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Review

Clinical aspects of urea cycle dysfunction and altered brain energy metabolism on modulation of glutamate receptors and transporters in acute and chronic hyperammonemia

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ABSTRACT

In living organisms, nitrogen arise primarily as ammonia (NH_3) and ammonium (NH_4^+), which is a main component of the nucleic acid pool and proteins. Although nitrogen is essential for growth and maintenance in animals, but when the nitrogenous compounds exceeds the normal range which can quickly lead to toxicity and death. Urea cycle is the common pathway for the disposal of excess nitrogen through urea biosynthesis. Hyperammonemia is a consistent finding in many neurological disorders including congenital urea cycle disorders, reye's syndrome and acute liver failure leads to deleterious effects. Hyperammonemia and liver failure results in glutamatergic neurotransmission which contributes to the alteration in the function of the glutamate-nitric oxide-cGMP pathway, modulates the important cerebral process. Even though ammonia is essential for normal functioning of the central nervous system (CNS), in particular high concentrations of ammonia exposure to the brain leads to the alterations of glutamate transport by the transporters. Several glutamate transporters have been recognized in the central nervous system and each has a unique physiological property and distribution. The loss of glutamate transporter activity in brain during acute liver failure and hyperammonemia is allied with increased extracellular brain glutamate concentrations which may be conscientious for the cerebral edema and ultimately cell death.

Contents

Abbreviations: N_2, nitrogen; NH_3, ammonia; Ca^{2+}, calcium; CPS-1, carbomyl phosphate synthetase-1; OTC, ornithine transcarbomylase; ASS-1, argininosuccinate synthetase-1; ORNT, ornithine transporter; HHH, hyperornithemia, hyperammonemia, homocitrullinemia syndrome; ASL, argininosuccinate lyase; GABA, γ-amino-butyric acid; CNS, central nervous system; mPT, mitochondrial permeability transition; HE, hepatic encephalopathy; ONS, oxidative/nitrosative stress; PTP, permeability transition pore; NMDA, *N*-methyl-D-aspartic acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NOS, nitric oxide synthase; sGC, soluble guanylate cyclase; mGluRs, metabotropic glutamate receptors; GDH, glutamate dehydrogenase; GS, glutamate synthetase; ATP, adenosine tri phosphate; TCA, tricarboxylic acid; PDH, pyruvate dehydrogenase; OAA, oxaloacetate; cGMP, cyclic guanosine monophosphate; EAAT, excitatory amino acid transporters; CN, calcineurin; CM, calmodulin; GLUT, glutamate transporters; DHPG, (*S*)-3,5-dihydroxy phenyl glycine; α-KGH, α-ketoglutarate dehydrogenase.

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1. Introduction

Like carbon dioxide and oxygen, atmospheric nitrogen was discovered in the late 18th century. In the earth's atmosphere, nitrogen (N_2) (78.08% by volume of dry air, 75.3% by weight in dry air) is abundantly present as a gas in organic forms and as an ionic form in plants and microorganisms. Continuous cycling of N_2 occurs between the soil, plants, animals and atmosphere. Molecular nitrogen (N_2) has to be reduced to ammonia (NH_3) by nitrogen fixation bacteria (rhizobium) living separately in the soil or in the root of leguminous plants before it may be utilized by humans [1]. As part of the symbiotic relationship, the plant converts the 'fixed' ammonium ion to nitrogen oxides and amino acids to form proteins and other molecules.

Nitrogen compounds are basic building blocks of all proteins in animal biology. Protein comprise not only structural components of muscles, tissues and organs, but also enzymes and hormones essential for the functioning of all living things. Animals use nitrogen-containing amino acids from plant sources as starting materials for all nitrogen-compound animal biochemistry, including the manufacture of nucleic acids. Ammonia is a precursor molecule for nitrogen from which it is incorporated into the animal tissues, it is a most required substrate for biosynthesis of amino acids, proteins and nucleic acids. Ammonia is a unique molecule which can act both as a weak base (NH_3) or weak acid (NH_4^+) has electrolytic conductance, and both of which are transportable across phospholipid bilayers (cell membranes). This in turn alters intracellular as well as extracellular pH [2]. In normal human plasma, the concentration of ammonia ranges between 11 and 50 μmol/L and varies in venous, arterial or capillary blood [3]. Despite the importance of ammonia in metabolism, an excess of ammonia (50 μM) may result in toxicity [4].

In mammals at least 20 metabolic reactions produce ammonia, by the enzymes, glutaminase and glutamate dehydrogenase, and purine nucleotide cycle pathways also producing most of the ammonia [5]. Ammonia is an important metabolic end product and intermediate of several biochemical pathways in the body, its appearances in the systemic circulation from a number of sources such as gut, muscle, kidney and brain [6]. It is usually well thought-out to be a waste product of the metabolism of amino acids and other nitrogenous compounds. It has to be eliminated for normal function of an organism as quickly as possible, otherwise the consequences of its toxicity may be life threatening.

The ammonia is both excreted in the urine and converted to urea, with urea conversion representing the major form of nitrogen disposal from the body. This urea is produced by the liver and then either travels to the kidneys where it is removed in the urine, or diffuses into the intestines where it is spliced into carbon dioxide and ammonia by urease-producing bacteria, and then either excreted in the feces or reabsorbed [7].

2. Liver

The vital role of the liver in regulating normal ammonium metabolism is crucial. The fate of the ammonium present in the bile is not clear, however, it may be released into the lumen of the intestine being subsequently transported by the portal vein to the liver. In healthy persons, nitrogen-containing compounds from the intestine, generated by gut bacteria from food, are transported by the portal vein to the liver, where 80–90% are metabolised through the urea cycle and/or excreted immediately. Approximately one-third of the total portal blood ammonia is detoxified by glutamine synthesis, although this percentage can vary depending on the acid-base status [8]. In addition, ammonium in a concentration ranging from 45 to 240 μmol/L (average 110 μmol/L) has been detected in the hepatic bile in healthy humans [9]. The ammonium concentration measured in the portal vein has been found higher than the concentration of ammonium in the hepatic vein, representing that the ammonium is used by the liver, which substantially reduces the high ammonium content present in portal blood [10]. Ammonium homeostasis and the interorgan trafficking of ammonium are altered in liver disease. Hepatocellular dysfunction results in impaired clearance of ammonium by the liver. Diminished ammonium clearance by the cirrhotic liver is recommended by the increased ammonium concentration present in the hepatic vein in patients with liver disease.

3. Urea cycle

At high concentration, ammonia is converted to urea through the urea cycle in the liver prior to excretion of urea via the kidneys [11]. Urea has low toxicity even at high concentration, in contrast to its precursors, particularly ammonia. There are different causes of increased ammonia levels in blood and tissues, including brain. Excretion of excess ammonia is necessary for life, and animals have