Does Exposure to Chronic Stress in Rodents Alter the Level of SIRT1 in the Nucleus Accumbens?

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Introduction

- Depression is a life-threatening disorder and a leading cause of disability worldwide.
- Studies have indicated that SIRT1, a class III histone deacetylase, may play a role in mediating depression like behaviors.
- The nucleus accumbens is a region in the brain that is involved in motivation and reward and is thought to play an important role in depression.
- In this study, we induce depression like behaviors in rodents and measure levels of SIRT1 in the nucleus accumbens.

Research Question

Does exposure to chronic stress in rodents alter the level of SIRT1 in the nucleus accumbens?

Materials and Methods

This is a randomized controlled trial where rodents are exposed to chronic social defeat stress in ten minute increments for a period of ten days and then observed and measured on several tests. For this study 27 animals were needed in the control group and the test group to detect a 25% difference in protein expression for 80% statistical power with an alpha of 0.05.

The rodents tested in this study are male C57BL/6J mice at 7-9 weeks old obtained from Jackson Laboratory. They were housed on a 12 hour light-dark cycle with free access to food and water and acclimated to the facility for one week prior to experimentation. The aggressor species is male CD1 retired breeder mice at 9-13 months old obtained from Charles River Laboratories. The test mice were exposed to an aggressive unknown CD1 retired breeder mouse for ten minutes per day for up to ten days. After this exposure the test mouse remained in the cage but was separated from the breeder mouse by a barrier that allows sensory but no physical exposure to the aggressor mouse. After the last interaction the test mice were observed and measured on the open field test to measure stress response and then divided into susceptible or resilient phenotypes. In the open-field test the mice were exposed to the CD1 retired breeder in a cage and EthoVision video tracking based methods (Noldus) were used to record how much time was spent by the mice in different areas of the enclosure. After the animals underwent social defeat and social interaction testing they were euthanized and the NAc was harvested. mRNA and protein levels were measured at 48 hours and ten days.

Results

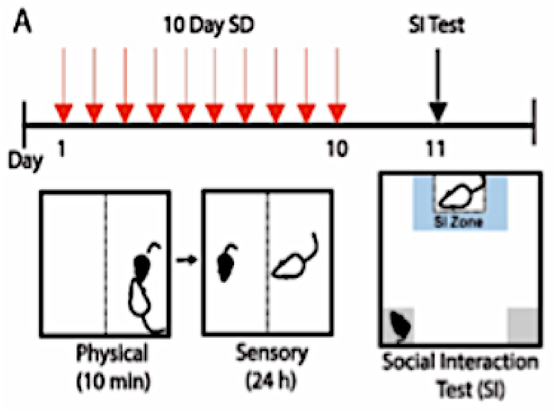

Figure 1: Male C57BL/6J mice rodents were first subjected to chronic social defeat stress by male CD1 retired breeder mice for a period of ten days.

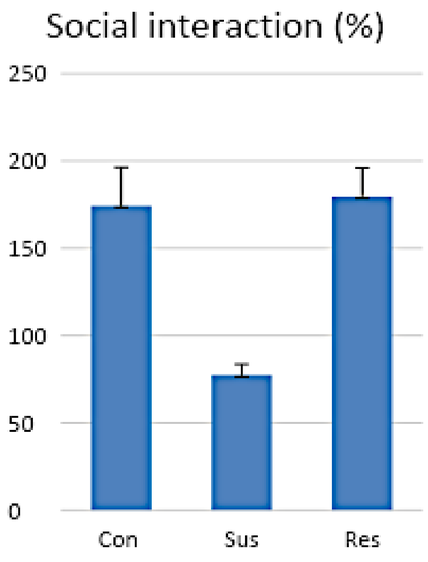

Figure 2: We observed a significant difference in the percentage of time spent in the interaction zone between the control and resilient groups versus the susceptible group (F =12.913, p = 0.0016). Mean ± SEM

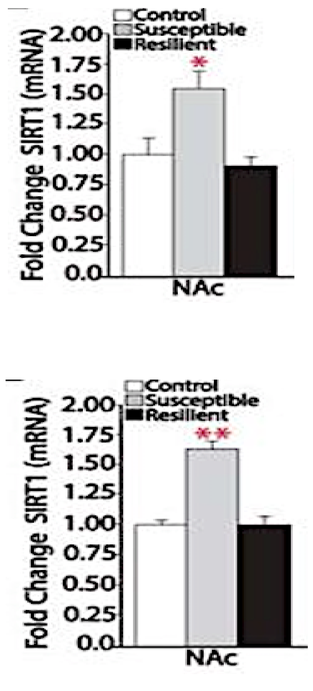

Figure 3: We observed that chronic social defeat stress induced SIRT1 mRNA levels in the NAc of susceptible mice at 48 hours (top graph, F= 9.75, p = 0.001). and 10 days (bottom graph, F = 5.99, p = 0.01) with no change seen in resilient mice. Mean ± SEM

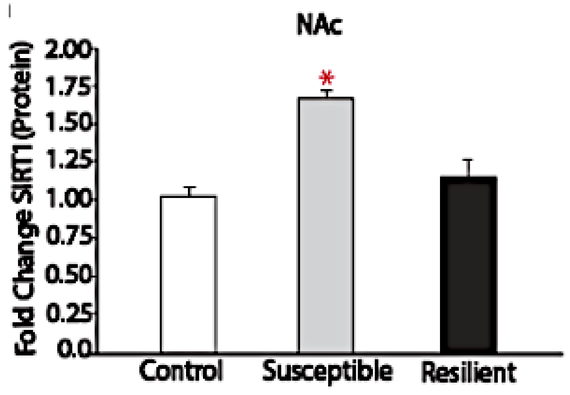

Figure 4: We also observed that the induction of SIRT1 mRNA in the NAc at 48 hours was paralleled by increased protein expression in the same region in susceptible mice but not resilient mice (Figure 6, F = 4.13, p = 0.03). Mean ± SEM

Conclusion

- Our results demonstrate that chronic social defeat stress stably induces SIRT1 expression in the nucleus accumbens of susceptible mice.
- Recent studies have linked SIRT1 to Major Depressive Disorder in humans.
- This correlates with our results demonstrating that SIRT1 levels in the nucleus accumbens are associated with depression and anxiety-like behaviors induced by chronic stress.
- These results could possibly introduce a new pharmacological target for the treatment of Major Depressive Disorder.

Summary

- This study demonstrates that chronic stress induces depression and anxiety related behaviors in susceptible rodents.
- These depression and anxiety related behaviors were shown to stably induce levels of SIRT1 mRNA and protein levels in the nucleus accumbens.

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