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Neuroprotective effects of nanodelivery of cerebrolysin with mesenchymal stem cells in high altitude induced exacerbation of brain injury

Military personnel are highly vulnerable to concussive head injury (CHI) during combat operation either at ground level or at high altitude mountains. High altitude induced brain edema development and alterations in cognitive dysfunctions are well known. However, effects of head injury at high altitude as compared to sea level are still not known. In this investigation we examined CHI at laboratory-simulated condition of high altitude and compared the results on identical head injury at normal laboratory conditions. Rats were exposed to simulated high altitude (HA) equivalent of 5000 m in an altitude chamber (hypobaric chamber) 11.2% O_2 at 0.53 Atm for 6 h daily for 1 week. The temperature of the hypobaric chamber was maintained at 21±1°C. The humidity (45 to 50%) and airflow was maintained at 4 liter per hour. Control rats kept at room temperature at standard laboratory conditions. Control or HA arts were provided food and water ad libitum before experiment. CHI was inflicted in control and HA rats under Equithesin anesthesia (3 ml/kg, i.p.) by dropping an iron tapered cylinder (114.6 g) through a guide tube from 20 cm height over the exposed right parietal skull inducing an impact of 0.224 N over the skull surface without making any fracture. The method simulates counter coup injury and results in profound cellular damage in the left uninjured hemisphere as compared to the injured side 12 to 24 h after the primary insult. In these rats blood-brain barrier (BBB) breakdown to Evans blue albumin and radioiodine was examined together with edema formation using brain water content. Nissl stain on paraffin sections was used to evaluate neuronal injuries. Our results showed that CHI in HA rats resulted in 250% exacerbation of BBB breakdown, 3-to 4-fold higher brain edema development and 2- to 2.5-fold greater neuronal injuries in the cerebral cortex, hippocampus and cerebellum as compared to rats kept at room temperature. Co-administration of cerebrolysin 2.5 or 5 ml/kg, i.v. with mesenchymal stem cells (MSCs, 1 million) 4 to 6 h after trauma was able to induce profound neuroprotection in CHI arts at room temperature. However, this dose was only slightly effective in reducing brain pathology following CHI in HA rats. On the other hand when TiO_2 nanowired cerebrolysin (2.5 ml) was co-administered with 10^6 MSCs 4 or 6 h after trauma significant reduction in the BBB breakdown, edema formation and neuronal injuries were seen in HA rats. Taken together our observations are the first to point out that CHI in HA results in exacerbation of brain pathology and under such situations nanodelivery of suitable drugs are needed to achieve better neuroprotection not reported earlier.

Biography

Hari Shanker Sharma is the Director of International Experimental Central Nervous System (CNS) Injury and Repair (IECNSIR) at University Hospital, Uppsala University, Sweden. He is a qualified Neuroanatomist and experimental Neurpathologist trained in Germany, Switzerland, Hungary, Sweden and USA. His main research interest is currently focused on neurotoxicity of nanoparticle and nanowired drug delivery of agents for enhanced neuroprotection in a variety of CNS insults or neurodegenerative diseases in relation to the blood-brain barrier (BBB) function. He has authored more than 250 original research papers and edited several book volumes or progress in brain research series.

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