# Does modulation of glymphatic system reduce delirium via waste clearance?

Dear Editor,

The glymphatic system is primarily responsible for maintaining homeostasis at the cellular level in the brain. It is involved in the delivery of nutrients and drug molecules via transcellular transport. It forms a perivascular transit in the brain. This system intercommunicates with interstitial fluid via aquaporin water channels of astrocyte end-feet. It regulates the waste clearance of drugs or metabolic by-products, amyloid proteins such as amyloid-β, and tau protein. The movement of endogenous macro-or micromolecules is maintained by the cerebrospinal fluid (CSF) inflow.[1] The sleep–wake cycle modulates the glymphatic activity. The NREM stage of sleep upregulates the glymphatic-associated waste clearance and the REM stage, or awake condition, downregulates its activity. The influx of CSF tracer was greater while sleeping than when awake. This phenomenon was explained by the slow-wave oscillation of deep NREM sleep. By adjusting noradrenergic tone in the cerebral circulation, the slow-wave

oscillation enhances the clearance by reducing the barrier to interstitial fluid movements.[2] This mechanism results in the expansion of the interstitial space volume.[3] The upregulation of glymphatic activity is biologically required during the slow-wave oscillation of NREM sleep. In two recent papers, the influence of anesthetic medications on glymphatic activity has been highlighted. The first paper, "Dexmedetomidine enhances glymphatic brain delivery of intrathecally administered drugs," was published in the Journal of Controlled Release by Lilius *et al.*[2] (2019), and the second paper, "Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia," was published in the journal "Science Advances" by Hablitz *et al.* (2019).[3] Based on these findings, it can be assumed that sedative or anesthetic drugs that induce deeper anesthesia states could boost glymphatic activity. Slow-wave oscillation during NREM sleep with prominent spindles and delta waves enhances the glymphatic activity and CSF tracer removal.[2,3] Dexmedetomidine acts at the locus ceruleus of the midbrain and blocks noradrenaline release. It also lowers the adrenergic tone of brain vessels. Lilius *et al.* compared the glymphatic activity in the two groups of rats that were exposed to similar experimental conditions and remained asleep.[2] They were able to demonstrate that the percentage of delta oscillation and spindles in the same time span were higher in the Dex + Iso group when compared to pure isoflurane. Ketamine and dexmedetomidine reduce postoperative delirium and postoperative cognitive disorder in human subjects; however, their mechanisms are still unknown.[4] The inhalation agent reduces CSF redistribution; however, wakefulness has prolonged the waste accumulation phase without compromising CSF dynamics. There is no substantial evidence of alteration in the glymphatic activity or waste clearance from hypnotics and sedative agents. The inhalation agent reduces CSF redistribution; however, wakefulness has a prolonged waste accumulation phase without compromising CSF dynamics.[5] Further research into the influence of delta waves and spindle type oscillation in EEG on glymphatic modulation in the context of sleep or anesthesia will be needed.

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## Conflicts of interest
There are no conflicts of interest.

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