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BIOENERGETICS OF ACETATE, GLUTAMINE, GLUTAMATE AND NEUROPROTECTION

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Júlio César Gomes Graça[1], Marizia Trevizani[2], Laís Lopardi Leal[3], Pedro Henrique Dutra da Silva[4], Carlos Magno da Costa Maranduba[5] and Fernando de Sá Silva[6]

ABSTRACT

Glutamate, a non-essential amino acid, is an excitatory neurotransmitter of the central nervous system (CNS), released during the nerve impulse. In situations of brain pathology, the accumulation of glutamate in the extracellular space causes neuronal damage and, eventually, apoptosis. Many studies have reported that glutamate cytotoxicity is associated with several neurological diseases. In this context, acetate, a short-chain fatty acid, can benefit the CNS energetically and structurally. Acetyl-coenzyme A, a metabolically active form of acetate, is used as a substrate in biochemical pathways involved in the metabolism of carbohydrates, lipids, and proteins, in addition to increasing histone acetylation, altering the expression of inflammatory genes. In this way, the review brings a look at the bioenergetics of acetate, glutamine glutamate and neuroprotection for a better understanding and treatment of neuropathologies, such as neuroinflammation and neurodegeneration.

Keywords: Acetate. Glutamate. Glutamine. Neurotoxicity. Neuroprotection.

[1]Master. Laboratory of Human Genetics and Cell Therapy, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora Campus, Juiz de Fora, MG, Brazil. jcesarjf@yahoo.com.br
http://lattes.cnpq.br/6759572904367981
[2]Doctor. Laboratory of Human Genetics and Cell Therapy, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora Campus, Juiz de Fora, MG, Brazil
marizia_tr@yahoo.com.br
http://lattes.cnpq.br/1543665156752981
[3]Doctor. Laboratory of Human Genetics and Cell Therapy, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora Campus, Juiz de Fora, MG, Brazil
lais.lopardi@hotmail.com
http://lattes.cnpq.br/7223029548923303
[4]Graduating. Laboratory of Human Genetics and Cell Therapy, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora Campus, Juiz de Fora, MG, Brazil
pedutra255@gmail.com
http://lattes.cnpq.br/2589607207034898
[5]Doctor. Laboratory of Human Genetics and Cell Therapy, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora Campus, Juiz de Fora, MG, Brazil carlos.maranduba@ufjf.br
http://lattes.cnpq.br/4763153859701731
[6]Doctor. Department of Basic Life Sciences, Federal University of Juiz de Fora, Governador Valadares Campus, Governador Valadares, MG, Brazil
fernando.silva@ufjf.br
http://lattes.cnpq.br/5425429447928911
Corresponding author

INTRODUCTION

Glutamate is the most abundant amino acid in the mammalian brain (SARLO and HOLTON, 2021) and acts as the brain's main excitatory neurotransmitter (ANDERSEN *et al*., 2021) through pre- and postsynaptic receptors (CHEN *et al*., 2023). In situations characterized by pathologically high levels of glutamate in the extracellular medium, there is constant activation of glutamate-dependent postsynaptic receptors which, added to the excessive entry of calcium into the postsynaptic cell, can lead to cell death and tissue damage (GREEN, SANTOS and FONTANA, 2021). As it is the most common excitatory neurotransmitter, the abnormal elevation of its levels is often associated with neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's, as well as ischemia and hypoglycemia (GLASER *et al*., 2022).

Glutamine is a very common amino acid in the blood and extracellular fluid of the nervous system, where it is the main precursor of glutamate (ZHANG, HUA and LI, 2024). Glutamine metabolism is regulated by two enzymes: glutamine synthetase, which catalyzes its synthesis from glutamate and ammonia, and glutaminase, which catalyzes the hydrolysis of glutamine into glutamate (NEWSHOLME *et al*., 2023).

Acetate is a short-chain fatty acid (LYMPEROPOULOS, SUSTER and BORGES, 2022) and its metabolically active form is acetyl-coenzyme A (acetyl-CoA), a metabolite composed of an acetate molecule linked to coenzyme A, through a thioester-like bond (CAI and TU, 2011). Acetate concentrations can increase with ethanol consumption, a high-fat diet, intermittent fasting or acute bacterial infection, by acetyl-CoA hydrolysis, and histone deacetylation, being primarily generated by the breakdown of dietary fiber by the gut microbiota (SIVANAND, VINEY and WELLEN, 2018).

Although glutamine and acetate perform distinct metabolic functions, they are both interlinked in the regulation of essential cellular processes, such as the synthesis of neurotransmitters and the modulation of biochemical activities. Increased acetate concentrations, whether from the diet or from specific metabolic processes, may influence the availability of acetyl-CoA, a key cofactor for several metabolic pathways, including energy production and epigenetic modulation. In turn, glutamine, with its precursor function of glutamate, is directly involved in the control of neuronal metabolism and may interact with the effects of acetate on the nervous system, illustrating the complex network of biochemical interactions that regulate the homeostasis of the human body (ZHANG, HUA and LI, 2024).

Acetate and Acetyl-CoA are related to several metabolic pathways, such as lipid synthesis, energy production, and protein acetylation (BOSE, RAMESH, and LOCASALE,

2019). Acetyl-CoA is the acetyl donor for acetylation reactions, citrate synthesis, cholesterol and fatty acid synthesis, among other functions that involve metabolism or cell signaling (CAMPBELL and WELLEN, 2018). Studies have shown a positive relationship between acetyl-CoA and histone acetylation levels, implying that its concentration also influences DNA architecture and gene expression (SIVANAND, VINEY and WELLEN, 2018).

Acetyl-CoA participates in ketogenic metabolic pathways, increasing brain energy metabolism as well as synaptic functions, resulting in neuroprotective effects in situations such as cerebral ischemia or hypoxia (JANG *et al*., 2024). An example of its neuroprotective effects are observed in the ketogenic diet, which induces the body to use ketone bodies as an energy source (state of ketosis) (ANDERSON *et al*., 2021). Because it consists of foods with few carbohydrates and a high concentration of fat, the ketogenic diet and, consequently, the ketogenic metabolism promotes the production of energy by the oxidation of fatty acids in the mitochondria of hepatocytes, with the synthesis of Acetyl-CoA and subsequent release of ketone bodies into the circulation, which reach the central nervous system, providing it with energy (RUSEK *et al*., 2019). This form of diet is used in the treatment of several neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases (GOUGH *et al*., 2021).

The present study sought to revisit, through a narrative review, characteristics of the bioenergetic metabolism of glutamate, glutamine and acetate, for a better understanding of their impact on neuropathologies, as well as an application of this knowledge in the development of future clinical treatments.

MATERIAL AND METHODS

The present narrative review was conducted with the objective of synthesizing and analyzing the available scientific literature on the effects of glutamate, acetate and glutamine on the central nervous system (CNS), focusing on their implications in neuropathologies, such as neuroinflammation and neurodegeneration. The review aimed to understand the biochemical mechanisms involved in glutamate cytotoxicity and the neuroprotective potential of acetate, particularly with regard to histone acetylation and modulation of inflammatory gene expression. The search for relevant articles was carried out in the main scientific databases, including *PubMed, Scopus, Google Scholar* and *Web of Science*. The selection was focused on articles that addressed the effects of glutamate, acetate and glutamine on the CNS, focusing on biochemical mechanisms, neuroprotection and neurotoxicity. Experimental, observational studies, and reviews were included, as long

as they directly addressed the effects of glutamate and acetate in the context of neuropathologies.

The following inclusion criteria were considered: articles that investigated the role of glutamate as an excitatory neurotransmitter in the CNS and its relationship with neuropathologies such as neuroinflammation and neurodegeneration, studies that explored the biochemical mechanisms of acetate, especially its conversion to acetyl-CoA and the effects of histone acetylation on the modulation of inflammatory genes, works that discussed the implications of glutamate accumulation and the possible therapeutic effects of acetate in neurological diseases. The following were excluded: studies that did not directly address the relationship between glutamate, acetate, and neurological diseases, articles that discussed only the effect of glutamate or acetate in isolation, without considering their interaction in the context of neuropathologies, studies not published in peer-reviewed scientific journals, or with questionable methodologies, such as very small samples or without adequate control groups.

The research was carried out using keywords such as "glutamate", "acetate", "acetyl-CoA", "neuroinflammation", "neurodegeneration", "glutamate cytotoxicity", "neuroprotection" and "histone acetylation". The search strategy was refined using filters of year of publication and language (articles published in English). The search was adjusted periodically to ensure that relevant articles were included.

After selecting the studies and analyzing the data, the information was synthesized in a narrative manner. The review focused on the biochemical mechanisms related to glutamate and acetate, exploring the interactions between these substances in the CNS and their implications for the development and progression of neuropathologies. The qualitative analysis of the studies allowed us to highlight the main findings on the cytotoxic effects of glutamate and the potential neuroprotective mechanisms of acetate, providing a broader understanding of possible therapeutic strategies for neurological diseases.

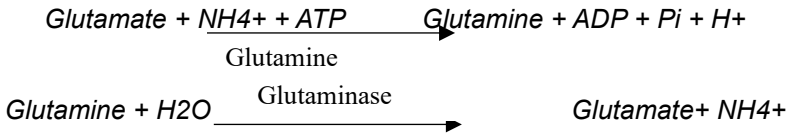
RESULTS AND DISCUSSION

GLUTAMINE, GLUTAMATE, AND NEUROTOXICITY

Amino acids are obligatory components of all cell culture media, as they are the starting point for protein synthesis. They are necessary for cell proliferation and their concentration determines the maximum achievable cell density. (FRESHNEY, 2010).

L-glutamine, a non-essential amino acid, is particularly important as it provides nitrogen to NAD, NADPH, and nucleotides, serving as a secondary energy source for metabolism (LANE, PAX and BENNETT, 1987).

Glutamine is an unstable amino acid that, over time, converts into a form that cannot be used by cells (PASIEKA and MORGAN, 1959). Its degradation results in the accumulation of ammonia, which can have a deleterious effect on some cell lines. Two enzymes are responsible for the synthesis of glutamine from glutamate or, conversely, its degradation into glutamate: glutamine synthetase and glutaminase, respectively (ROWBOTTOM, KEAST and MORTON, 1996; NEWSHOLME, PROCOPIO*, et al.*, 2003), as shown below:



Through the conversion of glutamate into glutamine and the use of ammonia as a source of nitrogen, with the consumption of adenosine triphosphate (ATP), glutamine synthetase is the key enzyme for glutamine synthesis and for the regulation of cellular nitrogen metabolism (NEWSHOLME, LIMA*, et al.*, 2003). It is an aminotransferase widely distributed among living organisms, and its activity is fundamental for the maintenance of life in microorganisms and animals (HISCOCK and PEDERSEN, 2002). The factors that regulate glutamine synthetase activity are diverse, such as glucocorticoids (SANTOS, CAPERUTO and COSTA ROSA, 2007), thyroid hormones (HISCOCK and PEDERSEN, 2002), growth hormone, and insulin (ARDAWI, 1990), resulting in numerous functions in the body (LABOW, SOUBA and ABCOUWER, 2001). In the brain, it is used as an important agent in reducing the concentration of ammonia, with consequent detoxification and synthesis of glutamine for new synthesis of glutamate (ROWBOTTOM, KEAST and MORTON, 1996). In the lungs and skeletal muscle, it is responsible for maintaining plasma glutamine concentration, being essential in pathological or stressful situations (PINEL *et al.*, 2006). In the kidneys, glutamine synthetase is essential for controlling nitrogen metabolism and maintaining pH in the body (LABOW, SOUBA and ABCOUWER, 2001).

Glutaminase is the enzyme that catalyzes the hydrolysis of glutamine into glutamate and ammonium ion. It is involved in several metabolic processes and can be found in bacteria, plants, and animals (RENNIE *et al.*, 2001). In mammals, this enzyme can be found in two isoforms, one (less abundant) in the liver and the other in other tissues, such as kidneys, brain, leukocytes and gastrointestinal tract. However, its most active form is mainly found in the mitochondria (LABOW, SOUBA and ABCOUWER, 2001). Through glutamate, the synthesis of other amino acids and antioxidants such as glutathione (GSH), the main non-enzymatic cellular antioxidant can occur (LU, 2013).

Glutamate is an excitatory neurotransmitter of the CNS, the most common in mammals (MELDRUM, 2000), being stored in vesicles at synapses. The nerve impulse causes the release of glutamate in the presynaptic neuron, which, in turn, causes the activation of N-methyl D-Aspartate (NMDA) receptors in postsynaptic terminals, causing the influx of calcium into these cells. The membranes of astrocytes, as well as neurons, have glutamate transporters that rapidly remove this amino acid from the extracellular space (DANYSZ and PARSONS, 2012; HOLMSETH *et al.*, 2012).

Calcium is a fundamental ion for the physiological functions of neurons, but in large quantities it causes injury and cell death (SZYDLOWSKA and TYMIANSKI, 2010). In situations of brain pathology (damage or disease), transporters can work in reverse and cause the accumulation and excessive concentrations of glutamate in the extracellular space. This reversal causes the entry and accumulation of calcium ions into the cells, through NMDA receptors, leading to neuronal damage and eventually cell death (apoptosis) (SATTLER and TYMIANSKI, 2001). The cytotoxicity of glutamate, potentially lethal to neurons, can be caused by: 1) mitochondrial alterations resulting from an excessive and uncontrolled influx of calcium into the cell, exceeding its storage capacity, with subsequent apoptosis; 2) amplification or overexpression of transcription factors of pro-apoptotic genes or 3) repression of transcription factors of anti-apoptotic genes mediated by glutamate and calcium (SATTLER and TYMIANSKI, 2001; ARUNDINE and TYMIANSKI, 2003; CHEN, GUO and KONG, 2012).

The exacerbated release of glutamate, in turn, generates death by cytotoxicity of other cells, continuing a cycle of degeneration in the tissue (LAUBE *et al.*, 1997; SZYDLOWSKA and TYMIANSKI, 2010). Cytotoxicity due to glutamate accumulation is associated with neurological and neurodegenerative diseases, such as Huntington's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and stroke or traumatic brain injury (HYND, SCOTT and DODD, 2004; KOSTIC, ZIVKOVIC and STOJANOVIC, 2013), since it induces damage such as free radical production, mitochondrial dysfunction and cell death (PAPOUIN *et al*., 2012). The main receptors involved in this process are NMDA-type receptors, but AMPA/Cainate receptors are also activated, causing the influx of calcium, sodium, chlorine and water through the osmotic gradient, causing edema, cell lysis and, consequently, greater glutamate release (STOCCA and VICINI, 1998; CHEN, MUHLHAUSER and YANG, 2003; PAPOUIN *et al*., 2012).

ACETATE BIOENERGETICS AND NEUROPROTECTION

In this context, acetate, a short-chain fatty acid, can benefit the CNS energetically and structurally, basically due to the participation of acetyl-coenzyme A (Acetyl-CoA), the metabolically active form of acetate, in biochemical pathways involved in the metabolism of carbohydrates, lipids and proteins (AKRAM, 2014).

Metabolically active acetyl-CoA is an important precursor in numerous biological processes that are critical for mitochondrial energy delivery, fatty acid synthesis, and lipid metabolism (SCHUG, VANDE VOORDE and GOTTLIEB, 2016). For example, in the cytosol of oligodendrocytes, acetyl-CoA is the source of the two-carbon atom units used for fatty acid elongation, which occurs in parallel with myelin deposition (BOURRE *et al.*, 1977). It is also used for oxidation in the Krebs cycle and energy production after condensation with oxaloacetate to form citrate, as well as in the biosynthesis of ketone bodies, fatty acids, and cholesterol (FUKAO, LOPASCHUK and MITCHELL, 2004; AKRAM, 2014). In addition, acetyltransferases employ acetyl-CoA as an acetyl donor for post-translational acetylation reactions on lysine and arginine residues that can lead to structural and functional consequences on proteins (GLOZAK *et al.*, 2005). Acetylation of nuclear proteins, such as histones, can lead to architectural chromatin changes and thus changes in gene expression (BANNISTER and KOUZARIDES, 2011).

Endogenous sources of acetate found in the CNS, which can influence cellular acetate levels, include the acetylated amino acid compounds (N-acetylaspartate, N-acetylcarnitine, N-acetylcarnosine, and N-acetylcysteine), as well as acetylated proteins capable of modulating cellular acetate levels in response to regulatory protein deacetylation and/or protein degradation (SOLIMAN, PUIG*, et al.*, 2012). Peripheral shunt acetate, on the other hand, enters the bloodstream and crosses the blood-brain barrier by simple diffusion (OLDENDORF, 1973).

According to the Codex General Standard for Food Additives (NGAA), the main nutritional sources of acetate are foods such as cheeses and other dairy products, processed meats, bread, ethanol, and non-digestible carbohydrates. In addition, acetate can be released from acetylated compounds in the body (SCHUG, VANDE VOORDE and GOTTLIEB, 2016).

Acetate is produced by most species of gut bacteria through the fermentation of pyruvate via acetyl-CoA. In addition, acetogenic bacteria can produce acetate from CO2 and H2 via the Wood-Ljungdahl reducing pathway (SCHUCHMANN and MULLER, 2014). Such bacteria can produce three acetate molecules from one molecule of glucose or fructose (REY *et al.*, 2010). Acetate is used locally in the intestine, and the rest enters the

liver through the portal vein. From there, the remaining acetate is released into the bloodstream, where it is consumed and oxidized in the tissues (SCHUCHMANN; MULLER, 2014).

After cell uptake, there are two enzymes capable of using acetate as a substrate: acetyl-CoA synthetase 1, located in the mitochondria (ACSS1), and acetyl-CoA synthetase 2 (ACSS2), located in the nucleocytosol (LUONG *et al.*, 2000; FUJINO *et al.*, 2001). Acetyl-CoA-synthetases, by definition, catalyze the ATP-dependent binding of acetate to CoA for the production of acetyl-CoA, which is a central metabolite between glycolysis and the Krebs cycle, as well as an important substrate for several other biochemical reactions and pathways, such as the synthesis of sterols, hexasamines, and ketones (SCHUG, VANDE VOORDE and GOTTLIEB, 2016).

The incorporation of acetate into fatty acids involves three enzymatic steps: binding of acetate with CoA to produce acetyl-CoA by ACSS2, carboxylation of acetyl-CoA by acetyl-CoA carboxylase α (ACCα, also known as ACC1), and the condensation of acetyl-CoA and/or malonyl-CoA by fatty acid synthase (KIMURA, FUKUDA and IRITANI, 2005). On the other hand, acetate oxidation in the Krebs cycle provides reducing equivalents for energy production by oxidative phosphorylation (PUIG*, et al.*, 2012).

Altogether, these metabolic fates of acetate indicate that when mitochondrial oxidation of glucose is compromised (under conditions of hypoxia or low glucose) or the availability of exogenous lipids is limited, acetate can be used to generate acetyl-CoA, producing energy through the Krebs cycle and/or generating biomass (SOLIMAN, SMITH, *et al.*, 2012).

The versatility of acetate-derived acetyl-CoA extends beyond being a bioenergetic substrate and a lipogenic precursor, also including the acetylation of proteins and metabolites. Studies have shown that acetate treatment in murine models of lipopolysaccharide (LPS)-induced neuroinflammation was able to inhibit the activity of histone deacetylases (HDACs), enzymes that catalyze the removal of acetyl groups from histones, directly influencing gene expression (SOLIMAN and ROSENBERGER, 2011; BRISSETTE *et al.*, 2012; SOLIMAN, PUIG*, et al.*, 2012; SOLIMAN, SMITH*, et al.*, 2012). In these patients, the treatment caused an increase in histone acetylation, with an increase in the activity of histone acetyltransferases (HATs). There was also a reduction in the expression of IL-1β, a pro-inflammatory cytokine, suggesting that the treatment resulted in a reduction in neuroinflammation (SOLIMAN, SMITH*, et al.*, 2012). Research evaluating the effect of acetate in a model of neuroborreliosis in rats found similar effects, with reduced activation of microglia and brain expression of IL-1β (BRISSETTE *et al.*, 2012). Acetate was

also tested in microglia cultures stimulated with LPS. The treatment reversed the hypoacetylation of histone (H3K9) induced by LPS and reduced the protein expression of IL-6, IL-1β and TNF-α (SOLIMAN, PUIG*, et al.*, 2012).

However, the extent to which acetate availability can influence specific epigenetic marks and overall acetylation levels needs to be determined. Acetate can become a substantial source of cellular acetyl-CoA when other carbon sources (e.g., glucose and glutamine) are limited, and acetate utilization will depend on its availability, absorption efficiency, and expression of acetate-capturing enzymes (e.g., ACSS1 and ACSS2) (SCHUG, VANDE VOORDE and GOTTLIEB, 2016).

Dietary supplementation with acetate has been shown to increase its concentration by 17 times and acetyl-CoA by 2.2 times in the brains of mice (MATHEW *et al.*, 2005). Acetate crosses the blood-brain barrier (DEELCHAND *et al.*, 2009) and is preferentially assimilated by astrocytes, prior to activation of acetyl-CoA by acetyl-CoA synthetase (WANIEWSKI and MARTIN, 1998; HALLOWS, LEE and DENU, 2006).

Over the past few years, there have been advances in studies of the potential of dietary acetate supplementation as an anti-inflammatory and neuroprotective intervention in different models of neuroinflammatory diseases *in vivo* and *in vitro* (MATHEW *et al.*, 2005; ARUN *et al.*, 2010; SOLIMAN and ROSENBERGER, 2011; SOLIMAN *et al.*, 2012; BHATT *et al.*, 2013; SMITH *et al.*, 2014; SINGH *et al.*, 2016). A crucial point in relation to this supplementation is its safety and tolerability. In this respect, parenteral and oral administration in animals was not associated with toxicities or behavioural changes analysed in dogs (BAILEY, HEATH and MILES, 1989; BAILEY, HAYMOND and MILES, 1991)Mice (BAILEY, MILES and HAYMOND, 1993) or rats (SOLIMAN and ROSENBERGER, 2011; SOLIMAN, SMITH*, et al.*, 2012).

Acetate can increase acetyl-CoA levels and replenish two energy reserves in the CNS. It is speculated that the energy generated as a result of mitochondrial metabolism of acetyl-CoA is stored in the form of phosphocreatinine (PCr) (BHATT *et al.*, 2013) and, when required, it is quickly converted into ATP (MEYER *et al*., 1984). PCr proved to be neuroprotective in animal models (ARUN *et al.*, 2010) and the increase in their neuronal stock protects neurons from damage from hypoxia, glutamate-induced toxicity, and amyloid-β (BREWER and WALLIMANN, 2000; BALESTRINO *et al.*, 2002).

Another hypothesis is supported by the action of ketone bodies (acetoacetate and beta-hydroxybutyrate), which are synthesized in the liver from acetyl-CoA generated by the beta-oxidation of fatty acids, when acetyl-CoA levels exceed the capacity of use in the tricarboxylic acid cycle (JAWORSKI, NAMBOODIRI and MOFFETT, 2016). The ketogenic

diet, a high-lipid, moderate-protein, and low-carbohydrate diet, mimics fasting and significantly increases serum concentrations of beta-hydroxybutyrate and acetoacetate (HARTMAN and VINING, 2007). Recent studies show that ketone bodies and their components have a neuroprotective effect for acute and chronic neurological diseases, particularly in the treatment of epilepsy in children, pathologies related to the deficiency of GLUT-1 enzymes, pyruvate dehydrogenase and defects of cerebral glycolysis (HARTMAN and VINING, 2007; KIM and RHO, 2008; NEI *et al.*, 2014). The ketogenic diet is considered safe because ketone levels are self-limiting, since excess ketone bodies are excreted in the urine (JAWORSKI, NAMBOODIRI and MOFFETT, 2016).

The mechanism by which the ketogenic diet leads to the reduction of epileptic seizures is not yet clear; It is suggested that the excessive supply of fats is able to maintain the metabolic mechanism of starvation, because in this situation, this macronutrient is used as an energy source instead of stored fat, creating and maintaining a state of ketosis (PRASAD, STAFSTRÖM and HOLMES, 1996). The sedative effect of ketone bodies (acetoacetate and β-hydroxybutyrate), their concentration in plasma, the degree of acidosis, partial dehydration, the change in lipid concentration and the energetic metabolic adaptation of the brain resulting from this ketosis would be the main factors involved and responsible for the control of seizures (SWINK, VINING and FREEMAN, 1997; KATYAL *et al.*, 2000).

The demonstration that the CNS is capable of metabolizing ketone bodies suggests that these may be related to the effect of this diet (OWEN *et al.*, 1967). Ketone bodies contribute not only as an energy source to the brain, but also to glucose-dependent brain constituents (GABA and glutamate). Since the oxidation of fatty acids produces a large amount of ATP, it is suggested that the increase in brain energy reserves is a protective factor against crises (WHELESS, BAUMGARTNER and GHANBARI, 2001).

Another molecule related to energy storage is N-acetylaspartate (NAA). Recent studies, many of them focused on multiple sclerosis (MS), have shown the energetic and structural importance of NAA in neuroprotection. This is interesting, since the excess glutamate in MS causes cytotoxicity in neurons, as already mentioned, and the pathway for the formation of NAA uses this available glutamate. The acetylation of aspartate by the neuronal enzyme aspartate N-acetyltransferase results in the formation of NAA, which is exported by the mitochondria. The formation of NAA favors the conversion of glutamate to α-ketoglutarate, which is a mechanism in neurons to bypass the slow reaction of citrate synthase in the tricarboxylic acid cycle. NAA levels are considered to be a marker of mitochondrial function and axonal integrity (YUDKOFF et al., 1994; CAMBRON *et al.*,

2012). NAA produced in axonal mitochondria is released into the extracellular space and taken up by oligodendrocytes for myelin maintenance (ANDO *et al.*, 2003). In oligodendrocytes, aspartoacylase cleaves the acetate portion of NAA for use in the synthesis of fatty acids and steroids that are used as building blocks for the synthesis of myelin lipids (MOFFETT *et al.*, 2007). Axons that lose their myelin sheath are prone to degeneration, as occurs in MS (IRVINE and BLAKEMORE, 2008). A cycle of decreased glutamate presence, energy efficiency and myelin production is then created, with acetate as the main neuroprotective component.

Finally, according to the literature, acetate promotes a decrease in the cycle ofand, consequently, the decrease in cell proliferation (MATSUKI *et al.*, 2013; LONG *et al.*, 2015). Matsuki et al. (2013) showed that acetate is one of the main responsible for the transcriptional repression of cyclin D1 and cyclin E1 genes in intestinal epithelial cells. Such cyclins are essential for the progression of the G1/S checkpoint in the cell cycle, so that their repression causes the blockage of cell proliferation. This process is also closely linked to cell differentiation, which competes with cell proliferation (MATSUKI *et al.*, 2013). In this sense, acetate It can act on neuroprotection more by differentiating or maintaining cell integrity than by cell proliferation (LONG *et al.*, 2015).

CONCLUSION

In conclusion, the balance between glutamate and acetate in the central nervous system plays a key role in maintaining brain homeostasis. While excess glutamate can be toxic and is associated with several neuropathologies, acetate, through its active form, acetyl-CoA, regulates cellular and tissue bioenergetics, modulates epigenetic processes and participates in the formation of myelin, so that it can contribute to neuroprotection. A deeper understanding of the interactions between glutamine, glutamate, and acetate, as well as the bioenergetic-structural of these compounds, opens new perspectives for the development of therapeutic strategies aimed at the treatment of neurological diseases, such as neuroinflammation and neurodegeneration.

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