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Neuro-endocrine Deficits in Hypothalamic Regulation of Brain Energy Metabolism and Dysfunctions in Mitochondrial Bioenergetics Associated with Neurodegenerative Diseases

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1. Introduction

Neural regulation of body energy homeostasis depends largely on the internal feedback signals sent to and from the periphery, integrated in the hypothalamus and brain stem which in turn balances activation of behavioural, autonomic and endocrine pathways leading to changes in food intake and energy expenditure [1,2]. A predominant factor in maintaining homeostatic functioning in women especially, is estrogen that has diverse effects on the immune and endocrine system through various signalling molecules [3,4]. The overall body energy homeostasis is achieved by regulation of adiposity signals, leptin and insulin, and satiety hormone ghrelin whose combined equilibria determine a settling point [5,6]. The brain responds to the circulating signals such as nutrients, insulin, and leptin and adjusts food intake accordingly. In response to these signals, the brain modulates metabolism and energy production in various tissues including liver, muscle cells and adipose tissue through the autonomic nervous system [7]. The brain also plays an important role in maintenance of glucose homeostasis, regulated by insulin/glucagon secretion in the pancreas and glucose uptake by the cells. The autonomic nervous system integrates the outflow pathways from the brain to peripheral metabolic organs and vice versa [8]. Studies show that insulin stimulates glucose metabolism in the brain by crossing the blood brain barrier (BBB) during fasting conditions. But subjects with impaired insulin secretion and insulin sensitivity show decreased glucose metabolism in the brain and subsequently leads to neuronal death [9]. Improper diet and sedentary lifestyle increase saturated and trans-unsaturated fat accumulation in the body that can impair the metabolic signals required to maintain homeostasis [10]. Defective cross talk between the brain and peripheral metabolic organs pave way to various metabolic disorders such as obesity and type 2 diabetes and neurodegenerative disorders.

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Neurodegenerative brain disorders are a broad spectrum of fatal conditions characterized by progressive neuronal dystrophic structural changes and loss of function. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders, with amyotrophic lateral sclerosis and Huntington's disease (HD) being less prevalent. These diseases share several mechanistic similarities at the subcellular levels including atypical protein aggregation, failure of protein degradation pathways, impaired axonal transport, mitochondrial dysfunction, and programmed cell death [11]. Glucose is metabolized to yield ATP through a series of pathways- glycolysis, Kreb's cycle and electron transport chain (ETC). Glucose is known to cross the blood brain barrier (BBB) to the enter the brain through glucose transporters and similarly, insulin secreted by beta cells of the pancreas cross the BBB for cellular utilization of glucose contradicting earlier assumptions that brain metabolises glucose independent of insulin. Insulin resistance (IR) can lead to decreased glucose metabolism in the brain, and without subsequent energy demands being met by the cells they succumb, contributing to neurodegenerative disorders [12,13]. Increasing evidence suggests that metabolic alterations strongly influence the initiation and progression of neurodegenerative disorders. Studies with animal models for neurodegenerative diseases suggest that defects in synaptic mitochondrial function, caused due to disrupted mitochondrial dynamics are underlying causes of neurodegeneration [14]. Excess nutrients lead to the inhibition of fusion, resulting in fragmentation and an incomplete cycle of fusion, fission and autophagy leading to mitochondrial dysfunction [15]. Studies from our lab show that estrogen plays a neuroprotective role in the brain by increasing antioxidant enzyme activity and enhanced activity of enzymes in glucose metabolism which may have promoted mitochondrial function, energy metabolism and thus, may facilitate neuronal survival in the brain areas [16-18].

This review aims to provide an overview of some of the evidences for metabolic dysregulation in neurodegenerative diseases. Further, it discusses several potential mechanisms that may underlie the potential relationships between metabolic dysfunction and etiology of neurodegeneration.

1.1 Hypothalamic regulation of food intake

A fundamental requirement for an organism's survival is its ability to maintain a homeostatic internal metabolic environment. Substantial evidence indicates that the brain plays a central role in the homeostatic regulation of energy metabolism [19]. The brain integrates multiple metabolic inputs from the periphery such as nutrient content, gut-derived hormones- glucagon like peptide-1 (GLP-1), cholecystokinin and peptide YY, and adiposity signals- leptin and insulin, to regulate food intake and energy expenditure [22]. The hypothalamus synthesizes and secretes neurohormones, called releasing hormones which stimulate or inhibit the secretion of hormones from the pituitary gland. It also controls body temperature, hunger, thirst, fatigue, sleep and circadian rhythms [20,21]. The arcuate nucleus (ARC) within the hypothalamus plays a significant role in regulating feeding and metabolism [22]. The hypothalamic ARC is situated near the median eminence, which is an area that presents with a porous blood-brain barrier thereby, granting free access to circulating nutrients and hormones to enter the hypothalamus [23]. The ARC houses two distinct neuronal populations of importance: one group of neurons produce orexigenic neuropeptides- neuropeptide Y (NPY) and agouti-related peptide (AgRP), whereas another set of neurons express anorexigenic neuropeptides proopiomelanocortin (POMC) and cocaine- and amphetamine regulated transcript (CART) [22]. These neurons are first order neurons on which peripheral metabolic signals and hormones including leptin, ghrelin and insulin primarily act [24]. These first order neurons subsequently project axonal processes to second order neurons such as the paraventricular nucleus (PVN), ventromedial hypothalamus (VMH) and lateral hypothalamus (LH) and to autonomic preganglionic neurons in the brain stem and spinal cord. These second-order neurons further process the received information and project to multiple neurocircuits

outside of the hypothalamus (extrahypothalamic), leading to an integrated response on energy intake and expenditure [25]. Ablation studies in mice have shown that loss of NPY an AgRP neurons induce hypophagia, weight loss and starvation whereas loss of POMC and CART neurons promote obesity [26,27]. Both of these neuronal groups are targeted by the satiety hormone leptin, originating from the adipose tissue and ghrelin, hunger hormone emanating from the gastrointestinal tract [19]. Leptin inhibits AgRP/NPY neurons and stimulate POMC neurons. This leads to decreased hunger/appetite and increased energy expenditure mediated by the alpha- melanocyte stimulating hormone, a product of POMC neuron, that acts on melanocortin 3 and 4 receptors (MC3R and MC4R) [28]. Conversely, ghrelin activates AgRP/NPY neurons and inhibit POMC neurons, thereby stimulating appetite. The AgRP/NPY neurons are also capable of inhibiting POMC neurons directly by release of NPY and gamma amino-butyric acid (GABA) [29,30].

Hypothalamic neurocircuits connected to the mesolimbic reward system comprising the ventral tegmental area (VTA) and nucleus accumbens control aspects of food intake in connection with extrahypothalamic brain regions such as the nucleus of the solitary tract [24,31]. During fasting states, there is an observed decrease in glucose levels, which trigger the production of glutamate and orexin in the LH neurons. The LH neurons project to the VTA and stimulate excitatory signals in the dopaminergic neurons of the VTA [32]. Parallelly, the GABAergic signals from NPY/AgRP neurons also project to the VTA that promotes food intake and is referred to as caloric reward [33]. Recent studies show that activation of GABAergic signals to the VTA initiates what is called a 'sucrose seeking' behavior that contributes to increased food intake [34,35]. Thus, it is established that signals to and from the hypothalamus are integrated with mesolimbic pathways and decision-making centers such as the amygdala, hippocampus and prefrontal cortex to maintain energy homeostasis. (FIG. 1).

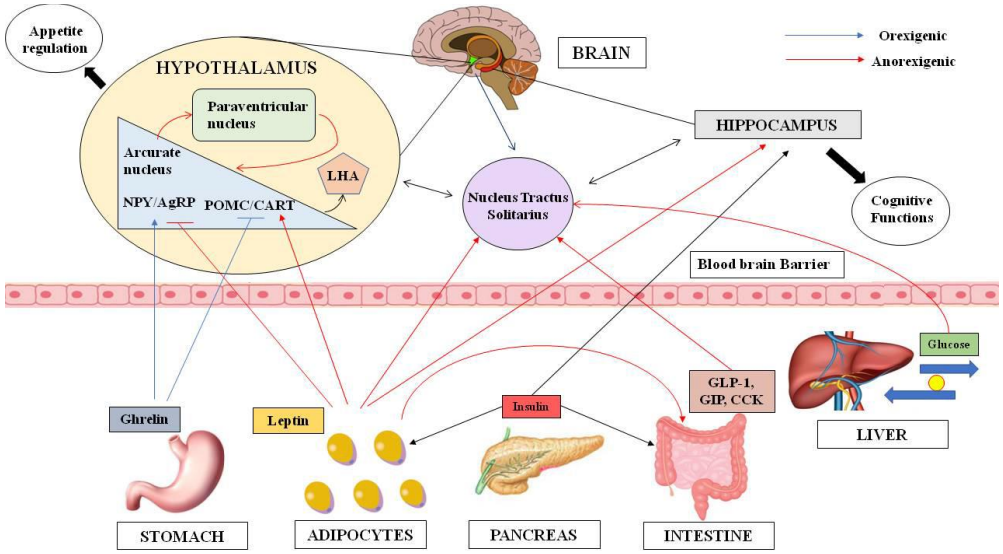

FIG. 1. **Energy homeostasis is maintained by integration of peripheral metabolic signals from the liver, pancreas, stomach, intestine and adipose tissues by the central nervous system. Specialized neuronal circuits in the hypothalamus coordinate the food intake and energy expenditure in response to signalling hormones leptin, ghrelin and insulin. The NPY/AgRP neurons and POMC/CART neurons in the arcuate nucleus primarily sense the energy requirements and project to the paraventricular nucleus and nucleus of the solitary tract in the brain stem which controls and regulates multiple aspects of maintaining homeostasis.**

1.2 Roles of Leptin & Ghrelin in energy metabolism associated with neurodegeneration:

The hypothalamus plays a key role in the regulation of energy metabolism and appetite in the body. This regulation is carried out with the help of molecules such leptin and ghrelin, which act directly on the hypothalamus [36,37]. Leptin is an anorexigenic signal hormone that suppresses appetite while ghrelin is orexigenic in nature that plays a role in appetite initiation [38]. Leptin and ghrelin thus exert antagonistic effects on food intake at the hypothalamic level, to regulate the energy metabolism, which is crucial for the overall homeostasis of the body [39]. Additionally, these are directly involved in neuronal death induced by diversified pathological conditions and also play a role in neuroprotection, making the cross talk between leptin and ghrelin, an important subject of research in the study of neurodegenerative diseases [40]. The discussion of this crosstalk requires a clear understanding about the action of each of these hormones individually.

Leptin is a satiety hormone, which is secreted in a pulsatile manner, mainly by white adipose tissue. The level of leptin secreted is positively correlated with the amount of fat in the body and the circulating concentrations of leptin decline rapidly in response to food intake, providing a dynamic measure of the size of fat storage and acute changes in energy balance [41]. Its primary metabolic function is to inhibit food intake and stimulate energy expenditure, by binding to the leptin receptors in the hypothalamus [42]. The crucial relevance of the leptin signaling in human energy homeostasis is can be observed in the phenotype of individuals who are homozygous for inactivating mutations in leptin or leptin receptor. Studies have reported that these people are clearly obese and extremely hyperphagic [43]. Apart from the hypothalamus, leptin receptors are also found in other regions, including the hippocampus, where leptin may play a role in controlling learning and memory. This is elucidated by the studies conducted on leptin receptor-deficient rodent models, which showed impairments in long-term potentiation in the Cornu Ammonis-1 (CA1) region of the hippocampus and poor spatial memory compared to controls dues to the lack of leptin [44].

This data indicates that leptin, besides its role in energy regulation, may also directly regulate the behavioral as well as the pathological progression of neurodegenerative diseases like AD and PD by exerting a neuro-protective effect. AD is one of the most common chronic neurodegenerative diseases, that is characterized by extracellular plaque deposits of the β-amyloid peptide (Aβ), neurofibrillary tangles of the microtubule binding protein tau, synaptic loss and neuro-inflammation [45]. It has been observed that the Aβ level is decreased both in brain extracts and the serum of transgenic mice after treatment with leptin [46]. This Aβ clearance has been shown to be promoted by the action of leptin which reduces β-secretase activity and increases apolipoprotein (ApoE)-dependent Aβ uptake [47]. Leptin can also reduce tau phosphorylation through inactivation of glycogen synthase kinase 3 β (GSK-3β) [48]. AMP-activated protein kinase (AMPK) is emerging as a central modulator of major pathological hallmarks of AD in the brain and leptin deficiency in AD can contribute to down-regulation of the AMPK system, causing increases in Aβ and phosphorylated tau [49,50]. This is proved by a study that shows primary neurons exhibit increased Aβ levels following leptin antagonist treatment [51].

These biochemical and pathological changes were also correlated with behavioral improvements, suggesting that leptin not only reduces AD pathology but also ameliorates cognitive symptoms [52]. Similar to the findings in AD, leptin has also shown to have a regulatory effect of the progression of PD as well. PD is another common neurodegenerative disease that is characterized by classical motor function deficits due to death of dopaminergic neurons in the substantia nigra and the accumulation of proteins into Lewy bodies in the neurons [53]. Studies have shown that leptin can reverse behavioral

abnormalities and reduce dopaminergic cell death in 6-hydroxydopamine (6-OHDA)-induced PD animal models. In the process of leptin-induced neuroprotection, extracellular regulated phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) plays a key role as a survival factor of dopaminergic neurons, which caused subsequently a MEK-dependent increase in cAMP response element-binding protein (CREB) [54].

Furthermore, another downstream product of leptin is brain-derived neurotrophic factor (BDNF), which can preserve the survival of dopaminergic neurons via activation of the ERK/CREB pathway [55]. Despite the neuroprotective effects, leptin has been shown to have a controversial role in the regulation of neurodegenerative diseases as it induces significant alterations in the immune system [56,57]. It is extremely powerful in regulating the activity of cells of the native and the adaptive immune system. It stimulates neutrophils, regulates phagocytic function of macrophages, activates dendritic cells and also promotes a pro-inflammatory cytokine pattern [41]. Animal studies show that there is an observed decrease in dopaminergic signals from the medial basal hypothalamus and lateral hypothalamic area, which may alter the neuroprotective functions of leptin and aid in progression of neurodegenerative diseases such as AD and PD [58].

It is suggested that leptin can potentially worsen blood–brain-barrier dysregulation, which is an existing feature of AD. This is proven by studies that showed reduced lymphocyte infiltration into spinal cord achieved by specifically blocking leptin signaling in the endothelium [59]. These observations indicate that leptin could represent a key mediator in the link between immune dysregulation and metabolism in neurodegeneration. This leads to the obligation to study molecules that interact functionally with leptin to modulate immune function in various ways depending on the metabolic status. Ghrelin is a hunger hormone produced by enteroendocrine cells of the stomach to assists in the stimulation of sensations of hunger before meals [60]. Its metabolic effects are opposite to those of leptin, as it stimulates food intake and decreases energy expenditure. In addition to these opposing metabolic effects, ghrelin also displays reverse action relative to leptin on immune activities. Ghrelin administration has been shown to significantly be associated with a reduced expression of pro inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6) [61]. This effect is shown to have a potential therapeutic application in AD, which is associated with increased pro-inflammatory cytokines, leading to chronic inflammation.

Additionally, ghrelin receptors are found to be expressed in a widespread manner in the central nervous system (CNS), showing that it is not only involved in metabolism and inflammation but also in other brain functions, such as learning and memory, anxiety control, reward, mood, and sleep [62]. This is elucidated by a study, wherein the administration of ghrelin into the rat hippocampus, amygdala, and dorsal raphe nucleus significantly and dose-dependently increased memory retention [63]. Circulating ghrelin was also demonstrated to bind to neurons in the hippocampus, where it promoted dendritic spine synapse formation, generated long-term potentiation (LTP), and enhanced spatial learning and memory [64].

Initial studies on ghrelin reported that it was also shown to protect cell viability, promote cell proliferation, prevent mitochondrial dysfunction, control apoptosis, reduce blood brain barrier dysfunction and reduce intracellular superoxide production following Aß oligomer-induced toxicity in varying cell models [65-67]. These data strongly support a role for ghrelin signaling in the maintenance of normal memory function and provide a motivation for the study of ghrelin regulation in AD [68]. Following this initial study, several recent studies were conducted and has shown that that the alterations in ghrelin

contributes to the severe cognitive deficit as observed in AD, since its expression was found to be strikingly reduced in one of the cortical regions most affected in AD, the temporal gyrus, when compared to healthy age matched controls [69]. Ghrelin concentration in plasma is also shown to be diminished in patients with PD when compared to healthy age-matched individuals [70]. This reduction is exhibited in the pre-motor stage of PD, suggesting a direct implication of ghrelin in disease progression, while administration of ghrelin has been shown to be able to protect dopaminergic (DA) neurons from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced death, diminish microglial activation and reduce the levels of TNF-α, IL-1β and Nitric Oxide (NO) [71-73]. AMPK senses cellular energy increases, adenosine triphosphate (ATP) production and suppresses energy consumption in conditions of cell stress [74]. Through AMPK, ghrelin is known to activate peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), which is a master regulator of mitochondrial biogenesis, which is known to be dysfunctional during PD progression [75,76]. The positive effect of ghrelin on PGC-1 determines enhanced mitochondrial health and may reduce dopaminergic cell loss. On the other hand, ghrelin target AMPK is central in the induction of autophagy, the process whereby damaged or unnecessary cellular components are digested. When the energy balance is low, AMPK activation leads to mammalian target of rapamycin (mTOR) inhibition and subsequent autophagy induction, which helps in ameliorating the disease condition [41].

While these mechanisms establish the utility of ghrelin as a therapeutic tool in neurodegeneration, further research is needed to address the interactions of ghrelin with other molecules like insulin and glucose is essential to determine the sensitivity and specificity of ghrelin as a potential peripheral clinical biomarker for the diagnosis and treatment of neurodegenerative diseases.

2. Glucose in Brain Energy Metabolism

Homeostasis maintenance is centered around a balanced energy metabolism regulated by the brain. Insulin and Glucagon are vital and antagonistic hormones essential for glucose maintenance and in turn have an influence on homeostatic functions. Glucose being an imperative substrate for energy production is required in adequate levels, and imbalances and disturbances in glucose homeostasis renders metabolic dysfunction causing disorders such as obesity, diabetes mellitus and IR. Metabolic signals reaching the brain stem and hypothalamus, control regulation following sensing of insulin, leptin, glucose and fatty acids [77]. Peripheral innervations controls organs by mediating insulin or glucagon secretion from the pancreas, glucose synthesis from the liver and glucose uptake from skeletal muscles which is also predominantly controlled by the hypothalamus [78]. Glucose sensing neurons in various brain regions are regulated by glucose levels where glucose excitatory (GE) and glucose inhibitory (GI) neurons increase and decrease their action potential respectively upon perception of increased interstitial brain glucose levels [79].

Ventromedial hypothalamus and glucose sensitive neurons protect the brain against energy deficits chiefly aiding in glucose hypersensitivity conditions of obesity and type 2 diabetes mellitus (T2DM). The brain identifies, detects and responds when alteration in glycaemia occurs, by inhibiting feeding and secreting insulin mediated by neuronal glucose sensors. Fueled by circulating glucose, the brain stores energy as glycogen and subsequent metabolism of glucose is undergone in the mitochondria producing adenosine triphosphate (ATP) [79-81]. The energy requirements of the brain are fulfilled through an uninterrupted supply of glucose in order to meet the physiological demands of the central nervous system. This could be accomplished by estrogen's ability to upregulate glucose transporter molecules on the cell surface and thereby increase glucose uptake by the neurons [82]. Energy requirements vary based on neuron physiology, with energy expended in maintaining synaptic function

and resting potential [83]. Variations in energy levels are represented in neurodegenerative conditions such as AD due to alterations in neuron structures, thus requiring high energy intake creating an imbalance in homeostasis and subsequent neuron death [84]. Progression of AD is also attributed to variations in lipid profile and bilirubin rates which may alter the energy homeostasis [85]. Disruptions in glucose metabolism and delivery connects with brain diseases due to its prime role as a precursor for ATP and neurotransmitter synthesis, regulation of blood blow and maintenance of a "body-brain" nutrient axis [86]. Claude Bernard's proposal of the brains participation in glucose homeostasis provides a substantial and plausible role of these energy molecules in neurodegenerative conditions. Normal brain aging is indicated by glucose hypometabolism and mitochondria dysfunctional as early indicators of functional changes [87]. In conditions of neurodegeneration, aging or ischemia, energy requirements are high increasing the vulnerability of neurons and synapses to dysfunction and degeneration due to insufficient ATP generation [88]. Perturbations in glucose homeostasis is attributed to a reduced expression of glucose transporters in the brain. A study on gerbils and mice indicated a decrease in glucose transporter 1 (GLUT1) levels and translocation of glucose transporter 3 (GLUT3) within the dentate gyrus [89]. Reduced GLUT1 levels have correlated with reduced glucose uptake and cerebral flow, strengthening hypometabolism to be a causative role in cognitive impairment over age [90]. Signaling pathways such as mTOR, promote dendritic protein synthesis and associate with memory are observed to be affected by disturbances in glucose-energy metabolism leading to neurodegeneration facilitated by autophagy and mitochondrial dysfunction [91].

Early-stages of AD or patients with mild cognitive impairment (MCI) are observed to have compromised blood brain barrier (BBB) integrity and decreased GLUT1 due to insulin receptor losses, decreases glucose transport across the BBB [90]. Similarly, decreased GLUT1 and GLUT 3 levels correlated with abnormal tau hyperphosphorylation in AD patients, accelerated by diminished brain glucose uptake and further cognitive decline [92]. Efficiency of key regulatory and rate-limiting enzymes in glucose metabolism such as phosphofructokinase (PFK), aldolase, glucose-6-phosphate isomerase and lactate dehydrogenase [93,94] are observed to be decreased in AD patients. Disruption of homeostasis of glucose metabolism induces neurodegeneration and affects production and clearance of Aβ and tau phosphorylation [95]. Pyruvate oxygenation, crucial for glucose metabolism oscillates due to decrease in activities of pyruvate dehydrogenase, cytochrome oxidase and α-ketoglutarate dehydrogenase complex and increase in malate dehydrogenase (MDH) in AD and HD [96,97]. Hypometabolism is implicated in PD, by decreased activity of the pentose-phosphate pathway for energy metabolism in the cerebellum of patients [98]. Glycolytic enzyme isomerase participates in dopamine metabolism, aggregation of proteins and neurodegeneration in animal models of PD, bolstered by mitochondrial dysfunction in similar neurodegenerative conditions. Glucose homeostasis is observed to have a variety of ramifications in normal physiology and neurodegeneration, which is further regulated by the synergistic action of insulin and glucagon in maintenance of this energy metabolism.

3. Role of Insulin and Glucagon in Brain Glucose Metabolism in Normal and Neurodegenerative Conditions

Insulin and Glucagon work synergistically to maintain normal blood glucose concentrations. Signals from the periphery to the brain via insulin aids in the regulation of glucose metabolism by the further secretion of insulin and glucagon. Regulation of insulin signaling in the CNS is vital for promoting neuronal survival and processes such as synapse density, plasticity and connectivity in learning and memory [99]. Brain glucagon is important in peripheral homeostasis regulation as observed in the medial basal hypothalamus [100]. AD and IR have a strong correlation due to a higher risk of aging hastened by glucose

intolerance, IR and metabolic syndrome. The brain as an insulin receptive organ has been established due to experiments indicating deletion of insulin receptors leads to obesity, hyperphagia and systemic IR; thereby exhibiting its importance in regulating metabolic homeostasis. Autonomic nervous system transitions towards the periphery are supported by brain insulin signaling pathways [101,102]. Abnormalities in brain insulin action is also manifested in diabetes and obesity. Flaws within the CNS insulin functions are reflected as defects in insulin signaling, transport of insulin across the BBB and impaired signaling in insulin receptor expressing cells [103]. Anxiety and behavioral disorders due to brain IR induced dopaminergic dysfunction reflect on the roles of insulin signaling in neuronal regulation [104]. Insulin receptor substrate 2 (IRS2) participates in the regulation of hippocampal-synaptic function and plasticity mediated through the phosphoinositide 3-kinase (PI3K) signaling pathway and N-methyl-d-aspartate (NMDA) receptor [105]. IR thus observed in memory impairment and cognitive dysfunction is owing to the defective signaling pathways within the brain. In hypothalamic neurons insulin activates IRS2 and PI3K pathways and signals adiposity to the brain and deletion of these insulin receptors and IRS2 increases food intake and diet-induced obesity speeding up age related processes [106].

In AD, IR is observed to be associated with higher tau levels in the cerebrospinal fluid and altering insulin and its signaling changes levels and clearance of Aβ from the brain via insulin-degrading enzymes [107,108]. Defective glucose metabolisms and IR cause diabetes mellitus, which has been studied to contribute to PD due to hyperglycemia causing neurodegeneration in the nigrostriatal pathway of Parkinson's patients [109]. Glucagon-like peptide-1 an incretin family hormone, enhance insulin secretions and synthesize glucagon. GLP-1 is studied to act as a neuroprotective agent, improves neuropathological features in AD and cognitive functions and GLP-1 receptor agonists (GPL-1RAs) were observed to protect motor activity and dopaminergic neurons in PD in neurodegenerative cases [110]. Phosphatidylinositol 3-kinase/ protein kinase B (PI3K/AKT) and RAS-extracellular signal-related kinase (ERK) pathways are induced upon activation of GLP-1R to mediate insulin action. Stimulation of GLP-1R improves IR in neurodegenerative conditions and inhibits apoptosis, oxidative stress and inflammation [111]. Blood glucose homeostasis is thus controlled by insulin and glucagon hormones with a broad action of anabolic insulin in peripheral organs such as the liver, muscle and adipose tissues. Insulin signaling is observed to be linked to neurodegenerative conditions and metabolic disorders associated with aging such as obesity and cardiovascular disorders. The hypothalamus being a key regulator of homeostasis and energy metabolism can contribute to defects in brain insulin action. Inflammation within the hypothalamus, reduces insulin sensitivity in the brain and impairs insulin transport from the periphery [112]. Insulin-glucagon signaling mechanisms supporting glucose energy metabolism, is imperative for the maintenance of homeostasis and glucose mechanisms, insulin signaling and receptor pathways, and GLP-1 prove to be novel in studying and targeting aging and affiliated neurodegeneration.

4. Mitochondrial Bioenergetics

An important criterion to maintain homeostasis is balancing the energy requirements of individual cells. Every cell must be able to constantly monitor and adjust its energy level and production of ATP based on its metabolic demand. Fulfilment of the energy demands depend on the ability of the cells to metabolize and convert nutrients to chemical energy. The main site for energy conversion is the cell organelle mitochondria which plays a critical role in maintaining this homeostasis. The bioenergetic alterations in the mitochondria were studied by using different approaches targeting the energy metabolism balance in response to nutrient supply [113]. Studies have shown that a nutrient rich environment results in fragmented mitochondrial network (fission machinery) whereas fasting conditions promote elongation of mitochondria (fusion machinery)

[114]. Therefore, in cells with increased energy requirements such as the neurons, proper mitochondrial machinery plays an important role in maintaining the energy balance to ensure proper functioning of cells. Alterations in mitochondrial energy metabolism contributes to the pathophysiology of various neurological conditions such as ischemia, brain injury and neurodegenerative diseases like Alzheimer's and Parkinson's disease [115]. Various alterations in factors such as ETC complexes, mitochondrial enzymes, reactive oxygen species and mitochondrial fission machinery contribute to mitochondrial dysfunction [116-118]. In addition to impaired ETC, mitochondrial dysfunction can also occur in response to inhibition of any enzyme necessary go energy production. Oxidative inactivation of mitochondrial matrix enzymes- pyruvate dehydrogenase and aconitase sow metabolic failure subsequently leading to cell death. Evidence also suggests that oxidative stress due to reactive oxygen species impairs adenine nucleotide transferase, enzyme required for the efflux of ATP. Closure of mitochondrial porins regulated by voltage gated channels, can lead to decreased aerobic respiration and subsequent energy production [119].

In hypothalamic neurons, neuronal activation of ArGP/NPY neurons and POMC neurons through leptin or ghrelin signals alter mitochondrial dynamics. Studies in mice show that during fasting conditions and in conditions where ghrelin is increased, the mitochondria in the ArGP/NPY neurons undergo fission whereas after feeding, mitochondria in the POMC neurons undergo fusion [120]. This further supports the theory that mitochondrial dynamics play a crucial role in maintaining energy homeostasis.

Mitochondrial dysfunction is a hallmark of aging, which leads to various biochemical alterations such as increased mTOR, production of proinflammatory cytokines that subsequently disrupt the BBB and disrupt normal homeostasis [121,122]. Mitochondrial dysfunction in neurodegenerative diseases have been linked to impaired glucose metabolism and oxidative stress. While mitochondrial dysfunction in PD is thought to mediate the increased generation of ROS and subsequent oxidative damage, another major consequence is energy failure linked to the inability of neurons to compensate their lack of capacity to generate ATP. Dopaminergic neurons in the substantia nigra are particularly susceptible to energy failure since they consume a significant amount of energy to maintain a basal dopamine tone in the striatum. This level of activity and energy consumption also leads to increased levels of basal oxidative stress. In addition, the numbers of striatal synapses established are expected to exert a high energy demand on the maintenance of plasma membrane potential (ionic gradients), protein/organelle (mitochondria) traffic and homeostasis [123]. Proteins involved in mitochondrial quality control, Pink1 and Parkin, are also mutated in familial forms of PD. The reduction of mitophagy efficiency by Parkin mutations causes an accumulation of dysfunctional mitochondrial and mitochondrial network fragmentation, which contributes to the progression of the disease [124]. In AD, increased accumulation of Aß peptides and neurofibrillary tangles mediate mitochondrial dysfunction [125]. Amyloid precursor protein (APP) is required for the clearance and Aß peptides and is primarily localized in the mitochondria. Evidence suggests that transmembrane arrest of APP promotes mitochondrial dysfunction by preventing Aß peptide clearance [126].

Post-mortem brain analysis of AD patients has also revealed decreased mitochondrial enzymes- pyruvate dehydrogenase, aconitase and cytochrome c oxidase in degenerative neurons thereby aiding the progression of the disease [127,128]. Age dependent increase of mTOR signaling molecule further attenuates mitochondrial dysfunction that may contribute to

neurodegeneration and cognitive decline in the elderly population [129]. The alterations in mitochondrial dynamics subsequently lead to mitochondrial dysfunction that aid and abet neurodegenerative diseases (FIG. 2).

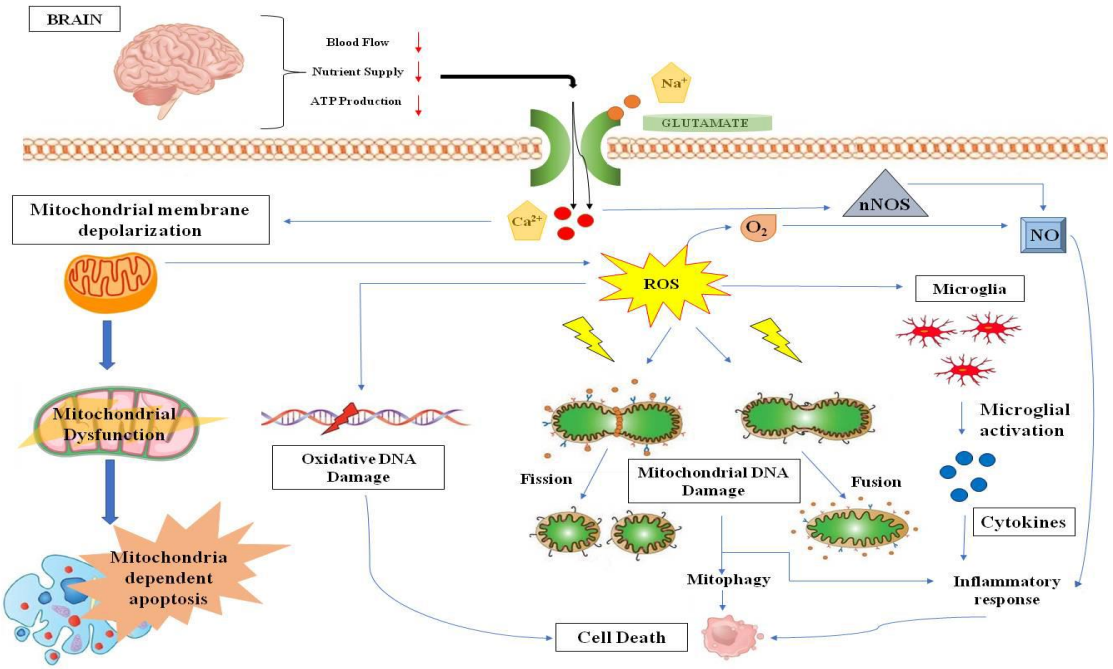

FIG. 2. **Blood flow and nutrient supply to the brain are crucial aspects in maintain homeostasis. Fluctuations in these conditions can lead to disastrous outcomes, primarily fuelled by mitochondrial dysfunction. Altered nutrient supply leads to mitochondrial membrane depolarization and production of nitric oxide species. The leads to a cascade of events such as production of reactive oxygen species, damaged mitochondrial machinery, microglial activation and production of pro-inflammatory cytokines all of which subsequently leads to mitochondrial dysfunction and mitochondria dependent apoptosis of the cell.**

5. Conclusion

Neurodegenerative diseases are characterized by progressive loss of structure and function of neurons. These diseases share the attributes of aging on multiple levels, including the motor and cognitive decline in addition to impaired molecular signaling. Another remarkable resemblance between these diseases is the display of metabolic dysfunction. This is explained by the neuronal damage due to the protein aggregation in the hypothalamus, which is the chief regulator of energy metabolism. Additionally, energy changes resulting from the disrupted connection between the peripheral organs that manage energy regulation and the CNS through alterations in leptin, ghrelin, insulin and glucagon signaling is also reported to contribute to the metabolic dysfunction occurring in neurodegenerative diseases. Further, mitochondrial dysfunction associated with neurodegenerative diseases also contributes to energy imbalance which leads dysregulation in the overall homeostasis. The established participation of these energy regulating mechanisms in neurodegeneration, has initiated the idea of using these as therapeutic targets in manipulating the metabolic factors to treat neurodegenerative disorders. An integrative approach to restore the metabolic energy balance and function may help in saving the vulnerable neuronal regions from advancing into in the path of neurodegeneration. Further research is needed to look into the combinatorial effects of metabolic hormones and neuronal signaling molecules to discover the potential of the metabolic factors in the treatment of various neurodegenerative diseases.

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