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The role of ammonia in human body

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بسم الله الرحمن الرحيم

(يَا أَيُّهَا الَّذِينَ آمَنُوا إِذَا قِيلَ لَكُمْ تَفَسَّحُوا فِي الْمَجَالِسِ فَافْسَحُوا يَفْسَحِ
اللَّهُ لَكُمْ ۖ وَإِذَا قِيلَ انشُزُوا فَانشُزُوا يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ
وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ).

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Abstract

Ammonia is produced by the metabolism of amino acids and other compounds which contain nitrogen. Ammonia exists as ammonium ion (NH4+). Under physiological conditions when the body is exposed to an acid environment, the kidney stimulates the production of ammonia and its excretion. The primary source of ammonia is glutamine which gets excreted in the urine. The blood level of ammonia must remain very low because even slightly elevated concentrations (hyperammonemia) are toxic to the central nervous system (CNS). Ammonia levels rise if the liver is unable to metabolize this toxic compound as a result of an enzymatic defect or hepatocellular damage. The levels may also rise if portal blood is diverted to the systemic circulation, bypassing the liver. In this review we discussed the etiology and harms of hyperammonemia on the body.

Keywords: ammonia, hyperammonemia , physiology

Introduction

Ammonia production occurs in all tissues of the body during the metabolism of a variety of compounds. Ammonia is produced by the metabolism of amino acids and other compounds which contain nitrogen. Ammonia exists as ammonium ion (NH4+) at the physiological pH and is produced in our body mainly by the process of transamination followed by deamination, from biogenic amines, from amino groups of nitrogenous base like purine and pyrimidine and in the intestine by intestinal bacterial flora through the action of urease on urea. Ammonia disposal takes place primarily by the hepatic formation of urea. The blood level of ammonia must remain very low because even slightly elevated concentrations (hyperammonemia) are toxic to the central nervous system (CNS). A metabolic mechanism exists by which nitrogen is moved from peripheral

tissues to the liver for its ultimate disposal as urea, while at the same time maintaining low levels of circulating ammonia [1].

Ammonia (NH3) plays a significant role in the human body and is considered to be an important biomarker. The molecule has been linked to liver and kidney function and the effects of exercise, bacterial activity, halitosis and to being an attractant for mosquitoes [2]. In nature, ammonia exists as both NH3 and in the ionic form of ammonia as ammonium ion (NH4+). A buffering reaction: NH3+ H+ --> NH4+ is used to maintain the relative amount of each form. Under biological conditions, the pKa of this reaction is about 9.15 and this reaction occurs almost instantaneously. As a result, the majority of ammonia under physiological conditions exists as NH4+, and only about 1.7% of total ammonia presents as NH3 at pH 7.4. Ammonia is a very small, uncharged particle. Due to this character of ammonia, it was initially believed that ammonia is highly permeable across the lipid membrane because of the maintenance of proper diffusion equilibrium [3].

Under physiological conditions when the body is exposed to an acid environment, the kidney stimulates the production of ammonia and its excretion. The primary source of ammonia is glutamine which gets excreted in the urine. The proximal tubule is the main site of ammonia formation, and the effective rate of delivery of glutamine in this site not only depends on the sufficient delivery of glutamine but also on the ability of proximal tubule to take up that particular glutamine delivered. The acidotic condition stimulates the delivery as well as augmenting the transport of glutamine into the kidney [4]. Enzymes responsible for the production of ammonia are upregulated by the acidotic condition that leads to augmented production of ammonia from proximal tubules of the kidney, which lead to preserve the acid base balance [1].

Aim of article

To highlight the physiology, metabolism, the effects on general health, the recent techniques in measurement, and how to use the ammonia as indicator for other diseases.

Hyperammonemia

Hyperammonemia is a metabolic condition characterized by the raised levels of ammonia, a nitrogen-containing compound. Normal levels of ammonia in the body vary according to age. Hyperammonemia can result from various congenital and acquired conditions in which it may be the principal toxin. Hyperammonemia may also occur as a part of other disorders that involve various other metabolic abnormalities. Normally, ammonia is produced in the colon and small intestine from where it is transported to the liver to be converted to urea via the urea cycle. Urea, a watersoluble compound, can then be excreted via the kidneys. Ammonia levels rise if the liver is unable to metabolize this toxic compound as a result of an enzymatic defect or hepatocellular damage. The levels may also rise if portal blood is diverted to the systemic circulation, bypassing the liver, or there is increased production of ammonia due to an infection with certain microorganisms [5].

Causes of hyperammoniemia

The etiology of hyperammonemia is vast. It is a part of numerous disorders that can be classified as congenital or acquired. The acquired disorders can further be classified as hyperammonemia due to hepatic causes and non-hepatic causes (causes other than a liver disease). Congenital disorders involving enzymatic defects include urea cycle defects, organic acidemias, congenital lactic acidosis, fatty acid oxidation defect, and dibasic amino acid deficiencies. Other disorders include

transient hyperammonemia of the newborn, neonatal Herpes simplex virus (HSV) infection, and severe perinatal asphyxia [6].

The urea cycle is an energy-dependent process responsible for the conversion of toxic ammonia into urea, which can then be excreted. Five major steps are involved, each requiring a different enzyme. These include N-acetyl-glutamate synthase, carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase, argininosuccinate synthetase (AS), argininosuccinic acid lyase (AL), and arginase. A defect in any of these enzymes results in impaired function of the urea cycle, leading to the accumulation of ammonia. All of the defects are autosomal recessive, except for ornithine transcarbamylase deficiency, which is X-linked recessive. This is also the most common type of urea cycle disorder, and its prevalence is estimated to be 1:140000 [7].

Transient hyperammonemia of infancy is possibly due to the slow maturation of the urea cycle function seen in premature infants. It usually presents with signs and symptoms of hypoxic-ischemic encephalopathy and intracranial hypertension within the first 24 to 48 hours of life. Severe perinatal asphyxia or neonatal HSV infection may also result in elevated ammonia levels. An acquired disease-causing hyperammonemia in children is Reye syndrome, a childhood disorder that occurs most commonly after influenza or varicella infection and ingestion of aspirin. Hyperammonemia is coupled with elevated liver enzymes and lactic acidosis. Hepatomegaly is usually seen on examination [8].

Effects of excess ammonia on the body

Its well known that the ammonia can cause neurotoxicity. The exact mechanism by which ammonia results in CNS damage has not been

established. It has been hypothesized that various alterations in the neurotransmitter system are responsible for the neuronal damage seen in both acute and chronic hyperammonemia. Animal studies have shown that acute ammonia intoxication in vitro results in elevated extracellular levels of glutamate in the brain. This results in activation of the N-methyl-D-aspartate (NMDA) receptors, which causes decreased phosphorylation of protein kinase C that results in the activation of Na/K-ATPase. The resultant ATP depletion is responsible for ammonia toxicity and is the most probable cause of seizures in acute hyperammonemia [9].

Hyperammonemia can cause irreparable damage to the developing brain, with presenting symptoms such as posturing, cognitive impairment (mental retardation), seizures, and cerebral palsy. The total duration of hyperammonemic coma and maximum ammonia level (but not the rapidity of ammonia removal), is negatively correlated with the patient's neurological outcome. This is concerning when ammonia levels at presentation exceed 300 mmol/L. If left untreated, the outcome can be fatal [10].

Clinical features of hyperammonemia

Symptomatology varies with patient age and ammonium level and may include, among the most common findings: hypotonia, vomiting, lethargy, seizures, coma, ataxia, anorexia, abnormal behavior patterns, dysarthria, weakness, liver enlargement, and dementia. Most patients with UCD present during the neonatal period with nonspecific symptoms (poor feeding, vomiting, somnolence, irritability, tachypnea, and lethargy) [11]. Acute and chronic hepatic encephalopathy (HE), in which hyperammonemia plays a pivotal role, can be seen as a complication of acute (i.e., drug toxicity, infections) and chronic liver disease. Swelling of astrocytes can lead to increased intracranial hypertension, cerebral edema,

brainstem herniation, and death. Chemical abnormalities include a generalized aminoacidemia (except for branched-chain amino acid levels, which are normal), hypoglycemia, hypovolemia, electrolyte disturbances, and hyperammonemia. Once the latter is reduced to normal levels, then clinical manifestations of hepatic encephalopathy reverse [12].

Measurement of ammonia level

Clinically, several conditions are related to changes of blood nitrogen levels and consequently ammonia levels. These are impairments in relation to the liver, brain, kidneys, stomach, duodenum, oral cavity, and lungs. In all cases, if ammonia levels in the blood are of a higher concentration than those found in the air, then ammonia can diffuse out of the blood and into the lungs. Doing so allows for potential clinical measurements of blood ammonia from a noninvasive perspective [13].

When it comes to quantifying ammonia gas, being able to isolate them from complex gaseous mixtures is important. Since the 1950's, techniques such as chemical ionisation, gas chromatography, laser spectroscopy, and chemical detection have emerged as the key methods. Their sensitivity, precision and accuracy have proven suitable for selectively detecting and identifying low molecular weight species in gaseous form. Furthermore, combining these methods with each other in various ways (e.g. with mass spectrometry) shows potential for strengthening their detection capabilities [14].

According to recent study, breath ammonia concentrations of 60 – 120 ppm were observed for candidates with kidney failure. Candidates with less severe cases of kidney failure had lower breath ammonia concentrations compared to those with advanced symptoms. Candidates without kidney failure had half the concentration of oral ammonia

compared to those with the disease. Also, it was observed that oral ammonia concentrations gradually decreased over the 10 second exhalation interval for all candidates tested. The results obtained using the proposed breath analyser show that breath ammonia analysis is an effective and accurate method of diagnosing kidney failure. It is therefore recommended that breath ammonia analysis be used by medical practitioners for the diagnosis of kidney failure [15]. arterial blood gas analysis used to determine acid-base status; respiratory alkalosis strongly suggests a urea cycle defect; it is the result of hyperventilation due to stimulation of the central respiratory drive.

Normal levels of ammonia vary according to age, being higher in newborns compared to older children or adults. In newborns, gestational and postnatal ages also affect the levels of ammonia [6].

Healthy term infants: 45±9 micromol/L; 80 to 90 micromol/L is considered to be the upper limit of normal.

Preterm infants: 71±26 micromol/L, decreasing to term levels in approximately seven days

Children older than 1 month: less than 50 micromol/L

Adults: less than 30 micromol/L

Neuroimaging with CT scan or MRI can be helpful for diagnosis, although it will only show the effects ammonia has on the brain. In hyperammonemic encephalopathy, MRI shows diffusion restriction in the insular cortex and cingulate gyrus. These changes may be reversible but may also lead to atrophy. In patients with chronic liver disease, cerebral atrophy with symmetric hyperintensities of the globus pallidus is seen. Asymmetric involvement of the thalami, parietal, occipital, temporal, and frontal cortices can also be seen [16].

Management of hyperammonemia

Toxin removal, enzyme induction, and anabolism are the main goals of emergency treatment. Normal patient growth and development should be the main goal of long-term treatment. Given the correlation between the duration of hyperammonemic coma and prospective neurocognitive function, it is imperative to institute treatment for hyperammonemia as soon as possible to prevent further neurological damage (even prior to a definitive diagnosis being made) [17]. Supportive treatment and correction of hydration, nutritional status, mineral (calcium, potassium), and electrolyte imbalances should be addressed. In patients with UCD, bacterial sepsis can lead to a fatal outcome due to catabolism, thus, antibiotic coverage should be considered even as prophylaxis, as patients often undergo multiple invasive procedures (such as line placements) that increase the infection risk [18].

Early in the treatment, dialysis should be prioritized, as it is the ideal method for rapid ammonia removal. Furthermore, dialytic interventions through acute dialysis in hyperammonemic patients leads to improved outcome. Upon confirmation of acceptable urine output, loading doses of ammonia scavengers to prevent ammonia from reaccumulating should be given initially, even when preparing to initiate dialysis. It is important to keep in mind that these agents often cannot remove the ammonia fast enough to keep up with the production rate, so dialysis plays a significant role in treatment [19].

Dialysis removes nutrients from plasma, creating a catabolic state, and plasma ammonia may rebound unless appropriate nutrition is concomitantly provided. Ammonia is a small molecule that can be cleared rapidly by diffusion. Therefore, the preferred dialytic methods are hemodialysis (HD) and/or continuous renal replacement therapy (CRRT).

It is of utmost importance to have a well-functioning catheter and adequate blood and dialysate flow in order to promote efficient ammonia clearance. Blood-flow rate should be set as fast as tolerated to enhance ammonia clearance [20]. HD as a primary therapy used for patients with severe hyperammonemia (>1,500 mmol/L), and once serum ammonia levels are <200 μmol/L, treatment should be transitioned over to CRRT for rebound control [20].

Interventions have been attempted in order to provide neuroprotective effects in the setting of acute hyperammonemia, with inconclusive evidence-based results. Some of the interventions described in the literature include the use of N-methyl-D-aspartate (NMDA) receptor antagonists (i.e., memantine), because death in encephalopathic hyperammonemic patients is thought to be mediated by activation of the NMDA type of glutamate receptors in the brain [21].

Lactulose is a disaccharide that is not metabolized in the small intestine and is transported intact to the colon, where colonic bacteria transform it to lactic and acetic acids, slowing the growth of enteric bacteria that would normally metabolize urea to ammonia. Lactulose also increases colonic peristalsis, thereby decreasing nitrogen absorption and increasing fecal ammonia. Neomycin is a poorly absorbed aminoglycoside that eliminates proteolytic bacteria and reduces nitrogen load [11]. And eventually liver transplant is needed

Conclusion

Ammonia contribute in major health issues such as hepatic encephalopathy and cerebral edema with high mortality rates. The use of

non-invasive methods to detect ammonia level should be established to all patients with renal failure and liver failure to prevent possible brain injury.

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