THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Eileen Parks

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Neuroscience

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"NEUROSTEROID SYNTHESIS IS ALTERED IN THE AGING BRAIN AND CONTRIBUTES TO COGNITIVE DECLINE"

COMMITTEE IN CHARGE: William E. Sonntag, PhD, Chair; David M. Sherry, PhD; Nicole M. Ashpole, PhD; Michael B. Stout, PhD; Willard M. Freeman, PhD

ABSTRACT: Provide an abstract of your dissertation here. As the average lifespan of humans is steadily increasing, so is the incidence of age-related cognitive impairment. Cognitive decline frequently involves deficits in processing speed, learning, and memory. In addition to the severe challenge to the individual, there are also significant costs to caregivers and the healthcare system. Several changes in the aging brain have been implicated in the development of cognitive decline including oxidative stress, cellular senescence, increased inflammation, and a reduction in neurosteroids. Progesterone is the initiating substrate for several neurosteroids including testosterone, corticosterone, and allopregnanolone. The neurosteroid, Allopregnanolone (AlloP), has been shown to be reduced in various models of *neurodegenerative* diseases. However, no studies have investigated the levels of AlloP in mice past the age of 14 months (middle-aged). We found that AlloP declines in the brain of aged mice, and that a single injection of AlloP improves working memory. Subsequently, we investigated the age-related changes in progesterone metabolism that mediate the decline in AlloP with age. Interleukin 6 is one of several inflammatory cytokines known to increase with age, and has been shown to increase the expression of corticosterone synthesizing enzymes in the adrenal glands. We hypothesized that IL-6 could also be regulating neurosteroid synthesis locally in the brain. Administration of IL-6 to young mice resulted in reduced AlloP synthesis and decreases in memory. Furthermore, inhibition of IL-6 in aged mice improved working memory. Further studies using in vitro cultures revealed that IL-6 reduces AlloP synthesis specifically in astrocytes. In our second study, we sought to investigate acute vs repetitive AlloP administration on working memory and healthspan. In contrast to the first study, we did not find that AlloP administration was effective in improving working memory. However, we found no age-related increase in IL-6 or decrease in AlloP in our control aged mice compared to young. From these studies, we conclude that increased IL-6 with age reduces AlloP synthesis, and treatment with AlloP is ineffective in the absence of elevated IL-6 levels.