Nutritional Brain Energy Enhancement for Reducing Mental Fatigue and Improving Mood and Cognition

Benjamin I. Brown, ND[1]

[1] Nutri Ltd United Kingdom, British College of Nutritional Health, email: BenBrownND@gmail.com

Abstract *Deficits in mental energy negatively impact mood, motivation and cognition, and may significantly affect quality of life in a large portion of the general population. Central to the maintenance of optimal mental energy is the role of the mitochondria in energy metabolism. The mitochondria play a fundamental role in maintaining neuropsychiatric function with evidence suggesting a relationship between impaired mitochondrial function and deficits in mood, cognition and mental vitality. The enhancement of brain energy metabolism with nutritional factors such as creatine, acetyl-l-carnitine, multivitamins and polyphenol rich diets may be a novel strategy for reducing mental fatigue and improving mood and cognition, having wider relevance to neuropsychiatric and neurodegenerative illness, such as major depression and Alzheimer's disease.*

Definition and Prevalence of Mental Energy Deficit

Mental energy has been defined as a three-dimensional construct consisting of mood (transient feelings about the presence of fatigue or energy), motivation (determination and enthusiasm), and cognition (sustained attention and vigilance).[1] Optimal mental energy, as reflected by such features as an enthusiastic outlook, abundant energy, clear thinking and a sharp memory, could be considered features of good mental health and healthy brain aging.[2]

It is conceivable that deficits in mental energy in this context would have subtle, but important relationships to work performance, social relationships, and quality of life in relatively healthy individuals although this has not been adequately investigated. However, features of low mental energy in the dimensions of mood, motivation and cognition are common features of prevalent mental health disorders and chronic illness such as depression, cognitive dysfunction and chronic fatigue, and are associated with considerable morbidity.

Major Depressive Disorder (MDD) is one of the most common psychiatric illnesses with a lifetime prevalence rate of 16.2%.[3] The diagnosis of MDD requires the presence of symptoms that fall within the construct of low mental energy including loss of interest, depressed mood, loss of energy and concentration difficulties.[4] Thus, MDD could be viewed as a common and pathological example of low mental energy.

Low mental energy in the cognitive domains of memory and attention is frequently found in the general population. Age-related cognitive dysfunction occurs across a gradual continuum of preclinical cognitive decline (PCD), mild cognitive impairment (MCI) and Alzheimer's disease (AD).[5] PCD precedes MCI and AD by several years and begins at least as early as 45 years of age.[6] The prevalence of MCI is 10% at 70-79 years and

25% at 80-89 years of age.[7] The frequency of AD is also high with prevalence rates in people over 60 years of age in North American and Western European populations estimated at 6.4% and 5.4% respectively.[8] The clinical characteristics of PCD and MCI are deficits in memory with more advanced cognitive impairment in AD.[9]

Fatigue is also a very common complaint, in one large survey amongst general practices in the United Kingdom some 38% of respondents reported substantial physical and mental fatigue and 18.3% reported that their fatigue had lasted six months or longer.[10] Population estimates of chronic fatigue syndrome (CFS), an illness characterized by severe debilitating physical and mental fatigue and cognitive dysfunction range from 1.85% to 11.3%.[11] Fatigue is frequently a non-specific symptom, and although often accompanies lifestyle issues, physical illness and mental disorders, the cause cannot be identified in one-third of cases.[12] Interestingly, there is evidence to suggest that mental fatigue may be central to the experience of peripheral fatigue symptoms.[13]

Considerable clinical overlap exists between symptoms of depression, cognitive dysfunction and fatigue. For example, up to 57% of CFS sufferers may have MDD disorder.[14] Therefore, it is conceivable that a deficit in metabolic energy metabolism might be the biological explanation for the clinical symptoms of low mental energy across seemingly disparate illnesses. Central to energy metabolism throughout the central nervous system are the mitochondria, organelles that generate the majority of energy in the form of adenosine triphosphate (ATP). Deficits in mitochondrial function have been implicated in several neuropsychiatric disorders characterized by low mental energy, including several mood and cognitive disorders.[15]

Neurological Roles of the Mitochondria

The brain consumes approximately 20% of the body's energy although it only represents 2% of absolute body mass. Energy in the form of ATP is essential to several neurological processes including the maintenance of neuronal electrical potential, neurotransmitter release in the synapse, the expression of cell receptors, cell signaling and gene expression. Accordingly, reductions in mitochondrial ATP production may result in rapid synaptic fatigue.[16]

Neuroplasticity is a broad term that encompasses adaptive structural and functional changes that occur in the nervous system in response to physiological or pathological perturbations. These changes include the generation of new neurons (neurogenesis) and the formation of synapses. The mitochondria are known to move dynamically along axons and dendrites where they provide energy and play a fundamental regulatory role in processes related to neuroplasticity.[17]

Calcium is a leading secondary messenger in the brain and calcium signaling is critical to neurotransmission and neuroplasticity. In neurotransmission, calcium releases into the synapse following neurotransmitter release and signals synaptic activity to the neuron. Calcium signaling is a highly energy dependent process and requires ATP to restore intracellular calcium levels. As a primary source of energy for maintaining calcium homoeostasis, the mitochondria play an important role in calcium mediated neurological processes.[18]

Cellular energy metabolism requires oxygen consumption, and consequently, the mitochondria are a major source of oxidant stress. The mitochondria also play a critical role in maintaining redox balance through the generation of antioxidant defenses.[19] Mitochondrial energy metabolism usually generates low-level oxidant production, but this can be up-regulated in pathological states.[20] Low-level oxidative stress plays an important role in neurological functions such as neurotransmission and neuroplasticity; however, excessive production of reactive oxygen species and/or reduced antioxidant defenses can result in neurotoxicity and cellular dysfunction.[21] For example, mitochondrial reactive oxygen species have been shown to inactivate neuronal nicotinic acetylcholine receptors (important for cognitive functions) and reduce synaptic transmission in a dose dependant fashion.[22]

Mitochondrial Dysfunction, Mood, Cognition and Fatigue

Several lines of evidence including experimental studies, brain autopsy investigations and functional assessment of mitochondrial activity and brain energy metabolism suggest that there are important behavioral and cognitive consequences of mitochondrial dysfunction that are expressed as clinical symptoms of low mental energy.

A number of post mortem studies of patients with depression have found evidence of mitochondrial dysfunction in various regions of the brain involved in regulation of mood and cognitive function, such as the prefrontal cortex.[23] Low levels of respiratory chain enzyme ratios and ATP production and increased mitochondrial gene deletions have been found in the peripheral muscle tissue of patients with chronic depression.[24] Interestingly, in these patients symptoms related to muscular dysfunction and mental fatigue predicted muscle ATP production rates suggesting that a sub-group of depression may be due to mitochondrial dysfunction.[25] There is even experimental evidence suggesting that common anti-depressant drugs may be working at least in part by improving brain mitochondrial metabolism.[26]

Reductions in brain glucose metabolism have been consistently documented and are characteristic of cognitive decline with age. Impaired glucose metabolism can be detected in earlier stages of AD including MCI and have been found to predate clinical symptoms by decades in individuals genetically susceptible to AD. Changes in brain glucose metabolism could be explained by underlying mitochondrial dysfunction.[27] A study of the brains in patients with autopsy confirmed AD found that alterations in citric acid cycle enzymes of the mitochondria significantly correlated with ratings of clinical disability.[28] Further, a study in mice with reduced mitochondrial gene expression indicated that normal mitochondrial energy production is essential for the retention and consolidation of memory.[29]

Deceased brain energy metabolism has been suggested to be a central feature of fatigue.[30] The severity of mitochondrial dysfunction in CFS has been shown to correlate with symptom severity, suggesting a primary role of impaired energy production in the peripheral and mental fatigue of this illness.[31] Mitochondrial dysfunction has also been suggested to play a role in age-related cognitive fatigue.[32] Also, in a group of volunteers a mentally fatiguing task was found to reduce brain phosphocreatine, a substrate for ATP production; suggesting, that the experience of mental fatigue may be related to a reduction in brain energy metabolism even in healthy individuals.[33]

Orthomolecular Restoration of Brain Energy

There is increasing interest in the use of nutrients known to improve the structure and function of mitochondria as a means to treat and prevent behavioral and cognitive illness as well as enhancing mental function in healthy individuals.[34-37] The term "mitochondrial nutrients" was coined to categorize nutritional compounds that enter the cells and mitochondria following exogenous administration, and protect the mitochondria from oxidative damage and improve mitochondrial function.[38] Mitochondrial nutrients have been shown to have a number of important effects including, reducing oxidative stress, enhancing energy metabolism, and increasing mitochondrial biogenesis.[39]

Examples of mitochondrial nutrients with established effects on mitochondrial function with the potential to improve mood, cognition and reduce mental fatigue include creatine, carnitine, coenzyme Q_{10} (CoQ_{10}) and lipoic acid. In addition, nutraceuticals containing combinations of mitochondrial nutrients, as well as multivitamin and minerals have shown evidence of benefit. This review will focus on creatine, acetyl-l-carnitine and multivitamins.

Creatine

Creatine is a dietary nutrient that directly influences phosphocreatine reserves in the brain.[40] Phosphocreatine plays an important role in energy homoeostasis by storing and

donating phosphate for ATP synthesis and regeneration. The importance of creatine in maintaining energy homeostasis in the brain is underappreciated.[41] Creatine supplementation is safe, well tolerated and has shown promise for neurological disorders with deficits in energy metabolism including neurodegenerative, mood and anxiety disorders.[42]

A number of short-term studies have investigated the ability of supplemental creatine to enhance mood (**Table 1**, below) and cognitive function (**Table 2**, p.181), particularly under conditions of high demand such as sleep deprivation or stress. Collectively, the current evidence suggests a promising role for creatine supplementation as a means of enhancing brain energy metabolism and improving mood and cognitive function.[55] There are no studies that have assessed the effects of creatine on mood in non-depressed individuals. Also, no studies have investigated creatine in dementia despite evidence that brain creatine is particularly low in those at high genetic risk.[56]

Acetyl-l-carnitine

Acetyl-l-carnitine (ALC) is a natural ester of the amino acid carnitine, is responsible for the transport of acetyl CoA into the mitochondria during fatty acid oxidation, and is thus crucial for cellular energy production. ALC is known to enhance neuronal energy metabolism although this is not necessarily its primary mechanism of action; ALC has several other established neurological effects, notably the enhancement of cholinergic neurotransmission through the donation of the acetyl moiety to the production of ace-

Table 1. Studies of Creatine on Mood

Reference	Study group	Intervention	Results
43	Women with major depressive disorder	5 grams of creatine per day for 8 weeks	Significantly improved depressive symptoms
44	Female adolescents with SSRI-resistant major depressive disorder	4 grams of creatine for 8 weeks	Reduced depressive symptoms and increased brain phosphocreatine
45	Unipolar and bipolar patients with treatment-resistant depression	3-5 g creatine per day for 4 weeks	Patients with unipolar (but not bipolar) depression improved
46	Case report of a patient with fibromyalgia and depression	3-5 g creatine per day for 8 weeks	Improved depressive symptoms
47	Patients with treatment-resistant posttraumatic stress disorder	Dose and duration unknown	Improved symptoms; greatest benefit in in patients diagnosed with comorbid depression

tylcholine, which is involved in cognition and mood.[57]

There is experimental data to show that supplemental ALC can enhance brain energy metabolism. Chronic feeding of ALC to healthy mice for example was able to improve brain glucose metabolism, increase metabolites involved in energy metabolism (adenosine nucleotides) and increase brain energy stores (phosphocreatine).[58] A number of human studies have also indicated beneficial effects of ALC on brain energy metabolism, mood, and cognitive function.

A meta-analysis of 21 studies of ALC for mild cognitive impairment (MCI) and mild (early) AD found a beneficial effect of ALC on both the clinical scales and the psychometric tests with benefits observed in memory, cognitive function, and mood. Doses were mostly 1,500-2,000 mg daily, and benefits were noticed within three months and increased over time.[59] Brain imaging has revealed that ALC treatment in subjects with AD improves high-energy phosphate levels.[60]

More recently ALC was shown to benefit age-related fatigue and functional impairment. Elderly subjects supplemented with ALC (2000 mg twice daily) had a sig-

Table 2. Studies of Creatine on Cognition

Reference	Study group	Intervention	Results
48	Healthy individuals subject to a repeated mathematical calculation	8 grams of creatine per day for 5 days	Attenuated of mental fatigue and increased oxygen utilization in the brain
49	Healthy young adult vegetarians	5 grams of creatine for 6 weeks	Improved working memory and intelligence
50	Healthy individuals subject to 24 hours sleep deprivation	20 g creatine per day for 7 days	Supplementation had a positive effect on mood state and tasks that place a heavy stress on the prefrontal cortex
51	Healthy individuals subject to 36 hours sleep deprivation	20 g creatine per day for 7 days	Improved performance of complex central executive tasks
52	Older age individuals	20 grams of creatine per day for 2 weeks	Significantly improved cognitive function
53	Healthy young adults (21±2 years)	0.03 grams creatine per kg body weight per day for 6 weeks	Supplementation did not improve cognitive function
54	Healthy individuals subjected to cognitive assessment tasks	5 grams of creatine per day for 2 weeks	Improved cognitive functions including reaction times and memory

nificant decrease in mental fatigue and improvements in cognitive function. They also had significant reductions in muscle pain, general and physical fatigue, post-exercise fatigue, and sleep disorders.[61]

ALC may also be effective for depression. Fourteen depressed elderly patients (between 70 and 80 years of age) were treated with 1,500 mg of ALC, while another fourteen received placebo. ALC reduced depression scores (in the Hamilton Rating Scale for Depression and Beck Depression Inventory) and behavioral aspects.[62] A significant antidepressant effect was similarly observed in an earlier study of elderly depressed subjects.[63]

There is also clinical evidence to show ALC can improve mood in patients with dysthymia.[64] In one such report ALC was compared to amisulpride for the treatment of dysthymia over 12 weeks and was found to be as effective as the medication, but with superior tolerability.[65]

Supporting a central role of enchantment in brain energy metabolism by ALC, a study in elderly patients with depression demonstrated a significant increase in brain phosphocreatine with treatment that directly correlated with symptomatic improvement in depressive symptoms.[66]

Overall, ALC appears to improve brain energy metabolism, cognitive function, and mood and reduce mental fatigue although most studies are limited to older age individuals with mild AD, unipolar depression or dysthymia.

Multivitamins

Vitamin and mineral intake is frequently deficient in modern diets, and due to the importance of micronutrients for neurological function, the restoration of optimal nutritional status with dietary supplements has been explored as an avenue for improving mood, cognition and reducing mental fatigue.

A recent review of the evidence for benefit from vitamin supplementation on cognitive function found that while interventions using one or only a few vitamins have largely demonstrated little benefit, there is relatively consistent evidence to suggest multivitamin and mineral formulations (multivitamins) can improve cognitive function, mood and reduce mental fatigue.[67] The authors identified nine studies of which all but one reported benefits from multivitamins on cognitive function. A number of these studies also reported positive outcomes on subjective measures of mental fatigue, mood, anxiety, and stress. In one such study a multivitamin formula taken over 33 days was found to improve ratings of stress, cognitive performance and reduce mental fatigue in healthy adult men.[68] A similar study of a multivitamin in women found that supplementation for nine weeks improved cognitive function and reduced mental fatigue during a mentally demanding task assessment.[69]

Extensive experimental evidence suggests that one of the primary effects of low micronutrient intake is decreased ATP synthesis and increased oxidative stress in the mitochondria, and that this can in-turn lead to accelerated cognitive dysfunction and chronic disease.[70] Multivitamin supplementation may therefore be a means of improving mitochondrial function, brain energy metabolism and enhancing neurological health.[71] "Tuning up your metabolism" with a multivitamin has been proposed as a safe, cheap and important way to enhance micronutrient intake, improve metabolic function and optimize wellbeing.[72]

Dietary Enhancement of Brain Energy Metabolism

A traditional dietary pattern characterized by foods that reflect those consumed by humans throughout the majority of recent evolutionary history (e.g. fruits, vegetables, herbs, spices, nuts, seeds, lean meats and seafood) has shown promise for enhancing mental health while modern dietary patterns (e.g. soda, sweetened desserts, fried food, processed meat, refined grains and high-fat dairy products) may negatively impact neurological function and are related to mental illness.

With regards to depression a "processed food" dietary pattern was found to strongly predict the development of depression within five years, while a "whole food" pattern

was protective.[73] Adhering to a traditional Mediterranean style diet also prevented depression over a 4-year prospective study.[74] A "traditional" dietary pattern (mostly vegetables, fruit, grass fed meat, fish, and whole grains) was associated with lower odds for major depression or dysthymia and for anxiety disorders compared to a "western" diet of processed or fried foods, refined grains, sugary products, and beer.[75]

There is also increasing evidence to suggest that a traditional diet can preserve or improve cognitive function with age. In particular, the traditional Mediterranean-type diet has been well studied with experimental, epidemiological and prospective data suggesting strong cognitive benefits.[76]

Few, if any, controlled intervention studies have investigated the effects of a traditional diet in subjects with depression or cognitive impairment. An important intervention study, however, did investigate the effect of a short-term (10-day) dietary intervention on mood and cognition in healthy, young women.[77] The subjects who followed a nutrient-dense Mediterranean diet showed significant improvements in self-rated vigor, alertness and contentment compared to a control group. Cognitive function was also assessed with evidence of small, but non-significant improvements.

The reasons for the benefits of a traditional dietary pattern on mental health are likely diverse, but do seem to be in part due to higher concentrations of phytochemicals, in particular polyphenols. For example, a strong relationship between the polyphenol rich foods typical of the traditional Mediterranean diet (olive oil, walnuts, coffee, wine and total urinary polyphenols) and measures of memory and cognitive function has been detected.[78]

Polyphenols trigger mild cellular stress, such as a free radical production and increased energy demands, which cause the cell to activate an adaptive response ultimately reducing oxidative stress and improving energy metabolism.[79] This occurs via a group of genes known as the vitagenes.[80] In the central nervous system the vitagenes play an important role in preserving neurological function and protecting against cognitive decline.[81]

Several neuroprotective activities of polyphenols have been identified including the ability to increase cellular detoxification enzymes, enhance the production of neurotrophic factors involved in nerve cell function and growth, and enhance levels of proteins that protect neurons and prevent cell death.[82] A traditional diet providing a high concentration of polyphenol rich foods may therefore stimulate genes involved in enhancement of neurological energy metabolism and function and improve cognition and mood.

Discussion

Healthy mood, cognitive vitality and minimal mental fatigue are undoubtedly desirable aspects of good mental health. One potential way to enhance mental energy is the use of targeted mitochondrial nutrients such as creatine and carnitine, particularly in people with functional or clinical evidence of impaired mitochondrial metabolism. More broadly, the use of a multivitamin may help optimize the daily supply of micronutrients important for brain energy metabolism and cognitive health in people exposed to modern, processed diets. Furthermore consumption of a phytonutrient dense traditional diet appears to augment brain energy metabolism and improve neurological function with clinical benefits noted in a matter of days and protective benefits extending over many years.

Beyond enhancing mental energy in otherwise healthy individuals there is considerable evidence to suggest that augmenting brain mitochondrial energy metabolism may have important therapeutic effects on mood and behavioral disorders. "Mitochondrial psychiatry," as it has been coined, may therefore emerge as a method of addressing wider mental illness.[83]

It is also intriguing to note that wider lifestyle changes associated with improved mental health have also been observed to influence brain energy metabolism. Stress management may be beneficial because chronic stress has been shown to impair mitochondrial structure and function in the

brain.[84] Also, an increase in regular physical activity increases mitochondrial biogenesis not only in skeletal muscle, but in the brain as well.[85]

Clinical interventions based on enhancement of mitochondrial function through nutritional supplements coupled with dietary and lifestyle change should be studied as a means of improving mental energy in people wishing to improve mood, cognition and reduce mental fatigue. The same approach could also be considered as a way to address the current epidemic of depressive illness and mitigate the increasing burden of age-related cognitive decline and AD.

Competing Interests

The author has been involved in the commercial development of dietary supplements including creatine, acetyl-l-carnitine and multivitamin products, and the facilitation of commercial training programmes in lifestyle medicine.

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