cortex were examined in LPS-treated mice. Pretreatment with LPS was associated with significantly prolonged duration of zolpidem-induced LORR compared to control mice. This effect was significantly attenuated by administering bicuculline, a $GABA_A$ receptor antagonist, or flumazenil, a benzodiazepine receptor antagonist, in LPS-treated mice. Compared to controls, LPS-treated mice showed no significant change in the expression of $GABA_A$ receptor subunits in the hippocampus or frontal cortex. Bumetanide, an Na^+-K^+-$2Cl^-$ cotransporter isoform 1 blocker, attenuated the extended duration of zolpidem-induced LORR observed in LPS-treated mice. LPS significantly decreased *Kcc2* mRNA expression in the hippocampus and the frontal cortex. These findings suggest that inflammation increases zolpidem-induced LORR, possibly through a reduction in KCC2 expression.

Keywords: lipopolysaccharide, zolpidem, $GABA_A$ receptor, K^+-Cl^- cotransporters