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·Minireview·

Dietary restriction and brain health

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Abstract: The benefits of dietary restriction (DR) on health and aging prevention have been well recognized. Recent studies suggest that DR may enhance brain functions including learning and memory, synaptic plasticity, and neurogenesis, all of which are associated with brain health. Under the stress stimulated by DR, a favorable environment is established for facilitating neuronal plasticity, enhancing cognitive function, stimulating neurogenesis and regulating inflammatory response. DR-induced expressions of factors such as heat shock proteins (HSPs), neurotrophic factors, and Sirtuin1 (SIRT1) are responsible for the effect of DR on the brain. Due to the difficulty in practising long-term DR in human, the potential mimics of DR are also discussed.

Keywords: dietary restriction; brain

1 Introduction

Aging is a very complicated process, accompanied with a decline in multiple organism systems, thus affecting reproductive, metabolic, physical, and cognitive functions and eventually, survival[1]. Aging can be regulated by changes of lifestyle such as dietary restriction (DR)[1]. DR is also named as caloric restriction, which refers to the dietary regimen low in calorie without a nutritional deficit that may cause increased disease risk[2]. There are 2 ways for caloric restriction. The first is to consume calorie 30%-40% less than the average intake level per day, and without malnutrition. In other words, for a person weighting 150 pounds and consuming about 2 200 calories per day, DR would limit the average caloric intake to 1 500-1 700 per day. The second way is by intermittent fasting (IF), or through every other day feeding (EODF). Animals in EODF are fed on an intermittent feeding regimen consisting of 24 h with normal food alternating with fasting for 24 h. Many studies indicate that implementation of the IF dietary regime results in an approximately 20%-30% reduction in calorie intake over time. Throughout the history, the beneficial effects of DR on health and general well-being have been realized. For example, "eat a 70% full diet" is an old saying concerning longevity in China. However, scientific studies on DR have not been conducted until 1935 when restricted diet and its ability to extend lifespan were reported by McCay and widely recognized[2]. In his studies, McCay shows that rats having a diet containing indigestible cellulose exhibit dramatically extended both mean and maximum lifespans[2], which has been confirmed and ex-

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tended to mice[3,4] and other species including fruitflies[5], nematodes[6], *etc.* Generally, the extension of lifespan has been shown to increase progressively with the reduction of caloric intake, until the point of starvation[7]. The time point of DR onset (pre- or post-pubertal) and the duration of DR are also determinant for the extent of lifespan extension[7].

Besides, DR has been shown to improve health and slow the aging process in many species[8], such as improving learning and memory, delaying age-related cognitive decline and reducing the risk of neurodegenerative disorders. In this review, the recent evidence on how DR affects the brain function and the underlying mechanisms were discussed. Then how DR protects the brain was discussed based on the hypothesis proposed by Mattson and Masoro[7,9]. Recent evidence demonstrates that DR can improve brain function via a pre-conditioning mechanism which increases the neuronal resistance to stress. Finally, recent studies on mimetic of DR were reviewed and future research in this area was also discussed.

2 Various brain function modalities are improved by DR

Besides lifespan extension, DR also has beneficial effects on general health[10,11]. Crucially, it has been found that DR can decrease the risk of diseases in many systems including the central nervous system (CNS)[12-14]. Various brain functions including learning and memory, synaptic plasticity, and neurogenesis can be improved by DR regime.

2.1 DR enhances learning and memory Studies in rodents have revealed robust effects of DR on aged animals, in which long-term DR can improve learning and memory, and counteract age-related behavioral impairment and disease-related mental decline[15-17]. For example, rats that have been on DR with a 40% reduction of calorie intake of normal level since the weaning age show decreases in age-related declines in stereotyped motor responses, motor coordination, and radial arm mazes[17], while rats maintained on unrestricted diet exhibit normal age-related deficits on cognitive tasks. Similarly, studies in non-human primates also demonstrate that 30% caloric restriction results in the reductions of the contents of peptides $A\beta_{1-40}$ and $A\beta_{1-42}$ in the temporal cortex of Squirrel monkeys, while $A\beta_{1-40}$ and $A\beta_{1-42}$ can cause mental deficiency in human[18]. However, due to the difficulties in performing DR in normal people, studies on human are at a very initial stage. Currently, there is no direct evidence from human study showing the protective effect of either short-term or long-term DR on cognition, such as memory, attention, processing speed and concentration[19,20]. However, both clinical and epidemiological evidence suggests that a high level of dietary fat is a risk factor for the development of Alzheimer's disease (AD)[21]. There is a significant negative correlation between low calorie intake and AD incidence. For example, people in China and Japan have a relatively low calorie intake (1 600–2 000 calories per day) as compared to the people in the United States and Western Europe (2 500–3 000 calories per day), and the AD incidence in China and Japan is approximately half of that in the United States and Western Europe[13].

Along with the improvement of performance in animal behavior, DR can also facilitate synaptic plasticity in the hippocampus, a key structure for spatial memory. Long-term potentiation (LTP) is the long-lasting enhancement in synaptic strength and is believed to be a cellular mechanism of learning and memory[22]. The effect of DR on age-related deficits in LTP has been reported. Eckles-Smith K *et al.*[23] have reported that caloric restriction prevents age-related deficits in LTP in the rat hippocampus. In addition, DR can inhibit the age-related decrease in the expression of NMDA receptor subunit NR1 in aged rats. In parallel with the effect of DR on hippocampal electrophysiological properties, DR also prevents age-related declines in the levels of synaptic protein synapsin[24], NMDA receptor subunit NR2B[25] and AMPK receptor (GluR1)[26] in the hippocampus, and levels of serotonin and dopamine in the cerebral cortex of rats. Preservation of LTP, synapse protein and neurotransmitter levels could provide a molecular and cellular mechanism by which DR enhances cognition and ameliorates age-associated cognition.

2.2 DR and neurogenesis Neurogenesis is a process during which progenitor cells develop into functionally integrated neurons. It is now believed to occur not only in the mammalian CNS during embryonic stages, but also in discrete re-

gions of the adult mammalian CNS[27,28]. In most mammals, active neurogenesis occurs throughout life in the subventricular zone (SVZ) of the lateral ventricle and in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus[29]. Evidence suggests that newly generated neuronal cells participate in processes such as learning and memory. For example, hippocampal irradiation for 8-21 d could block the formation of new neurons in the dentate gyrus (DG), resulting in deficiency in animal performance in a hippocampus-dependent place-recognition task[30]. This finding suggests that the newly generated neurons may be required for normal function of this area.

It has been shown that 3-month DR (IF) could increase the survival rate of new neurons in the hippocampus[31]. However, Bondolfi L *et al.* report that long-term DR (3-11 months, 60% of normal intake) does not inhibit age-related decline in hippocampal neurogenesis, but may increase the survival rate of glial precursors in the hilus[32]. The difference on the effect of DR on hippocampal neurogenesis may be due to the different protocols and time ranges of DR application in their studies. To fully realize the effect of DR on hippocampal neurogenesis, more systematic studies are needed.

2.3 DR is neuroprotective Extensive data demonstrate that DR can also attenuate brain injury and delay the onset of several neurodegenerative disorders. For example, epidemiological studies show that people taking low calorie or on a low-fat diet have significantly lower risks for AD and Parkinson's disease (PD) than those with higher calorie intake. This difference could be found especially in individuals carrying the apolipoprotein E4 allele (a risk factor for AD)[33]. In parallel with the epidemiological data, studies in animal models also support the beneficial effects of DR on age-related brain disorders such as AD and PD[34,35]. For example, DR is shown to improve the behavioral outcome in PD models[36], and enhance learning and memory in transgenic mouse model of AD[37]. Meanwhile, it can also delay the symptom onset in the transgenic mice of Huntington's disease[38]. The underlying mechanisms are associated with the neuroprotective effect of DR. For example, rats maintained on DR for 2-4 months show increased resistance to kainic acid-induced hippocampal damage[12]. What's more, in a model of PD, DR could reverse the vulnerability of midbrain dopaminergic neuron to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine toxicity and improve the motor function[36]. More interestingly, in the transgenic mouse model of AD, DR not only inhibits neuronal apoptosis caused by Aβ toxicity, but also decreases the production of Aβ plaque in the hippocampus and cortex[18].

In addition, DR has been shown to reduce several risk factors for cardiovascular diseases and stroke, such as insulin resistance, high levels of low-density lipoprotein (LDL) and cholesterol, and low levels of high-density lipoprotein (HDL) and hypertension[39,40]. The effect of DR on stroke has been tested in animal models. Application of DR for 3 months could attenuate brain damage and improve the behavioral outcome in a middle cerebral artery occlusion–reperfusion stroke model[13,41]. More interestingly, administration of 2-deoxy-*D*-glucose (a non-metabolizable glucose analog) in rats also reduces ischemic brain damage and improves behavioral outcome[42]. These results indicate that 2-deoxy-*D*-glucose may be similar with DR in some aspects. However, recent studies reveal that long-term application of 2-deoxy-*D*-glucose can cause congestive heart failure and even death. Thus, much work is needed to clarify the mechanisms underlying the effect of DR on brain and the possibility of applying the mimetic of DR in pre-clinical trial.

3 Mechanisms underlying DR effect on brain health

Although the effects of DR on lifespan and brain have been realized for several years, the underlying mechanisms still remain unclear. Several hypotheses have been proposed, including retardation of growth, reduction of metabolic, oxidative damage attenuation, alteration of glucose-insulin system, and alteration of growth hormone—IGF-1. Although those hypotheses can partly explain the effect of DR, they have some limitations. In 2005, Masoro *et al.* proposed a new hypothesis—"Hormesis Hypothesis"[43]. Hormesis is a term indicating generally favorable biological responses to low levels of toxins and other stressors. It is proved that a pollutant or toxin with hormetic properties may exert opposite effects at small doses, compared to that at large doses[44]. DR fits this criterion of hormesis in that a marked reduction in

food intake is obviously harmful to the point of being lethal, however, a long-term and moderate reduction in food intake can enable the organisms to cope with damaging environments and toxic agents more successfully[9]. Moreover, as a mild stressor, DR also induces the elevation of corticosterone level[45]. It is possible that under the condition of DR, individual cells and whole organisms are constantly forced to adapt to the stressful condition and at the same time develop multiple mechanisms to cope with stress[46]. Here the latest evidence supporting the hormesis hypothesis of DR at cellular and molecular levels was reviewed, including heat shock proteins (HSPs), neurotrophic factors, Sirtuin 1 (SIRT1), and peripheral hormones and proteins such as adiponectin and corticosterone.

3.1 HSPs Under stressed conditions, individual cells or organisms may have various adaptive measures for the resistance to the stress. Increasing the expressions of HSPs is one of the key mechanisms. The heat shock response is a highly conserved property of all living organisms[47,48]. During this response, the translation of non-stress-related proteins is decreased, and concurrent increases in transcription and translation of chaperones or HSPs are also observed, including HSP70, HSP90, HSP60, and glucose-regulated protein (GRP) 78 and GRP 94.

It has been reported that HSPs exert multi-functions on neurons. HSPs can prevent protein degradation and incorrect polypeptide aggregation induced by physiochemical stress. Also, HSPs are involved in antigen presentation, steroid receptor function, intracellular trafficking, nuclear receptor binding, and apoptosis[49]. Over-expression of HSP70 causes an increase in the expression of Bcl-2, the latter of which is an anti-apoptotic protein[50], and reduces the number of apoptotic cells under amyloid beta toxicity conditions[51]. Besides, *in vivo* administration of rhHSP70 is effective in extending lifespan, delaying the symptom onset, and preserving motor functions in an animal model of amyotrophic lateral sclerosis (ALS)[52]. Both *in vivo* and *in vitro* studies have shown that DR could stimulate the expressions of HSPs in neurons. Yu *et al*. have reported that short-term IF could cause significant increases in HSP70 and GRP78 expressions in the cortical, hippocampal and striatal neurons, compared to that in animals with AL feeding[42]. These data indicate the involvement of HSPs in the neuroprotective effect of 2-deoxyglucose.

3.2 Neurotrophic factors During DR, expression levels of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), are increased in the brain, a compensating mechanism to a chronic mild stress[38]. Similarly, the enhancement of BDNF expression is found in response to other stress conditions, such as hypoglycemia, ischemia, oxidative stress[53] and exercise[54] .

Generally, BDNF also has multi-functions in the brain. Firstly, BDNF promotes the survival and growth of neurons in various regions, including dorsal root ganglion cells[55], hippocampal and cortical neurons[56], via increasing the levels of proteins that suppress oxidative stress (antioxidant enzymes, glutamate receptor subunits and Bcl-2). Secondly, numerous studies have shown that BDNF is involved in the process of learning and memory. There is a positive correlation between hippocampal BDNF level and performance on hippocampal-dependent learning tasks[57]. In contrast, BDNF-knockout mice show impaired memory formation[58]. Thirdly, the elevation of BDNF expression in the hippocampus can improve neurogenesis. BDNF is also found to promote the survival and differentiation of progenitor cells in the hippocampus[59]. In DR animals, the expression of BDNF is increased in several brain regions, and the most robust and enduring responses occur in hippocampus and cortex[31]. Moreover, BDNF is required for basal neurogenesis and in part, mediates the DR-induced enhancement of neurogenesis in the hippocampus of adult mice[31]. Based upon the above findings, it is likely that the elevation of BDNF induced by DR is essential for the effect of DR on learning and memory in brain.

3.3 Silent information regulator 2 (SIR2)/ SIRT1 SIR2 or Siltuins is a family of nicotinamide adenine dinucleoitide (NAD)-dependent class III deacetylase[60], which are highly conserved from prokaryotes to human. As mediators of DR-induced lifespan extension in many species, the enzymes have gained much attention. SIRT1 is the mammalian homologue of SIR2, and catalyzes the deacetylation

of a variety of substrates, thus being involved in a broad range of physiological functions[61,62]. The downstream of SIRT1 pathway includes the tumor suppressor P53, the transcription factor nuclear factor kB (NF-kB) and Drosophila forkhead transcription factor (FOXO) family of transcription factors, and FOXO can control the cell proliferation and cell survival[61]. SIRT1 also deacetylates nuclear receptor peroxisome-proliferator receptor (PPAR-g) and PPAR-g co-activator a (PGC-a), which regulate a wide range of metabolic activities in muscle, adipose tissues and liver[62]. Thus, the expression of SIRT1 is crucial for DR function in glucose homeostasis, insulin secretion, fat metabolism, stress resistance and physical activity[63].

In the adult rat brain, SIRT1 expression is detected in the hippocampus, cerebellum and cortex. Studies demonstrate that DR or administration of resveratrol, a potential activator of SIRT1, could also increase the expression of SIRT1[64]. Recently, accumulating data have indicated the neuroprotective role of SIRT1. Firstly, SIRT1 may delay the onset of AD by inhibiting the generation of Aβ, which is one of the causes of AD. In primary cultured neurons, activation of SIRT1 can attenuate Aβ formation by stimulating the activity of α-secretase, the latter of which cleaves amyloid precursor protein (APP) in the fragment that would produce Aβ when APP is instead processed by α-secretase and γ-secretase[64]. In accordance with these *in vitro* data, upregulated secretase activity is found in rodent and non-human primates fed on a DR regimen[18]. Secondly, SIRT1 can indirectly protect neurons from Aβ-induced ROS production and DNA damage, thereby inhibiting apoptotic death *in vitro* through NF-κB signaling[65]. Moreover, elevated expression level of SIR1 has been found in pre-ischemic animal models. Pre-conditioning ischemia induces an increase in SIR1 expression in brain and protects neurons against the damage from ischemia, while sirtinol (an inhibitor for SIRTI) could abolish this protective effect[66], indicating that SIRT1 is crucial for the protection in pre-conditioning animal model. Therefore, the elevation of SIRT1 can contribute to the protective effect of DR.

3.4 Systemic mechanisms: DR reduces peripheral risk factors Currently, a fundamental concept has been proposed that brain health and cognitive function are modulated by the interplay of various central and peripheral factors. The peripheral risk factors for brain health include hypertension, obesity, dyslipidemia, impaired glucose metabolism, and inflammation[67]. Remarkably, DR can reduce all these peripheral risk factors, including improving cardiovascular function, restoring lipid–cholesterol balance and energy metabolism, enhancing insulin sensitivity, and inhibiting inflammation. Thus, besides the mechanisms mentioned above, DR improves brain health and function may also through reducing the peripheral (indirect) risks of cognitive decline.

3.4.1 DR and adiponectin DR improves brain health and cognitive function may through regulating endocrine changes in the peripheral system. Adiponectin is one of the candidates, since the concentration of adiponectin in the blood could be increased by DR[68]. Adiponectin is a 30 KD adipose tissue-derived hormone with anti-atherogenic, antidiabetic and insulin sensitizing properties[69-71]. Adiponectin is regarded as an insulin-sensitizing factor since it can decrease gluconeogenesis by increasing hepatic insulin sensitivity, glucose uptake in adipocytes and myocytes, and fatty acid oxidation in muscles. Moreover, studies in human show that a reduced serum concentration of adiponectin is correlated with high risks of obesity[72], insulin resistance and type 2 diabetes[73]. Collectively, these findings suggest that adiponectin could strongly counteract most of the risk factors of sporadic AD, such as insulin resistance, diabetes, obesity, vascular injury, atherosclerosis and metabolic syndrome[74,75]. Furthermore, other evidences indicate that adiponectin may have protective effects on the brain. For example, adiponectin-knockout mice show a larger infarct size after ischemia compared to the wild type, indicating that adiponectin attenuates the damage of cerebral ischemia[76]. In addition, adiponectin can decrease the expressions of pro-inflammatory cytokines such as IL-6[77], which is involved not only in immune dysfunction but also in AD pathogenesis[78].

Regarding the effects of adiponectin, recent studies in rodents suggest that adiponectin plays a role in the regulation of food intake, via the adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2), both of which are expressed in the hypothalamus[71,79]. Central administration of adiponectin can regulate food intake and decrease the body weight[79]. In

addition, our studies have observed the expressions of adiponectin and its receptors in the hippocampus (unpublished data), which indicate the participation of adiponectin in other brain functions locally, although further studies are needed.

3.4.2 DR and corticosterone Corticosterone is secreted in the adrenal gland in hourly pulses, which is thought to synchronize and coordinate sleep-related and daily events[80]. At any time, corticosterone response can be triggered by a stressor. DR is shown to cause a daily increase of the peak concentration of plasma corticosterone in rodents throughout the whole life[81]. This daily elevation of plasma corticosterone level indicates that DR causes a daily period of stress in these rodent species[82]. Moreover, DR-induced daily elevation of plasma free corticosterone level is slighter compared to the rapid, marked elevation caused by other stressors such as restraint[81]. Thus, DR can be regarded as a daily low-intensity stressor.

Corticosteroid hormones play an important role in energy hormesis of body via energy metabolism regulation, including stimulation of gluconeogenesis, mobilization of amino acids from extrahepatic tissues, inhibition of glucose uptake in muscle and adipose tissue, and stimulation of fat breakdown in adipose tissue[83]. Thus the DR-induced elevation of corticosterone could be regarded as a homeostatic response to the reduction of food intake and the need for an increase in gluconeogenesis. At the same time, corticosterone can enter the brain and bind to 2 types of intracellular receptors that regulate transcriptions of responsive genes: one is the mineralocorticoid receptors (MRs) with a high affinity and another is the glucocorticoid receptors (GRs) with an approximately 10-fold lower affinity. Both MRs and GRs are widely expressed in the brain[84]. The MRs are mostly restricted to limbic brain regions, such as the hippocampus, septal and amygdala nuclei and motor nuclei in the brainstem, while GRs are much more ubiquitous, in both neurons and glial cells[85]. Studies indicate that the effect of corticosterone on brain is very complicated. Corticosterone may act as a double sword in the regulation of brain function and the effect could be dose-dependent. Firstly, the physiological level of corticosterone is critical for neuronal survival. Adrenalectomy (ADX), which means removal of the major organism for synthesizing corticosterone, can induce cell death of granular neurons in the hippocampus, while replacement of corticosterone could then block this neuronal death[86]. Moreover, it is also found that the replacement of corticosterone can prevent the reduction of *bcl-2* gene expression after ADX[86]. Secondly, it has been found that corticosterone can facilitate and enhance memory consolidation[87]. For example, Morris water maze has revealed that rats subjected to cold water, a related stressor, learn faster and retain information longer[87]. On the other hand, over-expression of corticosterone *in vivo* is frequently associated with reductions of neuronal viability and neurogenesis, and cognitive impairment[88,89]. Longitudinal studies show that elevation of plasma cortisol level correlates with reduced hippocampal volume and memory impairment in aging subjects[89]. In fact, some subjects with a higher cortisol level develop into AD. Furthermore, Cushing's syndrome patients who exhibit dramatic elevations of glucorticosteroid level, are also characterized by memory impairment and hippocampal volume reduction[90].

Considering the bimodal effects of corticosterone on cognition, hippocampal pyramidal neurons, and learning and memory, it is really hard to clarify the exact role of corticosterone in DR functioning on the brain. Preventing the DR-induced elevation of corticosterone and examining the function of DR may be a good method to explore the role of corticosterone in the protective effect of DR on the brain.

4 DR mimetic

Although DR could extend lifespan, enhance cognition and reduce risks of neurodegenerative disorders, it may be hard to practise DR in the general public since it is very difficult to maintain long-term DR in human. Besides the requirement of adaption to a new diet habit, other side effects also occur. For example, DR can cause a decline in sex steroid due to the excessive loss of body fat, which may lead to menstrual irregularity, amenorrhea, bone thinning, and osteoporosis in female[20]. Therefore, some natural or pharmacological agents whose functions mimic that of DR have become the target of current research.

Moreover, studies have identified several compounds with similar effects to that of DR, including plant-derived molecules (e.g. resveratrol[91]), insulin-action enhancers (metformin)[92] and glucose analogue 2-deoxyglucose[93]. Among these compounds, resveratrol has been shown to increase the lifespans of *S. cerevisiae*, *C. elegans*, *D. melanogaster*, Northobranchius furzeri[91,94], a short-lived fish[95] and even rodents[96]. In addition, resveratrol could improve neuronal resistance to stress. *In vitro* studies indicate that resveratrol counteracts H_2O_2-induced oxidative damage, not only by its antioxidant properties, but also through the modulations of glial cell functions. Vieira[97] has reported that resveratrol can improve glutamate uptake and increase glutathione content and S100B secretion, suggesting that resveratrol may improve functional recovery after brain injury. Besides, resveratrol is found to protect the brain against excitoxtic insult in rodents[98,99]. Furthermore, resveratrol may mimic DR in its effect on SIRT1. *In vivo* studies reveal that resveratrol activates SIRT1 and induces many effects similar as that of SIRT1. Similar with SIRT1, resveratrol can deacetylate peroxisome proliferator-activated receptor-γ coactivator (PGC-1α)[100], promote cell survival by stimulating P53 deacetylation, inhibit adipocyte differentiation, activate fat mobilization by suppressing PPAR-γ, and sensitize cell tumor necrosis factor α (TNF-α)-induced apoptosis by stimulating NF-κB deacetylation[96]. However, further studies are needed to determine the exact role of resveratrol or other DR mimetic on lifespan and brain health in human. Hopefully, agents such as resveratrol could provide similar beneficial effects on lifespan and brain health, and reduce the risks of neurodegenerative disorders, just like DR.

5 Conclusion

Studies in animals and human indicate that DR improves many aspects of brain function and has broad effects on the overall brain health. The hormesis theory may well explain the possible mechanisms underlying the effect of DR on the brain. Under DR stress, a favorable environment is established for facilitating neuronal plasticity, enhancing cognitive function, stimulating neurogenesis and regulating inflammatory response. Many factors such as HSPs, neurotrophic factors, and SIRT1 induced by DR can be responsible for the effect of DR on the brain. Besides, DR might also induce many peripheral factors that are responsible for the effect of DR on the brain. Although the mechanisms underlying DR effect on the brain have not been completely understood, animal studies have provided valuable clues to explore compounds whose effects mimic that of DR. Further research is still required to confirm these findings for drug application in disease treatment in human.

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限制饮食和大脑健康

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摘要：限制饮食对健康和老化的益处已经逐渐被大家所认识。本文从学习、记忆、突触可塑性、神经再生等神经功能方面，回顾了最近有关限制饮食的基础及临床研究。目前认为限制饮食在神经功能方面发挥多种作用，其中较令人满意的解释是限制饮食作为一种应激原，能诱导机体内有利环境的形成。这个环境有利于促进神经可塑性，提高认知功能，刺激神经细胞再生和调节炎症反应。此外，许多分子包括热休克蛋白、神经营养因子、沉默调节蛋白1(SIRT1)等均参与了限制饮食对机体的保护作用。鉴于完全和长时间的限制饮食在人类实施的困难性，一些限制饮食模型的替代物开始被大家所重视。本文也对限制饮食模型的替代物的研究进行了分析和探讨。

关键词：限制饮食；大脑