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Veer B. Gupta
Edith Cowan University

Vivek K. Gupta

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Editorial Open Access

Impaired Energy Metabolism: Involvement in Neurodegenerative Processes and CNS Ageing

Veer B Gupta[1] **and Vivek K Gupta**[2*]

[1]*Centre of Excellence for Alzheimer's Disease Research & Care, School of Medical Sciences, Edith Cowan University, Joondalup, WA 6027, Australia*

[2]*Faculty of Medicine and Health Sciences, Macquarie University, 75 Talavera Road, Sydney, NSW 2109, Australia*

[*]***Corresponding author:*** *Gupta VK, Faculty of Medicine and Health Sciences, Macquarie University, 75 Talavera Road, Sydney, NSW 2109, Australia ,* ***Tel:*** *+61-2-98502760;* ***Fax:*** *+61-2-98502701;* ***E-mail:*** vivek.gupta@mq.edu.au

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Editorial

World is experiencing a consistent and steady increase in the ageing population with even higher proportional differences in the developed countries. Increase in ageing populations is directly correlated with the increased prevalence of age-related degenerative diseases of the central nervous system (CNS) such as Alzheimer's disease and various other forms of dementias, stroke, Parkinson's disease, retinal degenerative disorders, Huntington's' disease, multiple sclerosis, psychiatric and behavioural disorders amongst others [1]. The brain also undergoes a number of functional and structural changes during ageing, even when no contributing disease factors or genetic associations exist. A basic trait of ageing is impairment in cellular signalling pathways mediating requirement based cellular energy metabolism. This energy deficiency exerts a chronic negative impact on cellular functions and manifests itself in the form of degenerative processes in the CNS such as decreased clearance and repair of damaged proteins and nucleic acids, protein aggregates and other cellular debris. Brain and retina have highest energy requirements compared to all other tissues making them exceptionally vulnerable to metabolic stresses and therefore availability of energy substrates leading to optimal energy homeostasis is critical in these tissues [2]. Energy regulation in the brain is a major research area that includes the study of the transformation of energy substrates in cells and several associated biochemical processes like respiration and production and utilization of energy in the form of ATP. Since Peter D. Mitchell's discovery of ATP generation in the cellular organelles like mitochondria [3], many groups have identified various aspects of cellular survival, synaptic network formation, development, plasticity and neuronal function as some of the critical processes in living organisms that require steady supply of energy generation and utilisation.

During the last decade multiple groups have provided evidences about how changes in energy regulation and its impairment can have a modulatory impact on brain and retinal functions ranging from altered synaptic plasticity and network formation to developmental changes. Energy imbalance can also significantly alter the coupling of neuronal cells with glial cells and oligodendrocytes [4]. Glucose is recognised as the primary energy source but lactate, pyruvate and beta-hydroxybutyrate are some of the other substrates that mediate ATP generation in the CNS. Various growth factors and neurotropins play essential role in the maintenance of effective energy equilibrium in the neuronal tissues by their regulatory actions on glycolytic pathway, mitochondrial function as well as cellular uptake of energy substrates [5,6]. Neuronal energy demands are met by ATP production which in turn is linked to optimal energy substrate endocytosis and expenditure. Receptor mediated glucose uptake by neurons is tightly linked to activation of IR/IGF1R, EGFR and neurotropin pathways [7,8]. Their downstream effectors like PI3K/ Akt, MEK/Erk1/2 and PLCγ/ PKC/ NFκB in turn regulate various enzymatic catalytic steps involved in ATP generation [9-11]. Cellular signalling pathways extensively cross-talk with enzymes responsible for ATP production in the cytoplasm and mitochondria and regulate their activity through phosphorylation / dephosphorylation cascades involving various receptor and non-receptor phosphatases and kinases [12,13]. This line of research using cell biology and various animal models has helped to identify the mechanisms underlying regulation of metabolic machinery by the cellular signalling pathways. Human studies have also helped understand the association of brain cognitive and behavioural changes with metabolic disorders that primarily affect energy metabolism such as diabetes. Recent studies further suggest that modulating calorie intake helps preserve brain function and improve cognition and reduce the risk of various neurodegenerative disorders [14]. Nutritional changes to promote ketogenesis by altering the dietary ratio of protein / carbohydrate and lipids have also been shown to exert neuroprotective effects by providing higher quantities of ATP and phosphocreatine and inducing an increase in the mitochondrial number in the cells [15].

Other studies have reported various pharmacologically bioactive compounds such as Tropomyosin kinase receptor B (TrkB) agonists that help to modulate or preserve brain and retinal function. Modulators of neurotropin signalling such as 7,8 dihydroxyflavone and Deoxygedunin can activate Akt and Erk pathways which in turn modulate the activity of various phosphatases and kinases that play a role in cellular energy metabolism [16,17]. Apart from pharmacological approaches, gene therapy to modulate the neurotropin signalling can be used to target key enzymes involved in ATP generation as well as their upstream regulators and downstream effectors. Genetic approaches have already reached clinical practice in retinal disorders using AAV therapy in Leber's Congenital Amaurosis (LCA) [18]. The great advantage in using AAV is that it poses minimal antigenic responses and ensures long-term expression of the gene in the neuronal cells. In this regard, AAV9 serotype is particularly of the essence as it can cross the blood brain barrier following intravenous administration which has been the major challenge in the field [19]. Transgene expression in the neurons using specific promoters can be helpful to understand mechanisms underlying various CNS diseases, physiological processes and develop therapeutic tools and approaches. The effects of such gene therapy treatments can be investigated in animal model of disease with specific genes upregulated or knocked down. Similar studies can also be carried out in the transgenic animals

and tissue specific expression modulation using cre-lox or CRISPR technologies with inducible promoter expression system [20-22]. With the advent of new approaches and instrumentation we are now in a position to study the whole brain changes in a three dimensional network using techniques like small animal magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning in vivo and CLARITY technique in vitro to study cellular resolution of the whole connectome [23,24]. Bioinformatics and molecular modelling studies can also be of help to identify novel interacting partners and binding sites [25]. These studies will help to carry out unbiased research on synaptic and neuronal network and identify region specific changes moderated by the ageing / disease processes or their modulation by pharmacological or therapeutic approaches. Altogether, improved understanding of energy homeostasis in brain mediated through the network of various cellular signalling pathways using cutting-edge technologies has enormous implications in understanding the pathophysiological mechanisms and improved therapeutic targeting.

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