Abstract

Astrocytes are the most abundant and heterogeneous population of glial cells in the central nervous system (CNS). They have many roles including regulation of metabolic functions of the CNS and protecting neurons against infection or cellular damage. Their abundance and diversity of functions make knowing their contribution in CNS diseases essential. Quercetin (QH), a plant flavonoid, and Docosahexaenoic acid(DHA), an omega-3 polyusaturated fatty acid, have been documented to have health benefits in certain disease conditions by improving mitochondrial dysfunction and inflammation.

Methyl-CpG-binding protein 2 (MeCP2), a global transcription factor, mutations cause neurodevelopmental disorder-Rett syndrome. Several studies have shown mitochondrial impairment linked to ROS production and reduced ATP synthesis in Rett patients and models. Also, perturbed calcium homeostasis in neural cells have been documented in Rett syndrome condition. Importantly, the mitochondrial electron transport chain interconnects the paradigm of intracellular calcium and oxidative stress. Moreover, differential MeCP2 expression has been observed in neuronal and non-neuronal cells. Despite the existence of extensive research on pathogenesis underlying MeCP2 mutations/deficiency, its effects on ETC complexes in astrocytes have not been reported. Also, the evaluation of quercetin and DHA in MeCP2 knock-down astrocytes is first of its kind. The present study aims to investigate the effect of quercetin and DHA on mitochondrial respiratory complexes (Uqcrc1 & Ndufv2) genes expression, proteins expression and enzyme activities in MeCP2 knock-down astrocytes. Intracellular calcium, mitochondrial membrane potential and ROS were also observed in quercetin and DHA treated MeCP2 knock-down astrocytes. In C6 glial cells, modulated intracellular calcium and ROS were observed in quercetin and DHA treated MeCP2 knock-down cells. Data show favorable changes in quercetin treated MeCP2 knock-down astrocytes. DHA altered mitochondrial respiratory chain complexes genes expression, proteins expression and enzyme activities favourably in MeCP2 knock-down cells. Such research may lead to a deeper mechanistic understanding of cognitive deficits in autism spectrum disorders with early fatality in children.

Another study was to investigate the effects of quercetin and DHA in neuroinflammation and their underlying mechanisms in astrocytes. Here, primary rat cortical astrocytes were exposed to LPS

and inflammatory (IL-1β, IL-6, TNF-α, COX-2, HO-1, TLR-4) markers mRNA levels were determined in quercetin (25, 50,100, 200 μM) and DHA (25,100 μM) pre-incubated astrocytes. Their effects on phosphorylated forms of signaling proteins (phospho p38, p-IκB-α, pERK1/2) were also evaluated. In present study, quercetin down regulated pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), COX-2 and up regulated HO-1 genes expression and modulated p-IκB-α, pERK1/2, and phospho p38 activation in a dose dependent manner. DHA reduced IL-1β, COX-2 and TLR-4; and increased HO-1 gene expression in LPS induced astrocytes. TNF-α gene expression was significantly reduced in DHA treated LPS induced C6 glial cells. pERK1/2 protein level was also found to be increased in DHA treated LPS activated astrocytes. The demyelination and neurodegeneration-mediated disorders exhibit elevated pro-inflammatory markers and down regulating their expression has beneficiary effects. Thus, these observations suggest dose-dependent anti-inflammatory effects of quercetin and DHA in astrocytes.

In conclusion, these observations suggest positive effects of quercetin in mitochondrial dysfunction mediated by MeCP2 deficiency in astrocytes. They also serve as preliminary data to evaluate quercetin's effects in MeCP2 deficient/mutated conditions *in vivo*. The data also suggest anti-inflammatory effect of quercetin in inflamed astrocytes. DHA's modulatory effects need further attention to understand its beneficiary role. The *in vivo* study would help further to understand the therapeutic relevance of quercetin and DHA in ameliorating the diseases.