Impact of MDMA on CRH Gene Expression in the Dorsal Hippocampus and Amygdala

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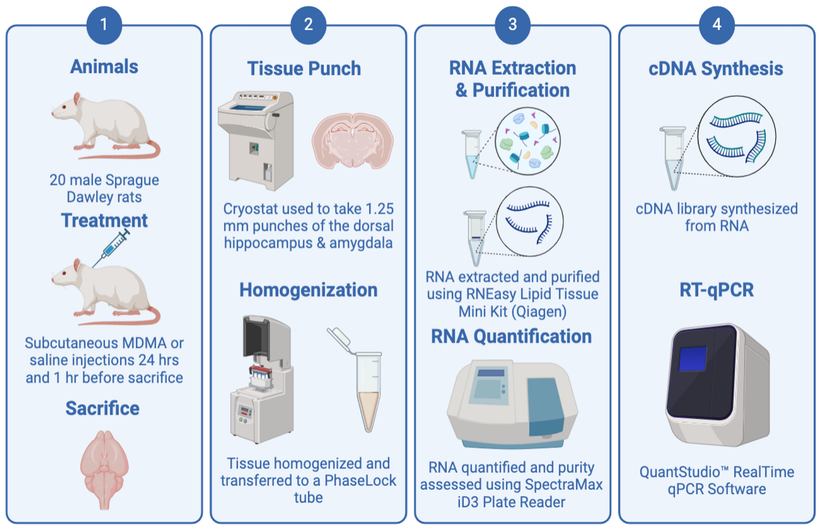
Introduction

- Post traumatic stress disorder (PTSD) is a psychological disorder that results from previous trauma and often manifests as extreme anxiety and depression upon witnessing a non-threatening stimulus.[1]
- Most PTSD patients fail to respond to conventional therapies.[2]
- 3,4-Methylenedioxymethamphetamine (MDMA) uniquely targets PTSD symptoms through HPA-axis activation, helping patients achieve remission.[1]
- HPA axis dysregulation has been observed in PTSD patients, marked by a decrease in cortisol and may promote maladaptive fear conditioning.[3]
- Corticotropin-releasing hormone (CRH) is an upstream regulator of cortisol release in the HPA axis pathway, the body's main stress response pathway.[4]
- The dorsal hippocampus and amygdala hippocampus have been associated with PTSD by affecting learning, memory, and fear-related emotions and behaviors.[5,6]
- The role of MDMA in the DH and amygdala and on CRH expression specifically has been understudied.
- Discovering mechanistic insight into how MDMA affects the HPA axis in these brain regions would provide insight into another mechanism by which it attenuates stress behaviors in PTSD treatment.

We hypothesized that CRH expression in the DH and amygdala will increase upon acute MDMA administration compared to a saline treated group in adult male Sprague Dawley rats.

Experimental Design



Figures

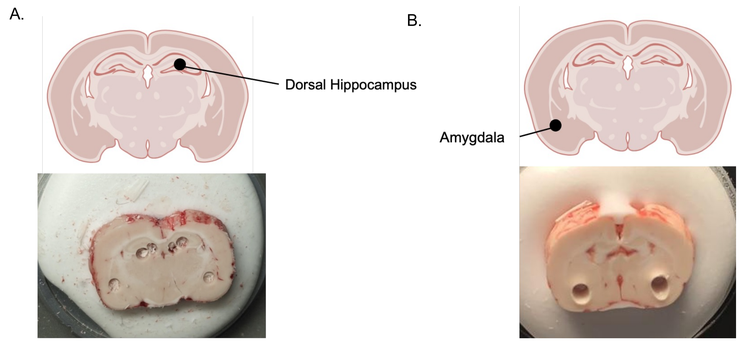


Figure 1. Brain Regions of Interest Obtained Through Tissue Punch. Brain regions identified using the Allen Brain Atlas. **A.)** Location of the dorsal hippocampus (DH) on male rodent. Below, DH punches removed. **B.)** Location of the amygdalar complex. Below, amygdala punches removed.

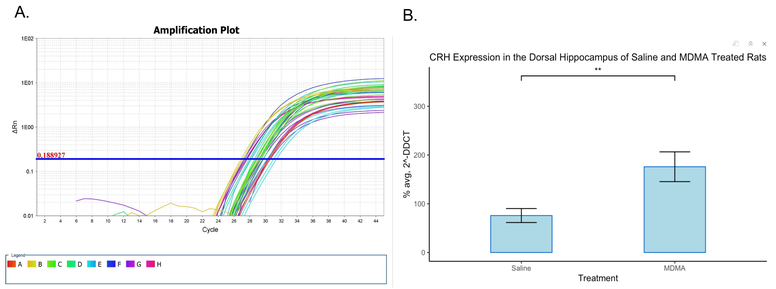


Figure 2. qPCR Amplification Plot and CRH mRNA Expression in the Dorsal Hippocampus (DH) Among MDMA- and Saline-Treated Male Rats (n=10 per treatment group). A.) The whole class amplification plot measuring CRH expression in the DH including the no template control (NTC) is shown. Letters A-H indicate the 8 rows of the 96-well plate, each with a different color to distinguish samples, which were run in triplicate. The automatic threshold determination was set at 0.188927. **B.)** A statistically significant difference is seen between saline and MDMA treatment groups (p=0.0111). Error bars indicate standard error of the mean to show precision. **, p<0.05.

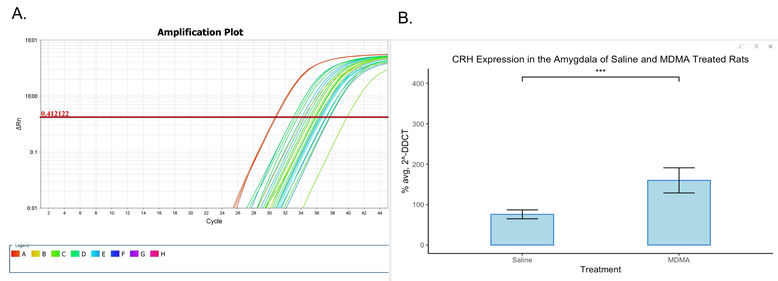


Figure 3. qPCR Amplification Plot and CRH mRNA Expression in the Amygdala Among MDMA- and Saline-Treated Male Rats (n=10 per treatment group). A.) The whole class amplification plot measuring CRH expression in the amygdala, including the no template control (NTC), is shown. Letters A-H indicate the 8 rows of the 96-well plate, each with a different color to distinguish samples, which were run in triplicate. The automatic threshold determination was set at 0.412122. **B.)** A statistically significant difference is seen between saline and MDMA treatment groups (p=0.0267). Error bars indicate standard error of the mean to show precision. ***, p<0.05.

Results

1) The results of Welch two-sample t-test for GAPDH gene were not significant, indicating there is no alteration on GAPDH expression in the DH and amygdala following MDMA administration (not shown in Figures).
2) MDMA-treated rats demonstrated a significant increase in CRH expression in the DH and amygdala compared to saline-treated rats (DH: p=0.0111, amygdala: p=0.0267).
3) **The results of RT-qPCR analysis support our hypothesis** that MDMA increases CRH expression in both the DH and amygdala.

Discussion and Future Directions

MDMA increased CRH expression in the DH and amygdala, potentially indicative of a mechanism by which it may attenuate fear conditioning during PTSD.

Future studies:

- Study this effect in female rats as well as male rats
- Incorporate behavioral stress paradigms and neuroimaging to visualize changes in CRH receptor expression alongside CRH mRNA expression
- Investigate the effects of MDMA on other downstream components of the HPA-axis pathway (ACTH and cortisol release) and CRH receptor expression

References & Acknowledgements

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