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Synergistic effects of lysergic acid diethylamide (LSD) and cannabidiol (CBD)

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Background: Serotonergic psychedelics and phytocannabinoids induce antidepressant effects [1, 2]. However, it is unknown whether they elicit synergistic antidepressant and/or euphoric effects. Therefore, we investigated whether cannabidiol (CBD) and lysergic acid diethylamide (LSD) generate synergistic antidepressant- and euphoric-like effects, and the electrophysiological and serotonin 2A (5-HT_{2A}) receptor correlates.
Methods: Forced swim test (FST), head-twitch response (HTR), and open field test (OFT) were performed. Dosage: Low-dose: 30 mg/kg CBD, 30 μg/kg LSD, or their combination. High-dose: 200 mg/kg CBD, 220 μg/kg LSD, or their combination. CBD was administered subcutaneously ∼45 minutes prior to testing, and LSD intraperitoneally immediately prior.

Acute pharmacological challenges were performed in the Dorsal Raphe Nucleus (DRN), and medial prefrontal cortex (mPFC) via in vivo single unit extracellular recordings. 5-HT_{2A} activation was assessed using a bioluminescence resonance energy transfer (BRET)-based biosensor monitoring 5-HT_{2A}-mediated diacylglycerol production in transfected HEK 293 cells.

Data was analysed with One-Way ANOVA followed by Dunnett's multiple comparison test. When SDs were significantly different and data passed the normality test, Welch's ANOVA was used. Electrophysiology: One-Way ANOVA followed by Dunnett's test. BRET: unpaired T-test test. Post-hoc tests were considered for significant ANOVAs.
Results: LSD and CBD alone had no behavioural effects at the doses tested ($P>0.05$). In combination, they elicited synergistic antidepressant-like effects in the FST at high ($F_{3,50}=6.213$, $P=0.011$, post-hoc CBD 200 mg/kg + LSD 220 μg/kg compared to CBD 200 mg/kg $P=0.0470$, compared to LSD 220 μg/kg $P=0.0068$), but not low doses ($F_{3,59}=2.991$, $P=0.0380$, post-hoc $P>0.05$).

CBD pre-treatment decreased the HTR induced by LSD both at low ($F_{3,67}=31.82$, $P<0.0001$, post-hoc CBD 30 mg/kg + LSD 30 μg/kg compared to LSD 30 μg/kg $P=0.0392$) and high ($F_{3.53}=73.86$, $P<0.0001$, post-hoc CBD 200 mg/kg + LSD 220 μg/kg compared to LSD 220 μg/kg $P<0.0001$) doses, suggesting an antipsychotic-like effect.

CBD pre-treatment prevented the LSD-induced hyperlocomotion (Dunnett post-hoc CBD 30 mg/kg + LSD 30 μg/kg compared to LSD 30 μg/kg $P=0.0099$) and anxiolytic-like effects (Kruskal-Wallis test $P=0.0005$, Dunnett post-hoc $P=0.0025$). High-dose CBD + LSD induce a sedative-like effect (post-hoc $P=0.0127$).

CBD and LSD in combination decreased spontaneous neuronal cell firing in the DRN ($F_{2,\ 11}=56.58$, $P<0.0001$) and the mPFC ($F_{3,\ 14}=44.45$, $P<0.0001$).

LSD acts as a partial agonist at the 5-HT_{2A} receptor, while CBD had no agonist effects alone. 10 minutes pre-treatment with CBD (10 μM) decreased LSD efficacy while increasing its potency (unpaired T-test $P=0.0002$ for efficacy and $P=0.0130$ for potency), illustrated by a downward left shift in the concentration-response curve.
Conclusion: Our findings suggest that CBD and LSD given in combination acutely might have greater antidepressant effects than each compound alone, potentially due to an allosteric modulation of the 5-HT_{2A} receptor by CBD, resulting in an abrupt attenuation of serotonergic and glutamatergic neurotransmission. Given the high doses required to achieve such effects, the translational value of these findings remains to be further elucidated. Our findings suggest that individuals seeking the combination of cannabinoids/psychedelics on the illicit market might be due to a fast relief from anxiety and depression which is not achieved with each compound alone.

Conflict of interest
Disclosure statement:
G.G. and D.D.G. are consultants at Diamond Therapeutics Inc, Toronto, ON, Canada. G.G. and D.D.G. are inventors of a provisional patent regarding the use of LSD.

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