Metabolic Response to Trauma: Can Specific Nutrients or agents Improve Outcome?
“Many types of injury produce a similar inflammation”

Hunter J (1794) A treatise on blood, inflammation and gunshot wounds

“The metabolic response to stress”
Heterogeneous Response: Factors influencing the metabolic response

- Age
- Gender
- Genetic influences
  - Gene SN polymorphisms
- Body habitus (obesity)
- Type and duration of stress
- Diet and nutritional state
  - Current “western diet”
- Route of feeding
- Lifestyle
Metabolic changes ICU setting

<table>
<thead>
<tr>
<th></th>
<th>Starvation</th>
<th>Trauma</th>
<th>Cancer Cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic rate</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Protein and muscle breakdown</td>
<td>↓</td>
<td>↑↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Glucose turnover</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Fat mobilization</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Liver synthetic activity</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Acute phase protein synthesis</td>
<td>↓</td>
<td>↑↑</td>
<td>↓↑</td>
</tr>
</tbody>
</table>
Metabolic Response: Starvation versus Stress

• Starvation
  - Preserve LBM
  - ↓ energy expenditure
  - ↑ alternate fuels
    - Adipose store primarily

• Hypermetabolism
  - Poor mobilization of alternate fuels
  - Catabolism LBM
    - Serve as gluconeogenic substrate
  - Impaired organ function
  - ↓ immune/repair function
What Endogenous Fuel is Available?

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Fuel</th>
<th>Energy (Kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>TG</td>
<td>140,000</td>
</tr>
<tr>
<td>Muscle</td>
<td>Protein</td>
<td>24,000</td>
</tr>
<tr>
<td></td>
<td>Glycogen</td>
<td>2,000</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>3,000</td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogen</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>500</td>
</tr>
</tbody>
</table>

Circulating Fuels

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Kcal/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free fatty acids</td>
<td>9.31</td>
</tr>
<tr>
<td>β-hydroxybutyrate</td>
<td>4.69</td>
</tr>
<tr>
<td>Glucose</td>
<td>3.72</td>
</tr>
<tr>
<td>Acetate</td>
<td>3.48</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>3.17</td>
</tr>
</tbody>
</table>

Cahill GF: Starvation in Man. NEJM 282:668.1970
Metabolic Response to Stress: Mobilization of Fuels

Muscle is metabolized as gluconeogenic substrate to supply the brain, kidney, tumor etc
Standard Energy and Protein is Not Enough! Acute Skeletal Muscle Wasting in Critical Illness

- Prospective study of 63 critically ill patients
  - Expected stay > 7 days, Vent > 48 hours
  - 3 methods to determine muscle loss
    - Serial US
    - Histology
    - Biochemistry – DNA/Protein ration and fractional synthesis breakdown rates. (Leucine uptake etc)

- Conclusions
  - CSA of Rectus Femoris decrease 10% US
  - CSA of muscle fibers decrease 17.5%
  - Ratio protein to DNA decrease 29%
  - >40% of patients showed myofiber necrosis
  - **Muscle wasting occurred in the face of adequate nutrition**
    - Significant inflammatory changes in muscle noted

Puthucheary ZA et al JAMA 2013
Loss of Lean Body Mass and Outcome?

“Sequential Metabolic Changes Following Induction of SIRS in Patients with Severe Sepsis or Major Blunt Trauma” 1

- ↑ over REE peaks 4-5 days
- Continues 9-12 days, still ↑ 21 days
- 16% TBP lost first 21 days (67% from muscle)
- ? Mechanism, not just pro-inflammatory cytokines

Loss of lean body mass clinical consequences 2

10% impaired Immune function
20% impaired wound and rehabilitation
30% pneumonia and pressure ulcers
40% Death (pneumonia)

1) Plank. WJS 24:630-638, 2000
2) Martindale R Physiologic Basis of Surgery 2008
The Perfect Storm:
Increase energy expenditure is not the only issue?

- Physical muscle unloading
  - Physical inactivity
  - Bed rest
  - Immobility

- Multiple models have evaluated
  - Bed rest
  - Space flight
  - Unilateral limb suspension
  - Joint immobility

- Decrease muscle protein synthesis ------- atrophy
  - Multiple mechanisms
    » Ca++ dependent proteolysis
    » ATP dependent proteolysis
    » Lysosomal proteolysis
    » All mxs leading to oxidative stress increase free radicals

Clinical example:
- TBI
- Spinal cord
- Casting

Burd NA J Appl Physiol 2011
Reaching balance!

- Balance between synthesis and degradation
- Muscle atrophy in ICU:
  - 3-4% per day of muscle fiber cross sectional area (1)
- Catabolic effects are prolonged 3 to 9 months
  - Burns have greatest duration of catabolism
  - Spinal cord injury and TBI prolonged catabolism
- Why:
  - Norepi increased 2 to 10 fold
  - Pro-inflammatory cytokines IL-1, directly inhibits GH axis, relative insulin resistance
  - Decrease availability of AA substrates
    - Shunted to gluconeogenesis

1. Jespersen PLOS 2011
More questions than answers

• Nutritional deficit in ICU associated with adverse outcomes –  
  No question !

• Prolonged starvation leads to death –  
  No question !

• Does “artificial” nutrition delivered during critical illness improve the outcome –  
  the question ?
Can Focused Timely Nutrition Attenuate the Catabolic Response?

- Early enteral feeding
  - Multiple mechanisms

- Decrease insulin resistance

- Supply protein and energy to meet increased demand
  - Specific amino acids to minimize protein loss
    - Glutamine, Arginine, Threonine
  - Fish Oils
  - Antioxidants
“Early Post Op Enteral Feeding Improves Whole Body Protein Kinetics in Upper GI Cancer”

- PRCT n=29
- iv fluids (SOC) vs early enteral feeding POD # 1
- labeled Leucine, REE
- Conclusion: early enteral feeding decreases net protein catabolism

Enteral Feeding Attenuates Hyperdynamic Response to Endotoxemia

- **Study Design:** PDBCT trial N=18 healthy volunteers
  - Study done to evaluate influence of EN on endotoxin induced metabolic response
  - 3 groups (nutrient infusion via FT 1 hr before and 6 hr after
    - Placebo – fasted (n=6)
    - Fed control – received standard 1 kcal/cc formula (n=6)
    - Experimental - High protein/high fat 1 kcal/cc formula (n=6)
  - All given hydration then E.coli endotoxin bolus (2ng/kg)
  - Multiple metabolic parameters monitored
    - Cytokines, vitals, CCK levels, etc

- **Results:** enteral fed group with experimental formula
  - Decrease in IL-6, TNF α, IL-1RA (p <0.05)
  - Increase IL-10 (p<0.0001)
  - Decrease iFABP (marker of mucosal damage) (p<0.05)

Lubbers T et al CCM 2013
The Gut as Regulator of Inflammatory Response

Gut disuse: inflammation

Feed the Gut: inflammation
So many Mechanisms?

- Brush border integrity to minimize bacterial or bacterial end products from entering the portal vein
- Feedback loops via vagus nerve
- Lymphocyte class differentiation
  - Th1 to Th2 shift from naïve T cells
- Anti-inflammatory action of the specific nutrients
  - Fish oils
  - Glutamine
  - Antioxidants
- Glycemic influence on mitochondria
- Enhancing blood flow to poorly perfused tissues
  - Exercise of muscle now shown to be anti-inflammatory
Can specific fuel delivery attenuate or modulate the metabolic response for better clinical disease outcomes?
Fuel utilization during metabolic stress!

**Calories** 20-35 Kcal / Kg / D

**Carbohydrates** 3-6 mg / kg / min
250 – 350 gm / D

**Protein** 1.25 – 2.0 gm / Kg / D
80 – 150 gm / D

**Lipids** 10 – 30 % of total calories
Variable based on source

**Vitamins / minerals / trace minerals**
Variable dependent on oxidant load
Branched Chain Amino Acids: are they just of historic interest only or the future of protein metabolism in stress and sepsis?

- **Leucine**, Isoleucine and Valine

- Goldberg et al (1972) studies BCAA serve a regulatory role

- Animal studies summary: BCAA favor nitrogen economy
  - Reduction in protein loss at the muscle
  - Possible improvement in visceral protein synthesis

- Human studies:
  - Early studies flawed (hypocaloric, poor outcome measures)
  - 2 RPCT\(^{(1,2)}\)
    - Improved nitrogen balance, 3MH, visceral protein
    - One of two reported improved mortality

- **Bottom Line**: jury still out, trends towards benefit
  - New data on ubiquitin, HSP

1. Jimenez J JPEN 1991,
2. Garcia-de-Lorenzo CCM 1997
Lipid Choices in Metabolic Stress: Does lipid choice alter the metabolic response?

- **Enteral vs Parenteral Lipids**
  - Enteral superior to parenteral
    - USA v Rest of World
  - Significantly more options enterally

- **Lipid Substrate**
  - **SCFA**
    - acetate, butyrate, propionate
    - Increase utilization
  - **MCT**
    - 6 to 12 carbons
    - Dual absorption via portal and lymphatics
    - no acyl-carnitine carrier required for MCT to enter inner mitochondria membrane for $\beta$ oxidation
    - Utilization MCT > LCT in times of metabolic stress
  - **LCT**
    - Omega 6
    - Omega 3
    - Utilization variable depending on Carnitine, oxygenation etc
EPA / DHA

Membrane Phospholipids

Membrane Fluidity

Eicosanoids

Signal transduction Pathways (NFkB)

ICAM 1
E-Selectin

Increase tissue perfusion

TLR4
Receptor binding

Resolvins
Protectins

Receptors
Enzymes

Cytokines

Increase tissue perfusion

Enhance diaphragm function

Increase vagal tone

Vagal tone

Enhance diaphragm function

Inflammation and Immunity
Resolvins

- Endogenous mediators generated from ω-3 PUFA’s that promote the active resolution of inflammation
- Each resolvin is a unique structure possessing precise stereochemistry that is essential for its biological activity
- Resolvins exert proresolving actions in physiologic (picomolar-nanomolar) dose ranges and have multiple cellular targets, including:
  - neutrophils, macrophages, dendritic cells,
  - vascular smooth muscle cells, and endothelial
- Primary mechanism of action of resolvins is to promote non-inflammatory efferocytosis (apoptotic cell removal)

• Zhang MJ et al Ann Rev Nutr 2012
Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects

Effects of fish oil on the neuro-endocrine responses to an endotoxin challenge in healthy volunteers

Burkhard Michaeli\textsuperscript{a}, Mette M. Berger\textsuperscript{a,*}, Jean-Pierre Revel\textsuperscript{y}, Luc Tappy\textsuperscript{b}, René Chioléro\textsuperscript{a}

Clinical Nutrition (2007) 26, 70–77
Arginine Supplementation

- Animal Models
  - Survival in sepsis
  - Survival in tumor bearing
  - Number and function of T cells
  - Delayed hypersensitivity
  - Allograft rejection
  - Macrophage phagocytic activity

- Human Studies
  - Improved wound healing
  - Net nitrogen retention during critical illness
  - Enhanced lymphocyte proliferative response to mitogens
    - 70 fold increase in arginine uptake with stimulation
  - Necessary for normal myeloid cell function
    - Macrophages, dendritic cells
    - ↓ Clinical infections
    - ↓ Postop length of stay
Metabolic Origin and Fate of Arginine In Critical Care / Surgery

- ADMA
- SDMA
- NMMA

Protein breakdown

Protein turnover yielding Arg

De novo
Syn and Citrulline recycle

Diet

Arginine

Arginase

NO + Citrulline

Urea
Polyamines
Proline
Glutamate

NOS

Creatine

Agmatine

Morris S 2009
Arginine in hemorrhagic shock

• Rodent model of 40% hemorrhagic shock
  – Sham, L-arg, L-arg with iNOS inhib, D-arg

• Results: Arginine supplementation
  • Increase arterial pressure
  • Decrease lactate
  • Improved small bowel histology
  • Increased survival

• Conclusion:
  • Arginine supplementation following shock improves perfusion globally
  • Regulation of iNOS or overriding the influence of ADMA appears to be the primary mechanism

Arora TK et al
J Trauma 2012
Arginine in Sepsis: Human Models

Luiking Y: Am J Clin Nutr 2009
- 10 patients septic – 7 critically ill – 16 healthy control
- Citrulline low sepsis, diminished de nova arginine synthesis
- No adverse effects of arginine

Vermuelen M: ESPEN 2009
- 24 patients with septic shock
- Higher Arg/ADMA levels increase CO

Kao D: Clinical Sci 2009
- 13 patients septic shock – 7 healthy controls
- Whole body NO synthesis in control same as sepsis
- Decreased plasma arginine in sepsis
- Inadequate de novo synthesis secondary to decrease citrulline production

Visser M: Br J Nutr 2012
- N=44 17 Cardiogenic shock, 27 septic shock
- Agr/ADMA is key to organ perfusion
- Increase ADMA or decrease Arg results in a decrease perfusion to organs and increase mortality

Gough MS: CCM 2011
- N=109 severe sepsis N=50 controls
- Declining Arg/ADMA ratio independently associated with mortality

Koch A J CC 2013
- ADMA levels on admission associated with mortality
A. Clinical Response

Early innate immunity

Pro-Inflammation

Anti-Inflammation

Fulminant death

Insult

Early

MOF

SIRS

PICS

CARS

Persistent Inflammation

Protein Catabolism/Cachexia

Indolent Death

Recovery

B. Individual Cell Response

Macrophage Activation

Macrophage Paralysis

TRegs

MDSCs

Dendritic Cells

T Effector Cell Number and Function

Persistent Inflammatory/immunosuppression Catabolism Syndrome (PICS)

Gentile L et al; J Trauma Acute Care Surg 2012

Slide courtesy of Fred Moore
Post op arginine deficiency alters T-cell function

- Arginine Deficiency
  - Rapidly develops following injury or surgery

- T-cell dysfunction
  - Anergy to recall antigens
  - Decrease T-cell receptor with loss of zeta chain
  - Decrease immunologic memory
  - Decrease production of interferon gamma

Zhu X et al Ann Surg 2013
A. Clinical Response

Insult → Early innate immunity → SIRS → Early MOF → Fulminant death → Persistent Inflammation → Protein Catabolism/Cachexia → Defects in Adaptive Immunity → Indolent Death

Pro-Inflammation → PICS

Anti-Inflammation

B. Individual Cell Response

Macrophage Activation → TRegs → MDSCs → Dendritic Cells → Macrophage Paralysis → T Effector Cell Number and Function

Courtesy of Fred Moore
Glutamine
(conditionally essential AA)

- Most abundant free amino acid
  - > 60% of free AA pool in muscle
- Interorgan nitrogen transfer
  - Purines, pyrimidine, nucleotides, amino sugars etc
- Acid Base balance
- Primary fuel for rapidly dividing cells
  - Enterocyte, lymphocytes
- Key substrate for gluconeogenesis
- Critical for synthesis of GSH, Arginine, glucosamine
- Decreases insulin resistance
- Regulator of Heat Shock Protein
Proposed mechanisms for glutamines influence within the cell

- **Tissue protection**
  - Heat shock protein
  - Anti-apoptotic effect
  - Fuel source for epithelial cells

- **Anti-inflammatory**
  - Attenuate NFkB
  - Enhanced PPAR activation
  - Attenuation of cytokine expression

- **Modulates immune function**
  - In-vivo and in-vitro
  - Ag presentation
  - Phagocytosis
  - Superoxide production

- **Preservation of tissue function in stress states**
  - Preserves ATP in sepsis and I/R
  - Preserves mitochondrial function
  - Favorable effect on apoptotic pathways

- **Antioxidant**
  - Enhanced GSH (MTX model)
  - Attenuates iNOS in sepsis and I/R
  - Reduction in oxidant stress

Wischmeyer, PE Curr Opin Clin Nutr Metab Care 2006
Is Glutamine Falling from Stardom?

Newer glutamine PRCT’s:

- Braga CRS 2009 (-)
- Scandinavian trial (2011) (+/-)
- Scottish Trial (SIGNET) (2011) (-)
- USA GLnD (NIH) Post-op Pts RCT (2013) (-)
- REDOX trial (2013) (-)

Why:

- Dosing ?
- Timing ?
- Delivered with other nutrients or as single agent ?
- Heterogeneity of population ?
  - If it work it appears to work better in higher APACHE and SOFA scores ?
REDOX trail now complete!

- Large Prospective Trial
  - >1200 patients
  - APACHE scores 26
  - Randomized w/in 18 hours of admission
  - Three groups:
    - Placebo
    - Antioxidants
    - Gln + antioxidants

Mortality

<table>
<thead>
<tr>
<th></th>
<th>AOX</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine</td>
<td>Yes</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>No</td>
<td>27.6%</td>
<td>24.5%</td>
<td></td>
</tr>
</tbody>
</table>

P=0.06

Highest risk: acute renal failure and MOF

Heyland D et al NEJM 2013
Meta-analysis antioxidant micronutrients in Critically Ill

- Literature included 1980 – 2011
- 21 RCT’s included

Results:
- Reduction in mortality ($p<.002$)
- Reduction in duration of mechanical ventilation ($p<.02$)
- Trends toward lower infections
- No overall effect on ICU or hospital length of stay
- Greatest influence in higher severity of illness
- > 500 micro gram of Se needed for maximum benefit

Manzanares W, Dhaliwal R et al Crit Care 2012
Caution with supplements! “Mother Nature may know best”

• “Large doses of antioxidants just prior to exercise prevent health-promoting effects of physical exercise in animal and human models”

• Bump in ROS in mitochondria appears to be needed to yield benefit

• Antioxidants prevent exercise induced mitochondrial biogenesis

• Blocking the rise blocks the long term beneficial effects.

• Gomez-Carbera MC Am J Physiol 2012
• Ristow M PNAS 2011
• Strobel NA Med Sci Ex Physiol 2011
Can the trauma team take some lessons from the body builders?

**Nutritional intake**
- Energy: 22 to 28 Kcal/kg/day
- Protein (2.0gm/Kg/D)
- CHO 300gm/day
- Lipid 0.7 gm/kg/d

**Timing of protein.**
- Protein with muscle resistance exercise

**Anabolic agents**
- Testosterone
- Beta blockers
- Insulin
- Growth hormone
- Grehlin
- Leucine, glutamine, fish oils
- Carnitine, creatine

**Nutritional Intake**
- Energy 30 to 40 Kcal/Kg/Day
- Protein 2.5 to 3.0 gm/kg/D
- CHO ????
- Lipid ????

**Timing of protein – immediately before resistance exercise**

**Anabolic agents**
- Testosterone - some to most
- Growth hormone – Few
- Leucine – most
- Glutamine – some
- Carnitine – Most
- Creatine – many
Potential Anabolic or Anti-Catabolic Agents in the ICU:

- **Pharmaceutical agents (non-hormonal)**
  - β-blockers
  - Statins
    - Pleomorphic influences
  - mTOR regulating agents of protein synthesis
    - Regulation of nutrients, growth factors, stress signals
    - Integrates input from AA, growth factors, intracellular clues to make for break muscle protein

- **Pharmaceutical agents (hormonal agents)**
  - Insulin
  - Growth hormone – IGF-1 Axis
    - IGF-BP’s
  - GLP-2
  - Anabolic steroids
  - Ghrelin

- **Nutrients**
  - Lipids – Fish oils
  - Amino acids – leucine, glutamine, arginine, other

mTOR = mammalian target of rapamycin
Muscle protein synthesis primarily determines changes in protein balance in healthy humans

Can resistance exercise overcome the anabolic resistance associated with immobilization and surgery?

- Exercise with appropriate AA and nutrition shown to be anabolic in multiple models
  - Burn (Wolfe 1990’s)
  - Cancer (Biolo 2010)

- Resistance exercise:
  - Increases nutritive blood flow to muscle (decreases precapillary shunting)
  - Anti-inflammatory
  - Lowers insulin resistance
  - Increase nutrient uptake in multiple tissue beds
  - Possibly decrease myofiber necrosis

  - Puthucheary ZA JAMA 2013
New approaches to protecting lean body mass ICU and post-op

- **Pohlman MC et al CCM 2010**
  - N=122 pts exercise program
  - Conclusion: Safe

- **Burtin, C et al CCM 2010**
  - N=90
  - Conclusion: enhanced recovery
    – 6 minute walk, muscle function, safe

- **Schweickert WD et al Lancet 2009**
  - RCT N=104 pts with PT/OT
  - 59 vs 35% left hospital functional status

- **Morris P et al CCM 2008**
  - RCT N=330 pts
    – OOB 5 vs 11.4 days
    – ICU stay 5.5 vs 6.9 days
    – Hospital stay 11.2 vs 14.5 days
Controversies continue

- Timing
- What to feed
- How much to feed
- Is all trauma cc the same
  - Sepsis
Potential Anabolic or Anti-Catabolic Agents in the ICU:

• **Pharmaceutical agents** (non-hormonal)
  - β-blockers
  - Statins
    - Pleomorphic influences
  - mTOR regulating agents

• **Pharmaceutical agents** (hormonal agents)
  - Insulin
  - Growth hormone – IGF-1 Axis
    - IGF-BP’s
  - GLP-2
  - Anabolic steroids

• **Nutrients**
  - Lipids – Fish oils
  - Amino acids – leucine, glutamine, arginine, other
Pharmaceutical agents

- Reported benefits supported by RCT’s
  - Wound healing
  - Protein synthesis
  - Immune function

- No major consistency showing benefits?
  - Heterogeneous populations
  - Variability of models
  - Inconsistent dosing
Beta Blockers (Propranolol)

- Propranolol
  - Reduced thermogenesis
  - Reduced marked tachycardia
  - Reduced energy expenditure
  - Prevents peripheral lipolysis
  - Decreases fatty infiltration of liver
  - Helps maintain LBM (stable isotope studies)
    - Mechanism unclear – increased protein synthesis in face of persistent protein catabolism and reduced lipolysis
    - Most of data from burn literature

Gauglitz GG et al Curr Opin Clin Nutr Met Care 2011
**Reversal of catabolism by β blockade after severe burns**

**Summary:**
Does well in very selective cases

---

**Average Heart Rate**

- **Treatment Days:** -10, 2, 4, 6, 8, 10, 12, 14, 28
- **Heart Rate:** 100, 120, 140, 160, 180

- **Control, N=12**
- **Propranolol, N=13**

Data presented as mean±SEM

* p<0.05

**Resting Energy Expenditure**

- **2 Week Treatment Course**
- **% Δ**:
  - Control
  - Propranolol

Data presented as mean±SEM

* p<0.05

**Lean Body Mass at Discharge**

- **%**:
  - Control
  - Propranolol

Data presented as mean±SEM

* p=0.01

---

Statins in the Perioperative Period

• Evidence for statins beyond the lipid lowering effects (pleomorphic effects)
  – Decrease cardiac arrhythmias
  – Anti-inflammatory properties
  – Decrease sepsis mortality (human and animal)

Multiple mechanisms involved;
  HMG-coA reductase
  Nitric oxide regulation via eNOS and iNOS
  Changes in TLR4 receptor expression
  others

Fauchier L JACC 2008
Brookes ZLS Br J Anes 2009
Stimulation of Muscle Protein Synthesis by Long-Term Insulin Infusion in Severely Burned Patients

Effect of Insulin Infusion on Net Protein Balance Across the Leg

- increase synthesis or decrease breakdown

Yoichi Sakurai, MD, PhD Ann Surg 1995
Protection of hepatocyte mitochondrial ultrastucture and function by strict glucose control with insulin in critically ill patients

Study design:
- 36 critically ill patients +/- strict glycemic control
- Enzyme activities respiratory-chain and oxidative-stress sensitive GAPDH muscle and liver
- Subset had mitochondrial EM

Findings:
- Hypertrophic mitochondria with abn cristae with decreased matrix electron density in control
- No difference in muscle between groups

Conclusion:
- Strict glycemic control prevented or reduced structural and functional abnormalities of hepatocyte mitochondria

Vanhorebeek I, De Vos R, Mesotten D et al
Lancet 2005;365:53-59
“Intensive Insulin Treatment in Critically Ill Trauma Patients Normalizes Glucose by Reducing Endogenous Glucose Production”

- Metabolic tracer study to evaluate WGD and EGP
- N=6 trauma patients (ISS > 15), 6 nl controls
- Tight glucose control with insulin
- EGP 30% greater in trauma
- Conclusion:
  - Intensive insulin treatment decreases EGP
  - Indirectly protecting LBM from being the substrate for glucose production

Thorell A et al JCEM 2004
Growth Hormone / IGF-1 / IGFBP-3 Axis

- **hrGH:**
  - nl release from ant pit is pulsatile in fasting, sleep, exercise, stress
  - Gh both lipolytic and anabolic
  - Improves wt gain, lean body mass, bone mineral content and cardiac function
    - Multiple early studies (0.2mg/kg/d)
    - Increased serum concentration of secondary mediators (IGF-1 and IGFBP-3)

- **IGF-1 and IGFBP-3**
  - Improvement in protein metabolism in catabolic patients
  - Improved gut mucosa integrity
  - Improved hepatic acute phase response
  - Less hyperglycemia than rhGH

- **Consistency of outcome between studies a problem**
  - +/- burns, no consistent benefit in adults, may be harmful
What stopped the rhGH rage?

- Takala J NEJM 1999
- Two RPMCDBPC trials (mixed surg – med ICU’s)
  - 247 pts in Finland
  - 285 pts from 8 EU countries
  - 5-7 days in the ICU (expected 10 days)
  - 0.1 mg/kg/d while in the ICU or 21 days
- Conclusions:
  - Hospital Mortality and days on Ventilator increased
    » 39 vs 20 % Finnish ; 44 vs 18 % in EU
- Etiology:
  - Most death from sepsis
  - Fluid retention, increase hyperglycemia, increase insulin requirements, decrease mobilization of glutamine from muscle, etc etc
Newer trials

- Three recent trials (relatively small)
  - +/- IGF-1, Gln,
  - All starting within 24 to 72 of admission
  - NO mortality increase
  - No major clinical outcome reported
Ghrelin

- 28 AA isolated 1999 in stomach
- Stimulates GH, food intake, weight gain
- Increase CO, enhance GI motility, anti-inflammatory

Looks promising:
Enhancing GI function,
Appetite,
Anti-inflammatory,
Improvement in CO

Ueno H Ann NY Acad Sci 2010
Testosterone analogs

• Well studied in non-ICU populations
  • Hypogonadal and non-hypogonadal males
  • Increased fat free mass (LBM)
  • Increased strength

• Prohormones
  • Dehydroepiandrosterone, androstenedione, and androstenediol

• Side effects not consistent with use in the ICU
  • LFT abn
  • Hyperglycemia
  • Fluid shifts
Anabolic Effects of Oxandrolone After Severe Burn


Protein Synthetic Efficiency

Fraction of Available Amino Acids Accreted into Muscle

Baseline
Control

Fractional Synthetic Rate of Muscle Protein Synthesis

% per hour

Baseline
Control
Oxandrolone

Data presented as mean ± SEM
†p<0.05 vs. Baseline
*p<0.05 vs. Time Control
**Oxandrolone**

- **Testosterone analog**
  - Only 5% of testosterone virilizing androgenic effects
  - Improves protein catabolism via enhancing synthesis
  - Decreases weight loss
  - Increases donor site wound healing (burns)

- **RCT’s**
  - 10 mg BID oxandrolone decreased hospital stay burns (1)
  - 0.1mg/kg/BID decrease LOS, maintained LBM, improved hepatic protein synthesis in burns (2)
  - Trauma / Surgery No clinical benefit (3)

- **Oxandrolone ICU**
  - Appears safe
    - Minor LFT abn
  - Data consistent in burns only

---

(1) Wolf SE J Burn Care Res 2006
(2) Jeschke MG Ann Surg 2007
(3) Gervasio J Pharmacother 2000
Nutrients with anabolic potential

- Anabolic vs anti-catabolic
- Key: preventing loss of lean body tissue
- Fish oil
- Amino acids
  - Leucine, glutamine, arginine
- Antioxidants
Leucine

- Reported for over 30 yrs to increase muscle protein synthesis
  - 1975 in isolated diaphragm model
- Leucine, isoleucine and valine make up more than one third of muscle mass
- Intracellular leucine increases muscle protein synthesis, and appears to regulate synthesis
  - Thought to act via mTOR
- Most data in aging, exercise, caloric deprivation
- Not well studied in ICU populations
  - Conflicting results ? of additional protein vs leucine

Koopman R Br J Nutr 2008
Pasiakos SM Emerging Sci 2011
HMB (β hydroxy-β-methylbutyrate)

- HMB = metabolite of leucine in muscle
- Mechanism: proposed
  - 1) increases substrate for repair of the sarcolemma via changes in cholesterol biosynthesis
  - 2) changes in the ubiquitin proteasome, decrease in overall activity
  - 3) alteration in mTOR (mammalian target or rapamysin)

- Most studies in body builders
- Clinical studies in AIDS, Ca, bed rest, trauma
- ICU studies
  - Improved pulmonary function in COPD ICU patients
  - HMB / arg / gln: 72 trauma pts improved N balance

Kuhls DA J Trauma 2007
Creatine

- Glycine-arginine-methionine
- Mitochondrial antioxidant, energy storage (CP)
- 50% diet   50% endogenous production
- Popular with intense athletics (post exercise recovery)
- Strict vegetarian supplement studies: increase cognitive function in DBPCXT (highest quality medical study)
- Animal stroke model 3 wk supplement decrease infarct by 40%
- Great theory for use in PD to support mitochondria
- Multiple studies RPCDBT (DATATOP trial)
- NIH Phase 3(NINDS) >1700 pts, 52 med centers 5 -7 yrs
- NO specific designed ICU studies
  » Animal models variable
What is the optimal formula in severe metabolic stress?

• *NO* single formula or route of delivery meets the need in all stressed patients

• Decision should depend upon:
  – Severity of stress
    – i.e. severe sepsis, septic shock
    – Hemodynamics
    – Oxygenation
  – Pre-existing co-morbidities
  – Timing of delivery
  – Route of delivery
  – Tolerance - Functional capacity of GI tract remaining
    – PN and Enteral
General Considerations: The Metabolic Response to Stress

- **Nutrition Support:**
  - Early enteral feeding reduces hypermetabolic response
  - Quality of nutrition appears more critical than quantity
    - Avoid overfeeding
    - Moderate glycemic control preserves LBM (target 150mg/dl)
    - Liberal use of EPA / DHA (omega 3 derivatives)

- Well controlled trials now support pre-op “nutritional preparation” prior to major elective cases can attenuate the metabolic response

- Specific receptors (i.e. TLRs) function to initiate the innate immune and inflammatory response in a variety of shared signal pathways
  - It appears specific nutrient modulation may be able to partially modulate the responses i.e. fish oils
Future directions manipulating the metabolic response to stress

- Controls on inflammatory response
  - Mitochondria approach
  - Fish oils
- Anabolic agents
  - Drug targets; mTOR, Akt, FOXO
  - Anti-myostatin monoclonal antibody (NCT01505530)
  - Selective androgen modulators, myostatin inhibitors
- Targeting ubiquitin proteasome
- New maintenance and resuscitation fluids
  - Glutamine
  - Anti-oxidants
- New attention to gut microbe interaction
  - Probiotics
- Genotype specific nutrient delivery
- Gender differences
  - Female survival > than males sepsis / trauma ?
- PICS
mTOR signaling in sepsis: where does it go wrong?

• mTOR
  • Intracellular regulator of protein synthesis
  • Simultaneously phosphorylates substrates to enhance protein synthesis while inhibiting proteosomal and autophagic protein breakdown

• Sepsis
  • Inflammation normally increases protein degradation
  • Sepsis in addition decrease synthesis
    – Defect in translation – increase free ribosomes
  • mTOR does not respond to increase Leu in sepsis
  • Teleologically this makes since “in you are going to make it don’t break it” concept

Frost RA et al Physiology 2011