Therapeutic Efficacy of Macamides on Fragile X Tremor/Ataxia Syndrome (FXT/AS)

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Fragile X-associated tremor/ataxia syndrome (FXT/AS) is a late-onset neurodegenerative disease associated with movement and memory problems, affecting 1 in 3000 males over 50 years of age. This syndrome is characterized by excess CGG (55-200) repeats of a trinucleotide sequence in the DNA for the Fragile X Messenger Ribonucleoprotein 1 (FMR1). It is suspected to induce mitochondria dysfunction in the CNS. Currently, no effective pharmacological treatments exist for FXTAS. The goal of this research was to test the ability of synthetic macamides, which are endocannabinoid-like compounds, to restore mitochondrial viability. Macamides were chosen as they have been shown to prevent mitochondrial membrane toxicity in Parkinson’s disease. To establish a rapid screening cell model to study the pharmacological efficacy of macamides, fibroblast baby hamster kidney (BHK-21) cell lines were treated with glucose oxidase (GluOx) at varying concentrations and times. Mitochondrial viability was assessed by the colorimetric Janus B Green Assay, which stains the mitochondria and enables assessment of cell numbers and the presence of oxygen in anchorage-dependent cell culture. GluOx treatment of BHK-21 cells caused a dose- and time-dependent increase in oxidative stress. There was a significant disruption in the morphology of BHK-21 cells at a high glucose concentration, i.e., 40 nM, between 2 and 24 hours post-exposure. The Janus B Green colorimetric assay confirmed the morphology data. In examining the effects of glucose on mitochondrial viability, we demonstrated that at 15, 30, 35, and 40 nM, glucose significantly decreased mitochondria viability compared to the untreated, with 40 nM having the most significant effect. Upon establishing this model of mitochondrial dysfunction, we next investigated the ability of three novel mitochondrial antioxidants (e.g., macamides) to protect mitochondrial viability. Macamides preserved the morphology of the BHK-21 cells at concentrations of 0.5µM, 1µM, and 5µM. Furthermore, in the presence of glucose, macamides at a low concentration of 0.5µM prevented the reduction of mitochondrial viability. This study provides evidence of the efficacy of macamides as novel therapeutic candidates in the treatment of mitochondrial dysfunction associated with FXTAS.

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