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Molecular Bases of Caloric Restriction Regulation of Neuronal Synaptic Plasticity

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Abstract Aging is associated with the decline of cognitive properties. This situation is magnified when neurodegenerative processes associated with aging appear in human patients. Neuronal synaptic plasticity events underlie cognitive properties in the central nervous system. Caloric restriction (CR; either a decrease in food intake or an intermittent fasting diet) can extend life span and increase disease resistance. Recent studies have shown that CR can have profound effects on brain function and vulnerability to injury and disease. Moreover, CR can stimulate the production of new neurons from stem cells (neurogenesis) and can enhance synaptic plasticity, which modulate pain sensation, enhance cognitive function, and may increase the ability of the brain to resist aging. The beneficial effects of CR appear to be the result of a cellular stress response stimulating the production of proteins that enhance neuronal plasticity and resistance to oxidative and metabolic insults; they include neurotrophic factors, neurotransmitter receptors, protein chaperones, and mitochondrial biosynthesis regulators. In this review, we will present and discuss the effect of CR in synaptic processes underlying analgesia and cognitive improvement in healthy, sick, and aging animals. We will also discuss the possible role of mitochondrial biogenesis induced by CR in regulation of neuronal synaptic plasticity.

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Brain plasticity refers to the capacity of the brain to modify its structure and function as a result of the interaction of individuals with their environment. Depending on the characteristics of such environment and the lifestyle of the individual, changes of the brain could be either strengthened or degraded. Aging is a process that produces a decrease of spine densities and neurogenesis [1, 2] and changes in different neurotransmitter systems ([3] and references therein), favoring a general neuronal dysfunction. These brain modifications are postulated as the major contributors to the functional decline observed with aging [4]. Learning and memory impairments, independent of overt pathology, are considered to be a normal component of aging. It is estimated that approximately 40% of people over the age of 65 experience some sort of age-related cognitive impairment [5]. The exact nature of the underlying neuronal changes that give rise to these age-related deficits remains unknown; however, there is mounting evidence that one brain region—the hippocampus—seems to be particularly sensitive to aging and is thought to be responsible, at least in part, for the age-related cognitive decline that occurs during normal aging [6]. Many age-related changes within the hippocampus have been documented, including altered mitochondrial function [7], oxidative stress [8], and alterations in glutamate transmission [9] and synaptic plasticity [10, 11]. Hence, an important aspect of aging research has been the quest for treatments that will prevent or ameliorate the memory deficits associated with aging. Although the long-lasting changes of synaptic transmission has been

studied extensively in the hippocampus and other cortical areas in the context of learning and memory processes, a similar phenomenon can be elicited in the spinal cord, comprising an activity-dependent, long-lasting homosynaptic facilitation of excitatory postsynaptic potentials in response to brief, high-frequency repeated trains of nociceptor input ([12, 13] and revised in [14]). These activity-dependent synaptic phenomena are relevant also in pathological conditions, including persistent pain, drug addiction, and emotional disorders [14–16].

Numerous studies have shown that a moderate reduction in caloric intake (caloric restriction—CR—of between 20% and 40%) might slow aging, reduce age-related chronic diseases, and extend the life span [17–19]. Also, the time between meals might be as important as the total food intake: mice following an intermittent fasting diet (IFD) showed metabolic changes similar to those in mice maintained on a CR diet [20, 21]. It is possible that the lengthy periods of fasting in this regimen bring about the physiological changes that extend life span. Although beneficial effects of CR on cardiovascular, immune, and endocrine systems have been demonstrated [19, 22–25], its effects on the central nervous system were not systematically studied until recently. Emerging data suggest that a similar scenario may apply to neurodegenerative disorders, including Alzheimer's and Parkinson's diseases (AD and PD), stroke, and nociception [26, 27]. Microarray and proteomic analyses have shown that CR actually forestalls many progressive changes that occur during aging [28, 29]. Studies in humans indicate that some metabolic markers of aging improve with CR diets [30–33]. These effects could be the result of a complex neuroendocrine response, in which are included the upregulation of trophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 [20].

Synaptic plasticity changes are required for the correct function of the central nervous system. Long-term synaptic plasticity changes in the hippocampus, such as long-term potentiation, have been postulated as a putative building block for memory formation [34, 35]. Also, changes in neurotransmission of nociceptive neurons in the dorsal horn of the spinal cord seems to be required for the modulation of some forms of pain [36, 37]. In this review, we will focus on recent results that show how CR modulates nociception and learning and memory processes in healthy mice. In addition, we will discuss recent data that relate CR with mitochondrial biogenesis and its possible role in learning and memory processes.

CR Provokes Analgesia in Healthy Mice

The experience of pain in response to noxious stimuli serves a crucial biological purpose: it alerts a living organism to environmental dangers, inducing responses that protect the organism from further damage. Since the discovery of an endogenous opiate system and the subsequent cloning of endogenous opioid ligands and their opiate receptors (reviewed in [38]) that mediate the effects of the prototypic opioid morphine, an intense effort has been made to characterize and understand the physiological and pathophysiological roles of each of its components. The classical opiate system comprises three receptor types (μ, κ, and δ) and their ligands are encoded by the endogenous opioid genes, proopiomelanocortin, proenkephalin, and prodynorphin, respectively [39]. A second endogenous system with an important role in pain modulation has also been described. The cannabinoid system comprises cannabinoid receptor types 1 and 2 (CB1-R and CB2-R) and their endogenous lipid ligands [40]. Because exogenous opioids and cannabinoids have traditionally been used for their analgesic properties, most studies on the endogenous substances have focused on their role in pain modulation, although participation in locomotive, cognitive, cardiovascular, neuroendocrine, and neuroimmune processes are known [41–43].

In the last 30 years, it has been well established that food deprivation diminishes acute nociception in laboratory rodents. Several neurotransmitter systems have been implicated in this effect, including μ-opioids and adrenocortical hormones [44–46]. Recently, it has been reported that both CR and IFD, which induce states physiologically distinct from food deprivation, induce analgesia in acute and chronic models of pain [27, 47]. The physiological processes underlying the effects of CR on pain are not well established. The mechanism could involve some of the substances implicated in the analgesic response to short-term food deprivation, such as glucocorticoids (corticosterone), opioid receptors, and adrenocortical hormones [45, 46]. In recent studies, we have reported that IFD in mice induces an increase in the expression and activity of the κ-opioid system components and a decrease in the CB1-R in spinal cord [27, 48]. Moreover, subchronic inhibition of CB1-R in mice provokes a κ-opioid receptor (KOR)-dependent hypoalgesia similar to that found in mice subjected to IFD [48]; in both cases, overactivation of the κ-opioid system provokes a block in nociceptive information flow at sensory neurons in the spinal cord, as was shown by a decrease in c-Fos immunoreactivity in spinal cord and superior centers involved in pain control.

The expression of the gene encoded for the main KOR ligand, prodynorphin, is regulated by several transcription factors in a tissue-specific manner [49–53]. In the spinal cord, DREAM is the main regulator of prodynorphin transcription [54], as was demonstrated using null mutant mice for DREAM. These mice show dramatic analgesia in acute and chronic pain models. In IFD mice, the increase in

prodynorphin transcription is mediated by a decrease in DREAM activity in the spinal cord [27], a result in agreement with that obtained with DREAM knockout mice [54]. The change in DREAM activity in spinal cord neurons could play a pivotal role in the change of the genetic program that leads to analgesia in IFD mice. In addition, our results with IFD mice, together with those in mice containing null mutation for DREAM, reinforce the idea that DREAM activity inhibition would be an attractive therapeutic opportunity because both groups of animals show persistent analgesia [55]. Various studies support the proposal of an antinociceptive action of dynorphin. Dynorphin-mediated analgesia has been ascribed to an inhibitory action on neurons through the activation of KOR. Cumulative evidence suggests that KOR activation impairs synaptic transmission in nociceptive neurons and diminishes substance-P release in the dorsal horn of the spinal cord [56, 57]. All these, together with the fact that the knockdown of CB1-R in the spinal cord produces changes in nociception and a high level of dynorphins [58], suggest that the balance between κ-opioid and cannabinoid systems determines nociception.

All these data indicate that dietary manipulation, CR or IFD, induces an attenuation of pain responses. At least, reduced pain behavior in IFD mice is attributable to enhanced KOR activity [27]. These findings highlight a new aspect of pain modulation—namely, that the activation of KORs blocks nociceptive information flow at the dorsal horn of the spinal cord. Taken together, the results indicate CR as an excellent model for the study of opioid-dependent analgesia.

Beneficial Effects of CR in Aging and Neurodegenerative Disease Models

Cells in the nervous system are affected by and respond to aging much as cells in other organ systems do, and so aging cells in the brain experience increased amounts of oxidative stress [8, 59], perturbed energy homeostasis [60], accumulation of damaged proteins [61, 62], and lesions in their nucleic acids [63, 64]. During normal aging, these changes in vulnerable populations of neurons are exacerbated in neurodegenerative disorders such as AD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [65–68]. Similarly, the accumulation of amyloid-β in AD, of α-synuclein in dopaminergic neurons in PD, and of Cu/Zn-SOD in motor neurons in ALS occurs to a lesser extent during normal aging [62, 69]. Alterations during normal aging have been described in numerous neurotransmitter and neurotrophic factor signaling pathways, and many such changes are amplified in neurodegenerative diseases. Examples include depletion of dopamine in substantia nigra neurons in normal aging and PD [70] and lower levels of BDNF in aging, AD, and HD [71, 72]. Lastly, at the cellular level, synaptic contacts, synaptic strength, and plasticity are reduced [1]. In addition, brain neurogenesis is diminished with aging [73, 74]. As a consequence, all the molecular and cellular alterations, described above, that occur in aging and in brain disease provoke degeneration of some very susceptible areas, such as hippocampus, perirhinal cortex, and substantia nigra (review in [4]). Loss of neurons in these brain areas provokes the cognitive, sensory, and motor impairments found in aging and in nervous system degeneration [75].

CR is one of the several experimental manipulations that have successfully restored a degree of plasticity and/or cognitive capabilities to aged animals [76–82]. Notwithstanding, the molecular bases underlying the amelioration of cognitive deficiencies induced by CR in aged animals are not well understood. The benefits of CR in aging mice may be a consequence of modifications in the pattern of gene expression and, in fact, it was recently shown that CR modifies the expression of many genes in the aged brain [83, 84]. Those studies provided the first insight into the pattern of gene expression in the aging mammalian brain and its modulation by CR. Transcriptional responses identified in human neurodegenerative disorders, such as the induction of lysosomal proteases, chaperones, and markers of oxidative stress and inflammation, have been identified in the aging mouse brain. Moreover, some of these events may play a central role in the pathology of AD [85]. While CR may partially suppress the development of this age-associated proinflammatory state, alterations of genes involved in neurotransmission were not observed in these studies. This may be due to the selection of genes present in the arrays analyzed, leading to the poor representation of some transcriptional classes and, perhaps, to the overrepresentation of others. However, it has recently been shown that aging does affect the expression of certain genes involved in neurotransmission (e.g. *N*-methyl-D-aspartate receptor (NMDA-R), BDNF, Trk-B, and α-synuclein), and, in many cases, these changes are counteracted by CR (reviewed in [26]).

Because advancing age is the major risk factor for AD, PD, and stroke, numerous studies have been performed during the past few years to determine the effects of CR in animal models of these disorders. In the case of AD, CR was effective in chemical models of neurodegeneration by administration of the neurotoxin kainic acid and in genetic models overexpressing a human presenilin-1 mutation. In both cases, animals subjected to CR for 2–4 months showed reduced neuronal vulnerability as well as reduced deficiency in learning and memory in both AD models [86, 87]. In both cases, the neuroprotective effect of CR was correlated with decreased levels of oxidative stress in the

hippocampus. CR was also beneficial in pharmacological models of PD, HD, and stroke. The vulnerability of midbrain dopaminergic neurons to MPTP or 3-nitropropionic acid toxicity is decreased and motor function is improved in mice maintained on CR [86, 88]. CR was also beneficial in a rat model of stroke in which the middle cerebral artery is transiently occluded, resulting in damage to the cerebral cortex and striatum and associated motor dysfunction [89].

Studies of human populations support a protective effect of CR against age-related neurodegenerative disorders. Studies of a large sample of people living in New York City reveal that individuals with the lowest daily intake of calories have the lowest risk for AD [90] and PD [91]. Also, in two populations of African, the incidence of AD decreased by more than 50% in those living in a community consuming a reduced caloric diet [92].

CR Enhances Learning Consolidation in Adult Mice

Memory enhancement is of interest primarily to older adults, in whom the ability to encode new memories declines measurably from the third decade of life onwards; by the fourth decade, the decline can become noticeable and bothersome to normal healthy individuals [93]. Memory difficulties in middle or old age are not necessarily a harbinger of future dementia but can be part of the normal pattern of cognitive aging. It is not clear whether the changes that underlie normal age-related declines in memory differ from those that underlie neurodegenerative disorders. Although the main objective of pharmaceutical companies is to look for pharmacological approaches to palliate cognitive deficiencies in aging and sick patients; currently, in our society, a new field is opening up for drugs that provoke memory enhancement in healthy individuals. The use of prescription stimulants (such as methylphenidate and dextroamphetamine) as study aids by high school and college students who do not have attention-deficit hyperactivity disorder has recently drawn attention and might involve as many as 16% of the students on some campuses [94]. Sales of nutritional supplements that promise improved memory in middle age and beyond have reached a billion dollars annually in the US alone [95], despite mixed evidence of effectiveness [96].

Many studies report that mild stress-behavior manipulation such as physical exercise, intellectual training, and CR have a protective role in brain aging and in the development of neurodegenerative disorder (reviewed in [71]). However, the beneficial effects on the nervous system of these manipulations have been much less studied in healthy adult animals. Recently, we have used IFD, as a variant of CR, to demonstrate that mice subjected to this dietary regime display improved cognitive functions, as well as an increased synaptic plasticity in hippocampal circuits. The benefits of IFD in mature mice may be a consequence of modifications in the pattern of gene expression. In fact, CR, in addition to reducing age-associated alterations in gene expression [83, 84], shifted the expression levels of several transcripts that did not alter with age [97]. CR increased the expression of 120 genes (1.9% of those surveyed) by 1.7-fold or higher in the neocortex. Detailed gene expression analyses indicate that CR modulates energy metabolism and affects oxidative stress, ion homeostasis, and inflammatory signaling pathways. However, alterations of genes involved in neurotransmission were not observed in these studies. On the other hand, it has recently been shown that aging affects the expression of certain genes involved in neurotransmission (e.g. NMDA-R, BDNF, Trk-B, and α-synuclein) and, in many cases, these changes are counteracted by CR (reviewed in [26]). We have reported that IFD causes a selective increase in the hippocampal expression of the NR2B subunit of the NMDA-R in adult mice [98], mimicking the expression of NR2B found in young mice [99, 100]. These findings indicate that IFD could be a form of CR able to slow aging in rodents [101–103]. The functional consequence of the selective increase of NR2B expression in hippocampus of IFD mice is a clear facilitation in the acquisition and consolidation of new tasks of these mice when compared with AL mice. These findings could be attributed to a decrease in hippocampal aging, as witnessed by the upregulation of NR2B NMDA-R subunit expression. Furthermore, NR2B expression probably confers on the hippocampus of IFD mice a better capacity for integrating information (better information acquisition and long-term changes in synaptic efficacy) and for consolidation. All these data also suggest that success strategies for neuronal plasticity enhancement in adult and aged or neurodegenerative animals could be different in the two cases.

CR, Mitochondrial Function, and Synaptic Plasticity

In neurons, mitochondrial activity plays a central role in processes such as neuron viability, membrane excitability, neurotransmission, and plasticity [104]. Studies carried out in pathological situations demonstrate that mitochondrial and metabolic dysfunctions develop in parallel [105]. Synaptic localization and activity of mitochondria are essential for synaptic activity and dendritic spine remodeling, and it seems that, reciprocally, synaptic activity modulates motility and fission–fusion balance in the mitochondria [106]. The maintenance of the proper activity of the mitochondria during aging thus seems to be a key factor in preventing the development of aging-related

neurodegenerative diseases. In a proteomic study carried out in the brain of aged animals under CR, most of the proteins affected by CR were involved in mitochondrial activity [29]. The same proteomic analysis detected an increase in the release of BDNF, a factor that protects against neurodegeneration and modifies neuronal plasticity [107]. BDNF can also modify brain metabolism and the efficiency of oxygen utilization, affecting mitochondrial activity [108, 109].

During aging, mitochondrial biogenesis dysfunction affects the whole organism but especially the central nervous system. The decrease in mitochondrial biogenesis would affect the turnover of mitochondrial components and benefit the accumulation of oxidized molecules. Thus, it is important that a high turnover of mitochondria is maintained during aging, thereby preventing the deleterious effect of mitochondrial malfunction. We and others have recently demonstrated that CR affects mitochondrial biogenesis in various cells and tissues, including liver, muscle, and brain [110, 111]. CR induces the activity of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α). PGC-1α activates several transcription factors involved in the regulation of mitochondrial biogenesis, lipid metabolism, and antioxidant response. In rat brain, PGC-1α protein is very abundant in the embryonic and early postnatal nervous system, suggesting a pivotal role for this protein in the developing central nervous system [112]. In fact, PGC-1α knockout mice exhibit behavioral abnormalities and progressive vacuolization in various brain regions [113]. It is therefore conceivable that CR can ameliorate neuronal activity during aging by maintaining mitochondrial turnover through slowing the age-dependent PGC-1α decline, as has been described in muscle under CR [114, 115]. In fact, the importance of PGC-1α would explain why its repression by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration, whereas its overexpression rescues cells from the deleterious effect of huntingtin [116].

Furthermore, mitochondrial activity is important during the learning processes [117], and its inhibition impairs cognitive performance [118–120]. Recently, using green-fluorescence-labeled mitochondria and confocal technology, Tong [121] have demonstrated that tetanic stimulation triggers a fast delivery of mitochondria to the synapse. The importance of mitochondrial delivery and activity is demonstrated by the suppression of both mitochondrial transport and potentiation of the synapse by rotenone. The use of mutant mice for porins, also called voltage-dependent anion channels, and cyclosporin A has demonstrated that the normal mitochondrial permeability transition pore complex function is required for synaptic plasticity and learning and memory processes [119, 120]. Thus, one of the molecular bases underlying the maintenance of cognitive capacity induced by CR during aging seems to be the maintenance of PGC-1α activity and, in consequence, a higher rate of mitochondrial turnover.

Future Direction: Toward a Chemical CR Mimetic

Food addiction is now the major cause of disease and death in industrialized countries. This problem could be solved simply by communicating the consequences of overeating to physicians and the public. In practice, however, it has proven very difficult to successfully implement prolonged CR regimens. In light of the inability of many people to reduce their food intake, research efforts are being made to identify ways either to reduce food intake or to mimic the beneficial effects of CR using drugs, dietary supplements, and even gene therapy approaches. The development of a chemical CR mimetic could be a promising therapeutic avenue for the treatment of neurodegenerative diseases and to delay the aging process. Because many of the beneficial effects of CR may result from a preconditioning effect and/or a decreased production of reactive oxygen species, agents that impair glucose metabolism were tested as candidates to induce a beneficial cellular response in animals fed ad libitum. The first positive results were obtained with 2-deoxy-glucose (2-DG), a nonmetabolizable analog of glucose. When rodents were administered with 2-DG for 2 weeks, neurons in their brains exhibited an increased resistance to dysfunction and death in experimental models relevant to the pathogenesis of AD, PD, and stroke [88, 89, 122]. More interestingly, the mechanism whereby 2-DG supplementation protects neurons may be similar to that of CR because levels of some stress-induced proteins, heat shock protein 70 and glucose-regulated protein 78, are increased in neurons of rats and mice given 2-DG [88, 89, 122]. Although prolonged treatment of 2-DG has shown similar neuronal protection to that produced by CR, few studies has been performed in order to determinate nociception. Studies at the 80s and the 90s have demonstrated that 2-DG administration provoke a central analgesia [123] mediated by serotonin receptor [124]. Moreover, continuous infusion of 2-DG in the ventromedial nucleus of hypothalamus provoked antinociception in the tail flick latency and threshold [125]. In both situations, the molecular mechanisms involved in the hypoalgesia induced by 2-DG administration still need to be elucidated.

Recently SIRT1, a class III histone deacetylase that requires NAD^+ as cofactor, has been shown to promote adaptation to CR by regulating the genetic programs for gluconeogenesis and glycolysis in the liver [126]. In addition, SIRT1 facilitates the reversal of changes in the nutritional status, which it senses via NADH/NAD^+ levels

[127–129]. Members of this growing family of deacetylases (SIRT1–7, also called sirtuins) have been implied as regulators of key activities in the cell such as stress responses and cell survival, aggregation and removal of damaged proteins, mitochondrial function, and inflammatory responses [130]. Sirtuin activation not only extends life span but also promotes longevity and healthy aging, as well as delays the onset of neurodegenerative disorders associated to aging. Recently, the protection of sirtuins against axonal degeneration and in several models of neurodegenerative diseases such as Alzheimer's disease has been reported [131]. However, to date, only SIRT1 and, in a lesser extent, SIRT2 seem to play important roles in aging and neurodegeneration whereas no information is available yet about the role of the other sirtuins in the nervous system [132].

It is clear that sirtuins emerge as important regulators of several key transcription factors and cofactors such as p53, FOXO proteins, PGC-1α, and also NF-κB. Between these factors, PGC-1α appears as the central regulator of mitochondrial activity and biogenesis [133]. However, it seems that, at least in liver, SIRT1 does not regulate mitochondrial gene expression by PGC-1α modulation [126, 134] although it does modulate the gluconeogenesis–glycolysis pathways. Furthermore, the importance of PGC-1α in the developing CNS is patent due to its special abundance in embryonic and early postnatal forebrain and cerebellum [112]. Thus, we can consider that higher activity levels of PGC-1α induced by SIRT or CR would sustain neuronal health during aging by maintaining the mitochondrial activity and turnover. Furthermore, the repression of PGC-1α activity due to a mutant version of huntingtin leads to mitochondrial dysfunction and neurodegeneration whereas overexpression of PGC-1α prevents those [116]. On the other hand, the presence of a remarkable amount of proteins acetylated at lysine residues in mitochondria indicates that sirtuins can also exert a direct role on the regulation and probably maintenance of mitochondrial functions during aging [135]. This regulation can be the reason why high levels of SIRT1 protect neurons against amyloid-β-induced reactive oxygen species production and DNA damage [136] and rescue neurons affected by Alzheimer's or Huntington's diseases [137].

Given the role of SIRT1 as a mediator of CR and longevity, the production of SIRT1 activators is of great interest in the field of aging [138, 139]. Resveratrol is a natural polyphenol found in the skin of grapes and is well known for its antioxidant properties [139], as a SIRT1 activator [140] and—recently—as a mitochondrial biogenesis activator in various cells and tissues, including liver, muscle, and brain [141–143]. All these findings are consistent with the fact that, in various species, resveratrol treatment mimics SIRT1-dependent life span extension during CR [140–145]. Furthermore, resveratrol has been shown to be effective in treating some neurodegenerative diseases associated with aging (reviewed in [146]). Amyloid-β neurotoxicity seems to be mediated by nuclear factor-κB (NF-κB) in AD [147]. NF-κB activation can be modulated by acetylation–deacetylation and SIRT1 [148]. Overexpression of SIRT1 or resveratrol treatment in neuronal cell cultures suppresses Aβ-induced NF-κB signaling and neurotoxicity [147]. Furthermore, resveratrol promotes neurite outgrowth and also stimulates mitochondrial biogenesis contributing to neuronal energy homeostasis and neuroprotection [142]. In p25 transgenic mice—a model of AD and tauopathies—a resveratrol treatment reduced neurodegeneration in the hippocampus, prevented learning impairment, and decreased the acetylation of the known SIRT1 substrates PGC-1α and p53 [135]. Activation of SIRT1 by overexpression or resveratrol treatment rescues the neuronal dysfunction phenotype in a *Caenorhabditis elegans* HD model and reduces the death of neuronal cells in a mammalian cell culture HD model, and this effect is blocked by sirtinol, a SIRT1 inhibitor [149]. Moreover, resveratrol and also quercetin, another sirtuin-activating polyphenol, protect against dopaminergic neuronal death induced by several different insults including mitochondrial toxics such as MPP^+ and complex VI inhibitors in brain slices [150]. Taken together, all these facts indicate that SIRT1 regulating PGC-1α and mitochondrial function is an essential factor in the maintenance of neuronal activity and the prevention of neurodegeneration. Hence, resveratrol and resveratrol derivatives or SIRT activators emerge as promising pharmacological agents against cognitive deficiencies and neurodegenerative progression during aging due to both their antioxidant activity or by activating sirtuins. Also, the effect of resveratrol has been proved in nociception. The first reports described that acute administration of the SIRT activator provokes a decrease in the hyperalgesia induced by local administration in the hind paw with carrageenan or formalin [151, 152]. In both cases, the resveratrol-induced analgesia seems to be due to cyclooxygenase inhibition. Interestingly, subsequent studies demonstrated that the antinociceptive effect of resveratrol in inflammatory models of pain also could involve opioidergic mechanism [153]. Lastly, chronic administration of resveratrol for 4 weeks provokes a significant attenuation in neuropathic pain associated to diabetes [154].

Concluding Remarks

There is much to be learnt about the effects of food intake (how much and how often) on the cellular and molecular biology of the nervous system and its functional capabilities. Recent investigations clearly show that CR induced

processes that decrease the levels of oxidative damage to cellular macromolecules in the brain and other organs. Data obtained from animal studies suggest that these processes may dramatically reduce the incidence and severity of aging and aging-related diseases such as AD, PD, and stroke. CR induces other beneficial effects, such as enhancing learning and memory capabilities and provoking analgesia, both in adult healthy animals. However, prolonged CR could cause side effects due to excessive loss of body fat. By this reason, the development of a chemical CR mimetic may be a promising therapeutic avenue to provide similar health benefits to CR, while circumventing the long-term need to reduce food intake. 2-DG and resveratrol are effective compounds that mimic CR effects on longevity, neurodegenerative resistance, analgesia, and cognitive properties. However, further and more detailed studies are needed to determine molecular mechanisms underlying the beneficial effects of these compounds. These studies will establish the rational use of these drugs in pain, aging, and neurodegenerative disorders and for enhancing cognitive capacities in healthy individuals.

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