SPECIFIC COMBINATION OF NEUROTROPHINS POTENTIATE NEUROPROTECTION AND FUNCTIONAL RECOVERY FOLLOWING TRAUMATIC INJURIES TO THE RAT SÅINAL CORD

Hari Shanker Sharma and Aruna Sharma

Laboratory of Cerebrovascular Research, Department of Surgical Sciences, Anesthesiology & Intensive Care Medicine, University Hospital, Uppsala University, SE-75185 Uppsala, Sweden.
E.mail: Sharma@surgsci.uu.se; Aruna.sharma@surgsci.uu.se

Experiments carried out in our laboratory in the last 20 years show that the blood-brain barrier plays a crucial role in neuroprotection and neuroregeneration [1,2]. Using various animal models of traumatic brain and spinal cord injuries in rats and mice, we found that the blood-brain and the blood-spinal cord barriers became leaky to various sized tracers ranging from 12 Å (Lanthanum ion) to 80 Å (serum proteins) as soon as 5 min after injury and continued up to 12 h after the insults (cut off time). Deposition of lanthanum seen at ultrastructural level and albumin evaluated using immunohistochemistry around 5-8 h after trauma showed a good correlation between breakdown of the blood-CNS barriers and cell damage in many parts of the brain and spinal cord [3,4]. Interstingly, the blood-CSF barrier also showed leakage to Evans blue-albumin complex as indicated by blue staining of the cerebroventricular walls and an increase in albumin concentration in the CSF [5]. Topical application of various growth factors, e.g., BDNF, IGF-1, GDNF, NT-3/4, CNTF or NGF selectively and specifically attenuated the BBB disruption and reduced cell injury [6,7]. This influence on cell injury and BBB disruption was most pronounced by GDNA, IGF-1 and BDNF treatments (either given 30 min before or 30 min after trauma). However, NT-3/4 and NGF were not able to significantly influence either the BBB disruption or cell damage. Only, a mild but significant reduction in BBB breakdown and cell injury was observed with the CNTF treatment, if given within 10 min after insult. On the other hand, a combination of BDNF and GDNF were able to induce neuroprotection even applied 90 min after injury. Whereas, other combination of neurotrophins, e.g., BDNF+CNTF, or NT-3/4 were not effective. BDNF together with IGF-1 was capable to induce neuroprotective affects within 60 min after trauma. These observations suggest that neurotrophins, if able to reduce the BBB disruption are capable to achieve neuroprotection. A combination of brain derived (BDNF) and glia derived (GDNF) neurotrophic factors appears to be most potent in attenuating BBB dysfunction in traumatic injuries to the CNS, and thus inducing neuroprotection. These results indicate a prominent role of BBB in neuroregeneration, a subject that requires additional investigation.

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