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Melatonin in ventricular and subarachnoid cerebrospinal fluid: Its function in the neural glymphatic network and biological significance for neurocognitive health

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Abstract

The central nervous system (CNS) is endowed with a specialized cerebrospinal fluid (CSF)/lymph network which removes toxic molecules and metabolic by-products from the neural parenchyma; collectively, this has been named the glymphatic system. It allows CSF located in the subarachnoid space which surrounds the CNS to enter the depths of the brain and spinal cord by means of Virchow-Robin perivascular and perivenous spaces. CSF in the periarterial spaces is transferred across the astrocytic end feet which line these spaces aided by AQ4 channels; in the interstitium, the fluid moves via convection through the parenchyma to be eventually discharged into the perivenous spaces. As it passes through the neural tissue, the interstitial fluid flushes metabolic by-products and extracellular toxins and debris into the CSF of the perivenous spaces. The fluid then moves to the surface of the CNS where the contaminants are absorbed into true lymphatic vessels in the dura mater from where it is shunted out of the cranial vault to the cervical lymph nodes. Pineal melatonin released directly into the CSF causes the concentration of this molecule to be much higher in the CSF of the third ventricle than in the blood. After the ventricular melatonin enters the subarachnoid and Virchow-Robin spaces it is taken into the neural tissue where it functions as a potent antioxidant and anti-inflammatory agent. Experimental evidence indicates that it removes pathogenic toxins, e.g., amyloid- β and others, from the brain to protect against neurocognitive decline. Melatonin levels drop

markedly during aging, coincident with the development of several neurodegenerative diseases and the accumulation of the associated neurotoxins.

Keywords: Aging; Amyloid- β ; Glymphatic system; Neural stem cells; Neurodegenerative diseases; Subventricular zone; Third ventricle; Virchow-robin spaces.

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