Differential effects of repeated treatment with DOI and psilocybin on the head-twitch response (HTR), locomotor activity and anxiety-like behaviour

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Introduction

Serotonin 5-HT2A receptors are widely distributed in the central nervous system and are thought to mediate the effects of psychedelic drugs (1). The 5-HT2A receptor has been identified as a potential therapeutic target for several psychiatric disorders, including anxiety and major depressive disorder (MDD) (1,2,3).

The aim of the present study was to investigate the effects of repeated administration of the psychedelic drugs DOI and psilocybin at two different treatment timepoints; 0h and 48h. For this purpose, we examined the head twitch response (HTR) which is widely used as a behavioral assay for 5-HT2A activation associated with rapid side-to-side rotational head movement. Locomotor activity and anxiety-like behavior were also assessed in the open field (OF).

Methods

Adult C57BL/6J male mice (n=56) were habituated to an open field arena (29cm x 36cm x 16cm) 30 minutes prior to testing.
The mice received a single i.p. injection of either saline, DOI (0.5 mg/kg or 1 mg/kg), or psilocybin (0.3 mg/kg, 1 mg/kg, 3 mg/kg or 5 mg/kg). Immediately post-treatment the mice were placed back in the test cage for 30 minutes.

- To assess HTR, the mice were observed for 20 minutes (n=3-4 per group).
- Mice were recorded using AnyMaze software for 30 mins to assess the effects of DOI and psilocybin on locomotor activity (m) and time (s) spent exploring the center of the arena (n=7-8 per group).

The above protocol was repeated 48h later to assess the effects of repeated treatment with either DOI or psilocybin on HTR, locomotor activity and time spent exploring the center.

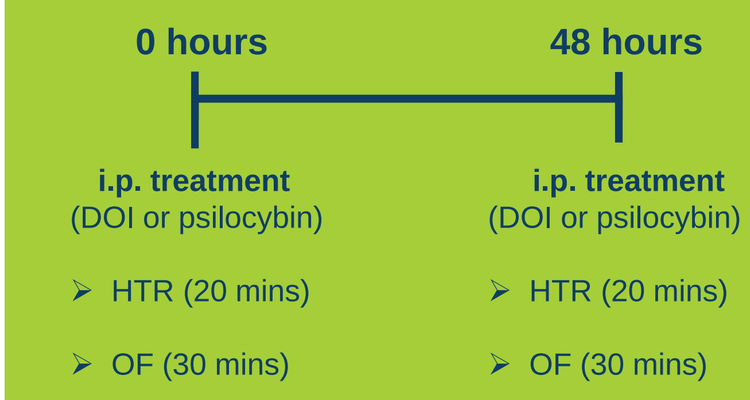

Figure 1: Experimental design timeline. Mice receive DOI or psilocybin (i.p.) and undergo HTR assessment and OF at 0h and 48h.

Results

Effect of DOI and psilocybin on HTR (number) post singular and repeated administration.

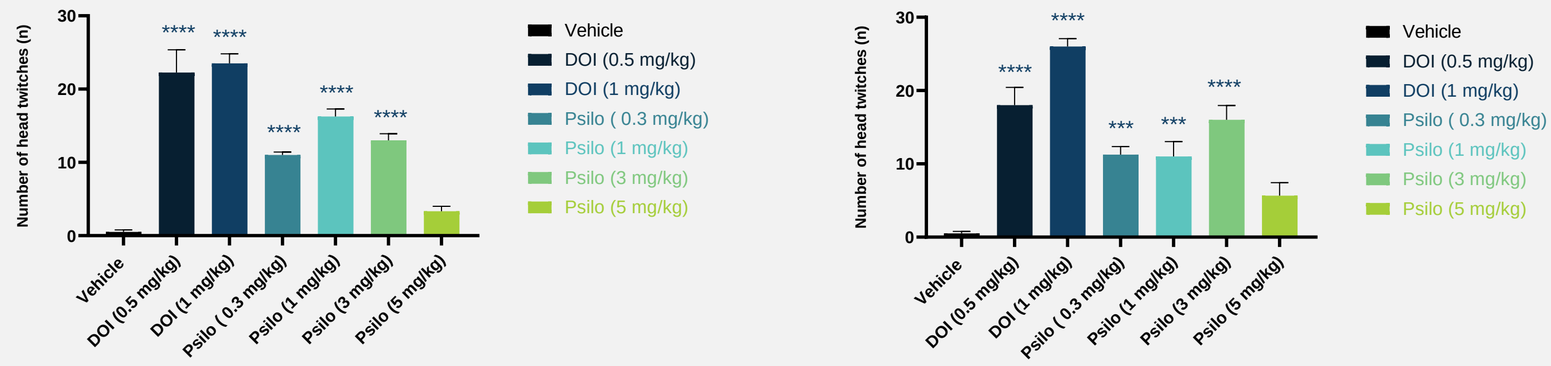

Figure 2: The effect of DOI and psilocybin on the HTR. A: 0h administration of DOI (0.5 mg/kg & 1 mg/kg) and psilocybin (0.3 mg/kg, 1 mg/kg & 3 mg/kg) significantly increased HTR. B: 48h repeated administration of DOI (0.5 mg/kg & 1 mg/kg) and psilocybin (0.3 mg/kg,1 mg/kg & 3 mg/kg) significantly increased HTR. Data expressed as mean ± SEM, n=3-4 per group. ***p<0.001, ****p <0.0001 vs. vehicle. One-way ANOVA followed by uncorrected Fisher's LSD test.

Effect of DOI and psilocybin on locomotor activity (m) post singular and repeated administration.

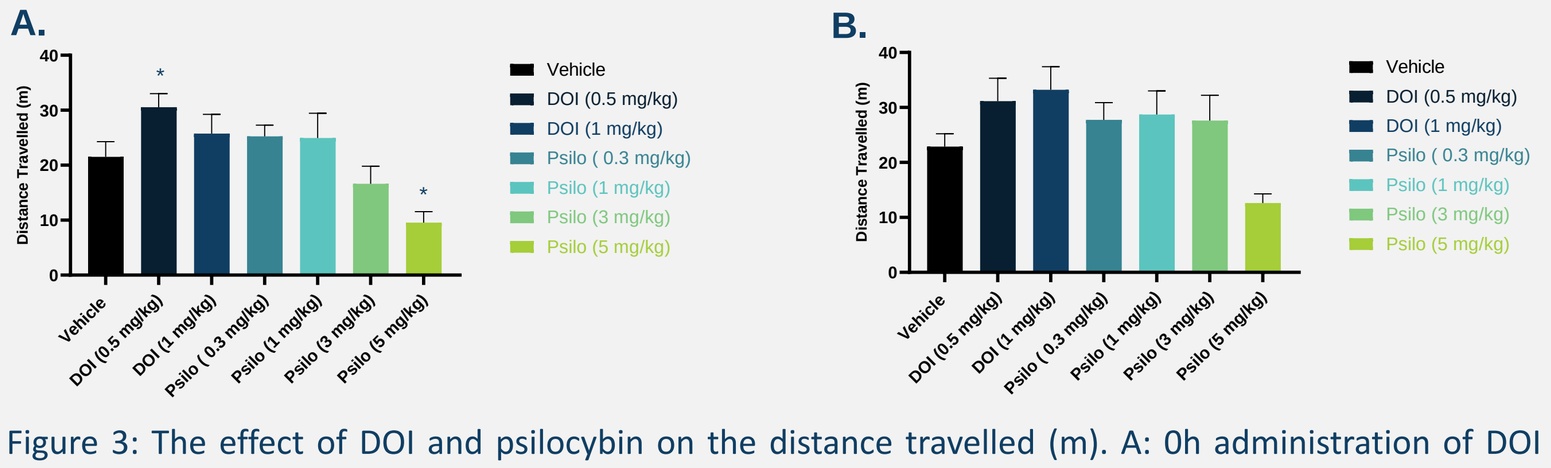

Figure 3: The effect of DOI and psilocybin on the distance travelled (m). A: 0h administration of DOI (0.5 mg/kg) significantly increased the distance travelled (m), whereas psilocybin (5 mg/kg) significantly reduced the distance travelled (m). B: 48h repeated administration of both DOI and psilocybin had no effect on the distance travelled (m). Data expressed as mean ± SEM, n=7-8 per group. *p<0.05 vs. vehicle. One-way ANOVA followed by uncorrected Fisher's LSD test.

Effect of DOI and psilocybin on anxiety (time in the center (s)) post singular and repeated administration.

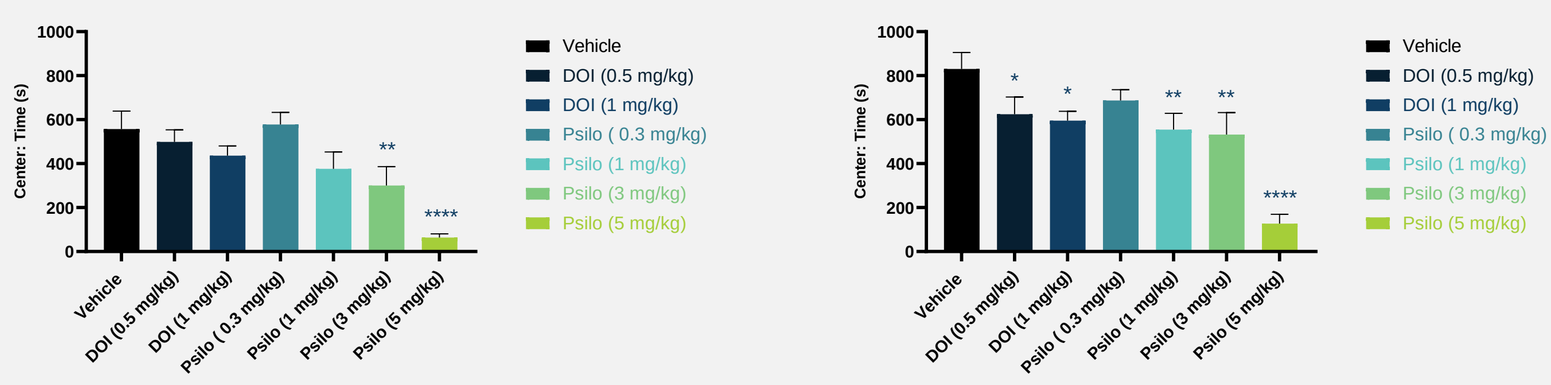

Figure 4: The effect of DOI and psilocybin on the time spent in the center (s). A: 0h administration of psilocybin (3 mg/kg & 5 mg/kg) significantly reduced time spent in the center (s). B: 48h repeated administration of DOI (0.5 mg/kg & 1 mg/kg) and psilocybin (1 mg/kg, 3 mg/kg & 5 mg/kg) significantly reduced time spent in the center (s). Data expressed as mean ± SEM, n=7-8 per group. *p<0.05, **p<0.01, ****p <0.0001 vs. vehicle. One-way ANOVA followed by uncorrected Fisher's LSD test.

Conclusion

This study demonstrates a significant increase in HTR following treatment with DOI (0.5 mg/kg & 1 mg/kg) and psilocybin (0.3 mg/kg, 1 mg/kg & 3 mg/kg) at the 0h and 48h time points, indicating that repeated exposure to the compounds at these doses did not decrease the 5HT2A receptor response. Psilocybin 5 mg/kg did not cause a significant increase in HTR, which was potential because of this dose's effect on mobility. Conversely, there were differences in locomotor activity and anxiety-like behavior between first and second exposure to DOI and psilocybin. The repeated treatment with both DOI and psilocybin either increased the anxiety-like behavior or impaired habituation to the arena. Taken together, this data suggests that prior exposure to DOI and psilocybin influences behavioral changes induced by the subsequent administration, which may have implications for clinical use.

References

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(3) Carhart-Harris, R., & Nutt, D. (2017). Serotonin and brain function: a tale of two receptors. Journal Of Psychopharmacology. doi: 10.1177/0269881117725915