CHRONIC CANNABIDIVARIN ADMINISTRATION RESCUES AUTISM-LIKE BEHAVIORS INDUCED BY PRENATAL VALPROIC ACID EXPOSURE IN MALE OFFSPRING

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Autism spectrum disorder (ASD) defines a group of neurodevelopmental diseases whose primary symptoms include impaired communication and social interaction with restricted or repetitive motor movements, frequently associated with general cognitive deficits. About 1 in 68 children aged 8 years receive an ASD diagnosis, and patients are expected to have a normal lifespan. Despite the critical medical need, no effective treatment for ASD is yet available.

Accumulated evidence suggests that the endocannabinoid system is a relatively less investigated piece of a puzzle that brings together several phenotypic features known to be altered in ASD (social reward responsivity, neural development, circadian rhythm, ASD comorbidities). As such, the potential therapeutic exploitation of this system certainly worth more careful investigation.

The non-psychotropic plant-derived cannabidinoid cannabidivarin (CBDV) has shown anti-seizure properties across a range of in vitro and in vivo models, and its administration was well tolerated with no serious or severe adverse events even at the highest tested dose. As many of the pediatric intractable epilepsy conditions share considerable overlap with ASD and early clinical observations suggest a potential role for cannabinoids in addressing problems associated with ASD, it can be hypothesized that CBDV might have a potential therapeutic value in autism.

In this study, we evaluated the efficacy of chronic CBDV administration in reverting/attenuating the autism-like phenotype induced by prenatal valproic acid (VPA) exposure in rats.

Pregnant Sprague-Dawley rats received a single intraperitoneal injection of VPA 500 mg/kg on the 12.5 day after conception, and control females were injected with physiological saline at the same time. Chronic treatment with CBDV 20 mg/kg/day i.p. was performed starting from PND 34 to PND 56 in male offspring. At PND 56, a battery of behavioral tests was carried out to assess the effect of chronic CBDV on 1) sociability and preference for social novelty, 2) short-term memory performance, and 3) locomotion and stereotyped/repetitive behaviors.

We found that CBDV administration was effective in counteracting deficits in sociability and social novelty preference, short-term memory impairment as well as compulsive self-grooming induced by prenatal VPA exposure. Importantly, in control animals CBDV per se did not affect any of the behavior under investigation.

Biochemical studies revealed that 1) prenatal VPA exposure altered the endocannabinoid system and triggered inflammatory processes in behaviorally relevant brain regions, and 2) chronic CBDV treatment was able to normalize these alterations.

Overall, these findings show for the first time the efficacy of chronic CBDV administration in ameliorating the autism-like phenotype in male rats prenatally exposed to VPA, possibly via

modulation of endocannabinoid signaling and neuroinflammatory processes in the brain of VPA-exposed rats.

Acknowledgements: funded by GW Pharmaceuticals (Cambridge, UK); CBDV was provided by GW Pharmaceuticals