Intranasal OT reduces conditioned locomotion and elicits changes in endocannabinoid receptors within the mesolimbic system

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INTRODUCTION

- **Oxytocin (OT)** is a neuropeptide commonly associated with social behaviors, stress responses, and drug-addiction. Previous studies have shown that OT has anxiolytic properties associated with cues in a cocaine-conditioning paradigm, but the underlying mechanism remains unknown. (Morales-Rivera et al., 2014)
- Pre-clinical studies show that endocannabinoids in the brain modulate emotional responses, appetite, mood, pain-sensation, and the effects of cannabis. (John et al, 2012)
- **Cannabinoid receptor type 1 (CB1)** is a G-protein receptor, whose activation reduces anxiety related behavior, also known as an anxiolytic effect.

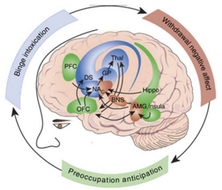


Figure 1. Neurocircuitry of Addiction (Koob et al. 2014)

OBJECTIVE

- Characterize possible mechanistic interactions between OT and the endocannabinoid system mediating cocaine conditioning and anxiety response, in particular the cannabinoid receptor type 1 (CB1).

HYPOTHESIS

- A cross-talk between the endocannabinoid system and oxytocin within the mesolimbic system is responsible for the anxiety modulation triggered by cocaine exposure.

METHODS

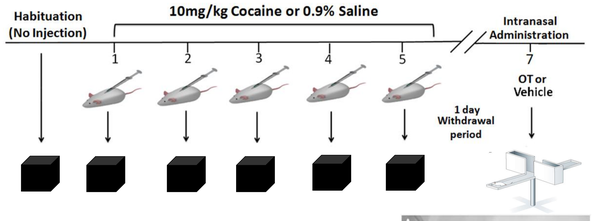


Figure 2. 36 Sprague Dawley male rats were exposed to activity chambers after receiving systemic intraperitoneal injections of with Saline 0.9% (Control) or Cocaine 10 mg/kg (Experimental). On the last day (D7), rats received intranasal infusions of OT (1 µg/µL) or vehicle 30 minutes prior being exposed to the cue-associated environment. Rats were then exposed to Elevated Plus Maze, euthanized, and brains were removed for Western blots or Immunohistochemical analysis.

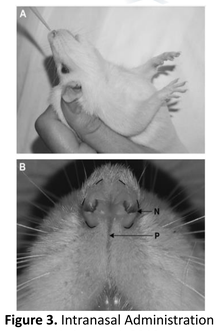


Figure 3. Intranasal Administration (Lukas et al. 2012)

RESULTS

Cocaine Conditioning

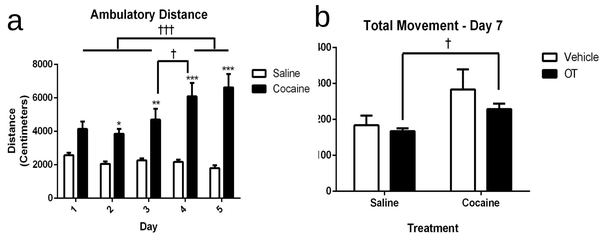


Figure 4. Intranasal OT impacts conditioned locomotion. (a) Cocaine increased the distance traveled during the first five days of training showing a cocaine-induced sensitization over time. (n=18) **(b)** Intranasal OT impacts cocaine-conditioned locomotion on the test day. (n=9) (*p<0.05, **p<0.01, ***p<0.001)

Elevated Plus Maze (EPM)

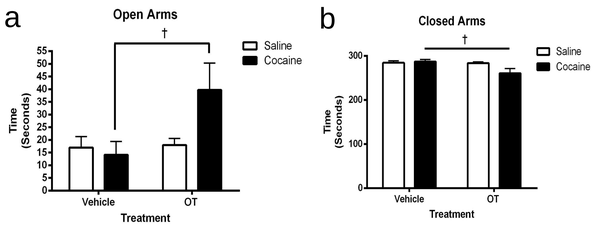


Figure 5. Intranasal OT reduces anxiety-like behaviors on cocaine conditioned animals. (a) Intranasal OT increases the time spent on the open arms on cocaine conditioned animals. (n=9) **(b)** Intranasal OT decreases the time spent on the closed arms on cocaine conditioned animals. (n=9) (*p<0.05)

Biochemical Assay

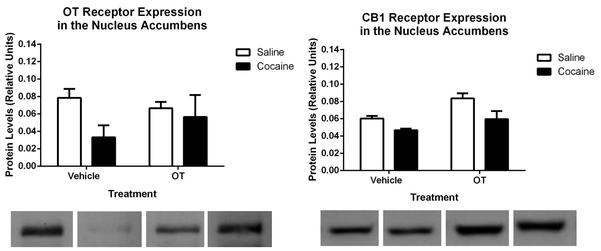


Figure 6. Cocaine-treated rats expressed less OT receptors than the Vehicle-Saline or the OT-Saline group. OT-Cocaine showed an increase in OT receptors compared to Vehicle-Cocaine.

Figure 7. Cocaine-treated rats expressed less CB1 receptors than the Vehicle-Saline or the OT-Saline group. OT group showed an increase in CB1 receptors compared to Vehicle.

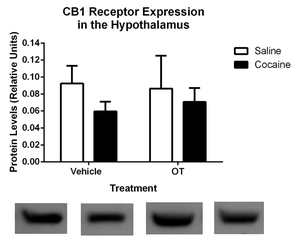


Figure 8. Cocaine-treated rats expressed less CB1 receptors than the Vehicle-Saline or the OT-Saline group in the hypothalamus.

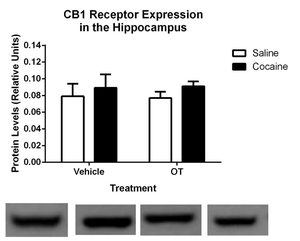


Figure 9. Cocaine- or saline-treated rats showed no significant receptor expression change in the hippocampus.

RESULTS (CONT.)

Immunohistochemistry

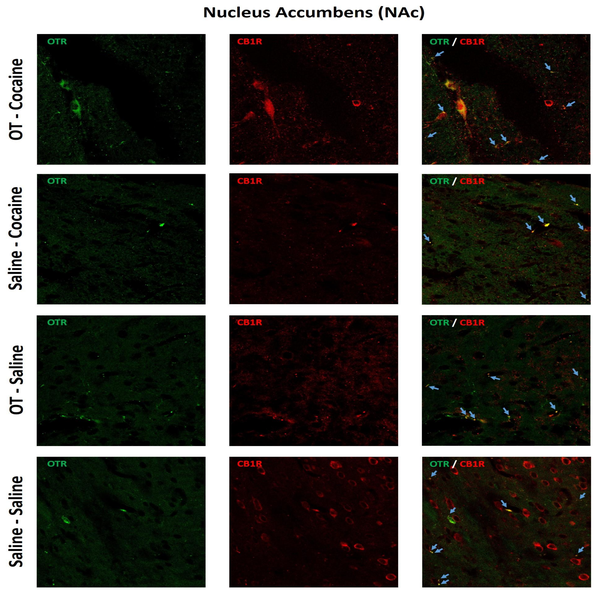


Figure 10. Colocalization of OT and CB1 receptors within the NAc. OT receptors are stained in green and CB1 receptors are stained in red. There is a colocalization of OT and CB1 receptors within the NAc in all treated animals. However, colocalization is pronounced when animals received a pretreatment of intranasal OT.

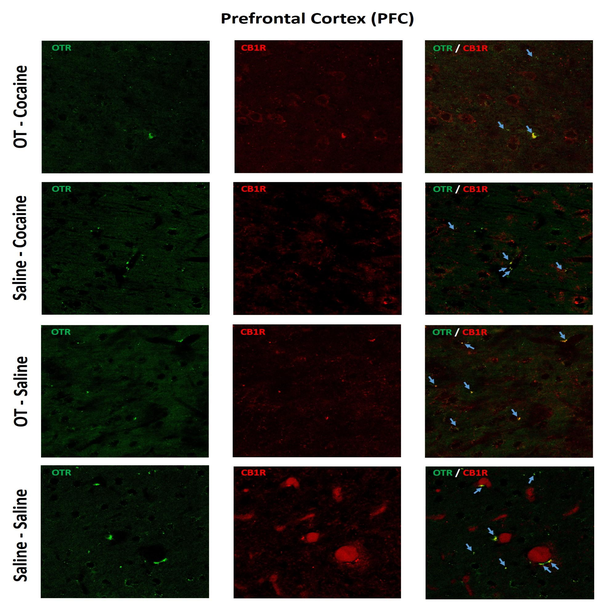


Figure 11. Colocalization of OT and CB1 receptors within the PFC. OT receptors are stained in green and CB1 receptors are stained in red. There is a colocalization of OT and CB1 receptors within the PFC in all treated animals.

SUMMARY AND CONCLUSIONS

- Intranasal OT administration impacts cocaine-conditioned locomotion and reduces anxiety-like behaviors on cocaine conditioned animals.
- There is a decrease of OT receptors when the animals are exposed to cocaine and a possible recovery with pre-treatment of OT in the NAc.
- Animals pre-treated with cocaine showed a decrease in CB1 receptor expression within the NAc and Hypothalamus compared to the saline group. No significant change was observed in CB1 receptor expression within the hippocampus.
- OT and CB1 receptors are colocalized within the NAc and PFC in all treated animals.

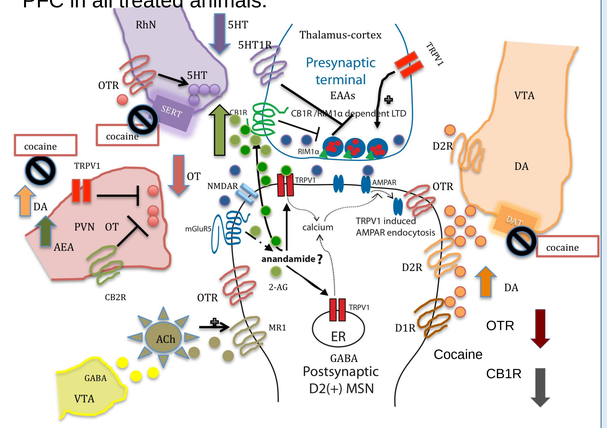
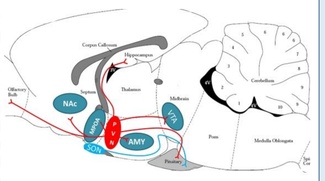


Figure 12. Proposed mechanism of cross-talk between OT and endocannabinoid system within NAc in cocaine treated animals. Cocaine blocks reuptake transporters of cathecolamines causing an increase in DA and OT. When OTR is activated exogenously, we propose an enhancement of endocannabinoid production leading to activation of CB1 in the presynaptic terminal.



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