Interorgan exchange of Amino Acids: What is the driving force?

NEP Deutz

Center for Translational Research in Aging & Longevity. Donald W. Reynolds Institute on Aging. UAMS, Little Rock

Interorgan exchange of Amino Acids

- Introduction
- Methods to measure interorgan exchange of Amino Acids
- Interorgan exchange Amino Acids during feeding
- Impact Diet on interorgan exchange
- Impact disease on interorgan exchange
- Conclusion

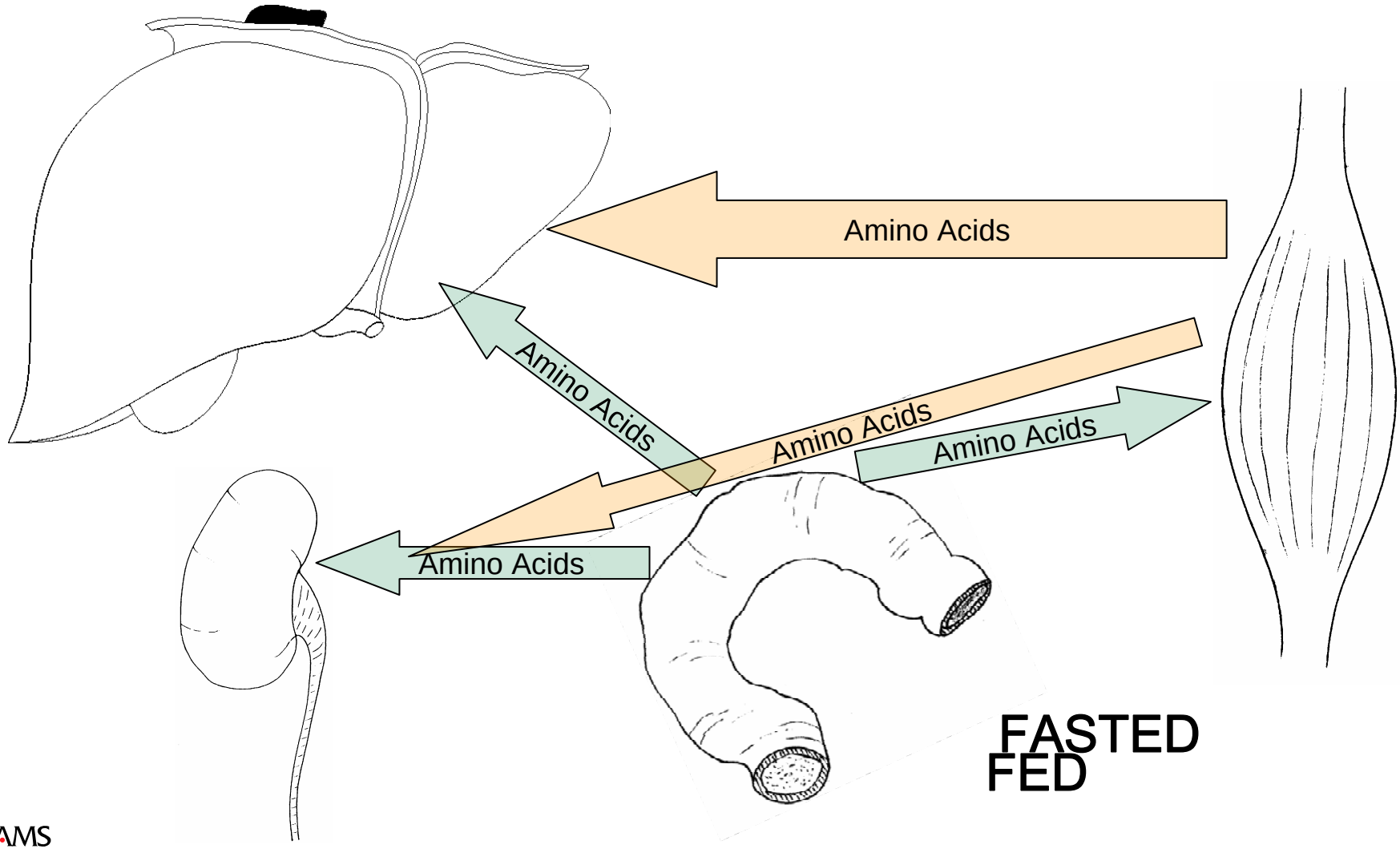
Interorgan exchange of Amino Acids

- Is highly active and regulated process
- Provides and delivers Amino Acids to all organs and tissues for
  - protein synthesis
  - Specific metabolic functions
- Plays a role in the maintenance of plasma Amino Acid homeostasis
- Major role of (patho)physiological state and nutrition

Interorgan exchange of Amino Acids

- After Feeding and initial phase of fasting
  - Dominant flux from the Gut to other tissues
- During prolonged fasting
  - Dominant flux from muscle to liver and kidney

Interorgan Amino Acid transport: Transition from feeding and early fasting period to prolonged fasting and starvation



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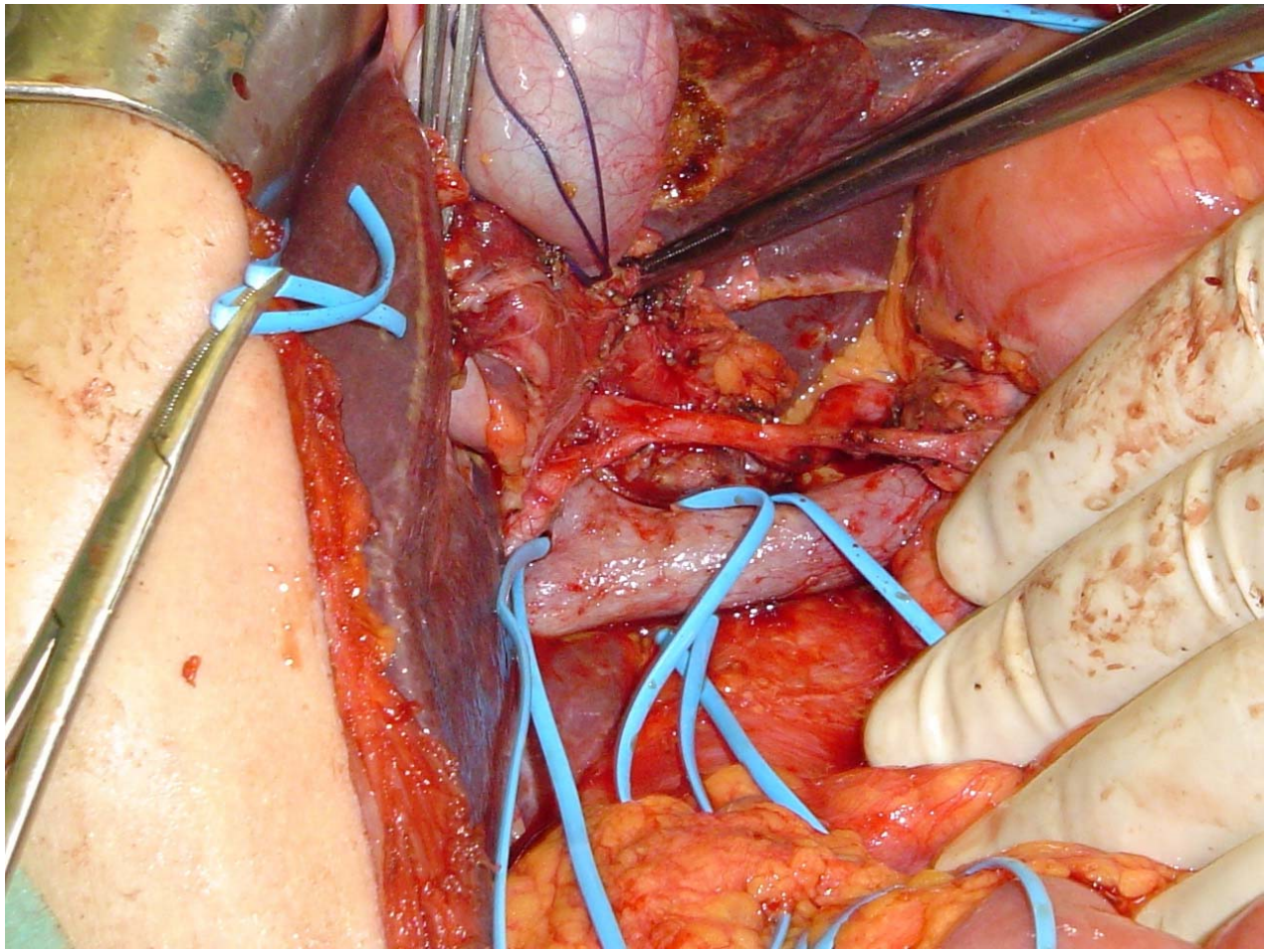
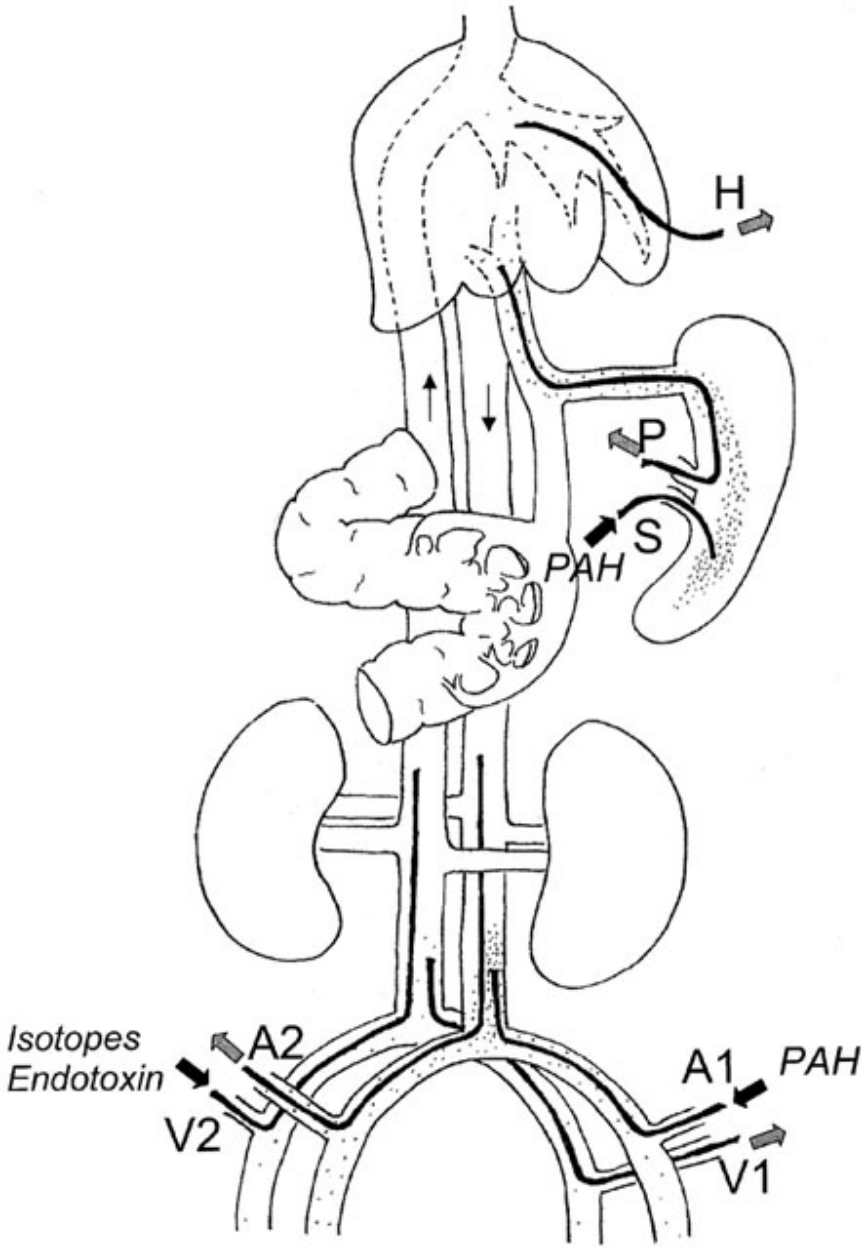
Peroperative Interorgan measurement



Direct puncture of portal vein (either blind or direct)

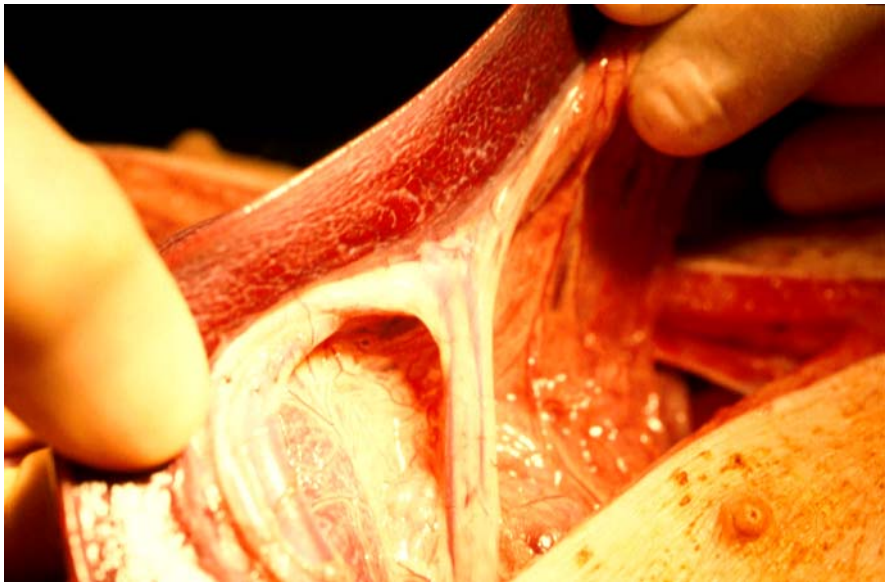
Catheter placement in the pig (full model)

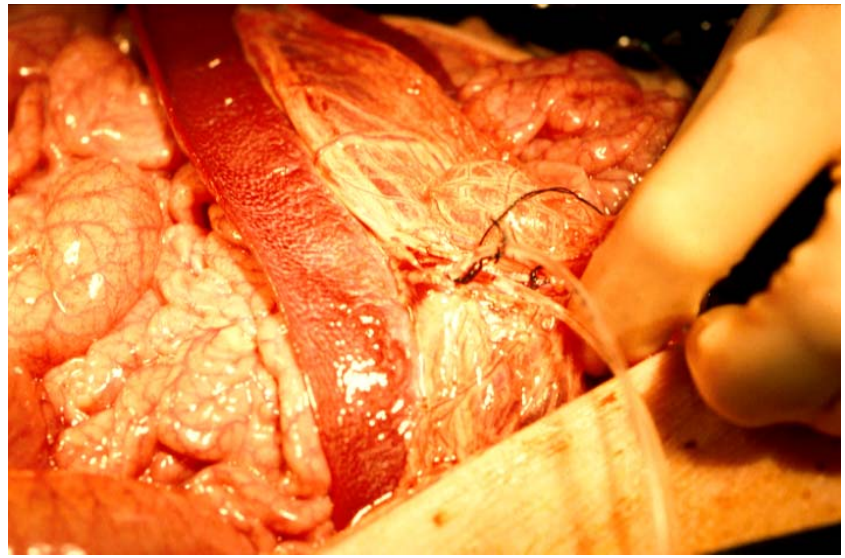
- To measure plasma flow, PAH is infused through the splenic vein (S) and abdominal aorta (A1)
- For turnover measurements, tracer is infused through the caval vein (V2) for turnover measurements
- Blood is sampled from the abdominal aorta (A2), caval vein (V1), hepatic vein (H) and portal vein (P)



Lab Anim **30**(4): 347-58

The Interorgan Pig Model





Implantation of the splenic and portal vein catheter

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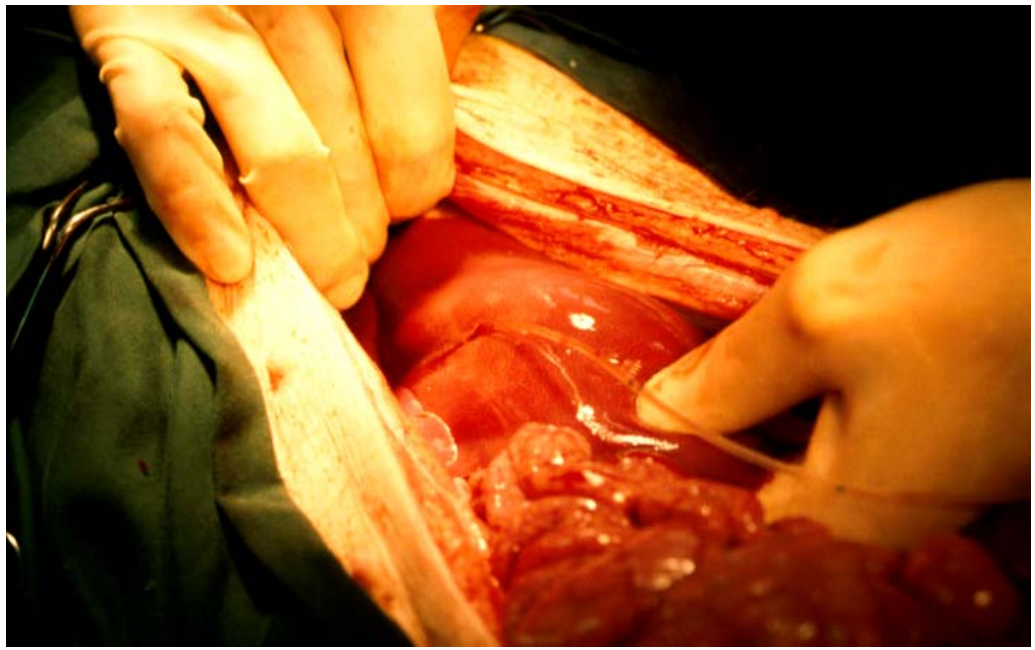
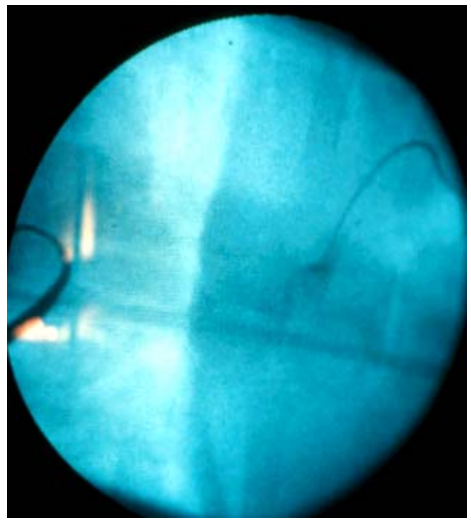
Lab Anim **30**(4): 347-58

The Interorgan Pig Model



Implantation and checking of the position of the hepatic vein catheter



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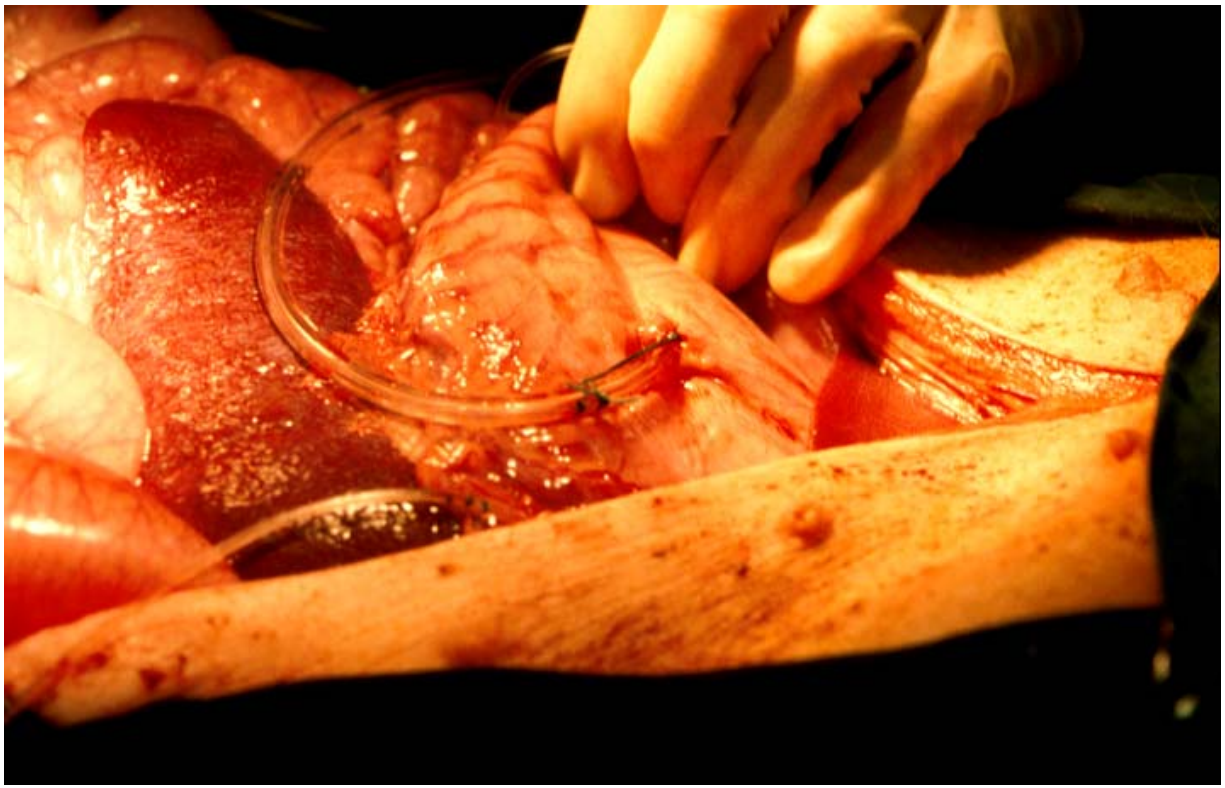
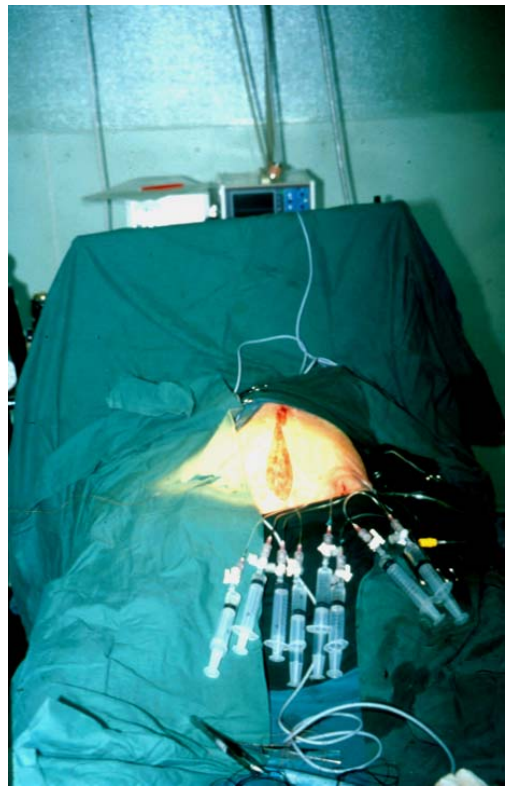
The Interorgan Pig Model

Implantation of the gastric catheter and closing





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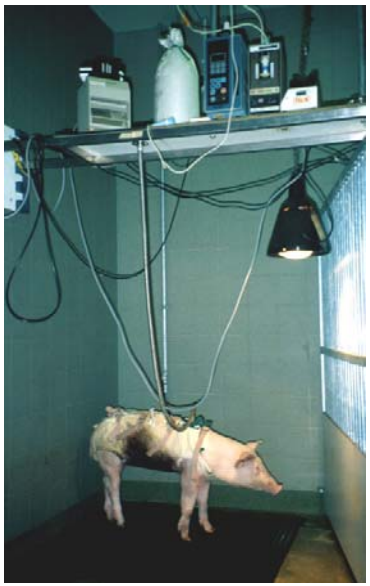
The Interorgan Pig Model: Nutrition and Sampling



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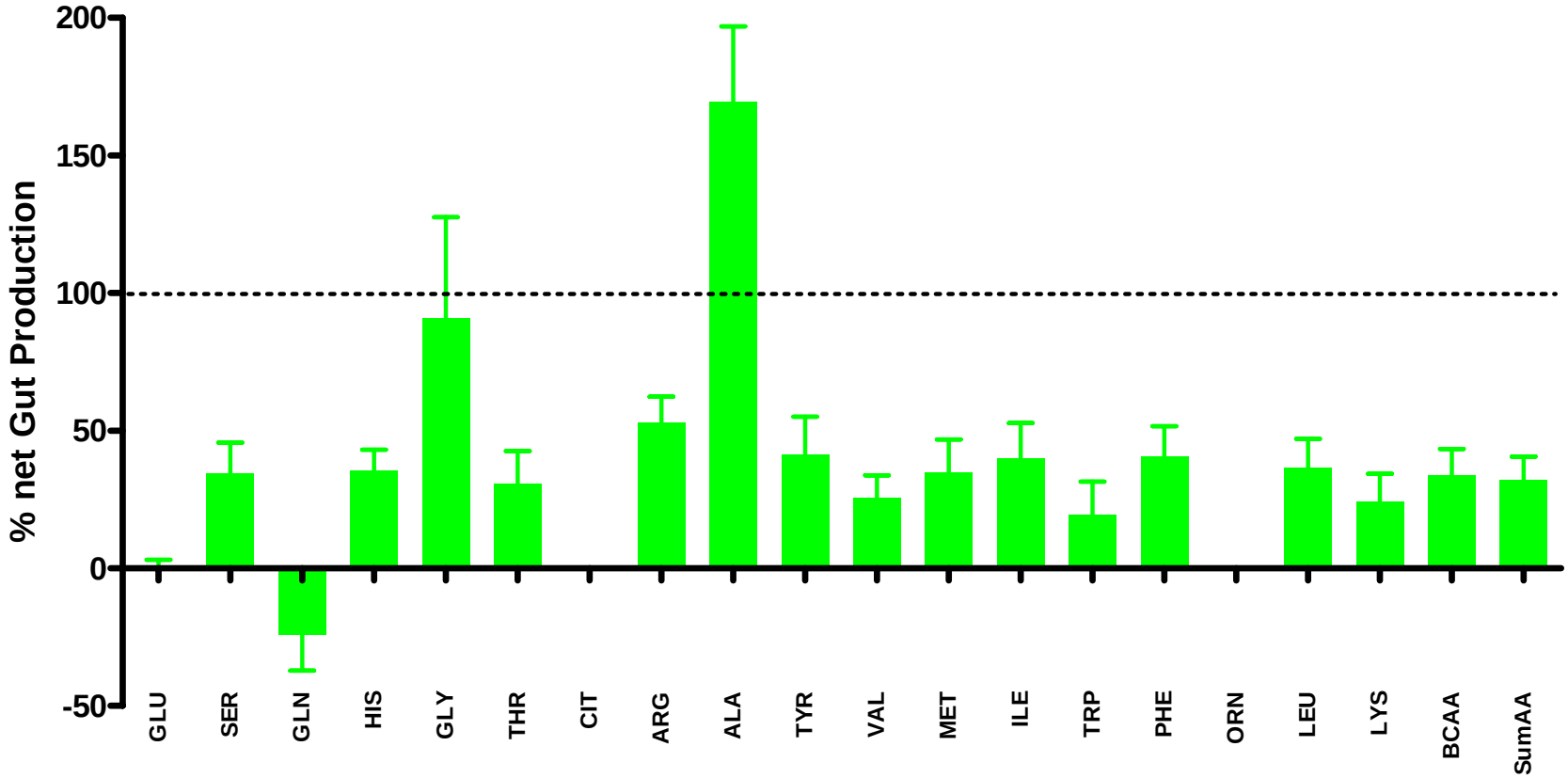
Interorgan exchange of Amino Acids: Flow from the Gut



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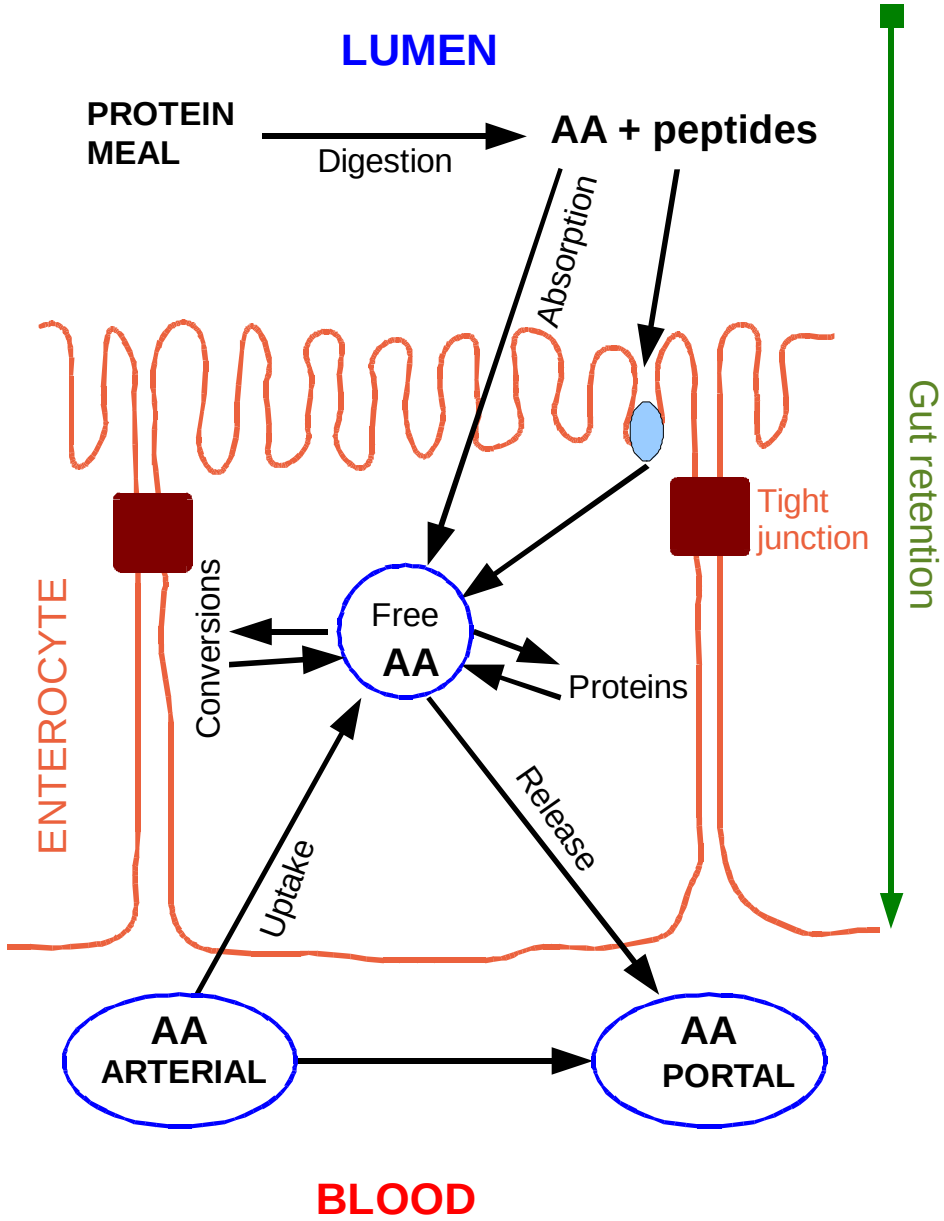
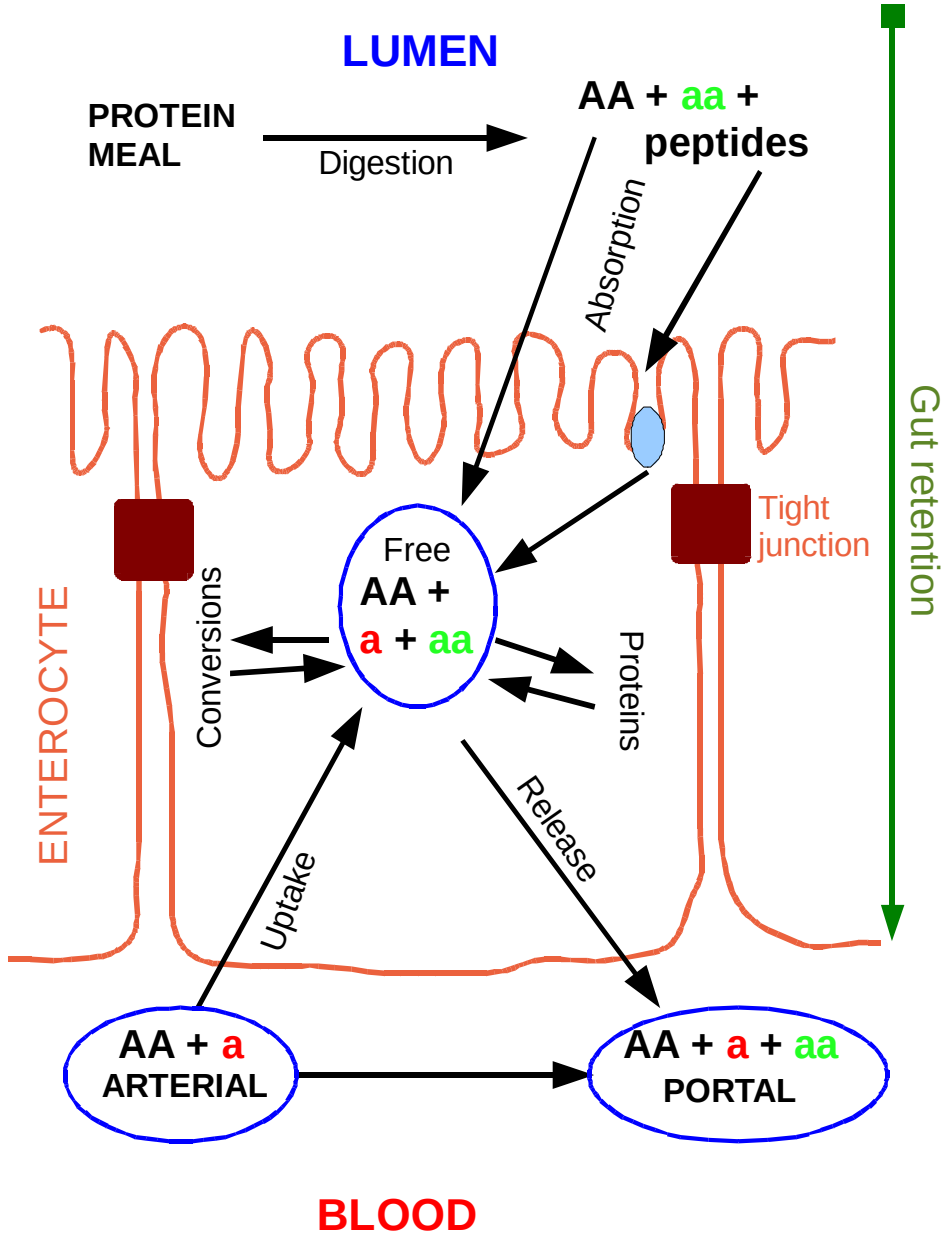
Bruins et al. J Nutr **130**(12): 3003-13.

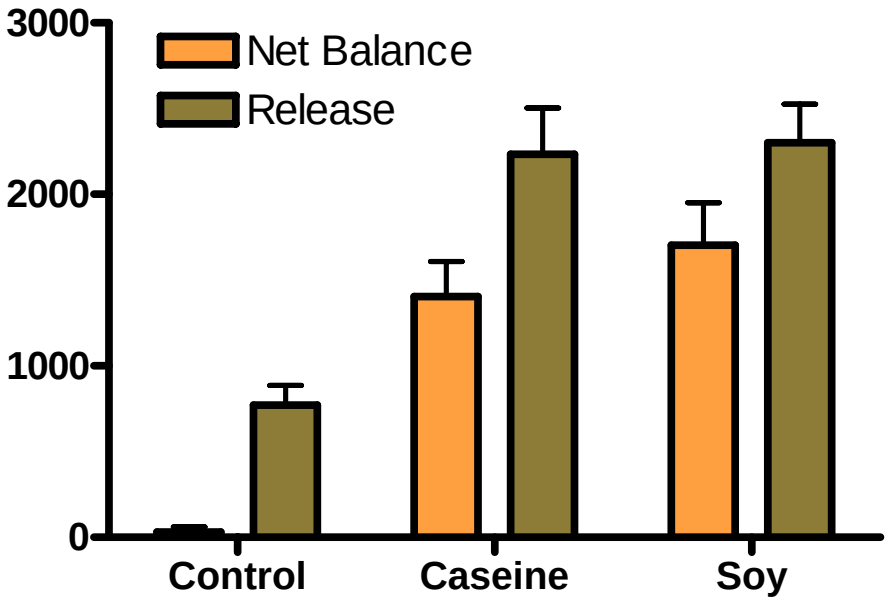
Delivery of amino acids from luminal and arterial site

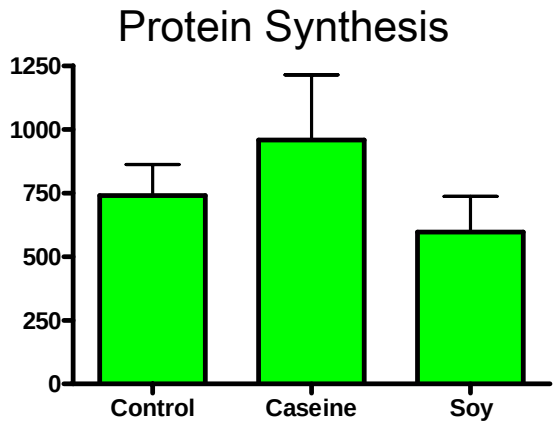


Use of tracers to study gut metabolism



Phenylalanine kinetics across the gut





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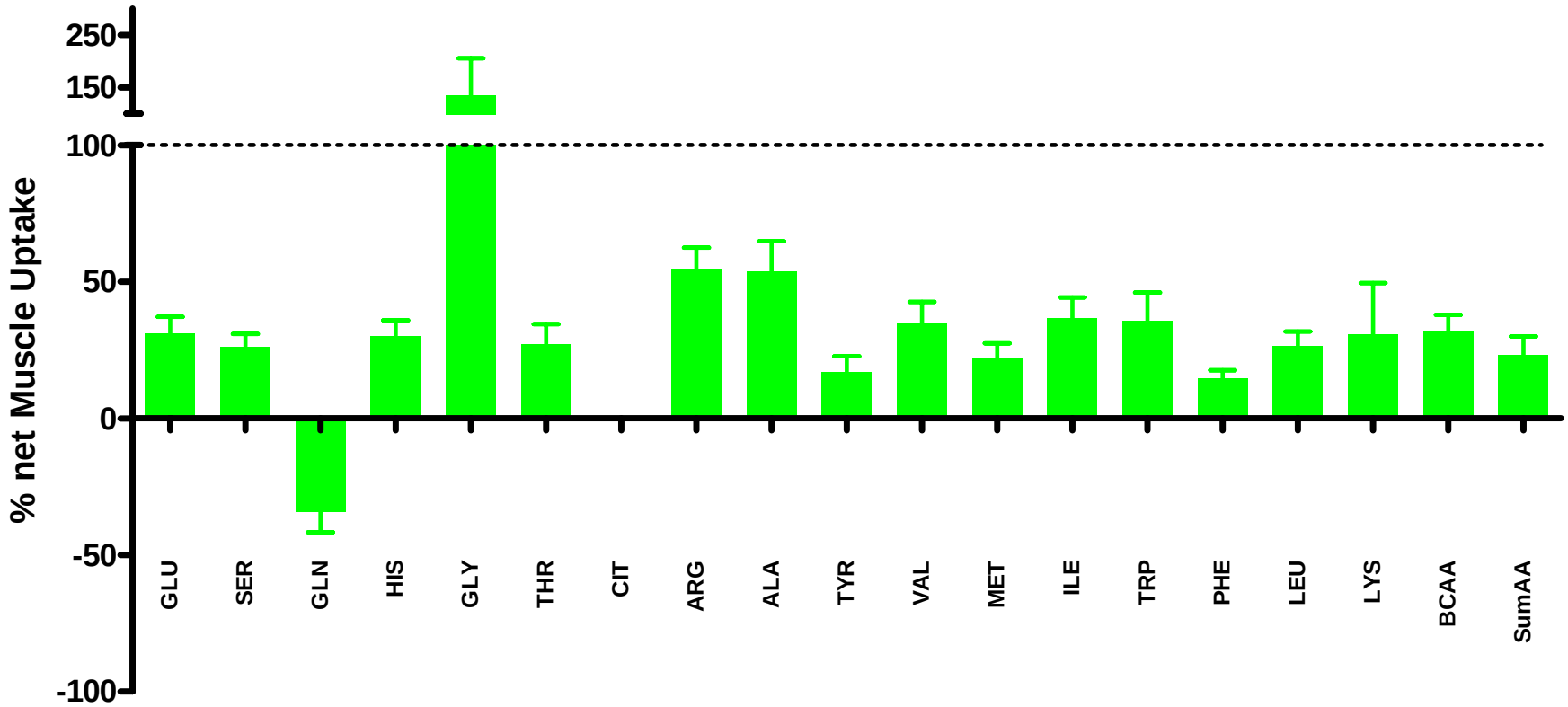
J Nutr **128**(12): 2435-45

Interorgan exchange of Amino Acids: Muscle - % uptake of intake



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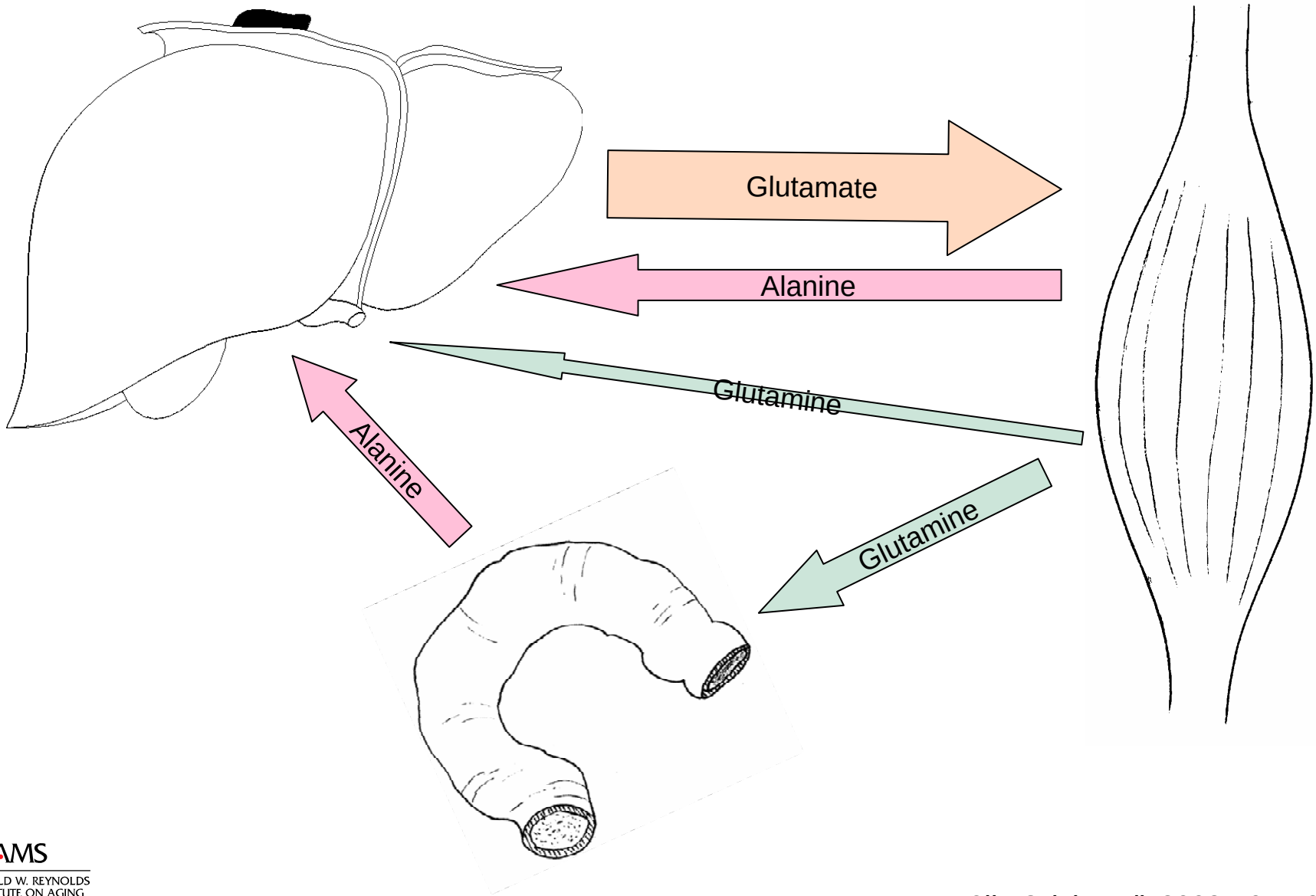
J Nutr **130**(12): 3003-13.

PIG Interorgan GLN and GLU transport



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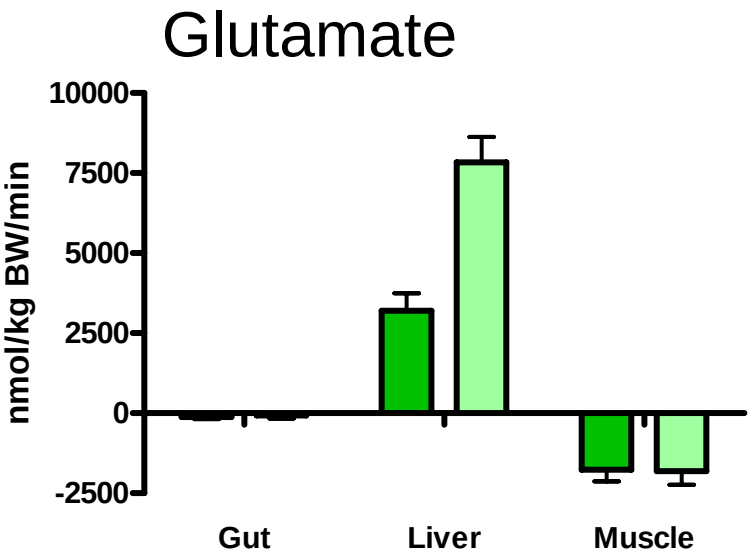
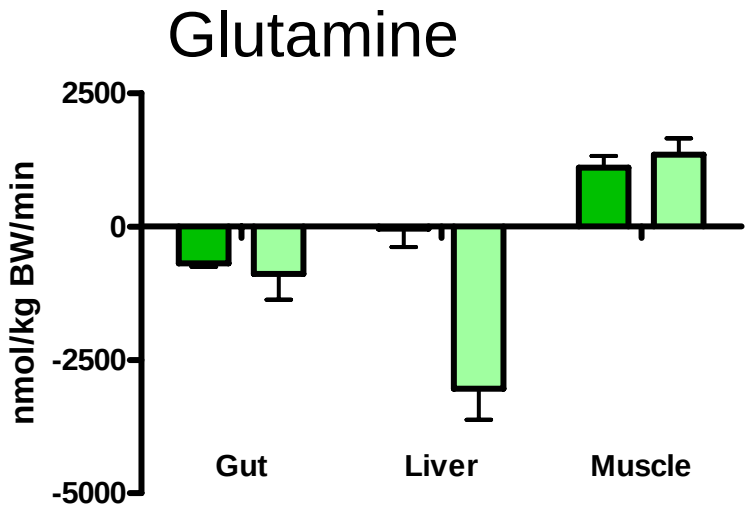
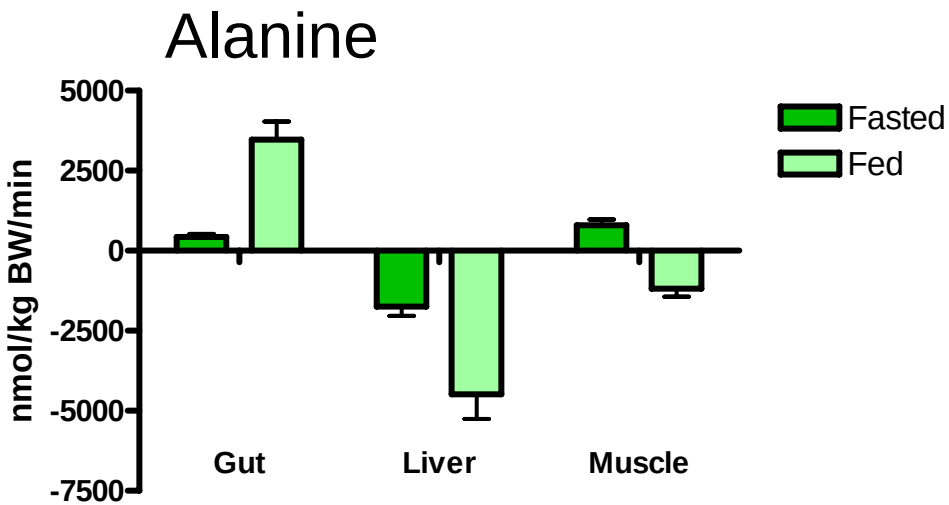
Clin Sci (Lond) 2003;104:127-41

Changes during fasted-fed state transition







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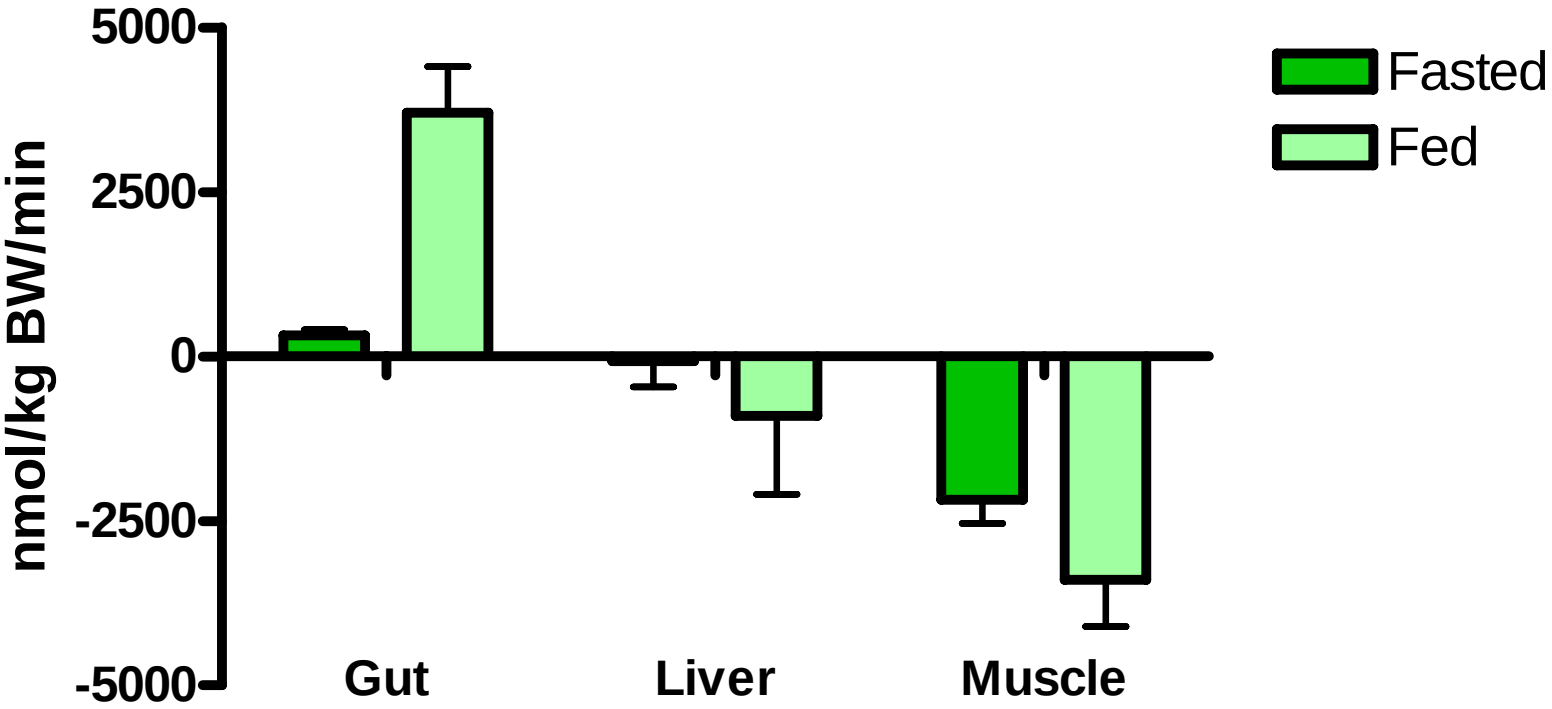
J Nutr **130**(12): 3003-13.
Clin Sci (Lond) **104**(2): 127-41

Changes in BCAA during fasted-fed state transition



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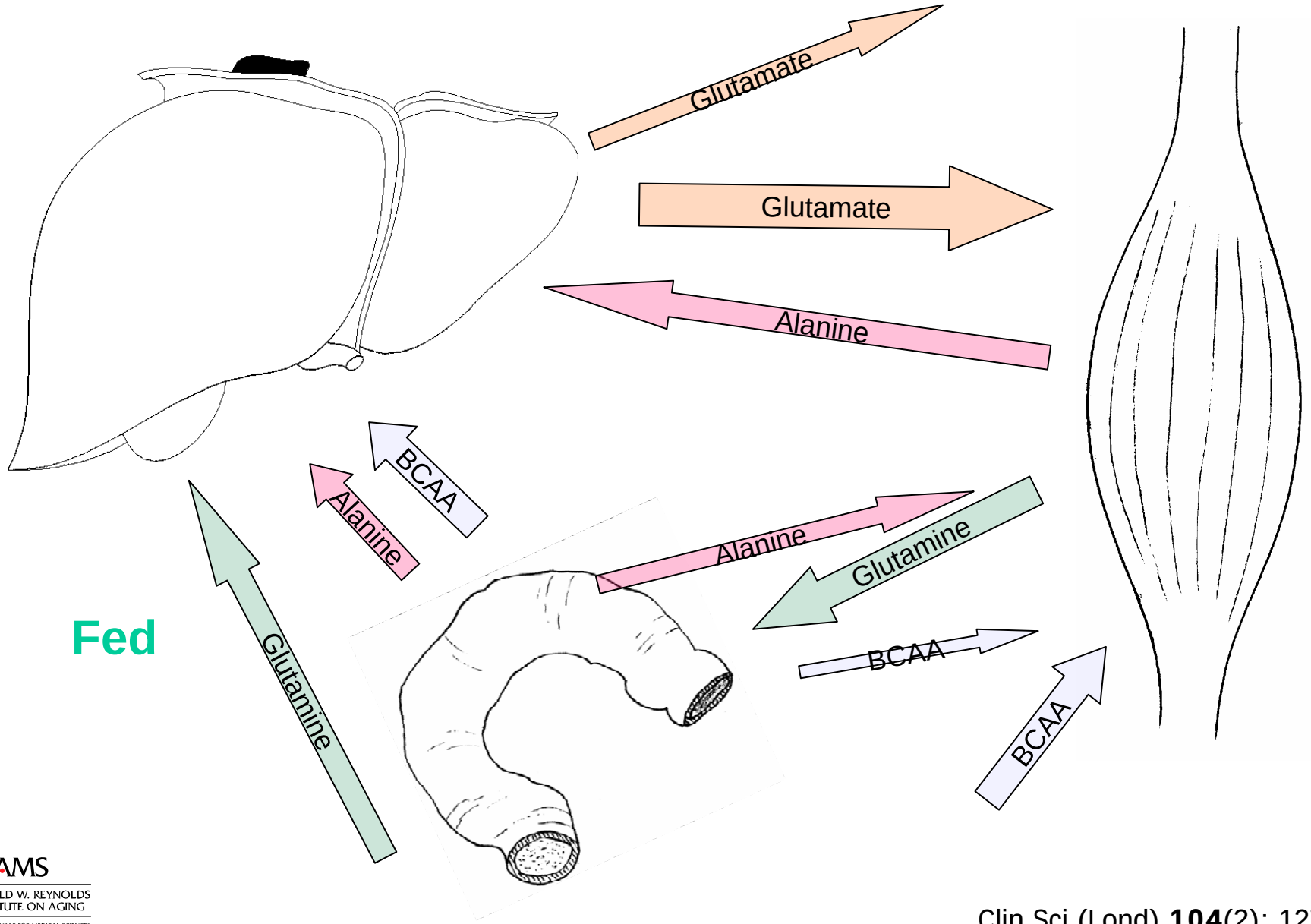
PIG Interorgan GLU, GLN, ALA and BCAA transport



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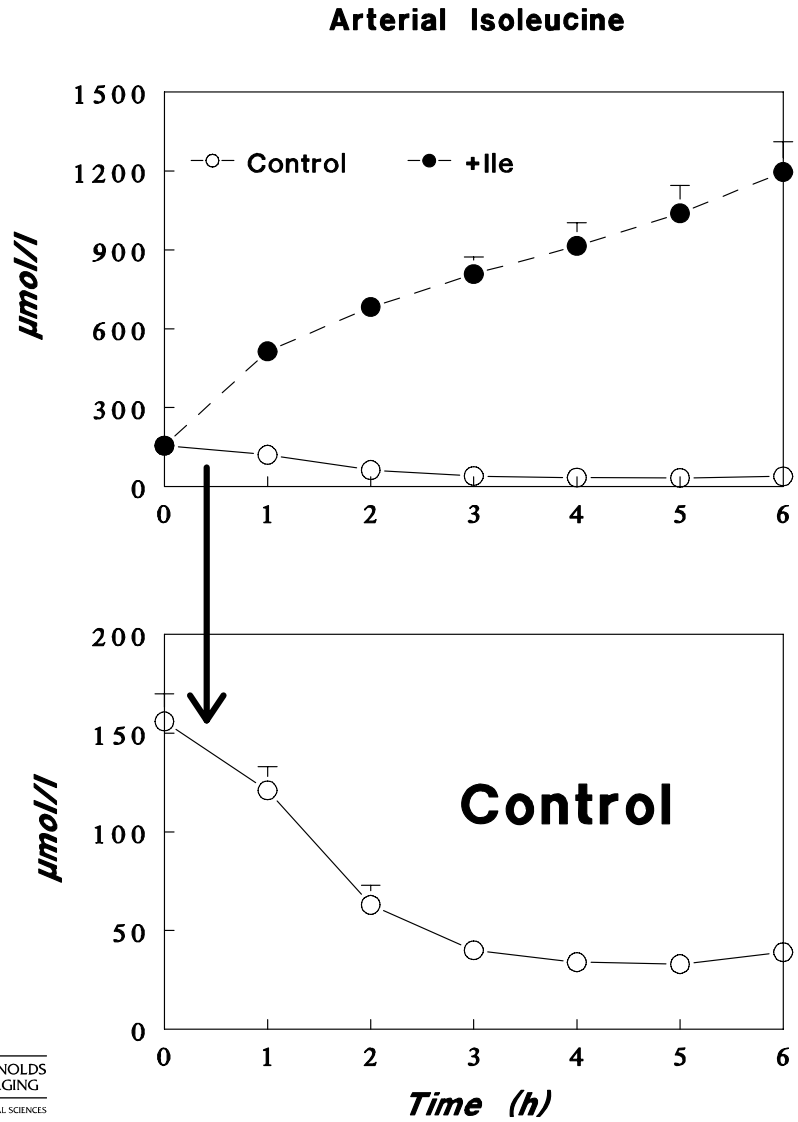
Amount of protein given

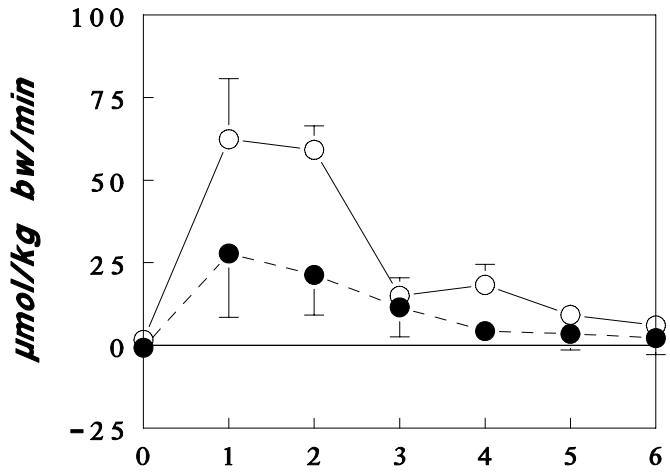
- With a balanced meal ±90% of the dietary amino acids are absorbed and about 30-50% will be used by the intestine itself and the rest released into the portal vein
- Excessive amount of proteins potentially could lead to limitation of gut absorption. However, it is more likely that the maximum that gut cells can use for own metabolism is reached faster and that consequently, higher protein intake will reduce the % amino acids extracted
- During a low protein intake, the % amino acids extracted by the gut will be higher, although the intestine can adapt to reduced protein intake by reducing its amino acid oxidation

Quality of the protein

- It is postulated that a high quality dietary protein stimulates the amino acid utilization in the gut and is therefore of benefit for the gut and for the rest of the body
- Metabolic utilization of amino acids in the gut also depends on the composition of the meal with respect to the presence or absence of (in)dispensable essential amino acids. Lack of an amino acid in a protein meal makes the protein of low quality
- For example, ingestion of an isoleucine-poor blood protein in pigs resulted in high amino acid release, while concomitant intravenous isoleucine infusion promoted amino acid retention in the gut

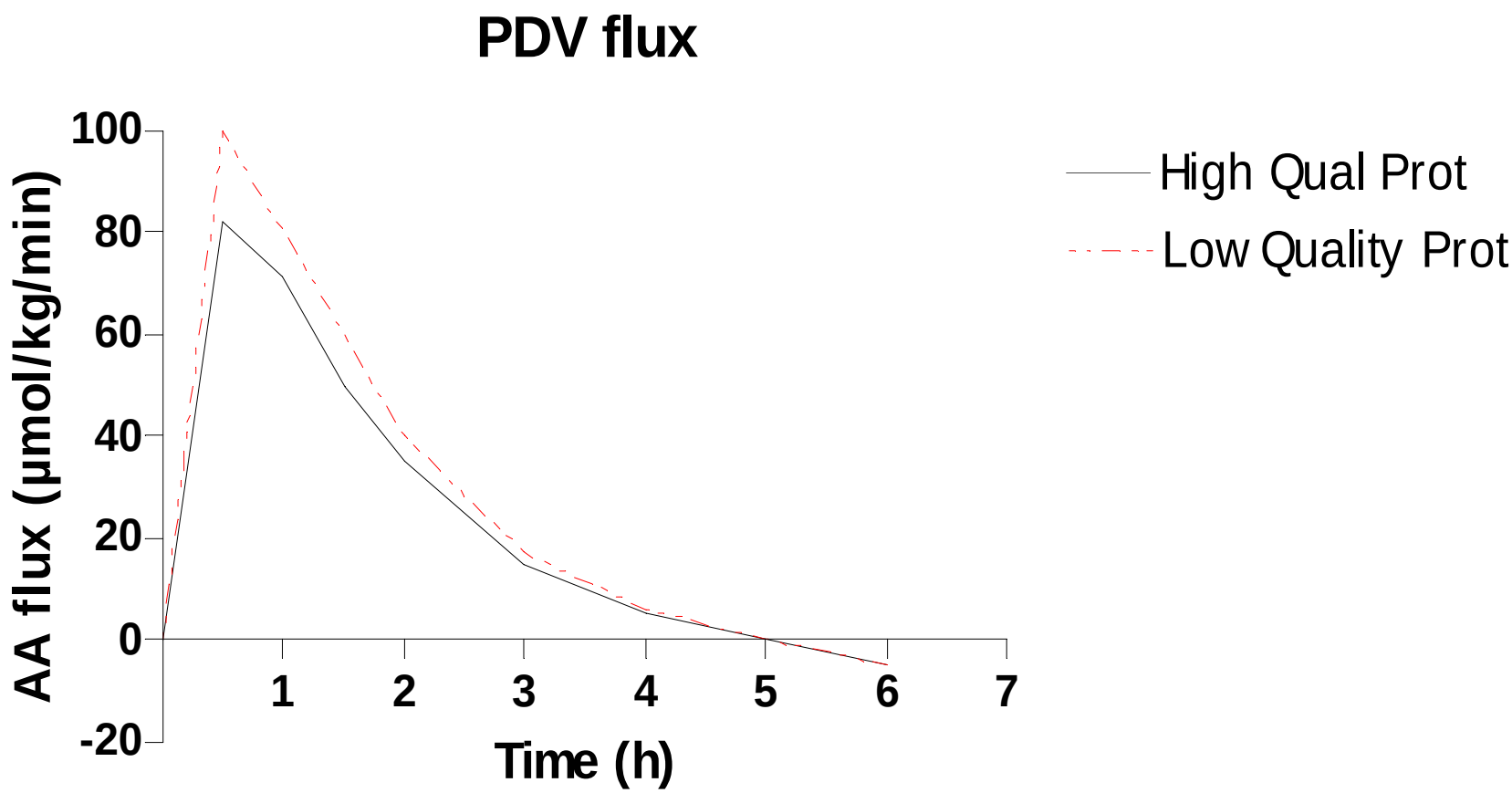
Making a low quality protein a better protein by infusion the limiting Amino Acid





Less amino acids come out of the Gut: More Gut protein synthesis!

Gastroenterology 1991;101:1613-20


PDV flux
AA flux (µmol/kg/min)
100
80
60
40
20
0
-20
1
2
3
4
5
6
7
Time (h)
High Qual Prot
Low Quality Prot

The gut as a metabolically-active organ during feeding

- Not all amino acids that pass the gut enter the circulation, since a part of the amino acids is used for local metabolism (e.g. oxidation, protein synthesis)
- There is also substantial use from arterial supply
- The gut has one of the highest protein synthesis rates

The gut as a metabolically-active organ

- About 50% of the dietary amino acid intake is used by the Portal Drained Viscera (PDV), but this percentage varies between different amino acids and other factors
- During feeding, amino acids that come from either the lumen or circulation contribute to protein synthesis, but at a different level
- Malnutrition or starvation, protein depletion or deficiencies of specific nutrients all inhibit the growth and turnover of the intestinal mucosa and therefore will affect absorption kinetics

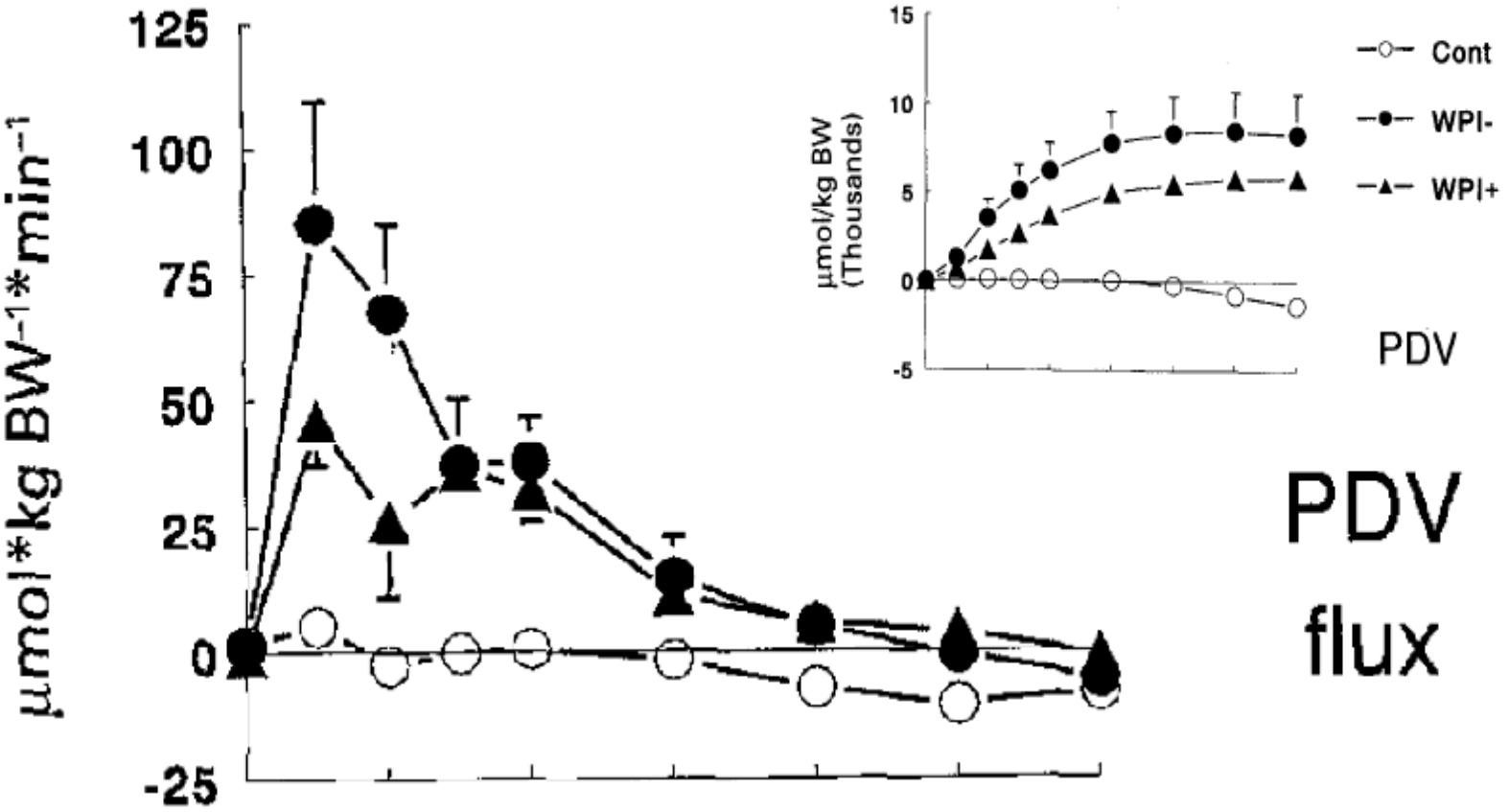
The gut as a metabolically-active organ

- The gut has a high protein synthesis rate that is affected during many conditions
- Special role of the Amino Acids
  - Glutamine: Main energy source in small intestine
  - Citrulline: Important source of Arginine in and out
  - Arginine: Role in NO production
  - Threonine: As precursor of mucus protein
  - Cysteine: As precursor of GSH

The gut as a labile pool of protein

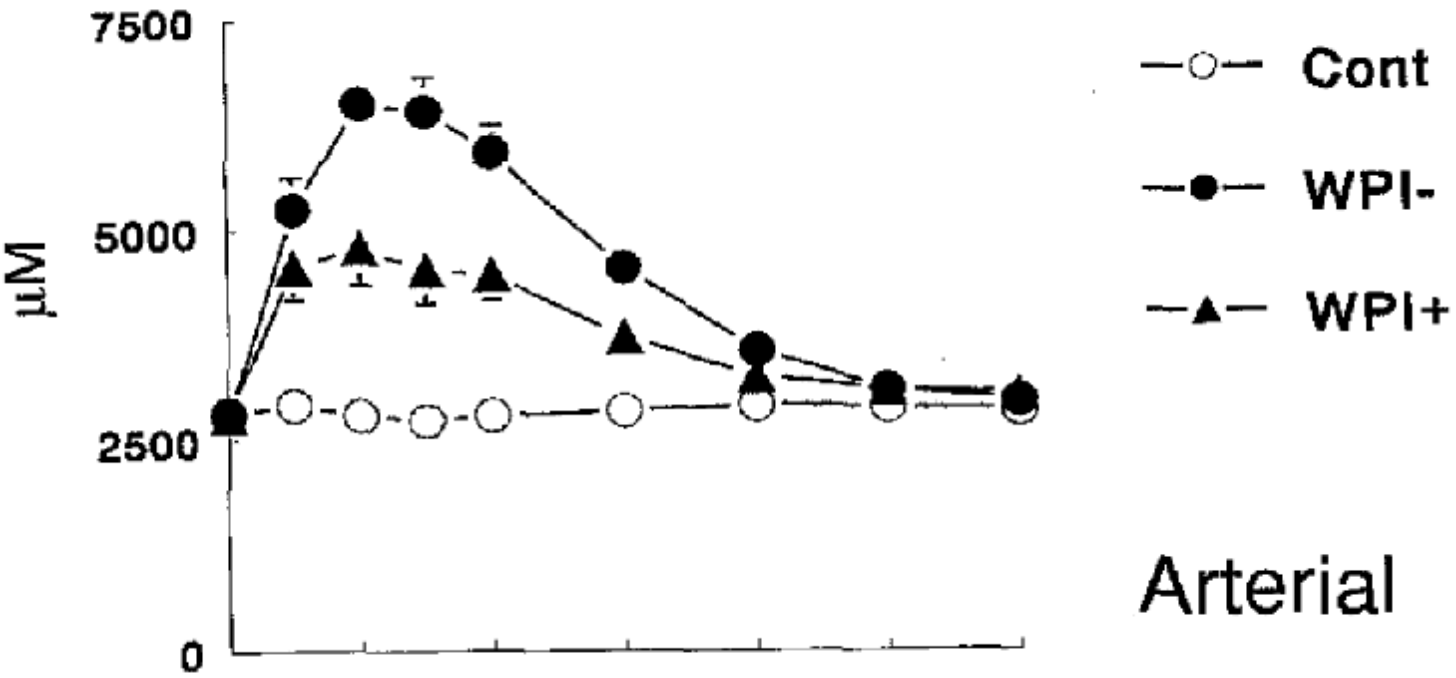
- After a meal there is a net accumulation of protein in the gut whereas in the post-absorptive state a net loss of protein takes place.
- When a protein is rapidly digested, absorbed and the amino acids are directly released to the portal system, this large flux of highly concentrated amino acids in the portal vein would give rise to a high rate of urea production, gluconeogenesis and amino acid oxidation
- A more gradual release of amino acids from the gut would ensure a more prolonged supply of amino acids in the portal vein, resulting in lower plasma concentrations in the portal vein, lower urea production and potentially more muscle anabolism

Addition of Macronutrient: CHO



In the multi-catheterized pig model, pigs were given a bolus meal consisting of Whey protein with and without carbohydrates (CHO)

Addition of Macronutrient: CHO



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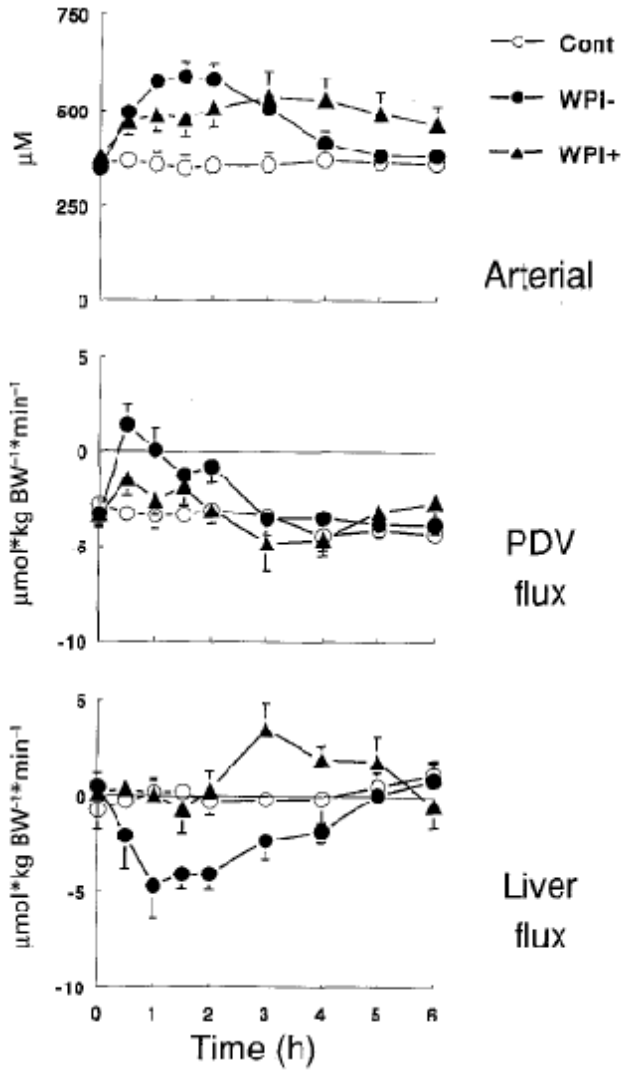
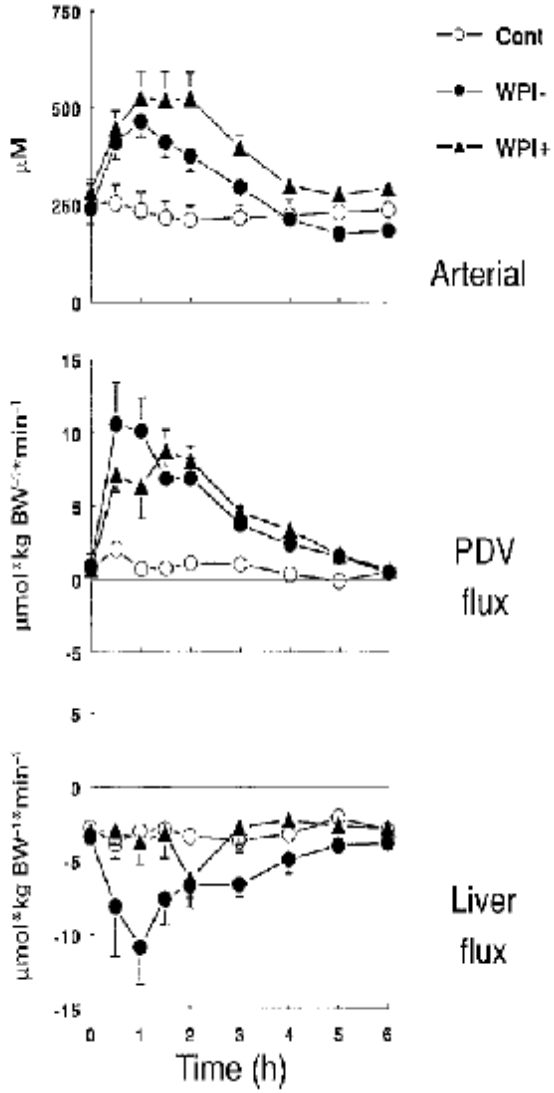


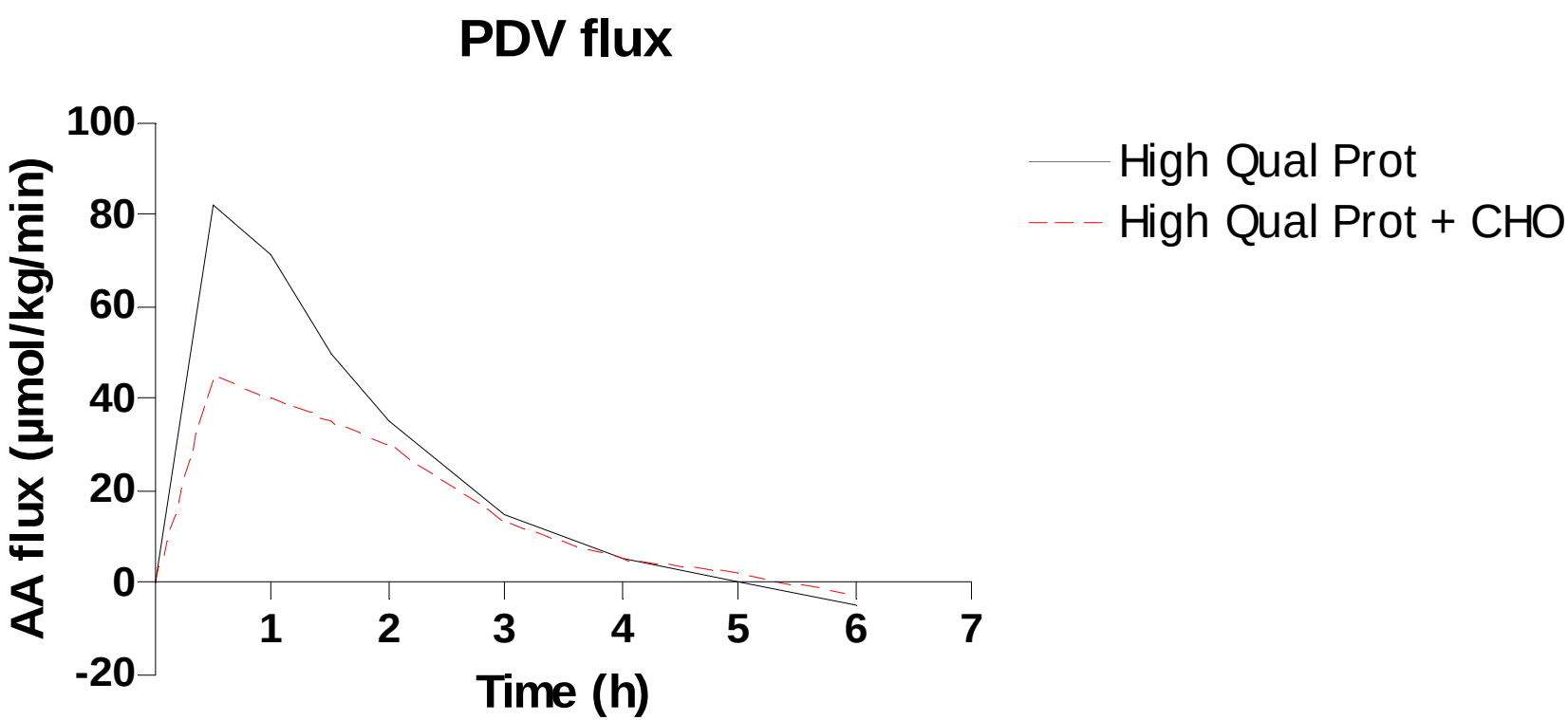
Glutamine



Alanine

Addition of CHO to a protein meal

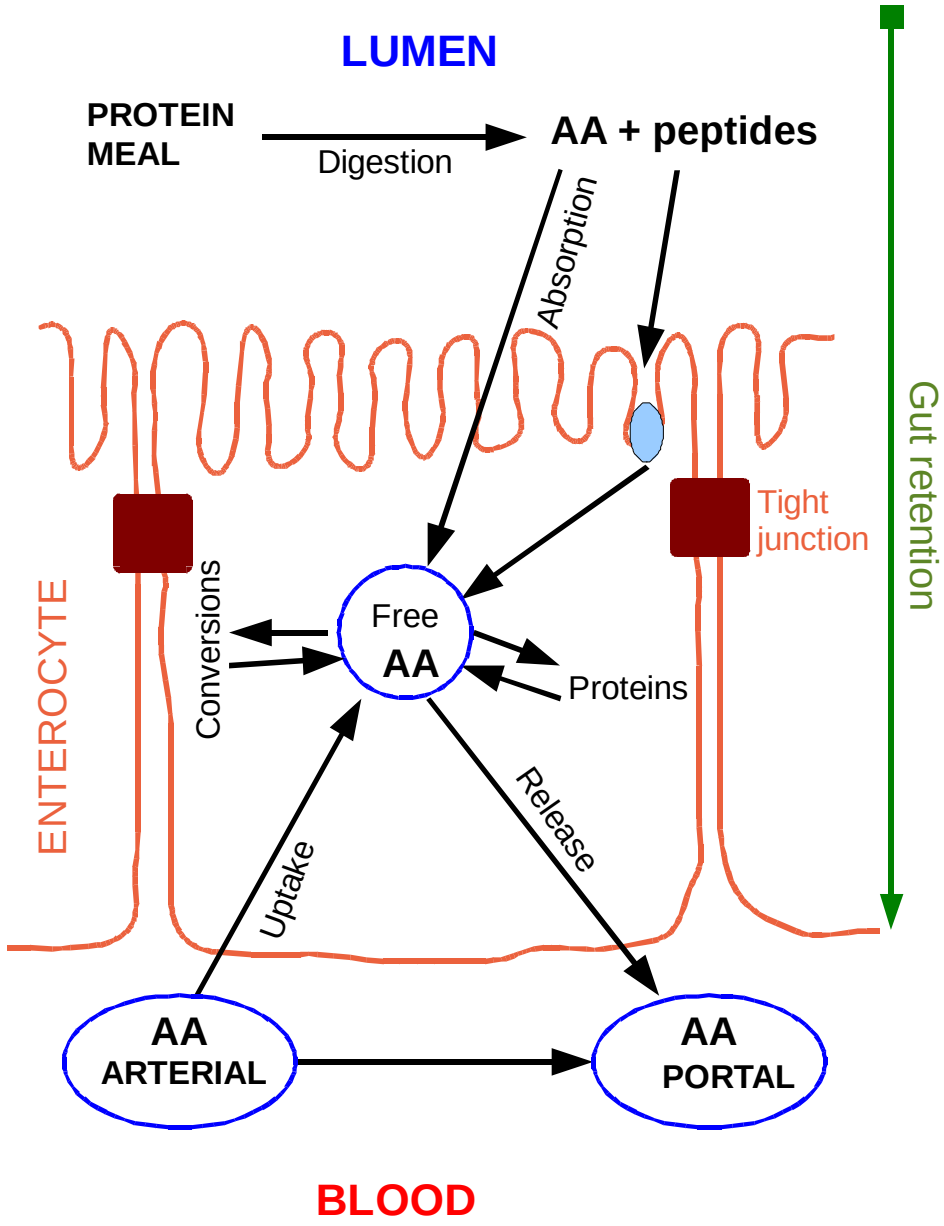
- Results in increased intestinal amino acid retention, increased Gut GLN uptake and ALA release, indicating stimulated gut metabolism
- Results in lower plasma concentrations, thus lower muscle delivery
- But, it improves the anabolic quality of a protein meal for the gut and probably on a day-to-day basis also whole body anabolism


PDV flux
AA flux (µmol/kg/min)
100
80
60
40
20
0
-20
1
2
3
4
5
6
7
Time (h)
High Qual Prot
High Qual Prot + CHO

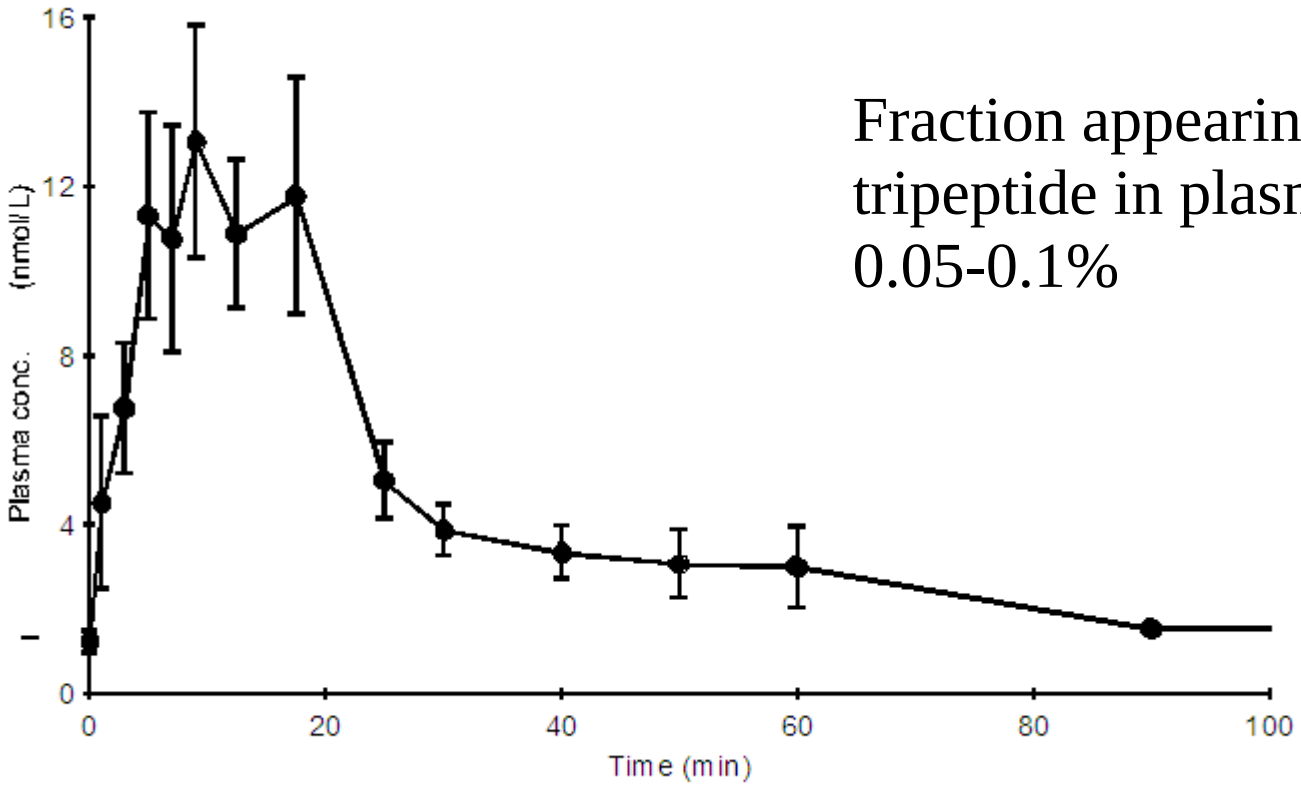
Slow vs fast protein

- A more prolonged positive net protein balance was observed with casein protein or with repeated meals of whey protein to mimic slow digestion rate
- When comparing protein sources, their digestibility and/or absorption rates can potentially have an effect on gut retention and consequently absorption kinetics

- Small peptides can be actively absorbed via a separate transporter in the enterocyte.
- In the enterocyte, the peptides are converted to single amino acids, released to the portal system or are utilized in the gut itself
- It is expected that only marginal amounts of peptides “escape” the mucosa cell to be released into the portal vein



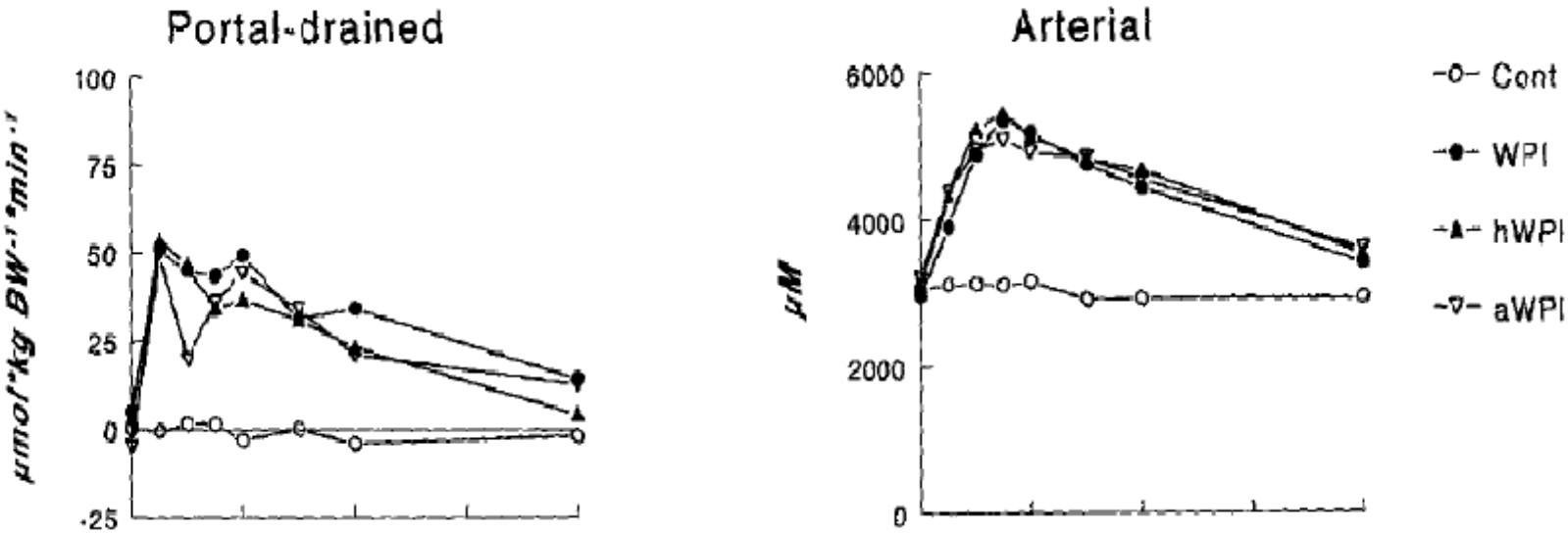
Absorption kinetics tripeptide



Fraction appearing tripeptide in plasma: 0.05-0.1%

Plasma concentration-time curve for tripeptide in pig after intragastric infusion of 4.0 mg tripeptide/kg BW

Does the form matter?



Whey protein as intact protein (WPI), partially hydrolyses (hWPI) and as mixture of free amino acids (aWPI) was given to pigs

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Clin Nutr 15(3): 119-28

Uptake of peptides and amino acid mixtures

- We did not observe a difference, because
  - whey protein was a fast protein with no digestion limitation
  - No limitation of peptidase activity in the mucosa (pigs have very high capacity?)
  - the amount of protein given was below daily intake

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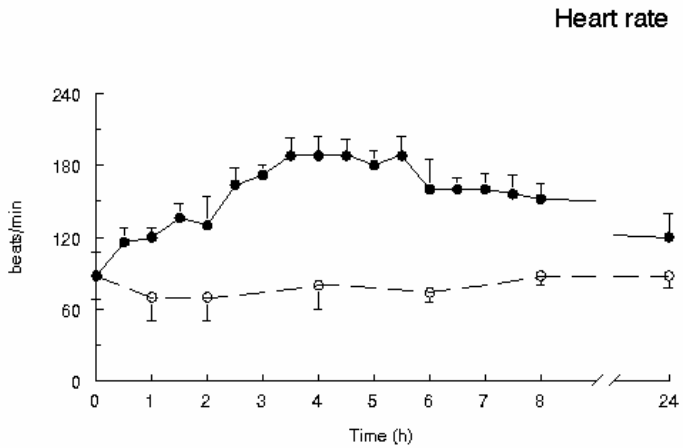
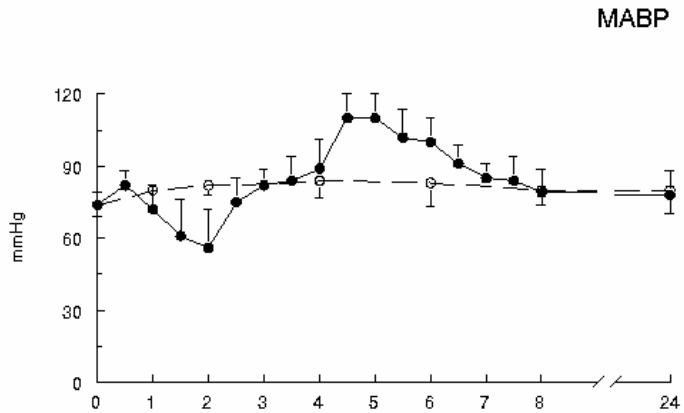
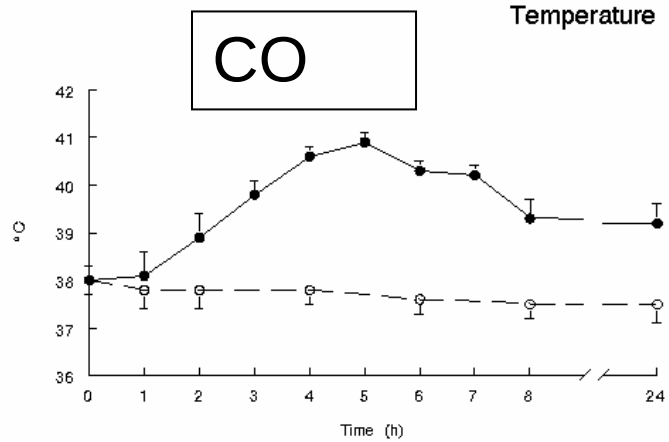
Septic pigs
Model validation

Hyperdynamic Sepsis model

- **LPS**
  - E.Coli 055:B5
  - 24h i.v. at 3 µg.kg $bw^{-1}.h^{-1}$
- **High Fluid Support**
  - 150 mM NaCl i.v.
  - 30 ml.kg $bw^{-1}.h^{-1}$ first 8h after start LPS
  - 20 ml.kg $bw^{-1}.h^{-1}$ 8-30h after start LPS
- **NO MORTALITY**
- **This pig model is good animal model for human sepsis**







J.Nutr.2000;130:2003

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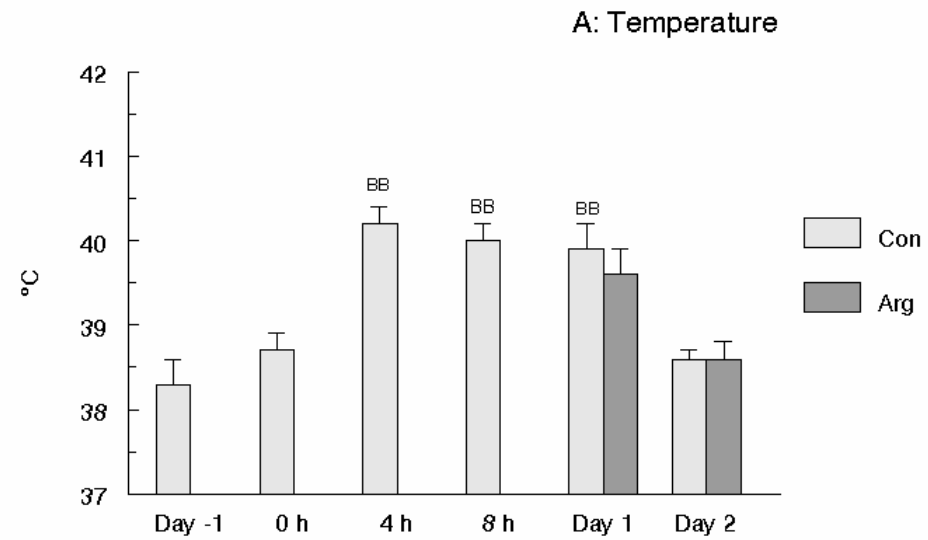
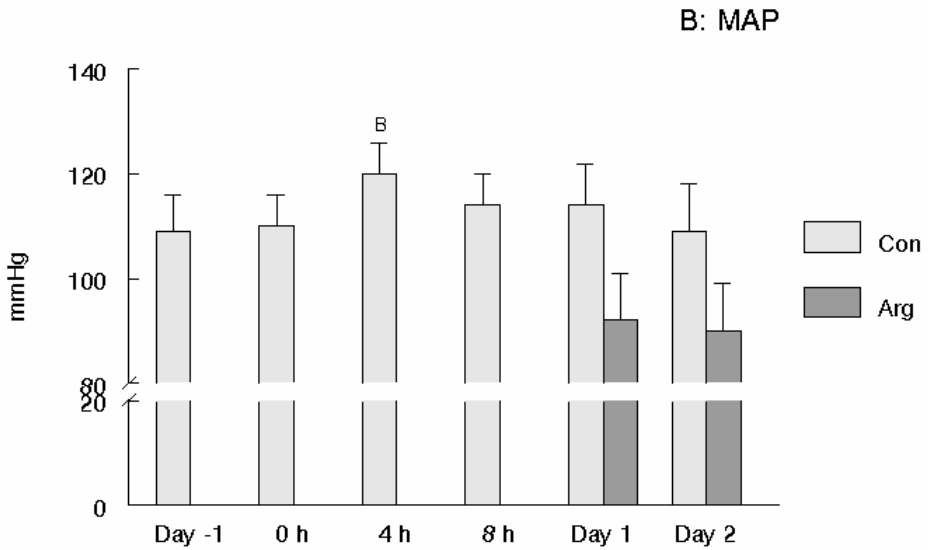
Body Temperature MAP





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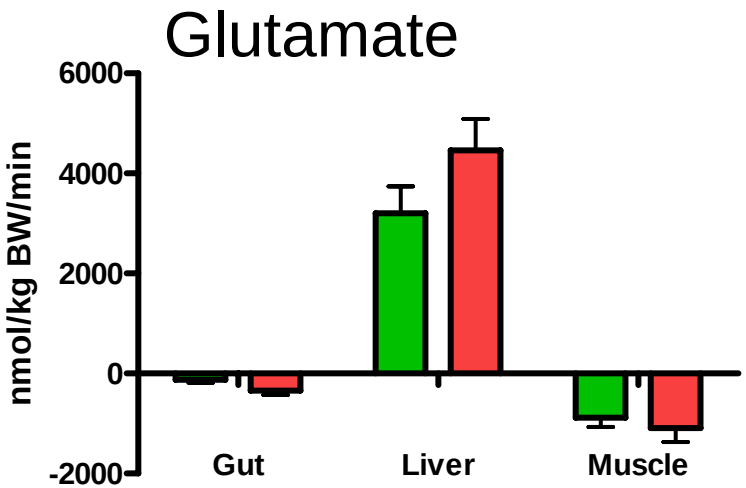
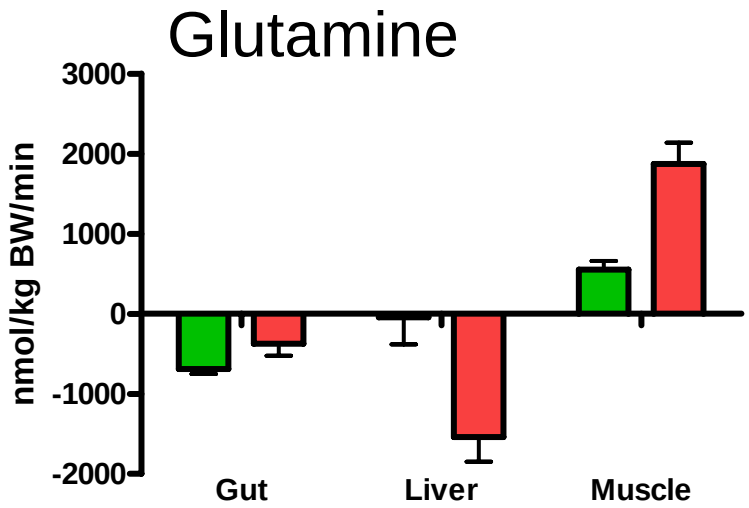
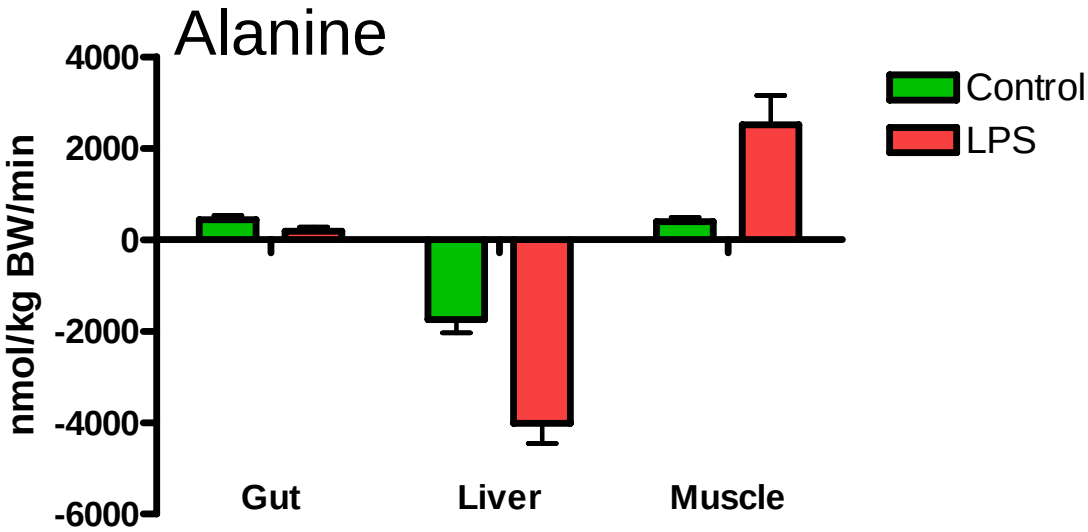
Crit.CareMed. 2002;30:508-17

Changes during sepsis in fasted pigs







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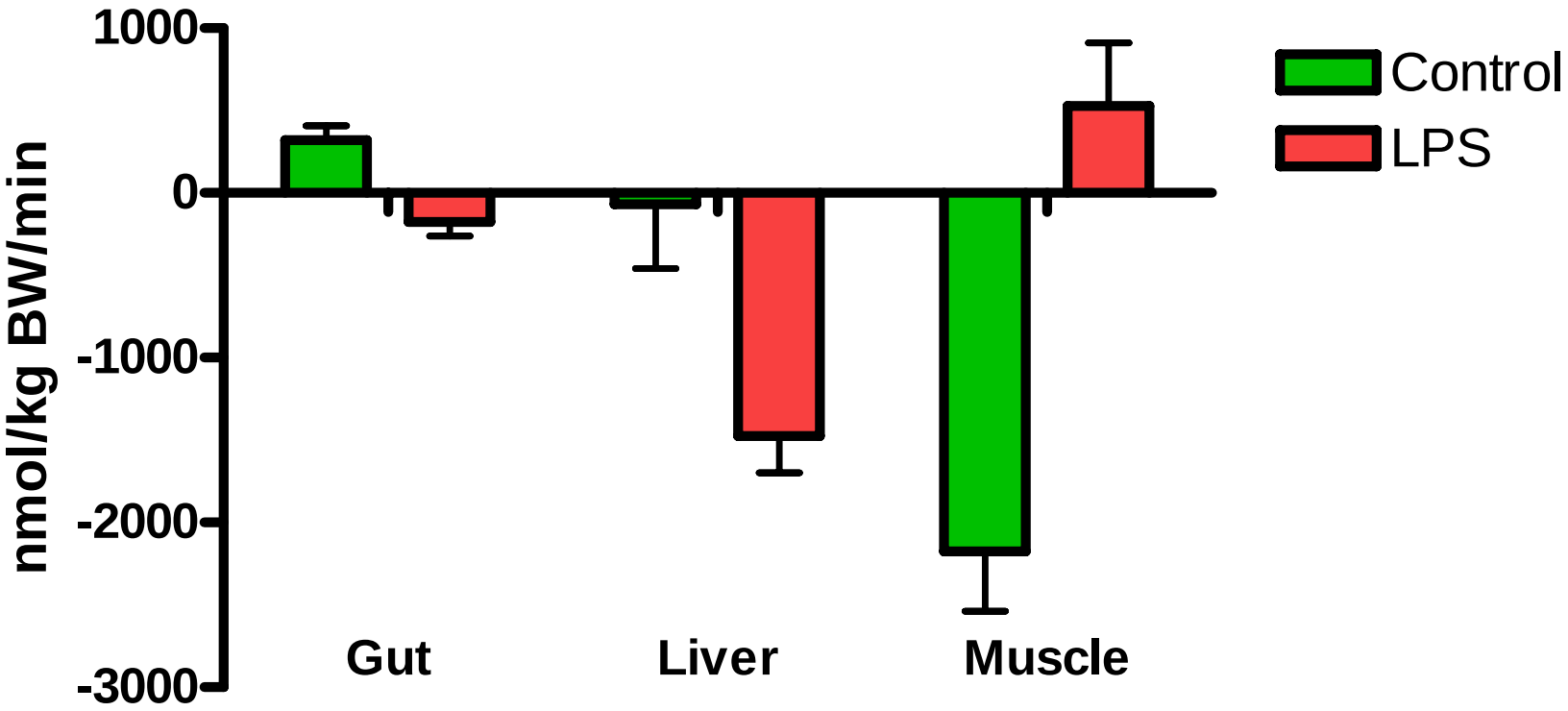
Clin Sci (Lond) **104**(2): 127-41

Interorgan BCAA in fasted pigs during sepsis



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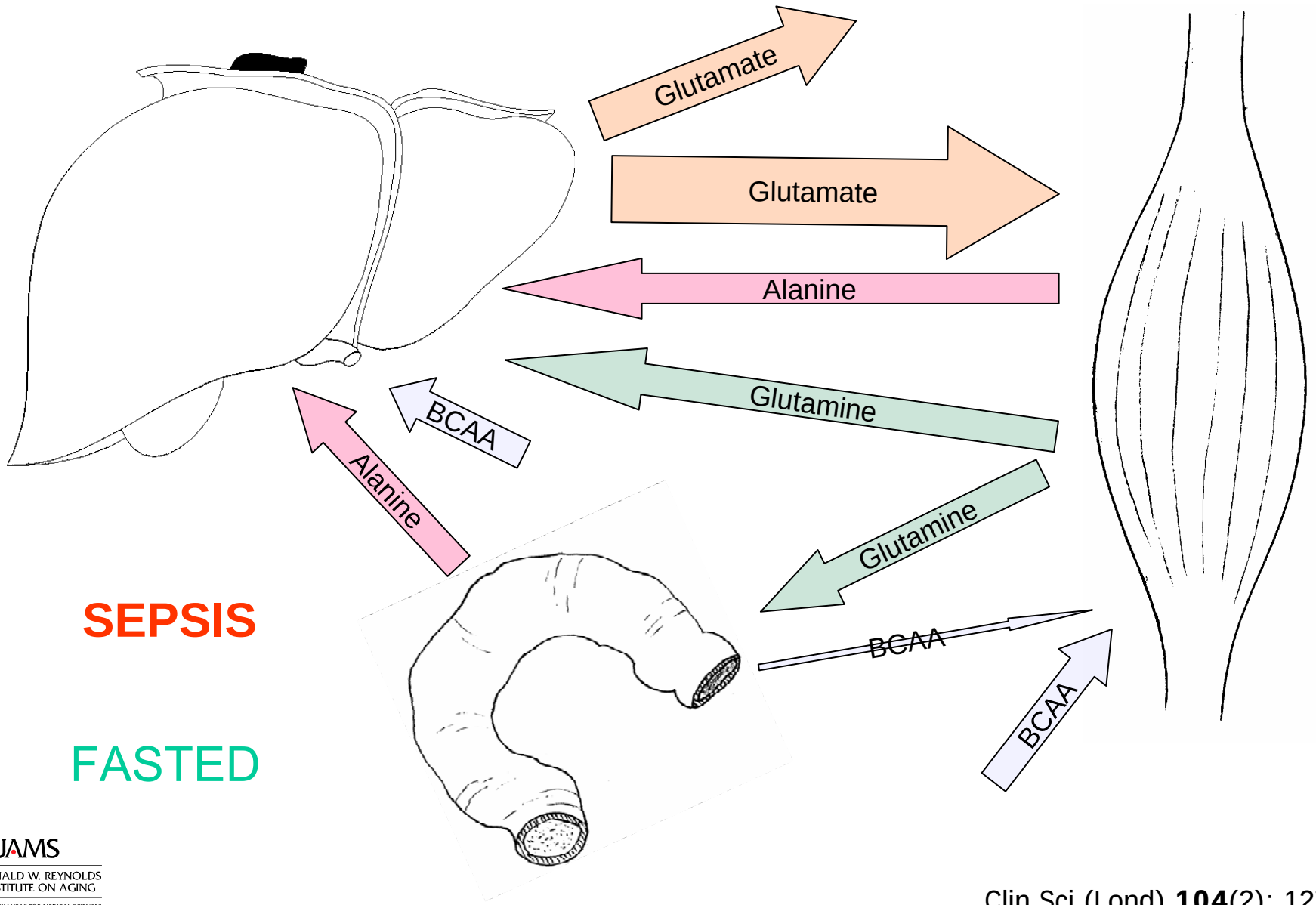
Clin Sci (Lond) **104**(2): 127-41

PIG Interorgan GLU, GLN, ALA and BCAA transport



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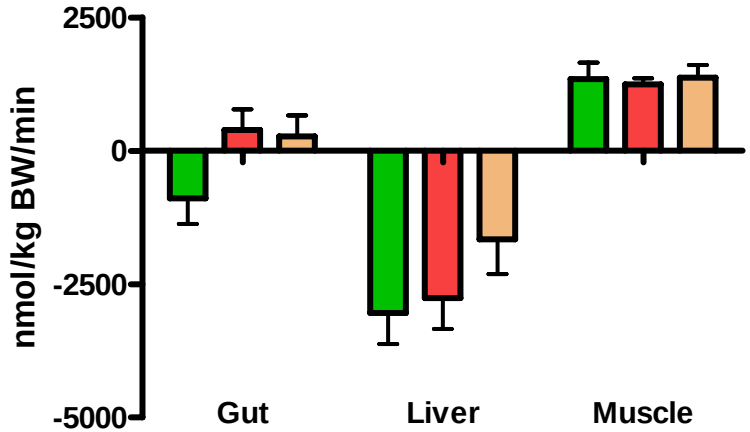
Clin Sci (Lond) **104**(2): 127-41

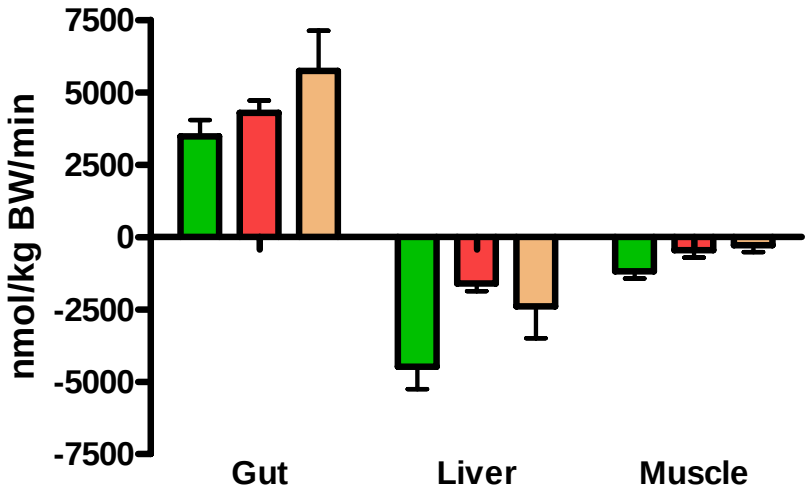
Changes post-sepsis in fed pigs

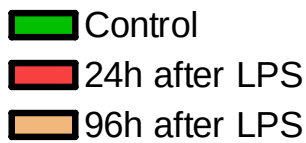
Glutamate

Glutamine



Alanine





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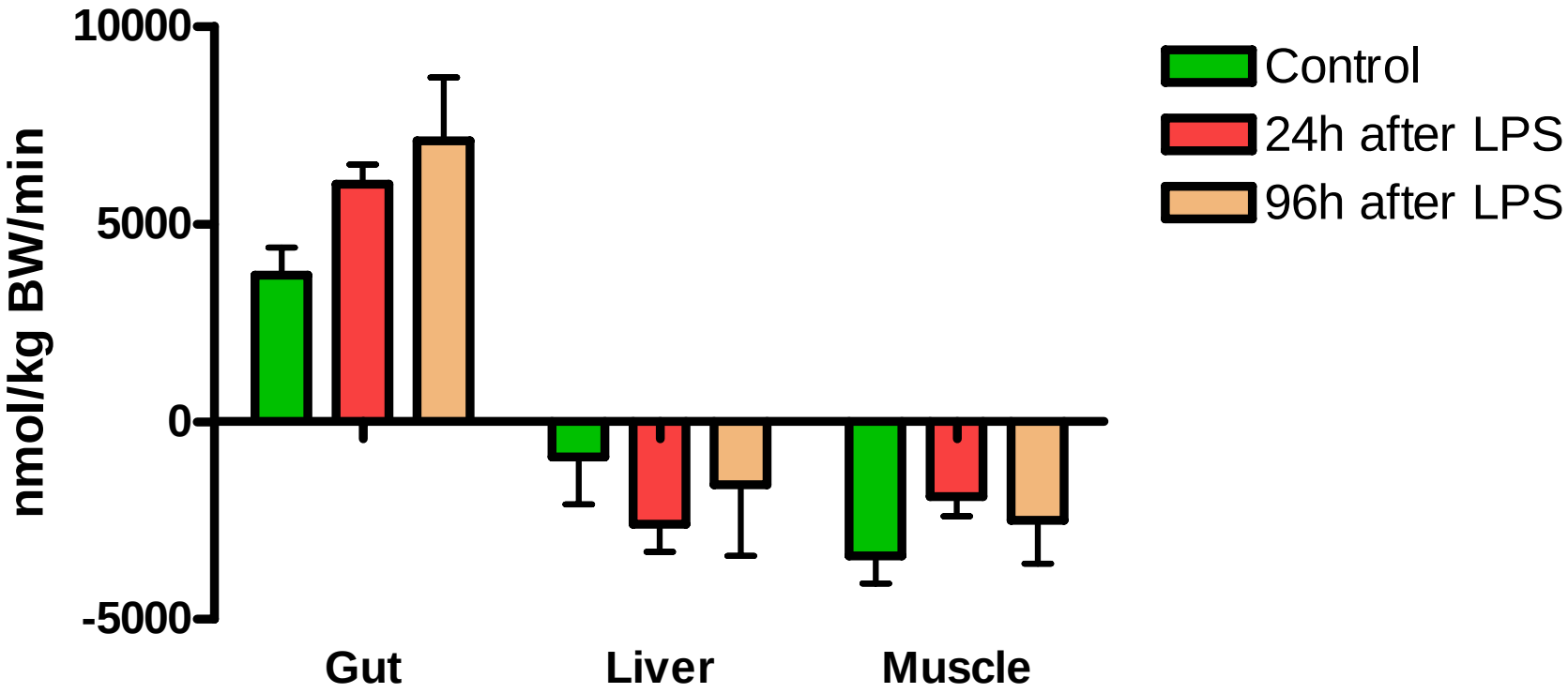
J Nutr **130**(12): 3003-13.

Interorgan BCAA Changes post-sepsis in fed pigs



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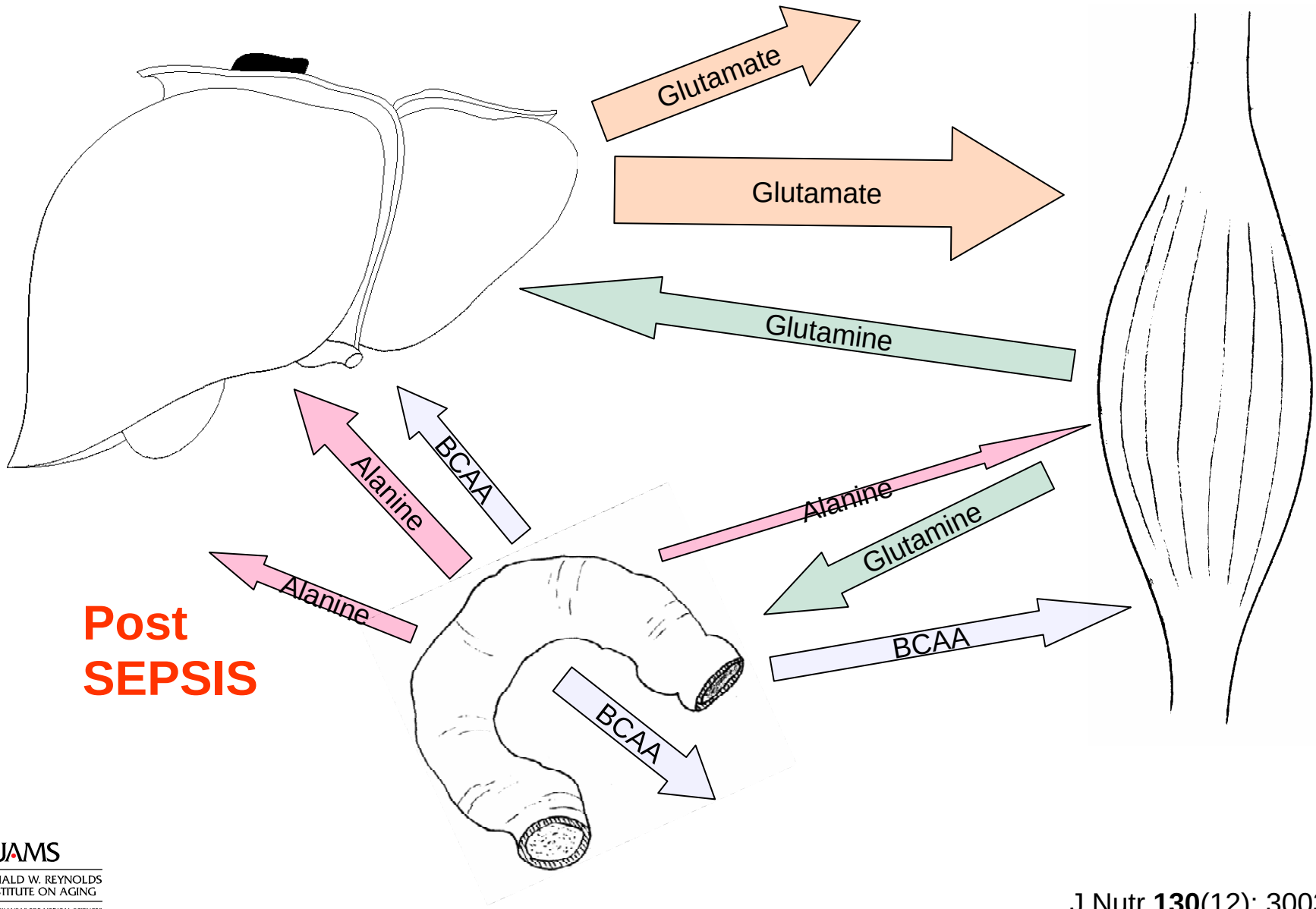

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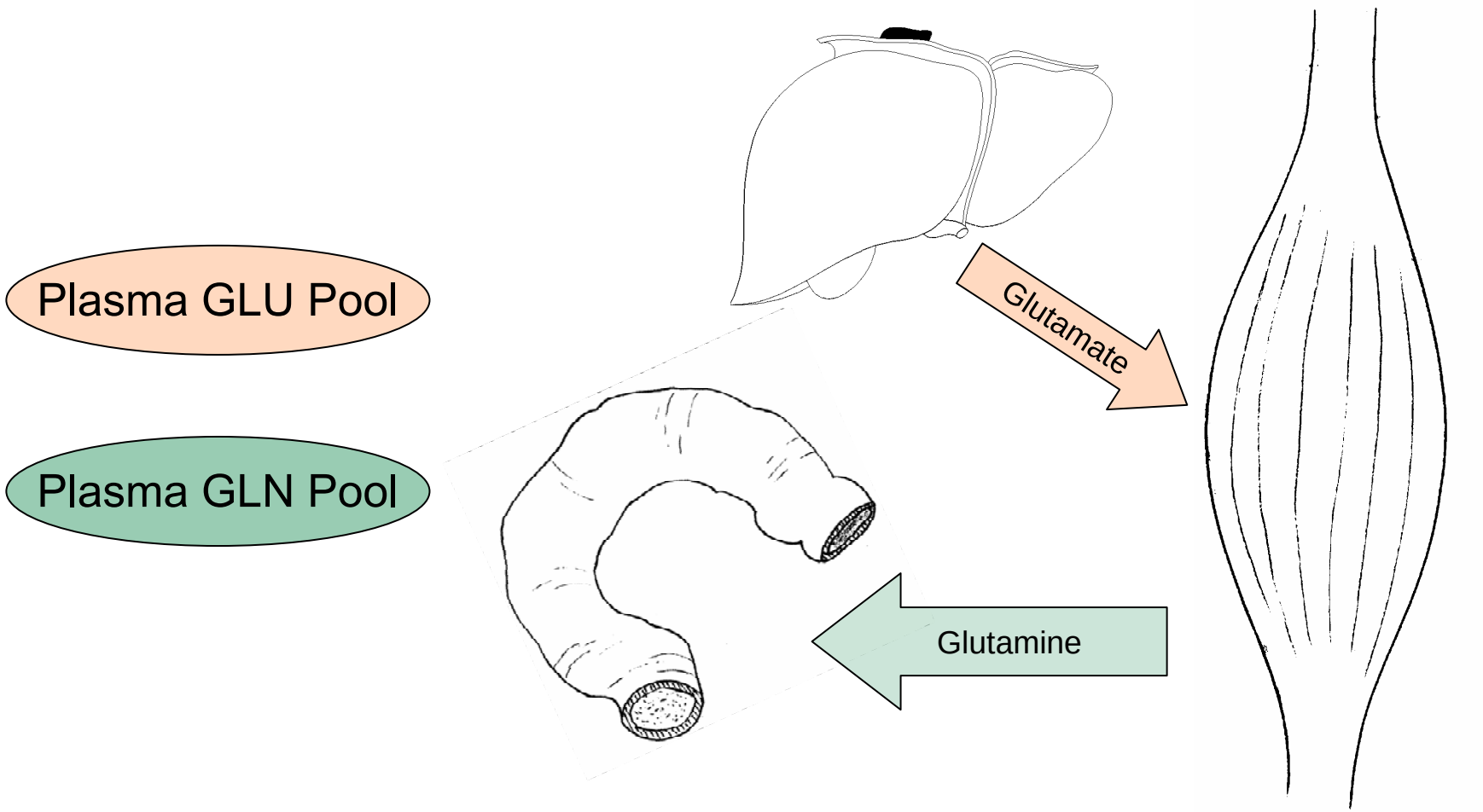
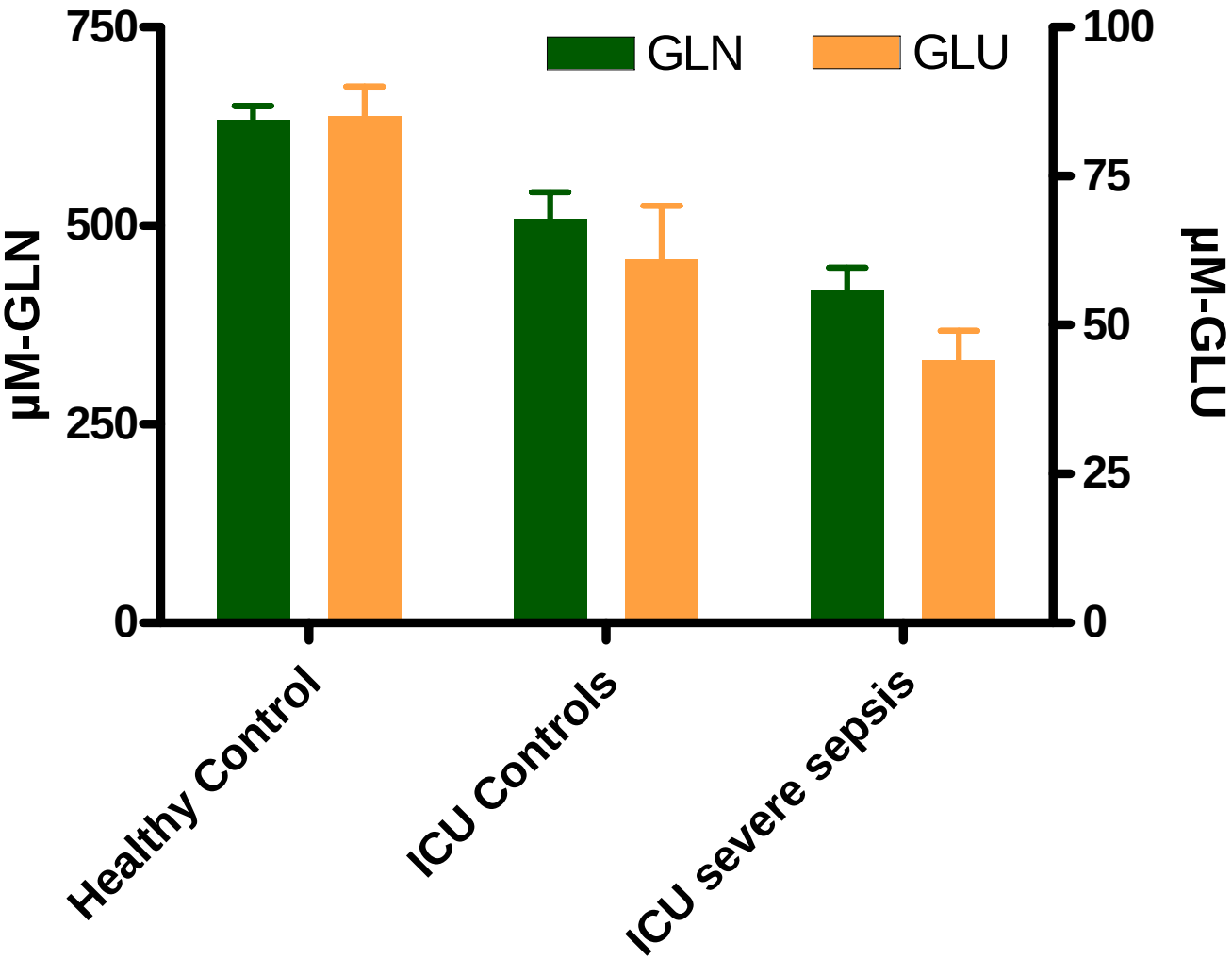
J Nutr **130**(12): 3003-13.

Interorgan GLU to GLN transport in humans



Severe sepsis in humans



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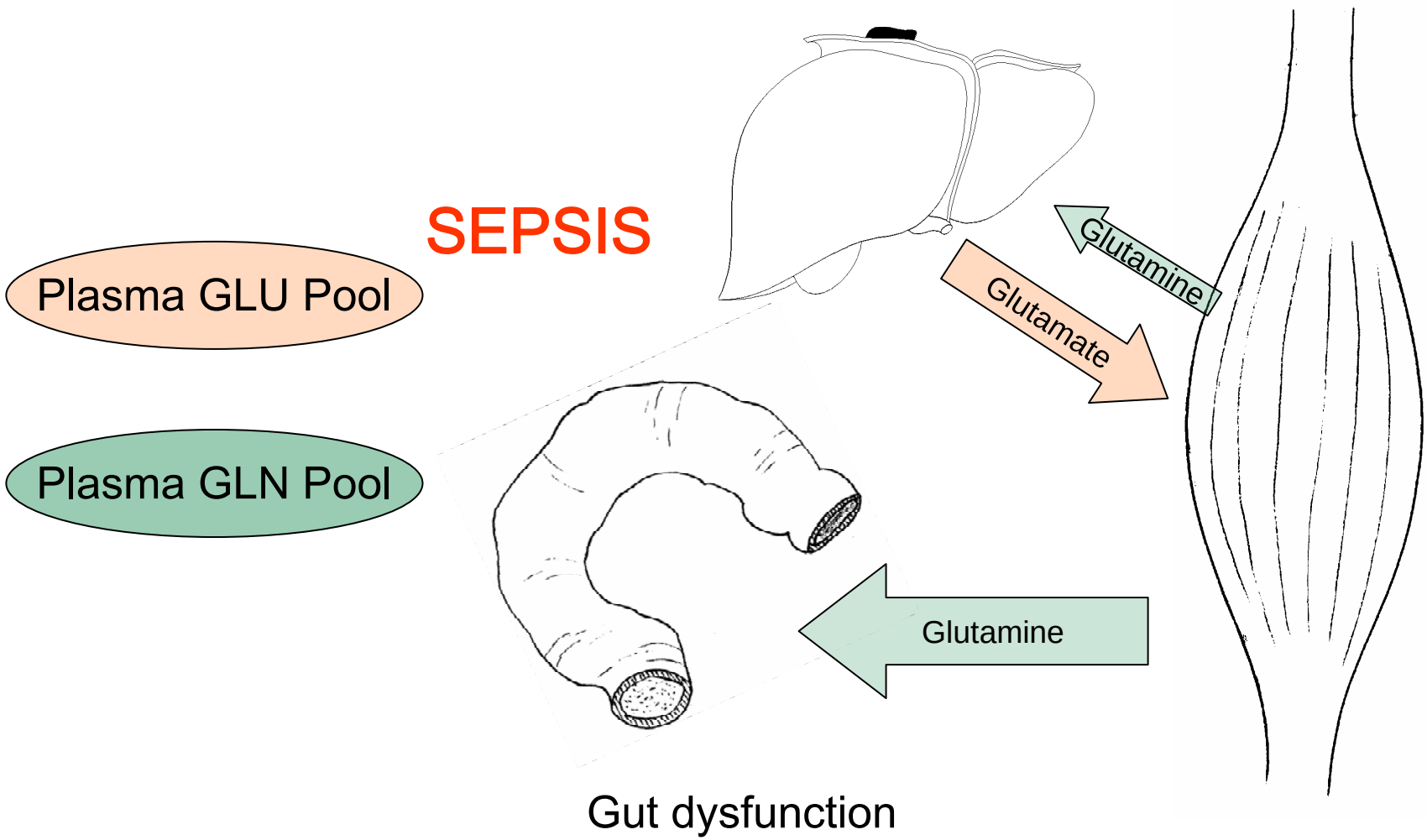
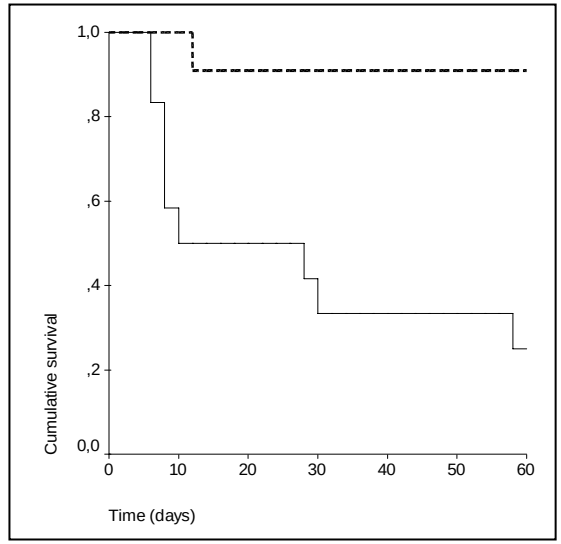
Interorgan GLU to GLN transport in humans

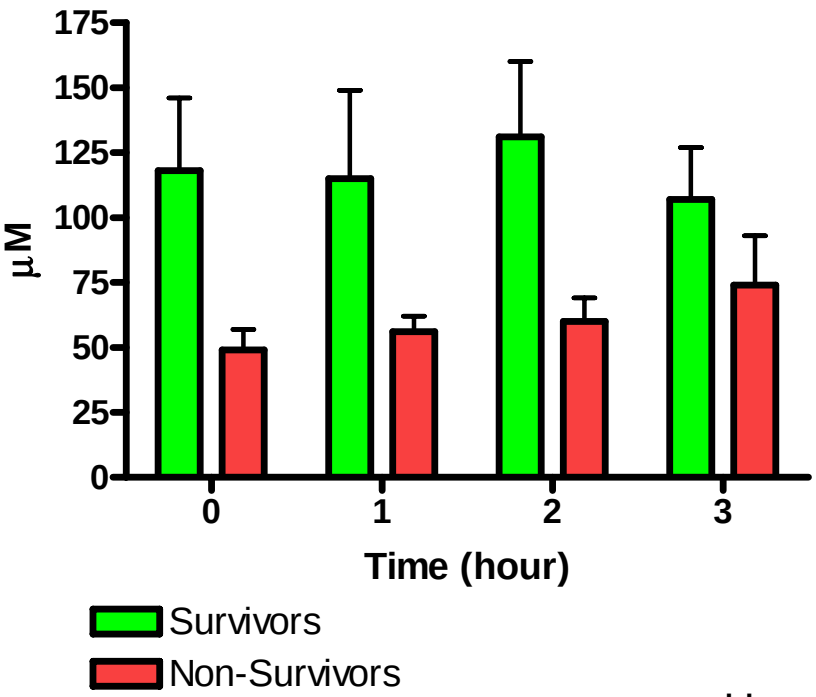


GLU as marker for survival during and after sepsis



	Survivors	Non-survivors	p-value
Number	12	10	
Age (years)	51.2 (3.7)	66.6 (5.3)	0.02
Gender (ratio M: F)	2.3	1.0	0.4
BMI	25.4 (1.1)	23.4 (1.0)	0.2
Diagnostic group Abdominal Pneumonia	 5 8	 7 3	 0.1
Liver OF score at 24 hrs	1.2 (0.8)	1.2 (0.9)	0.7
MOF-score after 24 hours	8.1 (0.5)	8.7 (0.6)	0.5
APACHE-II	26.7 (2.6)	33.9 (2.4)	0.06

All values expressed as mean (SEM). BMI, body mass index; (M)OF, (multiple) organ failure; APACHE, acute physiological and chronic health evaluation. Patients were grouped according to their 60-day survival.



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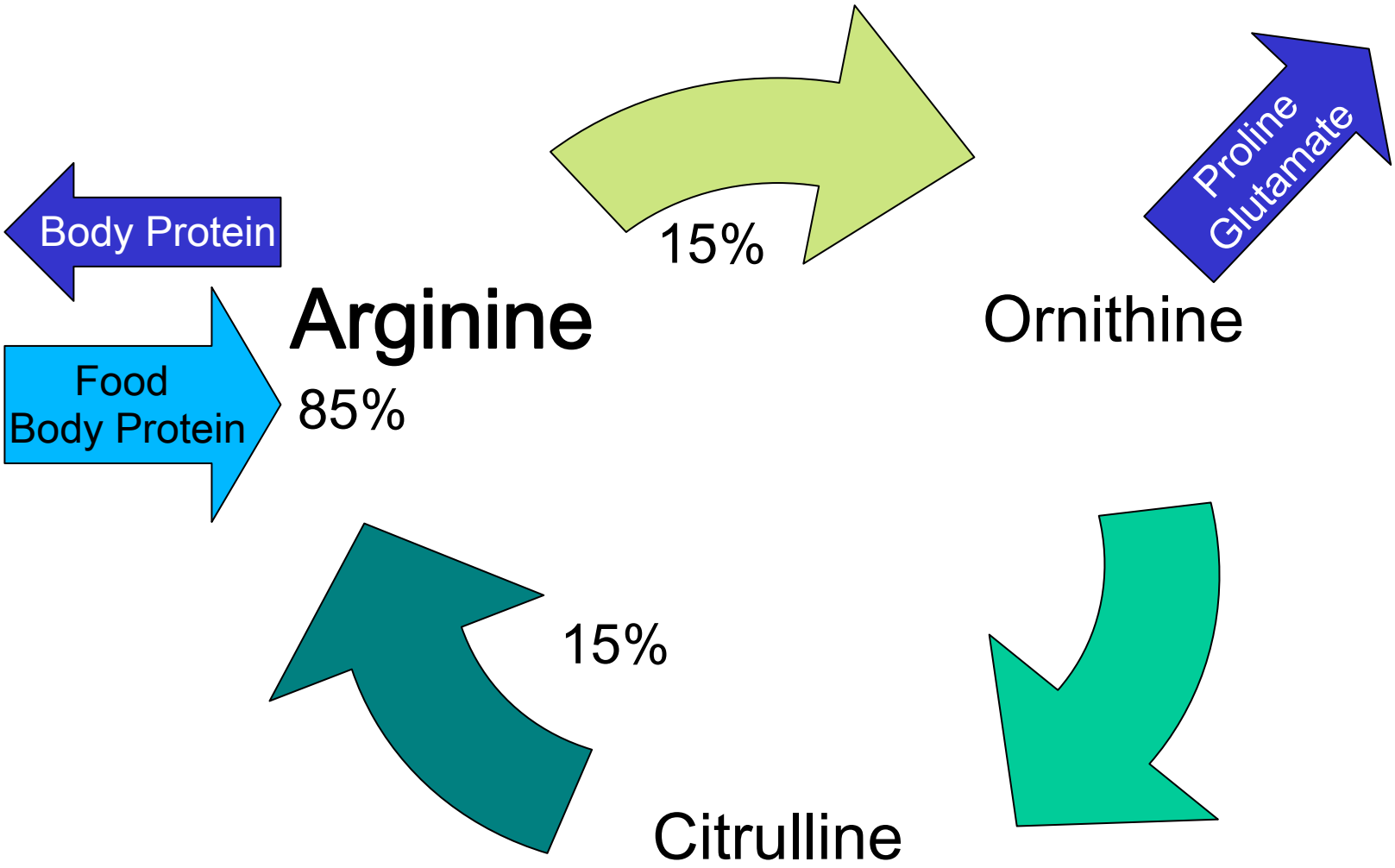
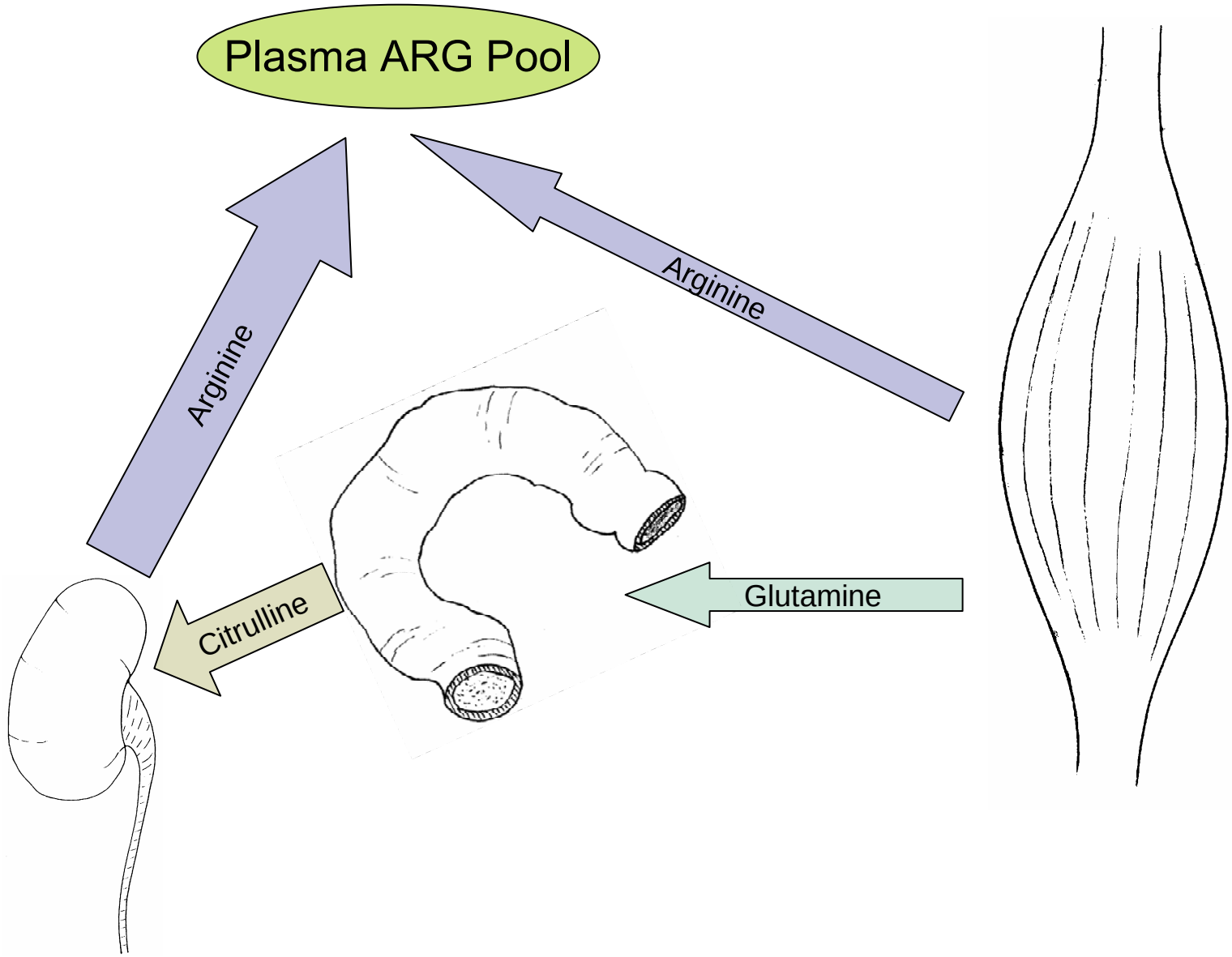
Arginine metabolism



Interorgan CIT and ARG transport



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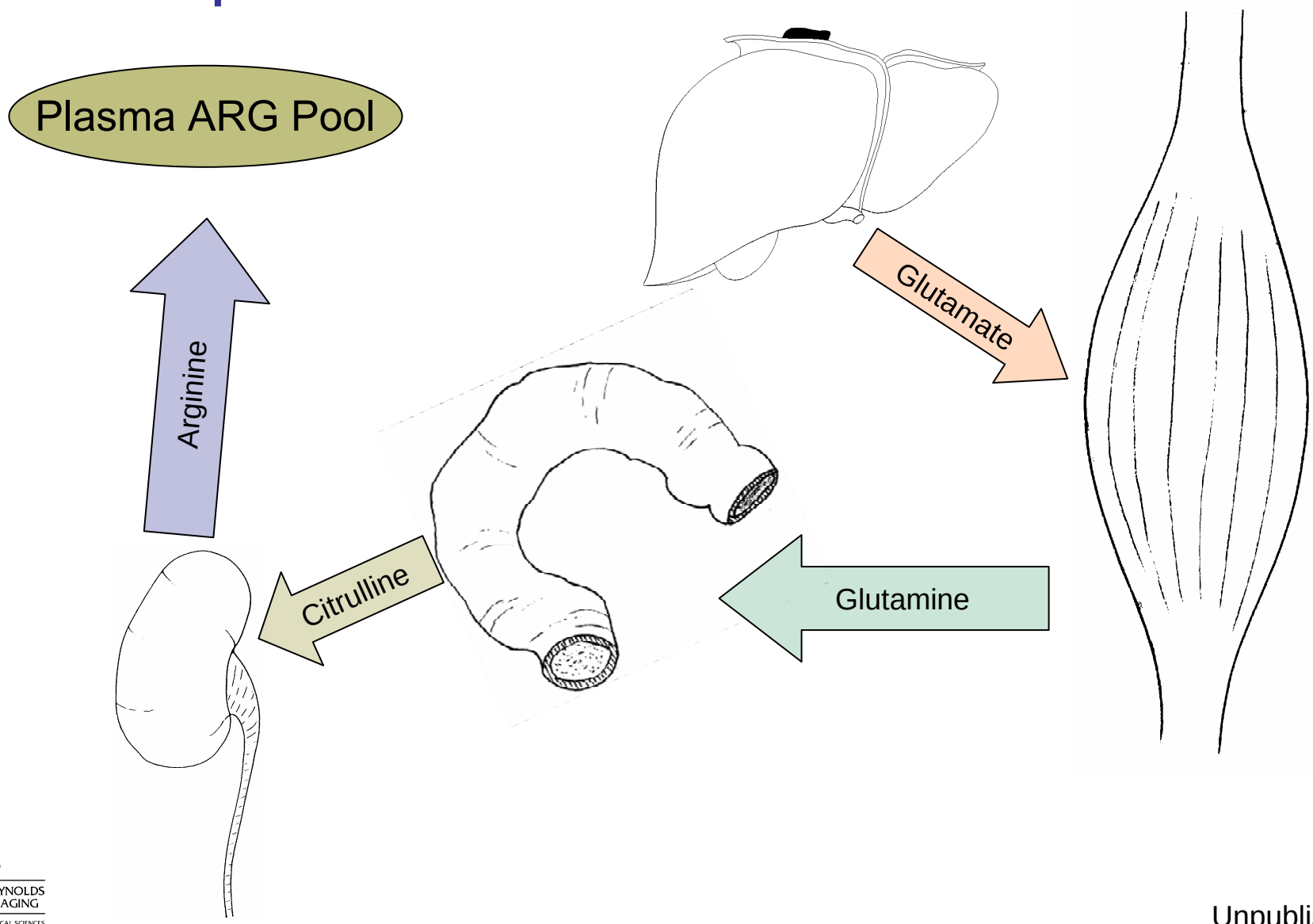
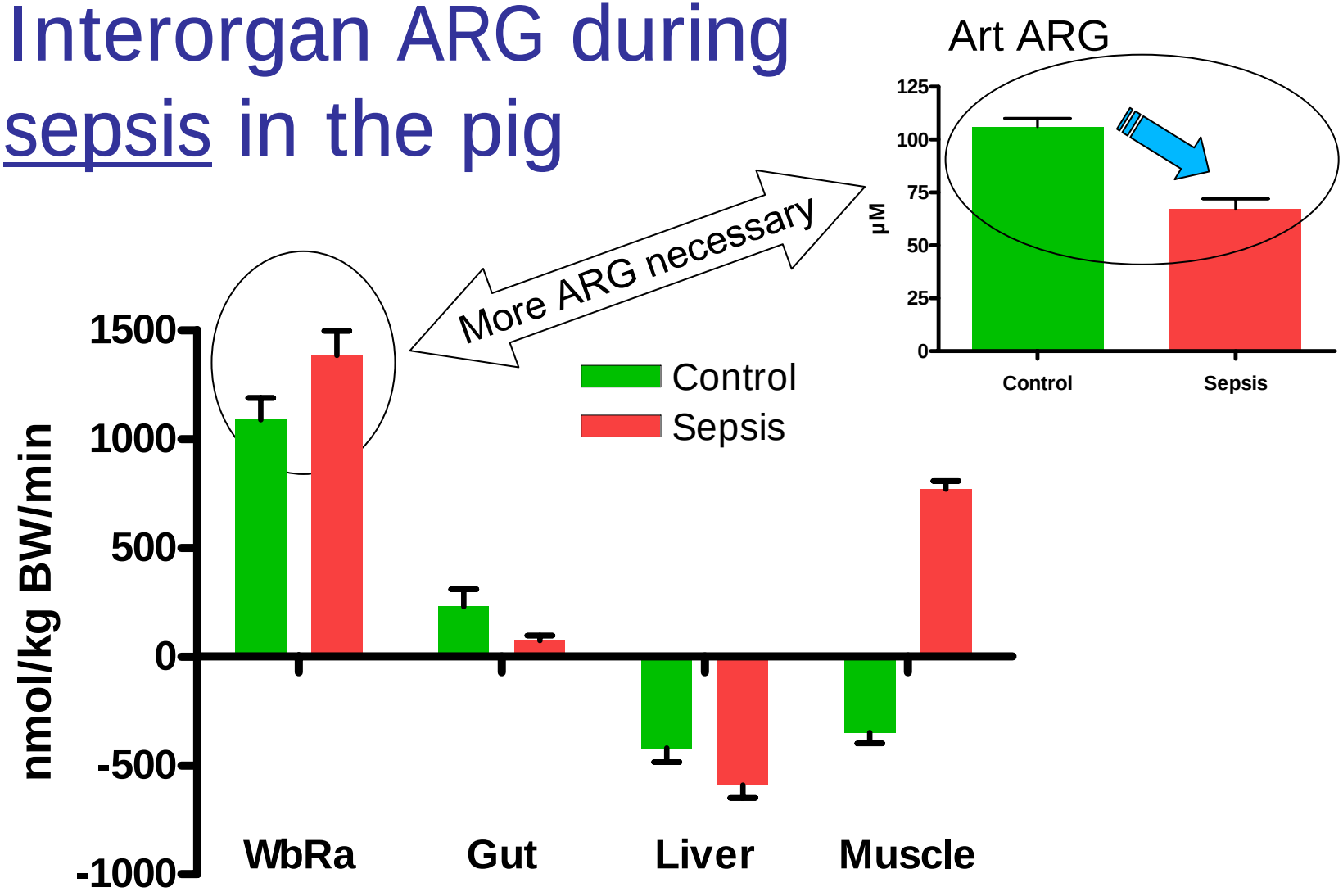
AJCN 2004; 79: 185-97

Interorgan GLU to GLN to Cit to ARG transport in humans



Interorgan ARG during sepsis in the pig



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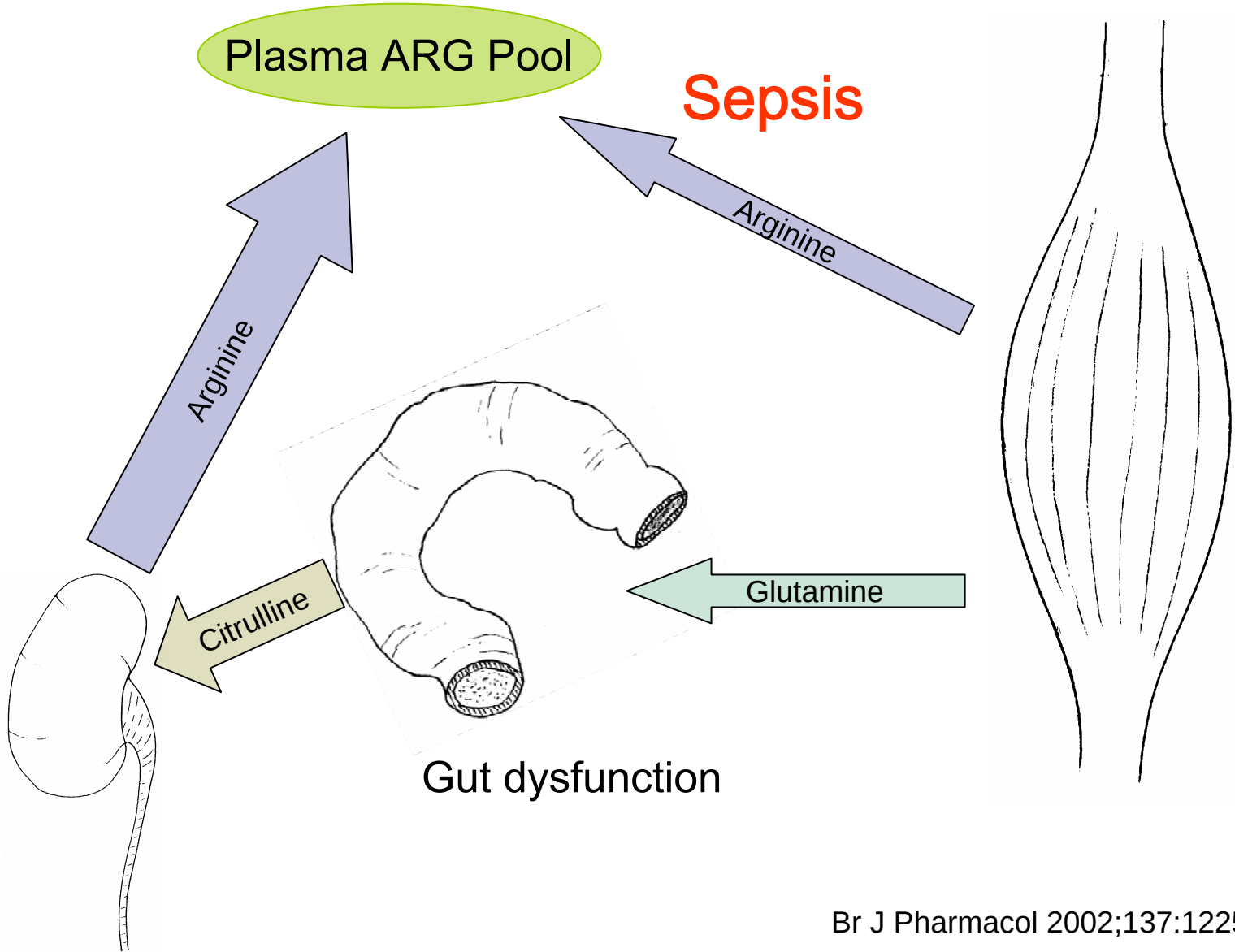
Br J Pharmacol 2002;137:1225-36.

Interorgan CIT and ARG transport in the pig



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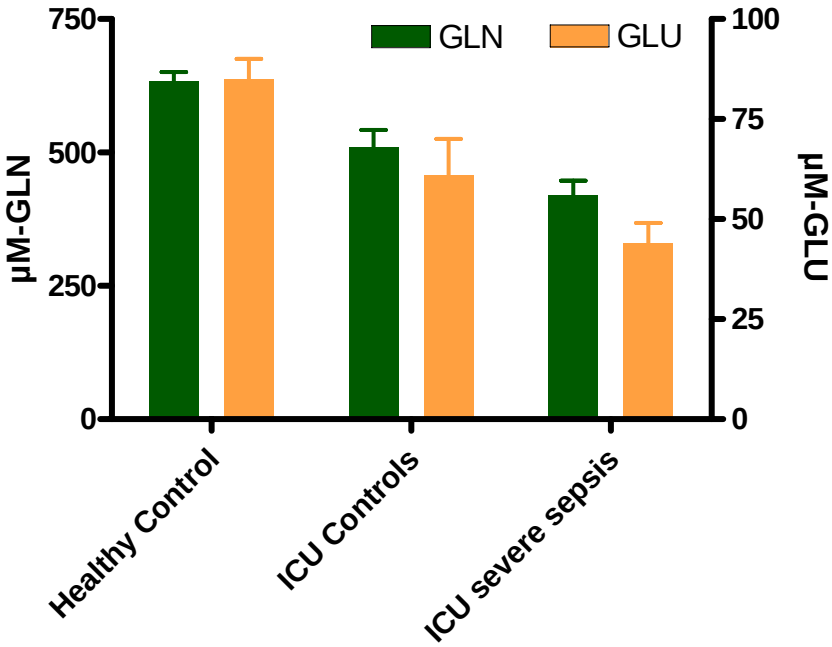

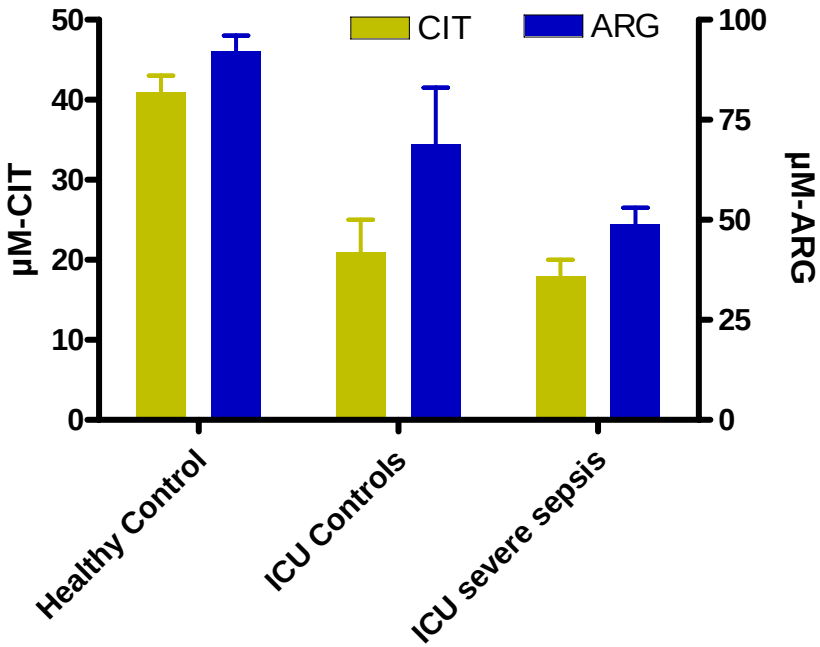

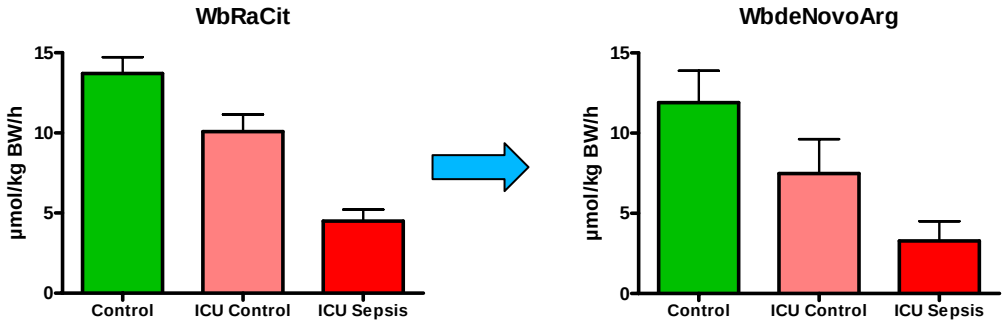

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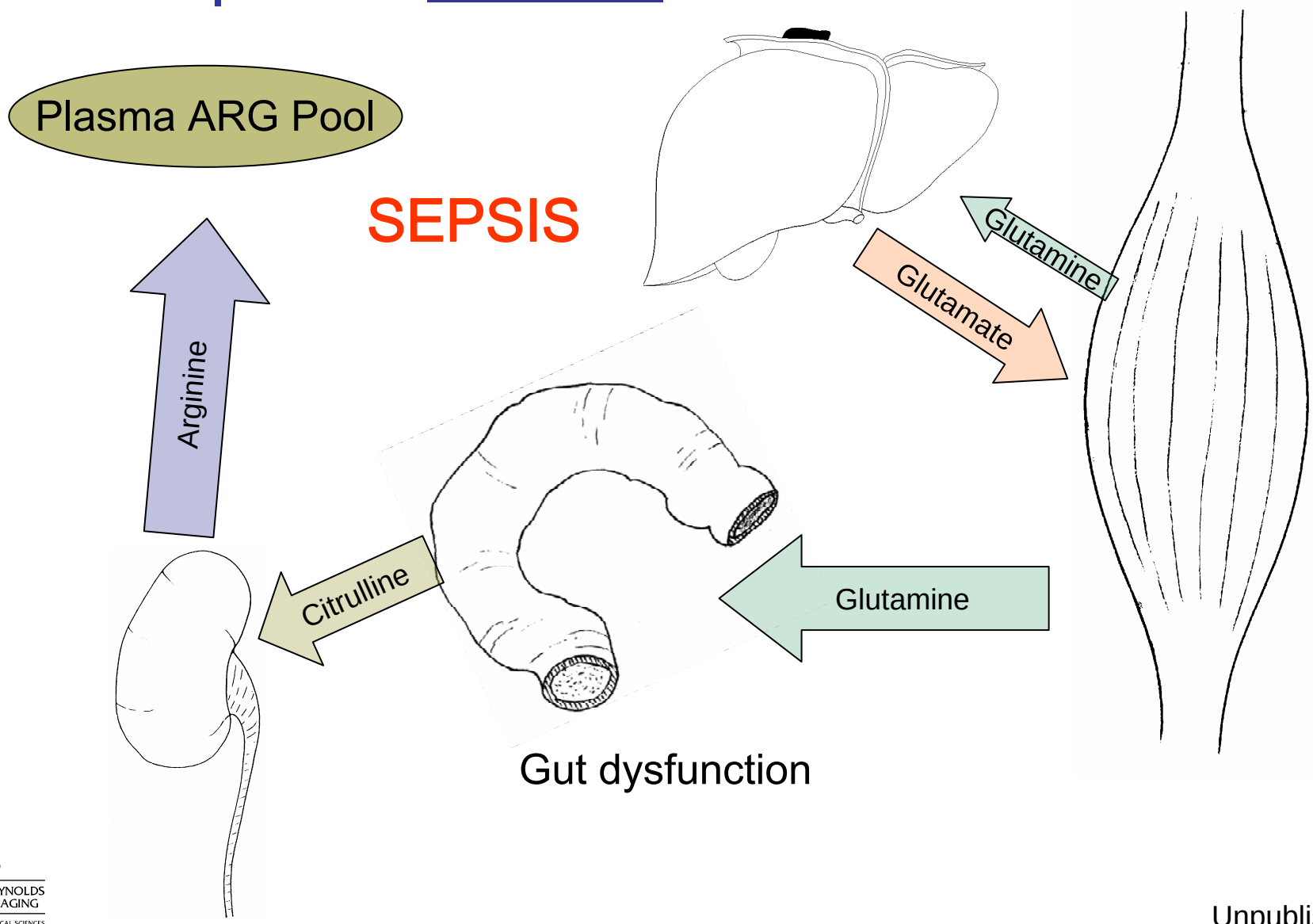
Interorgan GLU to GLN to Cit to ARG transport in humans



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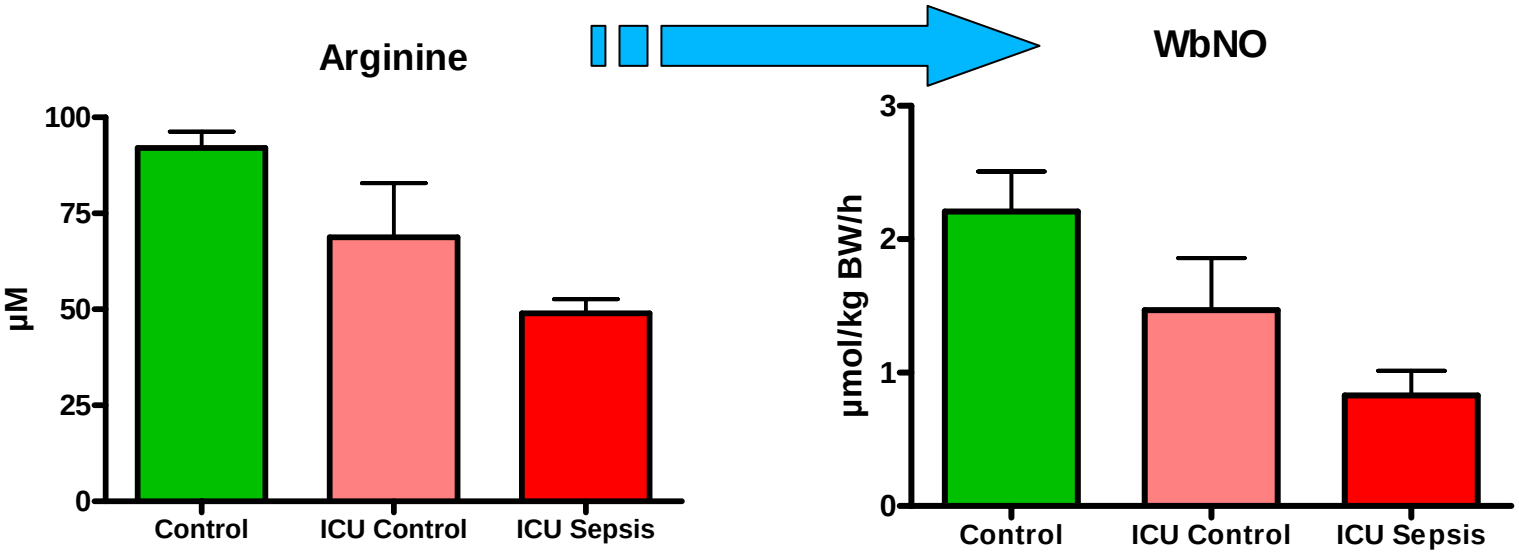
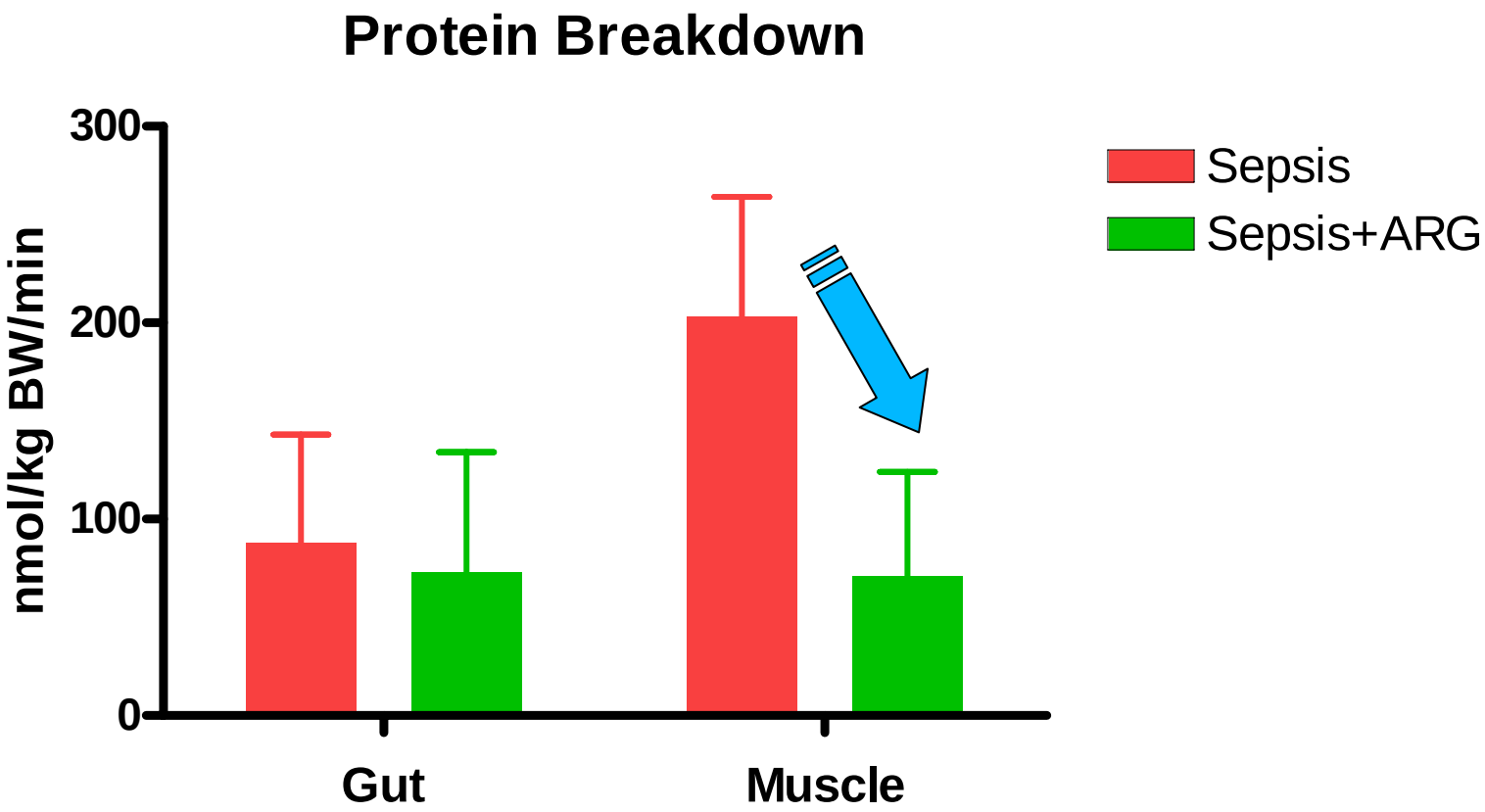
Lower plasma ARG during sepsis is related to reduced Nitric Oxide production



NO (Nitric Oxide) regulates vascular tone and microcirculation and is essential in the immune response

Arginine supplementation
after sepsis in the pig



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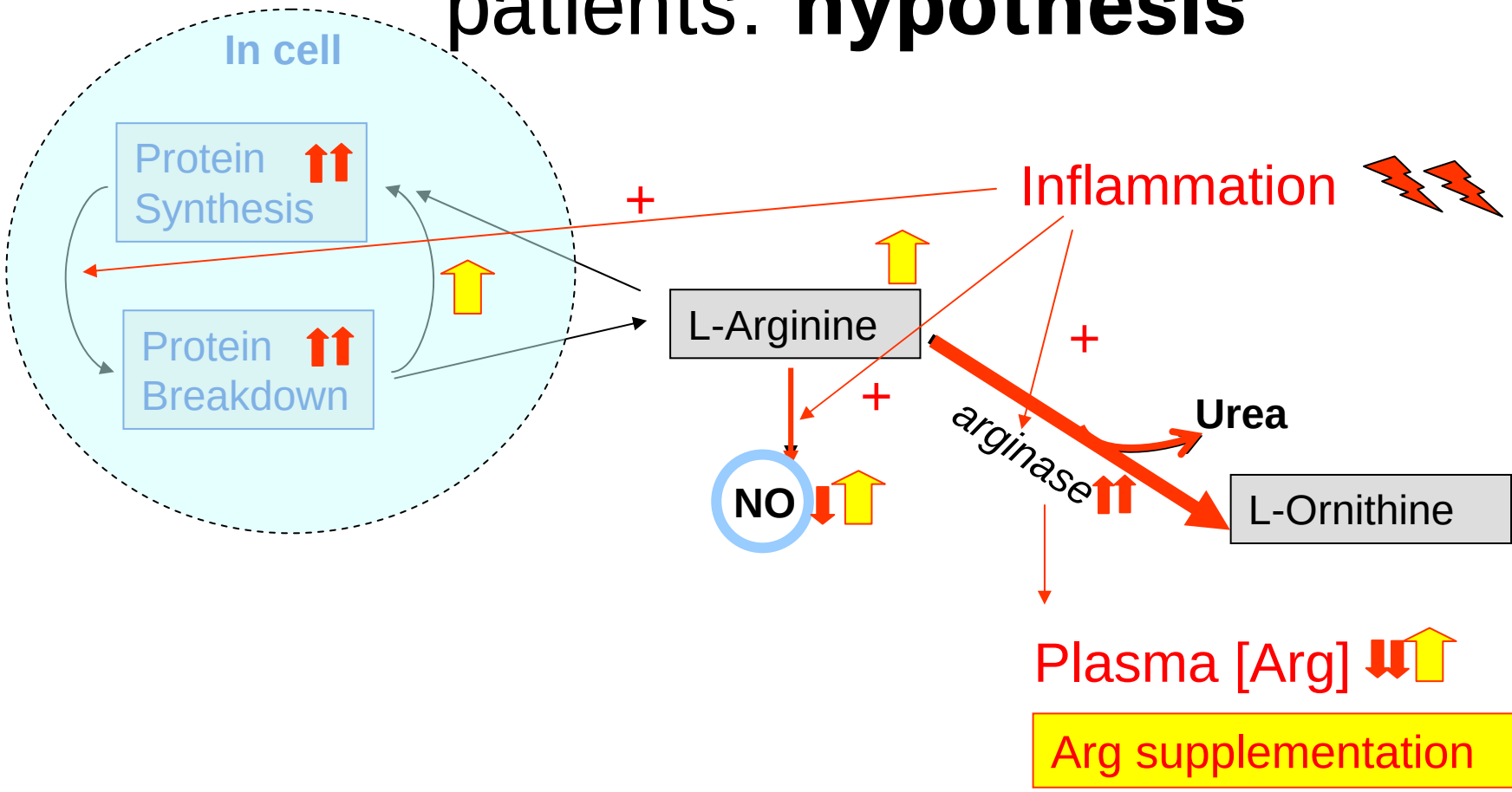
AJCN 2002;75:1031-44

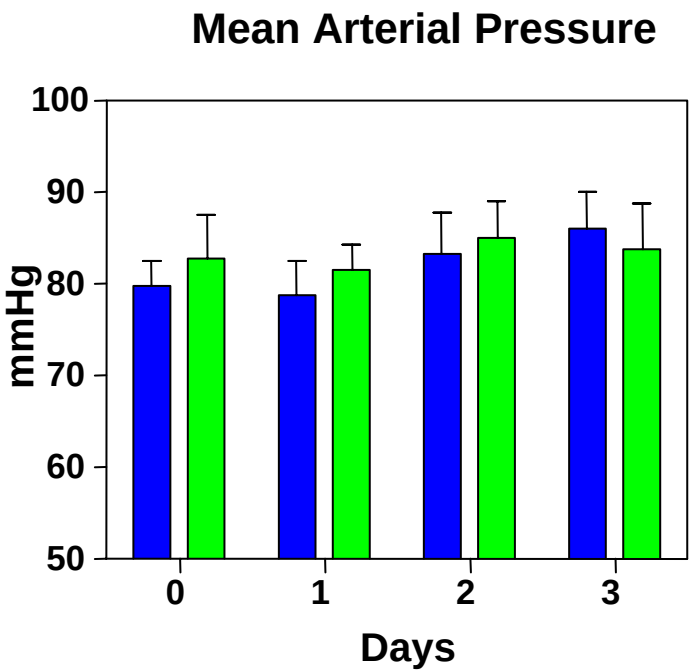
Arginine metabolism in septic patients: **hypothesis**



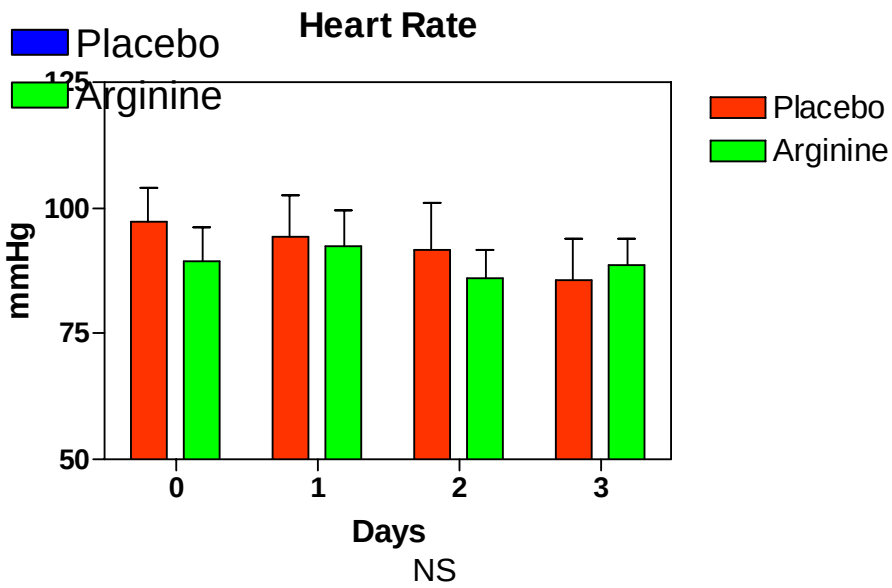
Crit.CareMed 2004;32:2135-45

Placebo-controlled Arginine infusion in septic patients: HAEMODYAMICS

Daily average values of 2h-interval measurements



P<0.05 for time effect (RM-ANOVA)



NS

- Significant increase in mean arterial blood pressure in both groups
- No effect of Arginine infusion

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Crit.CareMed2007; In press

Interorgan exchange of Amino Acids

- Introduction
- Methods to measure interorgan exchange of Amino Acids
- Interorgan exchange Amino Acids during feeding
- Impact Diet on interorgan exchange
- Impact disease on interorgan exchange
- Conclusion

Interorgan exchange of Amino Acids: What is the driving force?

- Driving forces
  - The fasting-feeding transition
  - Presence of disease
- Quantity of the driving forces
  - Role of the Gut as regulator!
  - Role of the quality and form/quantity of the dietary proteins
- Quality of the driving forces
  - The GLU → GLN → CIT → ARG route is important in relation to disease as it drives the ARG production and this also the Nitric Oxide production