



BIOMED CONFERENCE 2016

AMMONIA

Ammonia Toxicity in ASD, Causation
and Treatment Options

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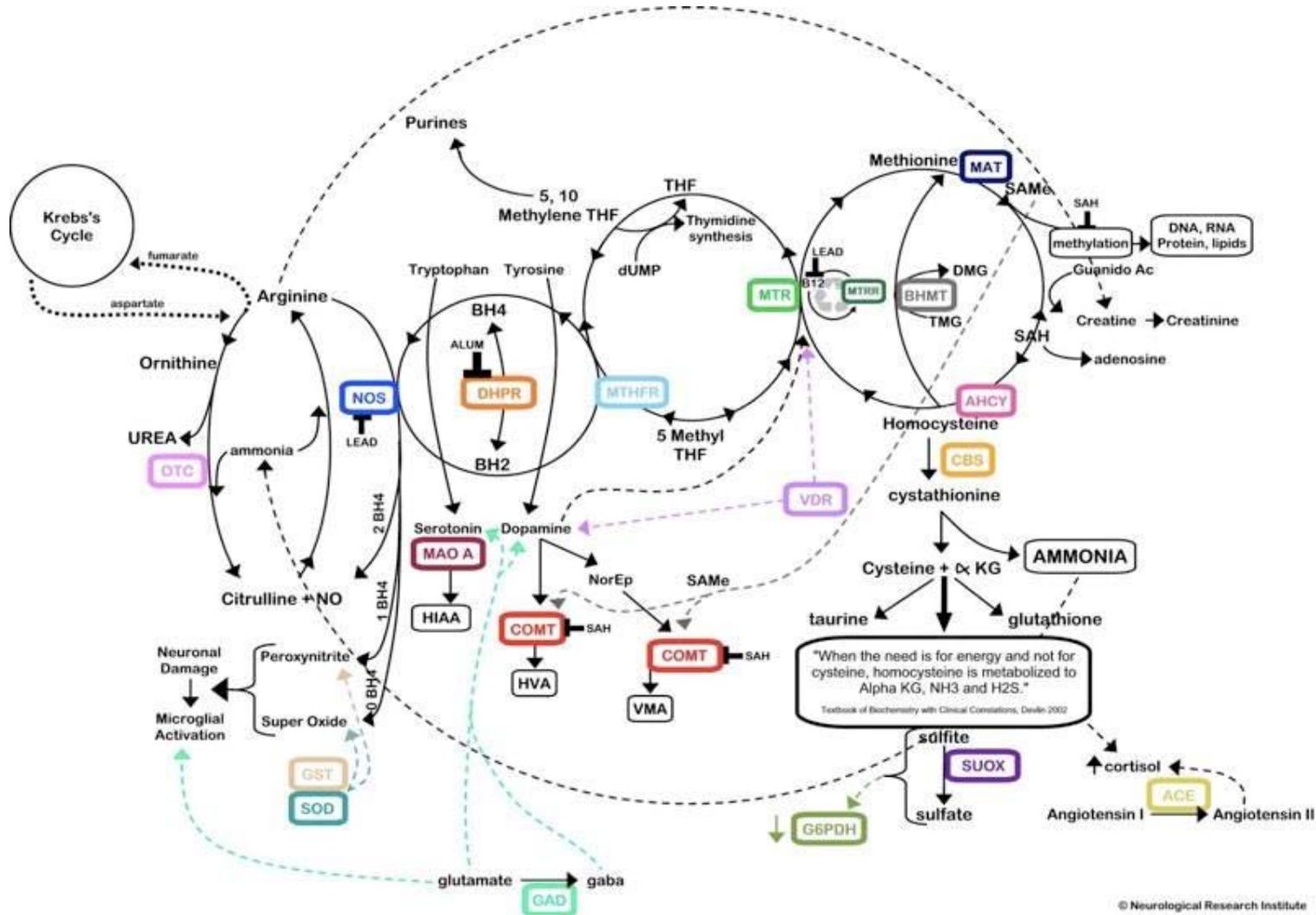
⌘ Ammonia in the Body and Natural Breakdown

- Ammonia is a by-product of the breakdown of protein.
- A healthy liver filters ammonia out of the blood and combines it with other compounds to render it inert and produce urea.
- Urea reenters the bloodstream and stays there until it reaches the kidneys for excretion.
- There is no medically sanctioned way to detox the body from ammonia.
- Keeping your liver healthy and strong will help to improve ammonia removal.
- Detoxing the liver may be one way to essentially detox ammonia from the body.

Necessity is the Mother of Invention Let's go back to 2006



⌘ Methylation Ammonia Cycle Map



⌘ Urea Cycle



Urea is the major end product of nitrogen metabolism in humans and mammals.

Ammonia is toxic in even small amounts and must be removed from the body.

The urea cycle or the ornithine cycle describes the conversion reactions of ammonia into urea. Since these reactions occur in the liver, the urea is then transported to the kidneys where it is excreted. The overall urea formation reaction is:

$2 \text{ Ammonia} + \text{carbon dioxide} + 3\text{ATP} \rightarrow \text{urea} + \text{water} + 3 \text{ADP}$

One indicator on testing of high ammonia is an elevated BUN Blood Urea Nitrogen, but it may not be captured at the time ammonia is high.

On OAT Organic Acid Test another indicator is higher 3-oxoglutaric than 2-oxoglutaric. 2-oxoglutaric is AKG and may be being used to clear raised ammonia and it is causing a deficiency.

Low Zinc, as zinc is involved in hundreds of enzymatic processes, may contribute to raised ammonia.



⌘ AKG and Ammonia

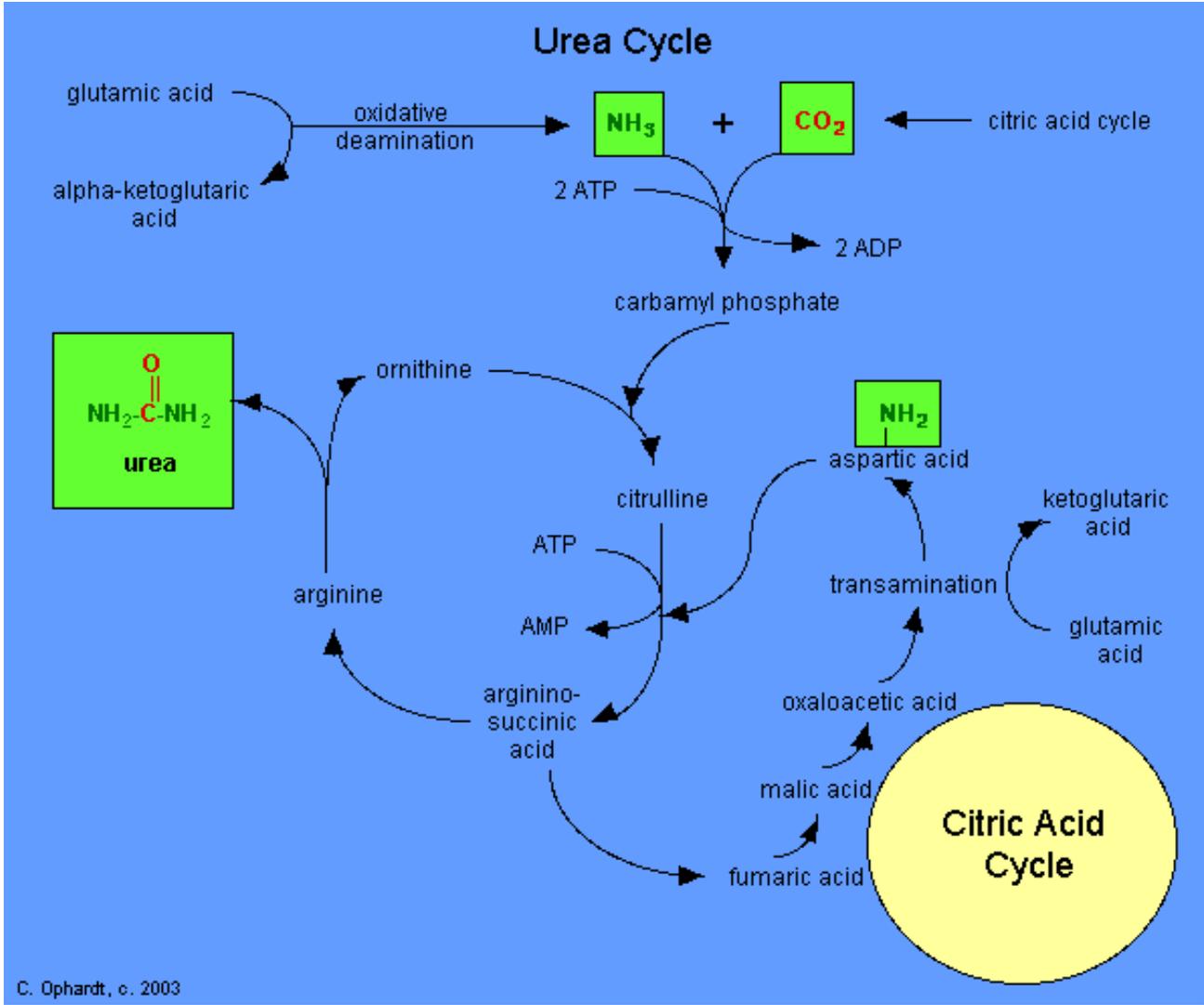
- AKG 2-oxoglutaric -Alpha Ketoglutaric acid and may also use Alpha Ketoglutarate.
- Alpha Ketoglutaric acid combines with the harmful ammonia to create glutamine. Problems with ammonia cause a depletion of the amino acid glutamine.
- Kids on the spectrum have been found to have low glutamine levels and supplementation was an early DAN! Treatment.
- “High [ammonia] would drive the Glutamine Synthase reaction (p. 1033). $\text{glutamate} + \text{ATP} + \text{NH}_3 \rightarrow \text{glutamine} + \text{ADP} + \text{P}_i$ This would deplete glutamate, a neurotransmitter and the precursor for synthesis of GABA, another neurotransmitter.”
- “Depletion of glutamate, as well as the high ammonia level, would drive the Glutamate Dehydrogenase reaction to reverse. $\text{glutamate} + \text{NAD(P)}^+ + \beta\text{-ketoglutarate} + \text{NAD(P)H} + \text{NH}_4^+$ The resulting depletion of α -ketoglutarate (AKG), an essential Krebs Cycle intermediate, could impair energy metabolism in the brain.”



⌘ Essential Amino Acid Co-factors

Essential Amino Acids must be consumed in the diet or supplemented because mammalian cells lack the enzymes to synthesize their carbon skeletons (α-keto acids). These include:

- **Isoleucine**
- **Leucine**
- **Valine**
- **Lysine**
- **Threonine**
- **Tryptophan**
- **Phenylalanine (Tyrosine can be made from phenylalanine. Some kids don't process Phenylalanine well.)**
- **Methionine (Cysteine can be made from methionine.)**
- **Histidine (Essential for infants.)**





⌘ Ammonia Toxicity in ASD as related to underlying Mitochondrial Dysfunction



Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis

D A Rossignol and R E Frye

Molecular Psychiatry (2012) 17, 290–314; doi:10.1038/mp.2010.136; published online 25 January 2011

“Indirect markers of mitochondrial function can also be abnormal in MD. For example, depletion in total and free carnitine can occur as a consequence of excessive unprocessed fatty acids. Ammonia may be elevated for at least two reasons.

First, under anaerobic conditions, ammonia is produced when adenosine monophosphate is broken down into inosine monophosphate in order to replenish ATP.

Second, as the urea cycle is partially located in the mitochondria, mitochondrial dysfunction can result in secondary urea cycle dysfunction and an elevation in ammonia.

In addition, the integrity of certain high-energy tissues, such as muscle and liver, can be compromised from mitochondrial dysfunction, resulting in elevations in indicators of tissue damage such as CK, AST and/or ALT.”



∴ Ammonia production by intestinal bacteria.

Vince A, Dawson AM, Park N, O'Grady F.

Abstract

Bacterial growth and the production of ammonia from urea and by deamination of peptone has been examined at various pHs in both conventional static bacterial cultures and in a continuous cultivation system. Growth occurred on primary testing of 93 out of 100 strains of aerobic Gram-negative bacteria at pH 5, and 48 out of 50 strains of *Esch. coli* at pH 4.6. Hydrolysis of urea by *Proteus mirabilis* decreased steadily from pH 7.2 to pH 5.3; below pH 5.3 little hydrolysis occurred. Ammonia production from peptones by *Esch. coli* decreased from pH 7.2 to pH 4.6. Considerable variation was noted in the ability of different strains to produce ammonia. Experiments with cultures containing both *Esch. coli* and *Pr. mirabilis* showed that more ammonia was produced at low pH than was produced by cultures of single organisms. At low pH reduction in the count of organisms was not found to be an essential prerequisite for reduction of ammonia formation.

PMID:4573343



:: Ammonia and Urea Cycle Dysfunction

Urea Cycle Disorders vs. Dysfunction

- Urea cycle disorders are inborn errors in metabolism.
- Dysfunctions are environmentally induced and may be repaired.
- UCD involve a deficiency in one of the enzymes required by the urea cycle that removes ammonia from the blood.

Even so, parents may have the same insufficiency and yet be asymptomatic. Meaning environment still may play a role. This is noted in adults going “undiagnosed” into adulthood.

The kids in the waiting room at the therapy centers.....



Ammonia Toxicity Description



Ammonia accumulates in toxic levels if the urea cycle does not convert nitrogen from protein metabolism into urea for excretion into the urine.

When an enzyme is missing or deficient, the cycle is interrupted and nitrogen accumulates in the form of ammonia. It cannot be excreted from the body and enters the bloodstream, damaging nervous tissues, including the brain.

In ASD and related disorders we find pathogens such as bacterial overgrowth, and genetic mutation areas of weakness in Methylation and the Urea Cycle allow for ammonia to accumulate.

Some Symptoms Include but are not limited to:

- Seizures
- Poor muscle tone
- Respiratory distress
- Mental retardation (developmental delays)
- Confusion
- Irritability
- Indecisiveness
- Periods of laughing and crying for apparently no reason
- Delirium
- Lethargy
- Ammonia smell in urine and/or feces
- Biting, mouthing, hitting
- Poor Feeding
- Abnormal Gait
- Coma
- Death



⌘ Ammonia Symptoms: Lacking Enzymes and Genetic Mutations

Symptoms may start to occur after events such as vaccination, use of seizure meds such as valproic acid, or viral infection. Most notably the viral infection mentioned in the literature is Chicken Pox. Note that the Chicken Pox, Varicella Vaccine, is a live virus vaccine. May be an example of Dysfunction and not Disorder.

Often times the symptoms may start to be more noticeable after a protein meal. Different enzymes may be lacking in the various forms of UCD.

The six major disorders of the urea cycle include:

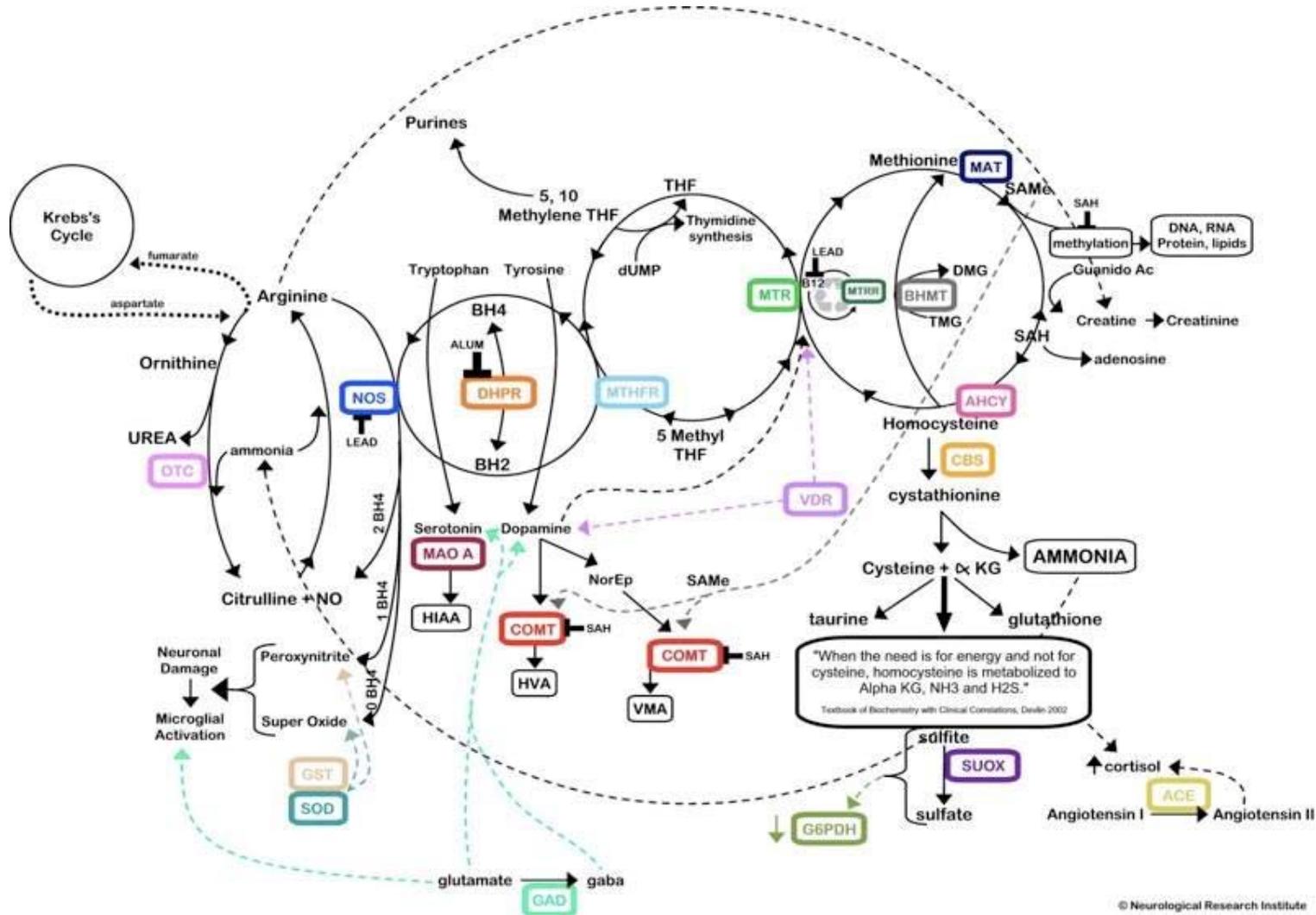
- CPS–Carbamyl Phosphate Synthetase
- NAGS–N-Acetylglutamate Synthetase
- OTC–Ornithine Transcarbamylase
- ASD–Argininosuccinic Acid Synthetase (Citrullinemia)
- ALD–Argininosuccinase Acid Lyase (Argininosuccinic Aciduria)
- AG–Arginase



∴ Genetic Mutations Notably Involved in Clearing Ammonia in Methylation & Urea Cycle

- CBS
- MTHFR A1298C
- SUOX
- NOS
- OTC
- SOD
- GST
- MAO
- GAD
- DHPR

⌘ Methylation Ammonia Cycle Map





⌘ Yasko and BH4 Ammonia

Ammonia burdens the urea cycle, thereby depleting a key intermediate called BH4, which plays a critical role in regulating neurotransmitters and therefore mood.

BH4 is needed for serotonin, dopamine, conversion of phenylalanine to tyrosine **and language-related function**.

The A1298C mutation in the MTHFR gene may also impact levels of BH4.

Lack of BH4 may result in mast cell degranulation and lead to higher histamine levels, which can produce symptoms such as red ears and other hypersensitivity reactions (and rashes.)

Elevated ammonia levels can cause flapping and other over-stimulatory behaviors. Each molecule of ammonia requires two molecules of BH4 for ideal detoxification.

Excess ammonia in the gut may alter the pH and aggravate imbalances in microbial flora = vicious cycle.

Helping to restore adequate levels of BH4 should also aid in serotonin synthesis, maintaining dopamine levels as well as ammonia detoxification in a more stable manner.



∴ Test Results Indicating Decreased BH4

- High hippuric
- Increased 8 hydroxy 2 deoxy guanosine (lack of SAME or high ammonia can also cause increased 8 hydroxy 2 deoxy guanosine)
- Elevated phenylalanine, phenyl lactate, phenyl acetate, and/or phenylethylamine
- Increased ammonia



⌘ Help for the BH4 Cycle

Low does BH4 (1.25mg)

Supplements that may help recycle, and thereby increase BH4 are:

- Folate
- Magnesium
- Copper (once Zinc/Copper ratios are corrected)
- Vitamin B6
- Vitamin C

The primary cofactors in BH4 reactions are:

- Iron (often low in ASD)
- Niacin (greater need for B3 as in No Flush Niacinamide for COMT)

Supplementation of products that are low due to impaired enzyme function such as:

- L-Tyrosine
- 5-hydroxytryptophan (5HTP)
- L-Citrulline

∴ Effects of ammonia on monoamine oxidase and enzymes of GABA metabolism in mouse brain.



Arch IntPhysiolBiochim 1978 Feb;86(1):67-82.
Sadasivudu B, Radha Krishna Murthy C.

Abstract

Acute and chronic ammonia toxicity was produced in the mice by intraperitoneal injection of ammonium chloride (200 mg/kg) and by exposure of mice to ammonia vapours (5% v/v) continuously for 2 days and 5 days respectively. The ammonia content was elevated in the cerebellum, cerebral cortex and brain stem and in liver. In acute ammonia intoxication there was a decrease in the monoamine oxidase (MAO) activity in all the three regions of brain. In chronic ammonia toxicity (2 days of exposure) a significant increase in the activity of MAO was observed in the cerebral cortex while in cerebellum and brain stem there was a significant decrease. In cerebral cortex and cerebellum there was a rise in the activity of MAO as a result of exposure to ammonia vapours for 5 days. A significant decrease was observed in the activity of glutamate decarboxylase (GAD) in all the three regions of the brain both in acute and chronic ammonia toxicity (2 days). There was a decrease in the activity of this enzyme only in the cerebral cortex in the animals exposed to ammonia for 5 days. The activity of GABA-aminotransferase (GABA-T) showed a significant rise in cerebellum and a fall in the brain stem in acute ammonia toxicity. In chronic ammonia toxicity GABA-T showed a rise in all the three regions of brain. Chronic ammonia toxicity produced a significant decrease in the content of glutamate in all the three regions without a significant change in the content of aspartate, GABA and glutamine. The content of alanine increased in all the three regions of brain under these experimental conditions. The ratio of glutamate + aspartate/GABA and glutamate/glutamine showed a decrease in all the three regions as a result of ammonia toxicity.

PMID:80199



⌘ Mechanism of arginine protection against ammonia intoxication in the rat.

Am J Physiol 1984 Sep;247(3 Pt 1):G290-5.
Goodman MW, Zieve L, Konstanitinides FN, Cerra FB.

Abstract

To examine the beneficial effect of arginine on ammonia intoxication, rats were injected intraperitoneally with a single dose of NH_4Cl (6.75 mmol/kg) with and without arginine (5.0 mmol/kg) or ornithine (5.0 mmol/kg). Arginine or ornithine reduced the blood ammonia nitrogen at 30 min after NH_4Cl injection from 3,288 \pm 800 micrograms/dl (mean \pm SE) to 538 \pm 90 and 575 \pm 34 micrograms/dl, respectively. In rats administered this dose of NH_4Cl , arginine or ornithine did not increase further the hepatic carbamoyl-phosphate synthetase (EC 6.3.4.16) activation by N-acetylglutamate beyond the effect of NH_4Cl . However, arginine or ornithine did increase the hepatic citrulline and urea content as well as the plasma urea concentration in these NH_4Cl -injected rats. In rats injected with four doses of NH_4Cl (2.5 mmol/kg), arginine or ornithine pretreatment increased the urea excretion and normalized the orotic acid excretion. These results indicate that arginine mitigates ammonia intoxication in the rat by increasing ornithine carbamoyltransferase activity through increased ornithine availability and not via activation of N-acetylglutamatesynthetase. By increasing ornithine carbamoyltransferase activity, ornithine enhances the conversion of ammonia to citrulline and urea.

PMID:6476119

∴ Zinc supplementation reduces blood ammonia and increases liver ornithine transcarbamylase activity in experimental cirrhosis.



Hepatology 1992 Sep;16(3):785-9.

Riggio O, Merli M, Capocaccia L, Caschera M, Zullo A, Pinot G, Gaudio E, Franchitto A, Spagnoli R, D'Aquilino E, et al.

Il Gastroenterologia, University of Rome La Sapienza, Italy.

Abstract

Zinc deficiency is common in cirrhosis and may be involved in the alteration of ammonia metabolism. Rats with carbon tetrachloride-induced cirrhosis have high plasma ammonia and low serum and tissue zinc levels. We used this model to examine the effects of oral zinc supplementation on activities of plasma ammonia and liver ornithine transcarbamylase (a key enzyme in the urea cycle). These parameters were examined in two consecutive experiments. Each experiment included two groups of rats treated with carbon tetrachloride; one group received zinc in the drinking water during the induction of cirrhosis, and another served as a control group. Regardless of zinc supplementation, all carbon tetrachloride-treated rats exhibited similar micronodular cirrhosis, with similar histological appearance and liver function impairment. Cirrhotic rats without zinc supplementation showed high plasma ammonia and low serum and hepatic zinc levels and reduced liver ornithine transcarbamylase activity. Serum, hepatic zinc and liver ornithine transcarbamylase activity increased significantly in the zinc-supplemented group, and these rats' plasma ammonia levels became normal. Plasma ammonia level was significantly inversely correlated with liver ornithine transcarbamylase activity and positively correlated with serum and hepatic zinc content. Our results suggest that zinc deficiency may modify hepatic ornithine transcarbamylase activity and, therefore, ammonia disposal.

PMID: 1505922



∴ Effects of valproate and citrulline on ammonium-induced encephalopathy.

Epilepsia 1994 Jan-Feb;35(1):164-71.

Stephens JR, Levy RH

Department of Pharmaceutics, University of Washington, Seattle 98195.

Abstract

Hyperammonemia is a recognized side effect of treatment with the antiepileptic drug (AED) valproate (VPA). Encephalopathic complications have also been observed in some patients receiving VPA therapy. The relation between VPA-induced hyperammonemia and encephalopathy is not clear, however. A model of ammonium (NH_4^+)-induced coma was used to investigate the contribution of VPA and to assess the efficacy of citrulline (a urea cycle intermediate) on hyperammonemia and encephalopathy. In groups of 6-12 rats, administration of VPA (2.5 mmol/kg) was associated with (a) a decrease in the dose of NH_4^+ that produces coma in 50% of the animals (CD_{50}) from 6.1 to 3.6 mmol/kg, and (b) significant increases in blood ammonia concentrations in NH_4^+ -treated animals. In addition, clear evidence also showed that in the presence of VPA, a lesser concentration of ammonia produced coma. Citrulline treatment (5.0 mmol/kg) was associated with (a) an increase in the CD_{50} value of NH_4^+ -treated animals from 6.1 to 8.6 mmol/kg, (b) a statistically significant decrease in ammonia concentration at all doses examined, (c) complete protection from encephalopathic effects of NH_4^+ at citrulline concentrations three- to tenfold greater than basal levels; and (d) a 24% increase in the CD_{50} value and a statistically significant decrease in ammonia concentration of VPA/ NH_4^+ -treated animals. These findings indicate that VPA has a dual effect on encephalopathy and that citrulline should benefit those patients treated with VPA who experience adverse encephalopathic effects.

PMID: 8112241

∴ Branched-chain amino acids and ammonia metabolism in liver disease: therapeutic implications.



Nutrition 2013 Oct;29(10):1186-91. doi: 10.1016/j.nut.2013.01.022. Epub 2013 Jun 4.
Holecek M.

Department of Physiology, Charles University Prague, Medical Faculty in Hradec Kralove, Czech Republic.

Abstract

The rationale for recommendation of branched-chain amino acids (BCAA; valine, leucine, and isoleucine) in treatment of liver failure is based on their unique pharmacologic properties, stimulatory effect on ammonia detoxification to glutamine (GLN), and decreased concentrations in liver cirrhosis. Multiple lines of evidence have shown that the main cause of the BCAA deficiency in liver cirrhosis is their consumption in skeletal muscle for synthesis of glutamate, which acts as a substrate for ammonia detoxification to GLN and that the BCAA administration to patients with liver failure may exert a number of positive effects that may be more pronounced in patients with marked depression of BCAA levels. On the other hand, due to the stimulatory effect of BCAA on GLN synthesis, BCAA supplementation may lead to enhanced ammonia production from GLN breakdown in the intestine and the kidneys and thus exert harmful effects on the development of hepatic encephalopathy. Therefore, to enhance therapeutic effectiveness of the BCAA in patients with liver injury, their detrimental effect on ammonia production, which is negligible in healthy people and/or patients with other disorders, should be avoided. In treatment of hepatic encephalopathy, simultaneous administration of the BCAA (to correct amino acid imbalance and promote ammonia detoxification to GLN) with α -ketoglutarate (to inhibit GLN breakdown to ammonia in enterocytes) and/or phenylbutyrate (to enhance GLN excretion by the kidneys) is suggested. Attention should be given to the type of liver injury, gastrointestinal bleeding, signs of inflammation, and the dose of BCAA.

PMID:23756281



⌘ Modified Citrus Pectin and Arabinogalactan Larch Tree (polysaccharides) both help against ammonia.

In one study in vitro faecal incubation system was used to study the metabolism of complex carbohydrates by intestinal bacteria. Homogenates of human faeces were incubated anaerobically with added lactulose, pectin, arabinogalactan, and cellulose, both before and after subjects had been pre-fed each carbohydrate. Fermentation of added substrate was assessed by the production of short-chain fatty acids and suppression of net ammonia generation over 48 h of incubation.

The effect of lactulose, pectin, arabinogalactan and cellulose on the production of organic acids and metabolism of ammonia by intestinal bacteria in a faecal incubation system.

Br J Nutr 1990 Jan;63(1):17-26.

Vince AJ, McNeil MI, Wagner JD, Wrong OM.



∴ Ammonia Toxicity: What to do about it?

Ammonia Treatments Include but are not limited to:
Kill gut bugs. Bacteria contributes to ammonia.

L-Glutamine

L-Citrulline

AKG Alpha Ketoglutaric Acid

Arginine (with Lysine)

Arginine/Ornithine (with Lysine)

RNA Ammonia (Yasko supplement)

Low protein diet

Molybdenum

Yucca Root with protein meals

Larch Tree

Modified Citrus Pectin

Activated charcoal

Supporting genetic mutations