Acute MDMA Exposure Increases BDNF Expression in the Amygdala and Dorsal Hippocampus

E. Bawden, A. Lanik, C. Scott, M. Windram

Shveta Parekh, PhD (Advisor)

UNC | COLLEGE OF ARTS AND SCIENCES
Psychology and Neuroscience

Acknowledgements

We would like to thank Dr. Donald Lysle for donating the rodent brain tissue and the College of Arts and Sciences as well as the Department of Psychology & Neuroscience for funding and support of the undergraduate NSCI laboratories. We would also like to thank the Office for Undergraduate Research for supporting our course's GRC: Jenny Fiedler who was instrumental in our course R analysis. Lastly, we extend our thanks to Dr. Shveta Parekh, Dr. Elena Vidrascu, Nina Song, Nathan Mothes, Connie Pei, Ashton Pierson, Neha Venkatesh, and Brandon Yoo for making this course possible.

Introduction

- Post-traumatic stress disorder (PTSD) is a psychiatric disorder experienced by people who experience or witness an overwhelmingly shocking/traumatic event. It affects approximately 4.7% of US adults annually and 6.1% over a lifetime[2]. Given the prevalence and clinical significance of PTSD, development of novel treatments are needed to address the limitations of current approaches.
- **3,4-Methylenedioxymethamphetamine (MDMA)**, which is a stimulant drug with some psychedelic properties, **shows promise in treating psychiatric conditions like PTSD.** There was a significant decrease in PTSD severity scores during the course of MDMA-assisted therapeutic treatment.
- In initial studies, **MDMA administration in adult male rats showed an increase in brain derived neurotrophic factor (BDNF) levels[1] [3]**, a gene implicated in learning, memory, neurogenesis, and synaptic plasticity.[5] [6]
- Combined, the increase and eventual down-regulation of BDNF in PTSD and **MDMA's modulation of BDNF could be an avenue through which MDMA-assisted therapy improves PTSD symptoms.**
- **This study aims to understand MDMA's effects on BDNF in specific brain regions related to fear learning and anxiety disorders such as the amygdalar complex (COA) and dorsal hippocampus (DH), as they have been implicated in conditioned fear responses.** It also seeks to illuminate the previously unknown relationship between MDMA treatment and BDNF gene expression.

Hypothesis: In response to acute MDMA administration in adult male rats, BDNF gene expression will be upregulated in both the amygdalar complex and the dorsal hippocampus.

Methods

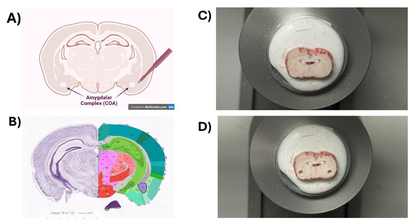

Figure 1: Sample Acquisition and Discussion of COA. A) Rodent brains were cut coronally to expose amygdalar complex (COA). Two 1.25 mm punches were taken of the COA from each brain. B) The COA was chosen as the brain region of interest due to links with stress, fear conditioned responses, and BDNF levels, as well as gaps in knowledge around MDMA and BDNF in the amygdala. BDNF levels were analyzed from tissue punches taken from the COA. C, D) Actual image of sample brain C) before and D) after COA punches.

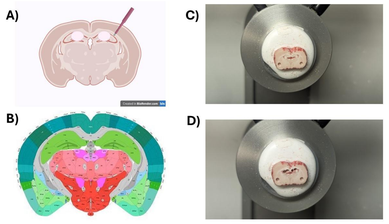

Figure 2: Sample Acquisition and Discussion of DH. A) Rodent brains were cut coronally to expose dorsal hippocampus (DH). 4-6 1.25 mm punches were taken of the DH from each brain. B) The DH was chosen as the brain region of interest due to links with stress, memory formation and BDNF levels. BDNF levels were analyzed from tissue punches taken from the DH. C, D) Actual image of sample brain C) before and D) after DH punches.

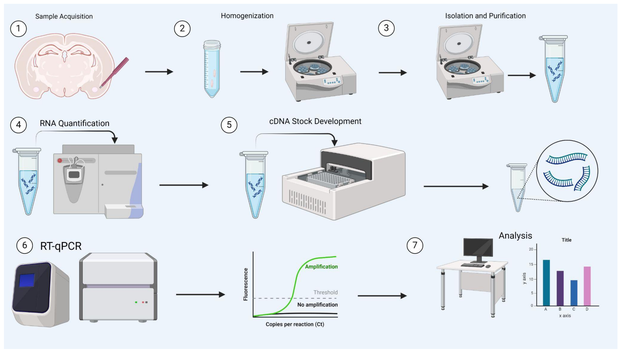

Figure 3: RT-qPCR Protocol. cDNA stock developed from RNA isolated from COA and DH tissue punches was reversed transcribed to obtain relative gene expression of BDNF in each respective brain region.

References

1) Ádori, C., Andó, R. D., Ferrington, L., Szekeres, M., Vas, S., Kelly, P. A. T., Hunyady, L., & Bagdy, G. (2010). Elevated BDNF protein level in cortex but not in hippocampus of MDMA-treated Dark Agouti rats: A potential link to the long-term recovery of serotonergic axons. Neuroscience Letters, 478(2), 56–60. https://doi.org/10.1016/j.neulet.2010.04.061
2) Goldstein, R. B., Smith, S. M., Chou, S. P., Saha, T. D., Jung, J., Zhang, H., Pickering, R. P., Ruan, W. J., Huang, B., & Grant, B. F. (2016). The epidemiology of dsm-5 posttraumatic stress disorder in the united states: Results from the national epidemiologic survey on alcohol and related conditions-iii. Social Psychiatry and Psychiatric Epidemiology, 51(8), 1137–1148. https://doi.org/10.1007/s00127-016-1208-
3) Koprich, J. B., Campbell, N. G., & Lipton, J. W. (2003). Neonatal 3,4-methylenedioxymethamphetamine (Ecstasy) alters dopamine and serotonin neurochemistry and increases brain-derived neurotrophic factor in the forebrain and brainstem of the rat. Developmental Brain Research, 147(1–2), 177–182. https://doi.org/10.1016/S0165-3806(03)00219-0
4) Martínez-Turrillas, R., Moyano, S., Del Río, J., & Frechilla, D. (2006). Differential effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on BDNF mRNA expression in rat frontal cortex and hippocampus. Neuroscience Letters, 402(1–2), 126–130. https://doi.org/10.1016/j.neulet.2006.03.055
5) Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G., M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mithoefer, A., Quevedo, S., Wells, G., Klaire, S. S., Van Der Kolk, B., … Doblin, R. (2021). MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. Nature Medicine, 27(6), 1025–1033. https://doi.org/10.1038/s41591-021-01336-3
6) Mitchell, J. M., Ot'alora G., M., Van Der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., Paleos, C., Nicholas, C. R., Quevedo, S., Balliett, B., Hamilton, S., Mithoefer, M., Kleiman, S., Parker-Guilbert, K., Tzarfaty, K., Harrison, C., De Boer, A., Doblin, R., Yazar-Klosinski, B., & MAPP2 Study Collaborator Group. (2023). MDMA-assisted therapy for moderate to severe PTSD: A randomized, placebo-controlled phase 3 trial. Nature Medicine, 29(10), 2473–2480. https://doi.org/10.1038/s41591-023-02565-4

Experiments

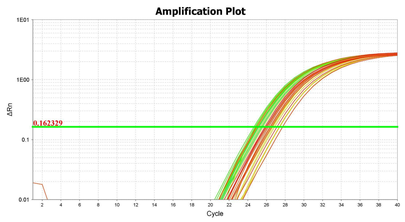

Figure 3: Amplification Plot of COA BDNF Gene Expression cDNA stock developed from RNA isolated from COA tissue punches was reversed transcribed to obtain relative gene expression of BDNF in this brain region. cDNA samples were run in triplicates.

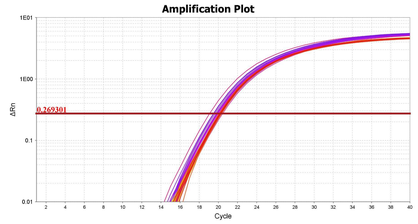

Figure 5: Amplification Plot of DH BDNF Gene Expression cDNA stock developed from RNA isolated from DH tissue punches was reversed transcribed to obtain relative gene expression of BDNF in this brain region. cDNA samples were run in triplicates.

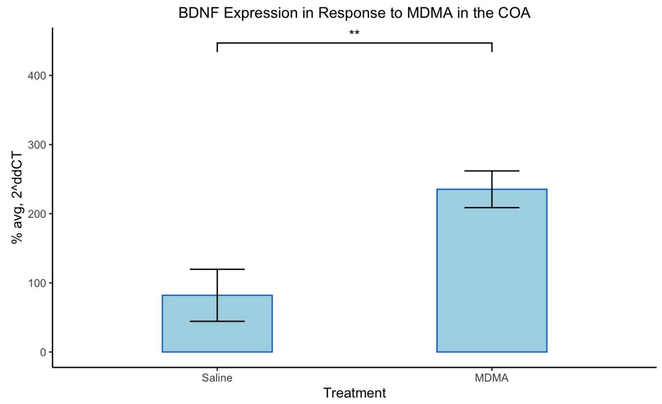

Figure 4: Percent Average Change in BDNF Expression Levels in the COA. Average percent change in COA between saline and MDMA-treated male rats. Saline: mean of 0.82, MDMA: mean of 2.35. P-value = 0.004, so reject null hypothesis. Gene expression was compared to the reference gene GAPDH. **p < 0.05.

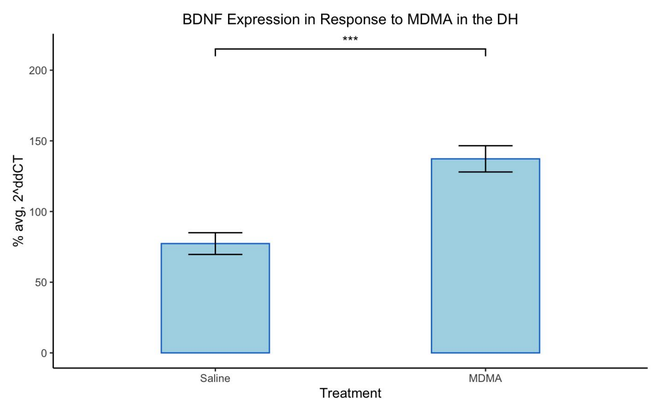

Figure 6: qPCR Amplification Plots and BDNF Expression Levels in the DH. Average percent change in COA between saline and MDMA-treated male rats. Saline: mean of 0.77, MDMA: mean of 1.37. P-value = 0.0001, so reject null hypothesis. Gene expression was compared to the reference gene GAPDH. **p < 0.001.

Results

- Successful experimental and control amplification plots from RT-qPCR
- Since $p < 0.05$ for the difference in BDNF expression, this means there are significant differences between MDMA and control groups in both the COA and DH
- The amygdalar complex had a Cohen's d effect size of 0.844, indicating a large effect size
- The dorsal hippocampus had a Cohen's d effect size of 0.921, indicating a large effect size

Key Finding: Acute MDMA exposure leads to a significant increase in BDNF expression in both the COA and DH

Conclusions

- MDMA exposure leads to statistically significant increases in BDNF expression in the COA and DH, indicating possible therapeutic uses of the drug for anxiety-related disorders such as PTSD
- These findings help us develop a better understanding of the molecular mechanisms that could make MDMA-assisted PTSD treatments effective
- Further investigation needed into how chronic (vs acute) MDMA exposure impacts BDNF in relevant brain regions, as well as how a longer treatment timeline would impact the overall efficacy of PTSD therapies
- A better understanding of MDMA and BDNF expression in individual brain regions will lead to more targeted PTSD treatments using MDMA