Metabolic Stress and Inflammation: Implication in Treatment for Neurological Disorders

Neurological disorders are described as a condition of functional deficits (depression, schizophrenia etc.) or structural damage of nervous system (peripheral neuropathy, Alzheimer’s disease, Parkinson’s disease etc.). Although the impact of metabolic disorders (obesity, diabetes etc.) on physical health is widely recognized, a recent and growing body of research suggested that this pathology is also associated with neurocognitive impairment, deficits in learning, memory and executive functioning, and increased incidence of neuropsychiatric disorders [1]. On the other hand, stressful life events deeply impact brain and bodily function and, in addition to representing major risk factors for neuropsychiatric disorders, also influence energy metabolism and feeding control. Further, chronic stressful condition considered as a major risk factor coexisting with the development of metabolic disorders. Neuronal system is metabolically very active and consumes enormous amount of energy to perform and sustain its physiological functioning [2]. Persistent high oxygen demand and consumption of huge energy, makes neuronal cell vulnerable to oxidative stress, a condition of imbalance of pro-oxidant/antioxidant homeostasis that leads to the generation of toxic Reactive Oxygen Species (ROS). Further, metabolism of excitatory amino acid and neurotransmitter in nervous system make them unique and serve as sources of oxidative stress. ROS attack glial cells and other neurons, which are particularly sensitive due to their post-mitotic nature. Overproduction of free radicals can cause oxidative damage to biomolecules, (lipids, proteins, DNA) and contribute to neuropathogenesis, eventually leading to many chronic neuronal dysfunction and diseases [3]. Moreover besides above, recent evidence has implicated neuroinflammation and Endoplasmic Reticulum (ER) stress as components of a novel form of neuronal metabolic stress that develop in neurological disorders and peripheral nervous system dysfunction over the time [4]. Among the possible underlying mechanisms whereby both metabolic stress and inflammation impair peripheral as well as higher neuronal functions and exacerbate neurological disorders. Given the high incidence of comorbidity and linked etiology, there is an urgent need to focus the latest development on the said area. This thematic issue presents detailed information on various neurodegenerative disorders and their connection with oxidative stress [5].

Recently, H2S received much attention due to its neuromodulatory role in diverse neurodegenerative diseases and plays important role in neurotransmission effecting learning and memory process. BACE1, Nrf2 and NF-κB have been implicated as molecular targets for H2S as described by Kumar and Sandhir. H2S has shown significant potential in free radical scavenging and activation of superoxide dismutase, suggesting its protective role in glutamate-induced cytotoxicity (Kumar and Sandhir, 2018). H2S bases therapeutics (S-Allyl cysteine, AP39, s-progallyl-cystine etc.) are under development for neuropathic pain, cancer and Aβ mediated neurodegeneration [6].

Mule and Singh discussed the role of oxidative stress in potentiating the deleterious effect of diabetes on nervous system (Mule and Singh, 2018). Several hypotheses and mechanistic evidence are discussed linking altered glucose metabolism to the risk of progressive dementia. This review specifically emphasized on altered metabolic pathway in condition of diabetes as potential contributor to persistent oxidative stress which culminates into neuronal dysfunction and dementia [7]. Targeting the various links downstream to oxidative stress and antioxidant-based therapies may be the possible putative target that is beneficial in combating development and progression of dementia associated with diabetes [8].

Mitochondrial function alteration is linked with changes in physiological homeostasis. Misfolded protein metabolism and increased oxidative stress leads to mitochondrial dysfunction in a big way to the pathogenesis of neurodegenerative disease such as Alzheimer’s, Parkinson’s and Huntington’s disease. It occurs early before losing cellular protein clearance homeostasis and finally mitochondrial autophagy (mitophagy). Kumar et al., emphasized the importance of targeting mitochondria and autophagy related proteins in combating neurodegenerative disorders [8]. Various antioxidants have shown potential in preclinical models but are found to be less effective in the clinical trials. The antioxidants, which not only focus on scavenging the existing ROS but also on the source of generation like mitochondrial dysfunction should be investigated. Further, research on interaction of old protein aggregates and involved proteins (such as Aβ, presenilin, ABAD, DJ-1, PINK-1, PARKIN, α-synuclein) with mitochondria may open new avenues for devising strategies against neurodegenerative disorders [9].

Khatri et al. have described how oxidative stress initiate and propagate secondary damage after Traumatic Brain Injury (TBI). It is argued that Ca2+ is very essential for numerous physiological functions but excessive calcium influx through glutamate-activated NMDA and AMPA receptors contribute to secondary damage after TBI. Calcium overload disrupts cellular free radical scavenging system like superoxide dismutase, catalase, reduced glutathione etc. and mitochondrial functions. These factors consecutively induce neuronal dysfunction and damage to structural component of neuronal cells viz. lipids, proteins, and DNA and finally leads to neuronal death. It is being concluded that further research focussed on the ways to overcome the
deleterious effects of TBI mediated oxidative stress and rescuing the brain cells from damage by secondary injuries and some serious disabilities [10].

Neuroinflammation is very well linked to metabolic disorders and oxidative stress. It has been implicated as a major contributor to the development of neurodegenerative disorders including Alzheimer’s disease (AD), Parkinson’s disease (PD) and Huntington’s disease (HD). Pandareesh et al., described the role of nutritional agent in mitigating the brain oxidative stress. Multiple neuroprotective pathways downstream to oxidative stress can be activated by natural agents/dietary supplement without causing severe adverse effects, which not only inhibit the neuronal damage but also help in tone-down the progression of neurodegenerative disorders [11].

Abnormal protein misfolding and aggregation are the hallmark of neurodegenerative disorders like AD and PD. It induces oxidative stress which further activates microglia and astrocytes promoting inflammation, ultimately aggravating neurodegeneration. Moreover, elimination of abnormal proteins aggregation without eliciting any adverse effects is the potential strategy and protein based biotherapeutics may provide opportunistic solution for the treatment of neurodegenerative disorders. In this issue, Chia et al., have described application of single-chain fragment variable antibodies (scFv) in inhibition and clearing of target physiological protein aggregates, such as amyloid-beta (Aβ) peptides, α-synuclein (α-syn) and Huntingtin (Htt). Further, research is needed to address brain penetrability, safety and stability which remains as the major concern for the scFv therapeutics [12].

The advent of modern tools with an improved in depth understanding of patho-mechanism of neurodegenerative disorders may help in developing strategies to tackle the problem of ageing world population. We should find means of not only treating the neurodegenerative disorder, but also in either delaying or halting the course of disease.

REFERENCES