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Review Article

Caloric Restriction Mimetics and Cerebral Pathologies

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Abstract

Caloric Restriction (CR) is widely recognized for its health benefits, including delayed aging and neuroprotective effects in age-related Neurodegenerative Diseases (ND). The development of Caloric Restriction Mimetics (CRM) has addressed some of the negative aspects of CR, opening new avenues for research, particularly in neurodegenerative diseases. This review focuses on CRM compounds, their mechanisms of action in preventing and treating neurodegenerative diseases, and their application to Alzheimer's disease, Parkinson's disease, and polyglutamine disorders such as Huntington's disease and cerebellar ataxia. The review also discusses the potential of CRM in future therapeutic strategies for traumatic brain injury, often resulting in long-term neurological deficits and cause of early neurodegenerative diseases.

INTRODUCTION

Neurodegenerative Diseases (NDD) affect millions of people worldwide, and the risk of developing these diseases increases with age. With the increase in life expectancy, NDD have become a major socio- economic burden. They are characterized by the progressive degeneration of the structure and function of the Central Nervous System (CNS) and/or the peripheral nervous system. These disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and cerebellar ataxia, are major causes of morbidity and mortality, particularly in the elderly. The main characteristic of NDD is neuronal loss in specific brain regions, often accompanied by protein abnormalities such as amyloidosis, tauopathies, or α-synucleinopathies. These protein abnormalities lead to a slowly progressive loss of function in specific neuron populations and their connections, resulting in movement disorders and cognitive or behavioral disorders [1]. Inflammation is also a significant characteristic of neurodegenerative diseases. It involves a complex biological response of the somatosensory, immune, autonomic, and vascular systems, promoting the elimination of damage, tissue repair, and the recovery of homeostasis. However, chronic inflammation can also lead to several diseases, including neurodegenerative disorders [2].

Despite extensive research and the dedication of the scientific community, there are currently no disease-modifying treatments for most neurodegenerative diseases. Most approved medications only help with associated symptoms [3]. In this context, Caloric Restriction (CR) and its mimetics have emerged as promising research areas. Since the early 1920s, CR has been the subject of increasing research, highlighting its health benefits and ability to prolong life [4]. CR has been shown to promote the resistance of neurons to chemically-induced neurodegeneration, appearing among other things on behavioral tests [5]. CR involves a dietary regimen that reduces calorie intake without inducing deficiency, implying the inclusion of all essential nutrients without malnutrition. It involves an active and dynamic conserved stress response that evolved early in life's history to increase the organism's chances of survival against adversity. This mechanism modulates many pathways and stress resistance signaling, including sirtuin-1 [6], mechanistic Target of Rapamycin (mTOR), and AMP-Activated Protein Kinase (AMPK), among others [7]. The mechanism also improves other beneficial effects, such as reducing inflammation, oxidative stress, improving insulin sensitivity, reducing the incidence of cancer, cardiovascular disease, obesity, and diabetes [8]. After this introduction, this paper is structured into several parts. Chapter 2 presents the main pathways involved in caloric restriction. Chapter 3 explains the concept of caloric restriction mimetics. Chapter 4 develops the application to

different neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and polyglutamine disorders such as Huntington's disease or cerebellar ataxia. We also present the potential of CRM in therapeutic strategies for traumatic brain injury. Finally, Chapter 5 concludes the review [9].

PATHWAYS

Despite the extensive knowledge about CR, research continues to discover new characteristics about its functioning. The main pathways involved in CR are well reviewed, and its main effects seem to have been established. Recent research tends to describe the molecular mechanisms through which CR acts in our cells. The main ways of action come through the activation of autophagy and inflammation, notably through mTOR or Sirt1 activation. CR also contributes to the reduction of oxidative stress, the regulation of gene expression, notably via FOXOs, and mitochondrial renewal and biogenesis [10].

Autophagy Regulation

Autophagy is a self-degradative cellular process responsible for degrading protein aggregates and damaged organelles, playing a housekeeping role. It degrades ribosomes, specific damaged organelles like mitochondria (mitophagy), endoplasmic reticulum, peroxisomes, and eliminates intracellular pathogens. Autophagy is closely related to the occurrence of various human diseases and can be considered a survival mechanism [11].

Autophagy occurs in response to various environmental stresses, such as nutrient stress, growth factor deficiency, and hypoxia. The induction of autophagy eliminates the damage caused by these stresses and helps return to normal levels after this [12]. Autophagy plays a crucial role in maintaining cellular homeostasis and is very important for development [13]. The functioning of autophagy involves producing double membrane vesicles, the autophagosomes, which engulf and transport cargo to be degraded after fusion with lysosomes [14]. In addition to eliminating intracellular aggregates and damaged organelles, autophagy promotes cellular senescence and cell surface antigen presentation, protects against genome instability, and prevents necrosis, giving it a key role in preventing diseases such as cancer, neurodegeneration, cardiomyopathy, diabetes, liver disease, autoimmune diseases, and infections [15]. In neurodegenerative diseases, the aggregation of misfolded proteins may impact autophagy. The fact that aging is a risk factor for neurodegenerative diseases and that autophagy decreases with age makes research on this mechanism a primordial tool for their treatment [16]. CR has been shown to induce autophagy through various pathways, including AMPK and SIRT1 activation. AMPK is a key energy sensor that regulates cellular metabolism to maintain energy homeostasis. It is activated by CR and plays a crucial role in regulating autophagy. AMPK activation inhibits mTOR, a master inhibitor of autophagy, thereby promoting autophagy [17]. SIRT1, a member of the sirtuin family, is also activated by CR and plays a crucial role in regulating autophagy. SIRT1 deacetylates various proteins involved in autophagy, such as ATG5, ATG7, and ATG8, thereby promoting autophagy [18]. SIRT1 also regulates autophagy through the deacetylation of FOXO3, a transcription factor that regulates the expression of autophagy-related genes [19].

Inflammatory Pathways

Inflammation is a protective biological response that can be induced by diverse injuries and infections, acting as harmful stimuli, such as viruses, bacterial infections, toxins, toxic compounds, or tissue injury. Inflammation involves a complex biological response of the somatosensory, immune, autonomic, and vascular systems, promoting the elimination of damage, tissue repair, and the recovery of homeostasis [20,21]. An acute inflammatory response is activated upon infection or tissue injury and involves the recruitment of immune cells to the site of damage. The coordination of immune cells mobilized from the bloodstream, in conjunction with tissue-resident immune cells, ensures the elimination of the damage followed by the resolution of the inflammatory process. Inflammation can thus be very useful; the innate immune system responds fast to a first damage, and the adaptive immune system will confer immunological memory and promote faster responses to repeated infections. These mechanisms are both crucial for a good inflammatory response [22]. However, under some conditions, failure in the mechanism can lead to an uncontrolled increase of pro- inflammatory cytokines, particularly in the brain. This risk factor increases with age and can, in some cases, lead to the development of neurodegenerative diseases [23]. CR has been shown to modulate inflammatory activity, reducing pro-inflammatory cytokines and improving chronic inflammatory and autoimmune disorders. This anti-inflammatory effect is mediated through pathways such as mTOR and NF-κB inhibition. CR inhibits the PI3K/AKT pathway and induces a younger transcription profile, reducing the age-related upregulation of NF-κB and consequently reducing inflammation [24]. CR also reduces the expression of genes linked to inflammation, the cytoskeleton, the extracellular matrix, and angiogenesis in mouse adipose tissue [25]. CR attenuates the age-related dysregulation of the cytokines TNF-alpha and IL-6, which are used as inflammatory markers [26].

Mitochondrial Function and Oxidative Stress

Mitochondria and oxidative stress play a central role in the metabolism and are deeply involved in the mechanisms of cell death in neurodegenerative diseases. Mitochondrial dysfunction and oxidative stress are key factors in neurodegenerative diseases and are involved in the generation of free radicals. Mitochondrial DNA mutations are implicated in aging mechanisms, which is one of the strongest risk factors for these diseases.

CR has been shown to ameliorate mitochondrial dysfunction, reducing protein carbonyl content, decreasing superoxide and hydrogen peroxide formation, and reducing the accumulation of mtDNA deletions [27]. CR also enhances mitochondrial biogenesis and reduces oxidative damage to mtDNA [28]. CR improves mitochondrial function by increasing the levels of SIRT3, a prominent regulator of mitochondrial activity. SIRT3 deacetylates proteins involved in diverse pathways of metabolism and mitochondrial maintenance, protecting against cerebral pathology and excitotoxicity [29]. CR also induces microRNAs to improve mitochondrial proteostasis, activating the protein expression of their mitochondrial targets. For example, miRND1 and miRCO1 specifically upregulate the expression of MTND1 and MTCO1, and miR-122 increases the expression of the OXPHOS subunits MTND1 and MTCO1 [30].

CALORIC RESTRICTION MIMETICS

Despite the beneficial effects of CR, its long-term application can be challenging, particularly in the elderly. Cr Mimetics (CRM) offer a practical alternative by mimicking the beneficial effects of CR without the need for strict dietary restrictions. CRM compounds, such as sirtuin activators, AMPK activators, and mTOR inhibitors, have shown promise in treating neurodegenerative diseases.

Sirtuin Activators

Sirtuins are a family of NAD+-dependent protein lysine deacylases that play a crucial role in CR's beneficial effects. Sirtuins target by CR are the SIRT1, 3, and 6 and are part of the sirtuins therapeutically targets in order to cure aged-related diseases, inflammation, or neurodegenerative diseases. These sirtuins, in addition to their anti-inflammation effect and neuroprotection, have been shown to act directly on mitochondria, and notably mitochondrial biogenesis and oxidative metabolism, but also reduce reactive oxygen species with a CR activation [20].

Polyphenols, such as resveratrol and curcumin, are natural sirtuin activators that have shown neuroprotective effects in various neurodegenerative disease models. Resveratrol, for example, has been shown to activate SIRT1 and AMPK, reduce oxidative stress, and improve mitochondrial function. Curcumin, on the other hand, has been shown to have anti-inflammatory, antimutagenic, antimicrobial, and immunomodulatory effects, as well as anticancer properties.

AMPK Activators

AMPK is a central regulator of cellular metabolism that plays a crucial role in CR's beneficial effects. AMPK activation increases the rate of catabolic processes while decreasing the rate of anabolic processes, regulating the energy metabolism of the cell. AMPK activators, such as metformin, have been shown to improve mitochondrial function, reduce inflammation, and enhance autophagy. Metformin, a drug primarily used for type 2 diabetes therapy, has been shown to have anti-aging, anticancer, and neuroprotective properties. Metformin has been shown to improve cognitive function, reduce inflammation, and enhance autophagy in various neurodegenerative disease models.

mTOR Inhibitors

mTOR is a serine/threonine kinase protein that plays a crucial role in regulating cell growth, proliferation, survival, and autophagy. mTOR inhibitors, such as rapamycin, have been shown to have neuroprotective effects by inducing autophagy and reducing inflammation. Rapamycin, for example, has been shown to improve mitochondrial function, reduce oxidative stress, and enhance autophagy in various neurodegenerative disease models. Rapamycin has also been shown to improve cognitive function, reduce neuroinflammation, and enhance autophagy in Alzheimer's disease models. Rapamycin has been shown to reduce amyloid-beta and tau pathology, key factors in Alzheimer's disease.

Polyphenols

Polyphenols are a vast category of phytochemicals present in many plants, including fruits, vegetables, nuts, seeds, and beverages such as tea and wine. They are known for their antioxidant and anti- inflammatory properties, making them potential candidates for the prevention and treatment of various diseases, including neurodegenerative diseases. Polyphenols can be classified into several subgroups, including flavonoids, simple phenols, stilbenes (such as resveratrol), and lignans. Resveratrol is a stilbene naturally present in the skin of grapes, berries, and peanuts. It is particularly abundant in red wine and is known for its health benefits, including its

antioxidant and anti-inflammatory properties. Resveratrol has been studied for its neuroprotective effects in various neurodegenerative disease models, including Alzheimer's and Parkinson's diseases. It acts by modulating several signaling pathways, including the activation of SIRT1 and the inhibition of NF-κB, leading to reduced inflammation and oxidation.

Curcumin

Curcumin is the primary active compound in turmeric (Curcuma longa), a spice commonly used in Indian cuisine. It possesses antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and immunomodulatory properties. Curcumin has been studied for its neuroprotective effects in various neurodegenerative disease models, including Alzheimer's and Parkinson's diseases. It acts by modulating several signaling pathways, including the inhibition of NF-κB and the activation of Nrf2, leading to reduced inflammation and oxidation.

Quercetin

Quercetin is a flavonoid present in many fruits and vegetables, including apples, onions, and berries. It is known for its antioxidant and anti-inflammatory properties. Quercetin has been studied for its neuroprotective effects in various neurodegenerative disease models, including Alzheimer's and Parkinson's diseases. It acts by modulating several signaling pathways, including the inhibition of NF-κB and the activation of Nrf2, leading to reduced inflammation and oxidation.

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is a catechin abundantly present in green tea. It is known for its antioxidant and anti-inflammatory properties. EGCG has been studied for its neuroprotective effects in various neurodegenerative disease models, including Alzheimer's and Parkinson's diseases. It acts by modulating several signaling pathways, including the activation of Nrf2 and the inhibition of NF-κB, leading to reduced inflammation and oxidation.

CALORIC RESTRICTION AND CEREBRAL PATHOLOGIES

Alzheimer's Disease

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder and the main cause of dementia in the elderly. It is characterized by loss of memory and loss of independence, with main risk factors including age, head injuries, genetics, or vascular diseases. AD is characterized by neuronal death, especially in the cortex and hippocampus, due to extracellular accumulation of Aβ peptides and intracellular neurofibrillary tangles composed of hyperphosphorylated Tau proteins [31]. CRM compounds, such as metformin and rapamycin, have been associated with a lower risk of AD. These compounds improve learning, memory, and cognitive function, reduce neuroinflammation, and enhance autophagy. Recent studies have shown that these compounds can reduce amyloid-beta and tau pathology, key factors in AD [32]. Metformin, for example, has been shown to reduce amyloid-beta and neuroprotein Tau accumulation by phagocytosis, ameliorating microglial autophagy [33]. Metformin has also been shown to improve neurogenesis in AD models, reducing hippocampal amyloid-beta plaque and neurofibrillary tangles load, suppressing inflammation, ameliorating mitochondrial dysfunction and oxidative stress, restricting apoptotic neuronal death, and inducing neurogenesis [34].

Rapamycin has been shown to reduce amyloid-beta and tau pathology, improve cognitive function, and enhance autophagy in AD models. Rapamycin has been shown to reduce the risk of AD, inhibit activation of AMPK-mTOR pathway, and improve AD lesion in the hippocampus in rats models.

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by motor symptoms such as tremor, rigidity, and bradykinesia, and non-motor symptoms such as Parkinson's disease psychosis. Environmental factors and genetic predisposition can be the causes of this disease. Symptoms originate from the degeneration of dopaminergic neurons of the substantia nigra, associated with a loss of dopamine and accumulation of Lewy bodies, inclusions that contain α-synuclein and ubiquitin [34]. CRM compounds have been shown to improve motor function and reduce dopaminergic neuron damage in PD models. Metformin, for example, has been shown to reduce damaged dopaminergic neurons and improve motor function in PD models. Metformin has also been shown to inhibit microglia activation by acting on inflammatory markers such as OX-6, IKKβ, and arginase immunoreactivity, minimizing the expression levels of some pro- and anti-inflammatory cytokines. Rapamycin has been shown to alleviate PD symptoms and reduce dopaminergic neuron damage in PD models. Rapamycin has been shown to decrease the level of the key protein p-4EBP1 in the striatum and substantia nigra, an abnormally elevated expression of this protein normally present in PD models.

Polyglutamine Disorders

Polyglutamine (polyQ) diseases are the largest group of hereditary neurodegenerative diseases caused by a trinucleotide repeat expansion (cytosine-adenine-guanine, CAG) in coding regions of the DNA. These expansions lead to RNA alterations, such as transcription, processing, nuclear exportation, and translation, leading to cellular dysfunction and consequent neurodegeneration in specific brain areas. Cognitive, motor, and neuromuscular deficits are the main hallmarks of these diseases. There are several neuromuscular and neurological diseases caused by repeat expansions in coding regions, such as Huntington's Disease (HD) and spinocerebellar ataxias (SCAs). Huntington's Disease (HD) is the most represented polyQ neurodegenerative disorder, characterized by gradual loss of neurons predominantly in the striatum, causing motor abnormalities and cognitive decline. The CAG mutation leads to the production of the htt with an abnormal protein-protein interaction named mutant polyglutamine htt (m-htt), which forms cytotoxic aggregates in neurons.

CRM compounds have been shown to decrease HTT levels and alleviate motor phenotypes in HD models. Metformin, for example, has been shown to reduce the number of nuclear aggregates of mutant huntingtin in the striatum, restore the expression of brain-derived neurotrophic factor, and reduce glial activation in HD models [35]. Rapamycin has been shown to reduce HTT levels and aggregates while rapalogs like rapamycin allosterically inhibit the mTOR Complex 1 (TORC1). ATP-competitive mTOR inhibitors suppress activities of TORC1 and TORC2 and are more efficient than rapamycin in inducing autophagy and in reducing protein levels and aggregates.

Machado-Joseph Disease (Spinocerebellar Ataxia Type 3)

Machado-Joseph disease (MJD), also known as Spinocerebellar Ataxia type 3 (SCA3), is a neurodegenerative disorder characterized by progressive cerebellar dysfunction, often accompanied by other neurological symptoms. It is caused by a CAG repeat expansion in the ATXN3 gene, leading to the production of a mutant ataxin-3 protein that forms aggregates in neurons [35]. Unlike the previous pathologies, the onset of the disease is generally early (average age of 24) and the symptoms progress rapidly.

Resveratrol has been studied for its potential therapeutic effects in MJD. In a study using a mouse model of MJD, resveratrol was shown to improve motor coordination and reduce the formation of ataxin-3 aggregates. The mechanism involves the activation of SIRT1, which enhances autophagy and reduces oxidative stress [36,37]

Traumatic Brain Injuries

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality worldwide, for children and the elderly alike, often resulting in long-term neurological deficits. The injury can lead to a cascade of cellular and molecular events, including inflammation, oxidative stress, and neuronal cell death. By modulating these pathways, CR may help preserve neuronal function and reduce the extent of tissue damage [38]. One of the most promising aspects of CR in the context of TBI is its ability to stimulate the proliferation of neural stem cells. These cells have the potential to differentiate into various types of neurons and glial cells, contributing to the repair and regeneration of damaged brain tissue [39]. CR has been shown to enhance neurogenesis in the hippocampus and other brain regions, which could be crucial for recovering cognitive and motor functions after TBI [40]. The molecular mechanisms underlying the beneficial effects of CR in TBI involve several signaling pathways, including: SIRT1 Activation that plays a crucial role in cellular stress responses [41]; AMPK and mTOR Pathways which are involved in energy homeostasis and cell growth [42]; reduction of Oxidative Stress, crucial for protecting neurons from further injury and promoting their survival [43-49].

CONCLUSION

CR has long been shown to be effective in treating and improving certain conditions of neurodegenerative diseases by targeting broad areas such as inflammation, redox balance, and mainly autophagy. Some benefits of CR are even specifically related to CNS function, promoting axonal regeneration, among others. However, the benefits, some mechanisms, and signalling pathways of CR remain to be uncovered. CR remains limited, notably through its need to be correctly designed and the resulting weight loss, which is a significant factor in the elderly, the main people affected by this type of disease.

The development of CRM has thus emerged to avoid the negative effects of CR while mimicking its beneficial effects. Research has been vast and prolific in this field, with many molecules mimicking specific effects or signalling pathways. Some of them are already used as adjuncts to certain diseases, and research in neuroscience and more specifically on NDs is not left behind with very encouraging results. New data are being discovered on a regular basis, showing the benefits of many CRMs in these fields. Although the most studied diseases such as AD or

PD benefit from more evidence, CRMs are an encouraging lead in the treatment of many brain diseases and are in some cases already in clinical use or are in the process of being clinically investigated for use as a treatment. Among the discoveries, some CRMs that have proven to be effective still have limitations. The search for analogs or the enhancement of the capabilities or bioavailability of these compounds through new formulations is very promising and is giving first good results. The research in the field of CRM is very encouraging, and many molecules, as well as many leads, remain to be exploited. The potential of CRMs is very important, and the discovery of new treatments is a major issue in ND research.

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