The effects of LSD and its non-hallucinogenic analogue 2-Br-LSD on murine behavior, sleep patterns, and quantitative EEG

Transpharmation
Science that translates into results

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INTRODUCTION

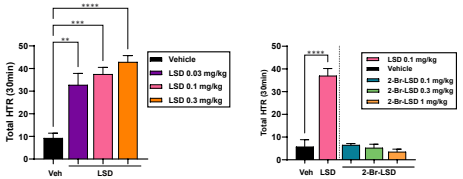
Pharmacotherapy for depression and anxiety faces challenges such as delayed onset of action, the necessity for long-term treatment, and treatment-resistant patient populations. Psychedelics offer an exciting, novel approach to tackling these issues. Nevertheless, intense hallucinogenic effects can limit therapeutic applications, highlighting the need for the development of non-hallucinogenic but therapeutically effective alternatives (Lewis et al., 2023). Here we compare the effects of LSD (Lysergic acid diethylamide) and its analogue 2-Br-LSD on sleep, neural activity and behavior in male C57Bl/6 mice.

METHODS

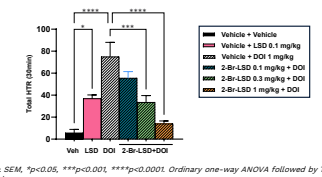
LSD was dosed subcutaneously at 0.03, 0.1, and 0.3 mg/kg. 2-Br-LSD was administered intraperitoneally at 0.1, 0.3, and 1 mg/kg. Hallucinogenic effects were measured in terms of head twitch responses (HTR). Locomotion and rearing were assessed using the LABORAS system. Wireless electroencephalography (EEG, DSI system) was used to monitor vigilance states and brain activity for 24 hours following dosing. Automatic sleep-wake scoring was performed, and the hourly distribution of wakefulness, non-REM sleep, and REM sleep was analysed.

RESULTS

I. Comparison of the Effects of LSD and 2-Br-LSD on Head Twitch Counts in the HTR Assay.



*n= 4-8 per group. Mean ± SEM, **p<0.01, ***p<0.001, ****p<0.0001. Ordinary one-way ANOVA followed by Dunnett's multiple comparisons test.*

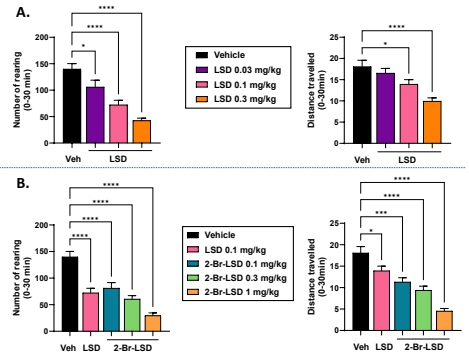


*n= 4-8 per group. Mean ± SEM, *p<0.05, ***p<0.001, ****p<0.0001. Ordinary one-way ANOVA followed by Tukey's multiple comparisons test.*

2-Br-LSD itself has no effect on the number of HTRs but significantly reduces HTR induced by DOI.

RESULTS

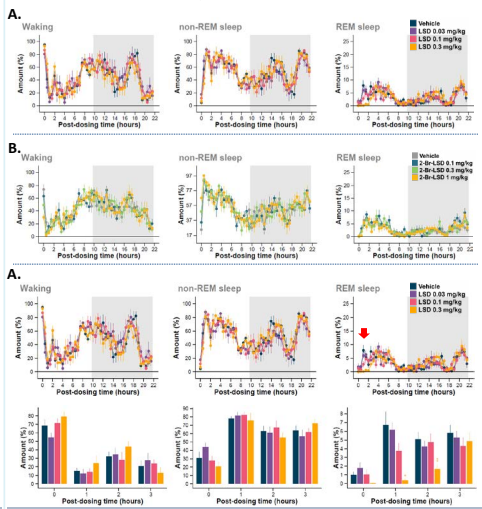
II. Effects of LSD and 2-Br-LSD on the General Locomotor Activity in Mice.



*n= 10 per group. Mean ± SEM, *p<0.05,***p<0.001, ****p<0.0001. Ordinary one-way ANOVA followed by Dunnett's multiple comparisons test.*

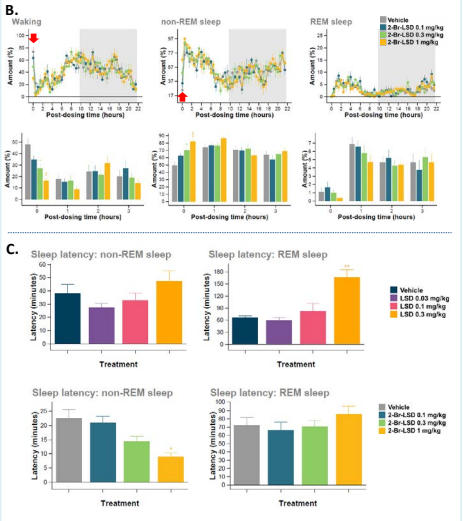
LSD (A) and 2-Br-LSD (B) significantly reduce distance travelled and rearing bouts compared to vehicle.

III. Comparison of the LSD and 2-Br-LSD Effect on Sleep EEG & Spectrogram in Mice (n = 8-9).

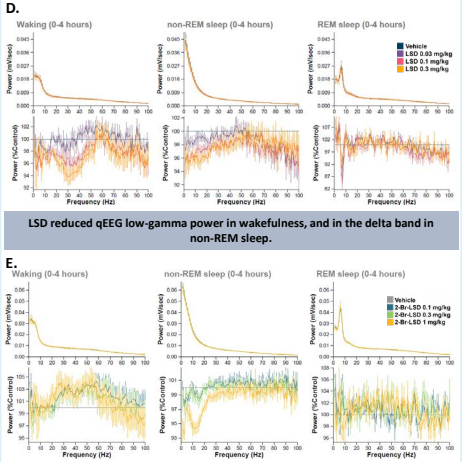


LSD but not 2-Br-LSD selectively suppressed REM sleep
2-Br-LSD enhanced non-REM sleep at the expense of wakefulness.

RESULTS



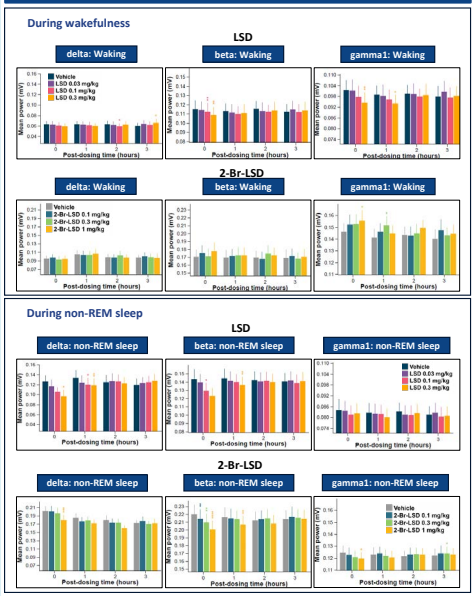
LSD lengthened REM sleep latency, while 2-Br-LSD reduced non-REM sleep latency.



LSD reduced qEEG low-gamma power in wakefulness, and in the delta band in non-REM sleep.

2-Br-LSD primarily reduced qEEG beta power in non-REM sleep, while increasing low-gamma power during wakefulness.

RESULTS



CONCLUSIONS

- **The lack of HTRs after 2-Br-LSD administration demonstrates its non-hallucinogenic properties, while attenuation of DOI-induced HTRs indicated its 5-HT2A receptor occupancy.**
- **While certain characteristics of LSD were recapitulated with 2-Br-LSD, such as reduced locomotion and the suppression of beta oscillations during non-REM sleep, others like REM sleep suppression were not.**
- **The results indicate new ways in which physiological biomarkers can be used to differentiate hallucinogenic and non-hallucinogenic drug candidates in this exciting new class of therapeutics.**

REFERENCES

Lewis V, Bonniwell EM, Lanham JK, Ghaffari A, Sheshbaradaran H, Cao AB, Calkins MM, Bautista-Carro MA, Arsenault E, Telfer A, Taghavi-Abkuh FF, Malcolm NJ, El Sayegh F, Abizaid A, Schmid Y, Morton K, Halberstadt AL, Aguilar-Valles A, McCorvy JD. A non-hallucinogenic LSD analog with therapeutic potential for mood disorders. Cell Rep. 2023 Mar 28;42(3):112203. doi: 10.1016/j.celrep.2023.112203. Epub 2023 Mar 6. PMID: 36894346; PMCID: PMC10012881.