Investigating the Role of MDMA on CRH and APP Expression: A Genetic Insight on MDMA's Modulation of Stress and Alzheimer's Disease

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References

Background

- **Alzheimer's disease (AD)** is a neurodegenerative disease that affects 5.8 million Americans.
- AD primarily affects the **dorsal hippocampus (DH)**, with symptoms including dementia, frontotemporal disorders, memory problems, and overall brain shrinkage.[1]
- It is hypothesized that AD stems from the accumulation of Amyloid-β-42 plaques, causing dystrophy in the DH. These plaques are formed by cleavage of the **amyloid precursor protein (APP).**[1]
- **Corticotropin-releasing hormone (CRH)** is an essential regulator of the stress response. CRH release stimulates elevated cortisol, a glucocorticoid hormone, which is a strong predictor of the pathogenesis of AD.[2]
- **3,4-Methylenedioxymethamphetamine (MDMA)** is a recreational drug that has been shown to modulate cortisol, although its relation to CRH is undefined.[3] The connection between CRH and amyloid plaques points to a potential link between MDMA and APP, potentially increasing AD propensity.

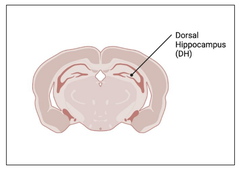
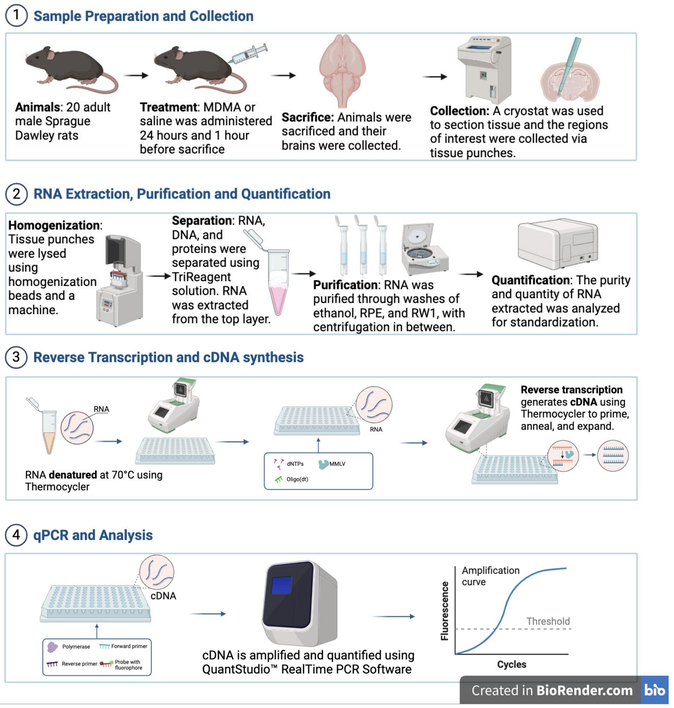


Figure 1. A coronal view of rodent DH (the region of interest).

Methods



Hypothesis

Acute MDMA administration will result in transcriptional upregulation of mRNA encoding CRH and APP in the male rat dorsal hippocampus.

Results

MDMA exposure *increases* APP Expression in rodents

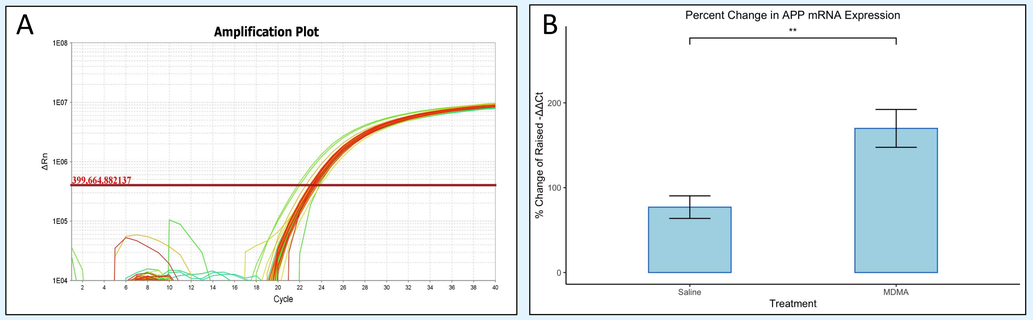


Figure 2. APP mRNA expression is increased in MDMA-administered rats. (**A**) Amplification plot of the extracted, purified and reverse transcribed mRNA, tagged with an APP primer, by subject, run in triplicate. (**B**) APP was shown to have increased expression using the $\Delta\Delta C_t$ method via a Welch two-sample t-test with GAPDH serving as a reference gene. There was no statistical difference in GAPDH mRNA expression across groups ($p>0.05$). With a p-value of 0.003, there is a statistically significant ($p<0.05$) difference in expression between MDMA and saline-exposed groups. A ΔRn of 400 was set using automatic threshold determination to derive Ct values. Error bars are included to represent the standard error of the mean.

MDMA exposure *increases* CRH Expression in rodents

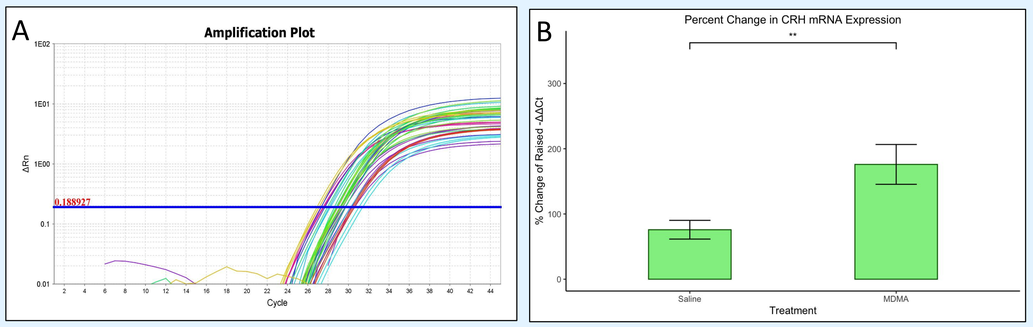


Figure 3. CRH mRNA expression is increased in MDMA-administered rats. (**A**) An amplification plot of the extracted, purified and reverse transcribed mRNA, tagged with a CRH primer, by subject, run in triplicate. (**B**) CRH mRNA levels were shown to be increased in the MDMA-treated male rats, using the $\Delta\Delta C_t$ method via a Welch two-sample t-test, with GAPDH serving as a reference gene. There was no statistical difference in GAPDH mRNA expression across groups ($p>0.05$). With a p-value of 0.023, there is a statistically significant difference ($p<0.05$) between the two saline and MDMA administered subjects. A ΔRn of 0.188 was set using automatic threshold determination to derive Ct values. Error bars are included to represent standard error of the mean.

Discussion & Future Experiments

- MDMA **increased** CRH ($\Delta\Delta C_t$ = 1.79) and APP ($\Delta\Delta C_t$ = 1.70) expression in the DH compared to control samples, supporting the initial hypothesis
- An increase in APP and CRH levels have been associated with increased amyloid plaque formation, which raises concerns for development of AD.[4,5]
- **A higher risk of developing AD would be a severe consequence of MDMA as a therapeutic drug**. Specifically, if consistent increases in APP and CRH are seen with chronic MDMA administration for therapeutic purposes, then there would be a greater concern for the development of AD.
- Future experiments should explore chronic MDMA usage to determine if these transcriptional increases are constant. Experiments using AD rodent models will elucidate long-term memory effects from MDMA.
- Future experiments should also elucidate the mechanism of action of MDMA's modulation of CRH and APP.
- **Limitations**: Rodents model used is not a sufficient model of AD. Study considers male rodents only.

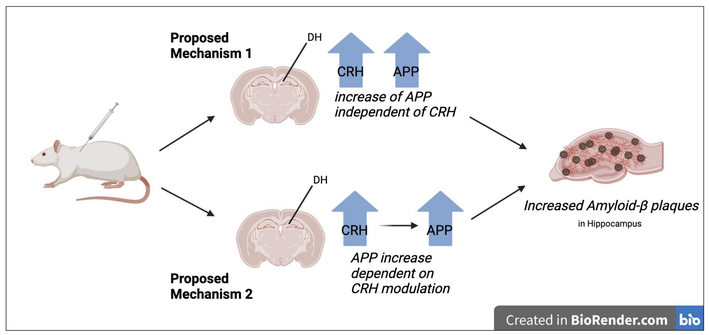


Figure 4. Summary of findings and presentation of 2 possible mechanisms of action for the increase in APP expression. Further experiments should elucidate MDMA's mechanism of action on the modulation of APP.

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