Cannabidiol (CBD) treatment improves spatial memory in 14-month-old female TAU58/2 transgenic mice

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Background
- Both Alzheimer’s disease (AD) and frontotemporal dementia (FTD) are associated with hyperphosphorylation of microtubule-associated protein tau (tau) as well as increased levels of neuroinflammation and oxidative stress.
- AD and FTD patients exhibit behavioural and cognitive deficits including apathy, social withdrawal, disinhibition and memory and spatial navigation deficits. Motor deficits are also observed in some cases of FTD and AD.
- Cannabidiol (CBD) - a plant derived cannabinoid - has been previously used to treat some forms of epilepsy and has minimal side effects in humans.
- CBD is able to inhibit tau hyperphosphorylation in vitro. It also has antioxidant and anti-inflammatory properties (in vivo).

Methods
- Mice: Female TAU58/2 (carrying P301S mutation) and wildtype-like littermates on a C57BL/6J background. Age: 14.5 months ± 2 weeks.
- Study size: n = 9-11 per group.
- Housing: Individually ventilated cages.
- Treatment: CBD at 100 mg/kg bodyweight (or vehicle), i.p. injections, daily starting 3 weeks prior to testing.
- Test schedule: Elevated plus maze, motor tests (accelerod, wire hang), social preference test, cheeseboard, fear conditioning.

Result: Both TAU58/2 and WT mice responded similarly to the conditioned foot shocks (data not shown). CBD treatment reduced context freezing in all mice, without any genotype effects. In the cue trial, TAU58/2 mice had an elevated freezing response to the cue without any significant effects of CBD treatment detected.

Conclusion: CBD may be effective in restoring sociability and spatial memory deficits in tauopathy-related neurodegeneration without adversely affecting motor performance, fear associated learning and anxiety related behaviours.

Summary
- CBD treatment normalised the sociability deficit and spatial memory deficit in TAU58/2 mice.
- CBD treatment decreased anxiety and fear-associated freezing (context trial) in all mice.
- TAU58/2 mice displayed intact learning during cheeseboard training, however, CBD treatment decreased the overall latency to the reward well in TAU58/2 mice.

Method: Mice were allowed to explore an elevated plus maze (two open arms and two enclosed arms forming a ‘plus’) for 5 mins where their movement was tracked.
Result: Time spent on the open arms was increased by CBD treatment. Time and percent distance on the open arms was higher in TAU58/2 mice.

Method: Sociability: Mice were allowed to explore and apparatus with a chamber containing a mouse (sex matched A/J) or an empty chamber for 10 mins. The percent time spent in the chamber with the mouse was analysed.
Result: Social preference of vehicle-treated TAU58/2 mice was impaired but restored by CBD treatment. All mice showed a preference for a novel mouse over a familiar mouse (social recognition memory).

Method: Spatial memory learning was tested on the cheeseboard (a dry land equivalent of the Morris water maze). The time for a mouse to find a food reward (sweetened condensed milk) hidden in one of the 12 wells on the board was recorded over 6 days (120 s cut-off time). The average of three trials per day was recorded.
Result: All mice displayed intact learning. Latency to the reward decreased faster in TAU58/2 mice (compared to WT) at the later stages of training. CBD treatment decreased the overall latency to the reward in TAU58/2 mice only.

Method: Accelerated: Mice were placed on an accelerating rotating rod (4-40 rpm over 30 s) and the latency to fall recorded.
Wire hang: Mice were placed on a 1 cm x 1 cm metal grid which was inverted 50 cm above soft bedding. The latency to fall was recorded.
Result: TAU58/2 mice, regardless of treatment, had poorer performance on both the accelerated and the wire hang test compared to WT. CBD did not impact motor function.

Method: Conditioning: Day 1 mice were placed into a box for 7 min where a tone (2 x 30 s) had a co-terminating footshock (2 x 0.4 mA).
Result: Two TAU58/2 and WT mice responded similarly to the conditioned foot shocks (data not shown). CBD treatment reduced context freezing in all mice, without any genotype effects. In the cue trial, TAU58/2 mice had an elevated freezing response to the cue without any significant effects of CBD treatment detected.

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