Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.48.007583

Creatine Transporter: A Review Focused on the Central Nervous System

Marco Machado*

Universidade Iguaçu – Campus Itaperuna, Brazil

***Corresponding author:** Marco Machado, Universidade Iguaçu – Campus Itaperuna, Brazil

ARTICLE INFO

Received: December 23, 2022

Published: January 10, 2023

Citation: Marco Machado. Creatine Transporter: A Review Focused on the Central Nervous System. Biomed J Sci & Tech Res 48(1)-2023. BJSTR. MS.ID.007583.

ABSTRACT

Creatine supplementation was initially used as a therapeutic resource that was forgotten for decades until it was "rediscovered" by coaches and athletes. However, its therapeutic applications have been increasingly highlighted, such as in diseases of the nervous system. Some gaps remain about the mechanisms linked to the possible therapeutic effects of creatine on the central nervous system. One of the ways to understand the mechanisms will certainly pass through the expansion of knowledge about creatine transporters. So far, we have broad but still limited knowledge of the interference that these transporters may have on the action of dietary creatine (supplemented or not) on neurons, astrocytes and the blood-brain barrier.

Abbreviations: ADP: Adenosine Diphosphate; AGAT: Arginine: Glycine Amidinotransferase; Akt: Protein kinase B (also called PKB) is a serine/threonine kinase; AMPK: Adenosine monophosphate-activated protein kinase; Arg: Arginine; ATP: Adenosine triphosphate; BB-CK: CK brain-specific isoform; CK: Creatine kinase; CNS: Central Nervous System; Cr: Creatine; CrP: Phosphocreatine; CrT: Creatine Transporter; GAA: Guinidinoacetate; GAMT: S-Adenosylmethionine: Guanidinoacetate Methyltransferase; Gly: Glycine; IOC: International Olimpic Committee; ISSN: International Society of Sports Nutrition; mTBI: Mild Traumatic Brain Injury; PKB: Protein kinase B (also called Akt) a Serine/Threonine Kinase; ROS: Reactive Oxigen Species

Introduction

The maintenance of the cell's energy charge is a priority for maintaining its operation. The numerous tasks that each cell has to maintain for itself and to fulfil the tissue and organ functions to which they belong demand high rates of energy consumption, obtained through food. Some metabolic pathways (a set of reactions that occur in a chain) are responsible for the production of energy, with emphasis on the reactions that occur within an organelle called mitochondria. However, when energy demand exceeds certain values in a specific system for short periods, the creatine phosphate (CrP) system becomes prominent in maintaining high rates of available energy.

Discussion

As initially summarized, cellular energy is primarily maintained by (a) glycolysis, (b) mitochondrial oxidative phosphorylation, and (c) ATP regeneration by CrP via the Lohmann reaction (ADP + CrP + H^+ → ATP + Cr) [1,2]. We can highlight that in skeletal muscles, Cr/CrP also works as an energy carrier between the mitochondria where ATP is produced and the cytosol, where ATP is used, but rapidly regenerated by Cr/CrP [1,2]. This elaborate scheme of Cr/CrP-mediated ATP regeneration and energy transport confers several advantages to muscle cells [3]. (Figure 1) can help better understand this process. CrP regenerates ATP at a rate 10 times faster than glycolysis and 40 times faster than mitochondrial oxidative phosphorylation, allowing muscle cells to handle sudden energy demands. On the other hand, 1 proton (H+) is released each time 1 ATP is hydrolyzed to ADP, which could cause acidosis (decreased cellular pH), but a proton will be immediately captured by the Lohmann reaction to regenerate ATP [4]. Due to the smaller

size of Cr (the molecular weight of creatine is ~130 daltons), skeletal muscle cells can store up to 10 times more Cr than ATP (the molecular weight of ATP is ~507 daltons, almost 4 times higher) as an energy reserve [1,2]. Last but not least, Cr stimulates oxidative phosphorylation when it reenters the mitochondria through voltage-gated anion channels, thus matching mitochondrial respiration with cellular demand for ATP [5,6]. (Figure 2) This function is also called an energy space buffer [3].

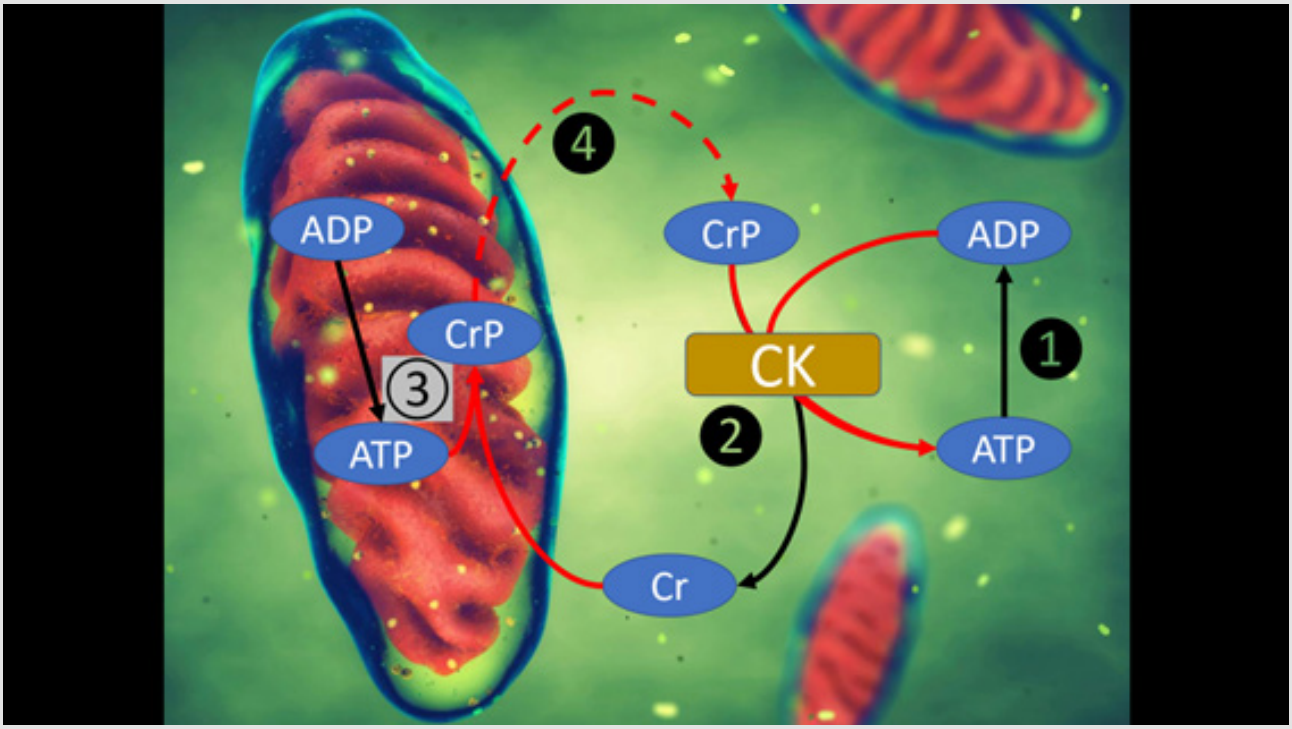

Figure 1: Energy metabolism of creatine
1. The hydrolysis of ATP into ADP + Pi + H^+.
2. The enzyme creatine kinase (CK) transfers a phosphate from phosphocreatine to ADP.
3. Inside the mitochondria, free creatine receives a phosphate group and energy from cellular respiration.
4. Creatine phosphate is transported to the cytoplasm and is available to donate the phosphate group to ADP.

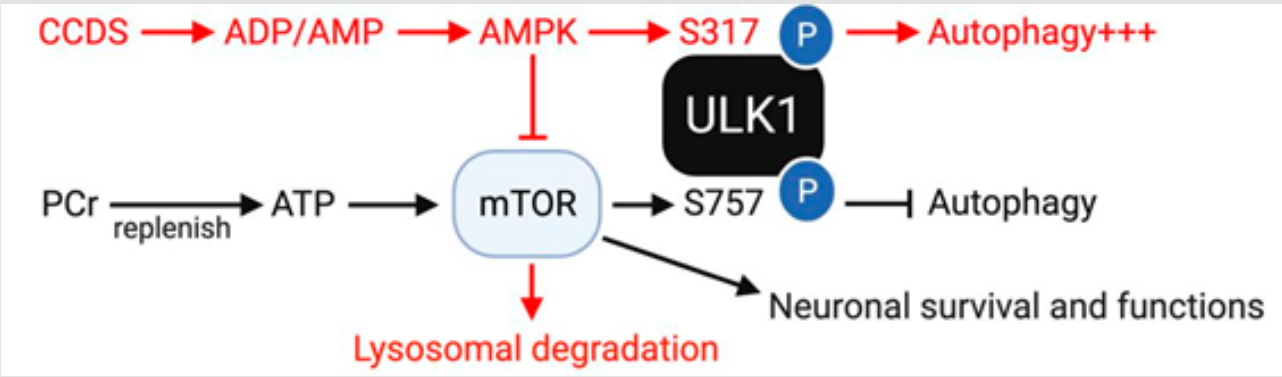

Figure 2: Schematic representations of CrP-mediated ATP regeneration and standard mTOR signalling responses under normal conditions (in black text and arrows, respectively) [7].

Under physiological conditions, Cr is obtained from food sources (beef, swine, poultry, fish, etc.) or endogenous synthesis. Endogenous synthesis is a two-step reaction catalyzed by the enzymes L-arginine: glycine amidinotransferase (AGAT) and S-adenosyl-L-methionine: N-guanidinoacetate methyltransferase (GAMT). AGAT converts glycine and arginine into guanidinoacetate (GAA) and ornithine. GAMT transfers a methyl group from S-adenosylmethionine (SAM) to GAA, generating Cr and S-adenosyl

homocysteine [1,4]. This seemingly simple pathway is complicated by the fact that most cells do not produce these two enzymes in equivalent amounts. In this way, the intermediate product (GAA) needs to leave the producing tissues and be transported to the tissues that produce large amounts of the GAMT enzyme [7]. For example, the mammalian kidney contains amounts of AGAT (which catalyzes large amounts of GAA) that must be transported via the bloodstream to the liver (which produces large amounts of the enzyme GAMT). Thus, in the liver finally, SAM can methylate GAA producing Cr. In contrast, the central nervous system (CNS) houses its Cr-synthesizing machinery (more on this later) [8]. After endogenous synthesis or nutritional supply, Cr is ready to fulfil its functions in other cells. Cr is a polar hydrophilic molecule incapable of crossing cell membranes (primarily nonpolar formed by phospholipids) so it requires a transporter, a protein capable of facilitating/permeabilizing the membrane for the passage of creatine.

The creatine transporter (CRT or Cr transporter) is Na+/Cl− dependent and specific for cellular uptake [9,10]. CRT is encoded by the SLC6A8 gene, which is located on the long arm of the X chromosome and has a coding sequence of 13 exons [9,10]. The protein consists of 635 amino acids with a molecular mass of about 70.5 kDa [11]. This transporter is a member of a protein superfamily (called SLC6), which includes transporters for the uptake of some neurotransmitters (eg, dopamine, GABA, serotonin) and amino acids (eg, glycine) [12]. The SLC6 family has a common three-dimensional structure, with 12 transmembranes (TM) domains, an extracellular loop between TM3 and TM4 with N-glycosylation and N- and C-terminal sites facing the cytoplasmic side of the membrane [13,14]. CRT is strongly regulated by extracellular levels of Cr, with high Cr reducing uptake activity [1]. Furthermore, cellular energy depletion inhibits CRT via the AMPK-mTOR pathway [15]. CRT is widely expressed in different tissues [9,14,16], including the brain, where it has been predominantly detected in cortical and subcortical regions involved in motor and sensory processing, learning and memory, and in the control of affective behaviour [9,17,18]. At the cellular level, CRT is expressed in oligodendrocytes and neurons, with notably high levels in fast-peaking parvalbumin inhibitory neurons [19,20]. It is also present in capillary endothelial cells that make up the blood-brain barrier (BBB), whereas it was detected only in smaller amounts in astrocytes [21].

Thus, Cr can enter the brain across the BBB, but blood-brain transport of Cr appears relatively inefficient, at least at a mature age [22-24]. Creatine (Cr) and creatine phosphocreatine (CrP) have the highest concentration in tissues that require a constant or rapid supply of energy, including skeletal muscle, heart and brain [1,25]. Cr/CrP accumulates functions of ATP resynthesis and transport of energy produced in cellular respiration. It also has neuroprotective effects and positively interferes with cognition [26,27]. There is already enough empirical evidence to support that both in conditions of hypoxia and normoxia it is advantageous to use oral supplementation of Crem in healthy adults [4,8,28]. On the other hand, when Cr/CrP concentrations and CK activity are low, they are correlated with neurodegenerative diseases [29]. Intellectual disability, autism or seizures in children also show changes in Cr concentrations [7,30]. Brain injuries seem to be more difficult to treat when Cr concentrations are low, mainly due to a slow blood-brain transport of Cr that is mediated by CRT [7,31,32]. Although Cr/CrP may have functions similar to those of skeletal muscle in the brain, the effects of CRT deficiency on stress adaptation and energy homeostasis remain unclear. CrP regenerates ATP at a rate 10 times faster than glycolysis and 40 times faster than mitochondrial respiration. This speed of catalysis allows muscle fibres to respond very efficiently to sudden energy demands [33-35].

Furthermore, it is important to remember that ATP hydrolysis releases 1 proton (H+) in addition to ADP, potentiating acidosis (decrease in cell pH), but the Lohmann reaction to regenerate ATP consumes a proton with each transfer of phosphate from CrP to the ADP [4]. As the molecular weight of creatine is low (about 130 daltons), skeletal muscle fibres can store up to 10 times more Cr than ATP (the molecular weight of ATP is ~507 daltons, almost 4 times higher) as a reserve of energy [1,2]. (Figure 3) Last but not least, free Cr after transfer of the phosphate group stimulates cellular respiration when ´w is transported into the mitochondria through voltage-gated anion channels, thus matching mitochondrial respiration with the cellular demand for ATP. [5,6]. This function is also called na energy space buffer [3].

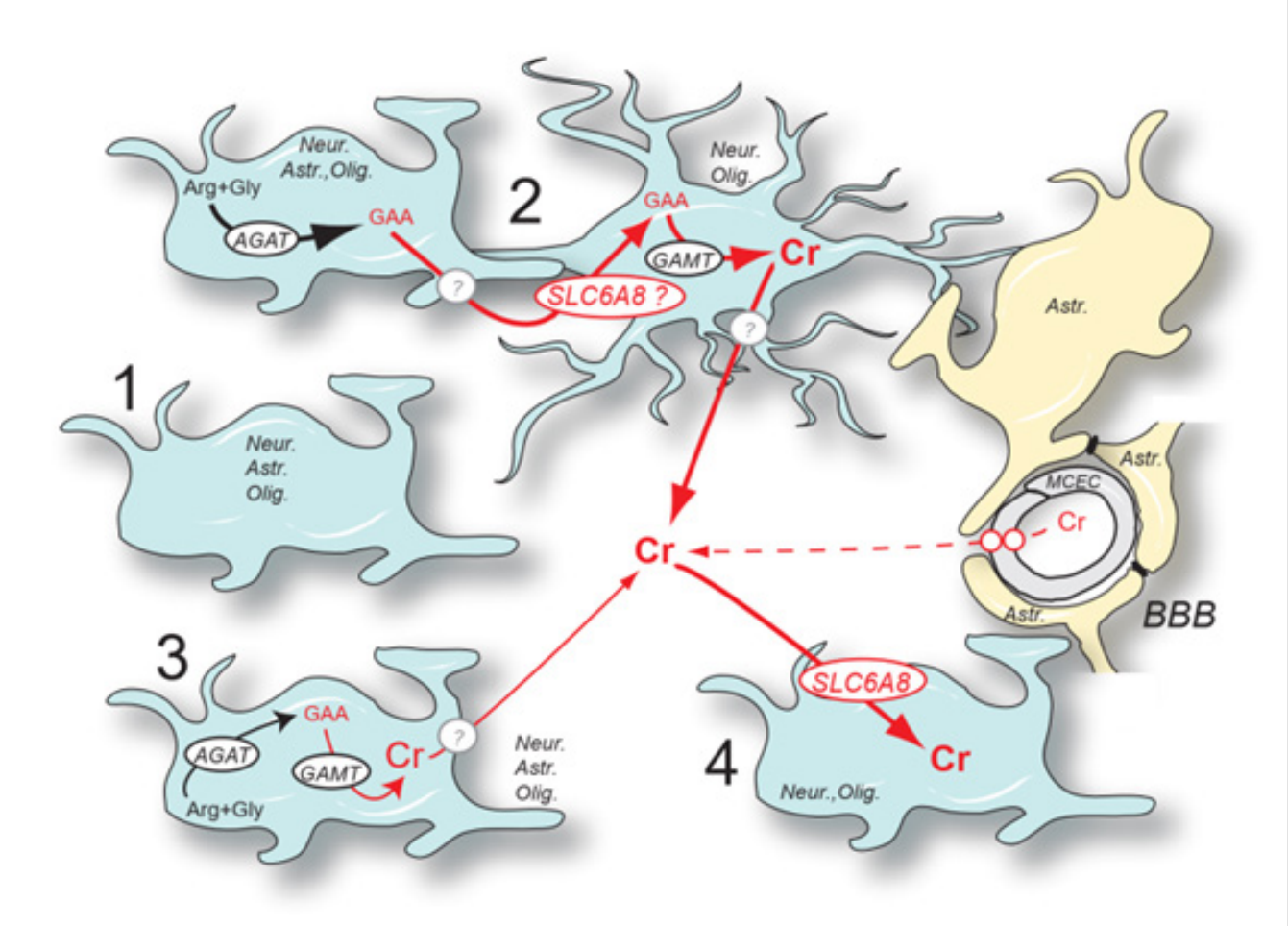

Figure 3: A proposed model for creatine synthesis and transport within the central nervous system. In normal conditions, a high proportion of cells do not express AGAT, GAMT, and SLC6A8

1. Endogenous synthesis of Cr within CNS can be achieved between AGAT- and GAMT-expressing cells and the concomitant trafficking of GAA between them
2. Or in cells co-expressing AGAT+GAMT
3. A low proportion of brain cells only express SLC6A8
4. i.e. Cr users-only.

Conclusion

As described, knowledge about the functions of creatine in energy metabolism themselves seems to be well described by science, especially in skeletal muscle. However, there are still limitations to the knowledge of creatine production and transport in the central nervous system. Understanding the mechanisms of creatine transport into the brain (crossing the blood-brain barrier) and the production of creatine by neurons, astrocytes and oligodendrocytes will be essential to develop strategies for the use of creatine in the prevention and treatment of various diseases and loss of cognition in older people.

Acknowledgement

This work would not have been possible without the contribution of the great scientists who made the discoveries described here. I also thank Dr Marcelo F Costa for his support and encouragement.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Consent of Publication and Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Wyss M, Kaddurah Daouk R (2000) Creatine and Creatinine Metabolism. Physiol. Rev 80(3): 1107-1213.

2. Persky AM, Brazeau GA, Hochhaus G (2003) Pharmacokinetics of the dietary supplement creatine. Clinical Pharmacokinetics 42(6): 557-574.

3. Machado M (2022) A Narrative Review on Athletic Performance and Safety Of Creatine Supplementation For Adolescents Biomedical Science. Open Access Journal of Biomedical Science 4(2): 1680-1685.

4. Rae CD, Bröer S (2015) Creatine as a booster for human brain function. How might it work?. Neurochemistry International 89(10): 249-259.

5. Monge C, Beraud N, Andrey VK, Tatiana R, Dan S, et al. (2008) Regulation of respiration in brain mitochondria and synaptosomes: restrictions of ADP diffusion in situ, roles of tubulin, and mitochondrial creatine kinase. Molecular and cellular biochemistry 318(1-2): 147-165.

6. Maughan RJ, Louise MB, Jiri D, Larson Meyer DE, Peter p, et al. (2018) IOC consensus statement: Dietary supplements and the high-performance athlete. British journal of sports medicine 52(7): 439-455.

7. Chen HR, Zhang Brotzge X, Yury MM, Yuancheng Li, Siming W, et al. (2021) Creatine transporter deficiency impairs stress adaptation and brain energetics homeostasis. JCI Insight 6(17): e140173.

8. Defalco AJ, Davies RK (1961) The Synthesis of Creatine by the Brain of the Intact Rat. J Neurochem 7: 308-312.

9. Nash SR, Giros B, Kingsmore SF, Rochelle JM, Suter ST, et al. (1994) Cloning, Pharmacological Characterization, and Genomic Localization of the Human Creatine Transporter. Receptors Channels 2(2): 165-174.

10. Joncquel Chevalier Curt M, Voicu PM, Fontaine M, Dessein AF, Porchet N, et al. (2015) Creatine Biosynthesis and Transport in Health and Disease. Biochimie 119: 146-165.

11. Guimbal C, Kilimann MW (1993) A Na(+)-Dependent Creatine Transporter in Rabbit Brain, Muscle, Heart, and Kidney. cDNA Cloning and Functional Expression. J Biol Chem 268: 8418-8421.

12. Chen NH, Reith MEA, Quick MW (2004) Synaptic Uptake and beyond: The Sodium- and Chloride-Dependent Neurotransmitter Transporter Family SLC6. Pflugers Arch 447: 519-531.

13. Dodd JR, Christie DL (2005) Substituted Cysteine Accessibility of the Third Transmembrane Domain of the Creatine Transporter: Defining a Transport Pathway. J Biol. Chem 280(38): 32649-32654.

14. Béard E, Braissant O (2010) Synthesis and transport of creatine in the CNS: Importance for cerebral functions. J Neurochem 115(2): 297-313.

15. Li H, Thali RF, Smolak C, Gong F, Alzamora R, et al. (2010) Regulation of the Creatine Transporter by AMP-Activated Protein Kinase in Kidney Epithelial Cells. Am. J. Physiol. Renal Physiol 299(1): F167-F177.

16. Iyer GS, Krahe R, Goodwin LA, Doggett NA, Siciliano MJ, et al. (1996) Identification of a Testis-Expressed Creatine Transporter Gene at 16p11.2 and Confirmation of the X-Linked Locus to Xq28. Genomics 34(1):143-146.

17. Mak CSW, Waldvogel HJ, Dodd JR, Gilbert RT, Lowe MTJ, et al. (2009) Immunohistochemical Localisation of the Creatine Transporter in the Rat Brain. Neuroscience 163(2): 571-585.

18. Lowe MTJ, Faull RLM, Christie DL, Waldvogel HJ (2015) Distribution of the Creatine Transporter throughout the Human Brain Reveals a Spectrum of Creatine Transporter Immunoreactivity. J Comp Neurol 523: 699-725.

19. Saunders A, Macosko EZ, Wysoker A, Goldman M, Krienen FM, et al. (2018) Molecular Diversity and Specializations among the Cells of the Adult Mouse Brain. Cell 174(4): 1015-1030.e16.

20. Tasic B, Yao Z, Graybuck LT, Smith KA, Nguyen TN, et al. (2018) Shared and Distinct Transcriptomic Cell Types across Neocortical Areas. Nature 563(7729): 72-78.

21. Braissant O, Henry H, Loup M, Eilers B, Bachmann C, et al. (2001) Endogenous Synthesis and Transport of Creatine in the Rat Brain: An in Situ Hybridization Study. Mol. Brain Res 86(1-2): 193-201.

22. Tachikawa M, Hosoya KI (2011) Transport Characteristics of Guanidino Compounds at the Blood-Brain Barrier and Blood-Cerebrospinal Fluid Barrier: Relevance to Neural Disorders. Fluids Barriers CNS 8(1): 13.

23. Perasso L, Cupello A, Lunardi GL, Principato C, Gandolfo C, et al. (2003) Kinetics of Creatine in Blood and Brain after Intraperitoneal Injection in the Rat. Brain Res 974(1-2): 37-42.

24. Braissant O (2012) Creatine and Guanidinoacetate Transport at Blood-Brain and Blood-Cerebrospinal Fluid Barriers. J Inherit. Metab Dis 35: 655-664.

25. Brosnan JT, da Silva RP, Brosnan ME (2011) The metabolic burden of creatine synthesis. Amino acids 40(5): 1325-1331.

26. Rae C, Alison LD, Sally RM, Timothy CB (2003) Oral creatine monohydrate supplementation improves brain performance: A double-blind, placebo-controlled, cross-over trial. Proceedings of the Royal Society B: Biological Sciences 270(1529): 2147-2150.

27. Riesberg LA, Stephanie AW, Thomas LM, Joan ME, Kristen MD, et al. (2016) Beyond muscles: The untapped potential of creatine. International Immunopharmacology. Elsevier BV 37: 31-42.

28. Tran NT, Kelly SB, Rod JS, David WW, Stacey JE, et al. (2021) Assessing Creatine Supplementation for Neuroprotection against Perinatal Hypoxic-Ischaemic Encephalopathy: A Systematic Review of Perinatal and Adult Pre-Clinical Studies. Cells 10(11).

29. Gualano B, Roschel H, Lancha Jr AH, Charles EB, Rawson E, et al. (2012) In sickness and in health: The widespread application of creatine supplementation. Amino acids 43(2): 519-529.

30. Merege Filho CAA, Maria Concepcion GO, Ana Lucia de SP, Maira Okada de O, Livia de SG, et al. (2017) Does brain creatine content rely on exogenous creatine in healthy youth? A proof-of-principle study. Applied Physiology, Nutrition and Metabolism 42(2): 128-134.

31. Rackayova V, Cristina C, Petra JWP, Olivier B (2017) Creatine in the central nervous system: From magnetic resonance spectroscopy to creatine deficiencies. Analytical Biochemistry. Academic Press Inc 529: 144-157.

32. Passi GR, Swati P, Akella RRD, Ramesh K, Abhisek Rj, et al. (2021) Cerebral creatine deficiency disorders – A clinical, genetic and follow up study from India. Brain and Development. The Japanese Society of Child Neurology 44(4): 271-280.

33. Cecil KM, Salomons GS, Ball jr WS, Wong B, Chuck G, et al. (2001) Irreversible brain creatine deficiency with elevated serum and urine creatine: a creatine transporter defect?. Annals of neurology, 49(3): 401-404.

34. Dunham TC, Jensen EM, Rebbaca EKM, Val Andrew F, Wendy EW, et al. (2021) Sex- and tissue-dependent creatine uptake in response to different creatine monohydrate doses in male and female Sprague-Dawley rats', Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 46(10): 1298-1302.

35. Pan JW, Takahashi K (2007) Cerebral energetic effects of creatine supplementation in humans. American journal of physiology. Regulatory, integrative and comparative physiology 292(4): R1745-50.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.48.007583

Marco Machado. Biomed J Sci & Tech Res