Arginine as an Example of a Conditionally Essential Nutrient: Sickle Cell Disease & Trauma

Claudia R. Morris MD, FAAP

Examining Special Nutritional Requirements in Disease States, A Workshop

April 1, 2018
When does a physiological state result in a unique nutritional requirement?

- Essential amino acids (AA) → diet dependent
- Non-essential AA → *de novo* synthesis
- *Conditionally essential* → Non-essential AA that become indispensable under stress/critical illness
  - *Capacity of endogenous synthesis surpassed*
Conditions Linked to Acquired Arginine (Arg) Deficiencies

- trauma
- critical illness
- burns
- surgery
- pregnancy
- sepsis
- pulmonary hypertension, asthma
- hemolysis: *sickle cell disease*, thalassemia, malaria…
What is Arginine?

- Conditionally essential amino acid in dietary protein
- Synthesized through the intestinal-renal axis
- Becomes essential in stress, catabolic states & hemolysis: trauma, sepsis, burns, sickle cell disease, malaria, PH, ?? asthma
- Found naturally in diet: meat, dairy, seafood, nuts, seeds +
- Normal adult ingestion: 2-7 grams/day
- Nutritional supplement with low toxicity
- **Obligate substrate for NO production**
Regulates vasodilator tone

Inhibits platelet aggregation and attachment

Immune response, anti-inflammatory

Signaling molecule

Inactivates superoxide: Diffusion-limited antioxidant
What Is Arginase?

- Important enzyme in urea cycle
- 2 mammalian isoforms
  - Arginase I (cytosolic)
  - Arginase II (mitochondrial)
- Present in most cell types, including RBCs and MDSC
- Induced by cytokines
- Competes with NOS for common substrate → Arginine
Ornithine

Arginase

- Arginine $\rightarrow$ Ornithine + Urea
- Orn & Arg use same cationic amino acid transporter (CAT-1 and CAT-2)
- ↑ Orn competitively inhibits cellular uptake of Arg
  - Limits Arg bioavailability
  - Translates to ↓ NO bioavailability
HEMOLYSIS
TRAUMA
Inflammation/cytokines
Liver damage
Genetic Polymorphisms

Glutamine → Citrulline → Kidney → ARGinine

Inflammatory cytokines → ↑NOS → ↓NO

↑NO CONSUMPTION:
- HEMOLYSIS: Cell free Hb
- Uncoupled NOS
  - ↑ADMA
- Superoxide → RNOS

Substrate Competition → ↑Arginase → ↑Ornithine

↑Arginase → ↑Ornithine → ↑Polyamines → Vascular smooth muscle proliferation
Airway remodeling

↑Polyamines

↑Proline → Collagen production/deposition
Lung fibrosis
Airway remodeling
Amino Acid Deficiencies

• Drop in any AA ≠ clinically significant deficiency
• For a nutritional deficiency to be present:
  ➢ Biological processes dependent on nutrient compromised
  ➢ Compromise leads to abnormal physiologic response causative of poor outcomes
  ➢ Poor outcomes reversed by amino acid replacement

  o **SCD**: model for distinctive nutritional requirement that arise from a chronic disease
  o **Trauma**: model for distinctive nutritional requirement in acute illness
What Is Sickle Cell Disease?

- An inherited disease of red blood cells
- Affects hemoglobin
- Hb Polymerization leads to cascade of effects ↓↓ blood flow
- Tissue hypoxia causes acute and chronic damage

- 8% AA carriers of Hb-S (trait)
- 1/400 AA, > 100,000 with SCD in USA, millions worldwide
- > 75,000 admits; annual cost > $470 million
Why Do Cells Sickle?

- Substitution of valine for glutamic acid in Hb molecule
- Polymerization of sickle Hb under the stress or deoxygenation
Cell Disease (SCD):  
*A Model for Vasculopathy & Endothelial Dysfunction*

An inherited red blood cell disease: hemolytic anemia

- Hemolysis
- Inflammation
- Nitric Oxide depletion
- Arginine depletion
Mechanisms of Vasculopathy & Endothelial Dysfunction
Renal Insufficiency
Arginine Insufficiency & Elevated Arginase in Sickle Cell Disease

(Morris et al, JAMA 2005)
Arginine-to-Ornithine Ratio

(Morris et al, JAMA 2005)
Arginine Therapy

Pulmonary systolic pressure (mmHg)

Changes in PASP before and after Arg

Results: ↓15.4 % in PASP

Morris et al. AJRCCM 2003
Dysregulated Arg Metabolism in Thalassemia

(Morris et al. Ann NY Acad Sci 2005)
Dysregulated Arg Metabolism in Thalassemia

(Morris et al, Brit J Haematol, 2015)
Survival Proportions

Low Global Arg Bioavailability $\uparrow$ Risk of Death

**Arg/Orn**

- High Arg/Orn
- Medium Arg/Orn
- Low Arg/Orn

**Arg/[Orn+Cit]**

- High Arg/(Orn+Cit)
- Medium Arg/(Orn+Cit)
- Low Arg/(Orn+Cit)

Follow-Up Time (Months)

Survival

**RR: 2.2 [1.0, 4.9], $p=0.02$**

**RR: 3.6 [1.5, 8.3], $p<0.001$**

(Morris et al, JAMA 2005)
Reduced GABR is Associated with Increased Incidence of MACE

MACE = Major Adverse Cardiovascular Events for n=991 patients (includes death, myocardial infarction, stroke)

JACC 53:2061-7 (2009)
How does a disease state impact nutrient metabolism & nutritional status?

Mechanisms of Arginine Dysregulation

- Hemolysis
- ↑ Arginase Activity
- Inflammation
- Myeloid-derived Suppressor Cells (MDSC)
- Intracellular Transport Abnormalities
- Renal Dysfunction
- Endogenous NOS inhibitors (ADMA)
- Uncoupled NOS
Arginine Deficiency Syndromes

Whether hepatic, immune or from hemolyzed RBC during hemolysis or transfusion, clinical consequences of excess extracellular arginase similar regardless of cellular origin

- **Endothelial dysfunction** – *sickle cell disease (SCD)*
- **T-cell dysfunction** – *trauma*
T-cell Dysfunction

- Linked to acute nutritional deficiencies in trauma patients
- Arginine essential for naïve T-cell activation
- T-cells sensitive to arginine depletion
  - *T-cell proliferation blunted*
  - *interferon-γ & IL-2 production inhibited*
  - *T-lymphocyte mediated cytotoxicity & memory responses nearly completely abolished*
- Provision of arginine to culture media restores T-lymphocyte function
Arginine Deficiency in Trauma

- > 15 million injuries/year in USA
- ~10% trauma pts develop wound infections
- Infection risk ↑ 30% for pts in ICU > 48 hrs
- Infections: Leading cause late organ failure; 10% of trauma deaths

- ↓↓ plasma Arg in trauma (in minutes to hours), low for ≥ 1 wk
- ↑ plasma arginase activity
- MDSC express arginase 1 after trauma
  - depletes Arginine → T-cell dysfunction
  - ↑↑ susceptibility to infection after injury

Strategies aimed at infection prevention after trauma should result in significant ↓ in morbidity, mortality and cost
How can nutritional interventions improve patient outcomes?

What is the Therapeutic Potential of L-Arginine?

SCD
- Improves perfusion, ↑ glutathione, ↓ inflammation, lung injury, microvascular vaso-occlusion and mortality in SCD mice
- ↓ Pulmonary hypertension in SCD; improved priapism
- Positive human phase 2 trials: leg ulcers; vaso-occlusive pain

Trauma
- Enhances wound healing after trauma & hemorrhagic shock
- Immunonutrition improves immune responses/T-cell function
- High Arg formulas: ↓ infection complications in critically ill
- Benefits greatest in surgical patients
- Evidence of harm in sepsis; following acute MI

Methodologic weaknesses in most studies; Paucity of data in children
Immunonutrition in Critically ill Children

- 2009 Cochrane review found insufficient evidence for or against nutritional support in children during 1st week of critical illness, mainly because appropriate studies not performed
- RCT Arg/Gln fortified formula in 40 vented children with TBI
  - No difference in mortality vs. standard formula (underpowered)
  - Positive nitrogen balance by day 5 in 69% vs. 31% (p<0.05)
  - Critically ill pediatric pts (n=1245): decreased 60-day mortality with adequate protein intake: <20%, intake ≥ 60% of prescribed goal associated with OR of 0.14 (95% CI:0.04-0.52, p=0.003) for 60-day mortality (enteral protein delivery, not overall calories)
  - Achieving delivery of >60% protein goals associated with ↓ mortality in mechanically ventilated children

Enteral protein delivery is a modifiable risk factor of mortality in dire need of a shift in current practice given the potential for improved outcomes
Therapeutic Strategies

- Arginine supplementation
- Arginine precursors: citrulline, glutamine
- Combination therapy
- Immunonutrition: targeted enteral formulas
  - Nutritional deficiencies rarely occur in isolation

Ideal formulas for trauma, critical illness, pediatrics do not yet exist. More research is needed.
Key Points

- Arg: conditionally essential AA → essential under conditions of stress & catabolic states - capacity of endogenous AA synthesis is exceeded
  - Includes critical illness, trauma, hemolysis
- SCD & trauma represent arginine deficiency syndromes
  - Distinct nutritional requirements; may benefit from arginine replacement therapy
- At least 2 broad categories of arginine deficiency syndromes:
  - T-cell dysfunction
  - Endothelial dysfunction
- GABR: ?? novel biomarker of Arg deficiency; warrants further study
- Arg-fortified immunonutrition: Treatment for acquired Arg deficiencies
  - Further study needed to identify sub-populations who will benefit while minimizing potential adverse events

Nutrition is Medicine!
Questions?

Emory University School of Medicine