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Mini review

Characteristics of the Amino Acid Pool in the Brain of Rats in the Postnatal Period

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Abstract

The brain, ensuring its functions, metabolism, and regulation of the rest of the body all this is largely provided by amino acids. This phenomenon has the following basis: the mediators necessary for nerve impulses have a raw material base - amino acids. The transmission of a nerve impulse through the synapse, which is the basis for the functioning of the brain and spinal cord, as well as the peripheral nervous system, is also largely provided by amino acids or those biologically active substances that are formed from these amino acids through their biological transformation in the nervous tissue.

Keywords: Amino acid; brain; rats; postnatal period

Introduction

The brain, ensuring its functions, metabolism, and regulation of the rest of the body all this is largely provided by amino acids. This phenomenon has the following basis: the mediators necessary for nerve impulses have a raw material base - amino acids. The transmission of a nerve impulse through the synapse, which is the basis for the functioning of the brain and spinal cord, as well as the peripheral nervous system, is also largely provided by amino acids or those biologically active substances that are formed from these amino acids through their biological transformation in the nervous tissue. In those conditions when the blood contains a small amount of oxygen and other energy substrates for neurons and glial cells, amino acids can be included in biological processes to provide energy for nerve cells. Thus, amino acids can play an important role in ensuring the occurrence of such energy-significant processes as the tricarboxylic acid cycle and the biosynthesis of cytochromes. There are 33.9 micromoles of amino acid pool for one thousandth of a kilogram of nervous tissue.

Normally and in several pathologies of the central nervous system and peripheral nervous system of humans and animals, it has the potential to maintain the balance of amino acids necessary to maintain its functioning. The amino acid content is highest in the mammalian brain. For example, their amount in brain homogenates exceeds that in plasma and cerebrospinal fluid by more than 9 times. Amino acids enter the brain through the blood-brain barrier from the blood plasma [1-3]. There are various mechanisms for their transportation. There are a number of carriers for this. Essential amino acids pass through the blood-brain barrier much more easily than non-essential ones. The isomerism of amino acids causes transport through the BBB, resulting in a large throughput of L-isomers. Three-quarters of the amino acids in the mammalian brain are non-essential amino acids that act as mediators. Different parts of the brain, regardless of the constancy of the total number of amino acids, have certain differences in their content.

The heterogeneity of the brain in various aspects is characterized by the compart mentality of amino acids in the structures of nerve cells and their subcellular structures. Brain neurotransmitters have the most diverse distribution of amino acids. Protein catabolism, metabolic rate in general, as well as the transport of amino acids determines their concentrating ability in the body. The balanced

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structure of amino acids of the organism is characterized by its normal activity. Diffusion against the concentration gradient, which entails the expenditure of a certain amount of energy, allows them to accumulate in the structures of neurons and glia of the brain by passing first the blood-brain barrier, and then into the organelles of brain cells. The cell membrane-bound γ-glutamyltranspeptidase affects the transport function of amino acids by being included in the γ-glutamyl cycle as the main reaction enzyme. The same amino acid is released by the enzyme γ-glutamyl cyclotransferase. Thus, they carry out the transfer of the intracellular group to the extracellular amino acid with the formation of the cysteinyl glycine dipeptide and, upon its cleavage, the final transportation of the amino acid into the intracellular medium [4].

For the transport to be carried out (due to the exceeding speed of transport, the rate of synthesis and degradation is not normally limited) with the help of the gamma-glutamyl cycle of one amino acid molecule, 3 ATP molecules are required. Therefore, there is an accumulation of amino acids in the brain, forming a pool, but with insufficient intake, its depletion occurs. Thus, it was found that the cerebral pool of free amino acids can be depleted in 30 minutes during the synthesis of proteins and neuroactive products, but during development there is a change in both the activity of the systems and the composition of their pool: in comparison with an adult organism, at an early age, large concentrations reach their peak much more easily. Free amino acids in the brain of baby rats can be conditionally divided into three main groups. The first group of AA includes glutamic acid, glutamine, aspartic acid, and GABA, which are present in the brain in relatively high concentrations and play an important role in the intermediate metabolism of proteins and their synthesis, control the speed of the tricarboxylic acid cycle and maintain the balance of its various components [5].

The second group of AA consists of many amino acids present in relatively low concentrations (serine, methionine, lysine, histidine, threonine, cysteate, cystathionine, cysteinsulfinic acid); these amino acids can be associated primarily with the synthesis and cleavage of tissue proteins that constantly occur during development. The third group of AA consists of usually unrelated AK, the number of which decreases during maturation (proline, valine, leucine, isoleucine, tyrosine, and phenylalanine) [6]. Rat brain mass increases significantly up to 21 days after birth. At the same time, there is an increase in the level of glutamic acid, glutamine, GABA and aspartic acid. Glutamine, which is in a dynamic relationship with glutamic acid, has a high level at birth, decreases by the seventh day, and then increases by 90 days of postpartum development. The GABA content gradually increases up to 30 days of postnatal ontogenesis. Since GABA is mainly formed in the central nervous system by decarboxylation of glutamic acid with decarboxylase glutamic acid, it is possible that the progressive growth of GABA may be the result of an increase in the content of glutamic acid in ontogenesis.

GABA is the most common mediator of inhibition in the nervous system. The cycle of GABA transformations in the brain includes three conjugated enzymatic reactions called GABA shunting. The GABA shunt is a branch of CTC in the section from α-ketoglutarate to succinate. With the participation of the enzyme glutamate decarboxylase (GDK), the first carboxyl group of L-glutamic acid is cleaved to form GABA. This enzyme is present only in the central nervous system, mainly in the Gray matter of the brain, and is a marker of GABAergic synapses. The enzyme is synthesized in the pericaryons of neurons, and then very quickly transported along the axon. Like most other amino acid decarboxylases, GDK needs pyridoxal phosphate as a cofactor, which is strongly bound to the enzyme. The level of GABA is regulated by the activity of GDK and does not significantly depend on the action of enzymes that break down GABA. GABA transaminase (GABA-T) is found mainly in the gray matter of the brain but is also found in other tissues. It contains pyridoxal phosphate as a cofactor and is strongly bound to it. GABA-T is localized in mitochondria, while GDK and GABA are localized in synaptosomes. The final enzyme GABA-shunt dehydrogenase of amber semialdehyde converts the latter into succinic acid, is metabolized with GABA–T in the mitochondria of CNS neurons, is specific to amber semialdehyde and NAD+, is activated by substances containing sulfhydryl groups [7-9].

The transamination reaction of α-ketoglutarate can lead to the synthesis of glutamate, which, in turn, under the action of the enzyme glutamate synthetase, forms a compound that removes ammonia from the body – glutamine, which proves the connection of glutamate with the Krebs cycle as a component of energy exchange. The further pathway of α-ketoglutarate consists in the reaction of amination or transamination with the formation of α-glutamate. Amination in this case is most frequent in the brain due to the utilization of ammonia in the amino acid composition, but the main way remains transamination, which depends on the normal functioning of the Krebs cycle and the number of macroergs in brain cells. Thus, glutamate plays a special role in the energy supply of the brain, which consists in maintaining a high level of α-ketoglutarate, and in the supply of mitochondrial synthetic processes with reducing equivalents [10]. Detoxification of ammonium occurs during the formation of glutamine from glutamic acid and aspartic acid from asparagine, which avoids hepatic coma in hepatic insufficiency. The enzyme of glutamine formation in the brain is deposited in glial cells and nerve endings.

In the latter, glutamine deamination occurs under the action of glutaminase, and, under the action of feedback, the products of this reaction inhibit the activity of the enzyme. Since glutamate is much harder to pass through biological membranes than glutamine, glutaminase is connected here, which allows the blood glutamine to turn into glutamate cells, in particular nerve cells. These data suggest that there is a glutamine cycle in the human body, that is, glutamine, being a glioneuronal transporter, is formed from glial glutamate and, when entering neurons, turns back into glutamate. Biologically active peptides and proteins are formed in the presence of glutamate since glutamate and glutamine make up about nine percent of the total amino acid residues of the brain. Glutamate is an integral part of glutathione, and its cyclic derivative pyroglutamate is contained in luliberin, tyro liberin, neurotensin

and other neuropeptides. Being the N-terminal residue of the latter, pyroglutamate protects them from proteolysis. Glutamate, compared to glutamine, when injected into the brain can cause seizures, and when administered intravenously can cause the death of neurons, especially in places where there is no blood-brain barrier, such as the ventricles. Since the BBB is not fully developed in new-borns, the neurons of the brain remain sensitive to damage by glutamate [11-13].

It was found that glutamate is associated with the phenomenon of glutamate excitotoxicity in cerebral ischemia, which is a pathogenetic link in the biochemical cascade that initiates the formation of divalent nitric oxide, oxidative stress, inflammation, and apoptosis. The negative role of glutamate excitotoxicity in the processes of neurodegeneration and demyelination in multiple sclerosis has also been established. After glutamate enters the synaptic cleft, its reuptake is carried out under the influence of Na-dependent high-affinity carriers by astrocytes and, to a lesser extent, by neurons. For optimal functioning of synapses with a neurotransmitter in the role of glutamate, its continuous supply to the nerve endings is necessary. The precursors of the glutamate transmitter pool are glucose and α-ketoglutarate. Glutamate can also be synthesized from ornithine and L-arginine (via glutamate-semialdehyde). The main source is glutamine, which is synthesized mainly in astrocytes, where glutamine synthetase is localized. After that, it passes unhindered through the membrane and with the help of carriers moves to the nerve endings [14-16]. At the same time, there is a decrease in the amount of several amino acids, such as: proline, valine, leucine, isoleucine, tyrosine, phenylalanyl.

Phenylalanine, being an essential amino acid, participates in transamination and decarboxylation. Also in the brain, it can hydroxylate to tyrosine, followed by the formation of 3,4-dihydroxyphenylalanine. With a deficiency of phenylalanine-4-hydroxylase, which is an enzyme for the formation of dioxyphenylalanine, phenylketonuria can be observed, which is characterized by a toxic effect on the brain of phenylalanine metabolites, namely: phenyl pyruvic and phenylacetic acids [17]. Brain catecholamines are formed mainly from tyrosine, which is the main way of its metabolism. Tyrosine also has several ways of transformation, as a result of which 3,4-dihydroxyphenylalanine, which has toxic properties of tyramine, as well as thyroid hormones and melanin, can be formed from it. It is an essential acid for phenylketonuria and affects nervous processes [18-20]. The concentrations of other amino acids and two peptides, glutathione, and sarcosine, remain unchanged throughout development. A decrease in the content of AA data may reflect changes in the internal environment of the organism, which is metabolically adapting to extrauterine life. These amino acids constitute the brain's prenatal reserve for postnatal adaptation. Their decrease in the postnatal period may be due to inclusion in protein synthesis or an increase in transport from the brain.

Decreased levels of tyrosine in the brain may be partly due to its use in the formation of catecholamines. The relative level of threonine in the entire rat brain is lower than in the rat cerebral cortex. In postnatal ontogenesis, there is a pronounced decrease in the product of AA metabolism - urea (by 63%), which is a consequence of passing through the blood-brain barrier. Given that the brain does not contain urease, its metabolic origin is not known. Thus, in the developing brain of rats, the content of several amino acids (tryptophan, glycine, alanine, glutamate, serine, methionine, lysine, histidine, threonine, tryptophan, phenylalanine, aspartate, asparagine, threonine, serine, histidine, arginine, cysteate, cystathionine, taurine, cysteine sulfonic acid) does not change [21-23]. There are several AAs, the content of which decreases (proline, valine, leucine, isoleucine, tyrosine, and phenylalanine) and several amino acids (glutamic acid, GABA, glutamine, and aspartic acid), the concentration of which increases in postnatal ontogenesis.

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