

Aging Induced ER Stress Alters Sleep and Sleep Homeostasis

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Introduction: Alterations in the quality, quantity and architecture of baseline and recovery sleep have been shown to occur during aging. *Drosophila melanogaster* shares several characteristics with mammalian sleep, including circadian and homeostatic regulation. Sleep deprivation induces endoplasmic reticular (ER) stress and upregulates a protective signaling pathway termed the unfolded protein response (UPR), which reduces the aggregation and accumulation of misfolded/unfolded proteins and shields the cell from injury. A key mechanism of the UPR involves increasing the levels of endogenous chaperones that bind to misfolded proteins. The effectiveness of this adaptive response, as well as other UPR elements including chaperone levels, is diminished by age. We have previously shown that increasing endogenous chaperone levels enhances recovery sleep in *D. melanogaster*. These results suggested that an exogenous chaperone could alleviate age-related sleep dysfunctions.

Methods: We compared sleep parameters in young and aged flies at baseline and after 6 h of sleep deprivation. Animals were either control or treated with 5mM PBA for 48 h. Molecular/biochemical studies were carried out to determine UPR markers induction over aging and with and without sleep deprivation.

Results: Acute administration of the chemical chaperone sodium 4-phenylbutyrate (PBA) reduced ER stress and ameliorated age-associated sleep changes in *Drosophila*. PBA consolidated both baseline and recovery sleep in aging flies. The behavioral modifications of PBA were linked to its suppression of the UPR. PBA decreased splicing of XBP1 and upregulation of p-eIF2 α , both markers of the UPR, in flies that were subjected to sleep deprivation. Directly activating ER stress through protein misfolding in young flies fragmented baseline sleep and altered recovery sleep.

Conclusions: Age-related alterations in baseline and recovery sleep were ameliorated by the chemical chaperone PBA. Inducing ER stress directly correlates to changes in sleep.

