2,5-Dimethoxy-4-iodoamphetamine (DOI) enhances motivation in low and medium but not high performers in the progressive ratio (PR) task in rats

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Introduction

People with depression and related disorders commonly show profound motivational impairments. Tasks measuring effort-based functions have been suggested as potential models for these motivational symptoms. The PR task is translational operant behavioural task used to objectively measure effort-based motivation. There has also been a renaissance of research in psychedelics as potential medicines particularly with a focus on depression. Previous work has demonstrated the effects of low-dose psilocybin in the PR task (1). Here we have evaluated a 5-HT2A agonist in higher or 'macro' doses in the PR task.

Methods

Male Sprague-Dawley rats (n=25) were trained in an operant progressive ratio task. The number of responses required to obtain a sucrose pellet is increased for successive reinforcers. The two main measures in the task are the number of lever presses and the breakpoint (trial that the animal reaches). A rat reached the break point if it failed to receive a reward for 20 minutes. After reaching a behavioural baseline rats were divided into subgroups (n=8-9) of tertiles representing "low", "medium" and "high" performers, based on lever press measures recorded over 3 days baseline prior to testing. Performance was assessed at 30 minutes post-administration and once daily over a 5 day period, all animals received 1mg/kg dose of DOI (s.c.).

Results

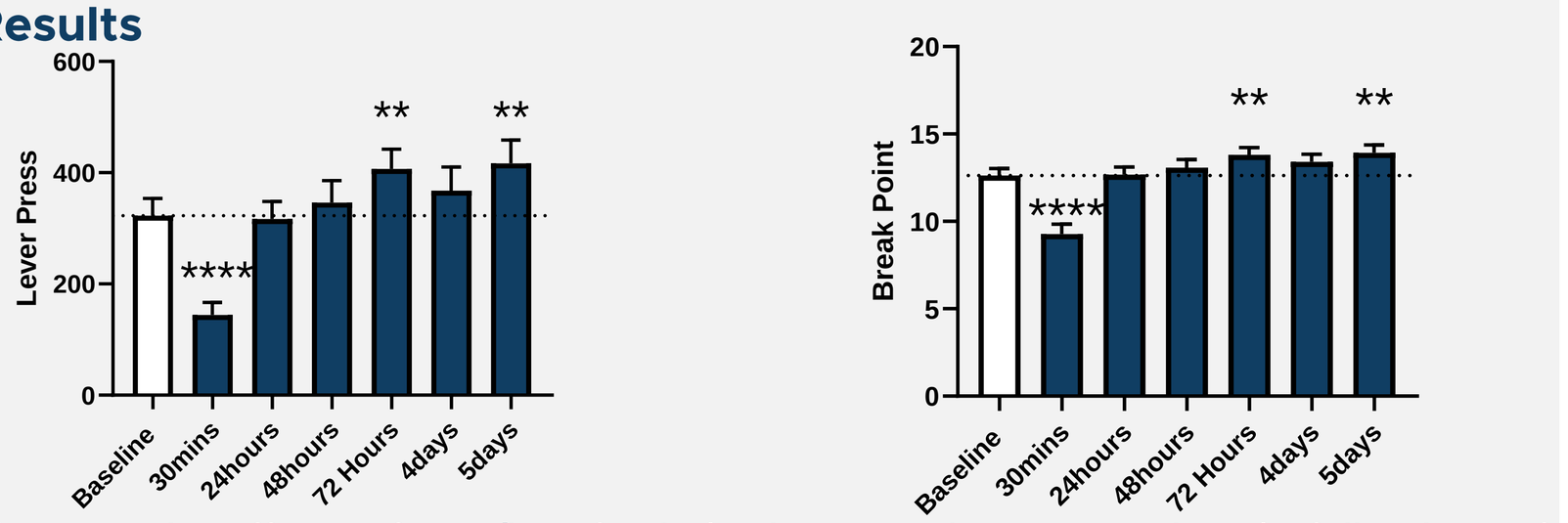

Figure 1: The effects of 1mg/kg of DOI in the PR task across 5 days in full cohort of animals: (A) Lever press in the full cohort: There was a significant decrease at 30 minutes ($p<0.0001$) and a significant increase at 72 hours ($p<0.01$) and 5 days ($p<0.01$). (B) Break point in the full cohort: There was a significant decrease at 30 minutes ($p<0.0001$) and a significant increase at 72 hours ($p<0.01$) and 5 days ($p<0.01$). Data expressed as mean ± SEM, n=25 per group. **p<0.01, ****p <0.0001 vs. baseline. One-way RM ANOVA followed by uncorrected Fisher's LSD test.

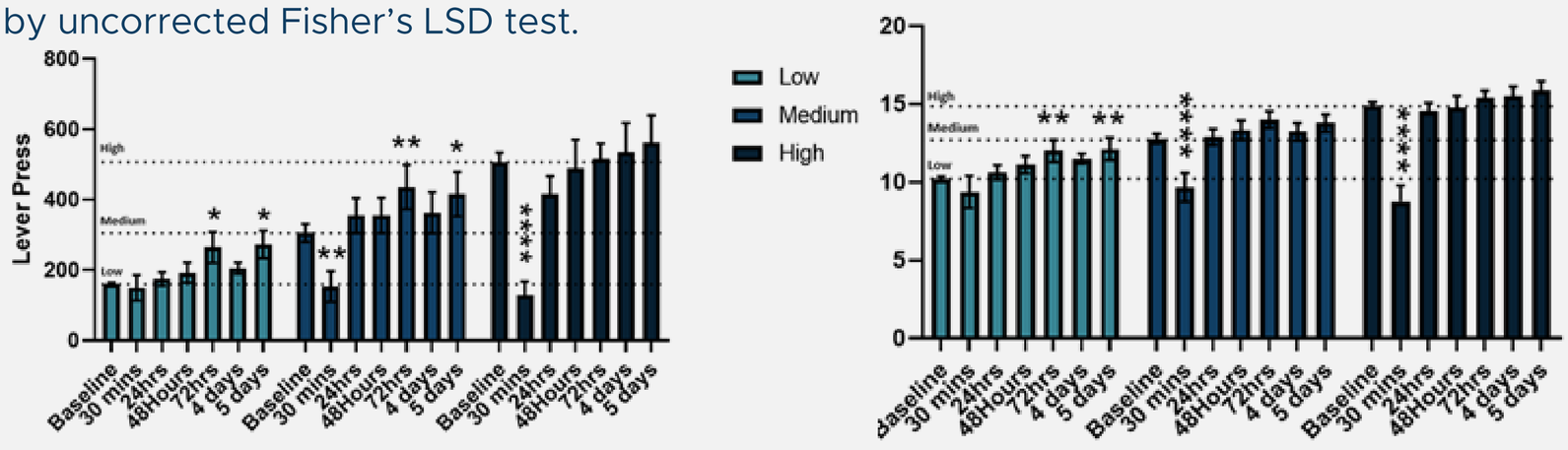

Figure 2: Lever press for each performance group. (A) : In the low performing group there was a significant increase at 72 hours ($p<0.05$) and 5 days ($p<0.05$). For the medium performing group there was a significant decrease at 30 minutes ($p<0.01$) and a significant increase at 72 hours ($p<0.01$) and 5 days ($p<0.01$). For the high performing group there was a significant decrease at 30 minutes ($p<0.0001$). (D) Break point for each performance group: for the low performing group there was a significant increase in at 72 hours ($p<0.01$) and 5 days ($p<0.01$). For the medium performing group there was a significant decrease at 30 minutes ($p<0.0001$). For the high performing group there was a significant decrease at 30 minutes ($p<0.0001$). Data presented as mean ± S.E.M. analysed using one or two-way RM ANOVA with Fishers post-hoc LSD. *p<0.05, **p<0.01, ****p<0.0001 compared to baseline. n=8-9 per group.

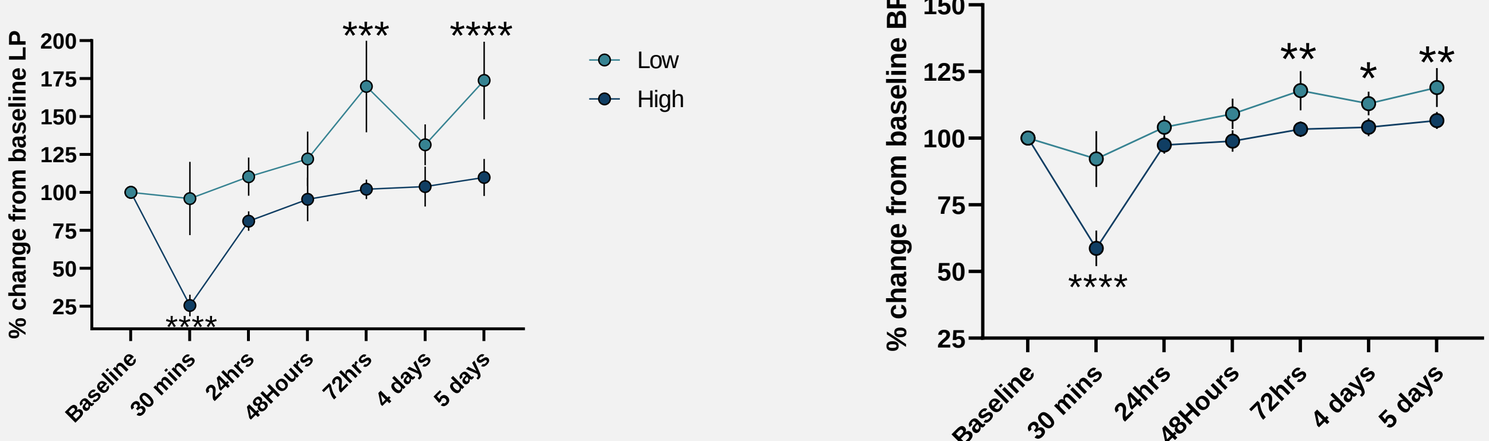

Figure 4: High vs Low performing groups as % change from baseline. A: Higher performers displayed a significant decrease at the 30 minutes compared to a baseline. Low performers displayed an increase at 3 and 5 days. **B:** Higher performers displayed a significant decrease at the 30 minutes compared to a baseline. Low performers displayed an increase at 3 and 5 days. Data expressed as mean ± SEM, n=7-8 per group. *p<0.05, **p<0.01, ****p <0.0001 vs. baseline. Two-way RM ANOVA followed by uncorrected Fisher's LSD test.

Conclusion

A clear and robust effect was observed at the acute time point of 30 minutes post administration, with a return to baseline at 24 hours when the drugs activity has dissipated. Another aspect of performance was examined with animals being split into 'Low', 'Medium' and 'High' performers. There is a clear differential effect of DOI between the performance groups. Animals in the 'Low' performing group displayed no acute reduction in performance at the 30 minute time point while having the largest improvement relative to their baseline. While the 'High' performing group showed almost the opposite behavioural profile, displaying the most severe acute deficit at the 30 minute time point and a marginal improvement in performance days later although this never reached significance. The 'Medium' performance group falls somewhere in between the two, exhibiting both a significant decrease acutely and significant improvement several days post administration. Although rats demonstrated a consistently lower level of lever pressing and break point compared to the 'High' performing group previous research has shown that these rats have similar body weights, free feeding measures and open field activity compared to their high responder counterparts, suggesting any differences are unrelated to general health status, neurological function or appetite (Higgins et al., 2021).

References

Higgins, G. A., Carroll, N. K., Brown, M., MacMillan, C., Silenieks, L. B., Thevarkunnel, S., Izhakova, J., Magomedova, L., DeLannoy, I., & Sellers, E. M. (2021). Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property [Original Research]. Frontiers in Pharmacology, 12(299). https://doi.org/10.3389/fphar.2021.640241