Abstract The purpose of this study is to determine the efficacy of drug mimics of the ketogenic diet on disease phenotypes in a mouse model of fragile X syndrome (FXS; Fmr1KO mice). FXS is a rare neurodevelopmental disorder and the leading known genetic cause of autism. The ketogenic diet is highly effective at attenuating seizures in refractory epilepsy and accumulating evidence in the literature suggests that it may be beneficial in autism. Our recent work investigated efficacy of the ketogenic diet in Fmr1KO mice. We tested chronic ketogenic diet treatment on seizures, body weight, ketone and glucose levels, diurnal activity levels, learning and memory, and anxiety behaviors in Fmr1KO and littermate control mice as a function of age. We found that the ketogenic diet selectively attenuates seizures in male but not female Fmr1KO mice and differentially affects weight gain and diurnal activity levels dependent on Fmr1 genotype, sex and age. Regarding the attenuation of seizures, we have tested several thousand mice for seizure susceptibility over the past decade in response to over two dozen pharmaceutical, dietary or genetic interventions. The ketogenic diet (3-day chronic treatment) was as effective as the mGluR5 inhibitors MPEP (30 mg/kg) and AFQ-056 (3–10 mg/kg) in attenuating seizures. Seizures were not reduced in female Fmr1KO mice. This is the first time we have observed a strong sex-specific response to an intervention in the seizure assay. We are currently testing the efficacy of drug mimics of the ketogenic diet (beta-hydroxybutyrate, 2-deoxyglucose, tributyrin) on seizure phenotypes in Fmr1KO mice. Methods include chronic drug dosing, testing susceptibility to audiogenic-induced seizures and assessment of hyperactivity by 24/7 actigraphy monitoring. Results indicate partial rescue of seizures in males with the ketone beta-hydroxybutyrate but no rescue with the glucose analog 2-deoxyglucose. Testing of tributyrin and actigraphy are in progress. We conclude that the ketogenic diet is highly effective in reducing seizures and hyperactivity in male Fmr1KO mice. Treatment with a single ketone, beta-hydroxybutyrate, partially recapitulates efficacy. Further studies are required to identify bioactive component(s) of the ketogenic diet and mechanism(s) underlying sex-specific effects.

6. Inhibiting Elevated GCPII Activity in Aging Mouse Muscle Reduces Frailty

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Abstract Glutamate carboxypeptidase II (GCPII) is a neuropeptidase that catalyzes the conversion of N-acetyl-aspartyl-glutamate (NAAG) into N-acetyl-aspartate (NAA) and Glu. In the PNS, GCPII is expressed in Schwann cells and activated macrophages and is involved in regulating the synaptic pruning of neuromuscular junctions (NMJs) during normal development. Recently, we observed increased GCPII expression in the muscle of the SOD1G93A mouse model of amyotrophic lateral sclerosis (ALS) that was selectively associated with infiltrating activated macrophages. When using 2-(Phosphonomethyl)-pentanedioic acid (2-PMPA), a potent and selective inhibitor of GCPII, we observed a significant delay in muscle function loss and denervation in the ALS mouse. ALS and aging share similarities including the loss of motor neurons and degeneration of the skeletal muscle resulting in reduced synaptic inputs and fine motor skills, muscle weakness or wasting, and neuro-inflammation. Due to these similarities, we determined whether GCPII levels were altered in muscle of aged mice similarly to ALS mice. We collected gastrocnemius and soleus muscle tissue from 4-, 12-, and 20-month-old C57BL/6 mice and examined GCPII protein expression and enzymatic activity levels. We observed low expression of GCPII in 4- and 12-month-old mice gastrocnemius muscle and significantly increased expression in 20-month-old mice. Like in ALS, we observed co-localization of GCPII staining on infiltrating activated macrophages in aged gastrocnemius muscle. We then began treating 15-months-old mice, with daily 2-PMPA, for 5 months. Monthly frailty scoring was performed using an index that tracks a spectrum of aging-related characteristics. After 5 months of treatment, 2-PMPA treated mice had significantly reduced frailty index scores compared with vehicle-treated mice. Additionally, there was a significant delay in body weight loss and body temperature decline. These studies demonstrate that blockade of GCPII activity has potential therapeutic benefits for slowing aging-related frailty.

7. Experimental Substantiation of New Target Links in Complex Therapy of Prenatal CNS Damage. Pharmacological Modulation of HSP70 – Dependent Mechanisms of Endogenous Neuroprotection

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Abstract Prenatal hypoxia (PH) causes pathological changes in the brain and can lead to irreversible long-term disorders of its development and the emergence of neuropsychiatric pathologies in children. Pharmacological correction of posthypoxic CNS disorders is a priority problem in modern medicine. The aim of this research was to study the neuroprotective action of drugs with an evidence-based effect on the expression – Angiolin ((S)-2,6–diaminohexanoic acid

3-methyl-1,2,4-triazolyl-5-thioacetate), Thiotriazoline (3-methyl-1,2,4-triazolyl-5-thioacetic acid morpholine), Tamoxifen, Glutoredoxin, Cerebrocurin (contains neuropeptides, S-100 proteins, reelin, nerve growth factor (NGF) (not less than 2 mg/ml) and amino acids), RAIL (selective IL-1b antagonist), Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) and L-arginine in comparison with the reference drug Piracetam in terms of their effect on the expression of endogenous neuroprotection factors to further substantiate their use in the treatment of prenatal CNS damage in a model of chronic hemic PH. Expression levels of mRNA of HSP70, HIF-1, c-fos and the content of HSP70 in the cytoplasmic and mitochondrial fractions of the brain of rat on the 60th day of life after PH were determined by real-time PCR and enzyme immunoassay. It has been established that chronic PH inhibits transcriptional processes in neurons and suppresses the synthesis of HIF1a, HSP70 and c-fos. The studied drugs are able to modulate HSP70-mediated mechanisms of endogenous neuroprotection. The most active among HSP70 modulators in conditions of chronic PH are Cerebrocurin (150 µl/kg) and Angiolin (50 mg/kg), which outperform other studied drugs in terms of increased expression of HSP70 mRNA, HIF-1α mRNA and HSP70 protein concentration in the brain of experimental animals and can be considered as promising neuroprotective agents in complex therapy after PH.

8. A Comprehensive Approach to Biomarker Discovery for Chemotherapy-Induced Peripheral Neuropathy (CIPN)

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Abstract Taxanes are a class of chemotherapeutics commonly used to treat solid tumors, including breast and ovarian cancers. Chemotherapy-induced peripheral neuropathy (CIPN) occurs in up to 70% of patients treated with taxanes, impacting quality of life both during and after treatment. CIPN typically manifests as tingling and numbness in the hands and feet and can cause irreversible loss of function of peripheral nerves, and can be dose-limiting, potentially impacting clinical outcomes. The mechanisms underlying CIPN are poorly understood resulting in limited treatment options, and no tools exist to identify which patients will develop CIPN in response to taxane therapy. Although some patients' genetics may predispose them to greater risk, genetic studies for CIPN are inconsistent, complicating the ability to develop definitive biomarkers. Moreover, other molecular markers (e.g., metabolites, mRNA, miRNA, proteins) may also be informative for predicting CIPN onset. To address the clinical gap of identifying patients at risk of CIPN, we initiated the Genetics and Inflammatory Markers for CIPN Study (GENIE) study, a multi-omic assessment of genetic and inflammatory markers of CIPN, as part of the National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) initiative (https://heal.nih.gov/). This study aims to use machine learning to build predictive biomarker signatures that identify patients at increased risk of developing CIPN during taxane treatment. Using pre-treatment, on-treatment, and post-treatment blood samples from 400 patients with breast cancer treated with taxanes, we are investigating genetic, transcriptional, epigenetic (DNA-methylation), protein, and metabolic associations with validated self-reported pain questionnaires that measure sensory, motor, and autonomic symptoms, and functional limitations related to CIPN. We hypothesize that there exist (i) molecular biomarker signatures that are indicative of patients with high probability of developing CIPN and (ii) molecular biomarker signatures that will change in the presence of taxanes and serve as a leading indicator for CIPN development. We anticipate that biomarker signatures can be used to identify susceptible patients early in their development of CIPN, enabling personalized dose adjustments to minimize adverse symptoms, optimize therapeutic outcomes, and improve quality of life.

9. The CURE Epilepsy Catalyst Award: Grant Opportunity for Translational Research in Epilepsy

Priya Balasubramanian, PhD; Laura Lubbers, PhD; CURE Epilepsy

Abstract CURE Epilepsy's mission is to find a cure for epilepsy, by promoting and funding patient-focused research. The CURE Epilepsy Catalyst grant program reflects our commitment to this mission by supporting the development