Progressive Tauopathy Disrupts Breathing Stability during Presumptive Sleep

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Sleep apnea occurs in over 50% of individuals with Alzheimer's Disease (AD) or related Tauopathies. While there have been investigations into sleep apnea and its potential to exacerbate AD, less is known concerning the role of progressive, age-related Tauopathy in the pathogenesis of sleep-disordered breathing. In this study, we tested the hypotheses that the rTg4510 murine model of Tauopathy: 1) exhibits breathing instability during presumptive sleep that is exacerbated with aging, reflecting Tauopathy progression and 2) that progressive Tauopathy impairs chemoreflex function during presumptive sleep. Type I and II post-sigh apnea, Type III (spontaneous) apnea, sigh and hypopnea incidence were measured in young (5-6 months) and aged (13-15 months) non-transgenic (nTg), monogenic control (tTA), and bigenic rTg4510 mice using whole-body plethysmography during presumptive sleep. Chemoreceptor sensitivity was assessed using transient exposures (5 min) to hyperoxia (100%O2) or hypercapnia (3% and 5%CO2, 21%O2). We report significant increases in Type I-III apneas ($p<0.001$), sighs ($p=0.002$) and hypopneas ($p<0.001$) in aged rTg4510 mice, but only Type III apneas in young rTg4510 mice ($p<0.001$) *vs* age-matched controls. Unlike aged nTg and tTA mice, aged rTg4510 mice exhibited impaired chemoreflex sensitivity. Hyperphosphorylated Tau was observed in brainstem regions known to be either directly or indirectly involved in respiratory control (*e.g.*, pontine respiratory group, medullary respiratory groups, retrotrapezoid nucleus) in aged rTg4510 mice. In contrast, similar extent of breathing instability or brainstem hyperphosphorylated Tau were not observed in young rTg4510 mice. Tauopathy in this model may directly contribute to impaired chemoreflexes and development of sleep-disordered breathing.

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