95355

Potential Drug Therapy for Fragile X Tremor/Ataxia Syndrome

Collis Brown, Tamaro Hudson and Sonya K.Sobrian
Howard University

ABSTRACT IMPACT: The ability to restore mitochondrial health in neurons derived from FXTAS patient-induced pluripotent stem cells by novel natural compounds is critically important to the management of patients experiencing this syndrome and other Fragile X associated disorders. OBJECTIVES/GOALS: The goal of this research is to assess the biological potency of MAM, NADA and MAM analogues' neuroprotective capacity with respect to mitochondrial damage, and antioxidant properties that can restore mitochondrial health in patients with FXTAS. METHODS/STUDY POPULATION: To establish mitochondrial dysfunction, normal human cell lines and human induced pluripotent cells will be exposed to multiple concentrations of glucose/ glucose oxidase (GluOx) at several time points to induce varying intensities of oxidative stress. The degrees of oxidative stress will be measured by apoptosis and mitochondrial reactive oxygen species (ROS) production. N-arachidonoyldopamine (NADA), macamides (MAM) and its analogue compounds, effective against oxidative damage in mitochondria, will be used to rescue glucose oxidase induced oxidative damage in both cell lines. To test the ability of these drugs to restore mitochondrial health, cell viability and cellular superoxide production will be assessed by propidium iodide and the MitoSox fluorescence assay, respectively. RESULTS/ANTICIPATED RESULTS: We anticipate that GluOx at varying concentrations and time points will proportionally increase levels of apoptosis and mitochondrial ROS, reflective of mitochondrial damage, with the most severe dysfunction occurring at the maximum dose of 40μM and the longest duration of 72-hr exposure. Moreover, administration of NADA, MAM, and MAM analogues at seven concentrations, ranging from 10-8 to 10-5 M in half-log increments, will successfully treat the oxidative defects induced in the cell lines by decreasing apoptosis, and superoxide production, and increasing cell viability. DISCUSSION/SIGNIFICANCE OF FINDINGS: This research allows for the development of an in vitro neuronal model of FXTAS, lends flexibility to testing therapeutics, and expands the discovery of mitochondrial biomedical markers for the syndrome. Data generated should inform mechanistic studies of the relationship between mitochondrial damage and FXTAS-induce neurodegeneration.

95923

TBI-on-a-chip: Linking physical impact to neurodegeneration by decrypting primary and secondary injury mechanisms

Edmond Rogers[1], Timothy Beauclair[1], Guenter Gross[2] and Riyi Shi[1]
[1]Purdue University and [2]University of North Texas

ABSTRACT IMPACT: This unique approach has the capability to elucidate the pathological mechanisms underlying traumatic brain injuries and neurodegeneration, both separately and in concert, while simultaneously providing a semi-high throughput model for investigating potential pharmaceutical interventions: discoveries that would have major translational implications and a significant impact worldwide. OBJECTIVES/GOALS: We aim to improve our understanding of the mechanisms behind the development of neurodegenerative diseases by utilizing the link between traumatic brain injuries and demonstrated biomarkers with our innovative TBI on a chip model. With this tool, we hope to provide new pathological insights and explore potential pharmaceutical interventions. METHODS/STUDY POPULATION: E16 murine cortical networks were cultured onto reusable, optically transparent MEAs (fabricated in-house), and subjected to a clinically-relevant range (30-300g) of impact g-forces, utilizing our exciting new in vitro model of trauma (TBI on a chip) with real-time electrophysiological and morphological access. Impacts were systematically applied at varying intensities, repetitions, and time points, and fixed 24-hours post. Basic immunocytochemical techniques were used to investigate post-impact levels of acrolein, an established biomarker of both post-TBI oxidative stress and neurodegeneration (ND), and compared to procedurally and age-matched non-impact control networks. In addition, several other TBI/ND biomarker investigations are in progress (βA42, α-synuclein, and phosphorylated tau). RESULTS/ANTICIPATED RESULTS: Impact experiments revealed significant, force-dependent increases of acrolein (acrolein-lysine adducts) at 24hrs post impact, indicative of impact-linked neuronal degeneration. These changes were amplified by the following manipulations: increasing g-force exposure (30-250 g); the rapid (4-6 sec interval) application of multiple impacts (1, 3, 5 and 10x); and exposure to 40 mM EtOH (10 min duration immediately following impact). Further, we demonstrate the enhancement of injury recovery as a function of: increasing time intervals between repeated hits; Hydralazine exposure. In addition, conditioned media from maximally-impacted cultures can cause acrolein elevation when introduced to non-impact, control networks, indicating acrolein's role as a diffusive-factor in post-TBI secondary injuries. DISCUSSION/SIGNIFICANCE OF FINDINGS: This novel approach provides unprecedented resolution, and is improving our understanding of the pathological mechanisms underlying both TBI and ND. Combined with our established in vivo models of trauma and computer modeling, we hope to better guide our translational laboratory endeavors and help improve clinical diagnoses and treatments.

Clinical Epidemiology

76352

Investigating the Association Between Intracerebral Hemorrhage (ICH) and Long-Term Encephalomalacia and Cortical Atrophy

Arjun Adapa[1], Siri Sahib Khalsa[2], Joseph Linzey[2] and Aditya Pandey[2]
[1]University of Michigan Medical School and [2]University of Michigan Department of Neurosurgery

ABSTRACT IMPACT: Investigating the relationship between ICH volume at presentation and cortical atrophy over time may help to explain the phenomenon of cognitive impairment after ICH. OBJECTIVES/GOALS: Non-traumatic intracerebral hemorrhage (ICH) is the most common type of hemorrhagic stroke. ICH causes both mechanical as well as oxidative injury leading to neurologic deterioration. However, the relationship between ICH volume and brain atrophy is not fully understood. To that end, we aimed to investigate this relationship. METHODS/STUDY POPULATION: A retrospective cohort of adult ICH patients over a 10-year study period were studied. Demographic data, ICH cause, location,

https://doi.org/10.1017/cts.2021.635 Published online by Cambridge University Press