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

Ashish Lalani, Caterina M. Hernandez, Indrani Poddar, Alvin V. Terry, Jr.

Department of Pharmacology and Toxicology, Augusta University, Augusta, Georgia

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

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 sides. 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 prefer 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.

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 these modifications are working together or independently.

Acknowledgements

- The Small Animal Behavioral Core Facility’s Research Associates (Samantha Sinha, Kristy Bouchard and Leah Vandenhuerk) for dosing animals and performing behavioral studies and Augusta University Honors Program