Inhibition of soluble epoxide hydrolase prevents lipopolysaccharide-induced inflammatory hyperalgesia in mice: Contribution of NLRC4 Inflammasome, NLRC3, NOX, iNOS, and nNOS

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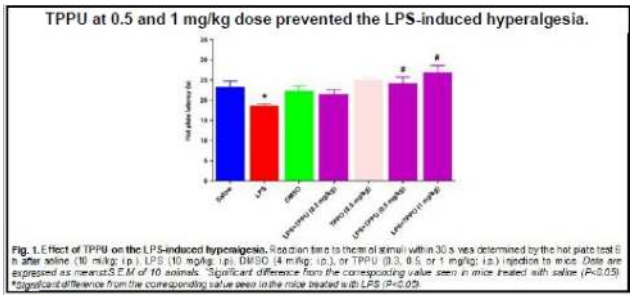
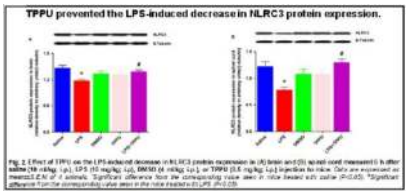
Background and aim: NLRC4 inflammasome and antiinflammatory NLRC3 has been implicated in the pathogenesis of several diseases associated with systemic inflammation such as septic shock. In recent years, it has also been suggested that sEH inhibitors may have a therapeutic potential in NLR-related inflammatory diseases. The aim of this study was to determine whether inhibition of sEH prevents inflammatory pain at the supraspinal level caused by bacterial LPS in mice as well as changes in expression of NLRC3, caspase-1/11, NOX, iNOS, and nNOS that may regulate NLRC4/ASC/procaspase-1 inflammasome formation and activity by using a selective sEH inhibitor, TPPU.

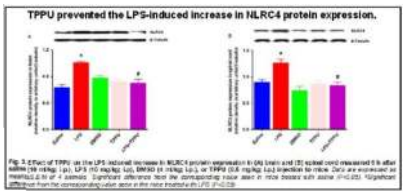
Methods: Male mice received saline, LPS (10 mg/kg), DMSO, and/or TPPU (0.3, 0.5, or 1 mg/kg). Reaction time to thermal stimuli within 30 s was evaluated after 6 h. The mice were euthanized and brains and spinal cords were collected for measurement of NLRC4, ASC, caspase-1/11, IL-1β, NLRC3, gp91^{phox}, p47^{phox}, nitrotyrosine, iNOS, nNOS, and β-tubulin protein expression by immunoblotting.

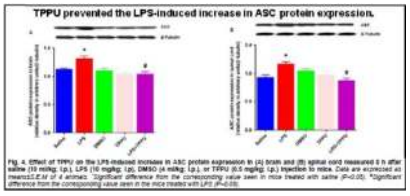
Results: LPS-induced hyperalgesia was associated with a decrease in NLRC3, iNOS, and nNOS protein expression as well as an increase in expression of NLRC4, ASC, caspase-1/11, IL-1β, NOX subunits (gp91^{phox} [NOX2] and p47^{phox} [NOXO2]), and nitrotyrosine protein expression. The LPS-induced changes were prevented by TPPU at 0.5 mg/kg dose.

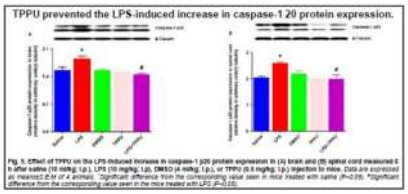
Conclusions: The results suggest that inhibition of NLRC4/ASC/pro-caspase-1 inflammasome formation and activity by sEH inhibition prevents inflammatory hyperalgesia induced by LPS in mice as well as changes in NOX2, NOXO2, iNOS, and nNOS expression/activity.

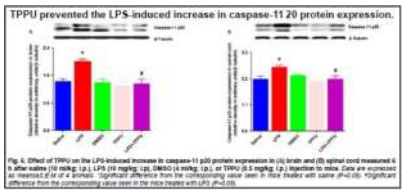


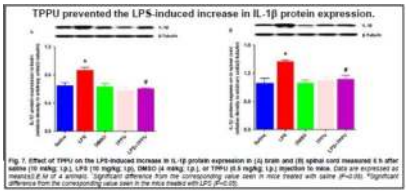


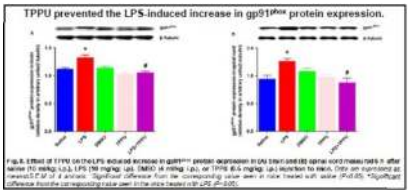


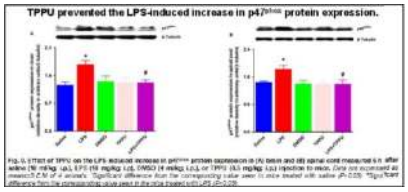


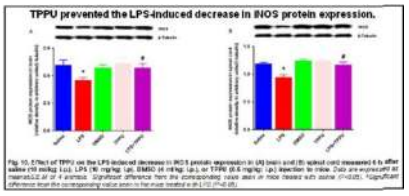


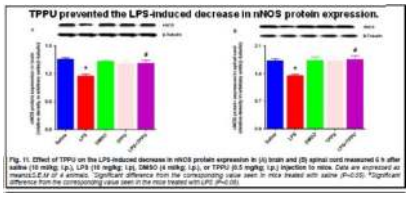


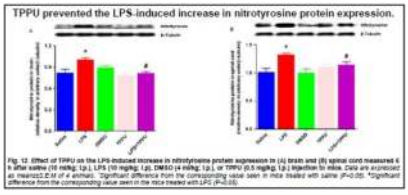


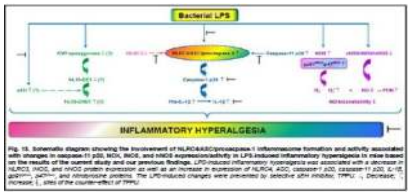












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