Comprehensive Therapeutic Potential of EPM301 for Hyperphagia, Anxiety, and Sleep Disturbances in Prader-Willi Syndrome

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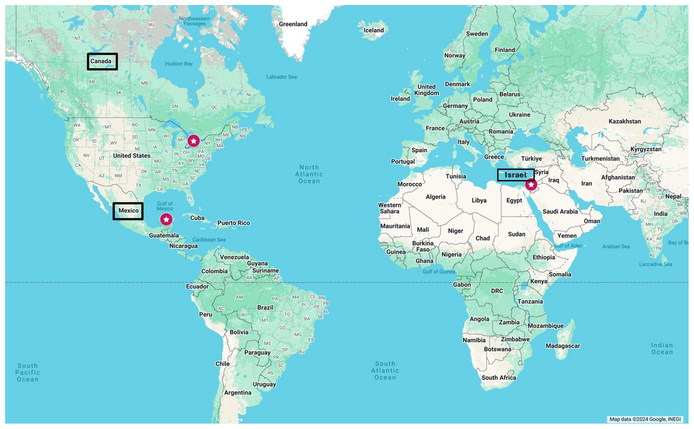
Background

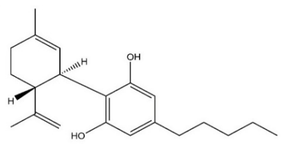
- Hyperphagia, which can lead to obesity if uncontrolled, is the primary unmet need patients with Prader-Willi Syndrome (PWS).[1,2] High levels of anxiety and sleep disturbances are also common among patients with PWS.[2]
- Current drugs in Phase III development target specific symptoms of PWS, such as such as hyperphagia (Carbetocin, DCCR) or sleep disturbances (Pitolisant).[2]
- EPM301, a novel cannabidiol (CBD) analogue in pre-clinical evaluation by EPM Therapeutics, shows potential as a comprehensive treatment for PWS.
- Early studies, conducted in Canada, Israel and Mexico, suggest EPM301 may address hyperphagia, anxiety, and daytime sleepiness.[1,3,4]



EPM301 (previously named HU-580)[1]

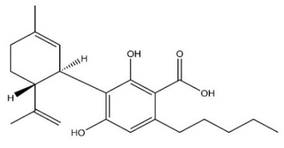
CBD

- Demonstrated positive effects on obesity-related mechanisms.
- Found to reduce body weight and hyperphagia in rat models.



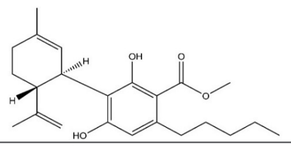
Cannabidiolic acid (CBDA)

- Precursor of CBD.
- Evidence suggests that CBDA can induce potent 5-HT_{1A} receptor-mediated anti-nausea and anxiolytic-like effects.
- Unstable, especially when subjected to heat – limited potential for development as a medicine.



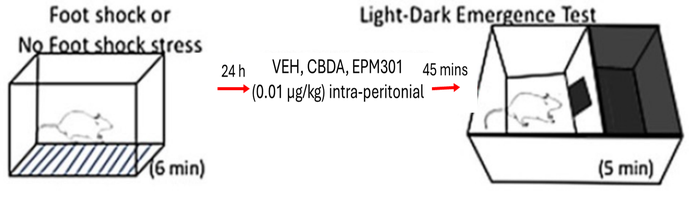
EPM301/HU-580

- CBDA-O-methyl ester.
- Stable analogue of CBDA.



EPM301 induces anxiolytic effects in a stress-induced anxiety-like behavior in rodents[3]

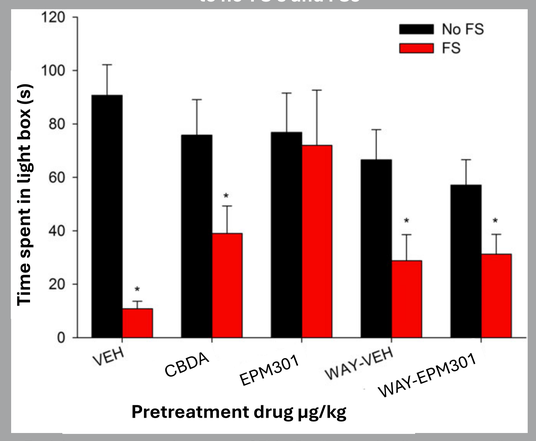
- The effect of **CBDA and EPM301 on anxiety-like responding** was evaluated using the light-dark box emergence test following either foot shock (FS) or No FS stress.



- Rats received a single FS stress session or No FS stress session 24 hours before the light-dark emergence test
- Rats in the FS group and the No FS group were pretreated with vehicle (VEH) 0.01 µg/kg, CBDA or 0.01 µg/kg EPM301. Forty-five minutes later, they were placed in the dark chamber of the light-dark box, and their movement was tracked for a 5 min test.
- Additional groups were injected with $5HT_{1A}$ receptor antagonist, WAY100635, 15 min prior to VEH or 0.01 µg/kg EPM310 to investigate the possibility that the effect of EPM301 was $5HT_{1A}$ receptor-mediated.
- The number of seconds spent in the light box was measured in the following groups:

No FS–VEH (n = 9)	FS–VEH (n = 12)
No FS–CBDA (n = 8)	FS–CBDA (n = 8)
No FS–EPM301(n = 8)	FS–EPM301(n = 8)
No FS–WAY–VEH (n = 8)	FS–WAY–VEH (n = 7)
No FS–WAY–EPM301 (n=8)	FS–WAY–EPM301 (n=8)

Mean time spent by rats in the light box, 24 h following exposure to no-FS's and FSs



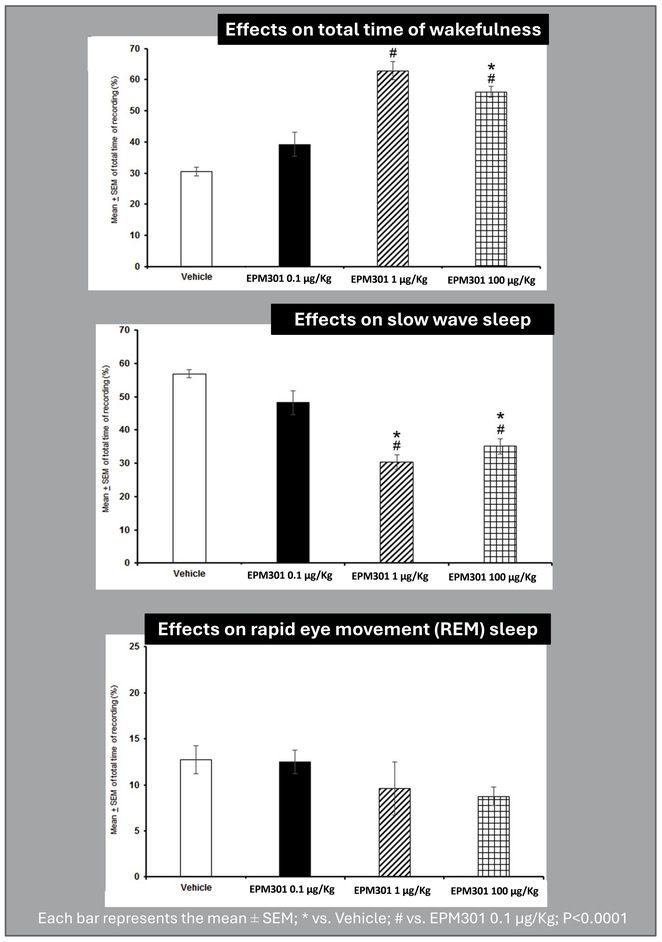
Each bar represents the mean ± SEM; *P < 0.05 and indicates a significant difference between FS and No FS stress groups.

- FS stress greatly enhanced the anxiety-like responding of decreased time spent in the light box.
- At a low dose of 0.01 µg/kg, EPM301 reversed the effect of FS on the anxiety-like responding of decreased time spent in the light box, while CBDA did not.
- Anti-anxiety effects of 0.01 µg/kg EPM301 were opposed by the 5-HT_{1A} antagonist, WAY100635.

EPM301 is more potent than CBDA at enhancing 5-HT_{1A} receptor activation, and inhibiting signs of anxiety

EPM301 exerts wake-promoting pharmacological effects in male Wistar rats[4]

- The effect of **EPM301 on the sleep-wake cycle** of male Wistar rats was evaluated.
- Rats were placed randomly into the following experimental groups: Vehicle (n = 8), EPM301(0.1, 1.0 or 100 µg/Kg, intra-peritonial [i.p.]; n = 8 each dose).
- The sleep-wake cycle data were sampled in periods of 12 s (epochs).
- EPM301 (0.1, 1.0 or 100 µg/Kg, i.p.) given to rats caused changes in the sleep-wake cycle.



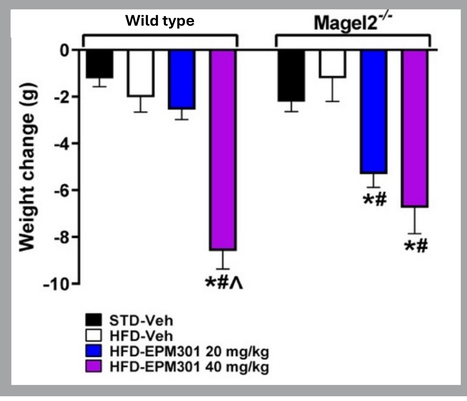
Each bar represents the mean ± SEM; * vs. Vehicle; # vs. EPM301 0.1 µg/Kg; P<0.0001

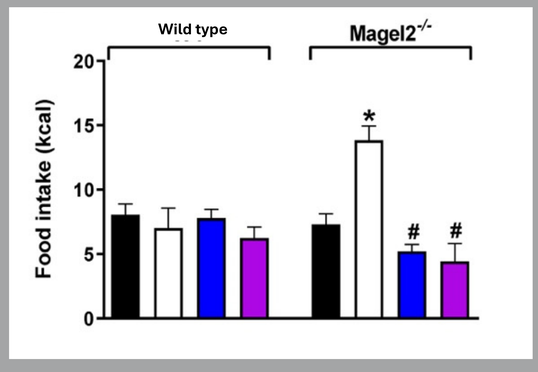
EPM301 1.0 and 100 µg/Kg, but not 0.1 µg/Kg, increased wakefulness and decreased slow wave sleep, with no change in REM sleep.

EPM301 (20 and 40 mg/kg/d, i.p.) reduced body weight and hyperphagia in a high-fat diet fed *Magel*^{2null} mouse model for PWS[1]

- The effect of **EPM301 on body weight and hyperphagia was evaluated in a high-fat diet (HFD) fed *Magel*^{2null} mouse model for PWS**. *Magel*^{2null} mice recapitulate various features of PWS, including hyperphagia, under high-fat diet.[5]
- *Magel*^{2null} mice and their wild-type littermates as controls were fed ad libitum with HFD or standard diet (STD) for 14–16 weeks.
- Next, mice were started with a daily treatment with EPM301 (40 and 20 mg/kg/day, i.p.) for 28 days.
- EPM301 was found to promote weight loss and decreased food intake in *Magel*^{2null} mice.

Change in body weight and food intake over 28 days





Data represent the mean ± SEM from 4–13 mice per group. *p < 0.05 relative to STD-Veh of the same strain; #p < 0.05 relative to HFD-Veh of the same strain, ^p < 0.05 relative to HFD-EPM301 20mg/kg of the same strain

Daily chronic treatment of obese *Magel*^{2null} mice with EPM301 (20 or 40 mg/kg/day, i.p.) for 28 days reduced body weight and caloric food intake at day 28.

These promising animal model results suggest that EPM301 could offer multiple therapeutic benefits for individuals with PWS and support the further development of EPM301 for clinical evaluation in humans.

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