Effect of N-acetyl-aspartate on microglia metabolism and inflammation

P-30-059

F. Felice[I], G. Lazzarino[II], F. Ciccarone[I], M.R. Ciriolo[I]

[I]Department of Biology, University of Rome Tor Vergata, Via della Ricerca Scientifica, Rome, Italy, [II]Departmental Faculty of Medicine, UniCamillus - Saint Camillus International University of Health and Medical Sciences, Rome, Italy

Neuroinflammation is an important feature involved in neurodegenerative diseases that initially protects the brain from insults, however, it becomes detrimental when sustained. Microglia are resident immune cells of the central nervous system (CNS) that play a central role in chronic inflammatory processes due to an imbalance between the neurotoxic (M1) and neuroprotective (M2) phenotypes. CNS homeostasis is strictly regulated by intricate communication between neurons and glial cells. N-acetyl aspartate (NAA) is among the most synthesized metabolites in the CNS; it is primarily produced by neurons and cleaved by recipient cells yielding acetate and aspartate. While existing data predominantly focuses on NAA's role in oligodendrocytes, where NAA-derived acetyl-CoA is used for myelin synthesis, we present findings on NAA's impact on microglial metabolism and activation. Our study demonstrates that NAA stimulates the mitochondrial oxidative metabolism sustained by an increase in lipid turnover. In particular, the acetate deriving from the catabolism of NAA can replenish the cell with cytosolic acetyl-CoA which then triggers lipid synthesis used by the cell for ATP production through oxidative phosphorylation. Furthermore, we investigated whether NAA could influence LPS/IFNγ-induced M1 polarization. Our findings reveal that NAA mitigates the expression of pro-inflammatory markers, as evidenced by the reduction in iNOS, TNF-α, and IL-6. These results are of particular interest considering that NAA is often considered as a marker of neuronal health. Reduced NAA levels are linked to neuronal loss and dysfunction, making it a potential prognostic marker in neurodegenerative diseases. This work was supported in part by PNRR “MNESYS” (MUR PE00000006).