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Mitochondrial Dysfunction: A Key Player in the Pathogenesis of Neurodegeneration Associated Neuropathic Pain Syndrome

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ABSTRACT

Neuropathic pain is one of the major neurodegenerative disorders. Neurodegeneration is caused by various etiological factors as age, diet, trauma and metabolic abnormalities of the nervous system. A hallmark of neurodegeneration is because of abnormal folding and accumulation of neurotoxic proteins in the nervous system. Moreover, protein changes led to neuronal cell death and failure of affected central and peripheral nervous system. The combined neurodegenerative process is caused by stimulation of various primary events as formation of free radicals, cytosolic calcium ions accumulation, loss of adenosine triphosphate (ATP) generation, and alteration of glucose metabolism. All these processes are closely related with mitochondria. Mitochondrial dysfunction produces neurodegeneration associated neurological disorders including neuropathic pain. Nervous system is a more vulnerable tissue because of high yields of glucose and energy using properties.

Mitochondrial mediators such as abnormal glucose metabolic products, ATP depletion and generation of free radicals enhance the opening of mitochondrial permeability transition pore (MPTP), calcium overload, and expression of apoptotic proteins led to mitochondrial dysfunction. Mitochondrial dysfunction has been documented in various neuropathic pain models, i.e., surgical

(chronic constriction injury of sciatic nerve and transaction & ligation of lumbar 4 and 5 nerve) and neurotoxic chemicals (2'3'-dideoxycytidine, didanosine, paclitaxal, oxaliplatin and vincristine). This review summarized the possible functional regulators for mitochondrial dysfunction. Also, it supports the evidence for the mitochondrial targeted medicines in ameliorating neurodegeneration and neuropathic pain.

Keywords: Mitochonrial dysfunction; Mitochonrial permeability transition pore; Calcium; Free radicals; Neuropathic pain; Neurodegeneration; Adenosine triphosphate; Deoxyribonucleic acid

INTRODUCTION

Neurodegeneration is one of the serious complications of human life. Various neurodegenerative disorders alter the functional and behavioural pattern that affects the quality of life [1-2]. Such neurodegenerative disorders are Alzheimer's disease (AD), Parkinson disease (PD), stroke, and amylotrophic lateral sclerosis (ALS) [3]. Recently, various reports revealed that mitochondrial dysfunction contributes in neurodegenerative disorders especially in neuropathic pain syndrome [4-5]. According to International Association for the Study of Pain (IASP) neuropathic pain is defined as "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system" [6]. Some research reports has been documented that various neurotoxic chemicals (it may be used as drugs for other disease) cause neurodegeneration associated with neuropathic pain in experimental animal and in human [7-8]. Various molecular mechanisms have been proposed and conformed in the pathogenesis of neurodegenerative pain disorders as generation of free radicals, pro-inflammatory mediators, activation of complement cascades, and formation of pro-apoptotic proteins [9-10]. All these and some other factors are closely linked with mitochondrial dysfunctions that cause neurodegeneration associated neuropathic pain [11-12]. Mitochondria is known as "powerhouse of the cell" because of the ability to generate adenosine triphosphate (ATP) and this term was coined by Philip Siekevitz in 1957 [13]. It is composed of various compartments as outer membrane, intermembrane space, inner membrane, cristae, and matrix. Each compartment has specialized function for various mitochondrial and cellular actions [14]. The five major mitochondrial functions that are essential for the homeostasis of cell are i) ATP generation; ii) few free radical generation; iii) maintainance of inactivate (i.e., closed) state of mitochondrial permeability transition pore (MPTP); iv) regulation of programmed cell death (i.e., apoptosis); and v) control intracellular calcium ions (Ca^{2+}) mobilization that produces healthy neuronal function and prevent neurodegeneration [15-16].

The primary function of mitochondria is to generate ATP by oxidizing major products of glucose, pyruvate and NADH through oxidative phosphorylation process [17-18]. This process is dependent on oxygen known as cellular or aerobic respiration of cell. When oxygen demand occurs, these glycolytic products will be switch over for the anaerobic metabolism and it is

independent of the mitochondria [18-19]. Furthermore, mitochondria also has other functions such as reactive oxygen species generation, regulation of membrane potential, calcium signal, apoptosis, cellular metabolism, heme synthesis reactions, steroid synthesis, hormonal signaling, and heat production processes [20-21]. Neuron needs functionally active mitochondria because of high metabolic activity and lack of efficient glucose backup system [22]. When there is mitochondrial dynfunction occurs in neurons, it faces severe problems in the body [23].

MOLECULAR MECHANISM OF MITOCHONDRIAL DYSFUNCTION

Neurodegeneration is the most common and serious problem of the nervous system. Mitochondria contributes to this process because of good relationship with energy production [24]. The nervous system uses several ATP because of its high rate of energy demand and metabolic activity. Mitochondrial dysfunction occurs by following manner i) generation of abundant free radicals, i.e., reactive oxygen species (ROS) and reactive nitrogen species (RNS); ii) mutation of mitochondrial deoxyribonucleic acid (mtDNA); iii) calcium ion dyshomeostasis; iv) abnormal import and tethering actions of mitochondrial proteins and lipids; v) protein misfolding associated mitochondrial damage; and vi) functional abnormalities of electron transport chain (ETC) complex [11,25-26]. Mitochondrial dysfunction also contributes in the pathogenesis of neurodegenerative disorders such as neuropathic pain [27]. This section focuses on the possible ways of mitochondrial dysfunction in the neurodegenerative process.

Role of Free Radicals in Mitochondrial Dysfunction

The small amount of free radicals is essential for the neuronal function because of stimulation of the nervous system and it carries neuronal impulse via synapse. Many free radicals like ROS and RNS are products from the mitochondria [11,28]. Usually normal amount of ROS is not harmful in the nervous system. It is involved in various cell signaling processes in the nerve tissue [29]. In contrast, neurodegeneration is caused by excessive mitochondrial free radical generation [30]. Also, ROS causes damage of mitochondria by decreasing mitochondrial enzymes like pyruvate dehydrogenase and cytochrome oxidase. These enzymes are responsible for ATP production by metabolism of glucose via Krebs cycle and ETC in mitochondria [18]. Absence of these enzymes causes mitochondrial dysfunction. ROS not only causes mitochondrial damage but also initiates apoptosis [18]. In pathological conditions, mitochondrial dysfunction is important steps involved in the process of apoptosis via opening of MPTP on the inner membrane of mitochondria that release cytochrome C protein [31-32]. Nitric oxide (NO) has protective role in the vascular system due its potential vasorelaxing property. The life span of NO is short in the nervous system and it serves as a gaseous neurotransmitter. Despite, it reacts with superoxide anion to form peroxynitrite ($ONOO^{\cdot}$-) and it causes potential lipid peroxidation of mitochondrial membrane and nitrosylation of various cellular proteins as nitrothyrosine, cysteine, c heme and cytochrome C that cause neurodegeneration [33-35]. Both RNS and ROS induce misfolded proteins' formation and accumulation in the nervous system that cause neurodegeneration. Accumulation of

misfolded proteins is because of two cellular signaling processes, i.e., i) destroying of chaperone process; and ii) alteration of proteasomal process [36-37]. Also, rise in the level of mitochondrial mediated ROS production and then it decreases production of antioxidant enzymes as superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione reductase (GR) and catalase in the nervous system with neurodegeneration [38]. These free radicals form macromolecules of cell membranes and damage nervous system through inducing lipid peroxidation [39-40]. In some case, free radicals directly act on mtDNA and enhance oxidization and mutations of mtDNA [41-42]. Further, it activates the glial cell mediated neuroinflammation through release of ROS and inflammatory mediators [12,43]. Activated glial cells of brain, i.e., astrocytes and cells in peripheral nerve, i.e., Schwann cells produce neurodegeneration [44-45]. Except free radical generation, mitochondrial calcium overload cause over activation of the glial cells that alter glutamate handling that cause abnormal neuronal excitatory processes and neurodegeneration [9,46].

Role of Mutated mtDNA in Mitochondrial Dysfunction

Mitochondria contain own DNA and it helps to form ATP [47]. In neurodegenerative conditions, the mutated mtDNA has been identified in cerbro spinal fluid (CSF) in circulation of aged person [48]. ROS produce damage of mitochondria through mutation of mtDNA that cause loss of ATP. This mitochondrial vicious cycle cannot be stopped once started, hence cause neurodegeneration [42]. This mutated mtDNA mediated lack of ATP generation and it also affects the normal cell-to-cell communication through release of deformed proteins [49-50]. It suggests that, mutation of mtDNA is one of the key factors in mitochondrial dysfunction that begin and produce neurodegeneration.

Role of Calcium in Mitochondrial Dysfunction

Mitochondria is one of the organelle in regulating cytosolic calcium concentration due to its calcium handling property [51]. Also, Ca^{2+} ions do not have direct effect on mitochondrial Krebs cycle and ETC process though mitochondrial Ca^{2+} overload enhance the release of mitochondrial ROS [52]. This is enough to alter mitochondrial function because of its more potential free radical actions. Also, Ca^{2+} stimulates metabolic rate, nitric oxide production, cytochrome C dissociation, cardiolipin peroxidation, opening of MPTP, and Ca^{2+}-calmodulin dependent protein kinases activation [53-54]. This fluctuation of cytosolic calcium can create sensitivity of apoptotic stimuli that express apoptotic proteins, i.e., Bax and Bcl [55]. Excessive accumulation of neuronal cytosolic calcium concentration enhances neuronal excitation and neuronal death [56]. Mitochondria control intracellular calcium concentration through mitochondrial calcium buffering action, activation of calcium pumps, calcium exchangers, and transporter actions. Altering these functions has been reported to produce neurodegeneration through opening of MPTP [57-60].

Role of Mitochondrial Proteins and Lipids in Mitochondrial Dysfunction

Import of abnormal protein into the mitochondria produces mitochondrial dysfunction.

Protein degradation and protein aggregation of mitochondrial proteins is because of the action of mitochondrial proteasome [25,61]. Import of proteins is essential for mitochondrial functions in the cells. Protein permeability is because of specific signaling process in outer mitochondrial membrane through specialised translocate complexes [62]. This membrane also contains various enzymes, i.e., monoamine oxidase, rotenone insensitive NADH cytochrome C reductase, kynurenine hydroxylase, and fatty acid Co-A ligase for diverse activities such as elongation of fatty acids, oxidation of epinephrine, and degradation of tryptophan [63-64]. Disruption of the mitochondrial outer membrane permits proteins import that causes cell death [65].

Furthermore, inner membrane doesn't contain porins and it is not permeable to all molecules [66-67]. It has five different types of functions such as i) perform redox reactions for oxidative phosphorylation; ii) ATP synthesis through activation of ATP synthase enzyme; iii) regulate metabolite passage in and out of the matrix; iv) regulate protein import machinery; and v) regulate mitochondrial fusion and fission protein [68-70]. Almost all ions and molecules require special membrane transporters to enter or exit the matrix. Proteins are ferried into the matrix through translocation in the inner membrane (TIM) complex [71]. Also, matrix contains highly concentrated mixture of enzymes like specialized mitochondrial ribosomes, mitochondrial tRNA and several copies of mitochondrial DNA (mtDNA) genome for oxidation of pyruvate, fatty acids, and parts of Krebs cycle [72]. Its own genetic material has an ability to produce RNAs and proteins biosynthesis that play an important role in the cell survival and cell death process [73-74]. The expression and release of mitochondrial mediated neurotoxic proteins cause neurodegenerative disorders like amyloid precursor protein, amyloid beta (Aβ), tau (τ), and neurofibrillary tangles proteins for Alzheimer's disease; α-synuclein and parkin proteins for Parkinson's disease; huntingtin proteins for Huntington's disease; and SOD1 proteins for ALS [75].

Mitochondrial inner membrane contains more than 151 different polypeptides known as phospholipid [76]. The outer membrane of mitochondria is closely linked with endoplasmic reticulum (ER) membrane known as mitochondria associated ER membrane (MAM). MAM is another structural element for regulating cellular physiology and homeostasis by transport of calcium and lipids [77]. MAM complex play a prominent role in regulating cellular lipid stores and signal transduction through enrichment of phospholipid exchange associated enzymes and calcium signaling process including apoptotic process [78-79]. MAM has enriched enzymes (phosphatidylserine synthase and phosphatidylserine decarboxylase) that supports biosynthesis of lipids and need for dynamic action (i.e., fission and fusion) of mitochondria [80-81]. In contrast, in the nervous system lipid transfer with standard vesicular mechanism is lipid flipping between opposed bilayers by MAM [82-83]. Altering lipid import can cause mitochondrial dysfunction associated neurodegeneration [84]. Furthermore, mitochondrial proteins have tethering action between mitochondria, ER, and other intra organelle membranes. It is required for lipid transfer at MAM and it also regulates lipid bilayer of intra organelle [85]. The mitofusins was first identified in mitochondria and it has fission and fusion events between the individual

mitochondria [86]. Various other mitochondrial proteins are also identified for this action and are also known as mitochondrial chaperone proteins [87]. These chaperone proteins restrict cellular activity through VDAC in mitochondria and ER membrane for Ca^{2+} fluxes; IP3R for efficient Ca^{2+} transmission in MAM [88]; stabilization of ER resident IP3R for communication of MAM during metabolic stress [89]; and elimination of accumulated polypeptides and molecular chaperone proteins to prevent aggregation of neurotoxic proteins [90]. Thus, it is reported that, calcium and mitochondrial associated endoplasmic reticulum tethering play a great role in the progression of neurodegenerative disorders as PD, AD and ALS [91]. Thus, tethering actions of mitochondria and ER change cellular and molecular functions cause neurodegeneration.

Role of Protein Misfolding in Mitochondrial Dysfunction

The protein misfolding is one of major key factor in the progression of neurodegenerative diseases [90,92]. The pathogenesis of many diseases is caused by mutation of genetic materials that cause abnormal expression of proteins and cause damage of cellular system. Moreover, DNA mutation induced expressed proteins misfold the own structure or induce structural changes of other proteins [41]. These misfolded proteins are able to cause various neurodegenerative disorders as alpha-synuclein induced Lewy bodies formation in Parkinson's disease and dementia; hyperphosphorylated tau protein induced neurofibrillary tangles formation in Alzheimer's disease; beta amyloid induced senile plaques formation in AD; parkin protein induced PD; and mitofusin 2 induced ALS [41,93]. The misfolded proteins mainly target to alter mitochondrial function that causes neurodegeneration. Recently, some molecular chaperones proteins such as heat shock proteins (Hsp) 70, Hsp90 and Hsp104 are identified to prevent neurodegeneration through inhibition of alpha-synuclein misfolding, oligomerization, and aggregation in animal models of Parkinson disease. Furthermore, Hsp104 is also able to resolve disordered protein aggregates and beta amyloid conformers [94-95]. Therefore, it may serve as a key target for amelioration of neurodegenerative disorders.

Role of ETC Complex in Mitochondrial Dysfunction

ETC is a major function of the mitochondria to generate ATP by oxidative phosphorylation of NADH, FADH, and succinate molecules [96]. Various organisms generate ATP by ETC reactions, while few organisms generate ATP by fermentation process [97-98]. The transfer of electrons generates energy. In this condition, ETC pump the protons from the matrix to inter mitochondrial membrane space that create mitochondrial membrane potential ($\Delta\Psi$) by electrochemical movement of protons across the inner mitochondrial membrane [69,99]. Then, it allows the activation of ATP synthase enzymes for the flow of H+ through matrix and generates ATP by using ADP and inorganic phosphate. This process occurs by four membrane bound complex reactions in mitochondria: Complex-I reaction accepts the electron from the Krebs cycle and complex-II with electron carrier factors, i.e., nicotinamide adenine dinucleotide (NADH) and coenzyme Q. Coenzyme Q is also known as ubiquinone (UQ), it passes electrons into complex-II

by succinate dehydrogenase enzymatic actions. Further, UQ also passes electrons to complex-III, i.e., cytochrome bc1 complex and it passes electrons to cytochrome C. This cytochrome passes electron to Complex-IV, i.e., cytochrome C oxidase. These complexes are embedded in the inner mitochondrial membrane [20,69]. The structures of these complexes are electrically connected by lipid (UQ, fatty acids, and glycerol 3-phosphate) and water soluble electron carrier (ubiquinol and cytochrome C) proteins [100]. Lack of mitochondrial functions by hypoxia, depletion of nutrient, release excitatory neurotransmitters enhance neurodegeneration through decreasing the capacity of mitochondrial ETC reactions and ATP generations [101-102]. The failure of mitochondrial ETC has been documented in the AD patient and rodent models of Alzheimer's disease. Also, alteration in ETC functions has also been identified in various neurodegenerative disorders as PD, ALS and Stroke [31,103]. Some reports suggested that, the inhibitors of mitochondrial ETC complexes attenuates dideoxycytidine, vincristine and streptozotocin induced neuropathic pain in rat [104-105].

RELATIONSHIP OF MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATION

Mitochondrial ROS, RNS and calcium changes cause fall in ATP production via alteration of ETC functions, MPTP opening and mitochondrial membrane potential. Furthermore, these factors also induce mutation of mtDNA followed by expression of proapoptotic proteins and caspase proteins. Also, misfolding of some neuronal proteins also affect mitochondrial functions by direct or indirect actions [37,106-107]. Combination of all these factors cause mitochondrial dysfunction via modifying anti-oxidative enzyme; chaperone, proteasomal, autophagy, and lysosomal processes that cause neurodegeneration [75,108-109]. Figure 1 shows the overview of mitochondrial dysfunction associated neurodegeneration.

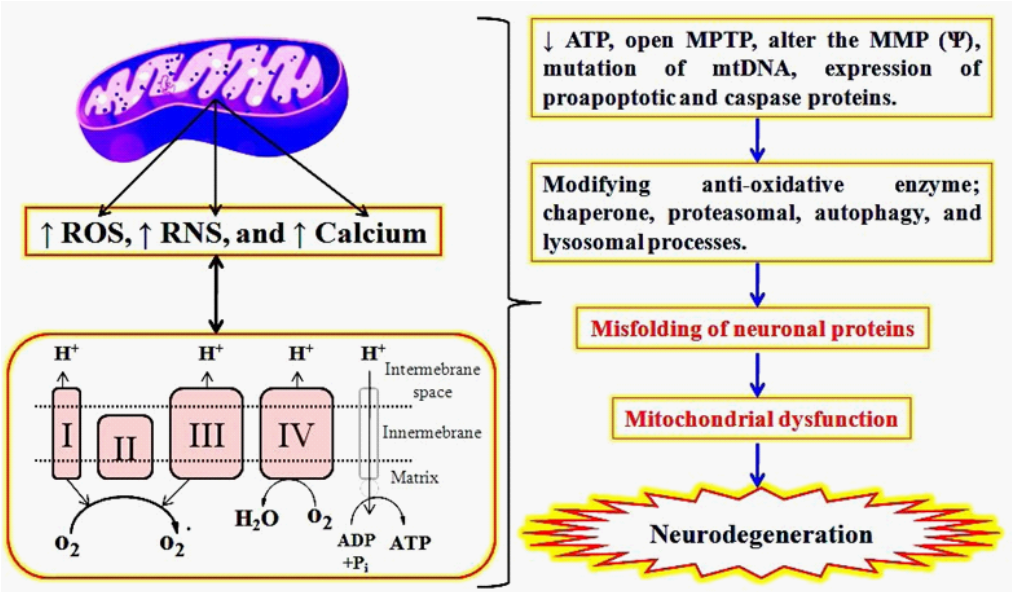

Figure 1: Overview of mitochondrial dysfunction associated neurodegeneration. The functional alteration of mitochondrial function leads to elevate the ROS, RNS and calcium levels which further alter the ATP production via functional defects of ETC actions. These processes are related with the opening of MPTP, mitochondrial membrane potential and mutation of mtDNA leads to induce the expression of proapoptotic and caspase proteins. Subsequently it also alters the actions of anti-oxidative defense enzyme; chaperone, proteasomal, autophagy and lysosomal function leads to modify the neuronal proteins (misfold). The combined all these process induces the mitochondrial dysfunction associated neurodegeneration.

ROLE OF MITOCHONDRIAL DYSFUNCTION IN NEUROPATHIC PAIN DISORDERS

So far we have discussed the role of mitochondrial dysfunction in neurodegeneration. Despite, the contribution of mitochondria in the progression of neuropathic pain remains to be elusive through complexity of neurodegenerative processes. The abnormalities of mitochondrial structure and function have been documented to produce nerve trauma and chemotherapy induced neuropathic pain in rodents [110]. Except mitochondrial dysfunction and mitochondrial dynamics also have a great role in the pathogenesis of neuropathic pain disorders [111]. Two kinds of mitochondria are observed in the nervous system in the pathogenesis of neurodegeneration, i.e., cluster and granule type of mitochondria. Granule type mitochondria protect the nervous system but cluster type mitochondria cause neuronal dysfunction. In the spinal nerve injury (SNI) neuropathic pain is induced by raising cluster type mitochondria and decrease granule type mitochondria in deep dorsal horn (laminas IIIV) neuron in mice [111]. The axotomy of peripheral nerve injury also cause alteration of cytosolic calcium ion concentration and their cell signal processes [58,112-113]. Accumulation of cell calcium has been documented to produce neurodegeneration

associated neuropathic pain in various experimental models [113-115]. Also, the axotomy of fifth lumbar (L5) nerve dorsal root ganglion and adjacent L4 neuron induce depletion of stored Ca^{2+} ions by enhancing sarco-endoplasmic reticulum Ca-ATPase activity [116]. The treatment of anti neuralgesic agent in DRG by way of intraneuronal injection modulates plasma membrane Ca^{2+} ATPase (PMCA) function in sensory neurons and produce potential relief of chronic neuropathic pain [117]. Recently, depolarization of normal peripheral nerve cause transient neuronal cytosolic Ca^{2+} concentration through blockade of mitochondrial Ca^{2+} buffering action. Though, the axotomy of lumar-5 (L5) spinal nerve cause lack of mitochondrial Ca^{2+} buffering action in L5 neuron [118]. Ligation and transection of spinal nerve (SNL & SNT) induce decrease in resting cytosolic Ca^{2+} ion concentration in sensory neuron. It occurs in large and capsaicin-insensitive axotomized neuron that is responsible to transmit non-nociceptive sensory information. Axotomy of L5 dorsal root ganglia produce degeneration of L5 and sciatic nerve neuron [116]. The platinum based cancer chemotherapeutic agent potentially causes mitochondrial damage and neurodegeneration. The treatment of caspase inhibitors ameliorates cisplatin induced neuropathic pain but treatment of mitochondrial ETC inhibitors and anti-oxidants attenuate oxaliplatin induced neuropathic pain [119]. Taxol has direct effect on mitochondria and it enhances mitochondrial dysfunction through mitochondrial ROS formation, opening of MPTP, altering mitochondrial membrane potential, and inducing cytochrome C release [120-121]. Administring acetyl-L-carnitine (a potential mitochondrial protective agent) ameliorates paclitaxel induced neuropathic pain syndrome [23]. The treatment of all five mitochondrial ETC complex inhibitors attenuate vincristine induced neuropathic pain in rat [119]. The treatment of streptozotocin causes changes of ETC function and ATP levels of mitochondria that cause ATP dependent neuropathic pain. The inhibitors of ETC complexes attenuate streptozotocin induced diabetic neuropathic pain in rat [119,122]. Administration of nucleoside reverse transcriptase inhibitors (NRTIs; i.e., 2'3'-dideoxycytidine, didanosine) induce mtDNA depletion and decrease ATP production in peripheral nerve that cause mitochondrial dysfunction associated neuropathic pain in HIV patients [123-124]. The inhibitors of mitochondrial ETC complexes attenuate 2', 3'-dideoxycytidine and tumor necrosis factor alpha (TNF-α) induced neuropathic pain in rat [119]. Many reports suggested that, mytochondrial dysfunction contributes in the central and peripheral neurodegeneration despite few research reports have evidenced mitochondrial dysfunction associated neuropathic pain in human and in rodents. Neuropathic pain is also one of the neurodegenerative disorders; therefore more focus is for mitochondrial targeted medicine in the management of neuropathic pain disorder.

TREATMENT OPTION FOR MITOCHONDRIAL DYSFUNCTIONS

Mitochondrial dysfunction can be abolished by many approaches, i.e., i) regulation of mitochondrial biogenesis through life style modification (exercise and diet), metabolic therapeutics (vitamins), pharmacological intervention (insulin sensitizers, angiotensin receptor blockers and angiotensin converting enzyme inhibitors, resveratrol, etomoxir) [125-126]; ii) controlling ROS production and oxidative damage through mitochondrial targeted anti-oxidants

like alkyltriphenylphosphonium cation, mitoQ and mitoVit E, tyrosine containing peptides and tempol [127]; iii) Gene therapy through gene transduction of nuclear DNA encoded with mitochondrial genes by three different approaches: a) import of normal mtDNA polypeptide genes to complement mutated mtDNA gene; b) reduction in proportion of mutant mtDNAs through heteroplasmy shifting; and c) direct modification of mtDNA [128]; iv) stem cell therapy (allogenic stem cells for producing thymidine phosphorylase enzyme); and v) organ transplantation [129]; vi) agent for modulation of MPTP i.e., cyclosporin A and nortriptyline [130-131]; vi) modulating mitochondrial Ca^{2+} overload [91,132]; and v) modulation of mitochondrial turnover by autophagy and mitophagy [133-134]. The summary of mitochondrial functional regulators is presented in table 1. Mitochondrial targeted drugs ameliorate mitochondrial dysfunction along with neurodegeneration and neuropathic pain. Such agents are summarized in table 2 and table 3.

Table 1: Summary of mitochondrial functional regulators for prevention of mitochondrial dysfunction associated neurodegenerative disorders.

	Class	Compounds	Mechanism	Neurodegenerative Disorder	References
Regulation of mitochondrial biogenesis	Direct Antioxidant	Aryl amines, carotene, lycopene, retinol, selenium, ebselen, flavonoids, stilbenes, hydroquinone, tocopherols, 17-estradiol, 5-hydroxytryptamine.	Non-enzymatic scavenging of ROS. Enzymatic recycling of free radicals with oxidoreductases.	AD	[30,127,35-136]
	Indirect antioxidant	Ion chelators; agonists of dopamine receptor; antagonists of calcium and glutamate receptor; inhibitors of amino acid oxidase and nitric oxide synthase enzyme.	Regulates metal homeostasis. Inhibits ROS and other free radical generation.Prevent the neuronal excitation.	PD and Dementia	[30,127,37-138]
	Metabolic antioxidant	N-acetyl-cysteine, L-arginine, vitamin C, glutathione, N-butyl--phenylnitrone, Carnitine, creatine, α-lipoic acid, ubiquinone, idebenone, triacetyluridine, dichloroacetate, and ketogenic diet.	Prevents the free radicals formation. Reduce the secondary metabolic burden in cell organelle. Improves the mitochondrial function.	Neurodenerative Diorders	[30,127,39-140]
	Metabolic substrates	Pyruvate, lactate, β-hydroxybutyrate, α-ketobutyrate, creatine, Ascorbate, glutathione, glutathione ethyl ester.	Prevents the mitochondrial dysfunction. Prevents the oxidative stress and motor neuron degeneration.	AD and PD	[141]
	Metal containing antioxidant	Manganese dependent catalase /superoxide dismutase	Prevents the protein-metal interaction.	AD and PD	[127,142]
	Controlled or regulated exercise and diet	Regular physical activity and supply of healthy natural foods fruits vegetables etc.	Improves the glucose tolerance, insulin sensitivity and calorie restriction; Stimulation of mitochondrial biogenesis.	Neurodenerative Muscle Diorders	[125-126,143]

Pharmacological approach	Insulin sensitizer	Pioglitazone, metformin, AR blockers, ACE inhibitors, resveratrol, and etomoxir.	Regulates the PPARγ activity. Mitigates the ROS generation Improves the mitochondrial biogenesis. Activates AMPK mediated mitochondrial proliferation. Inhibits the carnitine palmitoyltransferase 1 and promotes the mitochondrial β-oxidation process.	Diabetic neurodegenerative disorders	[144-146]
	Modulating Ca^{2+} toxicity	Neurotrophic factor like BDNF.	Inhibits MPTP opening.	Neurodegenerative disorders	[91,132, 147-148]
	MPTP modulators	Cyclosporin A and nortriptyline.	Inhibits MPTP opening.	ALS	[130,149]
	Mitochondrial turnover	PI_3K antagonists and Sirt-1 agonists.	Modulates the mitophagy Process.	Neurodegenerative disorders	[76,127]
	Gene therapy	ATP8, PNA.	Import the normal mtDNA polypeptide genes. Induce the heteroplasmy shifting. Modify the mitochondrial DNA.	Neurodegenerative disorders	[128,136,150]
	Stem cell treatment	TYMP gene developing tissue related stem cell.	Eliminates the toxic metabolites i.e., thymidine and deoxyuridine in blood and tissue.	MNGIE	[151-152]

ROS-Reactive Oxygen Species; AD-Alzheimer's Disease; PD-Parkinson Disease; BDNF-Brain Derived Neurotrophic Factor; ATP8-Aldehyde Dehydrogenase Targeting Peptide-8; PNA-Proteins for Nucleic Acid; PI_3K-Phosphoinositide 3-Kinase; TYMP-Thymidine Phosphorylase Gene; mtDNA-Mitochondrial Deoxyribonucleic Acid; MPTP-Mitochondrial Permeability Transition pore; AMPK-AMP-Activated Protein Kinase; MNGIE-Mitochondrial Neurogastrointestinal Encephalomyopathy.

Table 2: Summary of mitochondrial functional regulators for prevention of mitochondrial dysfunction associated neurodegenerative disorders.

Sl. No.	Class	Medicines	References
1	Antioxidants	Triphenylphosphonium derivatives	[153-154]
		Melatonin	[155-156]
2	Calcium chelators; Calpain inhibitors	EDTA, calpastatin, Taurine, SNJ-1945, E64, BDA-410, MDL-28170 and PD 150606	[157-159]
3	Activator of UPP	Proteasome inhibitors	[157,160]
4	CyPD dependent regulator of MPTP	Tacrolimus	[161-162]
5	Calcium dependent regulator of MPTP	Cyclosporine A	[149]
6	Anti-histaminergic drugs	Promethazine	[163]
7	mTOTs	MSDC-0160	[164]
8	Inhibitor of cardiolipin peroxidation	Melatonin	[155,165]

CyPD-Cyclophilin D; EDTA-Ethylene Diamine Tetraacetic Acid; mTOTs-Mitochondrial Targeted Thiazolidinediones; UPP-Ubiquitin-Proteasomal Pathway.

Table 3: Summary of mitochondrial targeted medicines for neuropathic pain.

Sl. No.	Class	Medicines	Comments	References
1	Sigma-1 receptor (σ1R) antagonist	BD-1063	Prevents the paclitaxel induced mitochondrial swelling and vacuolation. Ameliorates the paclitaxel induced neuropathic pain.	[166]
2	Acetylator of mitochondrial carnitine	Acetyl-L-arnitine	Enhance the mitochondrial CoA function. Eliminate the oxidative products. Facilitate the biosynthesis of acetylcholine. Prevents the HIV therapy induced neurodegeneration. Ameliorates the paclitaxel induced neuropathic pain.	[23,167]
3	Complement cascades inhibitor	Cobra venom factor (CVF)	Enhance the mitochondrial autophagy. Prevent the mitochondrial swelling, damage of cell membrane and fragmentation of mitochondrial cristae. Ameliorates the CCI of sciatic nerve induced neuropathic pain.	[168]
4	Benzodiazepine receptor antagonist	PK11195	Regulates the itochondrial metabolic process. Attenuates the spinal nerve ligation induced neuropathic pain.	[169]

CVF-Cobra Venom Factor; σ1R-Sigma-1 Receptor; CCI-Chronic Constriction Injury; HIV-Human Immunodeficiency Virus.

FUTURE SCOPE

Based on various research reports, it is summarized that; mitochondrial dysfunction potentially contributes in the pathogenesis of neurodegenerative disorders including neuropathic pain. Various newer compounds are now in clinical trials and expected to produce mitochondrial mediated neuroprotection in the treatment of neurodegeneration. Thus, mitochondria targeted drugs may be useful in the neuropathic pain disorders. And, mitochondrial targeted medicines are under investigation for the treatment of neuropathic pain syndrome in various clinical laboratories. Despite, more extensive studies are still required to explore their potential action in neuropathic pain patients because it has too complex phenomenon and pathological processs involved in the nervous system.

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