Sexual dimorphisms in Alzheimer's disease-related disruptions of circadian entrainment and a potential role for gonadotropin receptor signaling

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Alzheimer's disease (AD) is associated with progressive disruption of entrained circadian rhythms, and sexual dimorphisms in both AD and circadian function have been well established. However, whether sex differences in AD and circadian function share a common mechanism is unknown. Gonadotropin [follicle stimulating hormone (FSH) and luteinizing hormone (LH)] levels increase with menopause and have been suggested to contribute to the fact that two thirds of AD patients are women. Yet, it is unclear whether increased gonadotropin receptor signaling also contributes to sex differences in AD-related circadian dysfunction. In the TAPP (APPSwe-Tau) mouse model of AD, we recently showed that females develop AD-related pathology and disruptions of entrained circadian rhythms much earlier than males. Markers of circadian dysfunction were strongly associated with the development of hyperphosphorylated Tau (pTau) pathology in lateral parabrachial (LPB) neurons that project to the circadian system, including the suprachiasmatic nucleus (SCN, the master circadian pacemaker) and its primary axonal relay, the adjacent subparaventricular zone (SPZ). In this current study, we examine the sexually dimorphic role of gonadotropin receptor expression and signaling on entrained rhythms of core body temperature (Tb) and locomotor activity (LMA) in wild-type (WT) and TAPP mice. Additionally, we performed gonadectomy (GDX) at ages relevant for the development of AD pathology in TAPP mice. Our preliminary findings suggest that GDX increases variability in markers of circadian entrainment in WT mice compared to shams and increases circadian disruption and LPB pTau in GDX compared to sham TAPP mice. We also collected tissue from the LPB and SCN/SPZ regions and are using quantitative PCR to determine changes in gonadotropin receptor expression and how these differences correlate to circadian disruption. We hypothesize that there will be sexually dimorphic changes in gonadotropin receptor expression in the LPB, as both FSH and LH concentrations significantly increase with GDX and have been associated with increased deposition of AD pathology.