INTERNATIONAL
IV NUTRITIONAL THERAPY
GLOBAL PHYSICIAN EDUCATION

Parenteral Amino Acids

Advanced IV Therapy: Chronic Disease and Infections
by
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Brenden Cochran, ND and Shawna Kiker, ND

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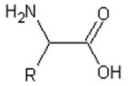
Parenteral Amino Acids



PARENTERAL AMINO ACIDS,
AND THE NON-AMINO ACIDS,
TAURINE, CARNITINE

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Before the Infusion

- Tailor the formulation to the patient's condition
- Obtain baseline lab testing: Comprehensive metabolic panel, CBC & urine dip
- Safe and effective use of parenteral nutrition requires nutritional knowledge and the ability to recognize and treat potential complications

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Vitamin-Amino Acid Interactions

B vitamins required for all amino acid formulations

- B vitamins all contain an amino group - nitrogen
- Pyridoxine, B6, is most important vitamin for amino acid metabolism
- B6 is cofactor for transaminase enzymes which metabolize amino acids
- Riboflavin, B2, is required by GSH reductase
- Niacin, B3, is synthesized from tryptophan
- Others will be covered with specific amino acids

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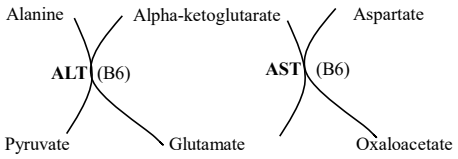

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Amino Acid Metabolism Review

- Amino acids that are not used for protein synthesis can be used for energy, either as sugars (glycogenic) or fats (ketogenic)
- Most amino acids are glycogenic, leucine is ketogenic and four are both: isoleucine, lysine, phenylalanine and tyrosine
- Amino acids also exhibit complementary or antagonistic relationships

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Amino Acid & Nutrient Relationships

Amino Acid	Complementary	Antagonistic
Arginine	Aspartate Citrulline Ornithine	Lysine
Carnitine	Lysine, Taurine Niacin	Tyrosine Vanadium
Cysteine	Methionine Taurine	Lysine, Copper Zinc

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AA & Nutrient Relationships

Amino Acid	Complementary	Antagonistic
Phenylalanine	Tyrosine Methionine Copper	Tryptophan
Taurine	Alanine, GABA Glycine	Aspartic acid Glutamic acid
Tryptophan	Niacin, Zinc Pyridoxine	Phenylalanine Tyrosine
Threonine	Arginine Proline, Glycine	Copper

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Neurotransmitter Precursors

Amino Acid	Neurotransmitter(s)
Cysteine	Cysteic acid
Glutamine	GABA, Glutamate
Histidine	Histamine
Lysine	Pipecolic acid
Phenylalanine	Dopamine, Norepinephrine, Epinephrine, Tyramine
Tyrosine	Dopamine, Norepi, Epi
Tryptophan, 5-HTP	Serotonin, Melatonin

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Amino Acids as Neurotransmitters

Amino Acid	Function
Alanine	Inhibitory or calming
Aspartic acid	Excitatory
GABA	Inhibitory or calming
Glutamate	Excitatory
Glycine	Inhibitory or calming
Taurine	Inhibitory or calming

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Brain Transmitter Physiology

- Uppers:
  - Serotonin
  - Acetylcholine
  - Norepinephrine
  - Epinephrine
  - Dopamine
  - Histamine**
  - [Glycine]**
- Downers:
  - GABA
  - Nitric Oxide
  - Neurosteroids
  - [Histamine]**
  - Glycine**

Balancing / Leveling: Serotonin – Glycine – Acetylcholine - Histamine

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Amino Acid Infusions, Crystalline

Combination Products

Examples

- Plenamine 15%
- Aminosyn , Aminosyn II, Aminosyn-PF
- FreAmine III
- Novamine
- Travasol
- Trophamine

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Note – Caution with severe liver disease

- Some patients with severely compromised liver function may experience increased blood ammonia levels on receiving amino acids
  - Dose related
- This can result in severe encephalitis and can require treatment with dialysis

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Plenamine 15%

Essential Amino Acids in mg/100 ml

Isoleucine 740
Leucine 1.04 gms
Lysine 1.18 gms
Methionine 749
Phenylalanine 1.04 gms
Threonine 749
Tryptophan 250
Valine 960

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Plenamine 15%

- mOsm/ml 1.38 (1358 per liter)
- pH 5.6

Non-essential Amino Acids in mg/100 ml

Alanine 2.17 gms
L-Aspartic acid 434
Histidine 894
Serine 592
N-Acetyl-L-Tyrosine 39
L-Glutamic Acid 749
Arginine1.47 gms
Glycine 1.04 gms
Proline 894

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Amino Acid Infusions, Crystalline

Combination Products

Indications & AA formulation based on condition:

- Total parenteral nutrition (TPN) for patients who cannot or will not eat
- Nutritional support for patients with hepatitis, cirrhosis, hepatic encephalopathy
- Nutritional support for patients with renal failure

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Combination Product Dosing For TPN

This information is available in the PDR and Nurses drug handbook.

- There are special formulations available for:
  - Liver disease
  - Renal disease
  - Patients on dialysis
- These formulations are used in in-patient settings or by home care nursing services
- Discussion of these applications is not appropriate for outpatient clinics

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Amino Acid Infusions, Crystalline

Combination Product Dosing

Nutritional IV Therapy

- Common dosage is 85 ml 15% Plenamine
- Limit peripheral infusions to 2.5% AA (Nurses Drug Handbook 2000, p. 1140)
- 85 ml diluted in 400-500 ml sterile water

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Amino Acid Infusions, Crystalline
Combination Product Adverse Reactions

- CV: thrombophlebitis, thrombosis, edema
- GI: nausea
- GU: glycosuria, osmotic diuresis
- Hepatic: increased liver enzymes
- Skin: flushing
- Other: hypersensitivity reactions, hyperglycemia, metabolic acidosis

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Amino Acid Infusions, Crystalline
Combination Product Adverse Reactions

- Other: alkalosis, hypophosphatemia, hyperammonemia, electrolyte imbalances, fever, weight gain
- Hyperosmolar hyperglycemic nonketotic syndrome

Drug-drug interactions: tetracycline may reduce protein sparing effects of infused AA due to its antianabolic activity

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Combination Amino Acid Infusions

Contraindications: patients with anuria or inborn errors of amino acid metabolism

- 39 inherited disorders at last count (Kelly's Textbook of Internal Medicine, 2000. Pp 2789-90.)

Administration considerations:

- Use caution in patients with renal insufficiency, cardiac disease, hepatic disease

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Combination Amino Acid Infusions

Administration considerations:

- In diabetic patients' insulin may be required to prevent hyperglycemia
- If patient has chills, fever or other signs of sepsis, stop infusion and retain bottle and IV tubing for microbiological culture – this is true for all IV infusions

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Single Amino Acid Infusions
Introduction

- See Therapeutic Application of Amino Acid Therapy page for clinical uses
- Commonly available AA's
- Commonly available concentrations
- Safe dosing for single amino acids given IV has a very wide safe range
- Gram doses are noted in literature
- Practicality and cost lead to mg or low gram dosing

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L-Arginine

- 50 mg/ml
- Conditionally essential AA
- Precursor to neurotransmitter nitric oxide
- IV doses of 20-35 grams releases growth hormone, glucagon and insulin
- Chelates ammonia (common issue with mold, SIBO, other infections)

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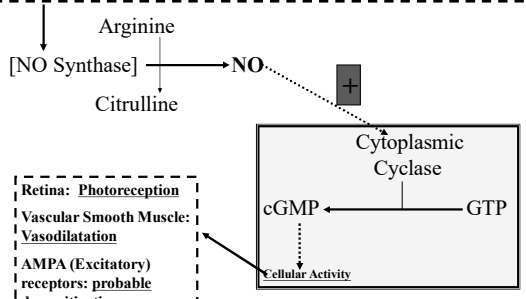
Nitric Oxide

NO Synthase is effectively inhibited by multiple heavy metals.
Mol Cell Biochem 1995 Aug-Sep;149-150:263-5



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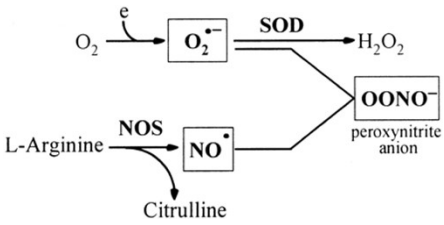
Peroxynitrite formation

- CAUTION in patients with high oxidative stress.



Picture taken from:
http://www.bloodjournal.org/content/97/11/3521?sso-checked=true

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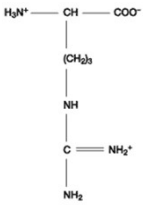
L-Arginine



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L-Carnitine

- 60 to 500 mg/ml
- Carnitine is an amine and an alcohol
- Not used in construction of proteins
- Increases rate at which liver burns fats, creates energy
- Primary role is regulation of fat metabolism

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L-Carnitine

- Acts by carrying fat across mitochondrial membrane – dose dependent
- Very important in providing energy to muscles, including heart
- Lysine loading raises Carnitine levels

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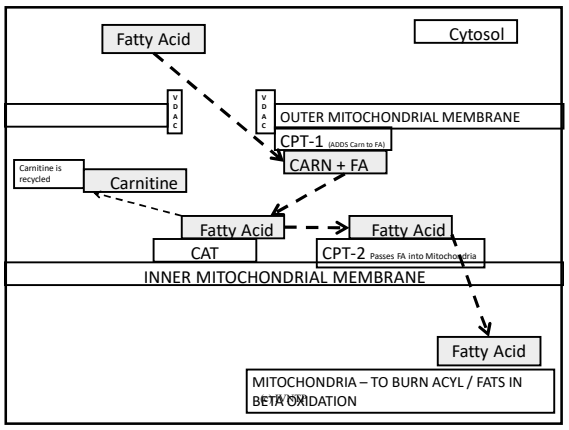

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N-Acetyl-Cysteine

- 100 mg/ml
- Increases intracellular Glutathione
- NAC increases GSH levels in liver, helps prevent oxidative drug damage
- Increase GSH levels in the kidneys.
  - Nephroprotective and regenerative

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N-Acetyl-Cysteine

- NAC is a weak chelator of heavy metals (HM)
- Transport mechanisms exist for movement of NAC:HM complexes both into and out of the brain

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NAC and the cystine-glutamate antiporter

- NAC (as CYS donor) can aid in CNS release of Glutamate.
- Dose at least 500 mg BID orally
- *Pow DV. Visualising the activity of the cystine-glutamate antiporter in glial cells using antibodies to aminoadipic acid, a selectively transported substrate. Glia. 2001 Apr 1;34(1):27-38.*

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N-Acetyl-Cysteine

- Typical dosage recommendations are in the range of IV is 250-1500mg of NAC daily for most therapeutic benefits.
- Typical oral can vary from 500 mg to 2000 mg

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N-Acetyl-Cysteine

- There is scientific confirmation that NAC supplementation does increase levels of glutathione in the liver, in plasma, and in the bronchioles of the lungs (ref last two bullets: http://www.nutritioninstituteofamerica.org/research/NutrientReview/N-Acetylcysteine.pdf)
- NAC is a useful mucolytic agent – has the ability to reduce disulfide bonds in mucoproteins found in mucus, leading to a thinning of viscous mucus

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Lancet. 2003 Aug 23;362(9384):598-603.
Acetylcysteine for prevention of contrast nephropathy: meta-analysis.

Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude FJ, Braun C.

BACKGROUND: Contrast nephropathy is associated with increased in-hospital morbidity and mortality and leads to extension of hospital stay in patients with chronic renal insufficiency. Acetylcysteine seems to be a safe and inexpensive way to reduce contrast nephropathy. We aimed to assess the efficacy of acetylcysteine to prevent contrast nephropathy after administration of radiocontrast media in patients with chronic renal insufficiency.

METHODS: We did a meta-analysis of randomised controlled trials comparing acetylcysteine and hydration with hydration alone for preventing contrast nephropathy in patients with chronic renal insufficiency. The trials were identified through a combined search of the BIOSIS+/RRM, MEDLINE, Web of Science, Current Contents Medizin, and The Cochrane Library Databases. We used incidence of contrast nephropathy 48 h after administration of radiocontrast media as an outcome measure.

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Acetylcysteine for prevention of contrast nephropathy: meta-analysis.

FINDINGS: Seven trials including 805 patients were eligible according to our inclusion criteria and were analysed. Overall incidence of contrast nephropathy varied between 8% and 28%. Since significant heterogeneity was indicated by the Q statistics (p=0.016) we used a random-effects model to combine the data. Compared with periprocedural hydration alone, administration of acetylcysteine and hydration significantly reduced the relative risk of contrast nephropathy by 56% (0.435 [95% CI 0.215-0.879], p=0.02) in patients with chronic renal insufficiency. Meta-regression revealed no significant relation between the relative risk of contrast nephropathy and the volume of radiocontrast media administered or the degree of chronic renal insufficiency before the procedure.

INTERPRETATION: Compared with periprocedural hydration alone, acetylcysteine with hydration significantly reduces the risk of contrast nephropathy in patients with chronic renal insufficiency. The relative risk of contrast nephropathy was not related to the amount of radiocontrast media given or to the degree of chronic renal insufficiency before the procedure.

PMID: 12944058 [PubMed - in process]

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N-Acetyl-Cysteine: Research Overview

(http://www.nutritioninstituteofamerica.org/research/NutrientReview/N-Acetylcysteine.pdf) 10/17/04

1. Is an antidote for acetaminophen poisoning
2. Prevents liver damage
3. Is a free radical scavenger
4. Is an antioxidant in methanol intoxication
5. Is effective in chemoprevention
6. Reduces endothelial dysfunction
7. Prevents cartilage erosion
8. Prolongs transplants
9. Slows tumor development in lungs
10. May prevent colorectal cancer
11. May reduce carcinogenic effect of tobacco smoke
12. Decreases ulcerative colitis
13. May inhibit esophageal tumors
14. Inhibits cancer progression in general
15. Limits susceptibility to HIV infection
16. Reduces heavy metal toxicity

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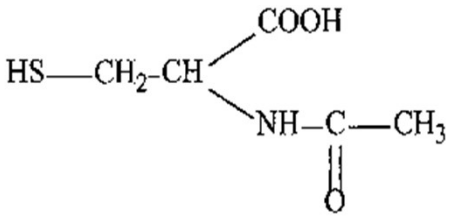
NAC



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L-Glutamine

- 30 mg/ml
- Most common AA in body
- Primary fuel source for immune system, intestines and colon
- Maintain and support GSH levels
- Conditionally essential amino acid

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L-Glutamine & The Brain

- Glutamine is a derivative of glutamic acid, chemical name glutamic acid 5-amide
- Glutamine can more easily pass through the blood brain barrier than glutamic acid
  - Glutamine + glutamate synthetase → glutamate
- Glutamate is the most common neurotransmitter in the brain and is always excitatory
- If patients receiving glutamine can't sleep, they may be over expressing the conversion to glutamate
  - This tendency can be decreased by giving organic lithium, e.g. Lithium orotate, 20 mg q.d.

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L-Glutamine & The Kidneys

- Glutamine is a major Nitrogen carrier in the kidney.
- The kidney can use glutamine to shuttle NH3 residues to be oxidatively deaminated where the NH3 joins local H+ and is secreted into the tubular system for removal from the body.
- This process is B6 dependent

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Glutamine Depletion

- Glutamine Peptides to Prevent Protein Loss After Surgery American Family Physician Date: July 1, 1989
  - Catabolic stress, such as surgery, trauma or infection, lead to nitrogen loss
  - This loss is thought to come from muscle protein breakdown, which leads to the transport of glutamine to visceral organs
  - Results in profound intramuscular glutamine depletion

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Glutamine Depletion (2)

- Muscle glutamine concentration strongly correlates with rate of protein synthesis
- Glutamine is known to promote protein anabolic processes
- Parenteral nutrition containing glutamine would likely conserve protein and promote healing

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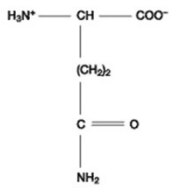
L-Glutamine



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L-Glycine

- 50 mg/ml
- Key metabolic agent
  - Helps in synthesis of nucleic acids, glycerol, phospholipids, cholesterol esters, skin proteins
  - Required for GSH synthesis
  - Enters into Krebs cycle via pyruvate
  - Encourages glycogenolysis
  - Required for creatinine synthesis
  - Required for glycine conjugation in phase 2 detox
  - Oral: sweetner

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Glycine Receptor

- CNS Activity:
- Receptor agonist: Glycine – AND - NMDA Receptors
  - Glycine is also agonist to NMDA receptor
    - **Contraindicated in Bipolar Disorders.**
  - Glycine receptor is probably a major cross regulatory mechanism for the excitatory receptor class

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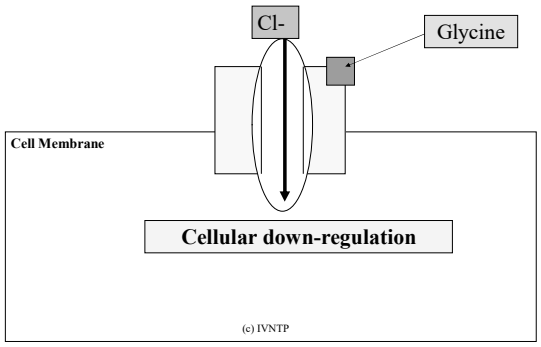
Glycine Receptor



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Glycine

Abstract: Accumulating lines of evidence suggest a possibility that glycine is useful as an immuno-modulating amino acid. Glycine most likely prevents the lipopolysaccharide (LPS)-induced elevation of intracellular Ca(2+) concentration in Kupffer cells, thereby minimizing LPS receptor signaling and cytokine production. Moreover, it was reported that dietary glycine inhibits the growth of tumors.

Vascular endothelial growth factor (VEGF) plays a critical role in cancer progression by promoting new blood vessel formation…. **The VEGF increased intracellular Ca(2+) concentration rapidly, but glycine blunted increases in intracellular Ca(2+) concentration due to VEGF. Further, the inhibitory effects of glycine were prevented by low concentrations of strychnine (1 micromol/L) or incubation with chloride-free buffer. Moreover, glycine increased influx of radiolabeled chloride into CPA cells approximately 10-fold. Furthermore, mRNA 92% identical to the beta-subunit of the glycine-gated chloride channel from spinal cord was identified in endothelial cells using reverse transcription-polymerase chain reaction. Finally, glycine significantly diminished serum-stimulated proliferation and migration of endothelial cells. [PMID:**17567469]

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Glycine

These data indicate that the inhibitory effect of glycine on growth and migration of endothelial cells is due to activation of a glycine-gated chloride channel. This hyperpolarizes the cell membrane and blocks influx of Ca(2+), thereby minimizing growth factor-mediated signaling. **Therefore, glycine can be used not only for treatment of inflammation, but also for chemoprevention and treatment of carcinoma.**

Glycine as a potent anti-angiogenic nutrient for tumor growth. Journal of Gastroenterology and Hepatology (2007) Volume: 22 Suppl 1, Pages: S62-S64 PubMed: 17567469

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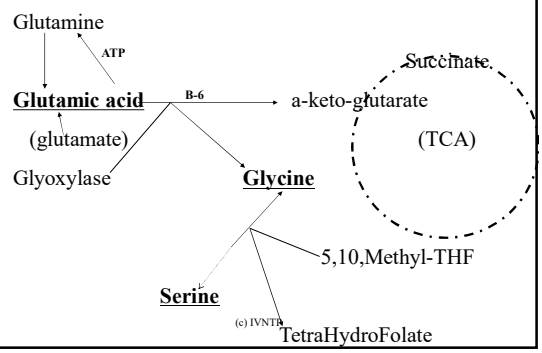
Glutamate and Glycine: CNS Metabolism



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L-Glycine

- Dosing
  - Start low (50-200 mg) and monitor somnolent response (generally higher in co-administration with Magnesium).
  - 1-4 grams have been used in research
    - Caution
    - Manic episodes

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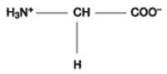
L-Glycine



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L-Histidine

- 50 mg/ml
- Can be synthesized from Glutamic acid, Carnosine, possible Biotin
- Precursor of histamine, neurotransmitter in brain and autonomic nervous system
- Low levels found in serum and synovial fluid of patients with rheumatoid arthritis
  - Treatment with 1 gram or more daily resulted in improved grip strength and walking ability

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Prog Neurobiol. 2001 Apr;63(6):637-72.

The physiology of brain histamine.Brown RE, Stevens DR, Haas HL.

Institut fur Neurophysiologie, Heinrich-Heine-Universitat, D-40001, Dusseldorf, Germany. brown@uni-duesseldorf.de

Histamine-releasing neurons are located exclusively in the TM of the hypothalamus, from where they project to practically all brain regions, with ventral areas (hypothalamus, basal forebrain, amygdala) receiving a particularly strong innervation. The intrinsic electrophysiological properties of TM neurons (slow spontaneous firing, broad action potentials, deep after hyperpolarisations, etc.) are extremely similar to other aminergic neurons. Their firing rate varies across the sleep-wake cycle, being highest during waking and lowest during rapid-eye movement sleep. In contrast to other aminergic neurons somatodendritic autoreceptors (H3) do not activate an inwardly rectifying potassium channel but instead control firing by inhibiting voltage-dependent calcium channels. Histamine release is enhanced under extreme conditions such as dehydration or hypoglycemia or by a variety of stressors.

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Histamine in the Brain

- H-1 (Stimulating)
  - Causes increased depolarization in hypothalamic and limbic areas
- H-2 (Stimulating)
  - Slows potassium conductance, increasing excitation in the hipocampus, amygdala and basal nuclei
- H-3 (Inhibiting)
  - Blocks calcium channels in the basal nuclei decreasing histamine release
- "H-4" (Inhibiting)
  - Slows / modulates NMDA receptor complex

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Histamine activates four types of receptors.

1. **H1** receptors are mainly postsynaptically located and are coupled positively to phospholipase C. High densities are found especially in the **hypothalamus and other limbic regions**. Activation of these receptors causes large depolarisations via blockade of a leak potassium conductance, activation of a non-specific cation channel or activation of a sodium-calcium exchanger.
   [H1 Blocking drugs inhibit this surge of depolarization – leading to somnolence and CNS depression]
2. **H2** receptors are also mainly postsynaptically located and are coupled positively to adenylyl cyclase. High densities are found in hippocampus, amygdala and basal ganglia. Activation of these receptors also leads to mainly excitatory effects through blockade of calcium-dependent potassium channels and modulation of the hyperpolarisation-activated cation channel.
3. **H3** receptors are exclusively presynaptically located and are negatively coupled to adenylyl cyclase. High densities are found in the basal ganglia. These receptors mediated presynaptic inhibition of histamine release and the release of other neurotransmitters, most likely via inhibition of presynaptic calcium channels.
4. Finally, histamine **modulates the glutamate NMDA receptor** via an action at the polyamine binding site.

The central histamine system is involved in **many** central nervous system functions: **arousal; anxiety; activation of the sympathetic nervous system; the stress-related release of hormones from the pituitary and of central aminergic neurotransmitters; antinociception; water retention and suppression of eating. A role for the neuronal histamine system as a danger response system is proposed.**

PMID: 11164999 [PubMed - indexed for MEDLINE]

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L-Histidine as Histamine Precursor

- Low histamine has been seen in:
  - Apthous stomatitis
  - Low libido and slow sexual response
  - Tension headaches
  - Grand plans but easily frustrated
  - Suspicious, paranoia
  - Ringing in ears
  - Low tolerance for medications
  - Frequent irritability
- High histamine has been seen in:
  - Hyperactivity
  - Obsessive-compulsive
  - Chronic depression with strong suicidal tendencies
  - Phobias
  - Low pain tolerance
  - Rapid metabolism with lean build
  - Excess sweating
  - Seasonal allergies
  - Frequent URI's

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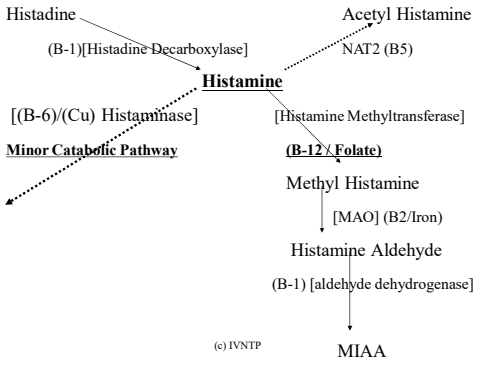
Histamine Metabolism



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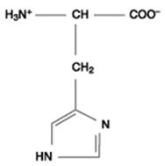
L-Histidine



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L-Lysine

- 50 mg/ml
- Metabolized by B2, B3
- Lysine, along with zinc, vitamin C suppress clinical manifestation of herpes virus
- Large doses IV, 1.9 gm/kg in rats was non-toxic unless aminoglycoside antibiotics were concurrently administered (renal tox.)

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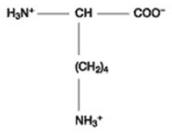
L-Lysine



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L-Methionine

- 50 mg/ml
- Essential sulfur containing AA
- Serves 3 major roles in body:
  - As a methyl donor for synthesis of many body compounds
  - Sulfur donor, e.g. phase 2 sulfation
  - Precursor for other sulfur AA
- Deficiency leads to temporary folate deficiency, folate is trapped in liver, important in allergic patients (high histamine)

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L-Methionine

- Critical to take adequate B6, B12, Folate when supplementing Methionine, otherwise homocysteine levels rise
  - MTHFR deficiency requires use of 5-MTHF, the bioactive form of folate
- Methionine is useful as part of a program for lowering high histamine levels

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L-Methionine

- SAMe is a cofactor for the neurotransmitter, epinephrine
  - Epinephrine opens up the blood supply to the heart, skeletal muscles and liver
  - Insufficient SAMe results in nor-epinephrine being formed leading to hypertension
- SAMe required for synthesis of carnitine

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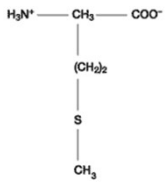
L-Methionine : Important methyl donor



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66

Taurine

- 50 mg/ml
- Sulfur containing organic acid, not incorporated into muscle protein, present in all cell membranes
- Major role in normal functioning of brain, other electrical excitable tissues (heart)
- Promotes pumping action of heart
- Useful for CHF: 3-5 grams (oral) + 30 mg COQ10 daily

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Taurine

- Taurine is a master osmolyte in the body – osmolyte function allows transport of excitable ions to the preferred side of the cell membrane (Na / Ca / Cl outside, Mg / K inside).
- Taurine is required in the cell membrane as well as in circulation to be effective as an osmolyte.
- Deficiency creates sub-optimal osmolyte activity

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Taurine

- Useful in patients who show increase of arrhythmias from IV magnesium
- Heart
  - Modulates activity of C-AMP which activates many cardiac enzymes
  - Contributes to muscle contractility
  - May affect entry of Ca into heart muscle cells
  - May be useful in treating arrhythmias

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Taurine

- Found in high concentrations in eye, useful for macular degeneration
- Required for synthesis of taurocholic acid one of the primary bile acids
- Mercury can significantly interfere in the trans-sulfuration pathway at many different locations, leading to a deficiency or reduction in available taurine

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Taurine

- Cysteine and B6 support synthesis in body
- Zinc enhances Taurine effects
- Zinc + vitamin A deficiency leads to loss of Taurine in urine – depleted tissue levels
- Has potent and long-lasting anticonvulsant action
- 15-20 grams IV given without toxicity

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Taurine: Research Overview

1. Slows development of heart failure
2. Prolongs life in those with CHF
3. Prevents EtOh induced hypertension
4. Improves glucose tolerance
5. Improves insulin utilization
6. Improves endothelial dysfunction
7. Prevents cell membrane damage
8. Decreases serum cholesterol
9. Antihypoxic
10. Decreases aortic lesions
11. Helps prevent atherosclerosis

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Taurine: Research Overview

12. Controls seizures
13. Treats EtOh induced amnesia
14. Helps cystic fibrosis fat absorption problems
15. Prevents cataract development
16. Protects against reperfusion injury
17. Reduces adrenal gland adrenaline output
18. Taurine is second only to GABA as inhibitory NT

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Taurine: Research Overview

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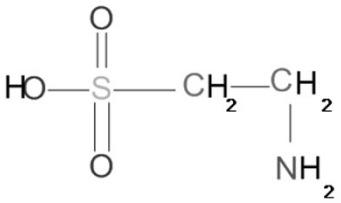
Taurine



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Tryptophan

- 30 mg/ml
- Essential AA
- IV administration supports production of serotonin
- Provides a calming effect on the brain
- CNS and peripheral effects
- Caution in people on serotonin medications
  Monitor for serotonin syndrome.
  - Fever, Hyperreflexia, HTN, Coma, Death
- Required for sythesis B6, B3, B5, B12, Folate

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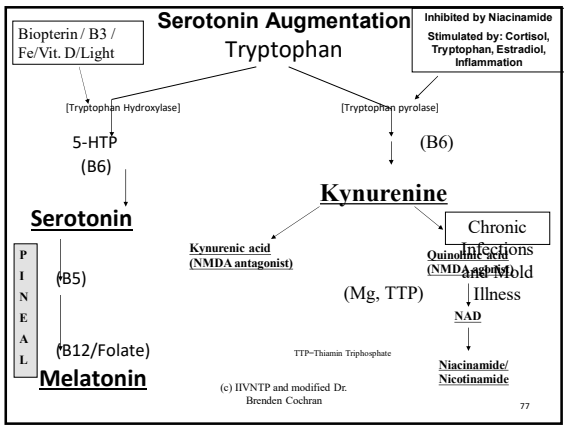

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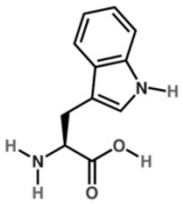
Tryptophan



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L-Threonine

- 50 mg/ml
- Essential AA
- IV administration raises Glycine and Threonine concentration in brain and spinal cord – 1 g bid orally for depression
- Threonine is essential for normal GABA receptor function
- B6 essential to metabolism
- Most studies found that Threonine is an immunostimulant, specific requirement by thymus

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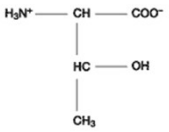
L-Threonine



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