Characterizing Non-Halloucinogenic Psychedelics: Phenotypic Fingerprinting of Lisuride and LSD

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Lisuride has strong effects on locomotion, HPA axis function cognition, and EEG activity that are not $5HT_{2A}R$-mediated

Background

- Psychedelics have therapeutic potential for a range of neuropsychiatric disorders, but their wide-spread implementation may be hindered due to their characteristic psychedelic effects.
- Psychedelics are potent agonists at many serotonin receptors (5HTRs), with $5HT_{2A}Rs$ specifically mediating their psychedelic effects.
- The head twitch response (HTR) is the primary preclinical measure of psychedelic responses, but is the lack of a HTR sufficient to identify a non-psychedelic compound?
- Here we compare the effects of the classic psychedelic LSD to lisuride, a supposed benign $5HT_{2A}R$ partial agonist that does not induce HTRs, on motor function, cognitive capabilities, EEG responses, and HPA axis function.
- We also tested the effects of LSD and lisuride in the presence of the $5HT_{2A}R$ antagonist MDL 100,907 (MDL) to determine which effects are $5HT_{2A}R$ mediated.

Hypotheses

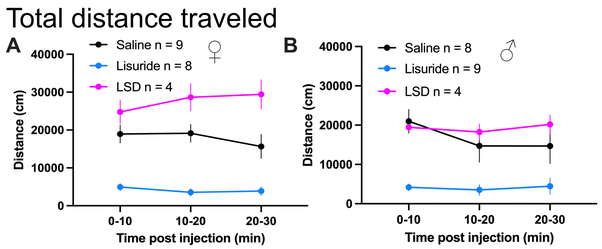
If lisuride is truly non-psychedelic, then LSD will, but lisuride will not:

1. affect locomotion, as measured by open field and rotarod,
2. impact cognitive performance on puzzle box,
3. increase corticosterone release,
4. impact brain activity in the prefrontal cortex (PFC), as measured by EEG.

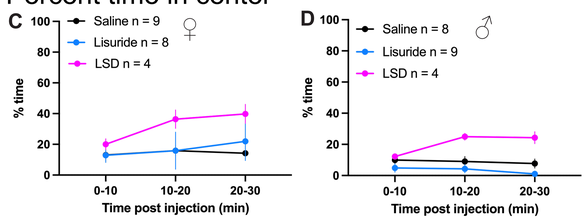
The $5HT_{2A}R$ antagonist MDL should block effects of LSD, but not lisuride. We also do not predict sex differences in LSD or lisuride effects.

Lisuride impacts locomotion

Total distance traveled



Percent time in center



Rotarod

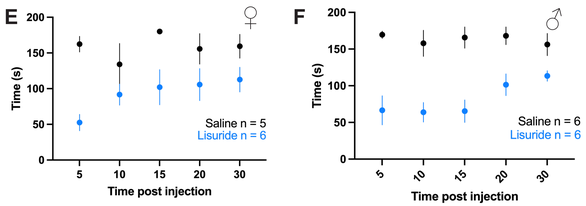


Figure 1: Lisuride (0.5 mg/kg) significantly decreased overall distance traveled in open field for females (C) and males (D) ($p<0.001$), and there was a significant sex*drug interaction ($p<0.003$). There was a significant sex*drug interaction for time spent in center, but no main effect of drug. Lisuride significantly impaired the ability of females (E) and males (F) to stay on the rotarod.

Lisuride elevates corticosterone

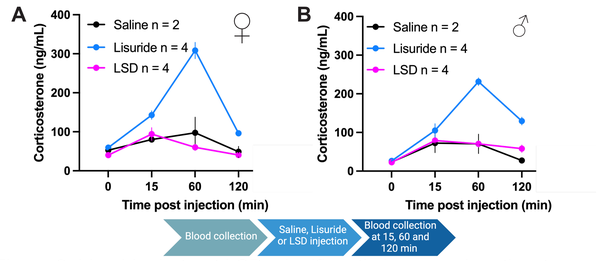


Figure 2: Lisuride, but not LSD, significantly increased corticosterone levels in females (A) and males (B), $p<0.001$.

Lisuride impacts cognition

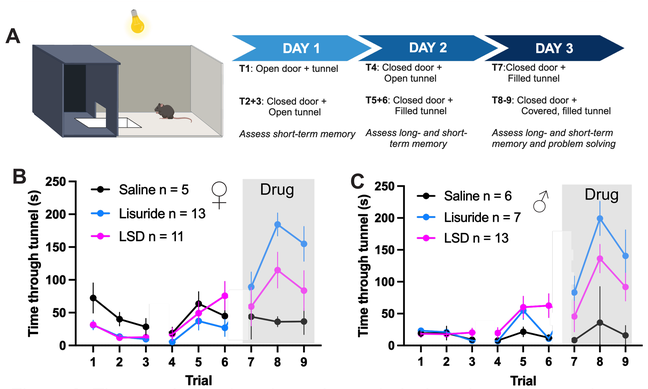
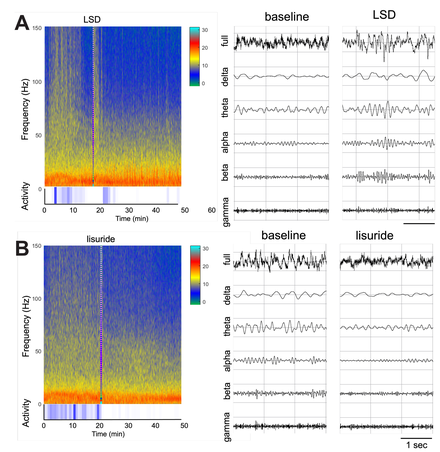


Figure 3: The puzzle box is a three-day task designed to measure short- and long-term memory, and problem solving. The mouse must go from the bright, open side of the box to the dark, enclosed side via a tunnel. Each day the tasks both get repeated and harder (A). Animals were tested 60 minutes after lisuride injection and 15 minutes after LSD. Both lisuride and LSD significantly decreased performance in the puzzle box compared to saline for females (B) and males (C) ($p<0.001$).

Lisuride affects PFC activity



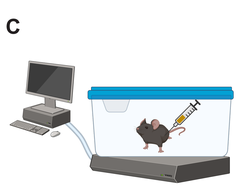


Figure 4: Lisuride injections promoted a desynchronized brain state (A) whereas LSD caused bursts of synchronized activity (B). Frequency bands (Hz): Delta 1-3, Theta 4-7, Alpha 8-12, Beta 13-29 and Gamma 30-80. (C) Mice were recorded from via wireless telemetry in their homecages

Conclusions

Lisuride may not be truly non-psychedelic because it:

1. Impaired locomotion.
2. Impaired cognition in the puzzle box.
3. Triggered a stress response.
4. Impacted PFC activity as measured by EEG.
5. Blocking $5HT_{2A}Rs$ had no impact on the effects of lisuride in any behaviors measured.

-HTR alone alone is not sufficient to identify psychoactivity and should not be relied upon in isolation.

-LSD had sex specific effects on locomotion.

-Blocking 5HT2ARs had sex specific effects on cognition

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$5HT_{2A}R$ antagonist does not block the effects of lisuride

Total distance traveled

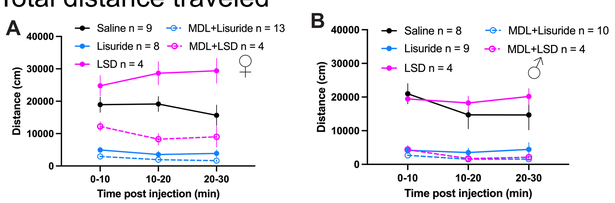
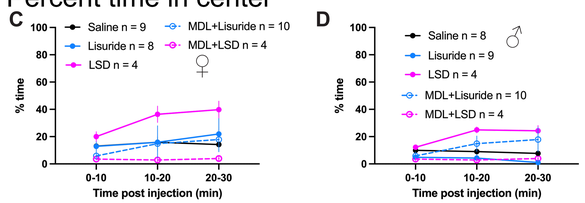


Figure 5: Blocking $5HT_{2A}Rs$ did not change how lisuride impacted total distance traveled, but did significantly decrease distance traveled when given before LSD, in both females (A) and males (B).

Percent time in center



Blocking $5HT_{2A}Rs$ did not alter lisuride's effects on time spent in center for females (C) or males (D). After $5HT_{2A}Rs$ were blocked, LSD caused both sexes spent significantly less time in the center (C-D).

Female Puzzle Box

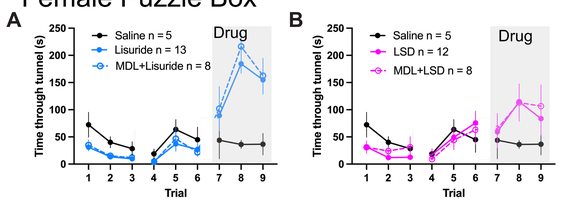
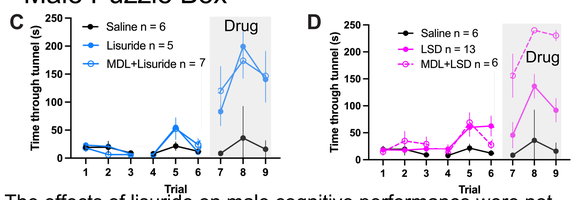


Figure 6: The effects of lisuride and LSD on female cognitive performance were not changed by blocking $5HT_{2A}Rs$ (A-B).

Male Puzzle Box



The effects of lisuride on male cognitive performance were not changed by blocking by $5HT_{2A}Rs$ (C), and their blockage worsened performance after LSD administration (D), a sex specific effect ($p<0.001$).