INTERNATIONAL
IV NUTRITIONAL THERAPY
GLOBAL PHYSICIAN EDUCATION

Parenteral Amino Acids

Advanced IV Therapy

by

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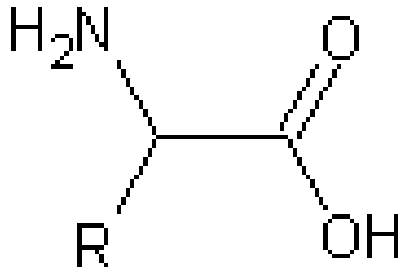
Parenteral Amino Acids



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

Pfeiffer's Law

"We have found that if a drug can be found to do the job of medical healing, a nutrient can be found to do the same job. When we understand how a drug works, we can imitate its action with one of the nutrients."

Amino acids have many applications under Pfeiffer's Law

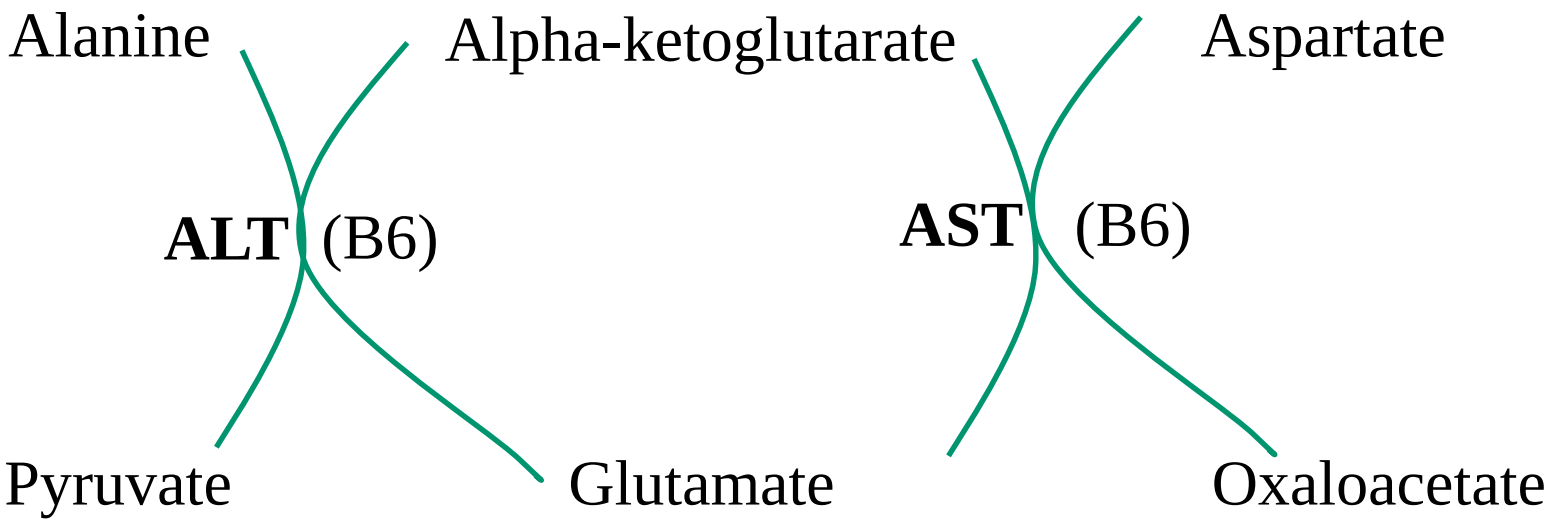
Before the Infusion

- 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

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



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

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

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

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

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

Brain Transmitter Physiology

- Uppers:
  - Serotonin
  - Acetylcholine
  - Norepinephrine
  - Epinephrine
  - Dopamine
  - Histamine**
  - [Glycine]**

- Downers:
  - GABA
  - Nitric Oxide
  - Neurosteroids
  - [Histamine]**
  - Glycine**

Balancing / Leveling: Serotonin – Glycine – Acetylcholine - Histamine

Amino Acid Infusions, Crystalline
Combination Products

Examples

- Aminosyn , Aminosyn II, Aminosyn-PF
- FreAmine III
- Novamine
- Travasol
- Trophamine

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

Aminosyn II, 8.5%

Essential Amino Acids in mg/100 ml

- Isoleucine 561
- Leucine 850
- Lysine 893
- Methionine 146
- Phenylalanine 253
- Threonine 340
- Tryptophan 170
- Valine 425

Aminosyn II, 8.5%

Non-essential Amino Acids in mg/100 ml

Alanine 844

Arginine 865

L-Aspartic acid 595

Glycine 425

Histidine 255

Proline 614

Serine 450

N-Acetyl-L-Tyrosine 230

L-Glutamic Acid 627

(Remember Glutamate and Tyrosine are excitable!)

FreAmine III, 10%

Essential Amino Acids in mg/100 ml

- Isoleucine 690
- Leucine 910
- Lysine 730
- Methionine 530
- Phenylalanine 560
- Threonine 400
- Tryptophan 150
- Valine 660

FreAmine III, 10%

Non-essential Amino Acids in mg/100 ml

- Alanine 710
- Arginine 950
- Cysteine 16
- Glycine 1400
- Histidine 280
- Proline 1120
- Serine 590

FreAmine III, 10%

Non-amino acid constituents per 100 ml

- Phosphoric acid NF 120 mg
- Sodium bisulfite < 100 mg
- SWUSP qs
- pH adjusted with glacial acetic acid USP to pH 6.5 (6.0-7.0)
- Calculated osmolarity 950 mOsm/L

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 cachexia, e.g. cancer patients
- Nutritional support for patients with hepatitis, cirrhosis, hepatic encephalopathy
- Nutritional support for patients with renal failure

Amino Acid Infusions, Crystalline
Combination Products

Action

- Provides substrate for protein synthesis
- Enhances conservation of existing body protein

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

Amino Acid Infusions, Crystalline
Combination Product Dosing

Nutritional IV Therapy

- Common dosage is 100 ml 10% FreAmine III or Aminosyn II, 8.5% solution
- Provides 8.5-10 grams AA
- Limit peripheral infusions to 2.5% AA (Nurses Drug Handbook 2000, p. 1140)
- 100 ml 10% diluted in 400 ml sterile water, is a 2.0% AA solution

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

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

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

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

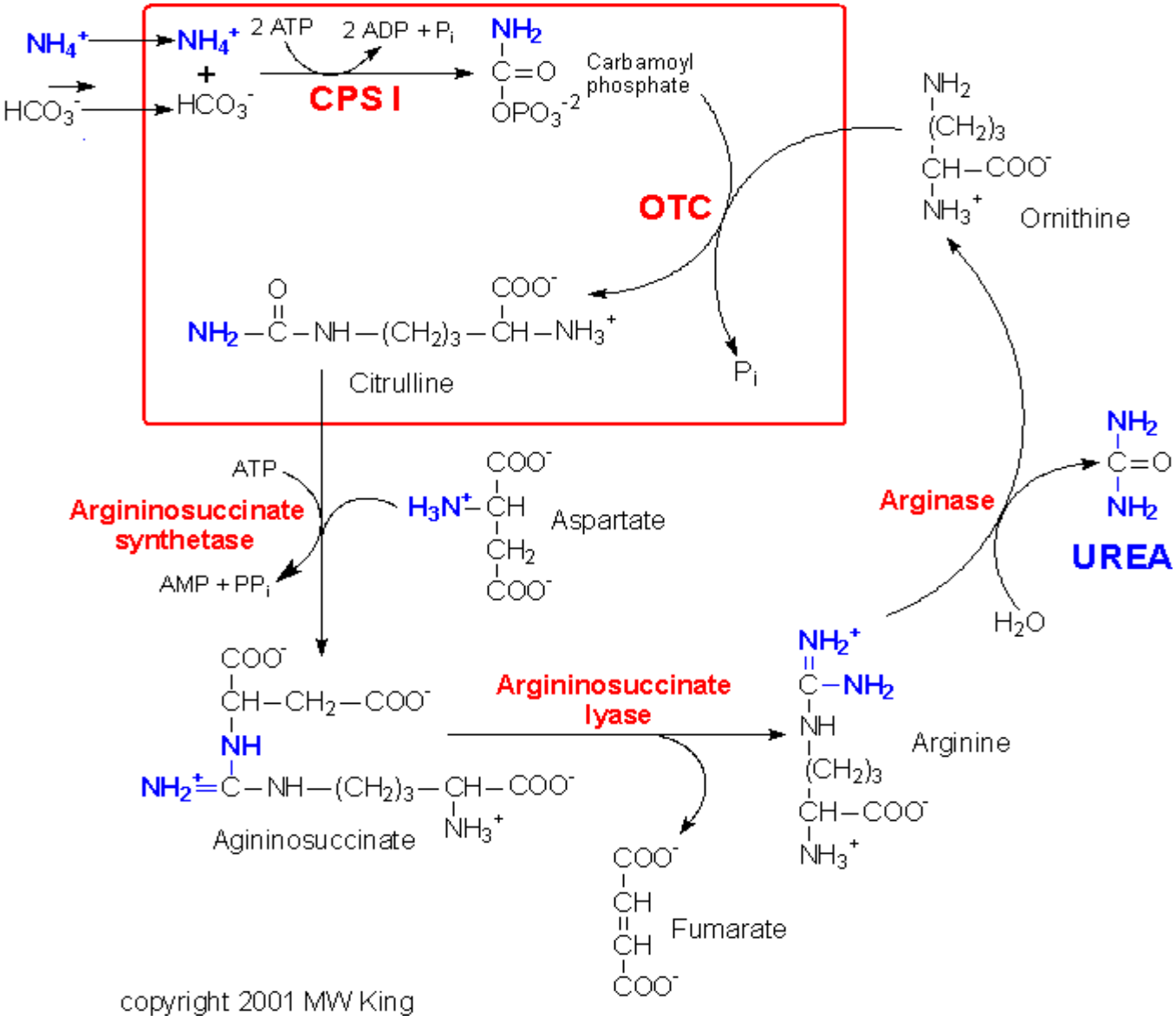
Single Amino Acid Infusions
Introduction

- 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

L-Alanine

- Non-essential amino acid
- Synthesized from lactic acid
- Precursor for pyruvate
- May help with reducing time of athletic fatigue.

Urea Cycle



http://themedicalbiochemistrypage.org/nitrogen-metabolism.html#urea

L-Arginine

- 50 mg/ml
- Conditionally essential AA
- Precursor to neurotransmitter nitric oxide
- Arginine stimulates carbamyl phosphate synthetase, which initiates urea cycle
- IV doses of 20-35 grams releases growth hormone, glucagon and insulin
- Chelates ammonia

A short history of nitric oxide

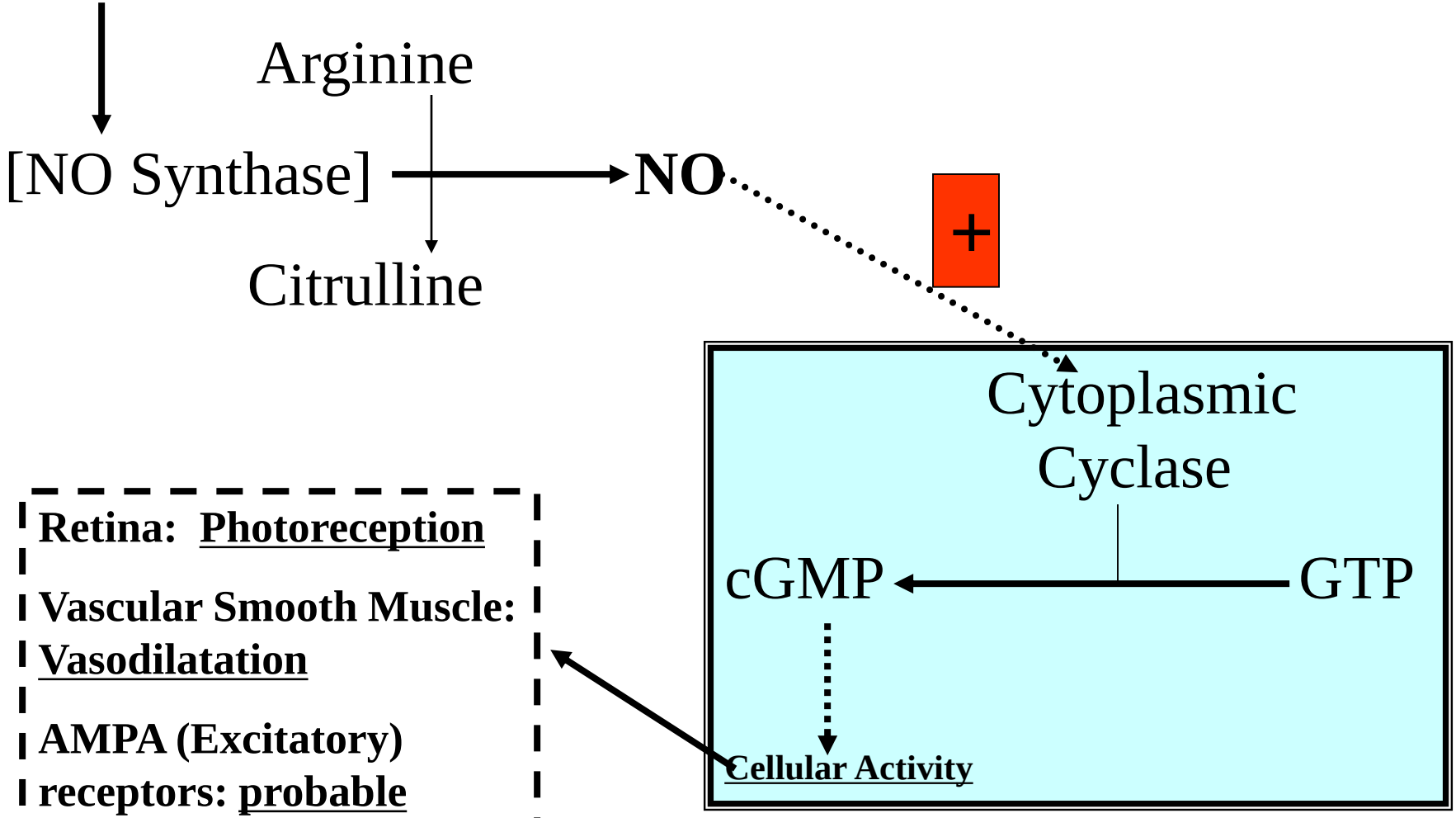
- Vasodilators, such as acetylcholine and bradykinin, do not exert their effects upon the vascular smooth muscle cell in the absence of the overlying endothelium. When acetylcholine (or bradykinin) binds its receptor on the surface of endothelial cells, a series of steps leads to the release of intracellular stores of Ca^{2+}
- The elevation in Ca^{2+} leads to the liberation of endothelium-derived relaxing factor (**EDRF**) which then diffuses into the adjacent smooth muscle,leading to smooth muscle cell relaxation
- Quite unexpectedly, EDRF was found to be the free radical diatomic gas, **nitric oxide**, **NO**
- So important was the elucidation of the pathway to and actions of NO that Drs. Murad, Ignarro and Furchgott were awarded the Nobel Prize in 1998 for their work on this system

Nitric Oxide Synthesis

- Nitric oxide synthase produces NO by catalysing a five-electron oxidation of a guanidino nitrogen of L-arginine (L-Arg). Oxidation of L-Arg to L-citrulline occurs via two successive monooxygenation reactions producing *N*ω-hydroxy-L-arginine (NOHLA) as an intermediate. 2 mol of O_2 and 1.5 mol of NADPH are consumed per mole of NO formed.
  - L-Arg + NADPH + H^+ + O_2 → NOHLA + $NADP^+$ + H_2O
  - NOHLA + ½ NADPH + ½ H^+ + O_2 → L-citrulline + ½ $NADP^+$ + NO + H_2O

Nitric Oxide

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



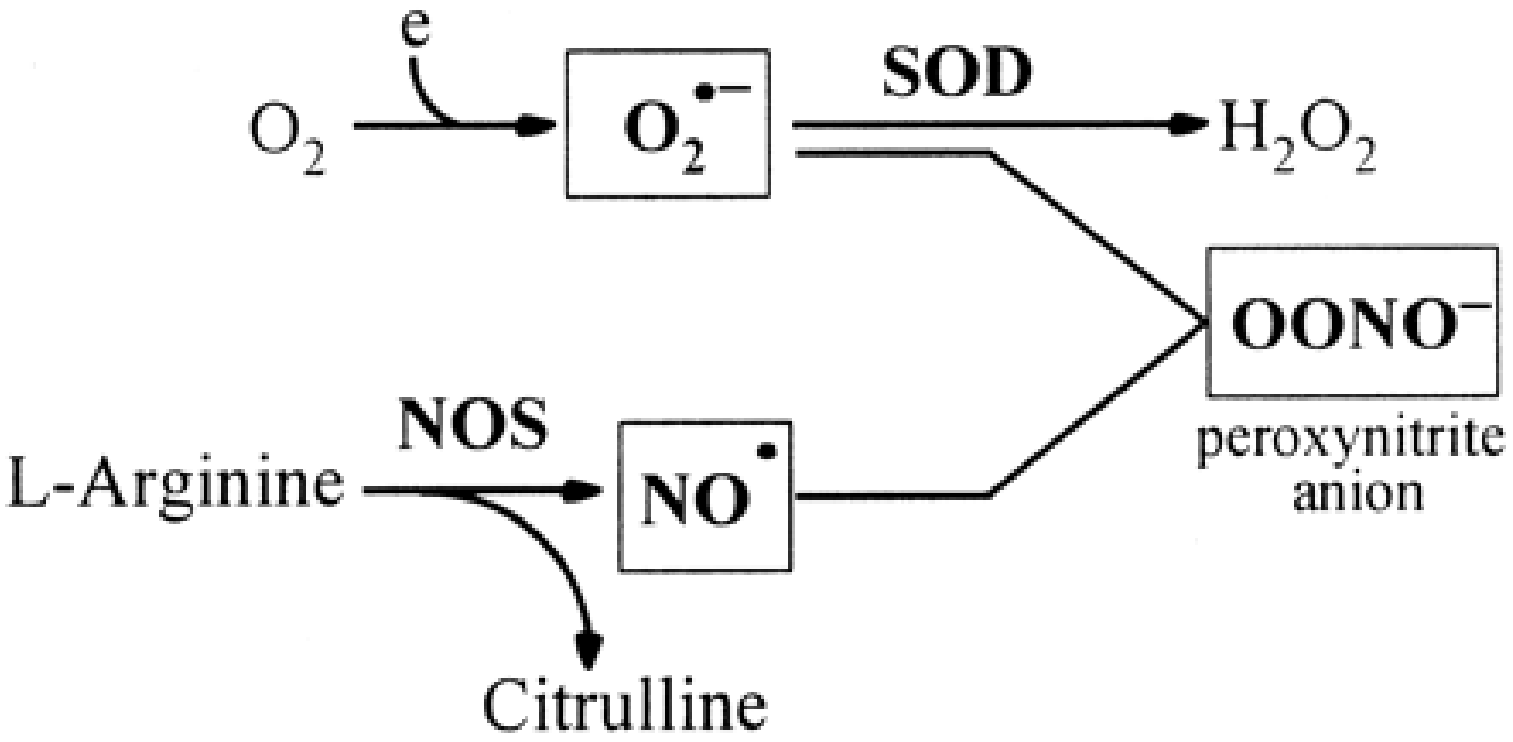
Retina: Photoreception

Vascular Smooth Muscle: Vasodilatation

AMPA (Excitatory) receptors: probable desensitization

Peroxynitrite formation

- CAUTION in patients with high oxidative stress.



Picture taken from:

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

Current Research Delineates many benefits of Oral or IV Arginine

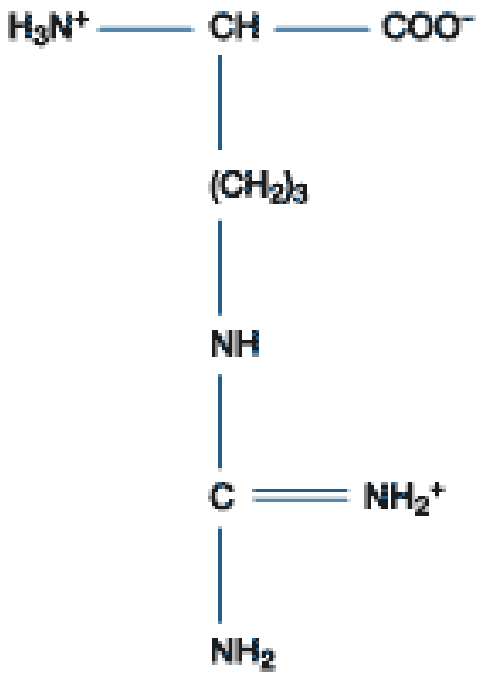
Arginine metabolism and nutrition in growth, health and disease.

Wu G, et.al.

Amino Acids. 2009 May;37(1):153-68

L-Arginine (Arg) is synthesised from glutamine, glutamate, and proline via the intestinal-renal axis in humans and most other mammals (including pigs, sheep and rats). Arg degradation occurs via multiple pathways that are initiated by arginase, nitric-oxide synthase, Arg:glycine amidinotransferase, and Arg decarboxylase. These pathways produce nitric oxide, polyamines, proline, glutamate, creatine, and agmatine with each having enormous biological importance. Arg is also required for the detoxification of ammonia, which is an extremely toxic substance for the central nervous system. There is compelling evidence that Arg regulates interorgan metabolism of energy substrates and the function of multiple organs. The results of both experimental and clinical studies indicate that Arg is a nutritionally essential amino acid (AA) for spermatogenesis, embryonic survival, fetal and neonatal growth, as well as maintenance of vascular tone and hemodynamics. Moreover, a growing body of evidence clearly indicates that dietary supplementation or intravenous administration of Arg is beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, as well as facilitating wound healing, enhancing insulin sensitivity, and maintaining tissue integrity. Additionally, Arg or L-citrulline may provide novel and effective therapies for obesity, diabetes, and the metabolic syndrome. The effect of Arg in treating many developmental and health problems is unique among AAs, and offers great promise for improved health and wellbeing of humans and animals.

L-Arginine



L-Carnitine

- 60 to 200 mg/ml
- Optimal health requires 250-500 mg in diet daily
- Carnitine is an amine and an alcohol
- Has been described as vitamin, amino acid, and essential metabolite
- Not used in construction of proteins

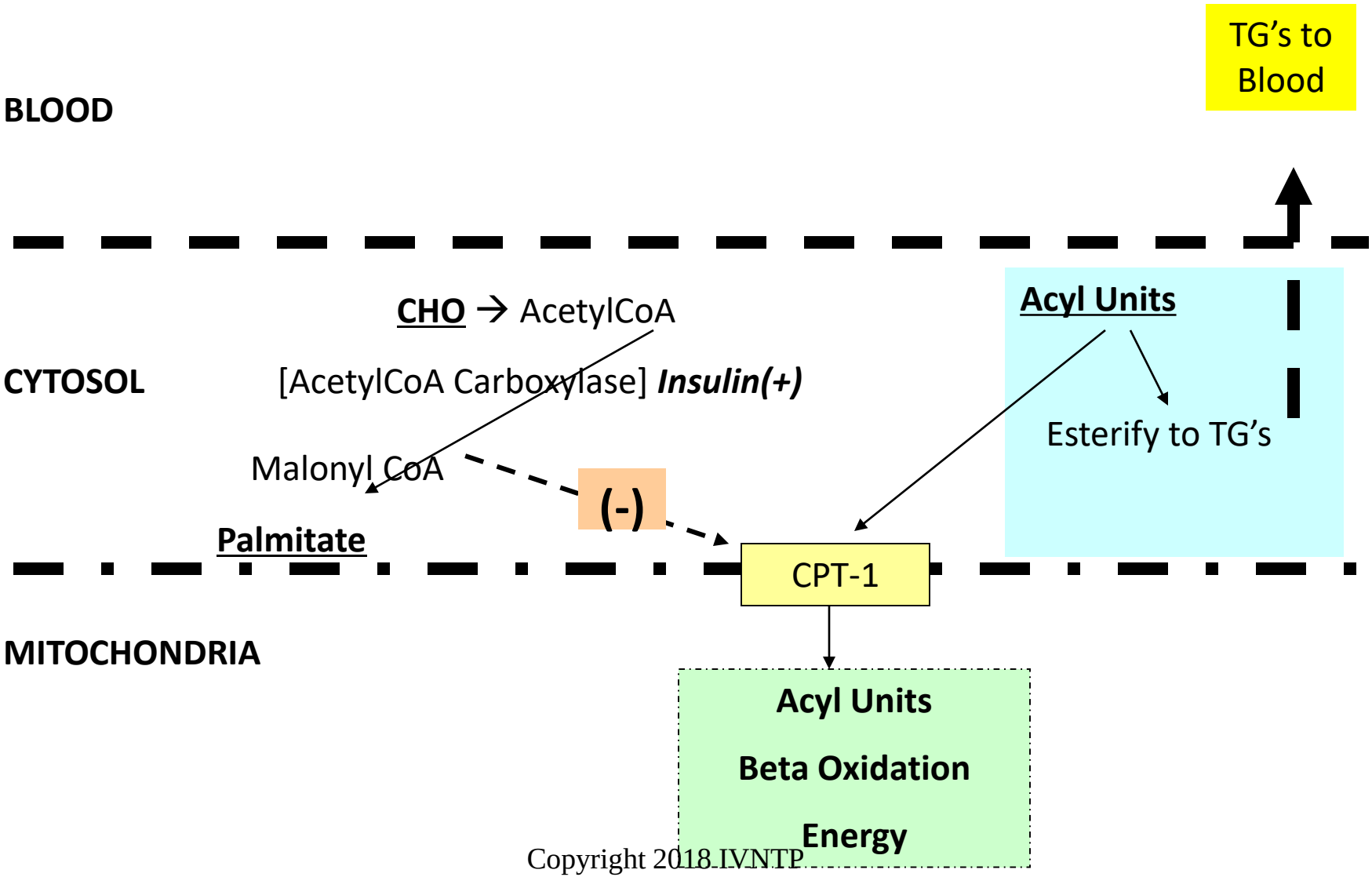
L-Carnitine

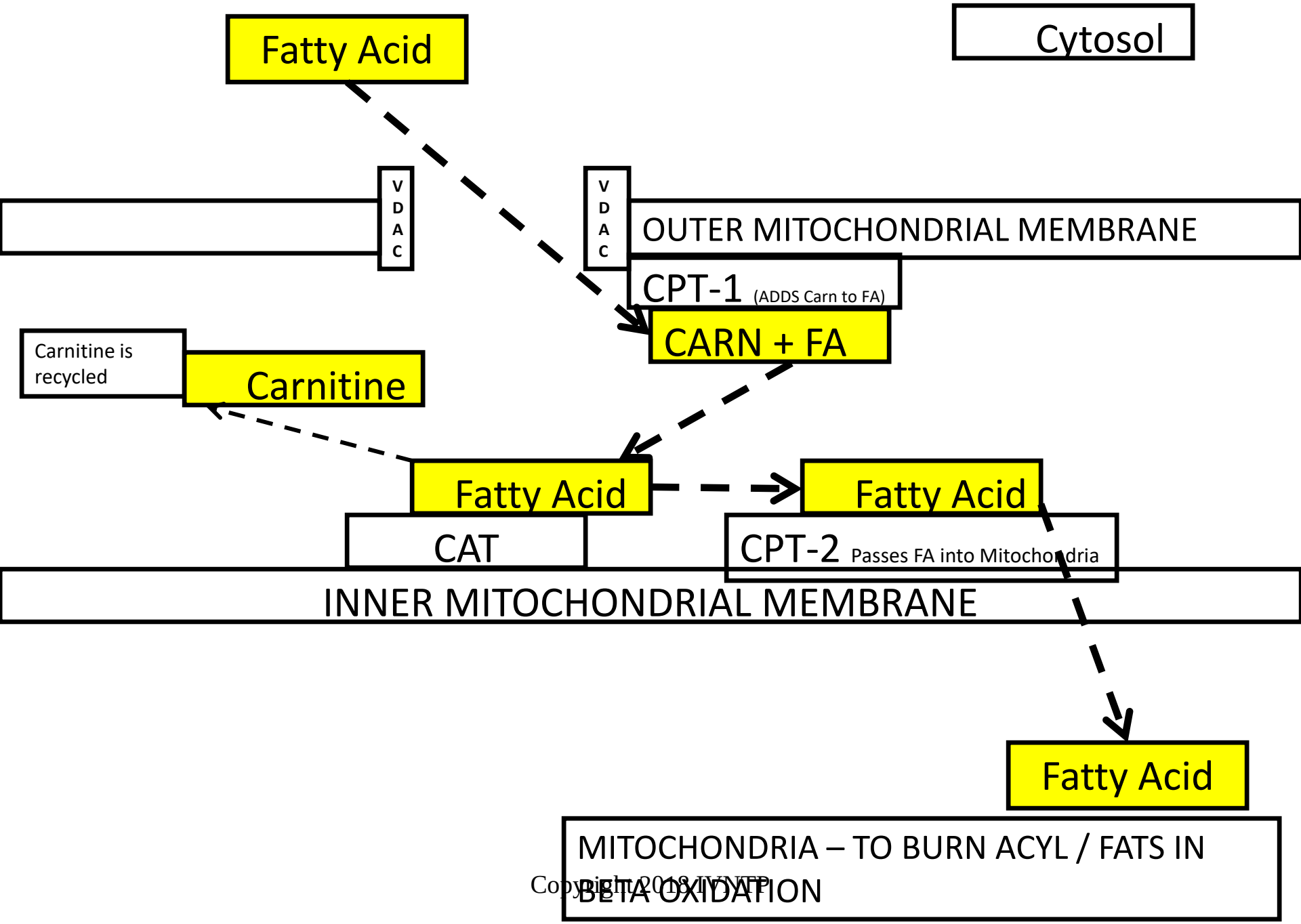
- Increases rate at which liver burns fats, creates energy
- Primary role is regulation of fat metabolism
- Acts by carrying fat across mitochondrial membrane – dose dependent
- Very important in providing energy to muscles, including heart
- Lysine loading raises Carnitine levels

L-Carnitine

- Lysine to Carnitine conversion requires methionine, niacin, pyridoxine (increases metabolism), vitamin C and iron
- Strict vegans are often deficient in Carnitine
- Elevated insulin levels can inhibit optimal Carnitine activity, e.g. high CHO diet
- Omega-3 fats improve Carnitine utilization

Sugar / Insulin and TG Synthesis





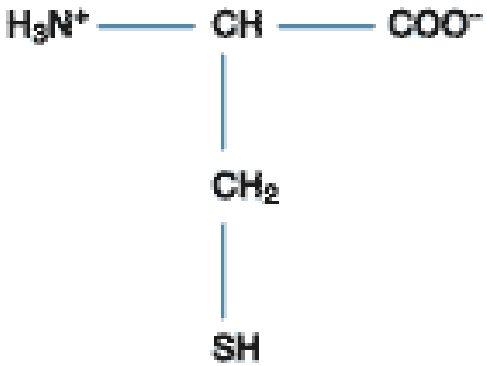
L-Cysteine

- 50 mg/ml
- Amino acid combined with thiol group
- Thiol compounds serve as reducing agents, e.g. help prevent oxidation of sensitive tissues, cysteine is oxidized in process
- Two oxidized cysteine residues link via disulfide bridge to form cystine

L-Cysteine

- Cysteine is major amino acid that will support-increase Glutathione levels
- It is the rate limiting substrate in glutathione production
- Large amounts of Phenylalanine and Tryptophan can lead to decrease in Cysteine levels – antioxidant levels decrease

L-Cysteine



N-Acetyl-Cysteine

- 100 mg/ml
- Closely related to L-Cysteine
- Water solubility is higher than Cysteine
- Increases intracellular Glutathione
- Enhances antitumor responses by Interleukin 2
- Helpful in detoxification of chemotherapy agents post treatment
- Antidote for arsenic and acetaminophen poisoning

N-Acetyl-Cysteine

- Acetaminophen overdose – usual treatment is oral dosing within 24 hours
- 140 mg/kg initially
- 70 mg/kg every 4 hours for 17 additional doses
- NAC increases GSH levels in liver, helps prevent oxidative drug damage

Ref: Davis Drug Guide for Nurses, 8th Ed. p. 1180

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
- Whey protein, and the amino acids Leucine and Methionine, help protect the BBB from HM movement into the brain during detoxification programs

N-Acetyl-Cysteine

- 400 mg NAC b.i.d. for a total of 800 mg daily p.o. has been recommended for patients at high risk for brain deterioration due to HM toxicity and oxidative damage
- Typical dosage recommendations are in the range of 250-1500mg of NAC daily for the majority of therapeutic benefits.
- 500 grams NAC given in a ADHD study
  - India

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

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.

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]

NAC and Chemotherapy

- Researchers used NAC either 30 minutes prior to or 4 hours after ototoxic chemotherapy (platinum agents) to reduce the ototoxicity with positive results.
- Common dose recommendations are 600 mg BID orally, beginning 4 hours post-chemo.
- An IV loading dose 4 – 6 hours post-chemo of 500 – 1000 mg would be appropriate as well.

Oregon Health & Science University (2005, December 12). Hearing Loss From Chemotherapy Underestimated. *ScienceDaily*.

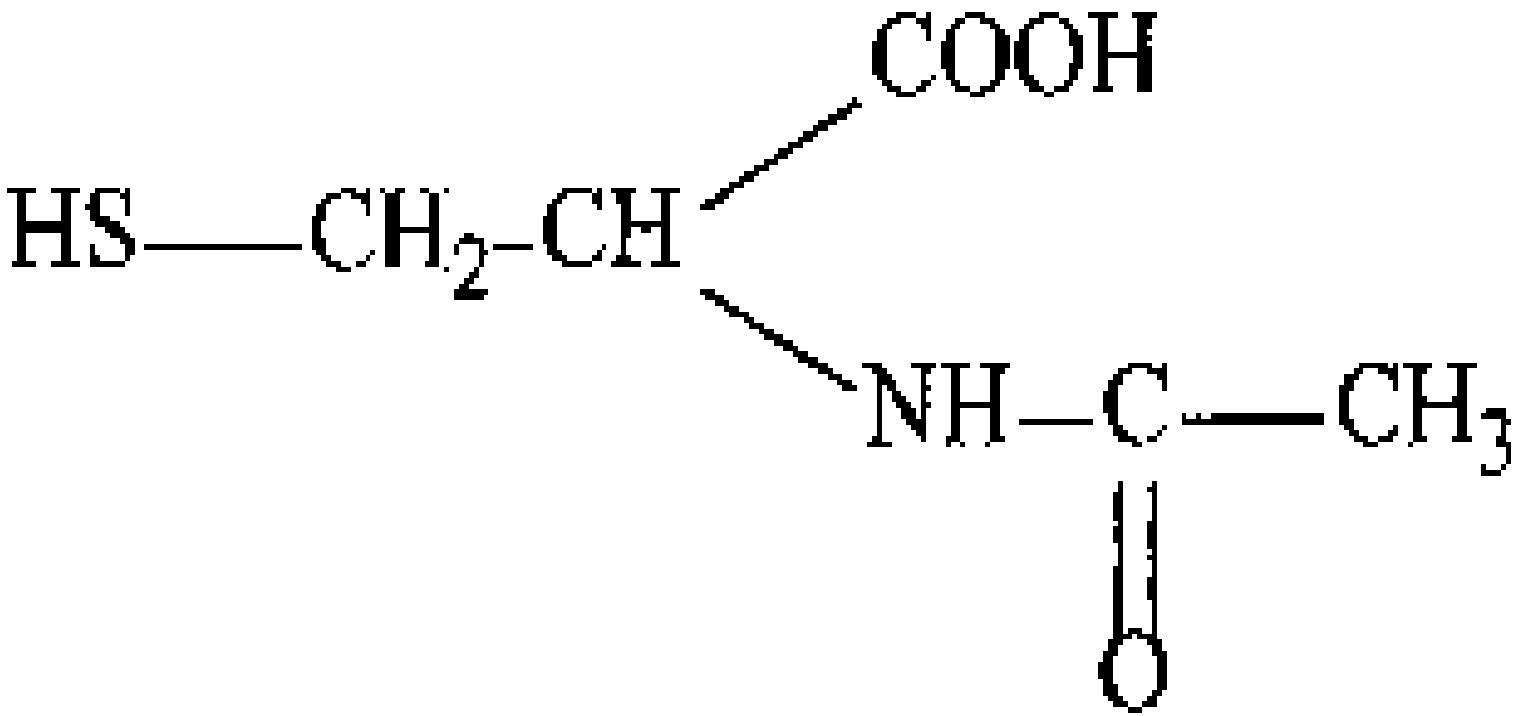
Doolittle ND, Muldoon LL, Brummett RE, et al. Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. Clin Cancer Res 2001;7:493–500

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

NAC



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
- Contraindicated in lymphatic cancers

L-Glutamine

- Glutamine is known to enhance replications of cancer cells
- Tumors did not grow but more tumor cell division took place, in spite of this it is used to:
  - Enhance chemotherapy effectiveness
  - Prevent development of mucositis during chemotherapy
  - Significantly lower infection rates in bone marrow transplant patients

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.

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

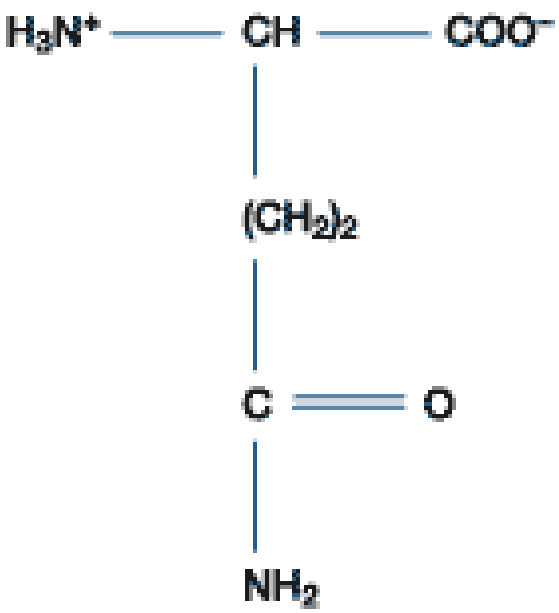
Glutamine Depletion

- 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

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

L-Glutamine



Glutathione

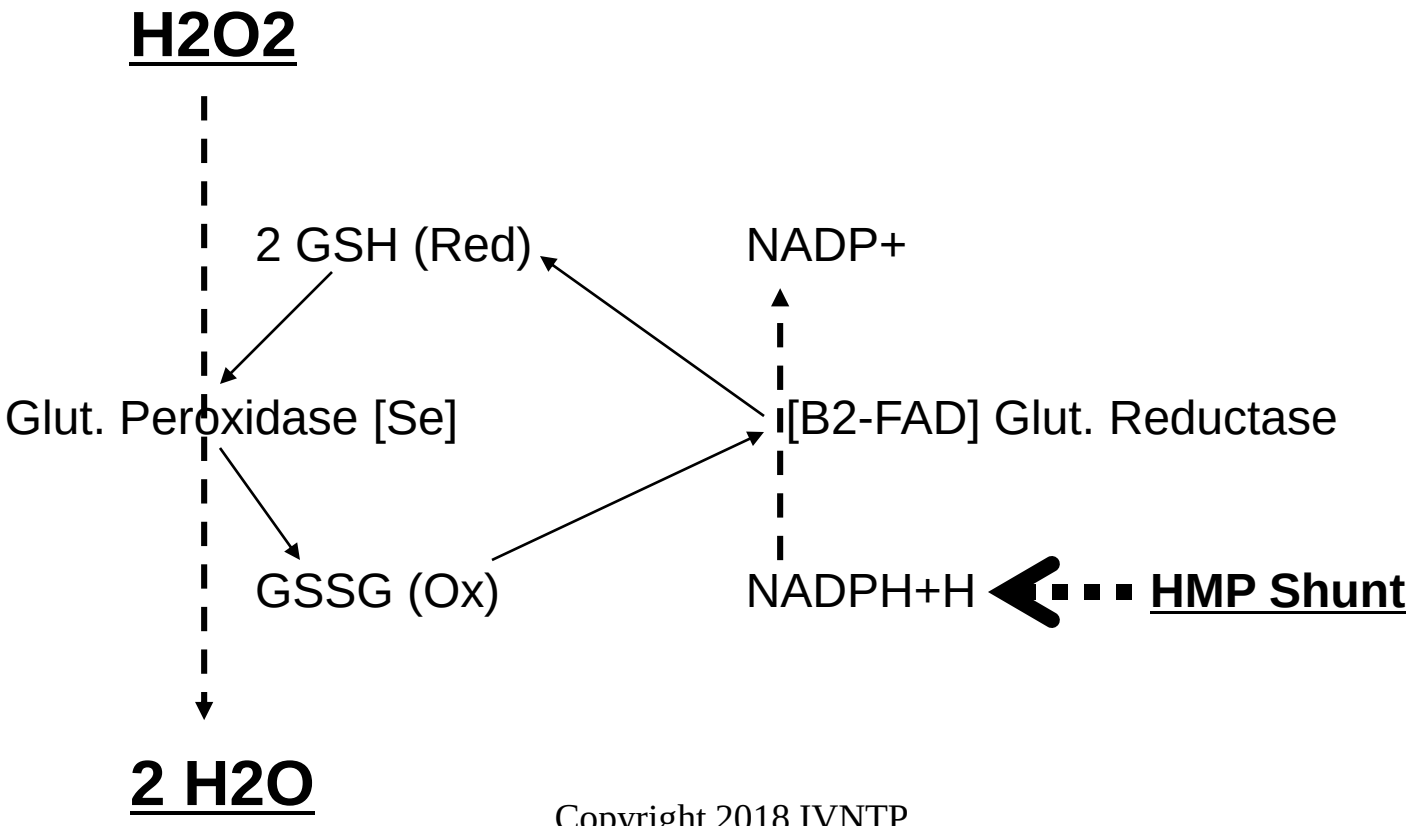
- 60 to 200 mg/ml
- A tripeptide synthesized from Glycine, Glutamic acid and Cysteine
- Primary intracellular antioxidant – essential to life
- Useful to prevent radiation injury BEFORE treatment is started
- Important chelator of lead, mercury, cadmium, arsenic

Glutathione

- Can prevent or reverse alcohol induced fatty liver, cirrhosis, hepatitis, liver tumors
- Inhibits chemical induced carcinogenesis
- Improves prognosis of stroke victims
- Useful in any condition where there is risk for oxidative damage

Glutathione

The Glutathione Redox Cycle and Peroxide



Glutathione (GSH)

- 500 mg is a reasonable starting dose for conditions benefiting from GSH
  - MCS patients may do better starting at 100-200 mg
- Evaluate how patient tolerates dose before giving high doses, e.g. build up dose over time incrementing 500 mg per infusion
- Protocols for the treatment of Parkinson's Disease use from 2400-3600 mg
  - This dose has been as high as 10,000 mg

Glutathione & Parkinson's Disease

- David Perlmutter, MD, has done extensive work with Parkinson's patients and finds GSH essential
- Dr Perlmutter's protocol
  - Typically starts GSH at 2400 mg twice weekly
  - Some patients require 3600 mg GSH daily
  - Given by push over 5-8 minutes following a nutritional IV

*Personal communication June 2007

l-dopa depletes sulfur amino acids

- Glutathione is a sulfur amino acid and a powerful antioxidant that neutralizes neurotoxins that may cause Parkinson's disease
- Implications of sulfur amino acid depletion relating to Parkinson's disease include depletion of:
  - Glutathione leading to progression of Parkinson's disease
  - The enzymes required to synthesize l-tyrosine to l-dopa
  - s-adenosyl-methionine, the body's one carbon methyl donor
  - Epinephrine

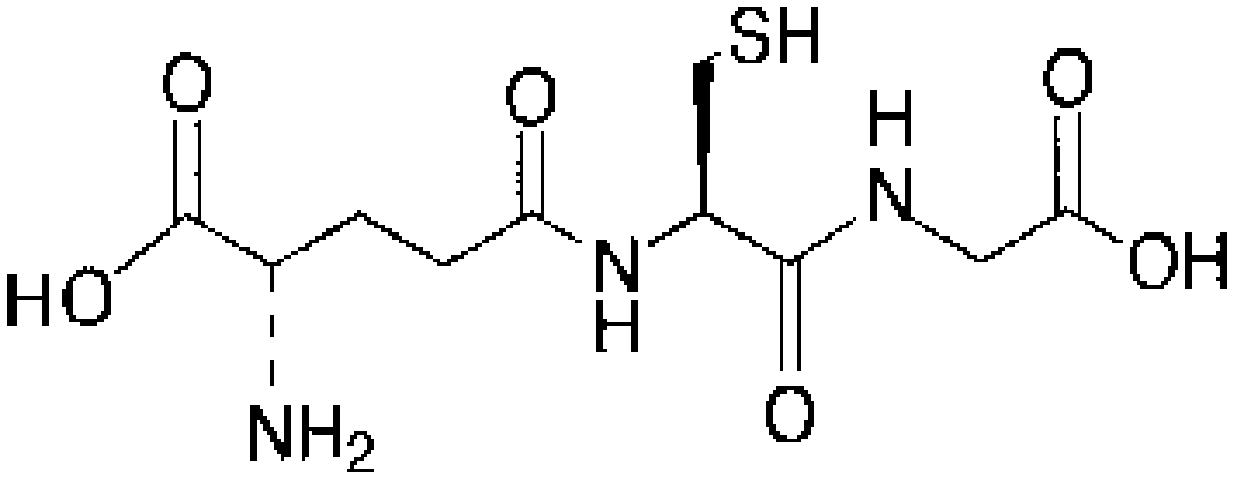
Ref: Hinz M, Stein A, Uncini T. Amino acid management of Parkinson's disease: a case study. Int J Gen Med. 2011; 4: 165–174.

Glutathione

- Important role in immune function via white blood cell production and is a potent anti-viral agent
- It is one of the strongest anti-cancer agents made by the body
- Glutathione levels decrease with age. It is involved in cellular differentiation and slows the aging process

Glutathione

Gamma-glutamyl-cysteinyl-glycine



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

Glycine Receptor

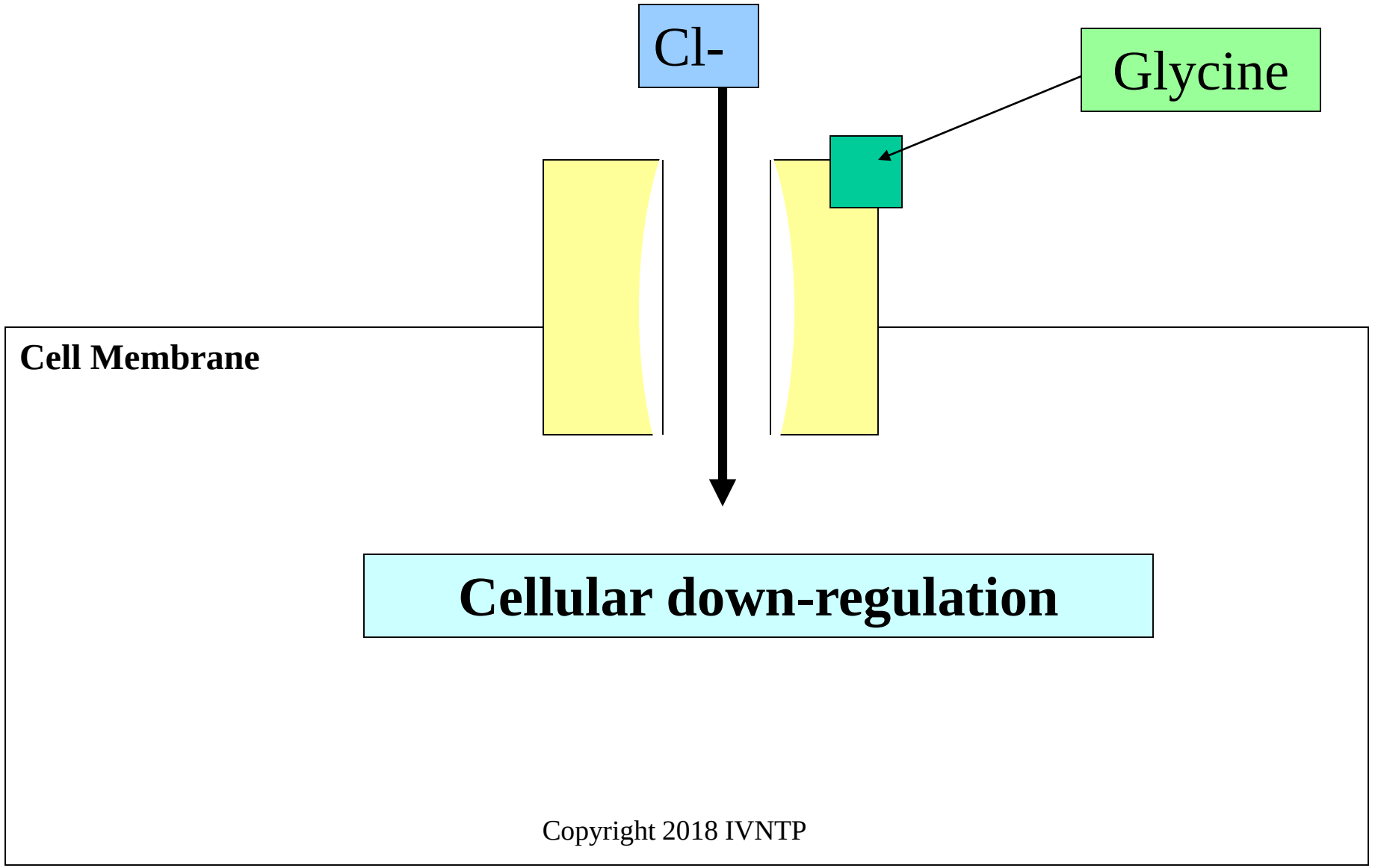
- CNS Activity:

- Receptor agonist: Glycine – AND - NMDA Receptors

  – Glycine is also agonist to NMDA receptor
    - **<u>Contraindicated in Bipolar Disorders.</u>**

  – Glycine receptor is probably a major cross regulatory mechanism for the excitatory receptor class

Glycine Receptor



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.

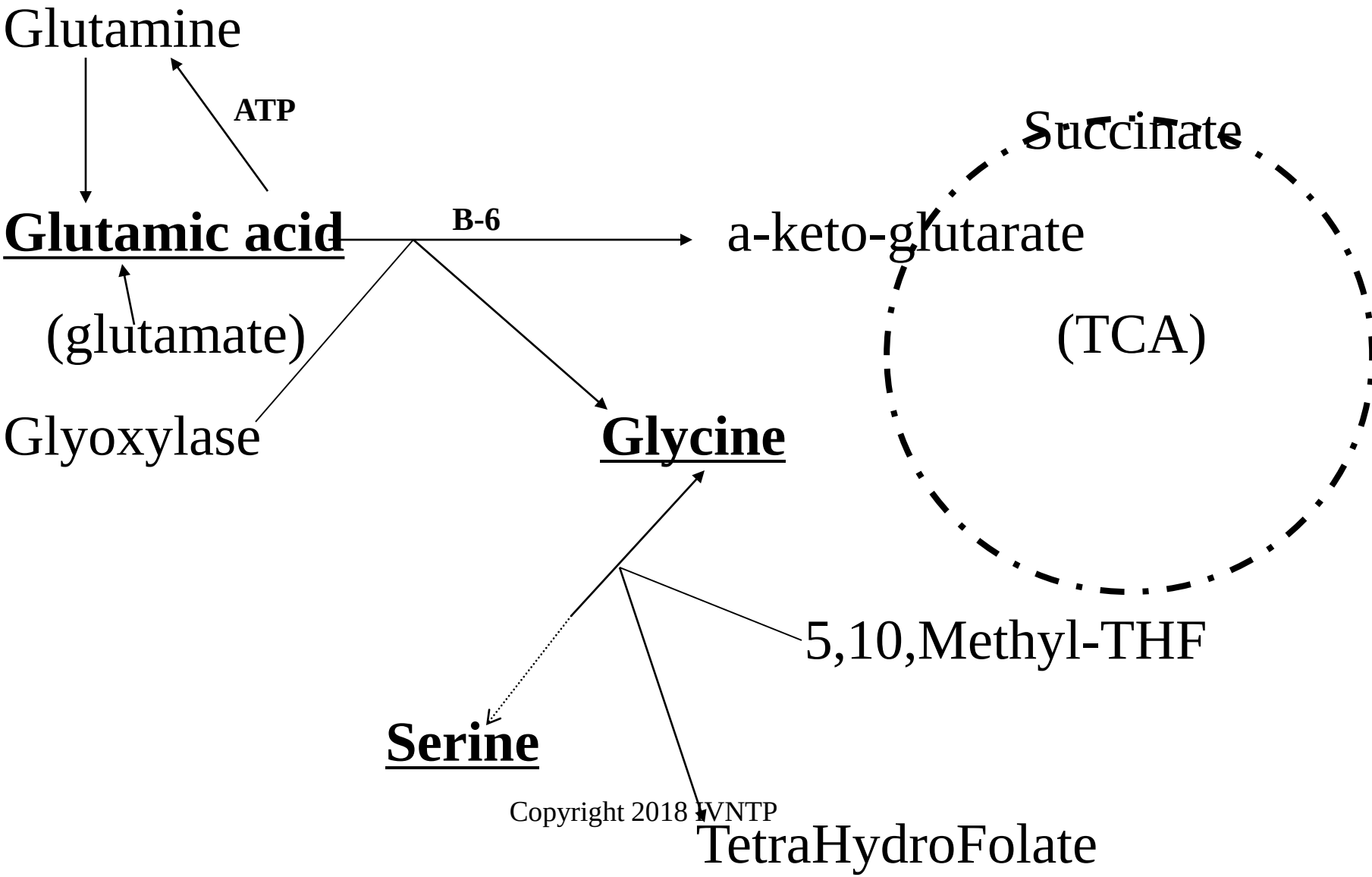
Vascular endothelial growth factor (VEGF) plays a critical role in cancer progression by promoting new blood vessel formation…. **The VEGF increased intracellular Ca(2+) concentration rapidly, but glycine blunted increases in intracellular Ca(2+) concentration due to VEGF. Further, the inhibitory effects 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]

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

Glutamate and Glycine: CNS Metabolism



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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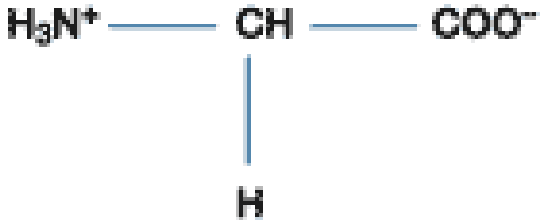
L-Glycine



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

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.

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

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.

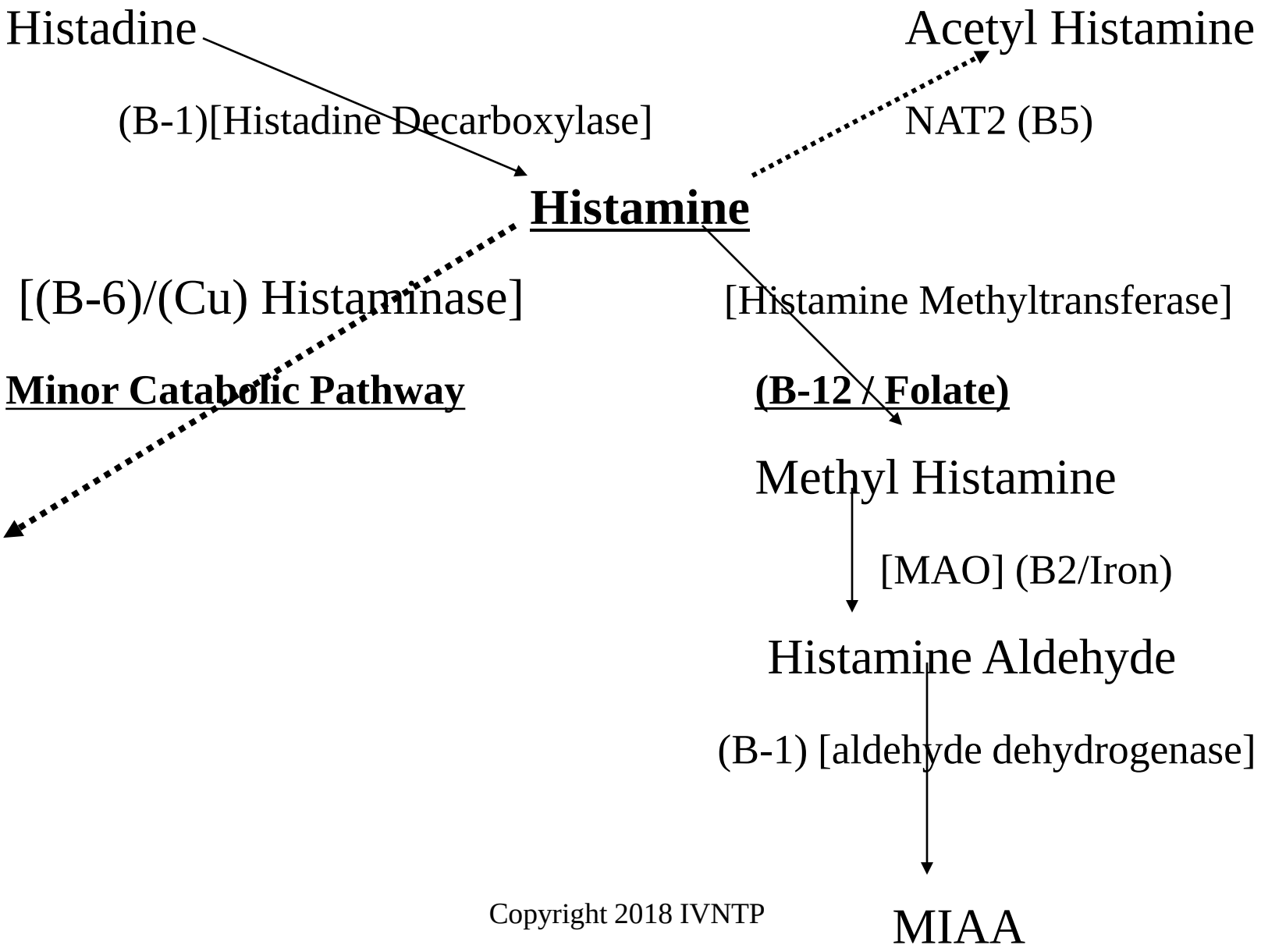
The central histamine system is involved in **many** central nervous system functions: **arousal; anxiety; activation of the sympathetic nervous system; the stress-related release of hormones from the pituitary and of central aminergic neurotransmitters; antinociception; water retention and suppression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

PMID: 11164999 [PubMed - indexed for MEDLINE]

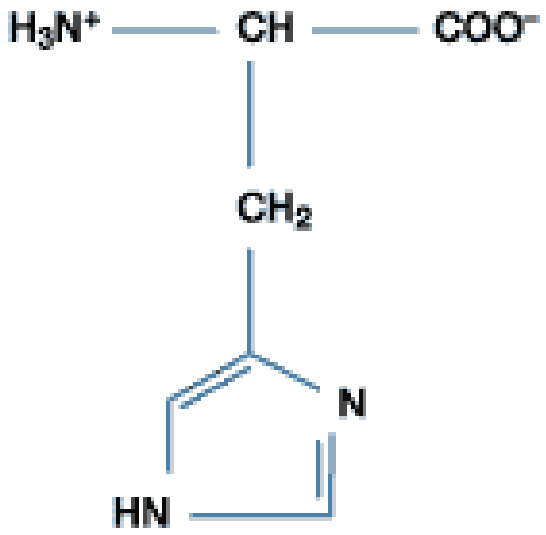
L-Histidine as Histamine Precursor

- 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

Histamine Metabolism



L-Histidine



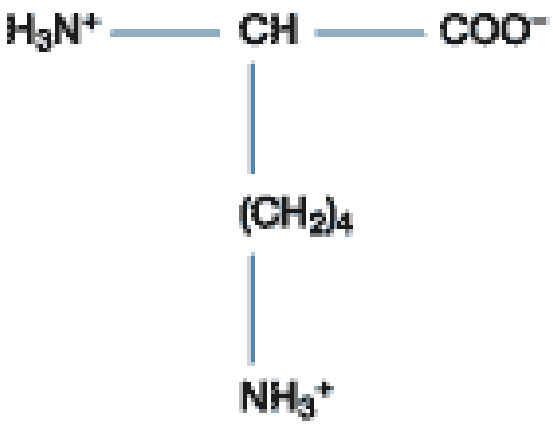
L-Lysine

- 50 mg/ml
- Metabolized by B2, B3
- Iron and ascorbate required to incorporate into collagen
- 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.)

L-Lysine

- Supports enzyme action of collagen development, inhibits breakdown and metastases. M.Rath MD

L-Lysine



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)

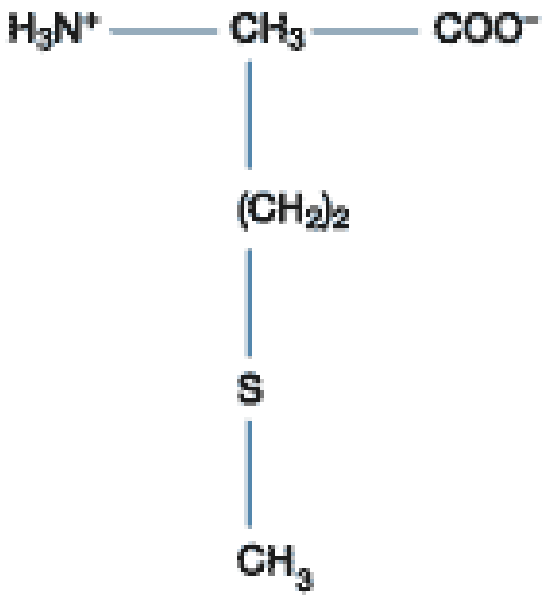
L-Methionine

- 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
- Depression – S-Adenosyl L-Methionine (SAMe) is synthesized in the body after supplementation of methionine
  - Study found IM injection of 45 mg SAMe had beneficial effect on depression, suicidal tendency and brain performance

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

L-Methionine : Important methyl donor



L-Proline

- 50 mg/ml
- Collagen is major Proline reservoir
- Vitamin C deficiency leads to increased Proline loss in urine
- It is useful in wound healing, injuries to ligaments, tendons
- Contraindicated in depression, seizures

L-Proline

- Enhances lysine ability to inhibit metastases
  - Greater effect when epigallocatechin gallate (polyphenol fraction of green tea EGCG) M. Rath MD
- “not wise” to use in cancer patients
  - Increases production of carcinogenic N-nitrosoproline in smokers

A Case for using arginine and proline post trauma/surgery

This paper demonstrated that nitric oxide (NO) derived from arginine and hydroxyproline derived from proline are both important for better healing from injury.

Organization of collagen bundles during tendon healing in rats treated with L-NAME.
Tomiosso, TC, et.al.
Cell Tissue Res. 2009 Aug;337(2):235-42. Epub 2009 Jun 9.
The Achilles tendon can support high tension forces and may experience lesions. The damaged tissue does not regenerate completely, with the organization and mechanical properties of the repaired tendon being inferior to those of a healthy tendon. Nitric oxide (NO) plays an important role in wound repair. We have examined the structural reorganization and repair in Achilles tendon after injury in rats treated with the NO synthase inhibitor L-NAME. The right Achilles tendon of male Wistar rats was partially transected. One group of rats was treated with L-NAME (~300 mg/kg per day, given in drinking water) for 4 days prior to tendon sectioning and throughout the post-operative period. Control rats received water without L-NAME. The tendons were excised at 7, 14, and 21 days post-injury and used to quantify hydroxyproline and for mechanical tests. Tendons were also processed for histomorphological analysis by polarized light microscopy, which showed that the collagen fibers were disorganized by day 7 in non-treated and L-NAME-treated rats. In non-treated rats, the organization of the extracellular matrix was more homogeneous by days 14 and 21 compared with day 7, although this homogeneity was less than that in normal tendon. In contrast, in injured tendons from L-NAME-treated rats, the collagen fibers were still disorganized on day 21. Tendons from treated rats had more hydroxyproline but lower mechanical properties compared with those from non-treated rats. Thus, NO modulates tendon healing, with a reduction in NO biosynthesis delaying reorganization of the extracellular matrix, especially collagen.

Amino acids & Hyaluronic acid in tissue healing

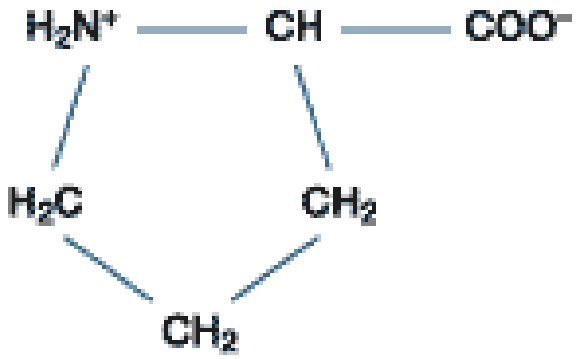
Enhancement of fibroblast proliferation, collagen biosynthesis and production of growth factors as a result of combining sodium hyaluronate and aminoacids.

Mariggio, MA, et. al.

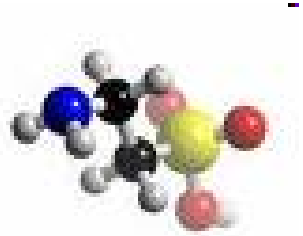
Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):485-92.

Fibroblasts play a key role in tissue healing by producing the majority of extracellular matrix components, favouring granulation tissue formation, and stimulating re-epithelialization. Hyaluronan is a component of ECM and its anti-inflammatory effects and properties in enhancing wound closure are well known. In this study, we examined the effects of Aminogam gel, a new pharmacological preparation suggested to improve wound healing, composed of hyaluronic acid, proline, lysine, glycine and leucine, on human fibroblasts. Results show that fibroblasts treated with hyaluronic acid plus aminoacid solution increased their proliferative activity, collagen I and III, and fibronectin synthesis. Moreover, HA plus aminoacid solution increased the expression of transforming growth factor beta, connective tissue growth factor, interleukin-6 and -8, assayed by RT-PCR. These results suggested that Aminogam gel, involved in several stages of wound healing, as fibroblast proliferation, granulation tissue formation, ECM component deposition, and production of cytokines, may be a useful device to favour and accelerate wound closure.

L-Proline



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

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

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

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

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

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

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

Taurine: Research Overview

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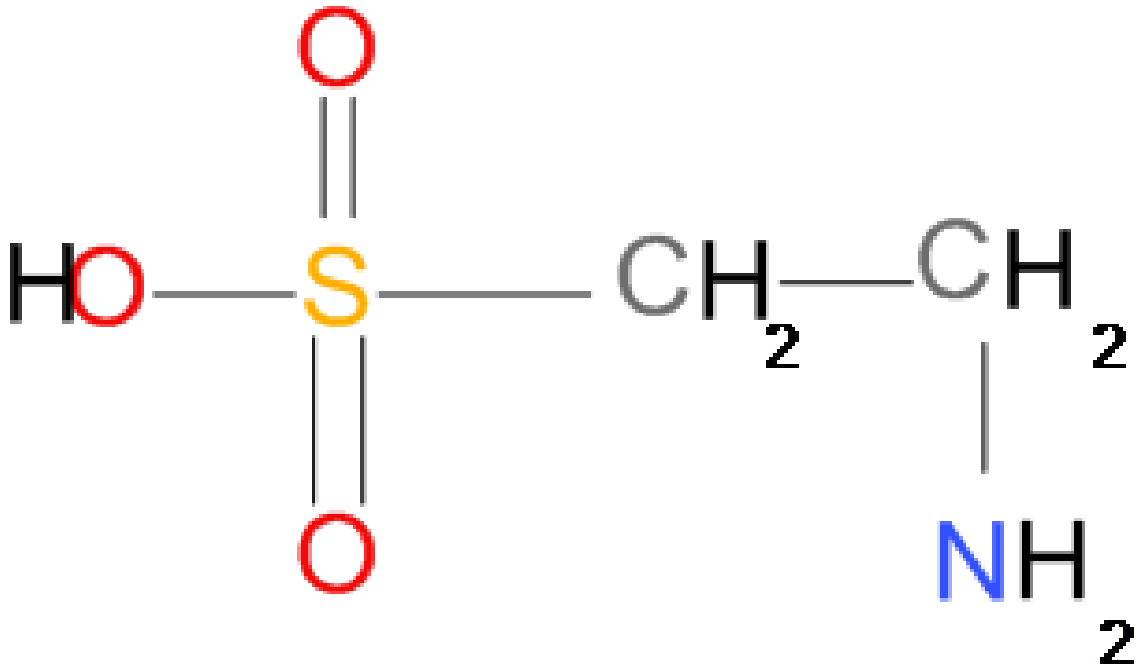
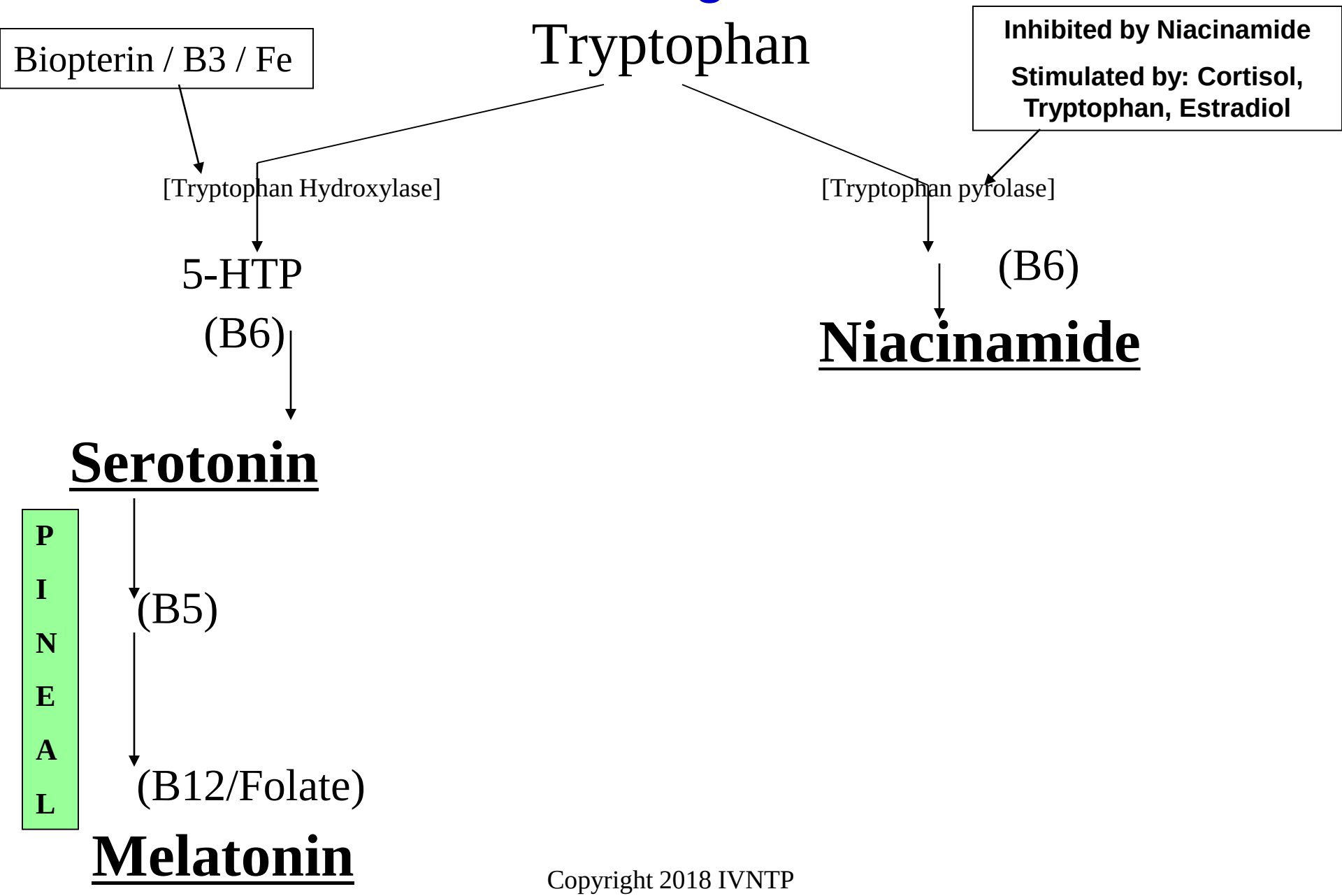
Taurine



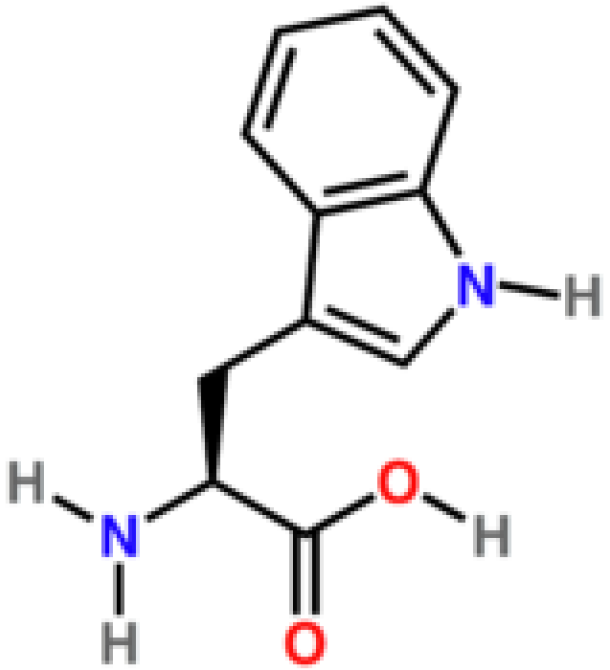
Tryptophan

- 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

Serotonin Augmentation



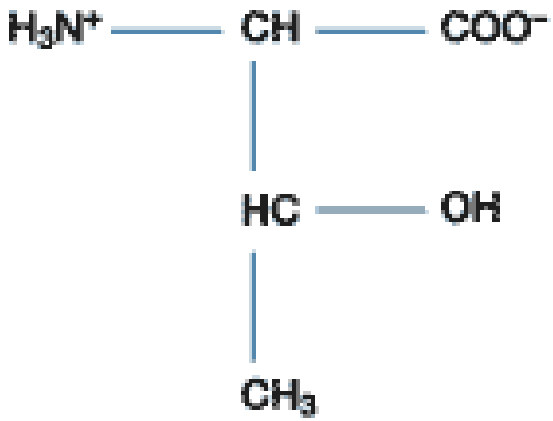
Tryptophan



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

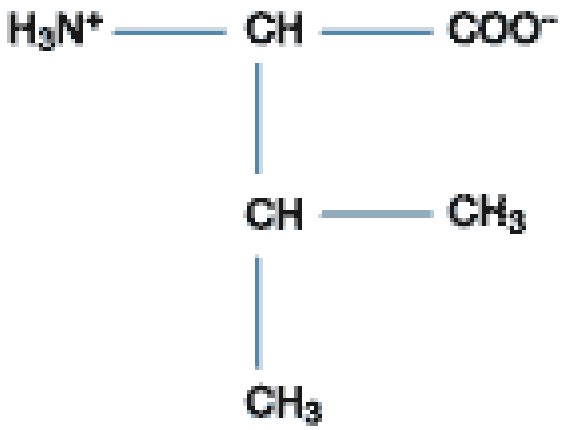
L-Threonine



L-Valine

- 50 mg/ml
- Essential branched chain AA
- Cofactors for metabolism: B1, B2, B6, Mg, Cu, Glutamic acid
- Useful in treatment of liver disease (5 mg/kg), muscle building (5-10 g daily, oral dose)

L-Valine



The Bottom Line
Practicalities

- Freamine III is good to replace those individual AA not used frequently in your clinic
- Essentials to have on hand
  - Glutathione
  - Taurine
- Less essential but useful: Proline, Carnitine, NAC
- Purchase others for specific patient applications

Reference

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