Apr 21st, 10:00 AM - 10:50 AM

Psilocybin prevents symptoms of hyperarousal and enhances novel object recognition in rats exposed to the single prolonged stress paradigm

Colin R. Del Valle
Ohio Northern University

Heather R. Sparkman
Ohio Northern University

Margaret M. Naylor
Ohio Northern University

Connor M. Cruea
Ohio Northern University

Rachel E. Rice
Ohio Northern University

See next page for additional authors

Presenter Information

Colin R. Del Valle, Heather R. Sparkman, Margaret M. Naylor, Connor M. Cruea, Rachel E. Rice, Claire E. Miller, Brooke E. Bramlage, Lillianna P. Puppel, Madison L. Brown, Aleece K. Al-Olimat, Elizabeth S. Dietz, and Phillip R. Zoladz

Psilocybin Prevents Symptoms of Hyperarousal and Enhances Novel Object Recognition in Rats Exposed to the Single Prolonged Stress Paradigm

Colin R. Del Valle, Heather R. Sparkman, Margaret M. Naylor, Connor M. Cruea, Rachel E. Rice, Claire E. Miller, Brooke E. Bramlage, Lillianna P. Puppel, Madison L. Brown, Aleece K. Al-Olimat, Elizabeth S. Dietz, and Phillip R. Zoladz

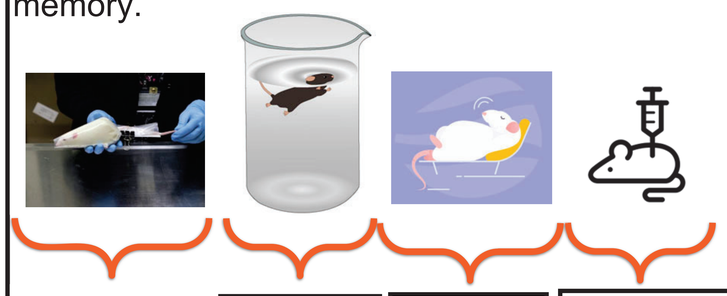
Behavioral Neuroscience, Psychology Program, Ohio Northern University, Ada, OH

Introduction

Post-traumatic stress disorder (PTSD) is a debilitating psychological condition that manifests after exposure to severe trauma. Although psychological and pharmacological treatments can help mitigate some PTSD symptoms, nonresponse rates can reach levels greater than 50%[1-3], emphasizing the need for more effective treatment options for the disorder. Recent work has demonstrated that psychedelic substances, such as psilocybin, exert antidepressant effects in preclinical models and can reduce symptoms of anxiety in patients with major depression and anxiety disorders[4-10]. Thus, we aimed to examine the ability of psilocybin, a 5-HT_{2A} agonist, in mitigating PTSD-like behaviors induced by the single prolonged stress (SPS) paradigm in adult rats.

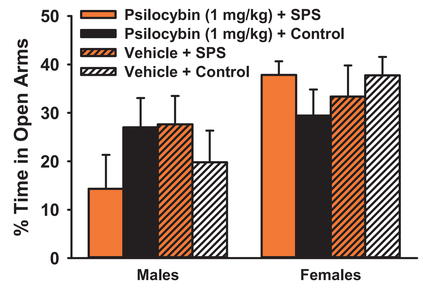
Method

Adult male and female Sprague-Dawley rats were subjected to the single prolonged stress (SPS) paradigm, including 2 hours of restraint, 15 minutes of forced swim, and ether vapor exposure until loss of consciousness. Five minutes following loss of consciousness, the rats were intraperitoneally injected with either vehicle (0.9% saline) or psilocybin (1 mg/kg). One week later, the rats underwent behavioral testing to assess their anxiety (elevated plus maze; EPM), startle response, locomotor activity (open field), and novel object recognition (NOR) memory.



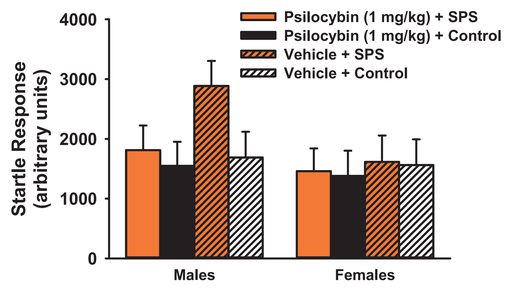
Results (all data are means ± SEM)

Elevated Plus Maze



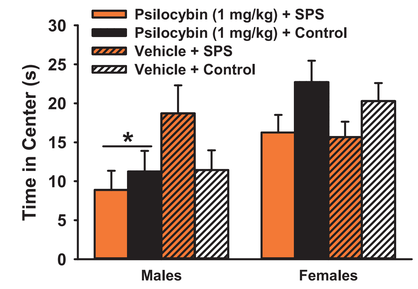
Female rats spent significantly more time in the open arms of the EPM than male rats. There were no other significant effects. *n* = 9-12 rats / group.

Startle Response



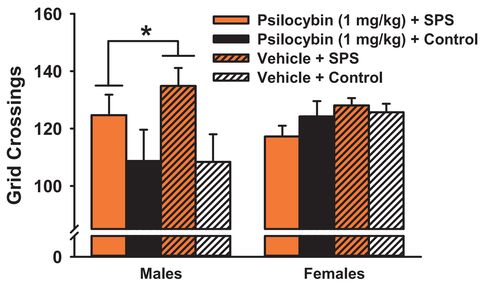
The analysis of startle responses to the first 5 noise bursts revealed a trend for the main effect of stress, $F_{1,69} = 3.48$, $p = 0.066$. Rats exposed to the SPS paradigm tended to display larger startle responses than controls, but this was driven by what appeared to be larger startle responses in male SPS rats treated with vehicle. This increase in startle response was seemingly mitigated by psilocybin. *n* = 9-12 rats per group.

Open Field – Time in Center



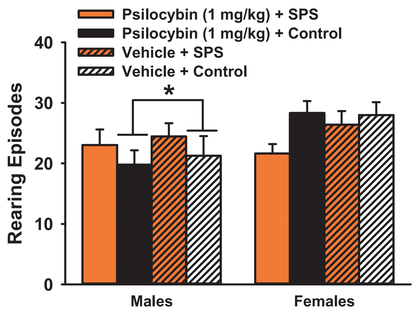
Under non-stressed conditions, males spent significantly less time in the center of the open field than females, $F_{1,69} = 5.98$, $p = 0.017$. Psilocybin caused males to spend significantly less time in the center of the open field than females, $F_{1,69} = 4.17$, $p = 0.045$. *n* = 9-12 rats per group; * $p < 0.001$ relative to females treated with psilocybin.

Open Field – Locomotor Activity



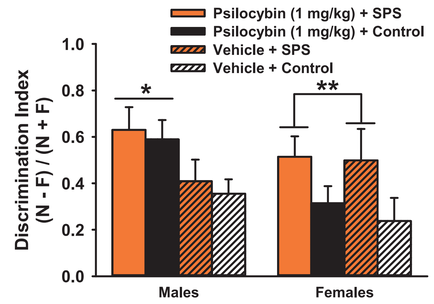
SPS exposure led to greater locomotor activity in the open field in males, but not females, $F_{1,70} = 5.32$, $p = 0.024$. *n* = 9-12 rats per group; * $p = 0.002$ relative to control.

Open Field – Rearing



Under non-stressed conditions, males displayed significantly fewer rearing episodes in the open field than females, $F_{1,70} = 5.24$, $p = 0.025$. Stress tended to increase rearing episodes in males, but not females, but this difference did not reach statistical significance ($p = 0.089$). *n* = 9-12 rats per group; * $p = 0.002$ relative to female controls.

Novel Object Recognition



Initial analyses suggested that psilocybin, $F_{1,67} = 4.31$, $p = 0.042$, and SPS, $F_{1,67} = 4.44$, $p = 0.039$, led to greater recognition memory. These effects appeared to be driven by males and females, respectively. Thus, we analyzed each sex separately and found that, in males, psilocybin led to greater recognition memory, $F_{1,33} = 7.01$, $p = 0.012$, whereas, in females, SPS led to greater recognition memory, $F_{1,34} = 5.35$, $p = 0.027$. *n* = 9-12 rats per group; * $p = 0.012$ relative to vehicle; ** $p = 0.027$ relative to control.

Conclusions

The SPS paradigm exerted sex- and test-dependent effects on rat behavior. Stressed males treated with vehicle tended to exhibit greater startle responses than controls, which was prevented by psilocybin. SPS exposure led to greater locomotor activity in males, but not females, and enhanced NOR memory in females, but not males. Psilocybin, independent of stress exposure, enhanced NOR memory in males, but not females. These findings suggest that the SPS paradigm exerts complex, sex-dependent effects on rat behavior and that psilocybin mitigates some of the behavioral alterations induced by stress. Future work should further examine the ability of psilocybin to prevent or reverse behavioral sequelae induced by intense stress exposure.

References

1. Akiki TJ, Abdallah CG. (2019). Are there effective psychopharmacologic treatments for PTSD? *Journal of Clinical Psychiatry*, *80*, 18ac12473.
2. Bernardy NC, Friedman MJ. (2017). Pharmacological management of posttraumatic stress disorder. *Current Opinion in Psychology*, *14*, 116-121.
3. Kar N. (2011). Cognitive behavioral therapy for the treatment of post-traumatic stress disorder: A review. *Neuropsychiatric Disease and Treatment*, *7*, 167-181.
4. Hibicke M, Landry AN, Kramer HM, Talman ZK, Nichols CD. (2020). Psychedelics, but not ketamine, produce persistent antidepressant-like effects in a rodent experimental system for the study of depression. *ACS Chemical Neuroscience*, *11*, 864-871.
5. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, … Nutt DJ. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *Lancet Psychiatry*, *3*, 619-627.
6. Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, … Nutt DJ. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports*, *7*, 13187.
7. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR. (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of General Psychiatry*, *68*, 71-78.
8. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, *67*, 1735-1740.
9. Roseman L, Nutt DJ, Carhart-Harris RL. (2017). Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Frontiers in Pharmacology*, *8*, 974.
10. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen, B, … Schmidt BL. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology*, *30*, 1165-1180.