Exploring the Therapeutic Potential of Psilocybin in a Mouse Model of Neuropathic Pain with Comorbid Depression-like State

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ABSTRACT

Chronic pain is a complex brain state that has comorbid mood changes, such as depression and anxiety. This constellation of conditions presents a formidable therapeutic challenge for patients, imposing substantial personal and socioeconomic burdens given the persistent lack of amelioration. Recently, emerging research signals the therapeutic promise of psychedelics across these distinct disorders when studied in isolation. To date, no study has studied the potential of a psychedelic in the treatment of chronic pain with comorbid mood changes. In our investigation, we shed light on the promising effect of the psychedelic psilocybin on chronic pain, coinciding with improvements in pain. We hypothesize that psilocybin induces rapid and durable changes in pain metrics, coupled with mood-related behavioral improvements. Our findings lay the cornerstone for a deeper grasp of Psilocybin's therapeutic potential, coupled with endeavors to illuminate its mechanistic underpinnings.

INTRODUCTION

Chronic pain, a pervasive health challenge, often intertwines with comorbid depression and anxiety, amplifying its impact. This necessitates innovative treatments that address both physical and emotional aspects. Across history, psychedelics have been used by ancient cultures for their transformative properties. Recent scientific interest rekindles exploration into their therapeutic potential, particularly for mood disorders. This study pioneers a novel dimension in psychedelic research, investigating Psilocybin's therapeutic effects in a mouse model of neuropathic pain with comorbid depression-like state. Integrating historical insights with modern methods, this research explores Psilocybin's potential to tackle neuropathic pain while ameliorating depressive symptoms. Bridging ancient wisdom with contemporary science, this study offers new insights into the intricate interplay of chronic pain and mood disorders, and the potential of psychedelics to provide an innovative therapeutic pathway.

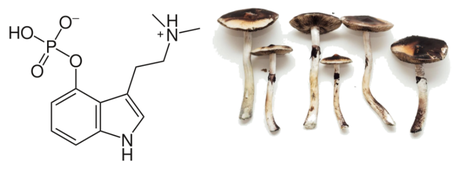

Figure 1. Psilocybin

CHRONIC PAIN MODEL

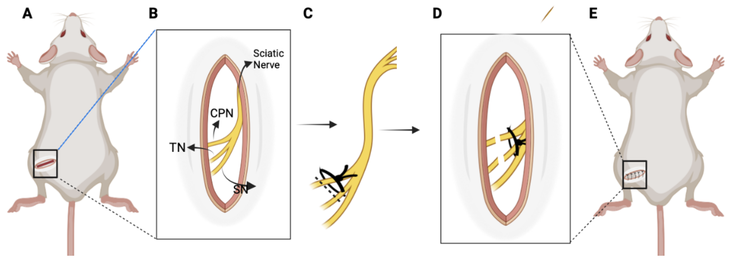

Figure 2. Spared nerve injury (SNI) surgical procedure to induce neuropathic pain in mice. A. Red line indicates incision site on left hindlimb. B. Biceps femoris muscle was exposed and a careful blunt dissection was made through it to expose the sciatic nerve and peripheral branches: common peroneal (CPN), tibial (TN) and sural nerves (SN). C. Ligation of CPN and TN was performed with a surgical knot. D. The ligated nerves were transected distally. E. Incision site is sutured. The surgical steps in panels C-D were not performed in the sham operation.

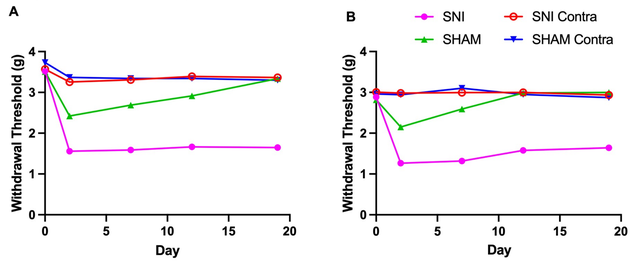

Figure 3. Measuring hindlimb paw withdrawal before and after SNI using Von Frey Test (VFT). A. Paw withdrawal threshold in *males,* measured in grams from ipsilateral and contralateral hindlimb. B. Paw withdrawal threshold in *females,* measured in grams from ipsilateral and contralateral hindlimb.

CHRONIC PAIN HAS COMORBID DEPRESSION AND ANXIETY

Figure 4. Force Swim Test (FST)

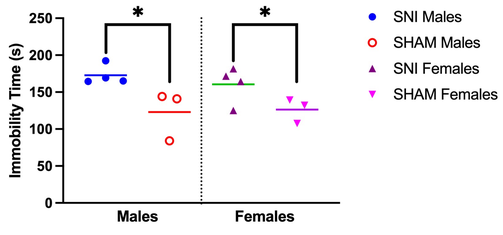

Figure 5. Comparing the immobility time under the FST. SNI animals tend to have greater immobility time which shows depression-like symptoms

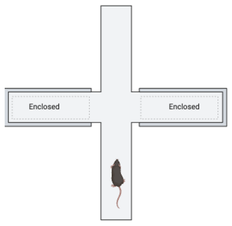

Figure 6. Elevated Plus Maze Test (E+M)

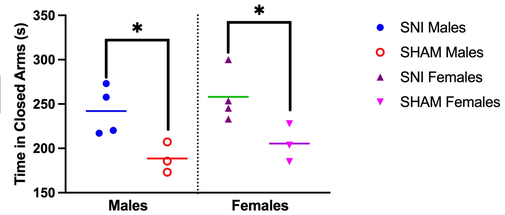

Figure 7. Comparing the time in close arms under the E+M. SNI animals tend to stay longer in closed arms of the maze which indicates anxiety-like symptoms.

EFFECT OF PSILOCYBIN

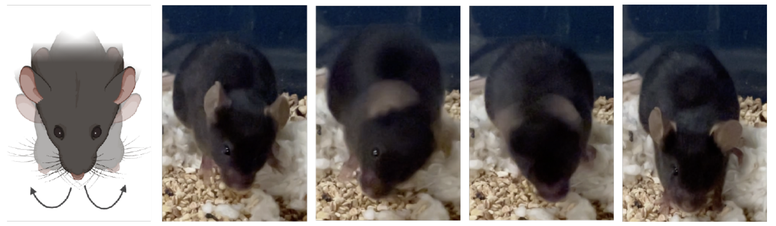

Figure 8. Head Twitch Response in Mice. The head twitch response is thought to be a result of the hallucinogenic effect of Psilocybin in mice.

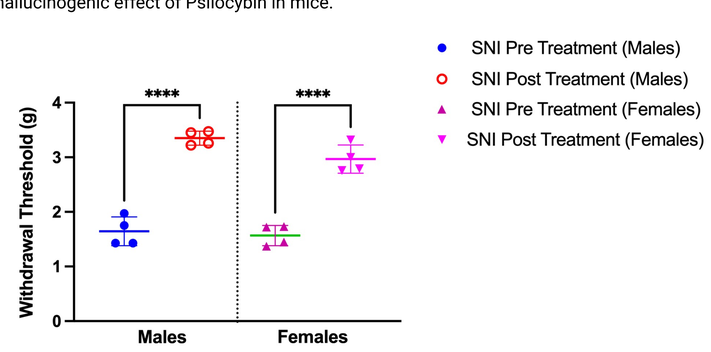

Figure 9. Comparing hindlimb paw withdrawal before and after treatment with Psilocybin in SNI mice using Von Frey Test. Both males and females show improved withdrawal threshold which indicates amelioration following the development of chronic pain (p<.0001)

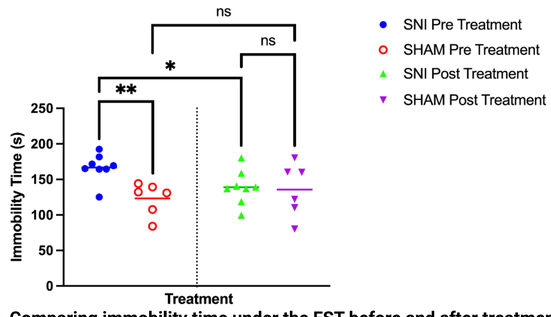

Figure 10. Comparing immobility time under the FST before and after treatment with Psilocybin. SNI animals show improved mobility after treatment, which indicates an improvement in mood (p<.05). SNI animals show no difference in immobility time compared to SHAM animals, which indicates a reversal of the depressive-like symptoms (p>.05).

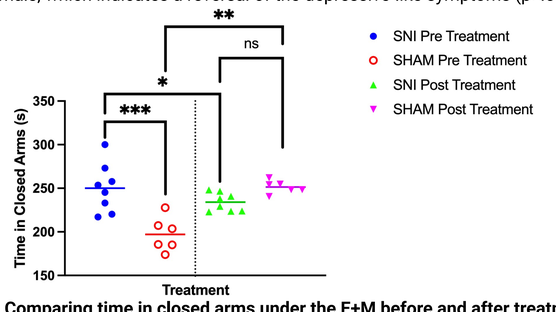

Figure 11. Comparing time in closed arms under the E+M before and after treatment with Psilocybin. SNI animals show less variability and less time spent in closed arms post treatment with psilocybin (p<.05). This indicates an improvement in stress-like symptoms following administration of Psilocybin.

CONCLUSION

This study unveils promising evidence of the significant impact of psychedelics on both chronic pain and mood regulation. These results hold the potential to revolutionize therapeutic strategies for individuals grappling with neuropathic pain accompanied by depression-like states. The observed improvements in hyperalgesia through the VF test show a reversal of the chronic pain effect. This is coupled with a reversal in depression like symptoms using the FST, and anxiety symptoms using the E+M. Further investigation and research serve as a stepping stone toward transformative interventions that fuse ancient wisdom with cutting-edge science, offering new avenues for comprehensive healing and well-being.

Next Steps

- Increase the animal cohort size (n)
- Further understand the mechanism of Psilocybin
- Discern potential sex disparities in mood and pain therapy
- Investigate how Psilocybin affects other mood behaviors in mice.
- Develop a centralized chronic pain model to delve deeper into Psilocybin's potential

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Cartoons were produced using BioRender

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