Serotonergic Influence on Leptin and BDNF in the Amygdala

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Introduction

•3,4-Methylenedioxymethamphetamine1 (MDMA), known for its hallucinogenic effects and serotonin (5-HT) stimulation, impacts synaptic vesicle release of serotonin via disruption of vesicular monoamine transporter 2, eliciting feelings of well-being and openness.[1]

•MDMA has also been known to induce appetite suppression, with one suggested pathway being the modulation of cocaine-and-amphetamine-regulated-transcript (CART) in the nucleus accumbens.[2]

•Leptin, involved in appetite regulation and a direct regulator of CART activity, shows reduced peripheral levels following MDMA administration, emphasized by a serotoninergic-dependent homeostatic pathway.[3,4]

•5-HT's modulation of synaptic plasticity involves enhancing brain-derived neurotrophic factor (BDNF) expression, promoting cell differentiation and survival.[5] MDMA administration has also been shown to influence BDNF levels.[6, 7]

•Leptin's role in energy homeostasis and cognitive processing, coupled with BDNF's role in neuroplasticity, suggests intertwined effects of cognitive homeostatic pathways on emotional processing, particularly in the amygdala, affected by MDMA.[8, 9, 10]

Hypothesis

Given MDMA's effect on serotonergic pathways and its downstream targets, acute MDMA administration will increase levels of both leptin and BDNF in the amygdala of male rats

Acknowledgements and References

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Experimental Design

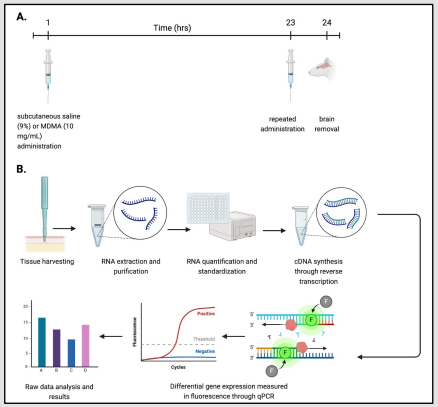


Figure 1. **Protocol Visualization of Preparation, Tissue Collection, and RT-qPCR performed on Male Rats in Amygdala Brain Regions. (A)** Timeline of MDMA administration before sacrifice. **(B)** Schematic of how differential gene expression was measured using RT-qPCR.

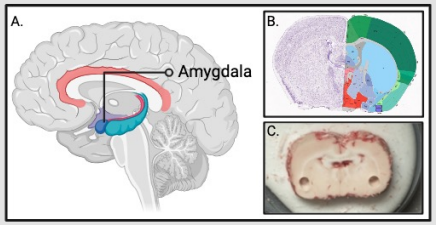


Figure 2. **Amygdalar Brain Tissue Acquisition. (A)** Visual representation of amygdala location in the human brain to show homology to the rat brain. **(B)** Representative image of Adult Mouse Brain from Allen Brain Atlas with purple highlight indicating the Amygdala. **(C)** Photograph of class rodent brain with two punches sectioned at the Amygdala .

Table 1. **Known Functions in the Amygdala from previous literature.**

Leptin	BDNF
• LTP attenuation[12, 27] • Neuronal cell migration[25] • volume maintenance[26]	• Fear extinction[11,18,19, 24] • Appetitive learning[18] • Mood regulation[20, 21] • Stress induced structural plasticity[22] • 5-HT neuron protection[23] • Memory[24]

Results

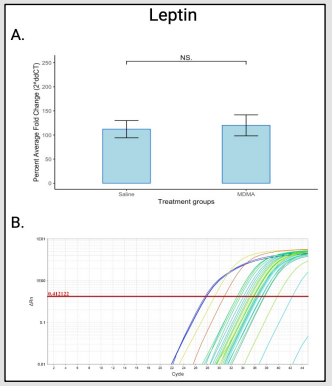


Figure 3. **Leptin Expression and Amplification Plot in Amygdala of Male Rodents. (A)** Comparison of Leptin expression between MDMA(n=10) and saline groups(n=10). Welch's two-sample t-test indicates no significant difference in means (2^-ΔΔCT) (MDMA: 1.200 ± 0.6881, saline: 1.212 ± 0.5647), with a p-value of 0.782, t-statistic of 0.28108, and df of 17.34. Cohen's D (0.1257) suggests a small effect size. Error bars indicate SEM. **(B)** Aggregated data collection of the amplification plot, with 20 samples run in triplicate, displaying key phases and threshold crossover. The threshold is automatically generated by the qPCR machine at a coefficient of 0.412122.

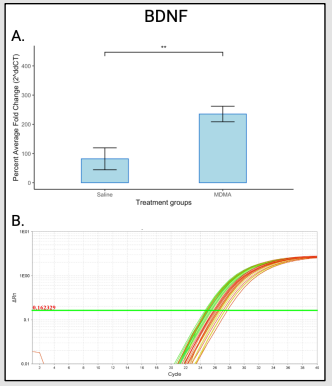


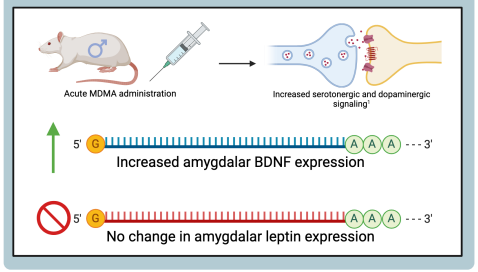
Figure 4. **BDNF Expression and Amplification Plot in Amygdala of Male Rodents.** (A) MDMA's effects on BDNF expression reveal a significantly higher mean (2^-ΔΔCT) test score in the experimental group (n=10) compared to the saline group (0.8199 vs. 2.353, respectively), with greater variability (SD=1.1898 vs. 0.8403, respectively). A large effect size (Cohen's D = 1.4888) and Welch's two-sample t-test (p = 0.004194, t-statistic = 2.0679, df = 11.952) confirm a substantial difference in gene expression between groups. Error bars indicate SEM. (B) Aggregated data collection of the amplification plot, featuring twenty samples run in triplicate, illustrates key phases and threshold crossover, with the threshold automatically generated by the qPCR machine at a coefficient of 0.162329.

Conclusion and Limitations

•While a significant increase in amygdalar BDNF was recorded, acute MDMA administration did not affect amygdalar leptin.

•The increase seen in BDNF expression levels upon MDMA administration suggests a role serotonergic signaling plays on memory and brain structure, also implicated in Young et al.[11]

•Experiments were only performed on adult male rats given ad libitum diets.



Future Implications

•Measure differential leptin expression in subregions of the amygdala based on the implications of Schepers et al.[12]

•Measure differential leptin and BDNF expression in the nucleus accumbens, to further clarify the observed increase in CART expression.[2]

•Investigate downstream targets of BDNF in the amygdala or in canonical amygdalar pathways, especially in the cerebral cortex.[15]

•Investigate the role of leptin in the hippocampus.

•Investigate differences in gene expression in models of chronic MDMA usage.

•In each of these future implications, restricted and/or controlled diet intake should be utilized to help further understand leptin involvement in inflammation[16].