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Evaluation of antipsychotic drug treatment and histone deacetylase inhibition on the behavioral and psychological symptoms of dementia (BPSD) in an alzheimer's disease mouse model

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Antipsychotic drugs are widely prescribed for the treatment of BPSD, especially psychosis and behavioral disturbances like aggression and agitation. However, antipsychotic drugs frequently produce serious extrapyramidal side effects (EPS) including bradykinesia, akinesia, tremor, and muscle rigidity. Developing novel treatment strategies that increase the efficacy of antipsychotics and reduce the side effects is essential in the treatment of AD. One such novel strategy currently being investigated is the co-administration of histone deacetylase inhibitors (HDACis) with antipsychotic drugs.

We first evaluated baseline BPSD-like behaviors in our adult (6 months) 5xFAD mice compared to age-matched controls. Behavioral evaluation was split into distinct domains: affective, hyperactive, apathetic and cognitive. We then evaluated behaviors in aged (11 months) 5xFAD mice to determine the impact aging has on BPSD-like behaviors. We then determined the impact chronic administration of risperidone has on BPSD-like behaviors and motor side effects in adult and aged 5xFAD mice. To test the effect of co treatment with an HDACi and antipsychotic, the HDACi MS-275 and antipsychotic drug risperidone were chronically co-administered to aged mice. 14 days following the start of drug treatment cognitive and behavioral function was assessed.

Our results revealed significant affective, hyperactive, and apathetic symptoms in 5xFAD mice compared to age-matched controls, but no significant differences in cognitive performance at 6 months of age . However, at 11 months of age, we found a significant increase in depressive-like behavior as well as impaired cognitive functioning in 5xFAD mice compared to age-matched controls. When 5xFAD mice were chronically administered risperidone, 11-month 5xFAD mice showed significantly increased sensitivity to risperidone-induced motor side effects compared to 6-month 5xFAD mice and age-matched controls, but these side effects were reduced by co-

treatment of HDACi MS-275. However, co-treatment of MS-275 and risperidone did not have an impact on BPSD-like behaviors.

Collectively, our results suggest that BPSD can be modeled in a mouse model of AD. Indeed, multiple tests within each behavioral domain showed significant disparities in BPSD-like behaviors between 5xFAD mice and age-matched controls. Additionally risperidone treatment did not significantly improve BPSD behaviors, but rather had a detrimental effect on motor side effects in 11 month age 5xFAD mice. Although co-treatment of MS-275 with risperidone did not mitigate BPSD-like behaviors in 5xFAD mice, it did significantly reduce the severity of risperidone-induced motor side effects.

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