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Nanoparticles exacerbate sleep deprivation induced brain pathology and functional disturbances. Neuroprotective effects of TiO_2 nanowired delivery of 5-HT_3 receptor antagonist ondansetron

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Military personals are often subject to sleep deprivation (SD) during combat operations or peacekeeping missions abroad that may affect brain function and reduce their ability to perform at optimal level. However, disturbances in brain functions following SD by additional exposure to nanoparticles (NPs) is unknown. In present investigation effects of SD on blood-brain barrier (BBB) breakdown and cognitive and sensory motor function was examined in a rat model. Furthermore chronic intoxication of engineered NPs from metal, e.g., Cu and Ag of two different sizes (20 to 30 nm or 50 to 60 nm) on BBB and behavioral functions were also examined in SD. SD was induced in young adult rats (age 12 to 14 weeks) using a model in which the animals are placed over an inverted flowerpot platform (ca. 7 cm diameter) in a water pool where the water levels are just 3 cm below the surface. Animals may sleep for brief periods but could not achieve deep sleep as they would fall into water. Normal animals subjected to SD showed leakage of Evans blue largely seen in the cerebellum, hippocampus, caudate nucleus, parietal, temporal, occipital and cingulate cerebral cortices and in the brain stem. The ventricular walls of the lateral and 4th ventricles were also stained blue indicating that SD disrupts both the BBB and the blood-cerebrospinal fluid barrier (BCSFB). Abnormal behavioral functions are also seen on Rota Rod, inclined plane angle test as well as walking on a wired mesh. The breakdown of the BBB, BCSFB and behavioral disturbances were progressive in nature from 12 to 48 h. However, no apparent differences in BBB or behavioral dysfunction were seen between 48 and 72 h of SD. When Cu or Ag NPs treated rats (50 mg/kg, i.p. daily for 7 days) were subjected to identical SD for 12 to 72 h, profound exacerbation of BBB disruption to Evans blue (+150% at 12 h; 260% at 24 h; 300% at 48 h and 360% at 72 h) was seen in similar brain regions. The ventricular walls showed much deeper blue staining indicating that BBB and BCSFB breakdown were exacerbated by NPs intoxication. The behavioral dysfunction in the NPs intoxicated animals was also exacerbated than normal animals. Small sized NPs induced most pronounced effects on BBB disruptions and behavioral dysfunction than the large sized NPs. In general, Ag NPs irrespective of their sizes exerted most pronounced effects on BBB and BCSFB disruption than Cu NPs of similar sizes. Ondansetron treatment (1 mg/kg, s.c.) 4 to 8 h after SD resulted in significant neuroprotection in 12 o 24 h SD rats. Interestingly nanodelivery of TiO_2 nanowired ondansetron (1 mg/kg) resulted in pronounced neuroprotection in 48 to 72 h SD rats. Taken together our observations are the first to point out that (i) small sized NPs may have more devastating effects on brain and behavioral dysfunctions during SD, and (ii) nanodelivery of a 5-HT_3 receptor antagonist ondansetron may alleviate most of the adverse effects of SD with our without NPs intoxication.

Biography

Aruna Sharma, MD is currently Secretary of Research at Uppsala University Hospital, Uppsala University, Sweden. She obtained her Bachelor of Science in 1971 and trained in Indian Medicine up to 1977 and engaged in medical research from 1978 to 1986 in India on hyperthermia induced brain dysfunction under University Grants Commission and Indian Council of Medical Research Programs. She is a qualified experimental Neurpathologist and received her training at Karl Marx University Leipzig, Institute of Neurobiology (1987-1988); Semmelweis University Medical School, Department of Human Morphology and Developmental Biology, Budapest, Hungary (1988-1989), Free University Berlin, Germany (1989-1991) and Neuropathology Institute Uppsala (1992-1995). She is member of various Distinguished American Organizations and elected to receive the prestigious award "Women of the Years Representing Sweden Award 2009" for her outstanding contributions towards society by American Biographical Research Institute, USA; and "Best Professional Business Women Award 2010" *For Setting Standard to Motivate, Excel and Inspire Others*, Raleigh, North Carolina, USA. She has published over 50 original research papers in Reputed *Neuroscience Journals* and is currently Acquisition Editor of *American Journal of Neuroproetction and Neuroregenartion.*

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