Acid-Base Regulation of Hepatic Glutamine Degradation

Renal AA Metabolism Plays a Key Role in Acid-Base Balance Regulation via Glutamine Hydrolysis and Ammonia Excretion

Change of Amino Acid Distribution (2)
BCAAs modifying large neutral amino acid transport at blood-brain barrier

Intraorgan cerebral ammonia, glutamine and glutamate transport

Effect of 7 d of Hyperinsulinemia (Concentration > 3000 pmol/L) on Phenylalanine Transport into Muscle from Blood, and Muscle Protein Synthesis

Rationale of Fat Addition to Glucose-Protein Solution
- Provision of utilized energy
- Provision of essential fatty acid
- High caloric content
- Lower thermic effect
- Reduction of carbohydrate respiratory load
- cell membranes phospholipid
- Modulating prostaglandins and leukotriens synthesis

Absorptive phase

Postabsorptive phase
release 1/3 whole body leucine production

Glutamine hydrolysis & ammonia excretion

Glutamine synthesis

BCAAs, Glutamine hydrolysis & ammonia excretion

Postabsorptive phase
release 1/3 whole body leucine production

Glutamine synthesis

BCAAs

Aromatic amino acid

PHE : phenylalanine
TYR : Tyrosine
TRP : Tryptophan

BCAAs

Leucine
Isoleucine
Valine

Effect of 7 d of Hyperinsulinemia (Concentration > 3000 pmol/L) on Phenylalanine Transport into Muscle from Blood, and Muscle Protein Synthesis

Phenylalanine transport
Muscle protein synthesis

Provision of utilized energy
Provision of essential fatty acid
High caloric content
Lower thermic effect
Reduction of carbohydrate
modulating prostaglandins and leukotriens synthesis

Clinical Nutrition 2006; 27: 321-327

Market facts on lipids

The history of industrially manufactured lipids started in 1961

1944
First industrially available lipid emulsion: Intralipid

1944
Helfrick & Abelson
Parenteral nutrition of a 5 month old girl with a 10% olive oil emulsion

1961
First industrially available lipid emulsion: Intralipid 100% soybean

1984
Launch of Lipofundin MCT Physic. Mixture MCT/LCT

1996
Launch of ClinOleic 80% olive 20% soybean oil

2000
Launch of Structolipid Struct. TG

2005
Launch of Lipoplus
Launch of SMOFlipid Soy/MCT/fish Soy/MCT/olive/fish

The history of industrially manufactured lipids started in 1961.

Understanding of the Biological Effects of FAs Has Evolved

That was then...

FAs
EFAs
Calories

This is now!

FAs
EFAs
Calories

- Lipid peroxidation

- Gene expression

Membrane phospholipids

Triglyceride synthesis

Signal transduction pathways

FAs are biologically active!!

Lipoproteins

- Triglyceride-Rich Lipoproteins
  - Chylomicrons
  - Very low density lipoproteins (VLDL)
  - Intermediate density lipoproteins (IDL)

- Cholesterol-Rich Lipoproteins
  - Lower density lipoproteins (LDL)
  - High density lipoproteins (HDL)
  - Lipoprotein X (Lp-X)

Composition of Parenteral Lipid Emulsions

- Fatty acids (FAs) are the primary biologically active component of parenteral lipid emulsions; these are usually supplied in the form of triglycerides
  - Fat-soluble vitamins (eg, vitamins E and K) and other fat-soluble compounds are incorporated along with triglycerides to form the core of the parenteral lipid emulsion particles
  - These 200-to-500-nm particles are intended to mimic naturally-occurring chylomicrons, which normally transport FAs in the blood-stream (although emulsion particles do not have protein on surface)
  - An emulsifier (ie, phospholipids [eg, egg yolk, or lecithin]) is added to enhance the stability and integrity of lipid globules in aqueous solution

- Parenteral Lipid Emulsion Particles in the Circulation
  - Once in the circulation, the lipid emulsion particles pick up proteins from other circulating particles (eg, high-density and low-density lipoproteins [HDL and LDL])
  - The emulsion particles are then hydrolyzed by the lipoprotein lipase enzyme, releasing FAs
  - The FAs are then transported to the tissues, where they are used by the cells primarily as an energy source for cell membrane development and as biologically active substrates

- Fatty Acid Classification: Chain Length
  - Long-chain FAs (forming long-chain triglycerides [LCTs])
    - FAs ≥14 carbons long
  - Medium-chain FAs (forming medium-chain triglycerides [MCTs])
    - FAs 6 to 12 carbons long
  - Short-chain FAs
    - FAs 2 to 4 carbons long
    - Not used in parenteral nutrition
Acute adverse effects
Most FAs in coconut oil\(^1\)

- Good energy source\(^2\)
- VFAs are found in LCTs\(^1\)
- ω-6 EFAs (eg, linoleic acid)
- ω-3 EFAs (eg, α-linolenic acid, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA])

Critical for cell membrane structure and function\(^1\)
Substantial variation in biological activity and physiologic effects among LCTs from different sources\(^1\)

SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; FA, fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; EFA, essential fatty acid.

1. Wanten GJA, Calder PC.
5. Kris-Etherton PM.
8. Eritsland J.

Fatty Acid Classification: Saturation

- Saturated FAs (SFAs): no double bonds in carbon chain
- Monounsaturated FAs (MUFAs): 1 double bond in carbon chain
- Polyunsaturated FAs (PUFAs): ≥2 double bonds in carbon chain

Medium-chain Triglycerides

- Primary triglyceride type in coconut oil\(^1\)
- Primarily serve as an energy source; rapidly and efficiently oxidized, providing large amounts of energy, but not incorporated into cell membranes\(^1\)
- No accumulation in adipose or hepatic tissue when given parenterally\(^1\)
- Bypass carnitine transport system for entry into mitochondria in the liver only\(^1\)
- Ketogenic and therefore should not be used in patients with diabetes or those at risk for acidosis or ketosis\(^3\)
- Must be administered in combination with LCTs to avoid EFA deficiencies, acidosis, and adverse neurologic effects\(^2\)
- Evidence suggests that MCTs may have pro-inflammatory effects\(^3,4\)

Fatty Acid Classification: Omega Nomenclature

- The ω nomenclature refers to the distance, in carbons, of the first double bond from the ω (non-carboxylic acid) end of the carbon chain
- ω-3: first double bond is 3 carbons from the ω end
- ω-6: first double bond is 6 carbons from the ω end
- ω-9: first double bond is 9 carbons from the ω end

- Oleic acid
- Linoleic acid
- α-Linolenic acid
- DHA
- EPA

Fatty Acid Classification: Saturation

<table>
<thead>
<tr>
<th>SFAs</th>
<th>PUFAs</th>
<th>MUFAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most FAs in coconut oil(^1)</td>
<td>Primary FA in soybean oil (linoleic acid) and fish oil (EPA and DHA)(^2)</td>
<td>Include oleic acid, the primary FA in olive oil(^1)</td>
</tr>
<tr>
<td>Increased risk of CV disease(^2)</td>
<td>Include EFAs(^2)</td>
<td>Olive oil is associated with favorable effects on risk factors for CV disease(^1,3)</td>
</tr>
<tr>
<td>Acute adverse effects include endothelial toxicity, apoptosis, and inflammation(^1,4)</td>
<td>Important for cell membrane structure and function(^2)</td>
<td>Require supplementation with a source of EFAs(^2)</td>
</tr>
<tr>
<td>Should be restricted in the diet(^1,5)</td>
<td>Primary FA that is oxidized(^2)</td>
<td>Should be the predominant FA in the diet (~50% of FA intake)(^3,5)</td>
</tr>
</tbody>
</table>

\(^1\) SFA, saturated fatty acid; PUF, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; FA, fatty acid; CV, cardiovascular; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; EFA, essential fatty acid.
\(^3\) Kris-Etherton PM.
\(^4\) World Health Organization.
\(^5\) López-Miranda J, et al.
Metabolism of Lipid Emulsion Particles

- Triglyceride-rich particles (TGRP)
- Phospholipid-rich particles (PLRP)
*impede lipid lipoprotein metabolism
*modify the lipid composition of cell membranes

Intravascular Hydrolysis of Exogenous Triglycerides and Remodeling

Removal of Exogenous Lipid Particle Remnants within Cell via cell-receptors and endocytosis

The Effect of Lipid Emulsion in ICU Patients
- Lipid emulsion are efficiently cleared from the circulation and do not exceeding increase plasma triglyceride
  - Directly oxidized as energetic fuels
  - Temporarily stored in adipose cells
- Lipids in meal—
  - Not ↑fat oxidation
- No effect in carbohydrate metabolism protein
- No replace endogenous fat as an energetic substrate

Fat Infusion in ICU Patients
- Fat solution alone
  - no effect in nitrogen balance
- Fat solution + Amino acid
  - Protein sparing effect

Soybean Oil Based Emulsion
- By comparison to recommendations for dietary FA intake in general populations
  - < 30% saturated
  - 30%-40% monounsaturated
  - ≤ 30% PUFA
- Soybean triglycerides contain
  - a much higher proportion (60%-65%) of PUFAs
  - 52%-54% of linoleic acid (C18:2 n-6)
Consequences of excessive linoleic acid intake

- Imbalance in fatty acid metabolism:
  - Inhibits the synthesis of active mediators
  - Imbalanced production of prostaglandins and other eicosanoids

- Battistella et al. (1997) J. Trauma 43, 52-60
- Linseisen J et al. JPEN 1997;21(1):21

Oxidative stress linked to high PUFAs may prolong recovery

Polytrauma patients (APACHE II av. 22) Standard glucose containing TPN with no lipid vs. Intralipid (10 days)

<table>
<thead>
<tr>
<th></th>
<th>No lipid</th>
<th>Intralipid</th>
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</thead>
<tbody>
<tr>
<td>Length of stay (d)</td>
<td>27</td>
<td>39*</td>
</tr>
<tr>
<td>ICU stay (d)</td>
<td>18</td>
<td>29*</td>
</tr>
<tr>
<td>Days on ventilator</td>
<td>15</td>
<td>27*</td>
</tr>
<tr>
<td>Pneumonia (#)</td>
<td>13</td>
<td>22*</td>
</tr>
<tr>
<td>Total infectious complications</td>
<td>39</td>
<td>72</td>
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</table>

NK cell activity

<table>
<thead>
<tr>
<th>% of baseline</th>
<th>P = 0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
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<tr>
<td>100</td>
<td>150</td>
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<td>150</td>
<td>200</td>
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<tr>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>250</td>
<td>300</td>
</tr>
</tbody>
</table>

Lipid

- Linseisen, J., et al. J. Trauma 43, 52-60

Medium-Chain Triglyceride Containing Emulsion

- MCFA \( \rightarrow \) perferentially oxidized
- \( \rightarrow \) sparing higher amount of EFA
- \( \rightarrow \) incorporation into cell membrane
- \( \rightarrow \) ketone body
- \( \rightarrow \) lymphocyte function \( \rightarrow \) (AIDS)

- Linseisen, J., et al. J. Trauma 43, 52-60

Entry and Cholesterol Loading of Macrophages in Atherosclerotic Lesions-2

- In early lesions, the cholesterol is stored as ACAT-derived cholesteryl esters and thus acquire a foamy appearance
- In advanced lesions, unesterified or ‘free’ cholesterol (FC) accumulates
- Macrophage apoptosis
- Necrosis

- Frederick R. Maxfield & Ira Tabas NATURE 2003;426:

Expression of CD11b/CD66b on Neutrophils and Monocytes after Incubation of Whole Blood at Various Lipid Concentrations for 1 h

- L.: long-chain triglycerides
- LM.: mixed long and medium-chain triglycerides
- FO.: fish oil


Impact of sepsis, lung injury, and the role of lipid infusion on circulating prostacyclin and thromboxane \( \text{A}_2 \)

Effects of LCT vs. Glucose on Immunity

Clinical Nutrition 2007;26: 302–313

Effects of LCT vs. MCT/LCT on Immunity

Clinical Nutrition 2007;26: 302–313

Effects of LCT vs. FO on Immunity

Clinical Nutrition 2007;26: 302–313

The Final Goal of Artificial Nutrition in ICU Patients

Current Opinion in Critical Care 2004; 10:449–455

Suppression of protein catabolism?
Glucose production achieved by carbohydrate or fat supply?
At which rates of nutrient administration
Do the type of nutrient and the route of administration play a role.
Are lipids administered as part of parenteral or enteral nutrition as effect as carbohydrates in achieving the same goals?
The effects of fat solutions on immunity, modulation of inflammation response and antioxidant status.
祝大家心想事成

THANKS