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Review Article

Association between autophagy and rapid eye movement sleep loss-associated neurodegenerative and patho-physio-behavioral changes

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ABSTRACT

Rapid eye movement (REM) sleep is a unique physiological process at least expressed in mammals. Its disturbance affects many psycho-somato-physiological processes including cardio-vascular-respiratory systems, brain excitability, neurogenesis, synaptic pruning, and memory consolidation. While it is altered in most neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD) and REM sleep behavior disorder (RBD), the detailed mechanism of inducing such action is unknown. Independent studies have reported that by clearing unwanted, dysfunctional intracellular debris, wastes, etc., autophagy maintains cellular health, integrity, and homeostasis. Abnormality in autophagy causes neuronal dysfunction including death, leading to neurodegenerative disorders. It has also been reported that by modulating noradrenaline (NA) levels, REM sleep maintains neuronal integrity and housekeeping functions of the brain. Using PUBMED, we surveyed the literature and found isolated, independent studies showing that autophagy dysfunction is associated with acute and chronic neurodegenerative and patho-physio-behavioral changes, which are also associated with REM sleep loss. We collated these scattered findings, which strongly support our contention that elevated NA associated with REM sleep loss is likely to affect autophagy in neurons, disturbing neuronal integrity and homeostasis and leading to altered brain functions and associated disorders.

1. Introduction

Autophagy is an intracellular process by which cytoplasmic materials are delivered to the lysosome in animal cells, or to the vacuole in plant and yeast cells, for degradation [1,2]. The word “Autophagy” was coined by Christian De Duve in 1963 and is derived from two Greek words “auto” meaning self and “phagy” meaning eating. Thus, autophagy is the process of self-eating inside the cell wherein cytoplasmic materials are degraded to simpler forms with the help of the lysosome. It is the primary intracellular recycling system by which unwanted proteins and cell organelles are degraded to simpler elements which are subsequently used as new building blocks and fed into the synthetic process for cellular development and maintenance of homeostasis in eukaryotic cells.

Autophagy can be categorized into three major classes: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy (CMA) [2]. Macro-autophagy is the primary autophagic process characterized by the formation of intermediate double-membrane structures called autophagosomes. They are formed by the sequestration of a small portion of cytoplasmic material by an isolated membrane, termed a phagophore. Autophagosomes then combine with the lysosome, leading to clearance of the cytoplasmic materials contained within them. In micro-autophagy, a small portion of the cytoplasm is engulfed by the lysosome by inward invagination of the lysosomal membrane. The third type of autophagy, chaperone-mediated autophagy, unlike the other two is highly selective for the proteins to be degraded and does not require the formation of the autophagosome nor the lysosomal membrane invagination. For a protein to be degraded by CMA, it must contain a KFERQ-like pentapeptide sequence which is explicitly recognized by the chaperone protein heat shock cognate 70 (Hsc70) and co-chaperones. After being recognized, the target proteins go to the lysosomal membrane where with the help of the lysosome membrane-associated protein 2A (LAMP-2A), which acts as the receptor, the unfolded proteins are delivered into the lysosomal lumen for degradation [3]. Of the three types of autophagy processes, macro-autophagy is more vital as it recycles a majority of

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damaged cell organelles, protein aggregates, and cytoplasmic materials. In our subsequent discussion, we focus on macro-autophagy and for convenience refer to it simply as autophagy.

Rapid eye movement (REM) sleep has been reported to maintain neuronal integrity, health, and function, while its loss is associated with neuronal damage; however, the precise mechanism of action is currently unknown. As autophagy plays a significant role in the maintenance of cellular health, we hypothesized that REM sleep loss associated neuronal damage and associated disorders could be mediated by the modulation of neuronal autophagy. Although our PUBMED search (until December 2018) did not yield direct evidence, we found many isolated, independent studies indirectly supporting our contention. In our PUBMED search, we used these keywords or phrases (alphabetical list): "Ageing", "Autophagy", "Memory", "Microglia activation", "Mitochondrial dysfunction", "Neurodegeneration", "Noradrenaline", "REM sleep", "REM sleep deprivation", "REM sleep loss" in 21 different combinations of two or three words/phrases each. Although 15 combinations containing either "REM sleep", "REM sleep loss" or "Autophagy" as one of the search keywords yielded ~20 to >3500 hits (citations), six combinations containing both "REM sleep loss" and "Autophagy" together with or without any other term either did not yield any or only yielded up to four citations, which were of no significance. In this article, we have collated those scattered, isolated pieces of information, which support our contention and form the basis for future studies in this direction.

2. Autophagy: molecular machinery, mechanism, and regulation

Several proteins, originally discovered in yeast and termed autophagy-related proteins (Atgs), are involved in the formation of autophagosomes [4]. They are conserved in mammals [5], and most of them function by forming various protein complexes [6–9]. Several reports and reviews have discussed in detail the different Atg proteins, their mechanism of action and regulation and also described the key molecular events leading to the formation of the autophagosome [1,2,4,5,10–13]. To avoid repetition we have refrained from re-narrating the phenomena; however, for a clearer understanding of the autophagy machinery and processes, we have summarized the information to reconstruct the accepted autophagy pathway as shown in Fig. 1.

Unlike other cells, neurons possess specific structural and functional properties including length, branches, neurotransmitter vesicles, their transport and fusion, the release of neurotransmitter, and vesicular re-cycling. Therefore the molecular events involved in the formation of membrane, its elongation, fusion, pore formation, and re-cycling, assume more significance in neuron than other cell types. As membrane formation along with its recycling is a fundamental element of autophagy [14,15], its dysfunction is likely to affect neuronal structure and function more seriously than other cells in the body. To further address this issue, we describe in brief membrane formation and its recycling concerning autophagy.

2.1. Source of membrane for autophagosome formation

The exact origin, growth, and formation of the isolated, double-membrane autophagosome are debatable. Notwithstanding this, in general it is accepted that the process of autophagy starts with the formation of a phagophore or the isolation membrane, which engulfs cytoplasmic materials, grows and finally closes around the sequestered materials to form an autophagosome [12]. The site(s) where the docking events (which lead to the formation of the phagophore) take place has been termed the pre-autophagosomal structure (PAS) [16]. Initially, it was proposed that the phagophore is derived either by de novo assembly machinery or from an existing membrane source like endoplasmic reticulum (ER), Golgi complex or the mitochondria. Current research more strongly favors the ER as the major source of the phagophore membrane [4,16–18]. Apart from the ER, the Golgi and trans-Golgi network, mitochondria, plasma membrane, and endosomal compartments have also been shown to act as possible sources of phagophore membranes under certain conditions [4,12,19,20].

2.2. Autophagosome-lysosome fusion in neurons

Once autophagosomes are formed, they either fuse with lysosomes resulting in the formation of autolysosomes or combine with late endosomes to generate amphisomes, which finally fuse with lysosomes for clearance. A majority of the autophagosomes are formed near axon terminals, while most of the lysosomes are located in the soma [13]. Therefore for the autophagosome-lysosome fusion to take place in neurons, a retrograde transport of autophagosomes to the cell body is necessary. As microtubules are the key structure for retrograde transport within the neuron, directly or indirectly they are likely to contribute significantly to optimum autophagy. Indeed, disassembly of microtubules with vinblastine has been shown to cause accumulation of autophagosomes within neuronal terminals [21]. Apart from microtubules, actin filaments have been suggested to be involved in the transport of autophagosomes [22]. Once autophagosomes reach the vicinity of the lysosomes, their membranes get fused; however, the molecular machinery and mechanism of membrane fusion are not yet clear. Three distinct families of proteins (ie, RAB GTPases, membrane-tethering complexes, and SNARE proteins) which are also involved in general intracellular membrane trafficking events, have been shown to participate in the fusion process [10].

2.3. Autophagy in controlling cellular -survival, -growth, -regeneration, -multiplication and -optimum health

Autophagy engulfs cytoplasmic materials into the autophagosomes followed by their degradation in the lysosomes. At first sight, it may appear that the autophagic process randomly encloses the cytoplasmic materials and degrades them non-selectively into simpler forms. Recent studies have shown that autophagy can be selective where a specific cargo is directed to autophagosomes for degradation to maintain cellular homeostasis [23]. Living cells continuously undergo wear and tear (under normal as well as abnormal conditions) due to exposure to various internal as well as external factors including oxidative load, resulting in the generation of metabolic wastes. The intensity and duration of exposure of the cells to extra- and intra-cellular factors, including metabolites and by-products, determines the damage inflicted to the cells. The adequate quantity of exposure depends on the effective availability of the factor(s), which in turn depends on their production and destruction (biological half-life), which remain in a dynamic equilibrium. If the waste keeps accumulating, resulting in clogging of the intracellular space, the cells would find it challenging to transport organelles within the cells (eg, vesicles) as well as other cargos including those necessary for cellular growth, maintenance, repair, and energy balance. Thus, destruction and/or clearance of toxic wastes from within the cells are necessary for the survival as well as the health of the living cell, including neurons.

Formation of new cells (by cell division) is an alternate way by which damaged, or dying cells can be replenished to compensate and retain the overall structure and functioning of tissues and organism and maintain homeostasis. However, the formation of a new cell is undoubtedly more complicated than if the same cell could neutralize the waste and continue to function. Unlike other cells, neurons have many projections of varying dimensions (length, diameter, volume,

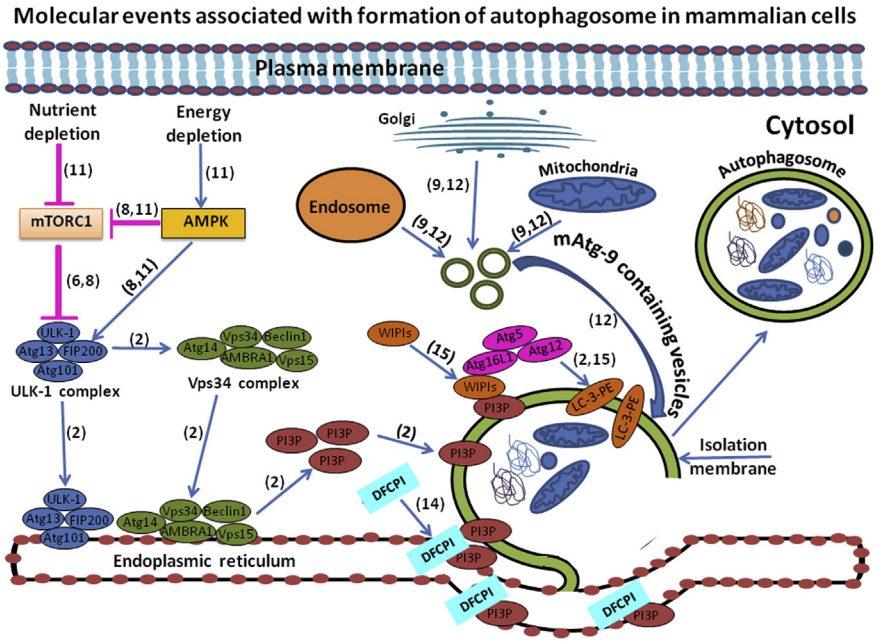

Fig. 1. Molecular events involved in the formation of autophagosome in mammalian cells. Nutrient deprivation and/or low cellular energy levels are sensed by mTORC1 and AMPK, respectively resulting in inhibition of mTORC1 and activation of ULK-1 complex. Once activated, ULK-1 complex further activates Vps34 complex that translocates into ER and produces PI3P making ER enriched with it. Isolation membrane originates from the PI3P enriched ER. Subsequently, WIPIs get translocated into the isolation membrane by binding with PI3P and recruit Atg12–Atg5–Atg16L1 complex, which facilitates elongation of the isolation membrane by recruitment of LC3-II. Finally, mATG9 containing vesicles, which originated from the endosome, mitochondria and Golgi complex, further help in elongation of isolation membrane and formation of the mature autophagosome. The reference numbers have been cited in parentheses. Abbreviations: mTORC1 (mammalian target of rapamycin complex-1); AMPK (AMP-dependent protein kinase); ULK-1 [(mammalian homolog of the C. elegans uncoordinated-51 kinase)]; PI3P (phosphatidylinositol 3-phosphate), WIPI (tryptophan–aspartic acid (WD) repeat domain phosphoinositide-interacting protein); Atg (Autophagy related proteins); LC3 (microtubule-associated protein one light chain three); ER (endoplasmic reticulum).

etc.) and they are terminally differentiated (ie, non-dividing); they are likely to be more vulnerable to the accumulation of waste substances and therefore elimination of the waste becomes more significant for neurons. In cells, autophagy is the primary intracellular recycling and degradation system; it plays a significant role in the removal of the waste including metabolic by-products as well as cellular debris, facilitating the repair process and maintaining homeostasis [2]. In conclusion, autophagy is likely to play the single most crucial role in maintaining neuronal health, integrity, functioning, and survival and in turn would be the primary process affecting the behavior of an individual. Next we discuss autophagy in relation to the maintenance of neuronal homeostasis.

2.4. Neuronal integrity, brain functioning and role of autophagy

Unlike most other cells in the body, neurons are unique in cytomorphology, shape, size, dimension, function, etc. They have several branches and through them contact other neurons at synapses to receive input or deliver output for communication and coordination. Most neurons do not divide; however, they possess a dynamic plasticity property, which allows them to snip or withdraw existing, or make new contacts (synapses), which are the basis of permanent memory. These contacts are responsible for new as well as learned coordinated activities including behavioral expressions controlled by the brain. Any factor which modulates neuronal plasticity including its growth, branching, breaking or making of neuronal connections would alter conditions and cause the expression of abnormal behaviors. Because neuronal actions depend on the release of neurotransmitters, any factor(s) which would affect the synthesis, transport, and release of neurotransmitters will affect neuronal functioning causing altered states. As per the previous isolated studies [13,24–26], all the factors modulating neuronal functions described here are affected by autophagy, which strongly indicates the role of autophagy in maintaining neuronal -growth, -development, -synaptogenesis, -structural and -functional integrity and in turn the functioning of the brain. We now discuss the molecular events involved in neurodegeneration and their association with autophagy.

2.5. Autophagy and neurodegeneration

Protein aggregation is a significant event associated with many neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD) [27]. Efficient clearance of unwanted proteins is necessary for the maintenance of structural and functional integrity of neurons. Neurons have vast expanses of dendritic- and axonal-cytoplasm, due to which it is more challenging for them to prevent the accumulation of protein aggregates over time [28]. Aggregated proteins result in synaptic impairment, increased oxidative load, and damage to intracellular organelles, leading to neurodegenerative conditions [27] due to neuronal dysfunction or death. Apart from protein aggregation, mitochondrial dysfunction is another factor contributing to apoptosis-mediated neuronal death and the development of neurodegenerative disorders [29]. Autophagy is the major intracellular pathway that assists in the clearance of protein aggregates and dysfunctional cell organelles including mitochondria, demonstrating its importance in the prevention of neurological disorders [2,30]. The role of autophagy in the clearance of damaged organelles, particularly mitochondria, is confirmed by published reports that mutations in PINK1 and Parkin (major proteins involved in the clearance of mitochondria by autophagy) have led to a defective clearance of the damaged mitochondria and caused a familial form of PD [31]. Further, genetic inactivation of essential autophagy genes (Atg5 or Atg7) in neurons results in the accumulation of protein aggregates, causing neurodegeneration [32,33]. Functional mutations of genes

involved in the lysosome-autophagy pathway were reported to result in neurodegeneration [34]. In addition, the autophagy pathway is altered in different stages of AD and PD, as shown by the accumulation of autophagosomes in the brains of patients suffering from these disorders [12].

Neurons require more energy than other cell types for the maintenance of electrochemical gradients across the cell membrane, conduction of nerve impulses, release and recycling of neurotransmitters; consequently the brain is metabolically more active than other organs in the body [35]. Previous reports have shown that apart from the clearance of waste materials, autophagy also contributes to maintaining energy metabolism and its balance in cells [36]. It has been shown that when cellular nutrient and energy levels are low, autophagy gets activated by mTOR and AMPK mediated pathways, respectively [11]. Once activated, autophagy degrades cytoplasmic waste materials, and produces amino acids that are re-used for cellular fueling and repair. Besides protein breakdown, autophagy also contributes to the mobilization of molecules from various cellular energy stores, including lipids and carbohydrates [36] and thus, helps to maintain energy homeostasis. We conclude that autophagy is instrumental in the maintenance of homeostasis in neurons by several mechanisms including clearance of misfolded-, aggregated-proteins, damaged organelles and by modulating energy metabolism, which helps to maintain normal neuronal health. The effects of dysfunctional autophagy could be more pronounced, particularly for long and branched neurons in the brain, an antioxidant compromised organ [37,38].

3. Rapid eye movement sleep (REM sleep)

Sleep and waking are instinctual behaviors; the former has been divided into non-REM sleep and REM sleep. Typically, REM sleep does not appear during waking and some amount of non-REM sleep precedes REM sleep; loss of non-REM sleep is usually associated with REM sleep loss as well, however significant loss of REM sleep with minimum loss of non-REM sleep is still possible. In the literature, we find experimental studies where the effects of either total sleep loss or loss of REM sleep alone has been reported [39]. Most often clinicians deal with patients after the latter have suffered sleep disturbances for a substantial time (ie, duration of sleep-loss) and associated symptoms and disorders are not in their initial state. Hence, very rarely does one encounter patients with disturbance of either REM sleep or non-REM sleep. REM sleep contributes significantly to the maintenance of neuronal homeostasis in the brain. Many of the sleep-loss-associated bio-molecular, patho-physiological, and behavioral changes have been found to recover upon undergoing compensatory recovery from the lost sleep and/or REM sleep as the case may be. It has been shown that a compensatory increase in REM sleep helps in the restoration of REM sleep-loss associated alteration in brain functions in the short and long run eg brain excitability [40], metabolism, energy balance and replenishment of biomolecules [41–44], neuronal regeneration, growth and repair [45–47], memory [48] and other altered behaviors [49]. Further, it has been shown that REM sleep-loss increases the level of noradrenaline (NA) in the brain [50–52] and many of the REM sleep-loss associated effects are induced by an elevated NA [40,53,54]. We now discuss the findings from earlier studies which led us to hypothesize that alteration in autophagy plays a crucial role in REM sleep-loss-associated cellular level changes in structure and function of the brain, leading to disorders.

3.1. REM sleep loss, aging and neurodegenerative diseases

Aging is a natural, time-dependent process experienced by living cells and organisms; senescence is often followed by death. In humans, aging is often associated with the progressive development of psycho-somato-neurobehavioral dysfunctions, including loss of concentration, muscular coordination, memory [55] and neurodegenerative disorders including AD and PD [56]. In humans, aging may be associated with disturbed non-REM and REM sleep [57]. In experimental animal models, REM sleep-loss has been shown to cause neurodegeneration [54,58–60], indicating a possible association between REM sleep-loss and the development of neurodegenerative disorders during aging. Reduced REM sleep has been reported in AD and PD patients [61], and an association between REM sleep-loss and AD as well as PD pathogenesis has been proposed [62–66]. Neurodegenerative disorders are often associated with memory and cognitive disturbances, which are characteristic features associated with REM sleep-loss [67–69]. Considering the aging-related association between REM sleep-loss and the development of neurodegenerative disorders (AD and PD), we find it attractive to propose and explore the existence of similar molecular events involved in the development of aging and REM sleep-loss associated neuro-patho-physio-behavioral changes.

Aggregation and/or defective clearance of β-amyloid and hyperphosphorylated tau are known factors involved in the pathogenesis of AD [65,67], while the defective clearance and accumulation of the α-synuclein protein aggregates is the major event involved in the development of PD [70]. A recent report showing increased aggregation of β-amyloid in the brain of subjects deprived of one night sleep further confirms the role of sleep loss in AD pathology [71]. As autophagy is the primary pathway for degradation and clearance of cellular debris and unwanted protein aggregates, it is likely to be modulated in AD and PD pathology. The expression of Beclin-1, which helps in the formation of autophagosomes, has been reported to be reduced in AD patients' brains [72]. Increased accumulation of autophagosomes in the brain of AD patients confirms a defect in the lysosome-mediated clearance of the autophagosomes in AD pathology [73]. Further, pharmacological activation of autophagy in animal models of AD has been reported to provide neuroprotection [74,75]. Lysosomal depletion and accumulation of autophagosomes are observed in post-mortem PD brain samples [76]. Other studies in animal models have suggested that pharmacological and genetic induction of autophagy reduces α-synuclein aggregation and prevents PD pathogenesis [77,78]. Functional mutations in the proteins involved in the autophagy pathway (including ATP13A2, PINK-1, Parkin) have been shown to result in the development of PD [79–81]. Thus, it may be proposed that autophagy plays an essential role in aging and REM sleep loss-associated neurodegenerative conditions. As a corollary, it may be proposed that REM sleep may modulate autophagy and maintain neuronal health in the brain. We discuss later that this effect may be induced by maintaining the level of NA in the brain.

3.2. REM sleep behavior disorder (RBD), synucleinopathies and autophagy

RBD is a neurological disorder characterized by excessive limb-motor activity and altered REM sleep [82]. Most RBD patients develop synucleinopathies (a class of neurodegenerative disorders, including PD, dementia with Lewy bodies, and multiple system atrophy) at various stages of life [82–86]. These associations suggest the possibility of similar molecular events involved in the pathophysiology of RBD and synucleinopathies.

The major events involved in the pathogenesis of synucleinopathies are aggregation and accumulation of α-synuclein proteins in neurons owing to poor clearance and resulting in neuronal death [87]. As autophagy is the primary cellular event involved in the clearance of aggregated, unwanted proteins [2], it is likely to be affected in this disease. Our contention may be supported by the

fact that over-expression of α-synuclein disrupts the trafficking of ATG9 and prevents the formation of autophagosomes [88]. Mutated α-synuclein (A53T and A30P) binds with the lysosomal membrane receptor LAMP2A more tightly than wild-type α-synuclein, which prevents its degradation and loading of other substrates into lysosomes by chaperone-mediated autophagy [89]. Accumulated α-synuclein aggregates also affect autophagosome transport within axons [90]. Moreover, the autophagy pathway is altered in the experimental models of synucleinopathies [91]. Defects, including mutation in the Glucocerebrosidase (GBA) gene that encodes for the lysosomal enzyme glucocerebrosidase, results in defective autophagy leading to the accumulation of α-synuclein aggregates [92]. GBA gene therapy has shown promising results in preventing synucleinopathies in animal models [93]. A recent study in RBD patients reported the presence of missense mutations in the GBA gene and those patients subsequently developed synucleinopathies; this supports the involvement of autophagy in RBD pathophysiology [94]. These findings suggest that RBD pathophysiology is associated with a dysfunction of autophagy and neurodegeneration; however, the sequences of events need to be studied.

3.3. REM sleep, memory, and autophagy

Memory formation (including the regulation of autonomic, voluntary and somatic functions) is an essential component of brain development; it involves two stages, encoding and consolidation. During encoding, perception of a stimulus results in activation and/or deactivation of a set of synapses (labile memory trace), which are highly susceptible to decay by many interfering factors. During consolidation, the labile memory trace is gradually stabilized and strengthened, resulting in the formation of long-term memory [95]. REM sleep plays a constructive role in memory formation [48,96,97], while REM sleep deprivation (REMSD) impairs [98–100] memory formation and its consolidation. Enhancement of REM sleep has been shown to improve memory retention [101]. Although these findings suggest that REM sleep is involved in memory formation and consolidation, the underlying cellular and molecular events involved in the process(es) remain to be deciphered.

Alteration in synaptic strength is a significant factor contributing to synaptic plasticity and memory formation. Autophagy has been shown to contribute to NMDA receptor-dependent synaptic -plasticity, -strength and -memory formation [102]. Recent independent studies have shown that the number of autophagosomes was increased in hippocampal neurons in rats following their training in a Morris water maze [103]. Stereotactic injection of an autophagy inhibitor, 3-methyladenine, in the hippocampus significantly impaired memory formation, while the intra-hippocampal infusion of an autophagy activator peptide (TAT-Beclin-1) improved long-term memory [103]. Autophagy also contributes towards brain-derived neurotrophic factor-mediated hippocampal synaptic plasticity and memory consolidation [104]. Recent independent studies have reported that while REM sleep-mediated selective pruning of synapses regulates memory consolidation [105], autophagy plays a pivotal role in selective pruning of the synapses [106]. Merging of these findings strongly suggests that autophagy is an essential molecular event involved in REM sleep-mediated memory formation, consolidation, and integration, which, however, needs to be confirmed with experimental evidence.

3.4. Selective pruning of synapses during development, REM sleep, and autophagy

Memory formation necessitates the establishment of a functional neuronal circuit in the brain, and to that end, the establishment of synapses is the single most crucial step, which serves as the hard-wired, structural correlate of memory. During this process, both new and old synapses are pruned sparing the remainder, which subsequently get matured and strengthened physically as well as functionally [107–109]. REM sleep plays a vital role in selective pruning and maintenance of new synapses [105]. Although it has been shown that REM sleep-dependent spine pruning and strengthening were mediated by NMDA receptor-dependent dendritic calcium spikes [105], the specific molecular events associated with this process remain unknown and need systematic investigation.

Pruning of synapses involves catabolic processes that need a specialized degradation mechanism. As autophagy is a major intracellular degradation process, it becomes the prime target likely to play a significant role in synaptic pruning. The role of neuronal and microglial autophagy in spine pruning has been proposed recently [106]. It has been shown that the size of the lysosome and its degradation capacity increase during synaptic pruning at the neuromuscular junction during early developmental stages. Increased protein levels of LC3-II along with increased spine density in the brain of patients who have autism spectrum disorders (ASD), indicates a strong correlation between impaired autophagy and deficient spine pruning. Conditional deletion of the Atg7 (a key protein involved in the autophagy process) has been shown to result in increased spine density and development of ASD like symptoms. Research showing that deficient autophagy in microglia impairs synaptic pruning during development and results in social and behavioral defects [110] and the loss of the mTOR-dependent autophagy pathway during early development which in turn results in deficits in synaptic pruning leading to ASD [111], also support our contention. Therefore, we propose that REM sleep regulates synaptic pruning during development by modulating autophagy; however, the precise mechanism and the molecular targets, as well as sequence of events necessary to mediate these actions, remain to be explored.

3.5. REM sleep, its disturbance, and neuronal integrity

One of the common instinctual behaviors, REM sleep plays a vital role in maintaining neuronal integrity, memory, and overall brain functions. It is affected in many disorders, including PD and AD; in fact, experimental REM sleep-disturbance has been reported to induce neuronal damage [54,58–60]. However, the detailed molecular mechanisms of REM sleep-disturbance-associated neuronal loss and related diseases are unknown. We now discuss how REM sleep disturbance can affect autophagy, which in turn would induce neurodegeneration and associated disorders.

3.6. REM sleep loss, NA, neurodegeneration, and autophagy

REM sleep plays a significant role in the maintenance of almost all brain functions, and its loss or disturbances lead to different neurodegenerative conditions (Fig. 2). Experimental REMSD has been reported to cause memory impairment and cytomorphological changes in the hippocampus of the rat brain [112,113]. Most RBD patients eventually develop neurodegenerative disorders including PD, AD, dementia with Lewy bodies, and multiple system atrophy [82,83,85]. In a series of experimental studies in animal models, it has been consistently shown that REMSD induces neuronal damage [58–60] by causing mitochondrial dysfunction through activation of the intrinsic apoptotic pathway [54]. As a mechanism of action, it has been shown that NA-ergic REM-OFF neurons cease activity during REM sleep, while they continue activity during REMSD [40,51]. This results in an elevated level of NA in the brain during REMSD [50], which by acting on alpha-

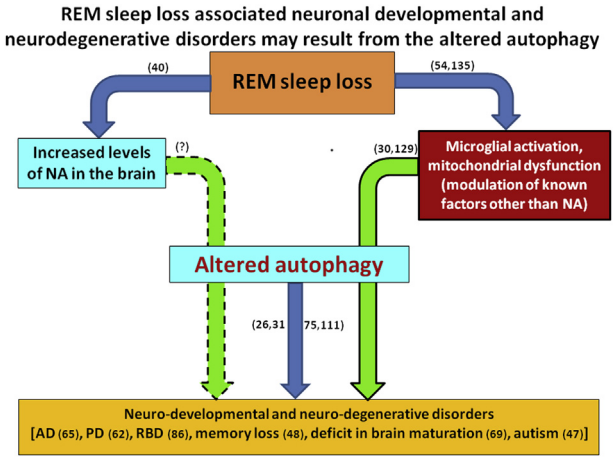

Fig. 2. REM sleep loss associated neuro-developmental and neurodegenerative disorders may result from altered autophagy REM sleep loss may cause or facilitate the development of neurodegenerative disorders by either or a combination of increased levels of NA, microglia activation, and mitochondrial dysfunction. Dysregulation of the autophagy pathway has been reported in neurodegenerative conditions, which has been reported upon REM sleep loss as well. Microglia activation and mitochondrial dysfunction are known events associated with altered autophagy as well as upon REM sleep loss. As NA level increases upon REM sleep loss, we propose that REM sleep loss associated increased NA would cause microglial activation and mitochondrial dysfunction and induce alterations in the autophagy pathway, which subsequently results in the neurodegenerative disorders associated with REM sleep loss (we are studying). The reference numbers have been cited in parentheses.

adrenoceptors causes REMSD-associated neurodegenerative changes in the brain [53,54,58–60,114].

Further, during REMSD an elevated NA causes decreased Ca2+-influx resulting in reduced intracellular Ca2+ [53,115–117]. Intracellular Ca2+ plays a crucial role in the activation of the autophagy pathway [118–121]. Previously, it has been shown that free cytosolic Ca2+ activates AMPK (a significant activator of the autophagy) via the Ca2+/calmodulin-dependent kinase kinase-β (CaMKKβ) dependent pathway, which subsequently activates autophagy by inhibiting mTORC1 through TSC1/TSC2 phosphorylation [118]. By consolidating the existing knowledge discussed above, we propose the likely possibility that REMSD-mediated elevated NA-induced decreased intracellular Ca2+ concentration, inhibits the autophagy pathway. This, in turn, causes an accumulation of dysfunctional and/or undesirable cell -organelles, -debris and -waste materials clogging the intracellular space and preventing the intracellular transport of molecules, resulting in neuronal death (Fig. 3). It is also possible, independently or simultaneously, that upon REMSD the elevated NA, by modulating intracellular Ca2+ level directly or indirectly, affects mitochondria and/or glia (the critical factors involved in neuronal survival or death) by modulating autophagy and facilitating neuronal damage. These proposals need to be confirmed.

3.7. REM sleep loss, NA, mitochondria, microglia, and autophagy: a possible mechanism of action

Mitochondria-generated ATPs are the major source of energy in cells, including the neurons in the brain. Apart from ATP formation, mitochondria also contribute to the generation of oxidative free radicals, regulation of Ca2+ dynamics, and the intrinsic apoptotic pathway [122]. Compared to other organs in the body, the brain consumes maximum energy and it is an antioxidant-compromised organ [37,38]. Therefore, for optimum homeostatic regulation and maintenance of a healthy body (cell or tissue for that matter), proper functional mitochondria along with the maintenance of an optimum energy balance are necessary. This becomes crucial for maintaining the health of neurons because they usually neither

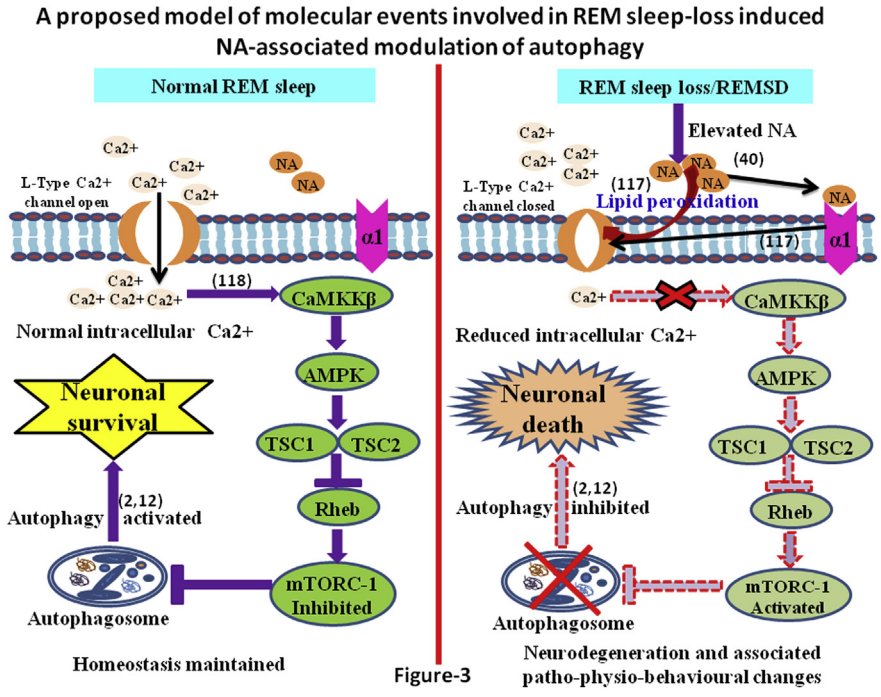

Fig. 3. A proposed model showing the molecular events associated with REM sleep loss-induced alterations in autophagy. Intracellular Ca2+ is one of the significant autophagy activators by modulating the AMPK-CaMKKβ dependent pathway. During REM sleep, normal/homeostatic levels of NA and intracellular Ca2+ are maintained in the cells resulting in neuronal homeostasis and survival (left panel). During REMSD the NA levels are increased in the brain, which by acting on α-1 adrenoceptor modulates plasma membrane lipid peroxidation and inhibits the L-type Ca2+ channels leading to reduced Ca2+ influx and reduced intracellular Ca2+. Decreased Ca2+ is likely to result in inhibition of autophagy, which subsequently would lead to reduced clearance of intracellular debris and waste molecules/products resulting in their accumulation, which would affect normal function and survival of neurons. The reference numbers have been cited in parentheses.

divide nor get replenished in the brain [35]. In support of this, it may be highlighted that mitochondrial dysfunction is a common event associated with an energy deficit, oxidative stress and cytochrome c-mediated induction of the intrinsic apoptotic pathway, leading to neuronal death and associated disorders [123–125]. REMSD-induced increased NA may alter basic neuronal functions, excitability, house-keeping functions [38] and energy metabolism [42], which, along with dysfunctional mitochondria, might facilitate neuronal death by activation of the intrinsic apoptotic pathway [54]. Therefore, efficient removal of damaged mitochondria, debris, and associated metabolic by-products (waste) through autophagy is likely to play an essential and decisive role for the maintenance of neuronal health, integrity, homeostasis, and functions.

Microglia are the resident macrophages in the central nervous system that play a vital role in maintaining neuronal health. Under normal conditions, they contribute to phagocytosis of damaged synaptic structures and actively help in the remodeling of the presynaptic environment. They also contribute to releasing soluble factors that help in maintaining the neuronal microenvironment [126]. Microglia get activated in most of the neurodegenerative conditions that subsequently result in neuronal inflammation-mediated apoptosis [127]. Activated microglia, characterized by enlarged cell bodies along with shortened and extensively branched processes and the increased expression of pro-inflammatory markers (COX-2 and CD11b), release several pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 and increase the generation of ROS, which are known factors contributing towards neurodegeneration [127].

Recent studies have shown alteration in microglial autophagy in neurodegenerative disorders [128,129]. Activation of autophagy in microglia downregulated the production of pro-inflammatory cytokines and protected neurons from lipopolysaccharide-as well as α-synuclein-mediated death [130], while inhibition of the microglial autophagy increased the production of ROS and pro-inflammatory cytokines leading to an inflammatory reaction [131]. Furthermore, in acute spinal cord injury, autophagosomes were found to accumulate in activated microglia in the dorsal white matter adjacent to the injury site [132]. Aβ protein aggregation and microglia activation are hallmark events associated with AD pathogenesis. Activation of the autophagy pathway in microglia has been shown to help the removal of Aβ protein aggregates in the brain, and this microglia-dependent clearance of the Aβ protein aggregates is mediated by autophagy [133]. Independent studies have shown that activation of microglia plays an essential role in REM sleep-loss-associated neurodegenerative changes [134–136]. Thus, because activation of microglial autophagy plays a pivotal role in limiting neurodegeneration thereby providing protection to neurons, we propose that REM sleep-loss-associated neuronal damage could also involve (at least partly) modulation of microglial autophagy. This may be supported by the fact that an elevated level of NA, as reported during REMSD [48], has been found to cause loss of glia (C6) as well as neurons [137]. Although the mechanism of action of cellular loss is unknown, the possibility of elevated NA inhibiting the autophagy of either glia or neurons or both is a prime suspect, and that needs to be investigated.

4. Summary

Wear and tear of cellular components, the effective clearance of unwanted debris along with the repair of damaged cells are automatic processes that play a significant role in maintaining normal cellular homeostasis and health, leading to cell survival and optimum functioning of the individual. This assumes an even greater significance for neurons, which are terminally differentiated cells, which possess long projections and branches, and which are metabolically highly active. In higher animals (including humans) REM sleep is an instinctual behavior, which plays a significant role in maintaining neuronal integrity; autophagy is the major intracellular recycling pathway involved in the maintenance of neuronal integrity and homeostasis. It has been shown that REM sleep, by maintaining NA levels, maintains neuronal integrity in the brain. Based on existing knowledge and subject to experimental confirmation we propose that REM sleep by modulating NA level in the brain, dose-dependently protects or damages the brain by modulating neuronal and glial autophagy.

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Conflict of interest

The authors declare no conflict of interest in this work.

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