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# Free radical scavenger edaravone administration protects against tissue plasminogen activator induced oxidative stress and blood brain barrier damage

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**Objective:** One of the therapeutics for acute cerebral ischemia is tissue plasminogen activator (t-PA). Using t-PA after 3 hour time window increases the chances of hemorrhage, involving multiple mechanisms. The other medicine that is used for cerebral ischemic patients is edaravone. Edaravone is a free radical scavenger that couples oxygen reactive species and reduces oxidative damage to brain.

**Material and methods:** 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 (4-HNE, HEL, 8-OHdG, AGE) as well as neurovascular unit markers (NAGO, occludin, collagen IV, MMP-9) were performed. Following in vivo study, in vitro study was performed, too. Blood-brain barrier (BBB) kit was used for evaluation of BBB in vitro. We examined neurovascular unit with immunocellular stainings for NAGO, occludin, claudin 5, GFAP as well as with transendothelial permeability assay.

**Results:** Plasmin and t-PA damaged rat brain with the most prominent injury in t-PA group on 4-HNE, HEL, and 8-OHdG immunostainings. Such brain damage was strongly decreased in t-PA plus edaravone group. For the neurovascular unit immunostainings, occludin and collagen IV expression was decreased in single plasmin or t-PA group, which was recovered in t-PA plus edaravone group. In contrast, matrix metalloproteinase-9 intensity was the strongest in t-PA group, less in plasmin, and was the least prominent in t-PA plus edaravone group. In vitro data showed a strong damage to tight junctions for occludin and claudin 5 in both administration groups, while there were no changes for endothelial (NAGO) and perivascular (GFAP) stainings. Such damage to tight junctions was recovered in t-PA plus edaravone group with similar recovery in Sodium-Fluorescein permeability assay.

**Conclusions:** 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 Univeristy of Novi Sad, Faculty of Medicine, Serbia at the age 24 years, and her Ph.D from Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan. She is currently resident of internal medicine at Faculty of Medicine, University of Novi Sad. She has published more than 10 papers (in two is first-author) in reputed journals and serving as a reviewer in a world recognised journal.

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