CHRONIC TREATMENT WITH RISPERIDONE MODULATES MOLECULAR SIGNALING IN THE PREFRONTAL CORTEX AND HIPPOCAMPUS

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INTRODUCTION

Risperidone is a commonly prescribed antipsychotic drug that is used to treat schizophrenia, bipolar disorder and relieve irritability in autistic children. Antipsychotics are believed to work by modulating neurotransmission events such as the neurotransmitter-synaptic membrane receptor interactions towards dopamine receptors to improve mood and behavior. However, chronic use of Risperidone negatively affects learning and memory through epigenetic changes to subcellular homeostasis, such as histone modifications in the prefrontal cortex and the hippocampus. Histone modifications are called post-translational modifications, and can include methylation, which generally decreases protein expression or acetylation, which generally increases protein expression among many others. These modifications are associated with changes in gene expression that are a prerequisite for memory consolidation. If the prefrontal cortex and the hippocampus are not working properly, then memory cannot be stored and retrieved, leading to issues such as short term memory loss. In our study, we surveyed rats given a 180 day dose of Risperidone and ran behavioral studies on them such as Novel Object Recognition Tasks and Passive Avoidance Tests then sacrificed them to determine any correlation between post-translational modifications and behavioral scores. The structure of Risperidone is shown to the right.

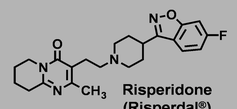
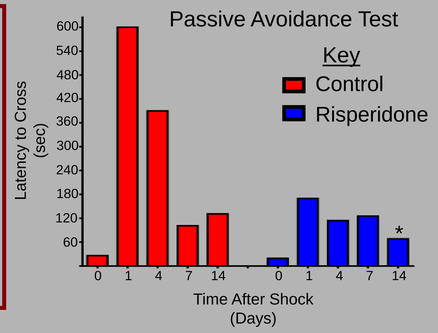


Fig 1. Structure of Risperidone

Risperidone (Risperdal®)

BEHAVIORAL RESULTS

Fig 2. Results of Passive Avoidance Test at 150 days indicate that the rats treated with Risperidone were more prone to walking into the shock inducing zone than the rats treated with the control, presumably because the rats given Risperidone had trouble remembering about the shock inducing side. The latency to cross was measured in seconds up to ten minutes. Day 0 is before the first shock. All values presented are mean ± SEM and normalized (norm) to VEH. n = 4-6 rats per group.



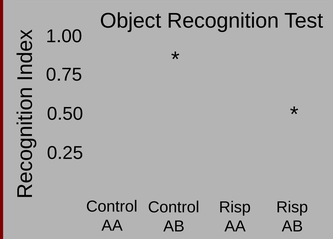


Fig 3. Results of Object Recognition Test done at 90 days show that the control rats did preferred the novel object over the familiar object they saw previously over the 6 hour delay. The rats subjected to Risperidone treatment, however seemed to forget what the familiar object was and focused on both objects almost equally. All values presented are mean ± SEM and normalized (norm) to VEH. n = 4-6 rats per group. '*' indicates significantly different ($p < 0.05$) than VEH.

MOLECULAR RESULTS

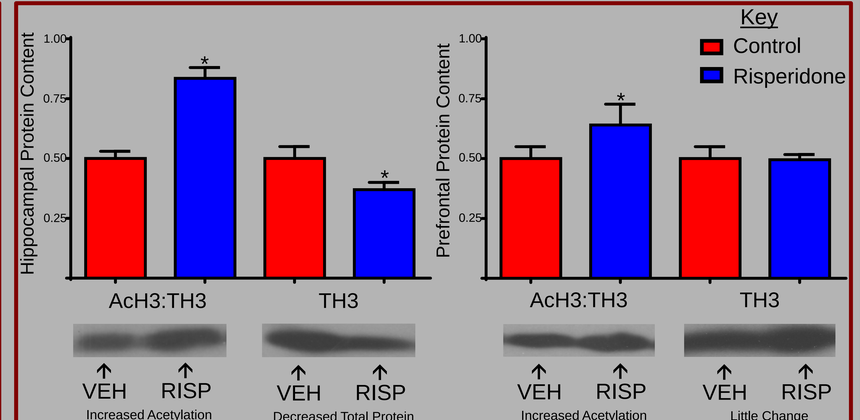
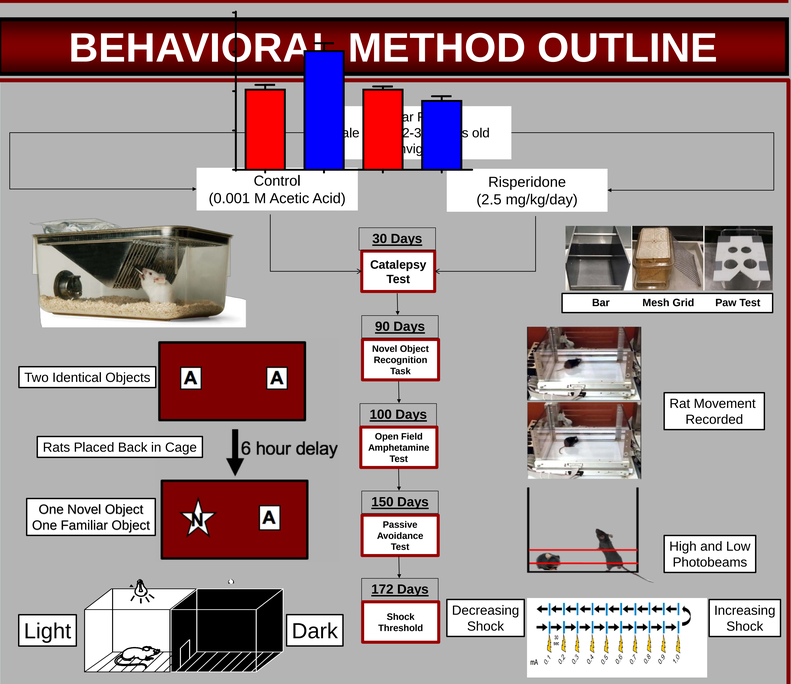


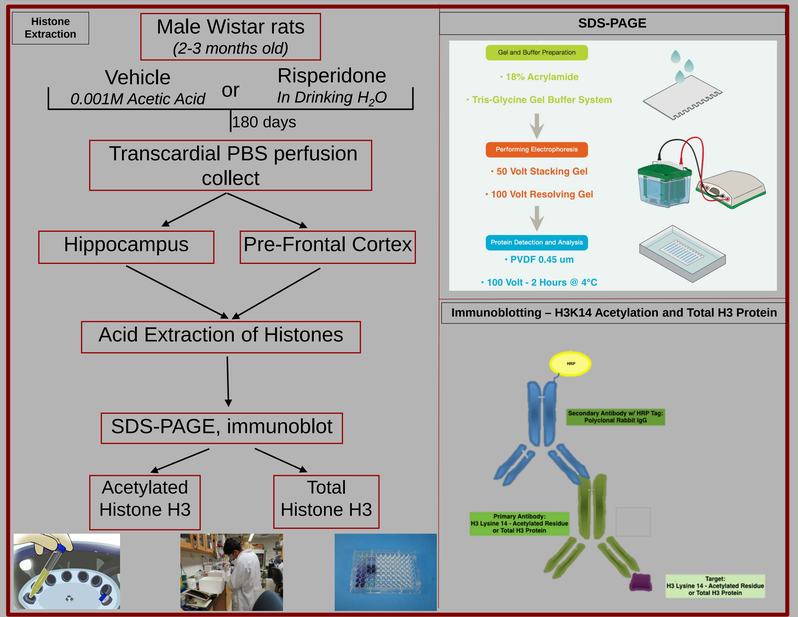
Fig 4. Effect of 180-day Risperidone treatment show increased Histone H3 Acetylation (AcH3) at lysine 14 and ratio (AcH3:TH3) in the hippocampus with Risperidone. All values presented are Mean ± SEM and normalized (norm) to VEH. n = 4-6 rats per group. Below histograms are representative immunoblots, which were used to determine protein expression.

Fig 5. Effect of 180-day Risperidone treatment show increased Histone H3 Acetylation (AcH3) at lysine 14 and ratio (AcH3:TH3) in the pre-frontal cortex with Risperidone. All values presented are Mean ± SEM and normalized (norm) to VEH. n = 4-6 rats per group. Below histograms are representative immunoblots, which were used to determine protein expression.

BEHAVIORAL METHOD OUTLINE



MOLECULAR METHOD OUTLINE



SUMMARY & CONCLUSIONS

- **The results show that there is a decreased amount of total H3 Protein in the hippocampus, but an increased amount of acetylation to proteins in both the prefrontal cortex and the hippocampus, presumably as a coping mechanism to increase the amount of protein available in these regions. The behavioral studies show that there is a statistically significant decline in memory performance, and the molecular studies back that up by showing decreased amount of total protein in the hippocampus. Further studies into other post-translational modifications such as methylation will be needed to determine if protein expression is indeed being suppressed. If so, then post-translational modifications of histones may underlie cognitive impairments previously observed in association with chronic antipsychotic (AP) treatment in animal models as well as the lack of sensitivity to pro-cognitive agents that have been observed in clinical trials in schizophrenia patients. These AP-related epigenetic modifications could be targeted for (adjunctive) drug development strategies to improve cognition in neuropsychiatric patients.**

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