Glycogen synthase kinase-3 inhibition reduces ischemic cerebral damage, restores impaired mitochondrial biogenesis and prevents ROS production.


Division of Pharmacology, Department of Biomedical Sciences & Biotechnology, University of Brescia, Brescia, Italy.

Abstract

This study was designed to test the hypothesis that improved mitochondrial biogenesis could help reducing ischemic cerebral injury. We found that levels of proliferator-activated receptor γ coactivator 1α and nuclear respiratory factor-1, mitochondrial DNA content and other markers of mitochondrial biogenesis and function were reduced in primary mouse cortical neurons under oxygen-glucose deprivation (OGD). The glycogen synthase kinase-3 (GSK-3) inhibitor SB216763 activated an efficient mitochondrial biogenesis program in control cortical neurons and counteracted the OGD-mediated mitochondrial biogenesis impairment. This was accompanied by the activation of an antioxidant response that reduced mitochondrial reactive oxygen species generation and ischemic neuronal damage. The in vitro effects of SB216763 were mimicked by two other structurally unrelated GSK-3 inhibitors. The protective effects of SB216763 on OGD-mediated neuronal damage were abolished in the presence of diverse mitochondrial inhibitors. Finally, when systemically administered in vivo, SB216763 reduced the infarct size and recovered the loss of mitochondrial DNA in mice subjected to permanent middle cerebral artery occlusion. We conclude that GSK-3 inhibition by SB216763 might pave the way of novel promising therapies aimed at stimulating the renewal of functional mitochondria and reducing reactive oxygen species-mediated damage in ischemic stroke.