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Short Term Sleep Deprivation Predicts Pharmacological Resilience Response to Aging

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Abstract

The ability of an organism to respond to physical stress with increasing age, defined as physical resilience, was measured by the effect of short term sleep deprivation (SD) in 17 month old CB6F1 male mice. Sleep loss induces histone deacetylation (HDAC), resulting in cognitive dysfunction. These mice were treated with phenylbuterate (PBA), an HDAC inhibitor, and then put through two physiological assessments. SD resistant mice had a weaker grip strength, but higher running distances than SD sensitive mice, suggesting these two physiological assessments have different pathway connections with PBA targeted hippocampal learning.

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Introduction

Physical resilience to aging is the continual ability to respond to physical stress with increasing age. Sleep deprivation (SD) is a physical stressor that affects more than 40% of seniors. Sleep loss induces an epigenetic change, specifically histone deacetylation (HDAC), resulting in cognitive dysfunction. This study set out to determine if the response to sleep deprivation could predict resilience to aging in mice treated with an HDAC inhibitor (phenylbutyrate, or PBA), using two physiological performance assays.

Methods

15 CB6F1 male mice aged 17 months were deprived of sleep 4 hours daily for 4 days. They were then tested in a Box Maze learning paradigm (Figure 1). 7 mice were then treated with 6g/L PBA solution through their drinking water while the control group of 8 mice ingested normal water for 12 weeks. After the 12 week PBA treatment, mice were tested for physiological performance using grip strength (Figure 2A) and 3-day wheel running distance (Figure 2B). Mouse tissues were then collected to test for the PBA target, acetyl-H4.

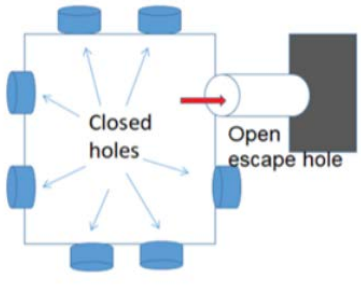

Figure 1. Box maze learning paradigm with four 2-minute trails.

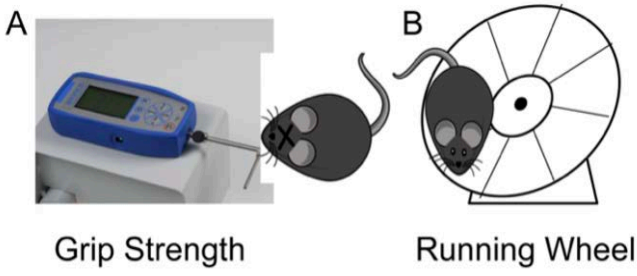

Figure 2. Physiological performance tests.

Results and Discussion

PBA was shown to effectively inhibit HDAC (Figure 3). After 12 weeks of treatment with PBA, SD resistant mice, quantified by their escape time of the Box Maze (Figure 4) had weaker grip strengths (Figure 5A) than SD sensitive mice (Figure 5B). They also had higher running distances (Figure 5C) than SD sensitive mice (Figure 5D).

Middle aged CB6F1 mice resistant to sleep deprivation performed better in wheel running as expected. In contrast, SD resistant mice performed worse in grip strength, suggesting these physiological assessments have different pathway connections with PBA targeted hippocampal learning. These observations suggest further study of sleep deprivation correlation with different activities; additional studies are being conducted to validate these preliminary findings.

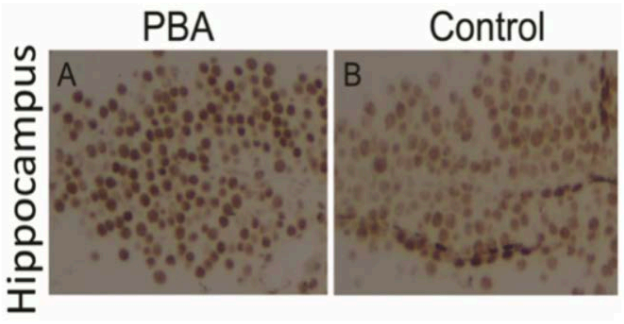

Figure 3. Hippocampus from a mouse treated with PBA for 12 weeks had increased labeling of acetyl-H4 compared to control, indicating HDAC inhibition. Similar findings were seen in 3 additional mice.

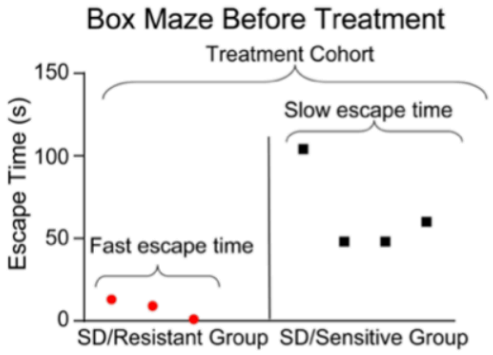

Figure 4. Mice with Box Maze escape times less than 50 seconds were considered resistant to SD, while mice with escape times greater than 50 seconds were considered sensitive to SD.

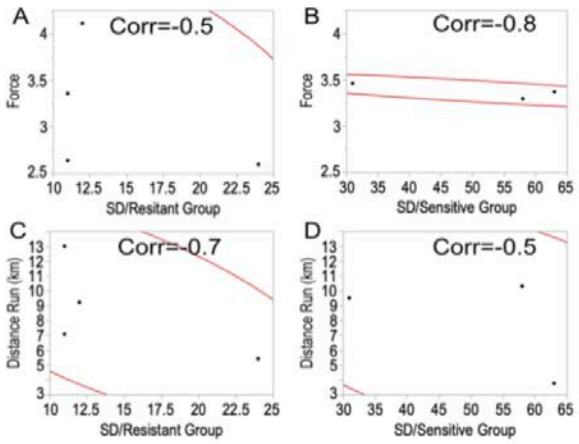

Figure 5. After 12 weeks of treatment with PBA, SD resistant mice had weaker grip strengths (A) than SD sensitive mice (B), and higher running distances (C) than SD sensitive mice (D), corr > -0.5.