GLYCOGEN SYNTHASE KINASE-3β INHIBITION REDUCES TRANSIENT CEREBRAL ISCHEMIA/REPERFUSION INJURY IN THE RAT HIPPOCAMPUS

Benetti Elisa[1], Collino Massimo[1], Thiemermann Christoph[3], Mastrocola Raffaella[2], Gallicchio Margherita[1], Dianzani Chiara[1], Danni Oliviero[2], Aragno Manuela[2] and Roberto Fantozzi[1]

[1]Dep of Anatomy, Pharmacol and Forensic Med., University of Turin, Turin, Italy. [2]Dep of Exp Med and Oncol, University of Turin, Turin, Italy. [3]Centre for Exp Med, Nephrology & Critical Care, William Harvey Research Institute, London, UK

The serine/threonine glycogen synthase kinase (GSK)-3β (EC 2.7.11.1) is abundant in the CNS, particularly in the hippocampus [1], and plays a pivotal role in the pathophysiology of a number of diseases, including neurodegeneration [2]. The study was designed to investigate the role of GSK-3β in the development of cerebral ischemia/reperfusion (I/R) injury. Involvement of GSK-3β was evaluated by assessing the effects displayed by the selective GSK-3β inhibitor, TDZD-8, against I/R injury in the rat hippocampus. TDZD-8 (1 mg/kg, iv.) was administered before and after ischemia (pre-plus-post treatment) or during reperfusion alone (post-treatment) to evaluate its potential as therapeutic strategy. Transient cerebral ischemia (30 min) followed by 1 h or 24 h reperfusion significantly increased generation of reactive oxygen species, modulated superoxide dismutase activity and induced apoptosis (determined as mitochondrial cytochrome c release and Bcl-2 and caspase-9 expression); 24 h reperfusion resulted in high plasma levels of tumour necrosis factor-α and increased expression of cyclooxygenase-2, inducible NO synthase and intercellular adhesion molecule-1. Prophylactic or therapeutic administration of TDZD-8 reduced oxidative stress, apoptosis and inflammatory response without affecting blood glucose levels. These beneficial effects were associated with a reduction of ischemia-induced activation of the mitogen-activated protein kinases JNK1/2 and p38 and nuclear factor-κB. Levels of S100B protein, a marker of cerebral injury used in stroke trials [3], were high in the hippocampi of rats exposed to I/R, but markedly reduced by TDZD-8. Taken together, these data suggest that GSK-3β inhibition attenuates cerebral I/R injury.

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