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Clinical and neurobiological effects of creatine supplementation in depressive disorders

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Abstract

Creatine is an endogenous compound that plays a role in cellular energy metabolism, particularly important in metabolically demanding tissues such as the brain. This article outlines the biochemical pathways controlling creatine synthesis through the orchestrated action of the enzymes L-arginine:glycine amidino transferase (AGAT) and guanidinoacetate methyltransferase (GAMT), its cellular uptake via the SLC6A8 transporter, and its intracellular compartmentalization as phosphocreatine—the primary energy store mobilized per unit of time. The literature is analyzed and the interface between these biochemical pathways and neurobiological processes of depression, through mitochondrial dysfunctions, biases of neurotransmission, and neuroprotection mechanisms, is discussed. Through these mechanisms, creatine appears to function as a modulator of mental health, shedding new light on potential treatments for depression. Such work bridges the gap between cellular biochemistry and neuropsychiatry, advancing an understanding of the metabolic role of creatine with emotional regulation.

Keywords: Creatine; Biochemistry; Depression; Energy Metabolism; Mental Health; Phosphocreatine; Brain

1. Introduction

Creatine, a nitrogenous compound synthesized endogenously from the amino acids arginine, glycine, and methionine, has long been recognized for its ergogenic role in sports and clinical settings. Traditionally, creatine has been associated with increases in muscle mass, strength, and physical performance (1). However, its bioenergetic and neuroprotective properties have generated considerable interest from researchers working in the fields of neuroscience and psychiatry. Starting in the early 2000s, scientific literature began to explore the effects of creatine on cognitive, emotional, and behavioral functions, particularly its potential adjuvant role in treating mental disorders, including depression, anxiety, and mood disorders (2–4).

Mental health disorders are currently among the most pressing global health issues. More than 970 million individuals worldwide suffer from mental health disorders, with depression and anxiety disorders among the most prevalent (5). Major depression alone affects approximately 280 million people and is the leading cause of disability globally. Although pharmacological therapies, such as selective serotonin reuptake inhibitors (SSRIs) and mood stabilizers, have improved diagnosis and treatment options, significant limitations persist regarding efficacy, response time, and side effects (6,7). Furthermore, treatment-resistant major depressive disorder (MDD) affects up to 30% of individuals diagnosed with MDD (8), emphasizing the need for safe and novel adjunctive treatments.

Creatine supplementation emerges as a promising strategy in this context. Creatine is vital for brain energy metabolism through the resynthesis of adenosine triphosphate (ATP) as part of the phosphocreatine–creatine kinase system (9). Adequate energy supply to brain tissue is essential for synaptic function, neurotransmission, neuronal plasticity, and

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neurogenesis—processes often impaired in psychiatric disorders, especially depression (4,10). Beyond its role in energy metabolism, creatine exerts antioxidant effects, stabilizes mitochondria, and modulates brain inflammation, all mechanisms implicated in the pathophysiology of mood disorders (11,12).

Recent studies suggest that creatine may also benefit anxiety symptoms by modulating stress reactivity and the hypothalamic-pituitary-adrenal (HPA) axis, mechanisms commonly disrupted in anxiety disorders (13). Both clinical and experimental evidence supports the role of creatine in maintaining neurochemical homeostasis and buffering the neurotoxic effects of chronic stress, a key risk factor for anxiety, panic disorder, and post-traumatic stress disorder (14,15).

Renshaw et al. (16) demonstrated that creatine supplementation in depressive patients altered cerebral glucose metabolism patterns, improving synaptic efficiency. These findings highlight a direct relationship between energy availability, synaptic transmission, and emotional regulation, positioning creatine as a potential neurochemical modulator.

2. Literature Review

2.1. Biochemical and Neuropharmacological Bases of CNS Creatine

Creatine (methyl guanidinoacetic acid) is a nitrogenous compound synthesized in the human body from the amino acids glycine, arginine, and methionine, primarily in the liver, kidneys, and pancreas. Once synthesized, creatine is transported via the bloodstream to tissues with high-energy demands, such as skeletal muscle and the brain (1,17).

2.1.1. Creatine–Phosphocreatine–Creatine Kinase System

Creatine's principal biochemical function in the central nervous system (CNS) relates to ATP regeneration. Via the creatine-phosphocreatine system, the enzyme creatine kinase (CK) catalyzes the direct transfer of a phosphate group from phosphocreatine (PCr) to adenosine diphosphate (ADP), rapidly regenerating ATP (9). This mechanism enables neurons and astrocytes—highly energy-demanding cells—to maintain adequate ATP levels even during periods of metabolic stress or intense activity (18).

This energy buffering capacity is vital for maintaining membrane potentials, supporting ion transport, neurotransmitter release, and facilitating synaptic plasticity (19,4). Impaired ATP regeneration has been implicated in the pathophysiology of several neuropsychiatric disorders, including depression, anxiety, and Alzheimer's disease (20).

2.1.2. Creatine and Mitochondrial Metabolism

Creatine acts synergistically with mitochondria, the primary organelles responsible for ATP production. Experimental models have demonstrated that creatine stabilizes mitochondrial function, prevents loss of mitochondrial membrane potential, reduces reactive oxygen species (ROS) production, and inhibits the opening of the mitochondrial permeability transition pore, a key event in neuronal apoptosis (11,21).

These protective effects are particularly significant under conditions of mitochondrial dysfunction, such as in severe depressive episodes, where reduced activity of mitochondrial complexes I and II have been documented in the prefrontal cortex (22). Magnetic resonance spectroscopy (1H-MRS) studies have shown decreased cerebral phosphocreatine levels in patients with depression, especially in regions critical for mood regulation, such as the hippocampus and anterior cingulate cortex (16,23).

2.1.3. Creatine Transport to the Brain

Creatine crosses the blood-brain barrier via a specialized transporter, SLC6A8. This transporter is crucial for creatine uptake into brain tissue, and mutations in SLC6A8 cause creatine transporter deficiency syndrome (CTD), characterized by intellectual disability, epilepsy, and behavioral abnormalities (24).

Even in healthy individuals, supplementation with oral creatine increases brain creatine and phosphocreatine concentrations, as measured by magnetic resonance spectroscopy (25,26). This demonstrates that oral creatine supplementation can effectively enhance cerebral energy reserves, providing the biochemical basis for its use in neuropsychiatric disorders.

2.1.4. Creatine and Neurotransmitters

Beyond its energy-buffering role, creatine modulates neurotransmitter systems. Experimental studies have shown that creatine increases the availability of serotonin, dopamine, and GABA, neurotransmitters that are crucial for mood, anxiety regulation, and cognitive processes (13,27). Additionally, creatine can modulate glutamate release and protect against excitotoxicity, a mechanism implicated in neurodegenerative and affective disorders (14).

2.1.5. Antioxidant and Anti-inflammatory Effects of Creatine

Creatine exerts indirect antioxidant effects by reducing lipid peroxidation, ROS, and reactive nitrogen species (RNS) levels. These antioxidant properties are intricately linked to its role in maintaining mitochondrial integrity and preventing oxidative dysfunction, key factors implicated in the pathophysiology of psychiatric disorders (11,12).

Moreover, creatine has been shown to modulate systemic and central nervous system inflammatory responses, reducing levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (28). Given the association between neuroinflammation and treatment-resistant depression, these anti-inflammatory properties further strengthen the therapeutic potential of creatine.

2.1.6. Creatine, Neuronal Plasticity, and BDNF

Creatine supplementation has been linked to positive modulation of synaptic plasticity and neurogenesis, particularly in the hippocampus. Studies have shown that creatine increases the expression of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), which promotes neuronal growth, differentiation, and survival (29).

This mechanism mirrors the neurobiological effects of conventional antidepressants such as SSRIs, which also enhance BDNF levels (30). Thus, creatine may exert similar or complementary effects, supporting functional recovery of corticolimbic circuits involved in mood and motivation regulation.

2.2. Evidence from Clinical and Experimental Studies on Creatine and Depressive Disorders

Major depressive disorder (MDD) is a complex psychiatric condition that profoundly affects mood, cognition, sleep, appetite, and motivation (31). Both genetic predispositions and psychosocial stressors contribute to its etiology, alongside several neurobiological abnormalities, including monoaminergic dysfunction, aberrations in glutamatergic and GABAergic neurotransmission, neurogenic inflammation, decreased neurotrophic support, and impaired cerebral energy metabolism (30,22).

2.2.1. Bioenergetic Hypotheses of Depression

Neuroimaging studies have consistently demonstrated reduced mitochondrial activity and decreased ATP production in key brain areas, including the prefrontal cortex, hippocampus, and anterior cingulate cortex, in patients with depression (16,4). The bioenergetic hypothesis of depression postulates that insufficient energy availability disrupts neurotransmission and synaptic plasticity, contributing to the persistence of depressive symptoms (20).

Creatine supplementation, by restoring ATP levels and optimizing cerebral energy metabolism, represents a promising novel adjunctive strategy for depression treatment (2,9).

2.2.2. Monoamine to Cell Metabolism

The classical monoaminergic hypothesis of depression, based on deficiencies of serotonin (5-HT), norepinephrine (NE), and dopamine (DA), dominated psychiatric research for decades. However, it does not fully explain delayed antidepressant responses or high rates of non-responders (8). Newer integrative models, including the neurotrophic, inflammatory, and bioenergetic hypotheses—highlight the cellular and metabolic underpinnings of depression (22,32).

Bioenergetic deficits, particularly mitochondrial dysfunction, ATP depletion, and oxidative stress, are now recognized as crucial contributors to mood disorders (22,4).

2.2.3. Mitochondrial and Energy Production in the Brain

Mitochondria are essential for neuronal energy production via oxidative phosphorylation and regulate apoptosis, calcium homeostasis, and ROS control. Neurons are particularly reliant on mitochondrial function due to their continuous high metabolic demands for maintaining membrane potential, axonal transport, neurotransmitter release, and synaptic plasticity.

In depression, mitochondrial dysfunction results in impaired oxidative phosphorylation, reduced ATP synthesis, and excess ROS production, leading to neuronal damage and impaired neurogenesis (22,33). Studies have shown reduced mitochondrial density and efficiency in post-mortem brain tissue and neuronal cultures from patients with depression (34,35).

Magnetic resonance spectroscopy (31P-MRS) studies confirm reduced levels of phosphocreatine and ATP in regions associated with emotional regulation, such as the prefrontal cortex, anterior cingulate, and hippocampus (16,23).

Oxidative stress from mitochondrial dysfunction damages lipids, proteins, and DNA, contributing to neuronal atrophy and impaired synaptic plasticity (36). Moreover, mitochondrial dysfunction activates innate immune responses, increasing pro-inflammatory cytokines like IL-6 and TNF-α, further aggravating neuronal damage (37).

These interlinked processes highlight mitochondria as central players in the pathophysiology of MDD and identify mitochondrial function as a promising therapeutic target.

2.2.4. Clinical Evidence: Changes in Depression Bioenergetics

Clinical studies have provided robust evidence for altered brain energy metabolism in depression. Brain spectroscopy studies have documented decreased phosphocreatine levels, indicating impaired energy buffering, and an increased lactate-to-ATP ratio, suggesting a metabolic shift toward anaerobic glycolysis (38).

In addition, decreased activities of mitochondrial respiratory chain complexes I and IV have been reported, reinforcing the concept of mitochondrial dysfunction (39). At the molecular level, reduced expression of mitochondrial biogenesis regulators, such as PGC-1α, and decreased activity of citrate synthase and succinate dehydrogenase have been observed in depressed patients (40).

Importantly, these metabolic alterations are even more pronounced in patients with treatment-resistant depression, suggesting that mitochondrial dysfunction not only underlies depressive symptoms but also contributes to therapeutic resistance (22).

3. Mechanisms Involving Creatine and Brain Energy

3.1. Creatine Kinase (CK) Brain Systems

Creatine kinase (CK) is a key enzyme in cellular energetics, catalyzing the reversible conversion of phosphocreatine (PCr) and adenosine diphosphate (ADP) into adenosine triphosphate (ATP) and free creatine. This cycle constitutes an effective energy-buffering system in tissues with high and fluctuating energy demands, such as the brain (9).

There are four major CK isoforms: CK-MM (skeletal muscle), CK-MB (cardiac muscle), CK-BB (brain), and mitochondrial CK (mtCK). In the central nervous system (CNS), CK-BB and mtCK operate synergistically to fulfill synaptic energy needs and maintain intracellular homeostasis (9,2).

3.1.1. CK-BB: Brain Cytosolic Creatine Kinase

The CK-BB isoform is expressed in neurons, astrocytes, and oligodendrocytes, particularly in regions of high synaptic activity such as the hippocampus, prefrontal cortex, striatum, and thalamus (19). CK-BB plays a crucial role in maintaining ATP supply during synaptic activity by catalyzing the rapid regeneration of ATP from PCr and ADP at presynaptic terminals (18).

Additionally, CK-BB contributes to maintaining cellular volume, cytoskeletal stability, and the structural integrity of synaptic proteins, which are essential for synaptic plasticity, learning, and memory (5).

3.1.2. CK-Mt: Mitochondrial Creatine Kinase

Mitochondrial CK (mtCK) is localized in the intermembrane space of mitochondria, where it transiently interacts with respiratory chain complexes and adenylate kinase. It phosphorylates creatine using newly synthesized mitochondrial ATP to generate phosphocreatine (9).

This phosphocreatine then diffuses into the cytosol, where it is used by CK-BB to regenerate ATP locally at sites of high-energy demand, forming the creatine–phosphocreatine energy shuttle system, which supports rapid energy transfer from mitochondria to synapses and axons (9,2).

3.1.3. The Creatine–Phosphocreatine Shuttle: Functional Synergy

The interaction between CK-BB and mtCK establishes a continuous energy production and delivery system essential for neuronal survival and function. mtCK uses mitochondrial ATP to phosphorylate creatine, forming PCr, which diffuses to areas of high-energy demand. There, CK-BB regenerates ATP from PCr and ADP to sustain synaptic transmission, plasticity, and adaptation during prolonged stimulation, learning, memory consolidation, and stress responses (9,2).

3.2. AMP and AMPK: Cellular Energy Sensing

AMP-activated protein kinase (AMPK) acts as a cellular energy sensor, becoming activated in response to increased AMP/ATP ratios. Once activated, AMPK initiates metabolic adaptations to restore energy balance, including the phosphorylation and regulation of CK activity (41).

AMPK activation also promotes mitochondrial biogenesis through upregulation of PGC-1α (42), enhancing oxidative phosphorylation, promoting fatty acid oxidation, and suppressing anabolic processes, thereby supporting neuronal survival during energy stress (41).

The cooperation between CK and AMPK ensures rapid local ATP regeneration and systemic cellular adaptation to energetic demands, contributing to cognitive resilience and emotional regulation.

3.3. Involvement of mTOR and CREB Signaling Pathways

The mechanistic target of rapamycin (mTOR) pathway integrates nutrient and energy signals to regulate cellular growth, protein synthesis, and synaptic plasticity. mTOR activation leads to phosphorylation of downstream targets, such as S6 kinase and 4E-binding protein 1 (4E-BP1), promoting protein synthesis and neuronal growth (30).

Creatine supplementation supports sustained ATP levels, maintaining mTOR activation and facilitating synaptic remodeling essential for mood regulation and memory (30). Furthermore, extracellular signal-regulated kinase (ERK) and cAMP response element-binding protein (CREB) pathways are vital for the transcription of neuroplasticity-related genes like BDNF, and their proper functioning depends on cellular energy status (29).

3.4. CK Impact on Oxidative Stress, Apoptosis, and Neuroprotection

The phosphocreatine system provides both rapid ATP regeneration and mitochondrial membrane stabilization. Under pathological conditions, disruption of this system leads to:

- Mitochondrial permeability transition pore (mPTP) opening,
- Caspase-3 activation and apoptosis initiation,
- Downregulation of anti-apoptotic proteins such as Bcl-2,
- Increased oxidative stress and lipid peroxidation (11,21).

Creatine supplementation has been shown to reverse these effects in experimental models by restoring mitochondrial integrity, reducing ROS production, inhibiting apoptotic pathways, and improving cellular energy management (11,21).

These neuroprotective properties make creatine a promising therapeutic adjunct in neurodegenerative and psychiatric disorders.

4. Conclusion

Creatine supplementation represents a promising adjunctive strategy in the treatment of depressive disorders, grounded in robust biochemical and neurobiological mechanisms. By supporting cerebral energy metabolism, enhancing mitochondrial function, modulating key neurotransmitter systems, and promoting neuroplasticity, creatine addresses multiple pathophysiological domains implicated in depression. Evidence from clinical and experimental studies supports the role of creatine in improving ATP availability, reducing oxidative stress, stabilizing mitochondrial integrity, and modulating neuroinflammatory responses—all of which contribute to improved emotional regulation and cognitive resilience.

The integration of creatine into psychiatric research marks a significant step toward metabolic-based interventions in mental health. Unlike conventional antidepressants that primarily target monoaminergic systems, creatine acts on foundational bioenergetic processes, potentially offering benefits to patients with treatment-resistant depression or those experiencing suboptimal responses to standard therapies.

While the current body of research is promising, further randomized controlled trials and longitudinal studies are needed to refine dosage protocols, elucidate long-term safety profiles, and identify specific patient populations who may benefit the most from creatine supplementation. Additionally, investigations into sex differences, dietary influences, and interactions with existing pharmacotherapies will be essential for optimizing the therapeutic application of creatine in clinical psychiatry.

In conclusion, creatine stands as a biologically plausible, accessible, and potentially transformative agent in the landscape of mood disorder treatments, bridging cellular bioenergetics and emotional health with compelling scientific rationale.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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