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Brain washing and neural health: role of age, sleep, and the cerebrospinal fluid melatonin rhythm

Russel J Reiter [1], Ramaswamy Sharma [2], Maira Smaniotto Cucielo [3], Dun Xian Tan [4], Sergio Rosales-Corral [5], Giuseppe Gancitano [6], Luiz Gustavo de Almeida Chuffa [3]

1 Department of Cell Systems and Anatomy, Long School of Medicine, UT Health San Antonio, San Antonio, TX, 78229, USA. reiter@uthscsa.edu.
2 Department of Cell Systems and Anatomy, Long School of Medicine, UT Health San Antonio, San Antonio, TX, 78229, USA. sharmar3@uthscsa.edu.
3 Department of Structural and Functional Biology-IBB/UNESP, Institute of Biosciences of Botucatu, Universidade Estadual Paulista, Botucatu, São Paulo, 18618-689, Brazil.
4 S.T. Bio-Life, San Antonio, TX, USA.
5 Centro de Investigacion Biomedica de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Mexico.
6 1st "Tuscania" Paratrooper Regiment, Italian Ministry of Defense, 57127, Leghorn, Italy.

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Abstract

The brain lacks a classic lymphatic drainage system. How it is cleansed of damaged proteins, cellular debris, and molecular by-products has remained a mystery for decades. Recent discoveries have identified a hybrid system that includes cerebrospinal fluid (CSF)-filled perivascular spaces and classic lymph vessels in the dural covering of the brain and spinal cord that functionally cooperate to remove toxic and non-functional trash from the brain. These two components functioning together are referred to as the glymphatic system. We propose that the high levels of melatonin secreted by the pineal gland directly into the CSF play a role in flushing pathological molecules such as amyloid-β peptide (Aβ) from the brain via this network. Melatonin is a sleep-promoting agent, with waste clearance from the CNS being highest especially during slow wave sleep. Melatonin is also a potent and versatile antioxidant that prevents neural accumulation of oxidatively-damaged molecules which contribute to neurological decline. Due to its feedback actions on the suprachiasmatic nucleus, CSF melatonin rhythm functions to maintain optimal circadian rhythmicity, which is also critical for preserving neurocognitive health. Melatonin levels drop dramatically in the frail aged, potentially contributing to neurological failure and dementia. Melatonin supplementation in animal models of Alzheimer's disease (AD) defers Aβ accumulation, enhances its clearance from the CNS, and prolongs animal survival. In AD patients, preliminary data show that melatonin use reduces neurobehavioral signs such as sundowning. Finally, melatonin controls the mitotic activity of neural stem cells in the subventricular zone, suggesting its involvement in neuronal renewal.

Keywords: Apoptosis; Brain metabolism; Brain ventricles; CSF flow; Dural lymphatics; Glioblastoma; Glymphatic system; Lumbar cistern; Neurodegenerative diseases; Redox homeostasis; Subventricular

zone; Tau protein; Virchow-Robin perivascular spaces.

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