



Traumatic Brain Injury and Branched-Chain Amino Acids

João Luís Pinheiro^{1*}, Armando Rocha¹ and João Pinheiro²

Abstract

Introduction: Traumatic brain injury is a major cause of death and disability in the youth population. It is not a common injury in sports practice but it is more frequent in modalities involving high energy movements at the cranial and cervical spine levels. Its neurological consequences can be serious, such as motor deficits and changes in the learning process and memory. This article discusses the role of branched-chain amino acids in improving cognitive functions after traumatic brain injury.

Methods: We conducted a literature search in PubMed / Medline, PEDro and Cochrane, up to 2016 with no limit on the starting date. Additional search were performed on other editors.

Results: A total of 23 articles were reviewed and various clinical elements were extracted to meet the objectives proposed.

Discussion and conclusion: After traumatic brain injury there is a decrease in the level of branched-chain amino acids in the central nervous system as well as an imbalance between excitatory and inhibitory potentials in the dentate gyrus in the cornu ammonis (CA) 1 and 3, with consequent impairment of neurocognitive functions. They are neurotransmitter precursors responsible for the balance of the hippocampal synaptic network. They are vital elements in metabolic reactions essential for neurotransmitters formation, and the cohesion of the synaptic network.

Human studies have demonstrated its efficacy in improving cognitive functions after traumatic brain injury. The impact of these amino acids may also be developed for other sequelae resulting from traumatic brain injuries, namely motor or sleep disorders.

Keywords

Traumatic brain injury; Branched-chain amino acids; Hippocampus; Limbic system; Glutamate

Introduction

In Western society, traumatic brain injury (TBI) is the primary cause of death and disability in adolescents and young adults. Recent data suggest that by 2020, TBI will be the third leading cause of death and disability in the world. In the USA and Europe together, there are approximately 13 million victims of TBI with various sequelae such as motor, cognitive and behavioral impairments [1].

The prevalence of sports-related TBI is not fully understood. It is estimated that every year approximately 3.8 million TBIs are related

to physical activity, including cases that are not submitted to specific medical evaluation [2].

The Glasgow Coma Scale (GCS) subdivides TBI into three categories: mild (13-15), moderate (9-12) and severe (3-8). Mild TBI, which includes cerebral concussion, is the most common group of sports-related traumatic endocrinal injuries, particularly in modalities such as rugby or fighting sports, while the moderate to severe group, which justifies emergency medical care, corresponds to 13.5% of sports TBI. Intracerebral, subdural or epidural hemorrhages are often associated with this type of trauma, caused mostly by the motorized sports, skiing and board sports. The therapy for moderate to severe TBI is mainly directed towards the relief of symptoms correlated with high intracranial pressure. It is also important to take into consideration the biomechanical characteristics of the attacking force. A high energy attack promotes several pathophysiological mechanisms responsible for severe modifications of neuronal activity that in turn promote several modifications of higher brain functions such as cognition [3,4].

Several efforts have been made by the scientific community to find substances able to limit and antagonize the biochemical changes resulting from TBI. In this context, branched-chain amino acids (BCAAs) appear to be a promising research line.

Methods

Electronic available literature was searched using PubMed / Medline, PEDro and Cochrane, up to 2016 with no limit on the starting date. Additional search were performed on other editors (Elsevier, Google Scholar). The research identified only articles specifically related to the main purpose of this review - role of branched-chain amino acids in improving cognitive functions after traumatic brain injury. The most common terms "traumatic brain injury, branched-chain amino acids" were combined with nervous central system words (i.e., hippocampus, limbic system, glutamate). The target populations were victims of TBI both in sports activities as well as in other daily activities. Considering the very specific nature of the subject, the number of eligible articles was greatly reduced by using only those who addressed the subjects "neural circuit of memory and learning", "brain metabolism and BCAAs" and "traumatic brain injury metabolic alterations and BCAAs". Characteristics and clinical contents of each article were extracted by the first author.

Results

A total of 23 articles were reviewed and various clinical elements were extracted to meet the objectives proposed. The details of the methodological quality of the 23 studies could not be obtained considering their characteristics essentially of literature review.

Discussion and Conclusion

In order to make the discussion more comprehensive we present the discussion subdivided into four items ("neural circuit of memory and learning", "excitatory and inhibitory neurotransmitters - Glutamate and gamma amino butyric acid (GABA) production", "brain metabolism and BCAAs", "traumatic brain injury metabolic alterations and BCAAs").

*Corresponding author: João Luís Pinheiro, Neurosurgery Service, University Hospital Centre of Coimbra, Portugal, Tel: + 351-239 857 700; E-mail: jpascoapinho@gmail.com

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Neural circuit of memory and learning

Anatomopathological studies and stereological counts have shown that TBI cognitive impairment is associated with localized lesions in the medial portion of the temporal lobe, more specifically in the hippocampal formation, a zone of the limbic system. This structure, which limits the floor of the lateral ventricle temporal horn, is divided into three sub-regions, namely the dentate gyrus (where the granule cells are located), the hippocampus and the subiculum.

The hippocampus, also known as the cornu ammonis (CA), is further subdivided into 4 portions (CA1, CA2, CA3 and CA4). Pyramidal cells are part of this structure [5].

The learning and memory-building process, also called working memory, involves a complex neuronal loop associated with a perfect balance between excitatory and inhibitory regional activity.

The first stimulus occurs in the so-called entorhinal cortex, located in the medial portion of the temporal lobe. From here, the signal is transmitted by axons that cross the subiculum to reach the dentate gyrus. This first pathway is called the “*perforant pathway*”. The granule cells of the dentate gyrus then synapse with the pyramidal neurons of the CA3 region. The axons of this region, called Shaffer collaterals, synapse in CA1 pyramidal cells. From here the signal goes to the subiculum ending in the entorhinal cortex, this being the end of the circuit. The so-called long-term potentiation (LTP) phenomenon is considered crucial in this process [6].

LTP is a mechanism related to synaptic plasticity, which aims to reinforce the connection between two neurons, in this case between CA3 (pre-synaptic) and CA1 (post-synaptic) neurons during the execution of complex cognitive functions. The neurotransmitter (NT) glutamate (Glu) is the key to the consolidation and strengthening of this process.

In the postsynaptic membranes of the CA1 neurons there are two receptors, the sodium-permeable (Na⁺) α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and the N-methyl-D-aspartate receptor (NMDA), also permeable to Na⁺ but to a greater degree to calcium (Ca²⁺). The latter is blocked by a magnesium ion (Mg²⁺). Both are sensitive to Glu [7].

It is well known that an action potential (AP) of a given frequency releases Glu from presynaptic vesicles of CA3 neurons into the synaptic cleft. In turn, Glu acts on the postsynaptic receptors AMPA and NMDA, both present in CA1 neurons. Activation of these neurons promotes the entry of Na⁺ by AMPA and the unlocking of NMDA, established by Mg²⁺. The opening of NMDA occurs at the expense of a mechanism called electrostatic repulsion, which is directly proportional to the Na⁺ input by AMPA.

It has also been verified that the greater the concentration of Glu released into the synaptic cleft, the higher the Na⁺ concentration entering the postsynaptic AMPA of the CA1 neurons, with a consequent increase in the number of Ca²⁺ permeable NMDA [8].

The increase in post-synaptic Ca²⁺ concentration promotes the reinforcement of the neuronal connection through two mechanisms. In the short term, the availability of AMPA increases, which might reinforce the phenomenon of electrostatic repulsion exerted on NMDA Mg²⁺.

In the long term, there is an increase in the transcription and synthesis of proteins such as AMPA, but also of brain growth factors

that participate in the formation of new synapses between the CA3 and CA1 neurons, reinforcing their connection [7].

This complex neuronal circuit, responsible for the enhancement of neurocognitive functions, namely memory and learning, has been particularly studied in animal models.

A behavioral test that evaluates the conditioned fear response has been the most frequently used. The model is placed in a separate compartment for a certain period of time and an electrical stimulus is applied. The ultimate goal is to evaluate the learning ability of the model by measuring the time it stay still when placed on the same side where the stimulus was applied. The percentage of freezing (% F) is directly proportional to cognitive efficacy [9].

Excitatory and inhibitory neurotransmitters (Glutamate and GABA production)

Glu is an amino acid (AA), consisting of two carboxyl groups (-COOH) and an amine group (-NH₂). It performs various functions at brain level, notably in astrocytes and neuronal cells. It contributes to the formation of high-energy molecules such as adenosine triphosphate (ATP).

Much of the ATP formed in brain cells comes from the Krebs cycle. The cytoplasmic enzyme aspartate aminotransferase promotes the reversible transamination of Glu with consequent formation of alpha-ketoglutarate (alpha-KG).

This is essential for the normal functioning of the Krebs cycle, a reaction that culminates in the formation of ATP molecules [10]. At the neuronal level Glu promotes post-synaptic excitatory potentials, responsible for the depolarization and subsequent development of an amyloid precursor protein (APP) that strengthens synaptic network efficiency through the LTP phenomenon.

In predominantly inhibitory neurons, Glu is converted into GABA through the enzyme Glu-decarboxylase. In this way, it is assumed that Glu is a precursor of the major inhibitory NT [7].

The glutamate-glutamine cycle is the primary mechanism for maintaining a constant pool of brain Glu. The Glu released into the synaptic cleft is taken up by the astrocytes and converted into glutamine (Gln), an ATP-dependent process catalyzed by the enzyme glutamine synthetase.

The astrocytic Gln is transported to the presynaptic neuronal portion and converted back into Glu by a mitochondrial glutaminase, thus closing the cycle. It is important to emphasize that not all of the Gln formed is used in the Glu recycling process, some of it being oxidized by the astrocytes, for example. The amount of Glu used by neurons is variable, depending on the complexity of the mental process [11].

It is thus concluded that the Gln-Glu cycle is not sufficiently effective in maintaining constant levels of Glu, and consequently of GABA, at the brain level. It is well known that there are other pathways which complement the production of these NTs.

Brain metabolism and BCAAs

AAs are organic compounds that contain an amine group (NH₂) and a carboxyl group (COOH-) associated with a side chain, the R group. The latter is specific for each AA group.

BCAAs have a side chain, called aliphatic, and are in the essential AA group. There are three types of BCAAs: leucine, isoleucine and valine.

They are not produced endogenously, so food or supplementations are the main sources for obtaining them. They correspond to 40% of the AAs required by the human body and approximately 40, 20 and 19 mg / kg / day of leucine, valine and isoleucine should be consumed, respectively.

BCAAs are considered essential elements in various metabolic reactions, namely the promotion of protein synthesis, glucose metabolism, and oxidation of free fatty acids, maintenance of an effective immune system and also in cerebral metabolism.

Regarding the practice of physical exercise, studies have been carried out to ascertain the role of these nutrients in the improvement of athletic performance.

Knowing that BCAAs stimulate protein synthesis through mammalian target of rapamycin dependent pathways, some trials have shown that BCAA supplementation may have some benefit in post-exercise muscle recovery, decreasing the intensity of delayed onset muscle soreness.

The participation of BCAAs in Gln metabolism and stimulation of lymphocyte proliferation, in particular cytotoxic T-lymphocytes, has led several investigators to demonstrate that daily supplementation with BCAAs in high-competition athletes may be important in the prevention of frequent oropharyngeal infections related to over training. Supplementation with BCAAs interferes with the degree of central fatigue related to endurance exercise, which includes ultra-trials and sailing. The term central fatigue is related to the cognitive alterations resulting from strenuous exercise that interfere with decision-making capacity and motivation.

These modifications are attributed to an increase in serotonin concentration in the CNS, more specifically, in the hippocampus. BCAAs cross the brain-blood barrier (BBB) through competition with aromatic AAs, namely the 5-hydroxytryptamine receptor (5-HT) precursor, tryptophan. A decrease in the tryptophan / blood BCAA ratio promotes a decrease in 5-HT in the central nervous system (CNS) and thus it is assumed that supplementation with BCAAs during endurance exercise could attenuate the degree of CNS-related fatigue. A study compared the short-term memory of athletes supplemented with BCAAs with placebo before and after a 32-hour sailing trial [12]. Although there were no differences in the tests performed before the trial, the group supplemented with BCAAs presented better results in the memory assay at the end of the competition, which corroborates the hypothesis described above.

After crossing the BBB, the BCAAs are involved in important functions, namely protein synthesis, energy production and NT formation [13].

Nearly 50% of the cerebral Glu contains nitrogen derived from the BCAAs, and 40% of the Glu released from the synaptic cleft is derived from the catabolism of these AAs [14]. Concerning the formation of new Glu, the catabolism of BCAAs in astrocytes essentially involves two types of processes.

The first occurs in the astrocyte mitochondria. The mitochondrial branched-chain aminotransferase enzyme the BCAAs in a reversible way, forming branched-chain alpha-keto acids (BKAAs). The amine group, together with alpha-KG, a ketonic acid from the Krebs cycle, gives rise to Glu. The second process involves the conversion of BKAAs into succinyl-Co, acetoacetate and acetyl-CoA, essential substrates for the Krebs cycle. From this cycle alpha-KG is produced, along with carbon molecules for the constitution of the COOH group

of Glu, and the ATP required for two reactions: the Gln-Glu cycle, and the conversion of Glu into Gln within the astrocyte for later use by the neuronal cell [15].

TBI metabolic alterations and BCAAs

Molecular and biochemical changes resulting from TBI have been studied through lateral fluid percussion injury, a technique approved by the Institutional Animal Care and Use Committee, which mimics mild to moderate TBI and cognitive deficits associated with animal models.

TBI causes specific changes localized in the medial portion of the temporal lobe, namely the hippocampus. After traumatic brain injury (TBI), aerobic glycolysis is compromised, with a consequent decrease in ATP production. The failure of several ionic carriers is observed, namely the Na + / K + ATPase pump, which in turn leads to an imbalance of the ionic homeostasis between the intra and extracellular space, with a consequent risk of neuronal lysis.

Through stereological quantification techniques, it is possible to demonstrate a 40% loss of neurons in the CA1, CA3 and hilar portion of the dentate gyrus (ipsilateral to the lesion) in the first month after a TBI [16]. Following a TBI, the concentrations of the required precursors for NT formation, such as Glu and GABA, are decreased. Among them are the BCAAs from the hippocampal region and those from the blood circulation [17].

Neuronal destruction, ionic imbalances and impairment of NT synthesis promote changes in the hippocampal excitability pattern. The excitability of the dentate gyrus is increased, unlike that of the CA1 and CA3, which is diminished. There is thus an impairment of the previously-described LTP, a phenomenon of synaptic plasticity, which in turn compromises the cognitive functions of the patient [18].

Other reactions dependent on high-energy compounds are also altered, in particular, protein synthesis. As a consequence, the formation of new synapses and the remodeling of damaged brain structures are compromised [19].

In rats submitted to local field potential analysis, a reduction in the hippocampal BCAAs ipsilateral to the lesion was observed. In humans with a GCS score between 15 and 3, chromatography techniques and mass spectrometry reveal that the three main BCAAs are decreased. The greatest reduction occurs in low GCS scores [17].

A study with experimental animals to find the benefits of BCAA supplementation after TBI was carried out using the Fear Conditioning Test. This supplementation was shown to increase % F after 5 to 10 days of treatment, approaching the values prior to the trauma. Intake of BCAAs for only five days has not been shown to be effective and there is a need for a continuous intake for at least 10 days.

It should also be noted that for a more sophisticated cognitive improvement, supplementation with 100Mm of BCAAs was necessary [20].

The Disability Rating Scale (DRS) is a 0-to-29-point scale applied to individuals with moderate to severe TBI (0 = normal, 29 = extreme vegetative state). It assesses the degree of disability caused by TBI, namely neurocognitive impairment, and the evolution of deficits. Aquilani et al. [21] used the DRS to verify cognitive improvement with BCAA supplementation. TBI victims with a DRS of 20 had improved scores and several therapeutic benefits after daily intravenous supplementation of 19.6 g of BCAAs over a 5-hour period. Later

in 2008, it was shown that the decrease in the DRS score was even more pronounced in individuals with initial values between 22 and 29 (68.2% of the traumatized patients had been considered as minimally conscious) [22].

These last studies suggest that BCAA supplementation can improve the cognitive function of the patient with TBI. On the other hand, one isolated study found that enteral supplementation with BCAAs promoted increased intracranial pressure and decreased oxygen saturation of the jugular vein in patients with severe TBI [23].

This review sets out to describe the therapeutic contribution of BCAAs in TBI. The phenomenon of LTP, responsible for synaptic neuroplasticity, is compromised in this type of lesion. The alteration of Glu and GABA levels, neuronal destruction and the imbalance of ionic homeostasis are key factors to be considered in order to understand the asymmetry between excitatory and inhibitory potentials in the hippocampus, with consequent LTP impairment.

BCAAs are vital elements in metabolic reactions essential for (NT) formation, the maintenance of neuronal health and the cohesion of the synaptic network responsible for neurocognitive functions. It has been shown that after TBI there is a decrease in the level of BCAAs in the CNS.

Human studies have demonstrated the efficacy of BCAA supplementation in improving cognitive functions after TBI. Since cerebral concussion is the most common TBI, future trials should focus on the benefit of taking BCAAs for compromised neuronal functions. Further studies should be performed so that BCAA therapy is instituted in the patient with TBI. The route of administration, dose and duration of therapy are variables that must be defined and correlated with the victim's characteristics, such as gender, age and cognitive ability prior to injury. The impact of BCAA supplementation may also be developed for other sequelae resulting from TBI, namely motor or sleep disorders.

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Author Affiliation

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¹Neurosurgery Service, University Hospital Centre of Coimbra, Portugal

²Physical Medicine and Rehabilitation, Faculty of Medicine, Coimbra University, Portugal

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