Nitric Oxide/Caveolin-1/MMP Pathway: A Novel Therapeutic Strategy for Drug Discovery from Herbal Medicine Targeting Blood-brain-barrier disruption during Cerebral Ischemia-reperfusion Injury

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Aims: Blood-brain-barrier (BBB) disruption is a crucial process in stroke, but no effective drug is available. Thus, drug discovery targeting BBB permeability becomes timely important. In this study, we hypothesized that Nitric oxide (NO)/Cav-1/Matrix metalloproteinase (MMP) pathway is important therapeutic targets in preventing BBB disruption. Following, we investigated the effects of CG, an active compound isolated from Astragali Radix on regulating this pathway and protecting BBB permeability and brain damage during cerebral ischemia-reperfusion injury.

Methods: SD rats were subject to different time courses of middle cerebral artery occlusion (MCAO). We investigated the expressions of cav-1 and NOS, the production of NO and peroxynitrite, activation of MMP-9, tight-junction (TJ) protein, BBB permeability and infarction volume in rat and mouse models of cerebral ischemia-reperfusion injury in vivo and hypoxic rat brain microvascular endothelial cells (BMECs) in vitro. CG (60 μmol/kg, i.p.) was used at 15 min before ischemia.

Results: (1) NO production reduced cav-1 expression, and the decreased cav-1 was associated with further increases of NO and peroxynitrite production, MMP-2/9 activation, TJ protein degradation and BBB hyper-permeability. (2) L-NAME, a non-selective NOS inhibitor, abolished the cav-1 reduction, MMP-2/9 activations, microvascular hyperpermeability and reduced infarction sizes in the ischemic brains. (3) Cav-1 knockdown by siRNA increased the secretion of MMP-2 to the culture medium. (4) After focal cerebral ischemia-reperfusion, cav-1 deficiency mice displayed higher MMPs activities and BBB permeability than wild-type mice. (5) The effects of L-NAME on MMPs activity and BBB permeability was partly reversed in cav-1 deficiency mice. (6) CG treatment decreased NO and MMPs activation, protected cav-1, reduced infarction volume, BBB permeability and brain damage.

Conclusion: Nitric oxide/Cav-1/MMP pathway is an important signal pathway in BBB disruption. The interaction of reactive nitrogen species, cav-1 and MMPs forms a positive feedback loop which provides amplified impacts on BBB dysfunction during cerebral ischemia-reperfusion injury. CG is a potential drug candidate for protecting BBB and reducing infarction volume in ischemic stroke treatment.

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