RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

Submission ID: 492
Mentor Name: Craig Ferris
Undergraduate

Center for Translational Neuro-Imaging

Mescaline-Induced Modulation of Fear and Reward Pathways: BOLD phMRI Study in Rats

S. Gallo[1], A. Brettler[1], N. Cavallaro, MS[1] P. Rai[1], D. Akins[1], R. Utama[1], A. Moore[1], B. Axe[1], R. Ortiz[2], PhD, P.P. Kulkarni[2], PhD, C.F. Ferris, PhD[1,3]

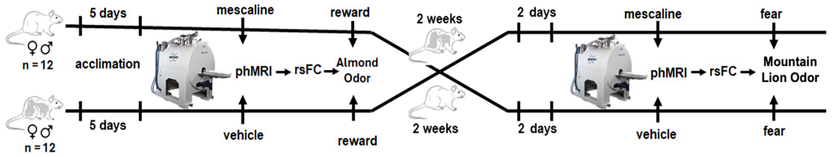
[1]Center for Translational Neuroimaging, Northeastern University, Boston, MA USA; [2]Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, NM USA; [3]Pharmaceutical Sciences, Northeastern University, Boston, MA USA

Background & Goals

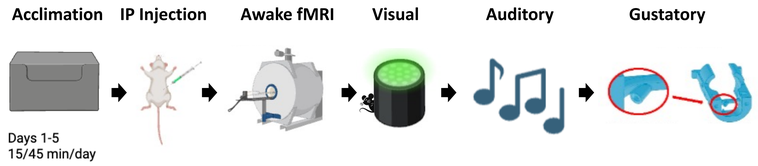
Mescaline is a psychoactive alkaloid found in peyote, acting as a 5-HT2A/2C agonist and inducing hallucinations and euphoria through its effects on sensory systems. Sensory perception, dominated by olfaction in rodents, processes and interprets external stimuli. The goal of this study was to examine mescaline's effects on responses to olfactory, gustatory, auditory, and visual stimuli in awake rats. Mountain lion urine and benzaldehyde were used to activate fear and reward pathways through the olfactory system, respectively, while additional paradigms were employed to probe taste, sound, and light sensitivity. This study aimed to address gaps in the current knowledge about mescaline and hallucinogens overall by offering insight into the neurobiological mechanisms underlying its broad sensory effects.

Process & Methods

Study 1. Sprague Dawley rats (12 male, 12 female) were split into 2 cohorts that received either 50 mg/kg Mescaline (Mesc.) or the same volume of vehicle (VEH). All experiments were conducted on reverse L/D cycles to preserve circadian rhythms. Rats were exposed to benzaldehyde during the first image acquisition and were then allowed 2 weeks to wash out. The Mesc/VEH cohorts were then swapped, and the same process was repeated with mountain lion urine.



Study 2. Sprague Dawley rats (12 male, 12 female) were split into 2 cohorts that received either 50 mg/kg Mescaline (Mesc.) or the same volume of vehicle (VEH). Acquisitions completed in a Bruker BioSpec 70/20 7.0T scanner 15 minutes post-injection. Three consecutive Rep120 BOLD fMRI scans (12 min each) were acquired, with visual, gustatory or auditory stimuli presented following an initial 6-minute baseline window.



Conclusion

Mescaline produced modality-selective effects on sensory processing rather than global disruption. Olfactory responses to rewarding stimuli were significantly blunted while aversive predator cues remained intact, suggesting mescaline preferentially disrupts valence-dependent processing of positive stimuli. Gustatory responses to sucrose were unaffected, pointing to a dissociation that may reflect differences in underlying neural circuitry, as olfactory reward networks overlap substantially with regions showing mescaline-induced hyperconnectivity while gustatory pathways through brainstem and insular cortex appear less vulnerable. PPI findings further support recalibration of specific sensory channels rather than global gating impairment. Together, these results position mescaline as a selective sensory filter disruptor, with the cerebellum as a likely mechanistic hub.

Future Directions

Behavioral Testing

- Effects on learning and memory: Barnes Maze, Open Field Test, Novel Object Recognition

Dose-Response Characterization

- Investigate dose-dependent effects by comparing sub-hallucinogenic, threshold, and suprathreshold mescaline doses on sensory-evoked BOLD responses

Temporal Dynamics

- Characterize the time course of mescaline's sensory effects by imaging at multiple post-injection time points to map the onset, peak, and resolution of neural activation changes

Acknowledgements

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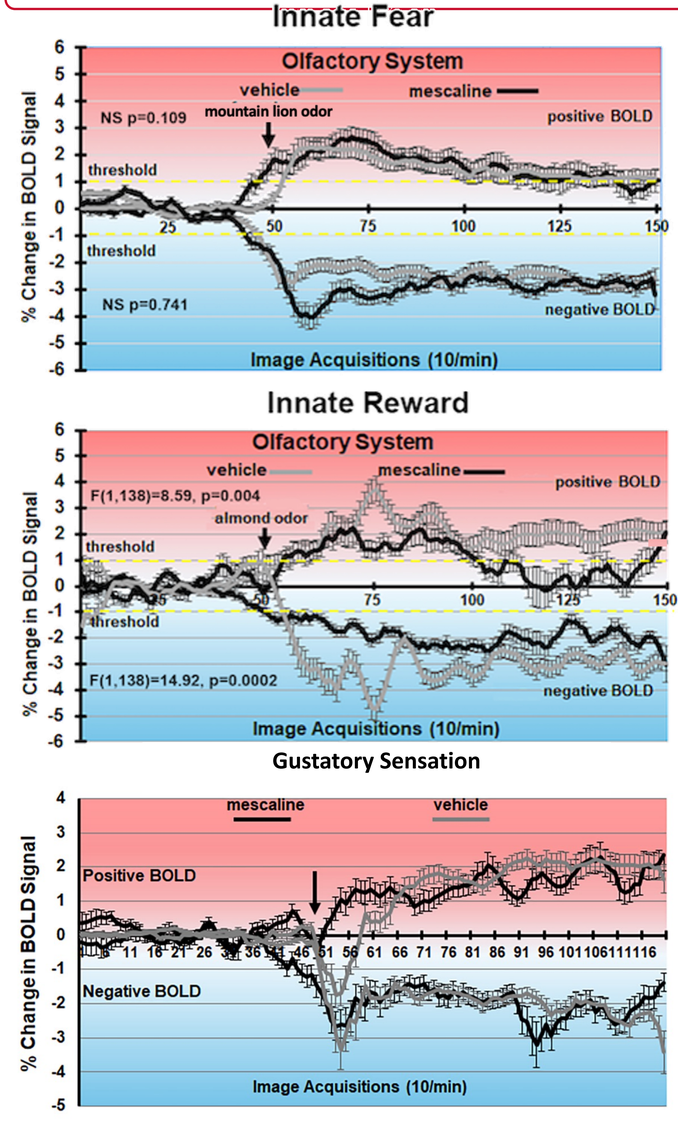
Significant Findings



Olfactory Sensory Processing: Reward vs. Fear

In response to a rewarding olfactory stimulus (almond odor), mescaline significantly attenuated both positive BOLD ($F(1,138) = 8.59$, $p = 0.004$) and negative BOLD ($F(1,138) = 14.92$, $p = 0.0002$) signal in the olfactory system relative to vehicle. In contrast, presentation of an aversive olfactory stimulus (mountain lion odor) produced no significant differences between mescaline and vehicle for either positive ($p = 0.109$) or negative BOLD ($p = 0.741$) Mescaline thus selectively disrupted olfactory processing of reward-associated stimuli while leaving threat-related olfactory processing largely intact.

Gustatory Sensory Processing

Following intra-oral delivery of 30% sucrose solution (at repetition 50), both mescaline (n = 9) and vehicle (n = 9) groups showed comparable increases in positive BOLD signal and decreases in negative BOLD signal in gustatory cortical regions. No significant differences were observed between treatment groups for either positive or negative BOLD

Sensory Gating (Pre-Pulse Inhibition)

Mescaline produced frequency-dependent effects on acoustic gating (Treatment × Frequency interaction: $F = 3.874$, $p = 0.028$, $\omega^2 = 0.098$). PPI was significantly enhanced at 4 kHz ($p = 0.037$) with a trend at 20 kHz ($p = 0.051$), but was not significantly different from vehicle at 12 kHz. Mescaline enhanced PPI by +27.6% and +27.3% at 4 and 20 kHz respectively, while impairing it by −16.4% at 12 kHz, producing an inverted U-shaped frequency response profile, indicating that mescaline did not alter gustatory sensory processing at this dose and time point.