Name: Palsamy Periyasamy Email: palsamy.periyasamy@unmc.edu

Epigenetic Regulation of NLRP6 Inflammasome in Methamphetamine-Induced Neuroinflammation and Astrocyte Pyroptosis

Abiola Oladapo[1,2], Shilpa Buch[2], Palsamy Periyasamy[2]

[1]Department of Genetics, cell biology and Anatomy, University of Nebraska Medical Center, Omaha, Nebraska, USA
[2]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, Nebraska, USA

Methamphetamine (Meth) abuse is a major public health issue, contributing to neuroinflammation and neurodegeneration by activating glial cells in the central nervous system (CNS). Recent evidence points to the inflammasome as a crucial mediator of cellular activation in this process. This study investigated the role of the astrocyte-specific inflammasome, NOD-like receptor family pyrin domain-containing protein 6 (NLRP6), in Meth-induced astrocytic pyroptosis and subsequent neuroinflammation. Using mouse primary astrocytes exposed to Meth, we demonstrated a dose-dependent upregulation of NLRP6 and glial fibrillary acidic protein (GFAP), accompanied by increased pyroptosis. Time-dependent studies further confirmed the upregulation of NLRP6 and its signaling mediators. Gene silencing experiments using NLRP6-specific siRNA verified the involvement of NLRP6-inflammasome signaling in Meth-induced astrocyte activation and pyroptotic cell death. Additionally, Meth exposure led to a reduction in brain-enriched miR-152-3p expression, which was inversely correlated with NLRP6 levels, indicating epigenetic regulation of NLRP6. In vivo experiments in Meth-administered mice validated these findings across the frontal cortex, striatum, and hippocampus, confirming the critical role of NLRP6 in mediating astrocyte-specific neuroinflammation. Collectively, this study highlights NLRP6-dependent pyroptosis as a key mechanism in Meth-induced neuroinflammation and underscores the therapeutic potential of targeting the NLRP6 inflammasome pathway to mitigate CNS damage associated with Meth abuse.

Hyperlink to relevant publication:

1. Oladapo A, Kannan M, Singh S, Buch S, Periyasamy P. Methamphetamine-Mediated Astrocytic Pyroptosis and Neuroinflammation Involves miR-152–NLRP6 Inflammasome Signaling Axis. Available at SSRN: http://dx.doi.org/10.2139/ssrn.4931000 (Preprint).
2. Oladapo A, Jackson T, Menolascino J, Periyasamy P. Role of pyroptosis in the pathogenesis of various neurological diseases. Brain Behav Immun. 2024;117:428-46. Epub 20240207. doi: 10.1016/j.bbi.2024.02.001. PubMed PMID: 38336022; PMCID: PMC10911058.