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Chronic Unpredictable Mild Stress Induced Cognitive Impairment: AMPK/mTOR Autophagic Signaling

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ABSTRACT

Chronic stress is linked to a variety of neuropsychiatric ailments, many of which are characterized by cognitional alterations. Stress animal models showed equivalent behavioural alterations, including working memory and cognitive flexibility impairment. It's consistent with morphological alterations in the hippocampus and frontal cortex, all of which play important roles in controlling these behaviours. Growing evidence suggests that changes in autophagy could be contributing to the disorders observed in neuropsychiatric diseases. Chronic stress can affect autophagy signaling in the hippocampus and frontal cortex; besides, this is believed to be related to changes in neuronal morphology. Recently, animal models have explained the function of autophagy signaling in behavioural changes caused by stress. Together, the findings indicate that autophagy plays an essential role in mediating cognitive impairment seen in the presence of stress. Increasing our knowledge of the effects of stress on AMPK/mTOR autophagic signaling will eventually support the discovery of more effective medications for people suffering from cognitive impairment.

KEYWORDS: CUMS, Cognitive impairment, Autophagy, AMPK/mTOR.

1. INTRODUCTION

Because of the complexity of today's living environment and the wide variety of pressures we face on a daily basis, stress has become an unavoidable part of life. The chronic unpredictable mild stress (CUMS) method is a well-known animal model for studying the pathogenesis of cognitive deficits in rodents, which are linked to inflammatory initiation, altered synaptic plasticity, impaired neurogenesis, and autophagy dysfunction [1].

Alzheimer's disease (AD) is a neurodegenerative disorder that leads to cognitive decline [2]. As shown in Fig.1, chronic stress is emerging as a major risk factor for AD, as evidence suggests that it can promote the onset and development of AD-related pathologies [3]. Relevant studies have shown that environmental factors, particularly prolonged exposure to chronic stress, can induce the onset of AD-related pathology in wild-type mice and exacerbate it in AD transgenic models [4–6]. Moreover, plenty of clinical data show that stress is closely related to the onset of many age-related diseases, including cancer, diabetes, depression, Parkinson's disease, cardiovascular disease, atherosclerosis, and coronary heart disease, as well as AD [6–10]. Chronic stress can alter neuronal properties in the brain, impairing learning, memory, and cognitive processes, implying that this event may serve as a trigger for AD pathology. In a

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study, CUMS promoted the expression of Aβ40 and Aβ42, and induced neuronal injury and cognitive impairment in APP/PS1 mice [11]. Also, it was found that CUMS significantly increased Aβ levels in the hippocampus of adult male rats [12]. This goes in line with epidemiological studies on the association of specific personality traits related to stress, posttraumatic stress disorder, and stress-related conditions of anxiety with AD. So, it might be assumed that lowering stress levels would have a beneficial impact on ameliorating the pathology and symptoms of AD in humans [13].

Autophagy, the process of phagocytosing and degradation of cytoplasmic proteins and organelles, is diminished in AD [14]. Chronic stress inhibits autophagy in a mTOR-dependent manner while increasing mTOR phosphorylation, which is the primary removal route for accumulated proteins. It was found that autophagy inhibition causes Tau protein aggregation and neuronal loss in the hippocampus and frontal cortex of mice [15]. Improved autophagic processes remove amyloid beta (Aβ) and tau accumulation, overcoming impaired cognition [16]. Autophagy is triggered by the membranes of cells. A phagosome is a two-layered membrane that stores proteins from the cytoplasm and organelle parts. The lysosome combines with the external membrane, creating an autolysosome, which breaks up the packaged contents [17]. Because autophagy is often weakened in AD, intended induction of autophagy is proposed as a possible treatment aid in AD since it enhances the clearance of Aβ deposition [18].

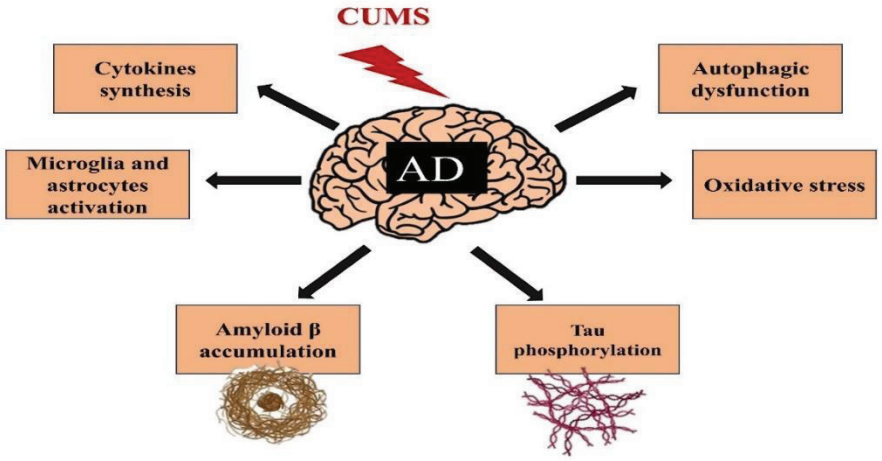

Fig. 1: Scheme summarizing the inflammatory pathways linked between CUMS and AD pathogenesis.

2. AIM OF THE REVIEW

Chronic stress has been linked to a number of neuropsychiatric disorders, many of which involve cognitive changes. Increasing proof suggests that autophagy changes may contribute to the disorder seen in neuropsychiatric diseases. AMPK/mTOR signaling has a crucial role in the modulation of the autophagic signaling cascade. Therefore, targeting AMPK and mTOR signaling represents therapeutic strategies for autophagy-related diseases, including cardiovascular diseases, ischemia-reperfusion injury, diabetic complications, depression, AD and so on. Thus, the present review was designed to define the effects of stress on cognitive impairment via AMPK/mTOR autophagic signaling.

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3. OVERVIEW OF AUTOPHAGY

Autophagy, a self-degradative procedure, is critical for managing the sources of energy throughout growth as well as in the aftermath of dietary stress [19]. It also helps to (i) remove misfolded or accumulated proteins, (ii) clean malfunctioning organelles like mitochondria, peroxisomes, and endoplasmic reticulum, and (iii) eliminate intracellular infection. Thus, autophagy is frequently considered an approach to survival, regardless of the reality that the process's disruption has been linked to the non-apoptotic death of cells [20].

Autophagy might be selective or non-selective in the elimination of specific organelles, protein fragments and ribosomes [21]. Also, autophagy helps to prevent diseases like cancer, dementia, major depressive disorder, cardiomyopathy, diabetes, liver disease, autoimmune diseases, and infections by promoting cell surface antigen presentation, protecting against genomic instability, and preventing necrosis [22].

Autophagy has three different forms that can occur: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA). Although everyone of them has a unique morphology, all of them play a role in the lysosomes degradation and recycling of cytosolic components [23]. Intrusions or projections of the membrane lysosome are used for capturing cargo during microautophagy [24]. The ingestion happens at the lysosome's restricted barrier and may include unaltered organelles. In contrast to microautophagy, which sequesters cargo using membrane-bound structures, CMA unfolds and translocates each substrate independently across the lysosomal membrane after being identified by chaperones as having a certain pentapeptide motif [25]. However, macroautophagy includes eliminating cargo from the lysosome. In the present instance, a new generation of vesicles with double membranes called "autophagosomes" is employed to store the cargo and move it across the lysosome [26].

The most prevalent form of autophagy is macroautophagy, and it's mainly a protective process. Nevertheless, excessive autophagic responses cause several pathological outcomes. As a result, autophagic disorders are linked to a wide range of people's illnesses, such as liver, lung, and heart disease, as well as neurodegeneration, cancer, aging, and metabolic disorders like diabetes [27].

4. REMOVAL OF AGGREGATE-PRONE PROTEINS VIA AUTOPHAGY IN NEURONAL DEGENERATION

Lately, many studies have shown that intracellular aggregates of proteins as well as misfolding have become a prevalent feature in numerous neuronal degeneration conditions like Parkinson's and AD [28, 29]. At this point, we do not have any viable treatments for curing or preventing neuronal degeneration in humans. As a result, a thorough understanding of the molecular processes underlying neuronal degeneration is critical. Typically, there are numerous approaches to treat neurodegenerative conditions that may improve the breakdown of susceptible proteins. The autophagy-lysosome and ubiquitin-proteasome routes are two of the most likely routes for misfolded protein clearance. Since the ubiquitin proteasome process mainly breaks down small-molecule proteins, this process is unknown, and it is unclear if it could be a potential therapy to clear aggregate-prone proteins. Furthermore, autophagic breakdown of aggregate-prone proteins is linked to decreased protein accumulation and toxic effects. Thus, improving autophagy could be an intriguing treatment option for

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neurodegenerative disorders, in which cumulative-prone proteins, like tau and α-synuclein, are used as autophagy substrates [30].

5. AUTOPHAGY IN AD, DEMENTIA AND COGNITIVE IMPAIRMENT

AD is a multifactorial, non-reversible progressive dementia that affects the majority of the world's elderly population. It's marked by a reduction in thinking and memory, as well as eventually the ability to perform any cognitive task [31]. AD is characterized by neurofibrillary tangles within the cell with excess phosphorylation of tau protein, self-accumulation of Aβ plaques outside the cell, a reduction in cholinergic signal activity, and ultimately autophagy impairment [32]. Neurodegeneration has been linked to the Aβ peptide, which is formed by the β-site amyloid precursor protein (APP) enzyme 1 (BACE1) and γ-secretase. This peptide has been shown to result in memory loss and damage to neurons in both the cortex and hippocampus throughout AD pathology [33]. Autophagosomes, which contain APP and presenilin-1 enzymes, can produce Aβ [34]. Autophagy may contribute to plaque accumulation by secreting Aβ into the extracellular space. According to numerous investigations, deleting Atg7 in transgenic mouse models of APP reduces Aβ extracellular substances and plaque development [35]. Thus, the enhanced autophagy will merely result in degraded Aβ secretion [35]. Research shows that autophagy serves as an element in removing Aβ during physiological states, highlighting the importance of maintaining Aβ homeostatic balance in an ideal brain [36]. In line with these studies, it has been shown that autophagy stimulation is reduced in AD animal models and human brains [37]. The association between autophagy reduction and Aβ accumulation in the brain highlights its role in AD pathogenesis [38]. To combat AD, targeting Aβ and tau proteins through autophagy upregulation is a promising therapeutic approach.

Cognitive impairment includes trouble concentrating and memory loss, completing tasks, remembering, understanding, following instructions, and solving problems. Cognitive impairment can be mild or severe [39]. AD is the most common type of dementia diagnosed in elderly people, and it is associated with cognitive impairment [40]. Dementia is typically diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning. In the brains of AD patients, the metabolism of Aβ is dysregulated, which leads to the accumulation and aggregation of Aβ. Metabolism of Aβ and tau proteins is crucially influenced by autophagy. Enhanced autophagic function can eliminate Aβ and Tau deposition, thereby reversing cognitive impairment [41, 42]. Thus, dysfunction of autophagy is suggested to lead to the accretion of noxious proteins in the cognitive impairment, dementia, and AD brain.

6. CHRONIC STRESS TRIGGERS TAU ACCUMULATION VIA AUTOPHAGY INHIBITION

There are multiple risk factors linked to AD, with recent research promoting the impact of long-term stress and the primary stress hormone, glucocorticoids (GCs). Studies have discovered that the HPA (hypothalamic-pituitary-adrenal) axis is impaired in AD, and the basal corticosterone level is significantly increased [43]. After stress, corticotrophin-releasing hormone (CRH) released by the hypothalamus acts on the pituitary gland to trigger the release of adrenocorticotropic hormone (ACTH), which then acts on the adrenal gland to increase the release of GCs [44]. Increasing in the production of CORT has been linked with impaired

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synaptic activity in AD. Experimental research has demonstrated the fact that prolonged stress as well as being subjected to elevated GC levels lead to increased Aβ, Tau phosphorylation, loss of cognitive and memory function and failure to function, resulting in its deposition and accumulation of toxic aggregates that produce neurological disorders [39, 40]. Furthermore, more recent findings show that elevated CSF cortisol in AD patients reflected the presence of the apoE4 allele [48], suggesting that apoE function was influencing circulating cortisol levels.

In addition, it was found that chronic stress and GC promote autophagy inhibition in an mTOR-dependent way, with elevated levels of p62 and a decline in LC3II, in addition to raising the phosphorylation of mTOR, which is the primary removal route for accumulated proteins. Autophagy blocking causes aggregation of Tau protein and neuronal loss in both the hippocampus and frontal cortex of mice [15].

As shown in Fig. 2, the hippocampus and the prefrontal cortex are the most affected brain areas in AD, revealing a characteristic deposit of pathological, aggregated Tau, which is strongly linked with cognitive impairment [45, 46]. Meanwhile, the number of pyknotic neurons at CA1 and the dentate gyrus of the hippocampus was significantly increased, and these changes may underlie the increased memory and cognitive impairment. Previous research has found that stress and GC cause abnormal hyperphosphorylation of Tau [41, 47]. These studies utilized the P301L-Tau transgenic mice expressing 4R0N human Tau that carried the aggregation-prone P301L-Tau mutation, which were then subjected to CUMS [52]. Stressed P301L-Tau animals displayed elevated levels of the GC. Furthermore, they showed deficits in behavioural flexibility and working memory in the Y-maze and Morris Water Maze, as well as anxious-like behaviour in the open field tests [43, 49].

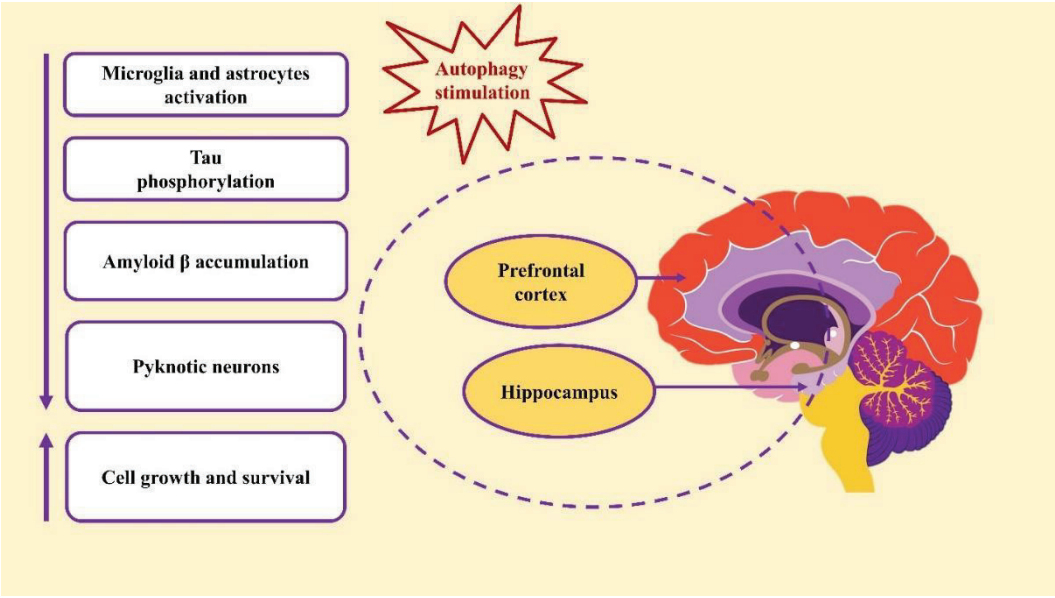

Fig. 2: Scheme summarizing the histopathological changes of the brain areas relative to autophagy stimulation.

The behavioural deficits in P301L-Tau transgenic animals were associated with higher levels of sarkosyl-insoluble Tau in both the hippocampus and prefrontal cortex of stressed animals. These Tau aggregates are biochemically like those found in neurofibrillary tangles, which characterize AD [50]. Moreover, P301L-Tau aggregates have been shown to be a significant cause of neurological damage in Tau pathology [52]. This is consistent with the

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reduced cell density that stressed P301L-Tau animals showed in the hippocampus and prefrontal cortex when compared to control P301L-Tau animals [53].

7. AMPK/MTOR SIGNALING CASCADE

As shown in Fig. 3, AMPK and mTOR are the main autophagy regulators. The second regulation, mTOR, negatively controls autophagy through the phosphorylation of the Atg1/unc-51-like autophagy activating kinase 1 (Ulk1) in order to block the beginning of autophagy [54]. AMPK is a positive regulator of autophagy via a decline in the mTOR complex 1 (mTORC1) action that happens in traditional and non-traditional ways [55]. AMPK can also attach and phosphorylate in order to stimulate Ulk1/2 and trigger autophagy. Ulk-1 activates Beclin-1 by binding to the autophagy proteins autophagy-related protein 101 (Atg101), autophagy-related protein 13 (Atg13), and focal adhesion kinase family-interacting protein 200 kD (fip200). Once Beclin-1 is activated, it binds to vsp18 and vsp34 to form phagophores. The matured autophagosome is formed by the phagophore enclosed upon conversion of LC3-I to LC3-II (autophagosomal marker). When transcription factor EB (TFEB) is activated, Rab-7 mediates autophagosome-lysosome fusion, which transports the specific protein to lysosomes for breakdown [56].

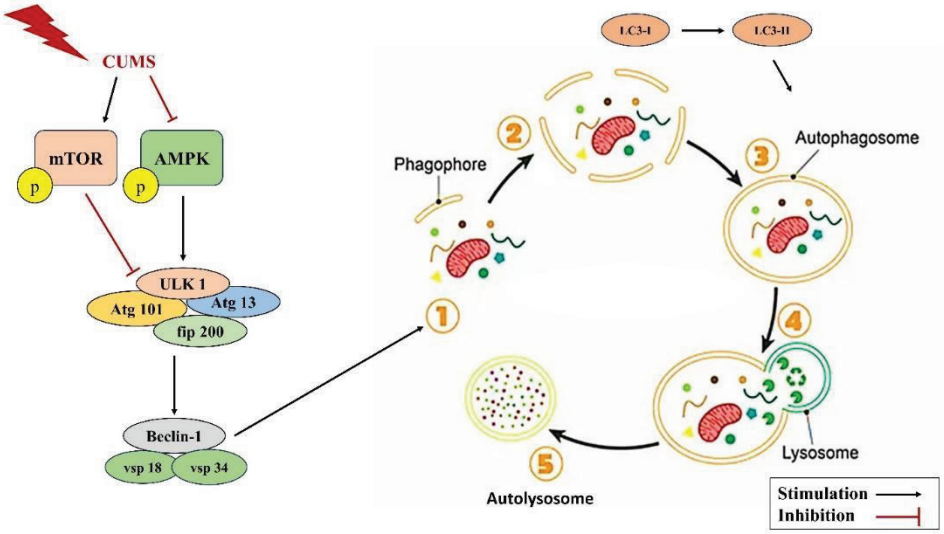

Fig. 3: Scheme summarizing the autophagy signaling pathway in response to CUMS.

8. AMPK/MTOR SIGNALING CASCADE AND AD

The mTOR pathway plays an important role in the pathogenesis of AD. The theory of amyloid plaques dominates AD pathogenesis and influences treatment development. In this regard, imbalanced Aβ production and clearance appear to trigger cascades leading to increased Aβ levels and plaque aggregation. The failure of synapses and the inflammation they trigger lead to oxidative injury, tau hyperphosphorylation, and intracellular neurofibrillary tangle formation [57]. The AMPK, protein phosphatase 2A (PP2A), and GSK-3β can interrelate with mTOR to induce the generation of Aβ plaques and hyperphosphorylation of tau [58]. Previous research has demonstrated that excessive mTOR stimulation can reduce autophagy and directly trigger increased phosphorylation of tau and its accumulation [37, 38]. Furthermore, the

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production of mediators of inflammation and microglial activation is associated with autophagy alteration and the production of two important autophagy regulators, mTOR and Beclin1 [57, 58].

9. CONCLUSION(S)

Inhibition of the AMPK/mTOR signaling pathway is considered a vital contributor to stress-induced cognitive impairment. Therefore, induction of the AMPK/mTOR cascade in order to initiate autophagy would have a protective effect against stress-induced cognitive impairment. This effect would be reflected in the improvement of major core behaviours associated with stress-induced cognitive impairment, as well as significant improvements in the histopathology of the hippocampus and prefrontal cortex.

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CONFLICT OF INTEREST

All of the authors listed have contributed significantly, directly, and intellectually to the work and have given their approval for publication.

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APPENDIX A: LIST OF ABBREVIATIONS

Aβ	Amyloid beta
AD	Alzheimer's disease
AMPK	AMP activated protein kinase
APP	Amyloid precursor protein
Atg	Autophagy related protein
CMA	Chaperone-mediated autophagy
CUMS	Chronic unpredictable mild stress
GCs	Glucocorticoids
MCI	Mild cognitive impairment
m-TOR	Mammalian target of rapamycin
Ulk1	Unc-51 like autophagy activating kinase 1

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