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The Effects of Calorie Restriction in Depression and Potential Mechanisms

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Abstract: Depression, also called major depressive disorder, is a neuropsychiatric disorder jeopardizing an increasing number of the population worldwide. To date, a large number of studies have devoted great attention to this problematic condition and raised several hypotheses of depression. Based on these theories, many antidepressant drugs were developed for the treatment of depression. Yet, the depressed patients are often refractory to the antidepressant therapies. Recently, increasing experimental evidences demonstrated the effects of calorie restriction in neuroendocrine system and in depression. Both basic and clinical investigations indicated that short-term calorie restriction might induce an antidepressant efficacy in depression, providing a novel avenue for treatment. Molecular basis underlying the antidepressant actions of calorie restriction might involve multiple physiological processes, primarily including orexin signaling activation, increased CREB phosphorylation and neurotrophic effects, release of endorphin and ketone production. However, the effects of chronic calorie restriction were quite controversial, in the cases that it often resulted in the long-term detrimental effects *via* inhibiting the function of 5-HT system and decreasing leptin levels. Here we review such dual effects of calorie restriction in depression and potential molecular basis behind these effects, especially focusing on antidepressant effects.

Keywords: Antidepressants, BDNF, calorie restriction, depression, orexin, serotonin.

1. INTRODUCITON

Major depressive disorder is the most commonly diagnosed neuropsychiatric condition with characteristics of low mood, reduced responsiveness to pleasurable stimuli, lack of appetite, insomnia and even suicidal intentions [1, 2]. Although the multitude of antidepressants has been developed, depression remains a significant cause of morbidity in the world [3].

Although insufficient to explain all aspects of depression, the monoamine hypothesis might be the most widely accepted one by the scientific community [4-9]. The monoamine hypothesis suggests that depression results from an aberrant neurotransmission of serotonin and noradrenalinein the hippocampus as well as subsequent hypothalamic pituitary adrenal (HPA) axis activation [10]. Thus, antidepressants, which increase these neurotransmitters in the synaptic cleft through blocking the monoamine reuptake or degradation, are able to elicit antidepressant efficacy in depression [11, 12]. Additionally, CREB (cAMP response element binding)/ BDNF (brain-derivated neurotrophic factor) is another well-identified signaling pathway pathway that involves antidepressant properties [7]. However, the pathophysiology of major depressive disorder seems extremely complicated and due to our limited understanding of depression etiology, current treatment of depression remains sub-optimal: complete remission only occurs in less than half of cases and even in the cases antidepressant reagents are effective, depressed patients often succumb to an immediate relapse of depression after drug withdrawal [13].

Calorie restriction (CR) refers to a reduction of calorie intake by 30-40%, while retaining protein, vitamin, mineral, water intake to maintain proper nutrition [14]. According to a randomized study of calorie restriction, six months of calorie restriction resulted in favorable physiological alterations, such as fat distribution, body temperature, fasting insulin, T3 and T4, as well as ghrelin levels [15]. Today, it has been well-established that calorie restriction produces numerous benefits to our health, such as reducing the risk of cardiovascular disease [16], improving insulin sensitivity in diabetes [17], alleviating oxidative stress [15] and enhancing cognitive functions [18]. As an alternative to calorie restriction, alternate day fasting (ADF), which allows participants to reduce food intake on certain days rather than on each day, showed similar benefits in clinical trials [19]. In addition, fasting could improve mood, sleep quality and daytime concentration [20]. Meanwhile, sports, which help consume the extra energy and increase endorphin release also result in great improvement in mood [21] and are adopted in antidepressant therapy [22].

At present, the calorie restriction has attracted increasing attention due to its evident effects on neuroendocrine system and mood condition. Both basic and clinical investigations demonstrated that calorie restriction triggered intracellular signaling pathway that involves stress response and neuron

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metabolism [23]. Most of them have been recognized as crucial regulators that intimately associated with the pathogenesis of depression. However, the question of whether calorie restriction causes positive or negative efforts on neuropsychological conditions remains in debate [24]. Short term and mild calorie restriction, as well as moderate exercise were likely to exhibit antidepressant effects, through activating neuroendocrine hormones to compensate energy deficiency. Whereas, most of the prolonged calorie restriction or severe dietary restriction, including fasting, often caused inevitable damage to neurons and exaggerated depressive behaviors.

In this article, we will discuss such controversial actions of calorie restriction in depression by presenting both experimental evidences and clinical findings, aiming to explore possible biological mechanisms behind these efficacies.

1.1. Anti-depressant Like Effects of Calorie Restriction

Clinicians found that prolonged fasting reduces negative emotions in patients suffering from eating disorders [15, 25]. Hussin *et al*. reported that fasting and calorie restriction markedly relieved negative moods like tension, anger and confusion and enhance the sense of euphoria among ageing men [26]. Furthermore, sustained calorie reduction by 25% for six months reduced depressive symptoms while producing no obvious negative effects on mood [27]. In a prospective uncontrolled trial, Michalsen and colleagues examined the effects of calorie intake of 250kcal/day for 2 weeks in patients suffering from chronic pain. They found that, notably, more than 80% of subjects showed an effective improvement in depressive mood [28]. It was found that such antidepressant effects were due to increased availability of neurotransimitters, such as serotonin, endogenous opioids [29]. In another study, 8 days of fasting (350 kcal/d) induced significant mood improvement *via* the polymorphism of GNB3 C825T [30].

Similar antidepressant effects of calorie restriction were also found in animal depression models. After calorie restriction, mice became more socially active than their control counter parts [31]. Manzanero *et al*. found that calorie restriction protected neurons against degeneration in rodent models, proposing that calorie restriction may benefit neurons [32]. Moreover, a recent study showed that 10 days of calorie restrictionled to a marked antidepressant-like response in rodents [23].

During Ramadan, Moslems tend to abstain from drinking and eating in the daytime. This religious activity provides a model of fasting and helps us investigate the effects of calorie restriction. According to a survey using this model indicated that depression score was improved in depression patients, without significant changes in lithium blood levels during Ramadan fasting [33]. However, the other studies showed contradictory results in the Ramadan fasting. Due to absence of adequate data, the effects of Ramadan fasting remain unclear.

Similar to diatery restriction, moderate sports also exerted positive effects on depression. It was reported that the adolescents participating in moderate sports had lower depression scores than those involving low sports [34]. Sports has been considered as a protective factor against depression as well as suicidal disposition [35]. Actually, sports had been adopted for the treatment of depression since it was found to benefit major depressive patients [36, 37].

1.2. Possible Mechanisms Underlying Antidepressant Efficacy of Calorie Restriction

1.2.1. Orexin Signaling Activation

Lutter *et al*. demonstrated that 10 days of calorie restriction induced antidepressant-like effects in rodent models of depression, *via* orexin signaling activation [23]. Orexin signaling is well known for its multiple functions, such as consolidation of arousal, metabolism regulation, food intake and mediating reward responses [38-41]. Although orexin absence alone did not reproduce the complete symptoms of depression, acute calorie restriction in orexin-null mice induced anti-depressant-like responses in social defeat model through increasing the activity of orexin neurons in their study.

Ghrelin is a peptide hormone produced by ghrelin cells in the gastrointestinal tract and functions as a neuropeptide in the central nervous system. Ghrelin plays a critical role in regulating the distribution and rate of use of energy [42]. In response of energy deficiency, it induces an effective feeding response by triggering growth hormone secret agogue receptors (Ghsr, ghrelin receptor) that exists in the central nervous system. Ghrelin activates orexin neurons *via* inducing c-FOS expression in orexin neurons. Ghsr polymorphism was detected in a number of major depression patients, and ghrelin administration showed favorable effects on mood in the patients with depression. Raising ghrelin levels through calorie restriction elicited an antidepressant response in the mice forced swim test (FST). The antidepressant effects of ghrelin are primarily dependent on direct and/or indirect activation of orexin neurons in the lateral hypothalamus. Such activation is essential for the antidepressant-like effect of calorie restriction. However, prolonged and repeated activation of the orexin neurons may downregulate prepro-orexin mRNA expression in the lateral hypothalamus, impairing the compensation capacity of orexin neurons.

1.2.2. CREB/BDNF Signaling Activation

Fusco group reported that phosphorylated cAMP responsive-element binding(p-CREB) was significantly activated in calorie restricted mice [43]. CREB is a key transcriptor critical for multiple signal transduction cascades, thus playing a central role in the neuronal plasticity and the neuronal transcription regulation induced by certain antidepressants. The activation of CREB/BDNF signaling pathway is triggered by the phosphorylation of CREB itself on Ser-133 site. The phosphorylated CREB then facilitates the transcription of target genes with the CRE motif. As a bona fide factor required for neuronal survive, Ser-133 phosphorylated CREB (p-CREB) can activate the transcription of its downstream genes encoding c-FOS protein and many other neurotrophins [44, 45]. Increased level of CREB and p-CREB is associated with the effects of several antidepressant components [46].

Feeding behavior was found to activate brain-derived neurotrophic factor (BDNF) and sustain brain neuronal plasticity, playing an essential role in the process of neurogenesis [47, 48]. The cerebral glucose decrease induced by calorie restriction also promotes neurogenesis, neurotrophin synthesis, neurotransmitter receptor expressions and BDNF activation. BDNF is a neurotrophin that plays a central role in the formation and plasticity of neuronal networks [49, 50]. Mature BDNF facilitates neuron survival and differentiation *via* the specific activation of TrkB, a tyrosine kinase receptor, accelerating the branching of axons and dendrites and stabilizing synaptic contacts [51]. The BDNF hypothesis of depression assumes that depression primarily results from a dysfunction of BDNF, thus its restoration can serve as an effective therapeutic strategy against depression. During these years, the BDNF hypothesis has been supported by considerable experimental evidences. Decreased serum levels of BDNF were found in depressed patient, increasing levels of BDNF were found in patients after the treatment with antidepressants.

BDNF also regulates the metabolism of serotonin and synaptic plasticity, improving cognitive function [52-54]. It was demonstrated that acute calorie restriction produced antidepressant-like effects *via* elevated p-CREB/CREB ratio. Thus, the combination of fasting and imipramine, which regulates 5-HT2 receptors, induced an additive antidepressant-like effect in animal model. Nevertheless, many other studies have generated evidences that contradict the BDNF hypothesis of depression. More detailed studies are still needed to elucidate the correlation between calorie restriction and BDNF function.

1.2.3. Endorphin Release

Endorphins have been established to produce sensations of analgesia and sense of euphoria. Studies on the correlation between sports practice and depression have demonstrated that during moderate exercise the brain undergoes a eustress, which activates the endorphin generation [55]. The release of endogenous endorphins was found in 5-10 days of fasting improved depression without significant loss of weight. In rat fasting model 5 levels of endogenous opiate production increased [56]. Consequently, it was proposed that antidepressant effects of calorie restriction might result from increased endorphin to some extent. However, more detailed evidences are still needed to prove this point.

1.2.4. Production of Ketone

Ketone plays a crucial role in improving mood, ameliorating pain, and protecting neurons against hypoglycemia [57, 58]. The antidepressant effects of calorie restriction might be dependent on the increased production of ketone. It was proposed that the anticonvulsant properties might involve its multiple effects on central neuronal system [59]. However, no direct evidence supporting such effects of ketone in depression has been yet reported.

1.3. The Association between Chronic Calorie Restriction and Depression

Food dietary below 500kcal/day leads to rapid mobilization of glycogen stores in the initial stage and 24h of fasting may result in the lipolysis of fat mass and even accelerated protein catabolism. Up to now, alterations of brain function induced by starvation have been studied systemically [60]. In earlier studies, intentional fasting and dietary calorie restriction to lose body weight per se was considered to facilitate the development of depression [61]. Excessive calorie restriction impaired cognitive abilities and thereby, lowered one's quality of life, leading to negative mood states [19]. According to some studies, the effect of calorie restriction was considered as a mild stressor on the elevation of corticosterone levels [62]. In response to energy stress, glucocorticoids are of tern elevated slightly and regress to normal when the stress subsides. However, excessive elevation of glucocorticoids may result in detrimental impacts on neurons [63].

As aforementioned, Ramadan fasting provides a plausible model to understand the actual efficacy of calorie restriction. Keys *et al*. reported that severe calorie restriction (45%) for six months duration increased depressive mood and tiredness in Ramadan fasters [42]. Likewise, Roky and colleagues determined the effects of Ramadan intermittent fasting on the mood and found that Ramadan intermittent fasting produced negative effects on moods and decreased the subjective alertness [64].

1.3.1. 5-HT System Deregulation

It was indicated that diet behaviors strongly trigger the regulation of serotonin system and long-term calorierestriction suppresses 5-HTergic activities in the brain [65, 66], inducing the dysfunctions of cerebral 5-HT system and the development of psychiatric disorders [67, 68]. Studies on rodent models showed that fasting enhanced the availability of brain tryptophan and serotonin [69]. Jahng and colleagues found 5 weeks of calorie restriction in young rats significantly increased the plasma level of corticosterone with HPA chronic activation, while lowering 5-HIAA/5-HT ratio in the hippocampus. In the raphe nucleus, where most of 5-HT neurons are localized, calorie restriction significantly inhibits 5-HTT mRNA expression [70]. Serotonin reuptake transporter (5-HTT) reuptakes 5-HT from the synaptic cleft once 5-HT is release, which is important for appropriate propagation of 5-HTergic signals. 2 weeks of 50% food restriction greatly reduced 5-HTT densities in the frontal cortex of rats [66]. Decreased 5-HTT expression was highly correlated with the development of depressive behaviors in rodent models [71,72] and human [73]. 5-HTT mRNA expression level was also declined in the raphe nucleus of anorexic mutant mouse with severe weight loss [74]. It has been suggested that 5-HTergic activities modulated by plasma glucocorticoids involves the pathophysiology of depression. Chronic food restriction elevating plasma corticosterone level in rodent model [75, 76] increases glucocorticoid receptors in the hippocampus as well [77]. A history of calorie restriction induced depression-like behaviors and neurochemical alterations in rats *via* dysfunction of monoamine system, and such effects persisted despite recovery of normal body weight and food intake [78].

1.3.2. Decreased Leptin Levels

In addition, fasting for over 8 days activates the HPA axis, through reduced availability of cerebral glucose, as well as decreased leptin levels [79-82]. Leptin, a hormone derived

from adipocyte, regulates adipose tissue mass and energy balance and resistance to it is held responsible for obesity [83]. Notably, decreased leptin level was suggested as a critical response to starvation and the aberrant plasma level of leptin is associated with certain mood disorders [84]. It was shown that changed leptin levels induced improvement in depression [85]. Animal studies indicated that decreased leptin level, was associated with depression-like behaviors, and leptin per se had an antidepressant-like efficacy [86]. Yet, no significant difference in leptin levels has been found in depressive patients [85] and high leptin levels was found in depressive women but not in men [87]. In another study, high leptin levels were found as an increased risk of depression onset in men [88]. Recently, rather than changes in leptin levels, studies began to focus on leptin resistance and impaired leptin function in the pathophysiology of depression [89, 90]. Still, the effects of leptin dysfunction in depression have not been well understood and are worth further investigation.

CONCLUSION

There is a great need to understand the mechanisms underlying depression to overcome the resistance to these therapeutic agents and develop new treatments. In this article, we discussed such dual effects of calorie restriction in depression and possible molecular basis behind them. The antidepressant efficacy of calorie restriction in depression has been found in increasing the number of experimental evidences and raised a promising therapeutic strategy against depression. Supported by certain clinical and preclinical studies mentioned above, the antidepressant effects of calorie restriction might be based on the molecular basis that involves orexin signaling, p-CREB/BDNF signaling and other neuroendocrine system. However, the opposite effects of long-term calorie restriction in depression were also found in many studies. Such different outcomes of calorie restriction in depression probably contribute to diverse depression models and heterogeneous genetic background of participants. Furthermore, absence of uniquely adopted degree of calorie restriction, including dietary time and reduced extent of calorie intake from mild to severe, we can hardly compare the different effects of calorie restriction. Even a single difference of recipe or ingredient may result in such dual effects of calorie restriction. Still, further investigation is required for better understanding of the links between the different effects of calorie restriction. In the light of multiple factors involved in the pathophysiology process of depression, such controversial issue is warranted to be elucidated, which may help to overcome the resistance to these therapeutic agents and develop new treatments.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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