MTU04-16

The oligosaccharide portion of ganglioside GM1 as mitochondrial regulator

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Functional data and clinical studies suggest the existence of a positive loop between the age-dependent GM1 deficiency and alpha-synuclein (αS) accumulation determining the neurodegeneration onset of sporadic Parkinson's Disease (PD). This loop is triggered by the plasma membrane GM1 deficiency, which leads to a failure of trophic signaling and to the αS accumulation, increasing the susceptibility to neuronal death. Recently we shed new light on the molecular basis underlying GM1 effects highlighting that GM1 oligosaccharide (OligoGM1) directly binds TrkA receptor, triggering TrkA-MAPK pathway activation which leads to neuronal differentiation and protection. Following its administration to B4galnt1$^{+/-}$ PD mouse model, OligoGM1 was found to completely rescue the physical symptoms, reduce αS aggregates and restore tyrosine-hydroxylase neurons. Since the mitochondrial dysfunction plays a central role in the exacerbation of nigrostriatal degeneration in PD, we decide to evaluate the putative OligoGM1 mitochondrial modulation in murine neuroblastoma cells, N2a. Following its exogenous administration, proteomic analysis revealed an increased expression of proteins involved in mitochondrial bioenergetics and in oxidative stress protection. By biochemical studies we found that OligoGM1 protects N2a cells from MPTP toxic effect as well as from mitochondrial oxidative stress. Moreover, by immunoblotting we identified an increased expression of TOM20/HtrA2 mitochondrial proteins, whose reduced expression has been associated with PD. At functional level, we found increased basal and uncoupled mitochondrial respiration following OligoGM1 administration. Collectively our data indicate a possible role of OligoGM1 as mitochondrial regulator that by inducing mitochondriogenesis and enhancing mitochondrial activity could determine mitochondrial restoration in PD neurons.

MTU04-17

Reductive reprogramming: a not-so-radical hypothesis of neurodegeneration

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Free radical-mediated oxidative stress, neuroinflammation, and excitotoxicity have long been hypothesized to contribute to the progression of Alzheimer's disease and other aging-related neurodegenerative disorders (NDD). Among these phenomena, the significance of oxidative stress and, more generally, redox perturbations, for NDD remain ill-defined and unsubstantiated. Here, I argue that (i) free radical-mediated oxidations of biomolecules can be dissociated from the progression of NDD, (ii) oxidative stress fails as a descriptor of cellular redox states under conditions relevant to disease, and (iii) aberrant upregulation of compensatory reducing activities in neural cells, resulting in reductive shifts in thiol-based redox potentials, may be an overlooked and paradoxical contributor to disease progression. In particular, I summarize evidence, from *in vitro* studies, which supports the view that reductive shifts in the extracellular space can occur in response to oxidant and inflammatory signals and that these have the potential to reduce putative regulatory disulfide bonds in exofacial domains of the N-methyl-D-aspartate (NMDA)-subtype of glutamate-gated receptors as well as other synaptic regulatory proteins, leading potentially to aberrant increases in neuronal excitability and, if sustained, excitotoxicity. Moreover, I provide data from my laboratory which establishes the presence in the brain, *in vivo*, of disulfide bonds in the NMDA receptor as well as other glutamate and non-glutamate-gated receptors. All of these are potential targets of reductive stress. This novel reductive reprogramming hypothesis of neurodegeneration provides an alternative view of redox perturbations in NDD and links these to both neuroinflammation and excitotoxicity.

MTU04-18

The role of monocarboxylate transporter-1 on cognitive deficits development during NAFLD

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Non-alcoholic fatty liver disease (NAFLD) is a major complication of obesity. Certain observations regarding NAFLD induced neuropsychiatric alterations have been reported but mechanisms are unknown. Monocarboxylate transporter-1 (MCT1) haploinsufficient mice, which resist high fat diet (HFD) induced hepatic steatosis represent an interesting model. Using a mouse model of NAFLD (HFD+high fructose/glucose in water [HF/HG]) we investigated the development of cognitive deficits and state of cerebral oxygenation and cerebrovascular reactivity.

Behavioural tests (open field/novel object recognition/forced swimming test [FST]) were performed in mice fed control diet (NC; WT/MCT1 + /- +NC) or HFD HF/HG (WT/MCT1 + /- +HFD HF/HG) for 16 weeks. Baseline cortical PO_2 and in response to systemic hypercapnia (10% CO_2) was monitored under anaesthesia by a fluorescence method. Microelectrode biosensors were used for lactate measurements by cortical slices. EchoMRI was performed to assess lean/fat mass.

Increased fat mass was observed in WT and MCT1 + /- mice on HFD HF/HG compared to NC controls. Liver mass was only significantly higher in WT+HFD HF/HG mice compared to controls. Behavioural tests revealed no significant differences between groups except for FST, which indicated a depression-related behaviour in the WT+HFD HF/HG group compared to controls. This was not observed with MCT1 + /-+HFD HF/HG mice. WT+HFD HF/HG mice had a lower cerebral PO_2 baseline and hypercapnia-induced PO_2 response compared to controls, while MCT1 + /- groups remained unchanged. Tonic lactate release was unaltered between all groups although the MCT1 + /-+HFD HF/HG group indicated a decreased lactate tone trend.

Our results suggest that NAFLD is associated with a depression-related behaviour and decreased cerebral PO_2 baseline. MCT1 haploinsufficient mice were resistant to the reported phenotypes, suggesting a link between liver metabolism and neuropathophysiological alterations.