

Sleep Deprivation Impairs Glymphatic A β Clearance by Disrupting AQP4

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Background

- The deposition of β -amyloid (A β) in the brain is a key pathogenesis of Alzheimer's disease (AD), and the Glymphatic system is an important pathway for clearing A β , and Aquaporin 4 (AQP4) polarity distribution in the foot of perivascular astrocytes is the main mechanism for maintaining the function of glymphatic system. Sleep disturbance is a risk factor for AD, however, the effects of chronic sleep deprivation (CSD) on glymphatic function remains unclear.

Methods

- Eighteen-month-old male C57BL/6J mice were randomly assigned to control (CON) or chronic sleep deprivation (CSD) groups. Mice in the CSD group were subjected to 20 h of sleep deprivation followed by 4 h of recovery sleep per day for 28 consecutive days. Cognitive function was assessed using the Y-maze, novel object recognition, and Morris water maze tests. Glymphatic function was evaluated by intracisternal and intrastriatal injection of fluorescent tracers to assess cerebrospinal fluid influx and interstitial solute clearance. Exogenous fluorescently labeled soluble A β was injected into the hippocampus to directly assess A β clearance. AQP4 perivascular polarization was analyzed using immunofluorescence combined with vascular labeling.

Results

- CSD impaired both the influx and clearance components of the glymphatic system.

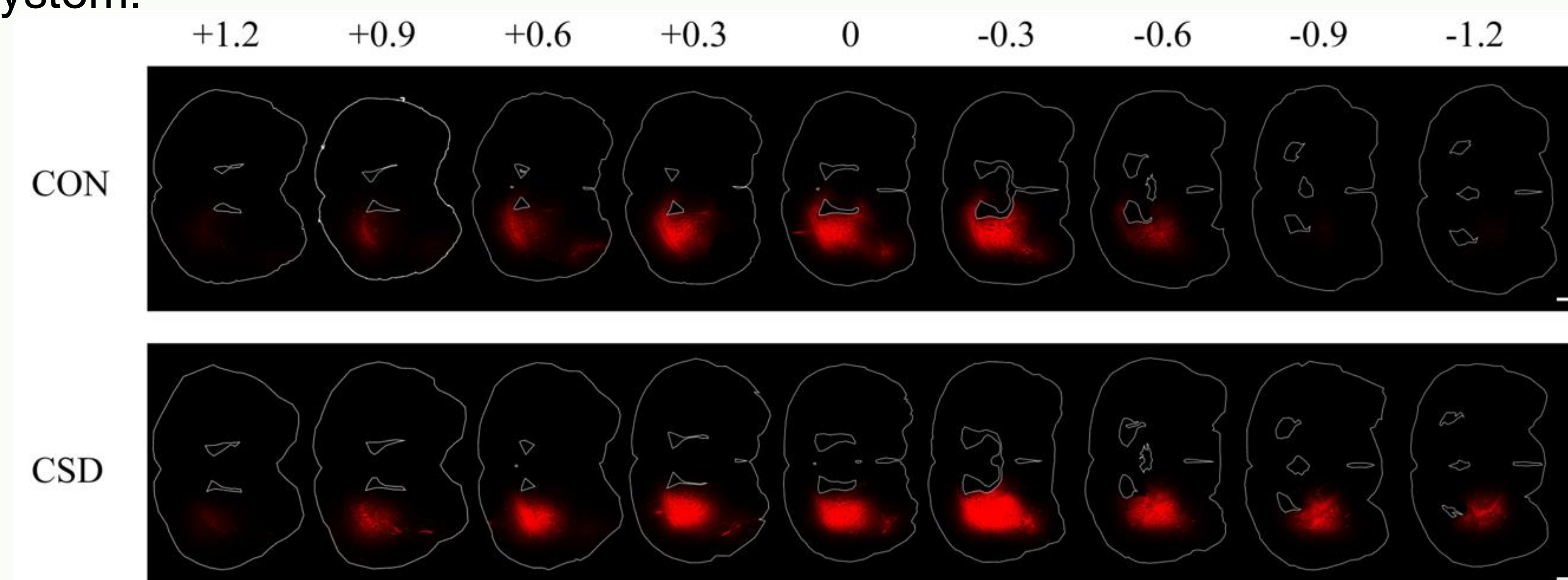


Figure 1. Representative images of glymphatic clearance of OA-555.

- CSD disrupted AQP4 polarization without changing total AQP4 expression. Pharmacological modulation of AQP4 polarization bidirectionally regulated glymphatic function and A β clearance in CSD mice.

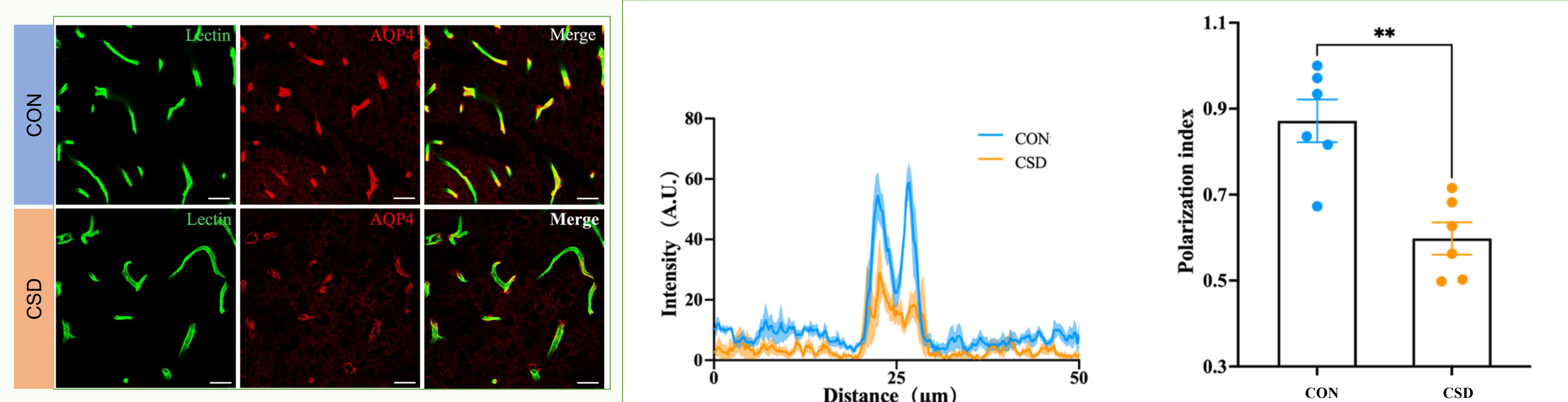


Figure 2. CSD Disrupts Perivascular AQP4 Polarization.

Conclusion

- Chronic sleep deprivation impairs glymphatic clearance and promotes brain A β accumulation and cognitive decline, potentially through disruption of AQP4 perivascular polarization. These findings identify AQP4 polarity as a key mechanistic link between sleep disturbance and AD-related pathology.