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Neuroprotective agents and thrombolytics in cerebral ischemia-focus on calcium channel blockers, edaravone and tissue plasminogen activator

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Searching for the new therapeutics in cerebral ischemia is the major goal for a lot of researchers. There are several drugs that are used for ischemic stroke treatment. The worldwide used medicine for ischemic stroke is tissue plasminogen activator (t-PA). T-PA is a thrombolytic, which is used to lysate the thrombus within the blood vessel during cerebral ischemia. Beside this drug some of the potential candidates for stroke treatment are calcium channel blockers (CCB) and free radical scavengers (edaravone) as the neuroprotective agents. The neuroprotective agents are employed to rescue the brain parenchyma, and to give the support to the cells involved in ischemia. The mechanism of their action is not yet revealed, but some of the supposed pathways are protection from oxidative stress damage for CCBs, and scavenging free radicals for edaravone.

We performed study with male Wistar rats that were subjected to 90 min of transient middle cerebral artery occlusion (MCAO) by a nylon thread. Animals were divided into 3 groups, vehicle, azelnidipine (CCB) and amlodipine (CCB) group. In the azelnidipine and amlodipine groups, rats were treated with azelnidipine (1 mg/kg) and amlodipine (1 mg/kg) by gastric gavage for 2 weeks before MCAO. Vehicle group was treated by solution of methyl cellulose for 2 weeks.

In this study is shown that pretreatment of azelnidipine and amlodipine has a neuroprotective effect in ischemic brain. The antioxidative property is one of the important profiles of CCBs that is implicated in the brain protection.

In order to show possible mechanisms of t-PA toxicity and the effect of the free radical scavenger edaravone, we administered vehicle, plasmin, and t-PA into intact rat cortex, and edaravone intravenously in *in vivo* experiment. Immunohistochemistry for oxidative stress markers as well as neurovascular unit markers were performed. Following *in vivo* study, *in vitro* study was also performed. Blood-brain barrier (BBB) kit was used for evaluation of BBB *in vitro*. We examined neurovascular unit with immunofluorescence cell staining as well as with transendothelial permeability assay.

Administration of t-PA caused oxidative stress damage to lipids, proteins and DNA, and led to disruption of outer parts of neurovascular unit, greater than the effect in plasmin administration group. Additive edaravone ameliorated such an oxidative damage by t-PA with protecting outer layers of blood-brain barrier (*in vivo*) and tight junctions (*in vitro*).

Biography

Violeta Lukic Panin has completed her MD from University of Novi Sad, Faculty of Medicine, Serbia at the age 24, and her Ph.D. from Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan in 2010. She is currently resident of internal medicine at the Faculty of Medicine, University of Novi Sad. She has published more than 10 papers (in two is first-author) in reputed journals and serves as a reviewer in a few world recognized journals.

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