

October 1, 2018 Speaker: Dr. Elaine Peskind, Professor, Dept. of Psychiatry and Behavioral Sciences, UW. *Drain the Swamp: Prazosin for Prevention of Neurodegeneration*. UW Health Sciences Building RR202, 4-5pm

Featured introduction video: **One more reason to get a good night's sleep** by Jeff Iliff, PhD, Oregon and Health Science University: TEDMED 2014

https://www.ted.com/talks/jeff_iliff_one_more_reason_to_get_a_good_night_s_sleep/transcript?language=en

Dr. Elaine Peskind introduced the topic of the glymphatic system in aging, as a way to understand age-related neurodegeneration.

Over aging, amyloid decreases in CSF, which signals that less is being removed from the brain and instead accumulating as AD pathology; Peskind's group thinks that amyloid decreases in CSF because it deposits in plaques, because of a slowing of amyloid beta clearance, in the bulk of the aging population. (Increased amyloid production occurs in carriers of certain gene mutations or people with Down syndrome.) Data from cerebrospinal fluid (CSF) in cognitively normal men and women aged 21 – 88 suggests that ages 50-60 is a critical zone of amyloid deposition.

Because the CSF functions as a sink for the waste chemicals produced by the brain, researchers feel that CSF analysis can yield the most accurate measures of pathology in the living brain, other than PET. For detail, the glymphatic pathway, a brain-wide perivascular network, clears waste products. For detail, glymphatic vessels are present in the dural sinuses, which are venous channels found between the endosteal and meningeal layers of dura mater in the brain. CSF is produced and secreted at choroid plexus, and it circulates through the brain. CSF is resorbed at arachnoid villi at top of brain.

Clearance via the glymphatic system is a function of the sleeping or anesthetized brain, and there is a circadian rhythm of amyloid clearance. This rhythm is disrupted by sleep deprivation and blunted with aging. CSF circulation is impaired in aging as well. In APP transgenic mice, sleep deprivation increased deposition of amyloid in plaques. And even a single night of sleep deprivation in adults increased amyloid burden detected by PET.

Intervention

Can we take advantage of glymphatic system and modulate it to increase clearance of neurotoxic proteins? The glymphatic system process of waste clearance appears to be under control of the alpha 1 adreno-receptor. Unsurprisingly, prazosin (which blocks this adreno-receptor) can increase clearance of abeta and tau (Is this because prazosin simply improves sleep?). Prazosin is inexpensive and safe, used since the 1970s for symptoms of benign prostate problems. Peskind's team has conducted a number of positive human trials at a wide dose range, for alcohol abuse, PTSD, and agitation in AD, and currently for prophylaxis of post concussive migraine. These are all disorders of the increased central noradrenergic function.

If the field wants to pursue primary prevention of AD, the window of opportunity is in middle age, below the age of 65, before people begin amyloid and tau deposition. After all, other risk factors, such as cardiovascular injury or loss of estrogen in menopause, have greatest effect in middle age. There is some evidence that women E4 carriers in the 50-60 age window have a worse dive.

Peskind emphasized the value of countering enhanced norepinephrine function in middle age, as it is reliably high in older adults and low in younger adults, but enormously varied in middle age adults. Despite the loss of locus coeruleus neurons in AD, the CSF norepinephrine is maintained in early stages and upregulated later. Could norepinephrine function be a precision medicine target for dementia prevention?

Dr. C. Dirk Keene of UW ADRC Neuropathology commented: “We’ve been tracking patients that have clear perivascular amyloid deposition vs. those who don’t. In the parenchyma around vessels, the amyloid is located adjacent to the glymphatic space, perhaps either stuck before it can get out, or getting filtered out as it comes in. So, from a precision medicine perspective, it would be interesting to use imaging to identify the people who would respond to this treatment.”

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