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Adenosine therapy in a mouse model of Dravet syndrome

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Statement of the Problem: More than 30% of patients diagnosed with Dravet Syndrome (DS) suffer from intractable epilepsy that put them at high risk for premature death. About 20% of DS patients die from Sudden Unexplained Death in Epilepsy (SUDEP). In addition, all DS patients experience at least some degree of autistic-like impairments and about 25% are diagnosed with full Autism Spectrum disorder (ASD).

Aim: The goal of this study is to test the long-term effects of a novel pharmaceutical approach that targets excitation, instead of inhibition, in a DS mouse model.

Methodology: Mice were administered N6-cyclopentyladenosine (CPA), an A1R agonist, twice daily by i.p. injection during early development. Two regimens were tested: A short-course from P11-20 and a long-course from P11-30. The long-term effects on viability, behavioral comorbidities and the astroglial environment were assessed for each regimen. Anxiety (open field), sociability (3-chamber) and long-term memory (contextual-fear conditioning) were quantified at 8, 9 and 10 weeks respectively. Confocal microscopy was employed to image brains of adult mice that had been labeled with anti-GFAP immunofluorescent staining techniques. Three-dimensional assessment of the astroglial environment was carried out with far sight image analysis software.

Findings: A short-course with CPA improved viability, while a long-course showed initial protection, but continued treatment reinstated decline in survival. The short-course improved sociability, restored long-term memory and blocked astrogliosis in adult mice.

Conclusion & Significance: Currently, no Anti-Epileptic Drug (AED) effectively controls seizures for one third of DS patients and these children can experience hundreds of seizures every day. The novel pharmaceutical therapy with A1R agonist CPA presented here protected against premature death and showed long-term improvements in comorbidities in a DS mouse model, making a case for exploring adenosine therapy during early development clinically.

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