ABSTRACT

Diabetes & its secondary complication have taken a toll over the past three decades. The picture is bleaker considering the elderly population is on rise. Endocannabinoid system (ECS) plays crucial role in bridging gaps between oxidative stress, calcium signalling, appetite regulation & accelerated aging mechanism in diabetic person. Current antidiabetic therapies have failed to address many relevant aspect of diabetes. The meshwork of various mechanism ECS participate in, provides many opportunities for development of new drugs for management of disorder like diabetes, dyslipidaemias, obesity, cognitive decline due to diabetes & many more. Some these have already been studied extensively. Still many pathways remain less highlighted. Reason for cognitive decline in diabetes appears especially more to do with endocannabinoid system, due to its widespread effects on all changes occur in cognitive decline.

Keywords: Calcium signalling, beta amyloid, endocannabinoid system, cognitive decline, aging, oxidative stress, diabetes.

INTRODUCTION

Ever since the research on diabetes and related diseases has increased there has been enormous development in the understanding the disease progression and its secondary complication. This lead to the development of different drugs, most popular of which are hypoglycemic drugs. It has been very clear that hyperglycaemia in not sole reason of all the complication of the disease, controlling which though increases the lifespan but does not reduces risks of developing secondary diseases particularly cognitive decline. However multiple mechanisms are modified in diabetes, which triggers changes in brain neuronal circuits involved in learning and memory and to which hypoglycemic drugs offer least help in diabetes. So this review article highlights scope for adjunct therapy, why these supplement would be able to provide benefits which is not possible with the existing drugs. In this review article we cite and relate all the mechanisms which get modified and their role in progression of cognitive decline and aging. The relation of these mechanism is very complex and there exist a fine tuning in a healthy human between these, this article shows how the changes in one or the other leads the changes of the other one in aberrant way. We see a relation between appetite, endocannabinoid system, oxidative stress, serotonergic transmission & calcium environment of neurons of hippocampal and many other apoptotic and replicative mechanisms, get deranged and leads to massive changes in learning and memory formation and aging.

Neurotransmitters in appetite & their relation

To begin with appetite, which involves highly regulated processes there many centre in brain and specific neurotransmitter involved in regulation of appetite. Consumption food leads to release of insulin and many neurotransmitters like NYP, AGRP, leptin and inhibition of ghrelin release. Along with these, endocannabinoid system also plays a major role in appetite regulation. So leptin and insulin release after the glucose load from meal, causes suppression of appetite by acting on appetite center; Leptin receptor-Ob-R, in arcuate nucleus, ventromedial, dorsomedial hypothalamus, lateral hypothalamic area, medial preoptic area, insulin receptors ARC, DM, PNV, suprachiasmatic and periventricular region and illicit activation of appetite suppressing signals & autonomic changes like slowing of GIT motility finally leads feeling of fullness. Before consumption of meal, concentration of ghrelin is increased which is reduced after meal, although in obesity it remains high even in well fed state. Leptin signalling is important to end the action of ghrelin. Activation of cannabinoid receptor-CB1 by respective agonist increases feeding in animal models. This is because endocannabinoid receptor CB1 activation leads to inhibition of interneurons which inhibits the release of NYP and AGRP, (potential orexigenic neurotransmitter) by release of gamma amino butyric acid (GABA). Leptin also suppresses appetite by inhibiting synthesis of endocannabinoids. In diabetes due to altered metabolism of lipid there is lipid peroxidation which hampers the caveolae structure & function, caveolae is present in leptin receptors and is important for downstream passage of leptin signalling. Insulin receptor too uses caveolae mediated signalling. So there is loss of these inhibitory signalling pathways in diabetes. Needless to say insulin and many other hypoglycemic medications do little to these derangements. Already many published data support the strong association between dysregulation of endocannabinoid system and diabetes. The relation between diabetes, oxidative stress, dyslipidaemia & cognitive decline may have many mediators which change each other but endocannabinoid system stands prominent as strongest player in all the above mention condition. What makes it so versatile in all of this is endocannabinoid system receives signal from each of them; diabetes, oxidative stress, dislipidemia or cognitive decline & at same time it is able to directly change all these conditions.

Endocannabinoid system making bridge between diabetes Oxidative Stress-Dyslipidaemia-Cognitive Decline

The dysregulation in synthesis of endocannabinoid in not only the result of loss of leptin signalling but also due to formation of a cycle; increase in likeness of palatable food, endocannabinoids reinforce the reward from consumption of high fat diet, this important as in dyslipidemia there is more...
and more unhealthy fat is available for conversion into endocannabinoids13,14. Use of CB1 antagonist reduces the consumption of high fat diet in animal models15,16. As said earlier there is association of cognitive disorder in patients with dyslipidemia and diabetes17, coexistence of both could double the chances of cognitive function. Dysregulation of endocannabinoid synthesis also has important relation with ceramide. Ceramide is another phospholipid derivative. Ceramide concentration increases in glialoma cell, signals apoptosis, a protective mechanism against cancer. However CB1 agonist can lead to sustained increased in level of ceramide even in normal cell which can produce same apoptotic signal an also lead to cell death in normal cells18. High level of endocannabinoids can directly interfere with the formation of new memories and recalling old memories19,20. This is very well established by use of CB1 agonist in animal models. Excessive endocannabinoid can directly compete with 5-HT for its action on its receptors 5-HT1A and 5-HT2C, interaction which is very crucial for the formation of new memories and recalling of them. Endocannabinoids, by acting on CB1 receptors can pre-synaptically inhibit the release of glutamate in parvocellular neurons, which again leads to memory impairment21. Other than above said mechanism, endocannabinoid synthesis dysregulation is also an act of altered calcium homeostasis in cytoplasm and in mitochondria.

**Calcium: more than just secondary messenger**

Calcium homeostasis inside of cell is crucial for many signalling pathways to run properly, as calcium acts as a secondary messenger for many processes22,23. With regard to synthesis of endocannabinoid synthesis and dysregulation, calcium concentration inside the cell per se is maintained by means of many calcium channels; voltage gated calcium channels on mitochondria and channels on cell wall of neurons24. It has been seen that brain cells of aged rat show heavily deranged calcium homeostasis24. Same observations have been there for animal models of memory and learning studies. Now calcium levels inside the cell can be altered in response to not just ligands but also due to oxidative stress, this the major reason in animal models of aging even if the animal are non-diabetic.24 – There is increase and decrease in calcium concentration in a cyclic manner; in response to a stimulus by a ligand, there is a slight increase in cytoplasmic calcium channels, this triggers the release of further calcium from endoplasmic reticulum, this second release of calcium leads an enormous increase in intracellular calcium ion. This high intracellular calcium levels is responsible for the action of any ligand; induction of gene expression, release of neurotransmitter so on.22,23 once the purpose of increased calcium is done, the level comes back to normal by effective buffering mechanism, endoplasmic reticulum plays important role in that24. However in oxidative stress, cell’s capacity to buffer cytoplasmic calcium level is hampered. This has been observed in neurons of aged rats that the resting calcium level in cytoplasm remains at higher level than neurons of young rats. Also upon the stimulus by respective ligands, the increase in cytoplasmic calcium in aged rat neurons is very feeble when compared to young rats, and which also fails to elicit any effective response. Then duration for which the calcium level remains increased in aged cell is also more than young neurons25. This also shows that the protein which responds to increased calcium level is also altered. The reason here too is same, free radical and oxidative stress, the ultimate weapons of aging. Use of calcium channel blocker in animal models have shown promising results in prevention of memory extinction17, which proves that there is involvement of impaired calcium influx and its buffering, in memory extinction.

**Alzheimer’s disease: role of calcium and others**

Increased calcium levels in cytoplasm of hippocampal cells also called excitotoxicity, is leading cause of Alzheimer’s disease. Calcium levels in Alzheimer’s disease have a different mode by which it is increased pathologically. The amyloid beta fibres of neurons which are degraded by beta- secretase and gamma-secretase leave the amyloid beta oligomers inside the cells. These amyloid beta oligomers form pores in the cell membrane of the neurons, causes influx of excessive calcium inside cells17. With this there exists the deregulation of L-type of calcium channels, as erratic increased calcium level in cell has damaging impact on function of calcium channel on mitochondria and endoplasmic reticulum. In Alzheimer’s disease, there is more direct role of oxidative stress. Oxidative stress interferes with correct folding of proteins in neurons. Although the cells have repairing mechanisms to correct the misfolded proteins. Chaperons, a group of proteins is involved in endoplasmic reticulum, also get damaged due to oxidative stress28,29. This leads to activation of unfolded protein response (UPR)30. Early and longer activation UPR is associated with impaired ubiquitin pathway, which ultimately leads to apoptotic signalling and cell death. Accumulation of misfolded proteins is again increase by the free radical as the react with the –OH group of amino acids in proteins. In normal proteins the active chemical groups of the proteins are hidden in inside of folded proteins, since there is misfolding these reactive proteins get exposed to each other. This leads to increases in interaction between different proteins, which ultimately leads to tangling of proteins with each other and accumulation17,03,11. The on-going damage in neurons is reinforced again by the dysfunction precinilin pathway. Aged rat’s hippocampal cell show there are more mutations in genes for precinilin. Oxidative stress alone directly interferes with repair mechanism of precinilin32,33. Other than above, the damages in hippocampal region is more due to oxidative stress than due to vascular diseases, which too is strong player for hippocampal atrophy but vascular dementia, mainly causes abnormalities in frontal cortex and entochondal cortex14,35. This is due to the fact that the other two regions (frontal cortex and entochondal cortex) are more dependent on major blood vessel’s branches.14 Then what makes the cells in hippocampal region more susceptible for oxidative stress is oligodendrocytes, these cells are rich in iron, have highly active metabolic process33. Which along with demyelination can be observed as hyperintensities in T2 weighted MRI scan reports of Alzheimer’s disease patients34. (Figure 1).

**Figure 1: White matter changes on MRI. The bright areas represent non-specific white matter changes in the periventricular and deep white matter areas, bilaterally."**

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*Shishir Mishra et al: Diabetes mellitus: A plotter of cognitive decline*
Oxidative Stress Mediated Activation of Neurohormonal changes & Its Consequences

There are changes which occur at hypothalamus due increase of oxidative stress. This results in increase release of ACTH so to increase synthesis of corticosteroids, as a compensatory response against stress body is facing. The increased levels of corticosteroid in healthy person causes feedback inhibition of release of ACTH, however this does not happen as finely so in diabetic person. So higher levels of corticosteroid for long time have negative impact on learning and memory formation26, as steroid have wide spread affect many transcription factors26. Since wide range of chemicals which are believed to hamper new memory formation inhibit the transcription factor, many protein synthesis inhibitors inhibit memory formation. Although not specifically proteins synthesis inhibitor, steroids do have similar effect on long term in higher concentration26. Other than this higher concentration of steroid for long time directly reduces the number of cells in hippocampal region. This has been proven by using mefipristone, corticosteroid antagonist. As use of this antagonist prevented the rats from inhibitory effect of corticosteroids on working memory. And the number CA1 cells in hippocampal region in group receiving mefiprstone was also found more than group which did not received antagonist27.

Significant Direct Role of Oxidative Stress on Cognitive Decline & Aging

So far in this article the biggest culprit for diabetes in cognitive disorder is oxidative stress. This is due to excessive production of free radicals and diminished capacity of body to fight against this. The major site of generation free radical is mitochondria. It is proven in animal models that knock-out gene for many complexes of respiratory chain38. The major reactions in which free radicals are generated are catalysed by complex I, III & IV. Electron here is transferred from one complex to other and during this the free energy is converted to ATP, the energy currency of cellular metabolism. The cell membrane faces significant lipid peroxidation in oxidative stress of the phospholipids of bilayer lipid membrane, this result in rigidity of cell membrane. Due to this their enormous increase in the level of formation of free radical, but instead of increase of fighting mechanism, there is decline in synthesis of free radical scavenging enzymes. Overall effect is many fold increase in free radical38. Free radical directly can damage DNA. Sometimes this leads to apoptosis. Also free radical can enhance the process of aging also by reducing the number of division a cell undergoes, by altering the function of telomerases39. Oxidative stress also reduces the generation of new cell from progenitor cell by damaging the genes of Foxo family. Foxo genes are crucial for signalling for new cell division in many parts of brain. So it's clear that there is increase in number of cell going to apoptotic stage than the number of new cell generation40.

CONCLUSION

In metabolic disorder like diabetes the major location for excessive free radical production is mitochondria, there is more mobilization of fat. These two contribute maximum damage. The free radical generated leads to lipid peroxidation of lipid membrane of mitochondria and cell membrane. As discussed earlier, this is the beginning point of all the oxidative stress mediated ailments. Lipid peroxidation of membrane not just renders the cell to dysfunctionality of membrane protein function but also to change in membrane potential. Change in resting potential of cell makes it unavailable to transmit the signals between the cells. Lipid peroxidation & changed membrane potential also leads to decrease in beta oxidation of fatty acids. All these lacunae in metabolism & cell signalling provide potential site of new intervention in therapeutics. Since the targets of diabetes mellitus in mediating cognitive decline is multifactorial, all contrived by diabetes, we believe that the preventive approach to this problem should be multi targeted. It should target all the assignee of oxidative stress and diabetes directly, as just targeting blood glucose level has been failed completely in preventing early sign of aging & cognitive decline. We speculate that supplementing the antioxidant medication with a potent antioxidant, free radical scavenging agent, correcting lipid peroxidation, may postpone the early onset aging & cognitive decline. Although this lacks support from molecular studies with elucidation of corrective mechanism in each pathways.

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