Betulinic acid protects against cerebral ischemia/reperfusion injury in mice

Dr. Li, Huige , Lu, Qing , Dr. Xia, Ning , Prof. Dr. Förstermann, Ulrich. Johannes Gutenberg University Department of Pharmacology, Obere Zahlbacher Str. 67, 55131 Mainz, Germany.

Increased production of reactive oxygen species and reactive nitrogen species following cerebral ischemia/reperfusion is a major cause for neuronal injury. In atherosclerotic apolipoprotein E knockout (ApoE-KO) mice, 2 h of middle cerebral artery occlusion (MCAO) followed by 22 h of reperfusion led to an enhanced expression of NADPH oxidase subunits (NOX2, NOX4 and p22phox) and isoforms of nitric oxide synthase (neuronal nNOS and inducible iNOS) in the ischemic hemisphere compared with the non-ischemic collateral hemisphere. This was associated with elevated levels of 3-nitrotyrosine, an indicator of peroxynitrite-mediated oxidative protein modification. Pretreatment with betulinic acid (50 mg/kg/day for 7 days via gavage) prior MCAO prevented the ischemia/reperfusion-induced upregulation of NOX2, nNOS and iNOS. In parallel, betulinic acid reduced the levels of 3-nitrotyrosine. In addition, treatment with betulinic acid enhanced the expression of endothelial eNOS, both in the ischemic and non-ischemic hemispheres. Finally, betulinic acid reduced infarct volume and ameliorated the neurological deficit in this mouse stroke model. In conclusion, betulinic acid protects against cerebral ischemia/reperfusion injury in mice. The reduced oxidative stress (by downregulation of NOX2) and nitrosative stress (by reduction of nNOS and iNOS), and enhanced blood flow (by upregulation of eNOS) may play an important role.