International Scientific Journal - ISSN: 1679-9844
Volume 21, Article nº 04 Continuous Publishing 2026
D.O.I: http://dx.doi.org/10.6020/1679-9844/v20a04
Accepted: 21/12/2024 Published: 09/06/2025

BDNF Gene Methylation and the Creatine-Phosphate System: A Translational Perspective for Neuropharmaceutical Innovation

Marco Machado [1] , Steven B Machek [2] .

Abstract - The maintenance of synaptic function and neuroplasticity relies on an intricate balance of genetic, epigenetic, and metabolic factors. Brain-Derived Neurotrophic Factor (BDNF), a key protein for neuronal health, is regulated by DNA methylation patterns that influence its expression. Concurrently, the creatine-phosphate (PCr) system serves as a critical energy buffer, especially in the brain during high metabolic demand. Here, we present a perspective on the potential interaction between creatine-mediated BDNF gene methylation and cerebral bioenergetics. While direct mechanistic data are still lacking, emerging evidence suggests that creatine supplementation may enhance BDNF expression and modulate synaptic energetics. These insights support the hypothesis that creatine-based interventions could be personalized through epigenetic biomarkers, offering novel opportunities for translational research and pharmaceutical innovation in the treatment of neuropsychiatric conditions.

Keywords: BDNF; creatine; epigenetics; brain metabolismo; neuropharmacology; biomarker; translational research

1 Introduction

Advances in neuropharmacology and molecular psychiatry have increasingly highlighted the importance of integrating epigenetic regulation and cellular energy metabolism in the development of new therapeutic strategies (Park et al., 2019; Quaioto et al., 2025). Among key neurotrophic factors, Brain-Derived Neurotrophic Factor (BDNF) plays a central role in synaptic plasticity, cognitive function, and neuronal resilience (Dwivedi, 2013). Its expression is modulated by epigenetic mechanisms, particularly DNA methylation in promoter regions (Januar et al., 2015). This post-translational modification is traditionally predicated on s-adenosyl methinone (SAM) synthesis and its regeneration through folate and vitamin B12 metabolism. SAM is the primary methyl donor, ultimately leading to hyper- and hypomethylation scenarios that repress or promote gene activity, respectively (Niculescu; Zeisel, 2002).

In parallel, the creatine-phosphate (PCr) system supports ATP regeneration in metabolically demanding tissues such as the brain (Braissant et al., 2011; Wallimann et al., 2011). Recent findings suggest that creatine supplementation can modulate brain function and potentially upregulate BDNF expression, offering a promising avenue for therapeutic innovation (Marosi; Mattson, 2014; Adriano et al., 2018). In this article, we explore the hypothesis that BDNF gene methylation may influence the brain's responsiveness to creatine-based interventions (Roitman et al., 2020). This perspective highlights an emerging interface relevant to the pharmaceutical and biotechnology sectors, where epigenetic biomarkers could guide the personalization of neuroprotective strategies.

[1]Fundação Universitária de Itaperuna, Itaperuna, RJ, Brazil
[2]California State University, Monterey Bay, Seaside, CA, USA

2 Epigenetic Regulation of BDNF and Its Clinical Relevance

DNA methylation in the promoter regions of BDNF, especially in exon IV, has been linked to decreased gene expression, impaired synaptic plasticity, and increased susceptibility to stress-related psychiatric conditions (Roy et al., 2017; Chen et al., 2017; Quaioto et al., 2025). Elevated methylation has been documented in individuals with major depressive disorder and anxiety, and is considered reversible through interventions such as physical activity, pharmacotherapy, tartgeted nutrional strategies, and/or environmental enrichment (Niculescu; Zeisel, 2002; Allison et al., 2021).

This reversibility suggests that BDNF gene methylation patterns could serve as dynamic biomarkers to monitor and personalize neuropsychiatric treatments (Quaioto et al., 2025). For the pharmaceutical industry, this opens the door to the development of diagnostic kits and epigenetically informed interventions.

3 The Brain Creatine-Phosphate System and Neurometabolic Health

The PCr system functions as a rapid-response energy reserve that stabilizes ATP concentrations in tissues with high metabolic flux. In the brain, creatine plays a crucial role in supporting synaptic transmission and plasticity. Impaired creatine metabolism, as seen in creatine transporter deficiency (CTD), leads to cognitive deficits and severe neurological impairments, further emphasizing its relevance (Braissant et al., 2011; Wallimann et al., 2011).

Prior investigations have demonstrated cognitive improvements in contexts such as sleep deprivation, reaction time-dependent physical endeavors, and even Parkinson's disease (Adriano et al., 2018). Pharmaceutical approaches targeting creatine biosynthesis, transport, or supplementation are already under consideration for a range of neurological disorders. Creatine use in neuropharmacology is a somewhat fledgling área of research, especially considering that its hepatic conversion via guanidino acetate methyltransferase is aptly dependent on methyl metabolism (Machek; Bagley, 2018). Neurochemistry is thus irrevocably tied to the intersection between methyl- and creatine-associated metabolic flux.

4 Evidence of Functional Interaction Between BDNF and Creatine

While no studies have directly examined the influence of BDNF gene methylation on creatine response, indirect evidence is compelling. In animal models, creatine supplementation enhances hippocampal BDNF expression and ameliorates behavioral deficits induced by chronic stress (Roitman et al., 2020). In clinical trials, creatine has shown efficacy as an adjunct to antidepressants, with improvements correlating with increased BDNF serum levels (Adriano et al., 2018).

Exercise, another BDNF stimulator, also enhances brain creatine capacity. This suggests a synergistic mechanism where energy metabolism and neuroplasticity co-adapt to external stimuli. These insights justify further translational research to explore this axis more concretely.

5 Translational Potential and Industry Implications

The convergence of BDNF epigenetics and the PCr system may lead to the development of novel therapeutic strategies. Potential applications include:

- Epigenetic screening tools to identify responders to creatine-based treatments;
- Combined formulations of creatine with neurotrophic agents;
- Personalized regimens integrating dietary, pharmacological, and behavioral interventions based on epigenetic profiles.

These developments align with the goals of the pharmaceutical and biotech industries to innovate patient-centered, precision-based therapies.

6 Proposed Framework for Experimental Validation

To validate these hypotheses, we propose a translational research model involving:

1. Preclinical studies using rodent models exposed to stress paradigms, with assessment of BDNF gene methylation and creatine responsiveness;
2. Human observational studies correlating BDNF gene methylation profiles with treatment outcomes in patients using creatine as adjunct therapy;
3. Clinical trials stratifying patients by epigenetic biomarkers to evaluate efficacy and safety of creatine supplementation.

Such studies could inform regulatory decisions and guide industry-academic partnerships.

7 Conclusion

Although preliminary, the theoretical link between BDNF gene methylation and the PCr system offers a promising target for neuropharmaceutical development. This interface encourages a multidisciplinary approach, integrating neuroepigenetics, metabolism, and translational neuroscience to create novel therapies for neuropsychiatric disorders. With appropriate validation, these insights may soon transition from hypothesis to clinical and industrial application.

References

ADRIANO, E. A. et al. Creatine as an adjunct treatment for depression in humans. **Frontiers in Nutrition**, v. 5, p. 1–8, 2018. DOI: 10.3389/fnut.2018.00014.

ALLISON, J.; KALISZEWSKA, A.; UCEDA, S.; REIRIZ, M.; ARIAS, N. Targeting DNA Methylation in the Adult Brain through Diet. **Nutrients**, v. 13, n. 11, p. 3979, 2021. DOI: 10.3390/nu13113979.

BRAISSANT, O.; HENRY, H.; BÉARD, E.; ULDRY, J. Creatine deficiency syndromes and the importance of creatine synthesis in the brain. **Amino Acids**, v. 40, n. 5, p. 1315–1324, 2011. DOI: 10.1007/s00726-011-0874-5.

CHEN, D.; MENG, L.; PEI, F.; ZHENG, Y.; LENG, J. A review of DNA methylation in depression. **Journal of Clinical Neuroscience**, v. 43, p. 39–46, 2017. DOI: 10.1016/j.jocn.2017.05.022.

DWIVEDI, Y. Involvement of brain-derived neurotrophic factor in late-life depression. **American Journal of Geriatric Psychiatry**, v. 21, n. 5, p. 433–449, 2013.

JANUAR, V.; ANCELIN, M. L.; RITCHIE, K.; SAFFERY, R.; RYAN, J. BDNF promoter methylation and genetic variation in late-life depression. **Translational Psychiatry**, v. 5, n. 9, e619, 2015. DOI: 10.1038/tp.2015.114.

MACHEK, S. B.; BAGLEY, J. R. Creatine Monohydrate Supplementation: Considerations for Cognitive Performance in Athletes. **Strength and Conditioning Journal**, v. 40, n. 2, p. 82–93, abr 2018. DOI: 10.1519/SSC.0000000000000369.

MAROSI, K.; MATTSON, M. P. BDNF mediates adaptive brain and body responses to energetic challenges. **Trends in Endocrinology & Metabolism**, v. 25, n. 2, p. 89–98, 2014. DOI: 10.1016/j.tem.2013.10.006.

NICULESCU, M. D.; ZEISEL, S. H. Diet, methyl donors and DNA methylation: Interactions between dietary folate, methionine and choline. **J Nutr**, v. 132, 2333s–2335s, 2002.

PARK, C.; ROSENBLAT, J. D.; BRIETZKE, E.; PAN, Z.; LEE, Y.; MCINTYRE, R. S. Stress, epigenetics and depression: a systematic review. **Neuroscience & Biobehavioral Reviews**, v. 102, p. 139–152, 2019. DOI: 10.1016/j.neubiorev.2019.04.010.

QUAIOTO, B. R. et al. Epigenetic impact of chronic stress: BDNF exon IV gene methylation in high-risk professionals. **Journal of Psychiatric Research**, v. 189, p. 295–300, 2025. DOI: 10.1016/j.jpsychires.2025.06.018.

ROITMAN, S. et al. Creatine and BDNF expression in the hippocampus of rats submitted to chronic mild stress. **Behavioural Brain Research**, v. 379, p. 112362, 2020. DOI: 10.1016/j.bbr.2020.112362.

ROY, B.; SHELTON, R. C.; DWIVEDI, Y. DNA methylation and expression of stress-related genes in PBMC of MDD patients with and without serious suicidal ideation. **Journal of Psychiatric Research**, v. 89, p. 115–124, 2017. DOI: 10.1016/j.jpsychires.2017.02.005.

WALLIMANN, T.; TOKARSKA-SCHLATTNER, M.; SCHLATTNER, U. The creatine kinase system and pleiotropic effects of creatine. **Amino Acids**, v. 40, n. 5, p. 1271–1296, 2011. DOI: 10.1007/s00726-011-0877-2.