Activated microglia enhance astroglial neuroprotective pentose-phosphate pathway through the activation of the Keap1/Nrf2 system by nitric oxide

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ABSTRACT

Objective: Both astroglia and microglia express toll-like receptor 4 (TLR4) that plays a pivotal role in the stroke-induced inflammatory response. Endogenous ligands for TLR4 in the ischaemic brain induce inflammatory responses. Both reactive oxygen species (ROS) and nitric oxide (NO) produced by TLR4 activation play harmful roles in neurovascular unit damage. Although astroglia exhibit pro-inflammatory responses upon TLR4 stimulation by lipopolysaccharide (LPS), they may also play cytoprotective roles via the activation of the pentose-phosphate pathway (PPP), reducing oxidative stress with glutathione. We investigated the mechanism by which astroglia reduce oxidative stress via the activation of PPP in concert with microglia.

Methods: In vitro experiments were performed using cells prepared from Sprague-Dawley rats. Coexisting microglia in the astroglial culture were chemically eliminated using L-leucine methyl ester (LME). Cells were exposed to LPS (0.1–100 μg/mL) for 12–18 h. PPP activity was measured using [1-14C]glucose and [6-3H]glucose. ROS and NO production were measured using fluorescent indicators.

Results: Cultured astroglia exposed to LPS elicited 20% increase in PPP flux, and these actions of astroglia appeared to involve Nrf2. However, the chemical depletion of coexisting microglia eliminated both increases in PPP and astroglial nuclear translocation of Nrf2. LPS-induced ROS and NO production were unaffected. U0126 also eliminated LPS-induced PPP activation in astroglial-microglial culture, indicating that microglia-derived NO mediated astroglial PPP activation in astroglial-microglial culture, indicating that microglia-derived NO mediated astroglial PPP activation. SNAP, an NO donor, did not induce PPP activation in astroglia.

Conclusions: Astroglia in concert with microglia may play a cytoprotective role for countering oxidative stress in stroke.

MAIN POINTS

DAMPs derived from damaged tissue stimulate microglial TLR4, resulting in NO production and neuronal damage. NO released from microglia (M1), in turn, activates astroglial Keap1/Nrf2 system, inducing neuroprotective roles of astroglia (A2).

REFERENCES


A model for the Kelchlike ECH-associated protein 1 (Keap1) nuclear factor erythroid 2-related factor 2 (Nrf2) interaction and activation (Takahashi S, et al: Clinical Neurology 52:41-51, 2012)

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