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Sex-dependent Microglia Response to Ischemic Injury in White Matter

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Abstract

White matter damage after ischemic injury contributes significantly to neurological impairments. Microglia survey the environment and maintain axon's function in normal physiological conditions. In grey matter, studies showed a duality of microglia after ischemic injury: exacerbating injury through pro-inflammatory markers or promoting neuroprotection. However, the role of microglia in WM axonal injury remains to be investigated. Nitric oxide synthase (NOS) activation contributes to oxidative damage in ischemia. The expression of NOS isoforms in WM is cell-specific and age-dependent. Particularly, microglia express NOS3 in young WM but both NOS2 and NOS3 isoforms in aging WM. Inhibition of NOS3 exerts functional protection against ischemia in young and aging axons. However, whether this protective effect is mediated through microglia has not been studied. We hypothesize that ischemic injury alters microglial activity and morphology in WM, and NOS3 inhibitor preserves microglial activity and function that contribute to axonal protection against ischemic injury. We used isolated Cx3Cr1-GFP mouse optic nerve, a pure white matter tract, to visualize and quantify the morphological changes of microglia in a model of ischemia.

Confocal live imaging of green fluorescent microglia was captured and quantified at baseline, during 1h of oxygen-glucose deprivation (OGD) with or without L-NIO, a NOS3 inhibitor. In males, OGD altered 90% of microglia quantified by a series of morphological parameters including the complexity of processes, size, and area covered by microglia. In contrast, only 25% of microglia are permanently altered by OGD with L-NIO. Interestingly, in females, OGD affected only 43% of microglia and L-NIO did not change the microglial response.

Our results show that microglia in WM undergo significant morphological changes in ischemic conditions in sex-dependent manners. Also, NOS3 inhibition only protects microglial morphology in males against ischemia-induced alterations. This study supports further investigation of sex- and age-dependent roles of microglia in protecting axonal function.