Effects of transrepression-selective liver X receptor (LXR) ligands on inflammasome activation of microglia and neural progenitor cells

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[Introduction] It is recently reported that sustained activation of inflammasomes (cytosolic protein complexes) in microglia and neural progenitor cells (NPC) may induce neuroinflammation and impaired neurogenesis in neurodegenerative diseases. While liver X receptor (LXR) activation induces transcription of lipid metabolism related genes through a mechanism called transactivation, the activation suppresses expression of genes, such as interleukin-6 (IL-6) and IL-1beta, a mechanism called transrepression. We have developed transrepression-selective LXR ligands which have anti-inflammatory actions without causing hypertriglyceridemia. We determined the effects of transrepression-selective LXR ligands on inflamasome activation of microglia and NPC.

[Materials and Methods] Activation of inflammasomes in 6-3 microglia cell clone or NPC stimulated by TNF and LPS was examined by the expression of inflammasome components (NLRP3 or caspase-1), IL-1beta, or IL-18 using Western blot analysis. The differentiation potential of NPC into neural cells was evaluated by NeuN expression using Western blot analysis. A transrepression-selective LXR ligand (AA70 or M2-76) were pretreated prior to the stimulation by TNF and LPS.

[Results] Stimulation with TNF and LPS induced caspase-1 activation and production of IL-1beta and IL-18 in microglia or NPC. Pretreatment with either AA70 or M2-76 significantly inhibited the inflammasome activation. In addition, stimulation with TNF and LPS significantly suppressed NeuN expression in the differentiated NPC. Pretreatment with either AA70 or M2-76 also significantly inhibited the suppressive effect.

[Conclusion] Pretreatment of microglia or NPC with transrepression-selective LXR ligands inhibited inflammasome activation and suppression of neural differentiation by TNF and LPS.