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Co-administration of cerebrolysin and 5-HT6 receptor antagonist induced superior neuroprotection following exacerbation of brain pathology in sleep deprivation by concussive head injury

Aruna Sharma[1], Dafin F Muresanu[2], José Vicente Lafuente[3], Z Ryan Tian[4], Asya Ozikzilcik[5] and **Hari S Sharma[1]**
[1]Uppsala University, Sweden
[2]Iuliu Hatieganu University of Medicine and Pharmacy, Romania
[3]University of the Basque Country, Spain
[4]University of Arkansas, USA

Sleep deprivation (SD) in military often leads to decline in cognitive and higher mental functions. Since military personnel are vulnerable to concussive head injury (CHI), it appears that SD may worsen brain pathology in CHI. Previously, we showed that 48 or 72 h SD alters serotonin (5-hydroxytryptamine, 5-HT) metabolism and induces brain pathology that is significantly reduced by 5-HT3 receptor antagonist ondansetron. Recent reports suggest that treatment with 5-HT6 receptor antagonists has also beneficial effects in attenuating behavioral and cognitive functions in brain injury. We found that cerebrolysin, a balanced composition of several neurotrophic factors and active peptide fragments when delivered through TiO_2-nanowired-technology results in superior neuroprotective effects on brain pathology in CHI. Thus, we examined whether CHI brain pathology that is aggravated in SD could be reduced by nanodelivery of 5-HT6 receptor antagonist SB-399885 together with cerebrolysin probably having a synergistic enhanced therapeutic effects. Male Wistar rats (age 20 to 25 weeks) were subjected to 72 h SD using an inverted flowerpot model placed in a pool of water maintained at 1 cm below the surface so that animals are deprived of restful sleep. After 72 h of CHI in these animals were inflicted by dropping a weight of 114.6 g from a 20 cm height guide tube inducing and impact injury of 0.224 N on the right skull. Our observation shows that CHI in SD rats resulted in marked exacerbation of brain pathology (2 to 3 fold higher) after 4 weeks of survival. In the brain, neuronal damages in cortex, hippocampus and cerebellum, blood-brain barrier (BBB) breakdown and edema formation was also aggravated by 2-3 fold in SD rats after CHI. These SD rats after CHI also showed much worse behavioral performances on Rota-Rod treadmill, inclined plane angle test, and water maze apparatus. TiO_2-nanowired delivery of 5-HT6 receptor antagonist SB-399885 (3 mg/kg) together with cerebrolysin (2.5 ml/kg) intravenously once daily for 2 weeks starting from 1 week after CHI in SD rats induced marked neuroprotection as compared to these drugs either given alone or without nanotechnology under identical conditions. Interestingly, nanowired delivery of drugs in combination also improved behavioral function remarkably in SD rats after CHI. These observations are the first to show that a combination of 5-HT6 receptor antagonist with cerebrolysin using nanodelivery has superior neuroprotective effects in CHI induced brain pathology in SD, not reported earlier.

Biography

Aruna Sharma's main interest is now focused on Indian Medicinal drugs and their effects on the Central Nervous System Function, toxicology, neurorepair and neuroprotection. She is also investigating neurotoxicological profiles of many Ayurvedic traditional drugs with special reference to those containing metal oxide or metal ashes.

Aruna.Sharma@surgsci.uu.se