Alpha and Beta Adrenergic Agonists Increase Hindrance to Diffusion of 3-kDa Dextran in Mouse Visual Cortex Extracellular Space

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Background: Sleep is believed to play a role in the clearance of potentially harmful substances that accumulate in the brain during wakefulness. One such harmful substance is beta-amyloid, a 4.5-kDa protein known to accumulate in the brains of patients with Alzheimer's disease. While it has been found that sleep causes a noticeable increase in the volume of the brain extracellular space (ECS), studies found no difference in the diffusion rate of small molecules in the brain ECS between awake and asleep mice. To determine how sleep/wake states impacts the diffusion of large molecules of comparable size to beta-amyloid, the diffusion rate of 3-kDa dextran was assessed before and after the addition of adrenergic agonists to the brain slices. Results: Fluorescently tagged 3-kDa dextran was pressure ejected into the ECS of visual cortex in mouse brain slices and diffusion rate was determined using Integrative Optical Imaging. The addition of either a beta agonist (isoprenaline) or alpha agonists (phenylephrine and clonidine) to mimic an awake state significantly reduced the rate of diffusion of the dextran. Conclusions: Large molecules diffuse slower through the ECS when adrenergic agonists are present (an awake-like state) and diffuse more rapidly when there are no agonists (an asleep-like state). These results support the idea that large and potentially toxic substances like beta-amyloid can be cleared at a much faster rate during sleep. In the future, it may be possible to develop drugs that allow for faster removal of toxins from the brain based on this concept.

Awards Won:

Third Award of $1,000