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Review Article

Changes in the pool of amino acids during cerebral ischemia. Review

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Abstract

Amino acids play an important role in metabolism and brain function. This is explained not only by the exclusive role of amino acids as sources of the synthesis of a large number of biologically important compounds (proteins, mediators, lipids, biologically active amines). Amino acids and their derivatives are involved in synaptic transmission as neurotransmitters and neuromodulators (glutamate, aspartate, glycine, GABA, taurine), and some AAs are involved in the formation of nervous system mediators: methionine - acetylcholine, DOPA, dopamine; tyrosine – catecholamines; serine and cysteine - taurine; tryptophan - serotonin; histidine - histamine; L-arginine – NO; glutamic acid – glutamate.

Their energy significance is also significant, especially in conditions of hypoglycemia. Despite the use of glucose as the main source of energy in the brain, amino acids are involved in energy metabolism through the formation of CoA and other components of the tricarboxylic acid cycle, as well as cytochromes.

Keywords: amino acid; cerebral ischemia; tryptophan

Introduction

According to the literature, with cerebral ischemia caused by occlusion of the middle cerebral artery, the content of alanine, glutamic acid, phenylalanine, threonine, lysine, tyrosine, arginine, tryptophan and glycine increases, while the content of taurine decreases.

Alanine performs inhibitory neurotransmitter functions in the cerebellum and brain stem, as well as in some ganglia of the peripheral nervous system.

Glutamate (glutamic acid) is formed from α-ketoglutarate and other amino acids in transamination reactions. With the participation of glutamate synthetase, glutamate is converted to glutamine, a compound that allows the removal of ammonia. A feature of the metabolism of glutamate in nervous tissue is its close connection with the intensively functioning energy cycle through the formation of its substrate α-ketoglutarate in transamination reactions, which allows glutamate to be considered a component of energy metabolism. Thus, already 30 minutes after injection of labeled glucose, more than 70% of the radioactivity of the soluble fraction comes from glutamate and its derivatives. This is facilitated by the extremely rapid interconversion of glutamate and α-ketoglutarate in the central nervous system. The high percentage of incorporation of radioactivity from glucose into brain amino acids has led to the assumption that glucose utilization in this organ occurs largely through amino acid metabolism. In turn, α-ketoglutaric acid can be converted to α-glutamate by direct reductive amination with the participation of glutamate dehydrogenase or by transamination. In the brain, the glutamate dehydrogenase reaction is predominantly involved in the synthesis of glutamate from α-ketoglutaric acid, thereby ensuring the continuous utilization of free ammonia into the amino group of amino acids. The main pathway for glutamate oxidation in the brain is through transamination. During normal functioning of the tricarboxylic acid cycle, the dehydrogenase pathway of glutamate oxidation is suppressed, and the transaminase pathway is active. When the number of high-energy compounds is reduced, for example, when the uncoupler of oxidative phosphorylation 2,4-dinitrophenol is added to mitochondria, the transaminase pathway is suppressed while the dehydrogenase pathway of glutamate oxidation is enhanced. Thus, glutamic acid performs an extremely important function in the energy supply of the brain, which is to maintain a high level of the α-ketoglutarate metabolite, as well as to supply mitochondrial synthetic processes with reducing equivalents. The formation of glutamine and asparagine from glutamate and aspartate, respectively, is an important mechanism for the detoxification of ammonium, the accumulation of which is detrimental. In liver failure, ammonium concentration increases, which causes hepatic coma, and its manifestations are mitigated by the administration of glutamate. The main part of glutamine synthetase is localized in glial cells and only a small proportion is located in nerve endings. Deamination of glutamine to form α-glutamate is catalyzed by glutaminase, an enzyme most active in neurons, where it is localized in mitochondria. It is assumed that this enzyme is involved in the membrane transport of glutamate, and its activity in the brain is low. The reaction products - glutamic acid and ammonium - inhibit the activity of the enzyme. Biological membranes are more permeable to glutamine than to glutamate,

and the conversion of blood glutamine into intracellular glutamate is carried out using glutaminase. The enzyme also plays an important role in regeneration changes in glutamate content in nerve endings. The fact that glutamine synthetase is localized mainly in glial cells, glutaminase is most active in neurons, and glutamine is the main precursor of glutamate and GABA, which perform a transmitter function, suggests the existence of a glutamine cycle. Glutamine serves as a glial-neuronal glutamate transporter. Glutamate, absorbed by glial cells, is converted into glutamine in a synthetase reaction, the latter enters neurons, forming glutamic acid there. Another important function of glutamate is its participation in the synthesis of proteins and biologically active peptides. Glutamate and glutamine together account for 8-10% of the total amino acid residues in brain protein hydrolysate. Glutamate is a constituent of a number of brain regulatory peptides, including glutathione and a number of γ-glutamyl dipeptides. Some neuropeptides (lyuliberin, thyroliberin, neurotensin, etc.) contain a cyclic derivative of glutamate - pyroglutamate as an N-terminal residue, which protects them from proteolysis. Injection of glutamate into various areas of the brain results in seizure activity. Glutamine does not cause this effect. When administered intravenously, glutamate can cause the death of brain neurons, especially in the ventricles. As is known, the phenomenon of glutamate excitotoxicity in cerebral ischemia is associated with glutamate, which is a pathogenetic link in the biochemical cascade that initiates the formation of NO, oxidative stress, inflammation and apoptosis. In addition, the negative role of glutamate excitotoxicity in the processes of neurodegeneration and demyelination in multiple sclerosis has been confirmed. After glutamate is released into the synaptic cleft, its reuptake occurs with the participation of Na-dependent high-affinity transporters by neurons and, to a greater extent, by astrocytes. For the functioning of synapses involving glutamate as a neurotransmitter, constant replenishment of its pool in nerve endings is necessary. The precursors of the glutamate transmitter pool can be glucose and α-ketoglutarate. Glutamate can also be formed from ornithine and L-arginine (via glutamate semialdehyde). The main source is glutamine, which is synthesized mainly in astrocytes, where glutamine synthetase is localized. Then it is easily transported through the membrane of astrocytes and, with the help of active carriers, reaches nerve endings.

Phenylalanine is an essential amino acid. In the brain, it undergoes transamination and decarboxylation. The main metabolic pathway of this amino acid in the body is hydroxylation to tyrosine with the participation of the enzyme phenylalanine-4-hydroxylase, followed by the formation of DOPA. With enzyme deficiency observed in phenylketonuria, the conversion of phenylalanine occurs through the formation of phenylpyruvic and phenylacetic acids, which have a toxic effect on the brain.

Lysine is an essential amino acid; its functions have been little studied. In the brain it is catabolized through the formation of pipecolic acid. The nervous system is extremely sensitive to disturbances in lysine metabolism in other tissues. The latter leads to severe destructive and demyelinating processes, accompanied by mental retardation.

Tyrosine acts as a source of catecholamines (adrenaline and norepinephrine). The conversion of tyrosine to catecholamines is the leading pathway of tyrosine metabolism in the brain. Under the action of the enzyme tyrosine 3-hydroxylase, tyrosine is converted to 3,4-dihydroxyphenylalanine (DOPA). The main pathway for tyrosine degradation is through hydroxyphenylpyruvate, homogentisic acid and ring cleavage. In the brain, active transamination of tyrosine occurs under the influence of the enzyme tyrosine-2-oxoglutarate amine transferase. It is formed from phenylalanine; therefore, it is an essential amino acid for phenylketonuria. Tyrosine also serves as a source of thyroid hormones and affects the activity of nervous processes. Capable of being converted into the mediator tyramine.

Tryptophan is an essential amino acid and is not synthesized in the human brain. Insufficient content of it in the diet leads to disruption of protein synthesis processes. Tryptophan produces nicotinic acid, which is a component of redox enzymes that play an important role in energy metabolism and a number of other metabolic transformations. In the body it can be transaminated as an amino group acceptor, and also decarboxylated to form serotonin and melatonin. The physiological significance of the first reaction is unknown. About 5% of the total tryptophan metabolism is used for the formation of the neurotransmitter's serotonin and melatonin. The content of tryptophan, and, consequently, serotonin in the brain is influenced by the nature of the food used; it increases with intake of complete proteins and carbohydrate-rich foods. Carbohydrates stimulate the release of insulin, which promotes entry into the muscles, and subsequently flax, removal from the circulation of branched amino acids - competitors of aromatic amino acids for the transport systems of the brain's BBB. Thus, a decrease in the level of branched-chain amino acids in the blood plasma leads to an increase in the transport of aromatic amino acids into the brain. The kynurenine pathway of tryptophan catabolism, which occurs in the liver, plays an important role in the regulation of tryptophan and serotonin levels in the brain. This pathway is initiated by tryptophan pyrrolase, a liver enzyme that utilizes primarily tryptophan from food and is induced by both its substrate tryptophan and glucocorticoids. Growth hormone, on the contrary, prevents the induction of tryptophan pyrrolase by tryptophan. Thus, liver tryptophan pyrrolase helps remove excess tryptophan from the blood plasma, which, in turn, minimizes changes in tryptophan content in the brain.

Glycine is involved not only in protein synthesis, but also in other biosynthetic processes - the formation of porphyrins, cytochromes, creatine, choline, glutathione and is an inhibitory neurotransmitter in the spinal cord. Inhibitory neurotransmitter of the brain. Causes hyperpolarization of postsynaptic membranes by increasing permeability to ions. Since the utilization of glycine in nervous tissue is relatively high, and its release from the blood occurs slowly, a significant part of its AA is synthesized in the brain de novo. The main sources of glycine are glucose and serine. De novo synthesis of glycine occurs in nervous tissue through the reversible methylenetetrahydrofolate-dependent transformation of serine with the participation of the enzyme serine hydroxymethyltransferase. In turn, serine can be formed from glucose through 3-phosphoglyceric acid and is relatively quickly released from the blood.

Taurine is an amino acid with mediator properties, has a number of other effects: regulates osmotic pressure in the brain, has an antioxidant effect. Like other short-chain amino acids (glycine, β-alanine, GABA), taurine suppresses neuronal excitability, causing hyperpolarization. Endogenous synthesis of taurine occurs in the brain mainly through the decarboxylation of cysteine sulfinic acid (cysteine oxidation product) and hypotaurine, from serine, methionine, and histidine. Inactivation of amino acids in brain synapses is carried out using high-affinity reuptake. The uptake of taurine by glial cells has also been described, indicating the role of glia in modulating its mediator function. The effects of taurine are associated with the regulation of calcium transport in nervous tissue. Taurine is a weak β-adrenergic agonist; it activates K+-stimulated release of norepinephrine in the cerebral cortex. The release of taurine from brain cells causes the release of adenosine into the cerebrospinal fluid, indicating the involvement of taurine in the modulation of synaptic transmission. Taurine is present in high concentrations in developing brain tissue and the retina. The transfer of taurine across cell membranes is associated with a change in cell volume. The release of taurine from cells is sensitive to Cl channel blockers. Taurine transport is reduced by tyrosine kinase inhibitors and increased by tyrosine phosphatase inhibitors. In the hypothalamus, the protective effect of taurine is realized with the participation of the adenylate cyclase mechanism. As an inhibitory neuroactive amino acid, taurine activates receptors in nerve endings on the membranes of neurohypophysis cells, causing partial depolarization of the cell membrane as a result of inactivation of Na+ channels. Taurine is involved in the regulation of the secretion of hormones, GABA and acetylcholine. In the neurohypophysis, taurine stimulates the release of vasopressin and oxytocin. Taurine is an inhibitor of GABA transaminase, a pyridoxal-dependent enzyme that catalyzes the breakdown of GABA, which contributes to an increase in the latter. As a glycine agonist, taurine reduces seizure activity, i.e. is a potential anticonvulsant. During brain development, taurine affects cell migration and modulates neurotransmission at synapses. Along with GABA, taurine has neuroinhibitory properties and restores the concentration of intracellular ions during brain hypoxia. In hepatic encephalopathy, a decrease in taurine content in the brain may be one of the reasons for its swelling. In addition, a number of researchers have revealed an increase in the levels of aspartate,

alanine, taurine, and asparagine in the cerebral cortex, as well as a decrease in the concentrations of glutamate, asparagine, gamma-aminobutyric acid, and tyrosine after subtotal and focal cerebral ischemia. Aspartic acid (aspartate) is found in high concentrations in the brain along with glutamate. In its mitochondria, up to 90% of glutamate is exposed to Fvania and PCA - aspartate aminotransferase is the most powerful transaminase in the brain. Two isoenzymes of aspartate aminotransferase, localized in mitochondria and cytoplasm, have been isolated. Their functional role is different. The mitochondrial fraction of the enzyme is associated mainly with the functioning of the TCA cycle, cytoplasm asmatic – determines the intensity of gluconeogenesis. Aspartate excites neuromuscular endings on synaptosomes containing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA receptors). This amino acid has several specific transport systems with different kinetic parameters. Aspartate uptake by brain synaptosomes is inhibited after treatment with neuraminidase, which reflects the participation of glycosylated proteins in neurotransmitter binding. At rest, the accumulation of aspartic acid is detected only in the nerve endings of excitatory neurons. Along with the direct stimulating effects of dicarboxylic amino acids, their inhibitory effect on the hydrolysis of phosphoinositides has been revealed. Some of the effects of aspartic acid on nerve transmission may occur at the level of second messengers. Along with glutamate, aspartate is also involved in the pathogenesis of brain damage during ischemia, affecting AMPA receptors. It is a glutamine mimetic. Gamma-aminobutyric acid (GABA) is the most widespread inhibitory mediator in the nervous system. The cycle of GABA transformations in the brain includes three coupled enzymatic reactions, called the GABA shunt. The GABA shunt is a branch from α-ketoglutarate to succinate. With the participation of the enzyme glutamate decarboxylase, the first carboxyl group of L-glutamic acid is removed to form GABA. This enzyme is present only in the gray matter of the brain and is a marker of GABAergic synapses. The enzyme is synthesized in the perikarya of neurons and then very quickly transported along the axon. Like most other amino acid decarboxylases, glutamate decarboxylase requires pyridoxal phosphate as a cofactor, which is tightly bound to the enzyme. The rate of glutamate decarboxylase reaction is the rate-limiting step in the formation of GABA. The level of GABA is regulated by the activity of glutamate decarboxylase and does not significantly depend on the action of GABA degradation enzymes. GABA catabolic enzymes are isolated from glutamate decarboxylase. GABA transaminase (GABA-T) is primarily found in the gray matter of the brain, but is also found in other tissues. It contains pyridoxal phosphate as a cofactor and is tightly bound to it. GABA-T is located in mitochondria, while glutamate decarboxylase and GABA are localized in synaptosomes. The final enzyme of the GABA shunt, succinic semialdehyde dehydrogenase, converts the latter into succinic acid, colocalizes with GABA-T in the mitochondria of CNS neurons, is specific for succinic semialdehyde and NAD+, and is activated by substances containing sulfhydryl groups. With partial cerebral ischemia, an increase in the content of valine and leucine and a decrease in tyrosine and tryptophan were found.

Thus, amino acids play an important role in metabolism and brain function. This is explained not only by the exclusive role of amino acids as sources of the synthesis of a large number of biologically important compounds, but also by their participation in synaptic transmission as neurotransmitters and neuromodulators, and involvement in energy metabolism through the formation of components of the tricarboxylic acid and cytochrome cycle. Determining the activity of enzyme systems of their metabolism can serve as an important diagnostic marker of the response of the central nervous system to damage in various cerebral and other pathologies