Effets régulateurs des acides aminés au niveau intestinal

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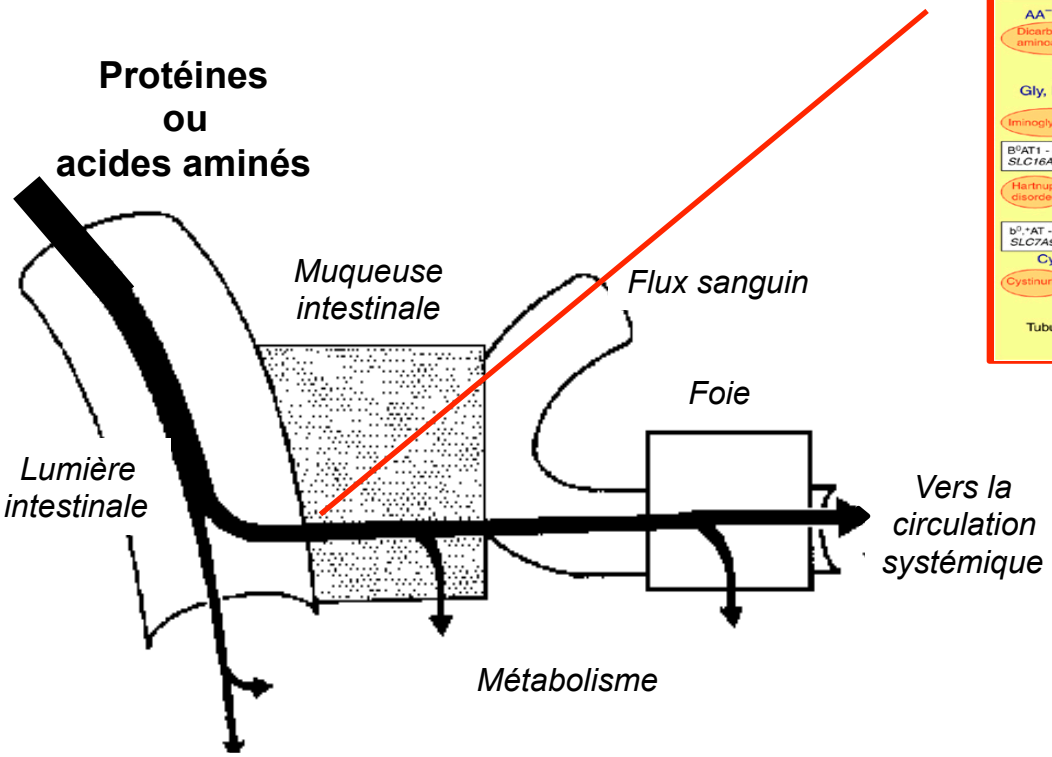
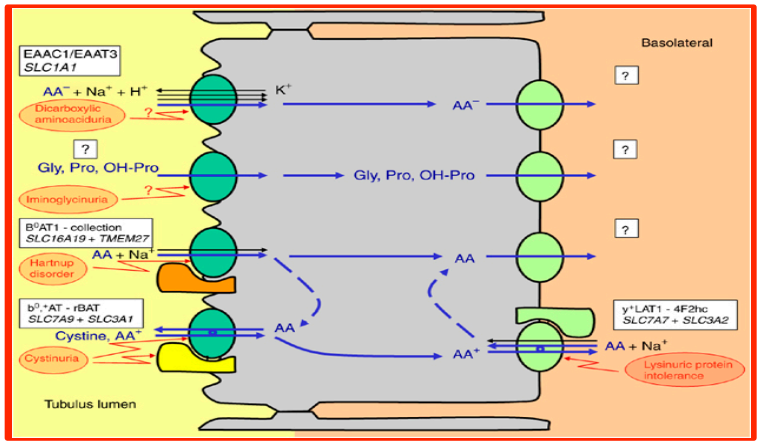
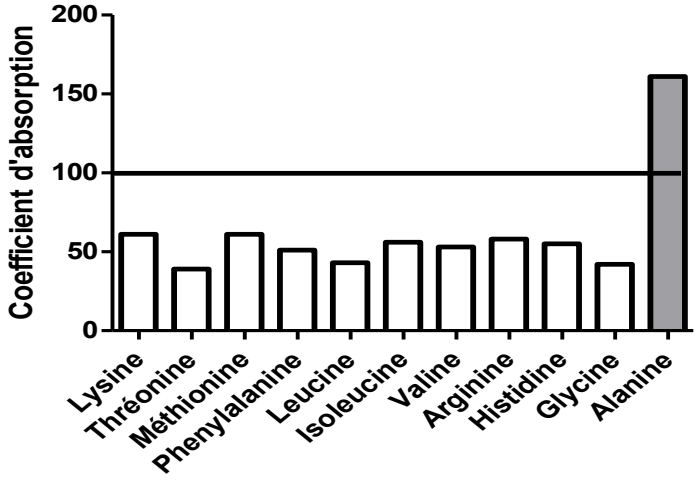
JFN 2013 - Bordeaux

Déclaration d'intérêts:

- **Activités de conseil, fonctions de gouvernance, rédaction de rapports**
  Non
- **Essais cliniques, autres travaux, communications de promotion**
  Non
- **Intérêts financiers (actions, obligations)**
  Non
- **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**
  Non
- **Réception de dons sur une association dont je suis responsable**
  Nestlé, Nutricia, Fresenius Kabi, Astra , MSD, Baxter , Bayer, Janssen-Clag, Roche, Ferring
- **Perception de fonds d'une association dont je suis responsable et qui a reçu un don**
  Non
- **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**
  Non

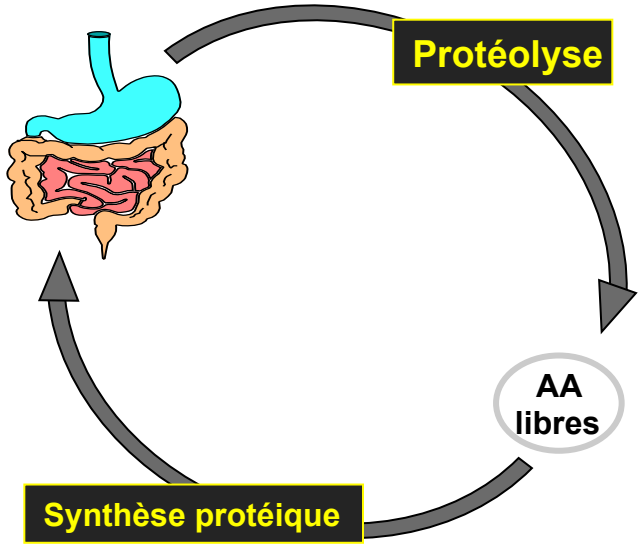

Protéines
ou
acides aminés
Muqueuse
intestinale
Flux sanguin
Foie
Lumière
intestinale
Vers la
circulation
systémique
Métabolisme


Basolateral
EAAC1/EAAT3
SLC1A1
Dicarboxylic aminoaciduria
Gly, Pro, OH-Pro
Iminoglycinuria
B0AT1 - collection
SLC16A19 + TMEM27
Hartnup disorder
b0,+AT - rBAT
SLC7A9 + SLC3A1
Cystine, AA+
Cystinuria
y+LAT1 - 4F2hc
SLC7A7 + SLC3A2
Lysinuric protein intolerance
Tubulus lumen


Coefficient d'absorption
200
150
100
50
0
Lysine
Thréonine
Méthionine
Phenylalanine
Leucine
Isoleucine
Valine
Arginine
Histidine
Glycine
Alanine

→ 50% des protéines sont renouvelées par jour.

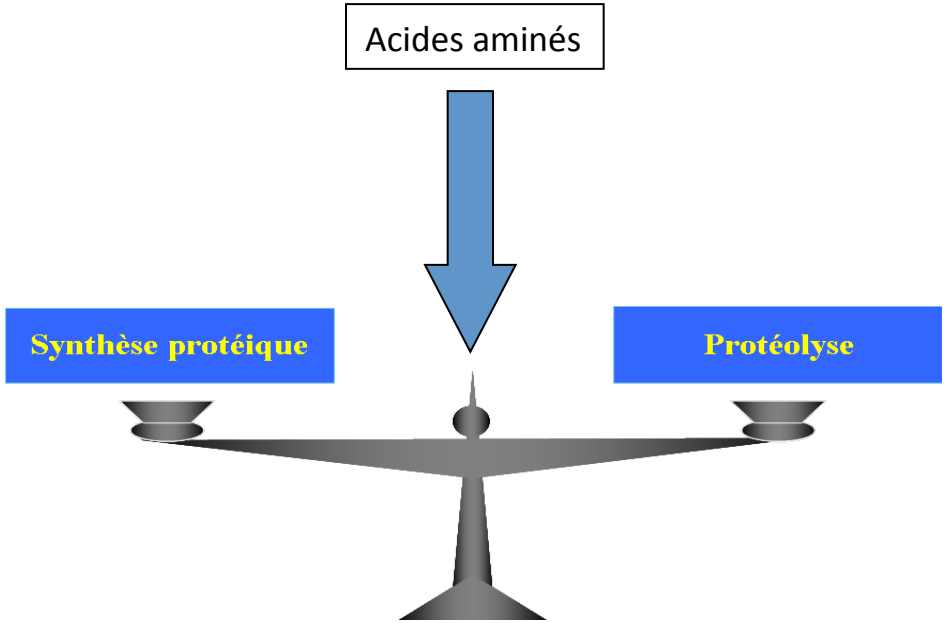
Nakshabendi et al, 1996

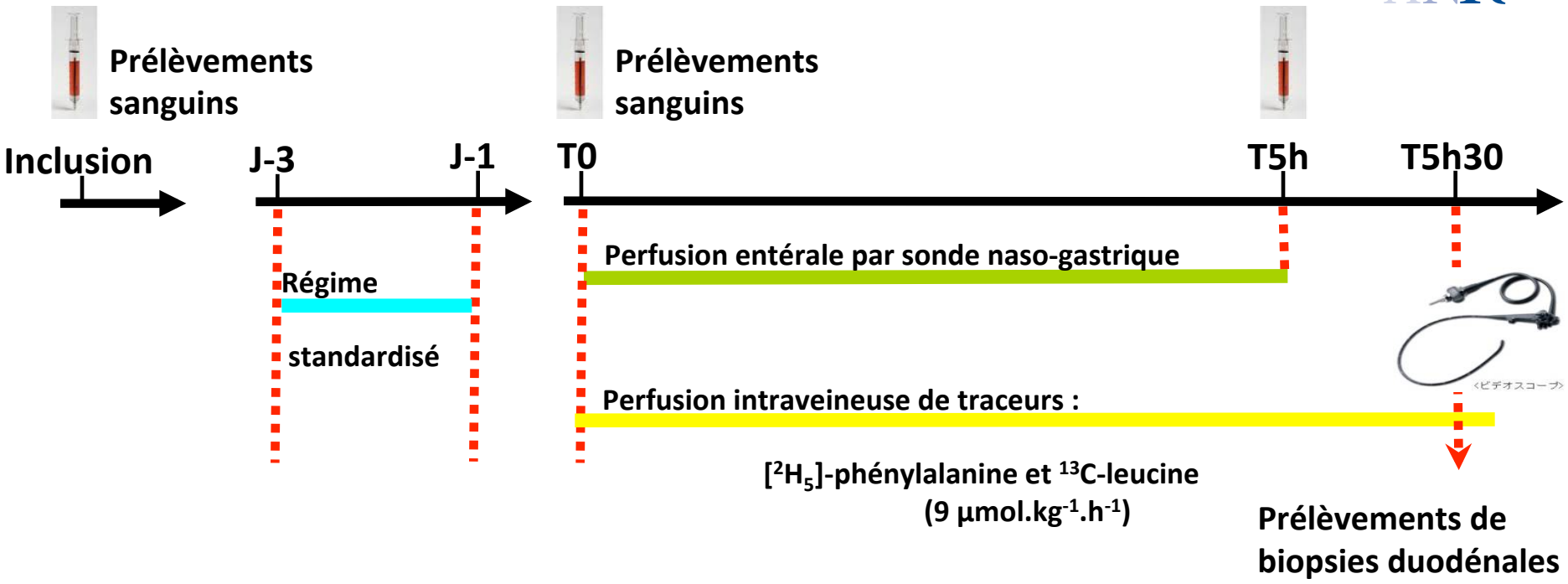


ATP-ubiquitine dépendante

Activée par le Ca^{2+} (calpaines)

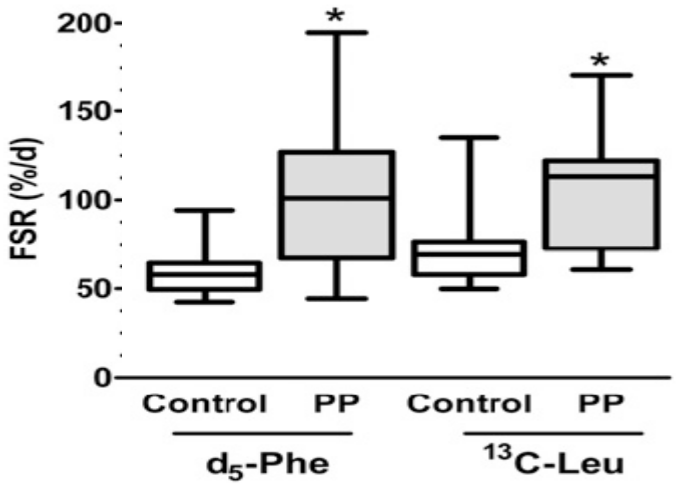
Lysosomale (cathepsines)



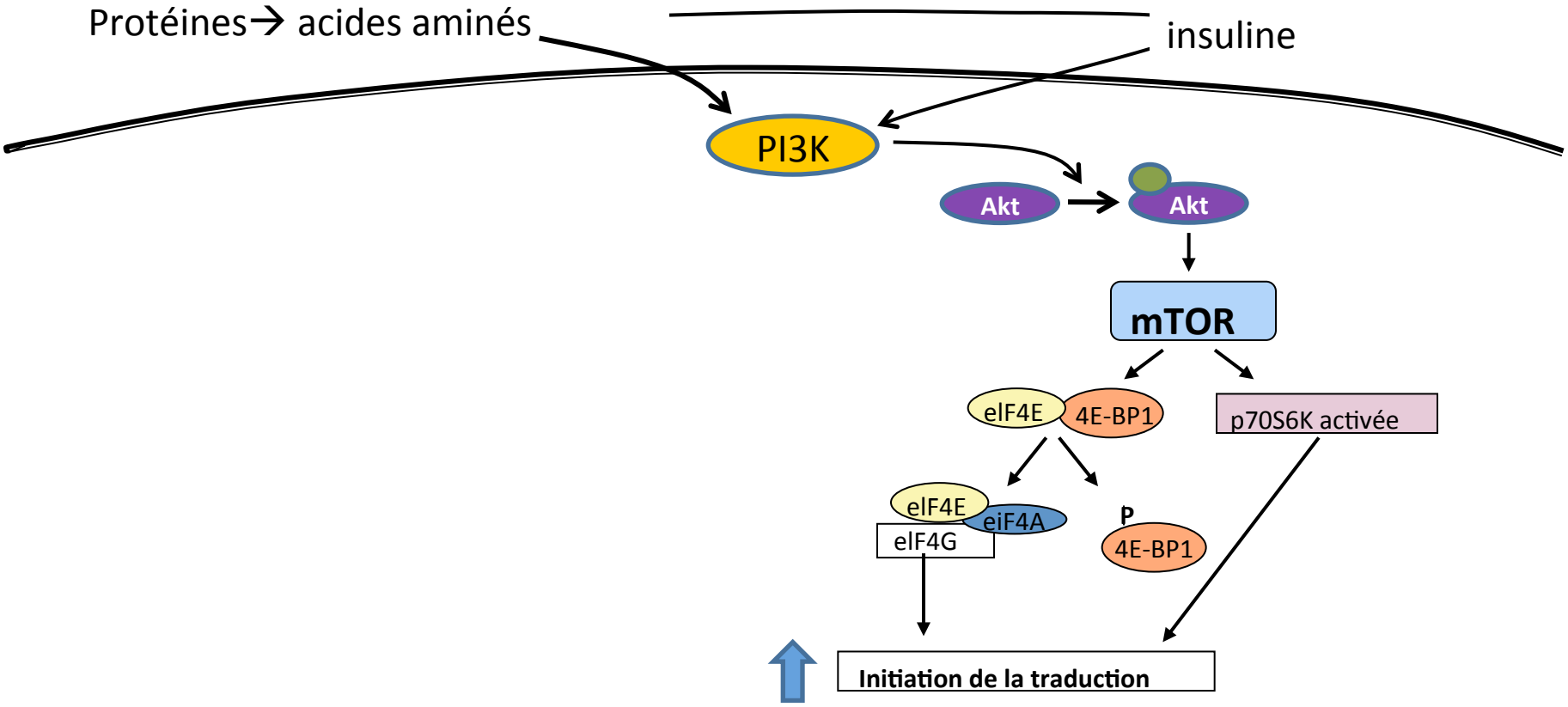


→Perfusion entérale de maltodextrines

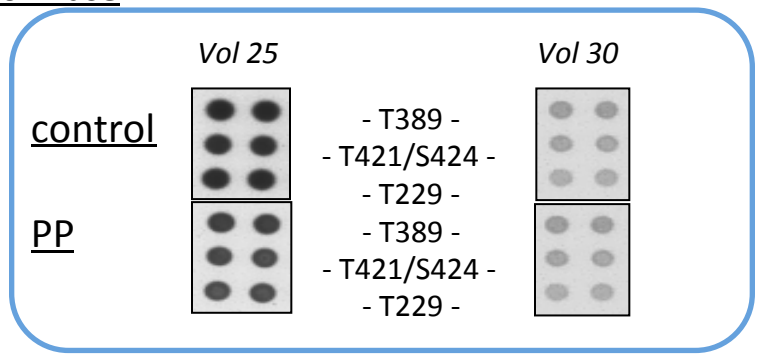
→ Perfusion entérale de maltodextrines + **poudre de protéines**



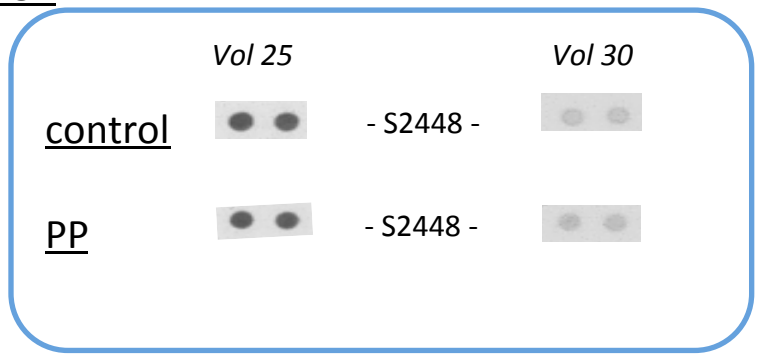
Coëffier et al, AJCN 2013


Protéines→ acides aminés
insuline
PI3K
Akt
Akt
mTOR
eIF4E
4E-BP1
p70S6K activée
eIF4E
eiF4A
eIF4G
P
4E-BP1
Initiation de la traduction

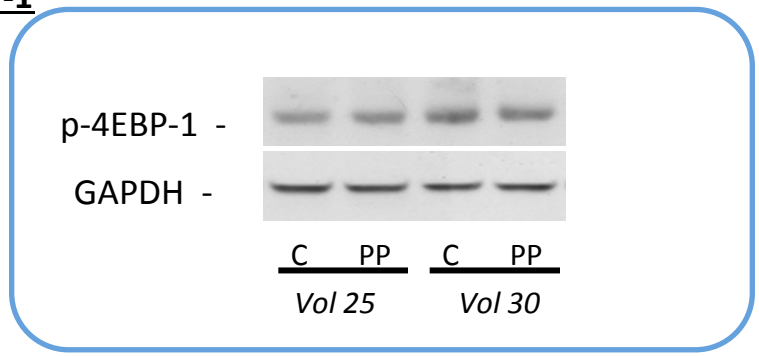
p70S6kinase



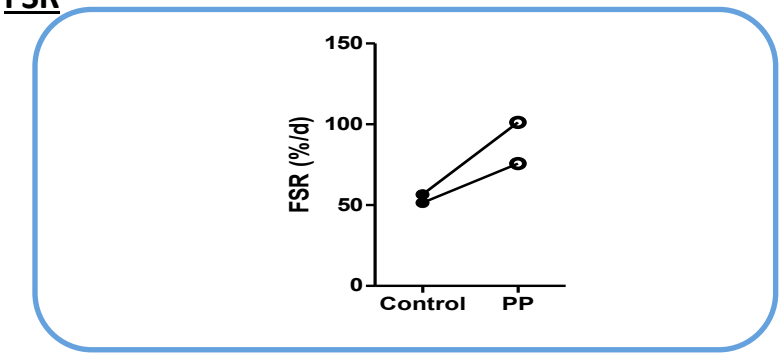
mTOR



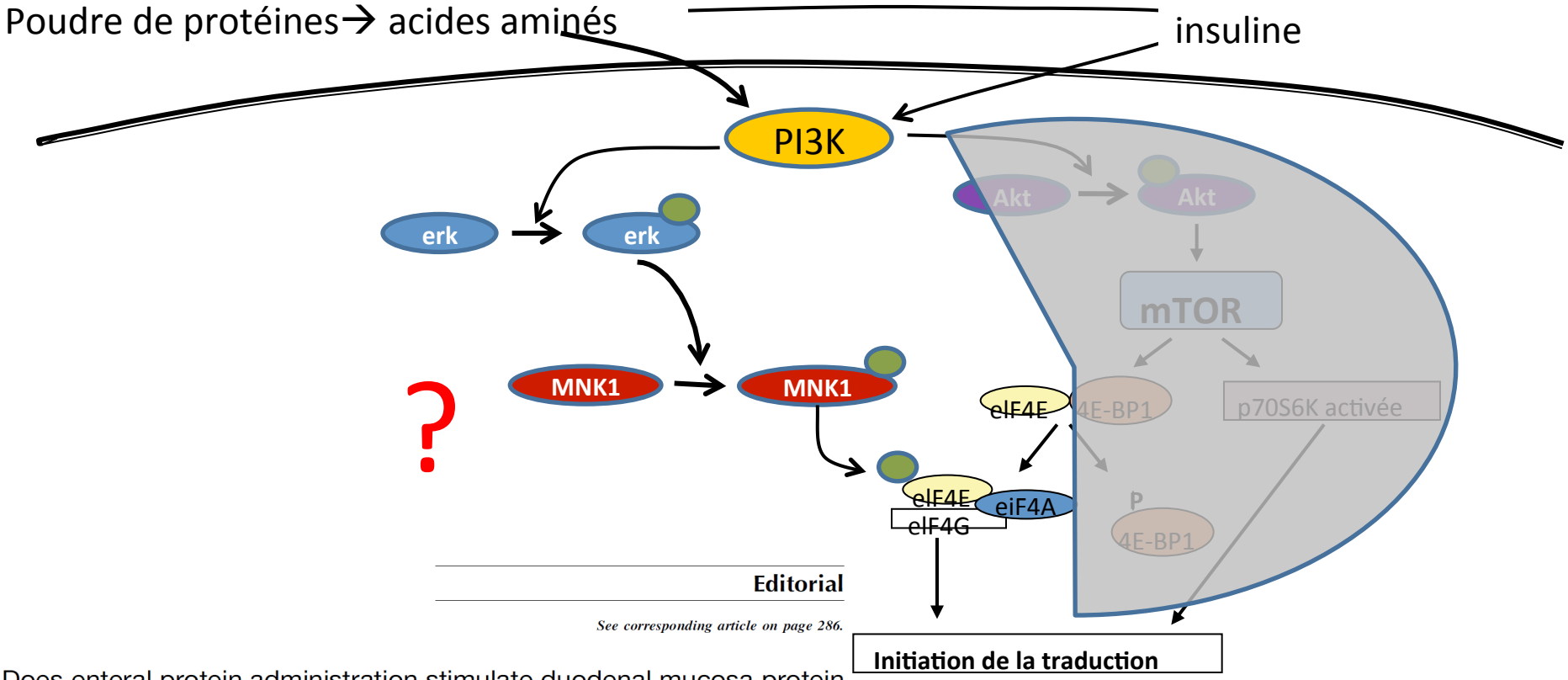
4EBP-1



FSR



Coëffier et al, AJCN 2013

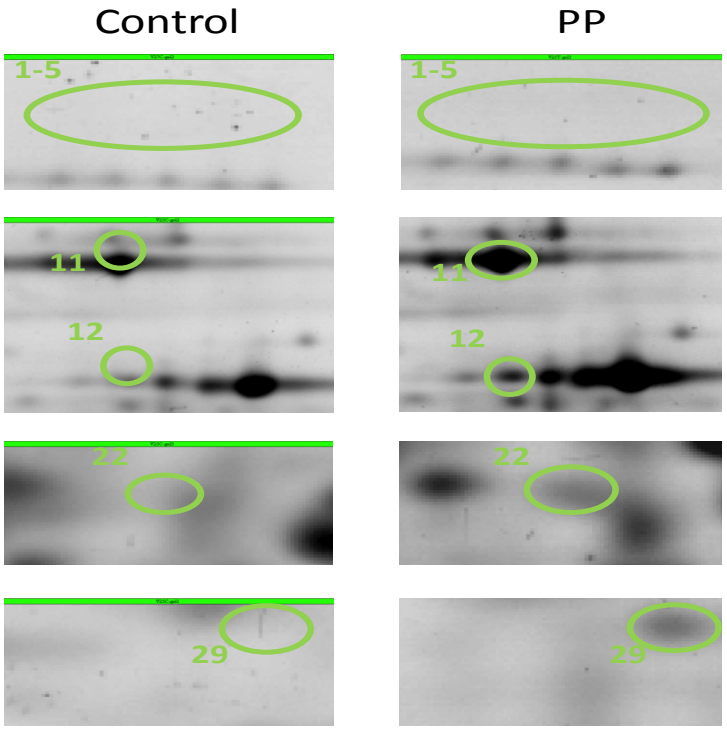


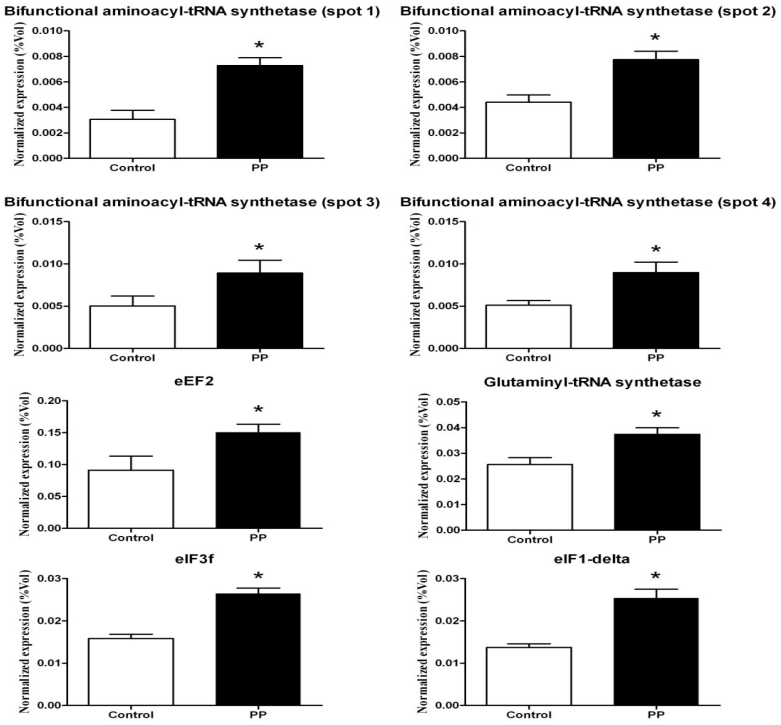
Editorial

See corresponding article on page 286.

Does enteral protein administration stimulate duodenal mucosa protein synthesis through an mTORC1-independent signaling pathway?[1–3]

Scot R Kimball





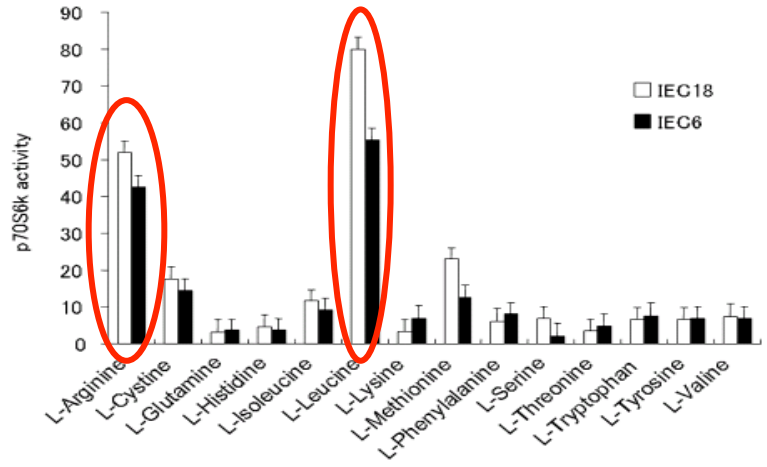
Goichon et al, JFN2013 – O35

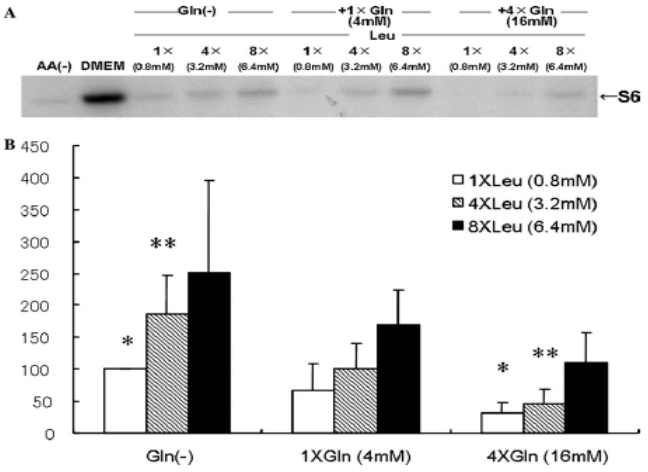
Table 1 Effects of individual amino acids on intestinal protein synthesis and involved signaling pathways

Models		Protein synthesis	Signaling pathways	References
Glutamine				
In vitro, Caco-2 cells (human)	Deprivation	Decreased	–	Le Bacquer et al. (2001)
In vitro, HCT-8 cells (human)	Deprivation	Decreased	↑ GCN2, ↑ mTOR	Boukhettala et al. (2012)
	Supplementation	Increased	↑ mTOR	
In vitro, IPEC-1 cells (porcine)	Deprivation	Decreased	↓ mTOR	Xi et al. (2012)
	Supplementation	Increased	↑ mTOR	
In vitro, Caco-2 cells (human)	Supplementation	Increased	–	Le Bacquer et al. (2003)
In vitro, Caco-2 cells (human)	Deprivation	–	↑ mTOR	Sakiyama et al. (2009)
In vitro, isolated enterocytes (rat)	Supplementation	Increased	–	Higashiguchi et al. (1993)
Jejunal segment (piglets)	Supplementation	Decreased	–	Adegoke et al. (2003)
In vivo, healthy humans	Supplementation	Increased	–	Coeffier et al. (2003a)
In vivo, malnourished rats	Supplementation	Unaffected	–	Tannus et al. (2009)
In vivo, hypercatabolic dogs	Supplementation	Increased	–	Humbert et al. (2002)
Arginine				
In vitro, IPEC-J2 cells (porcine)	Supplementation	Increased	↑ mTOR, NO independent	Bauchart-Thevret et al. (2010)
In vitro, IPEC-1 cells (porcine)	Supplementation	Increased	↑ mTOR	Tan et al. (2010)
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR, NO dependent	Ban et al. (2004)
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR	Nakajo et al. (2005)
In vitro, IEC6 cells (rat)	Supplementation	–	↑ mTOR	Rhoads et al. (2006)
In vitro, cdx2 cells (rat)	Supplementation	–	↑ mTOR, NO dependent	Rhoads et al. (2008)
In vivo, healthy humans	Supplementation	Unaffected	–	Claeyssens et al. (2007)
In vivo, rat (enteritis)	Supplementation	Increased	↑ mTOR	Corl et al. (2008)
Leucine				
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR	Ban et al. (2004)
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR	Nakajo et al. (2005)
In vitro, cdx2 cells (rat)	Supplementation		↑ mTOR	Rhoads et al. (2008)
In vivo, neonatal pigs	Supplementation	Increased	↑ mTOR	Murgas Torrazza et al. (2010)
In vivo, weaning pigs	Supplementation	Increased	–	Yin et al. (2010)
In vivo, healthy humans	Supplementation	Unaffected	–	Coeffier et al. (2011)

Bertrand et al, Amino acids 2013

→ Acides aminés et synthèse protéique intestinale.





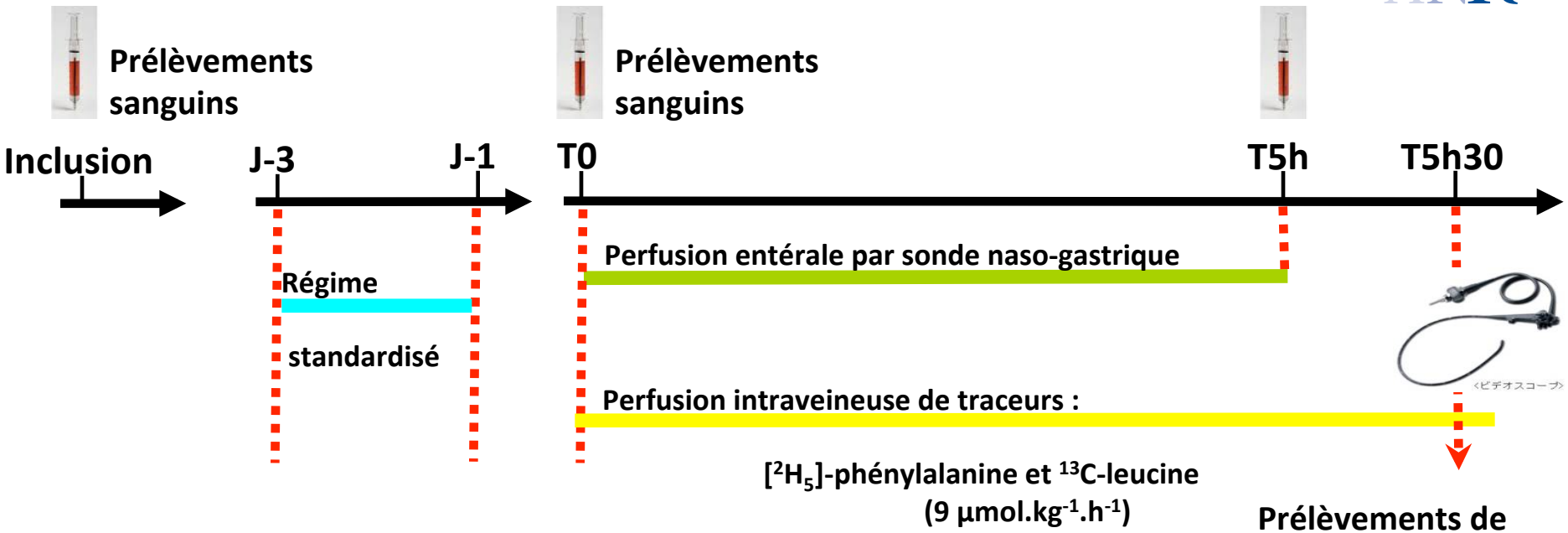
Nakajo et al, BBRC 2005

Dig Dis Sci (2007) 52:1826–1832
DOI 10.1007/s10620-006-9628-9

ORIGINAL PAPER

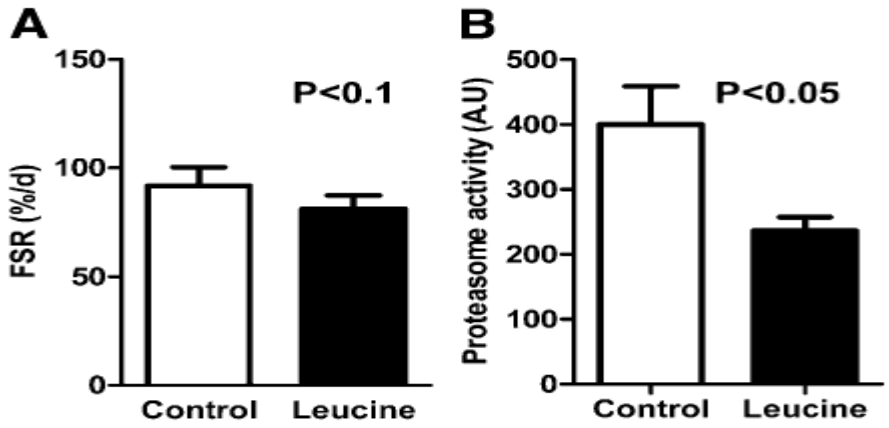
Lack of Effect of Acute Enteral Arginine Infusion on Whole-Body and Intestinal Protein Metabolism in Humans

Sophie Claeyssens · Stéphane Lecleire · Jonathan Leblond · Rachel Marion · Bernadette Hecketsweiler · Alain Lavoinne · Philippe Ducrotté · Pierre Déchelotte · Moïse Coëffier



→Perfusion entérale de maltodextrines

→ Perfusion entérale de maltodextrines + **leucine**

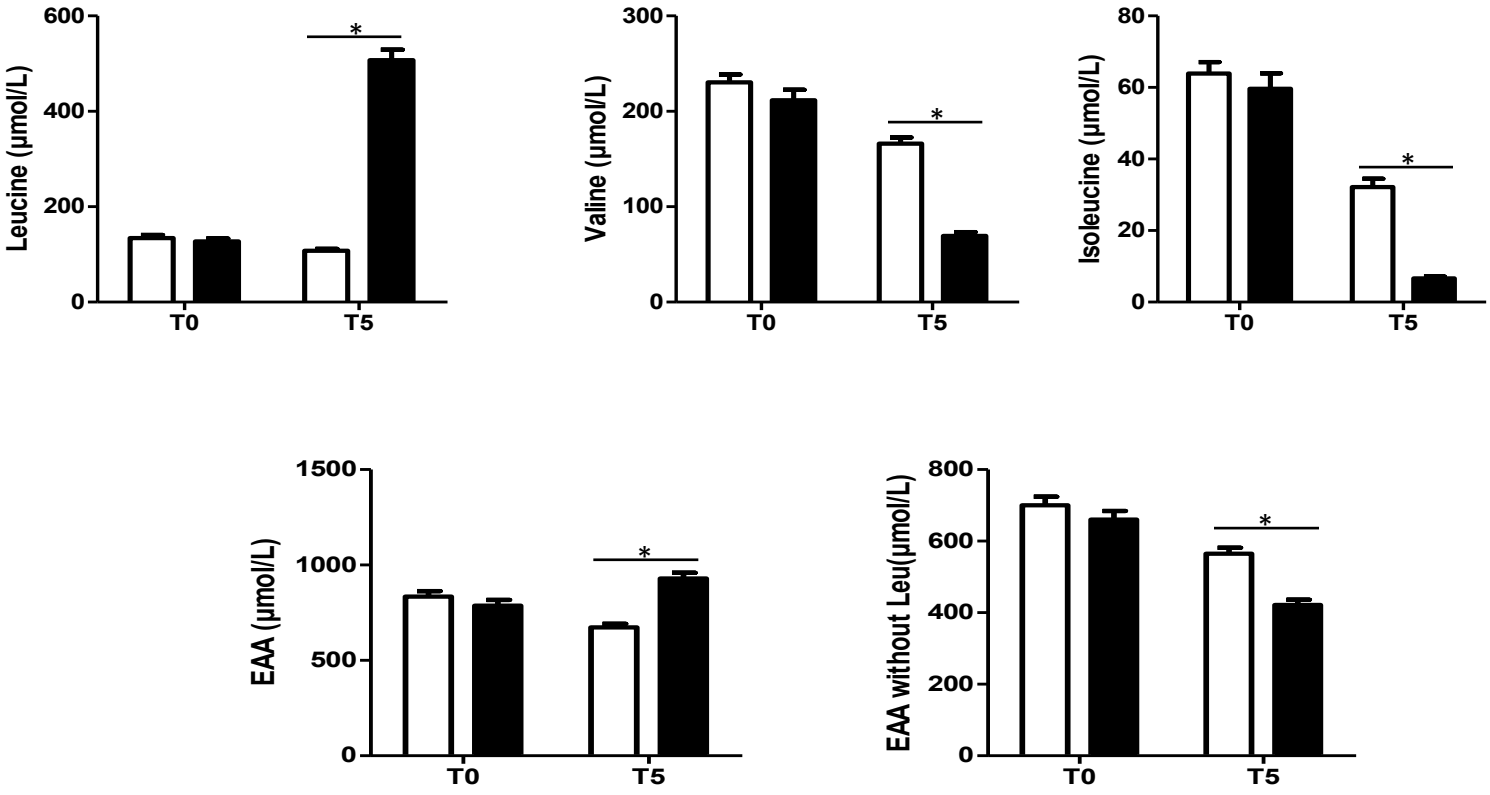


→ La leucine ne modifie pas le taux de synthèse protéique.

(→ Une tendance à une diminution !).

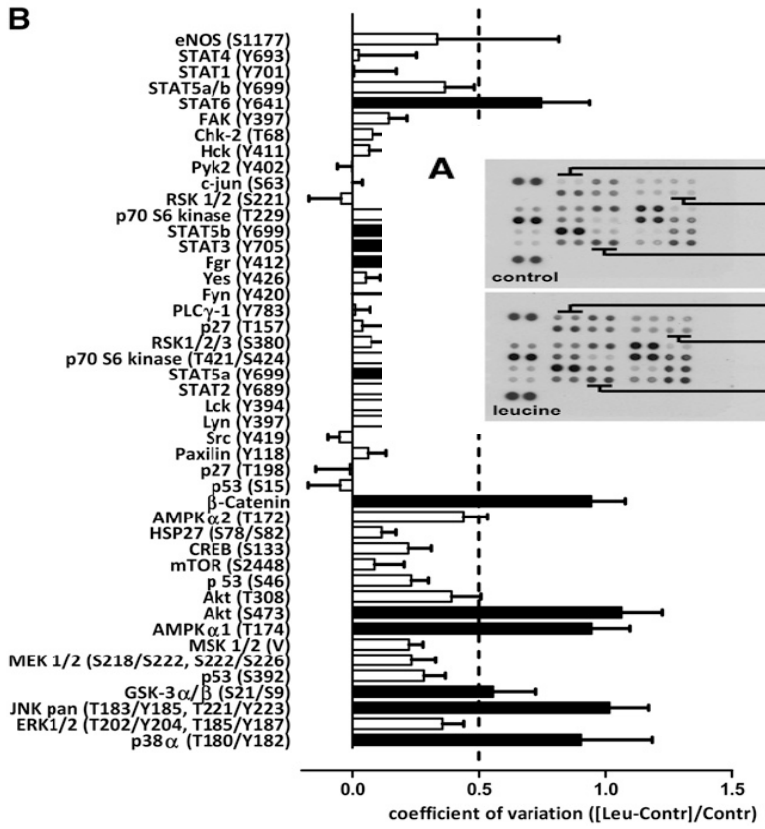
→ La leucine diminue l'activité totale du protéasome.

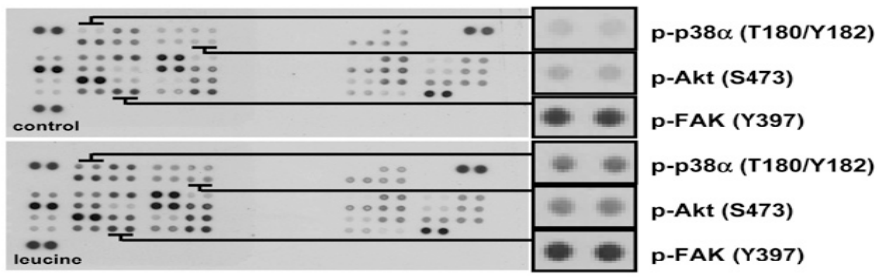
Coëffier et al, AJCN 2011



Coëffier et al, AJCN 2011

→Etude des voies de signalisation intracellulaire



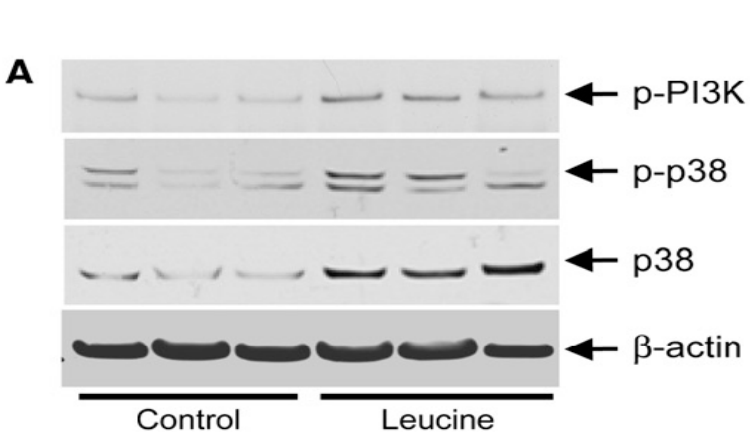


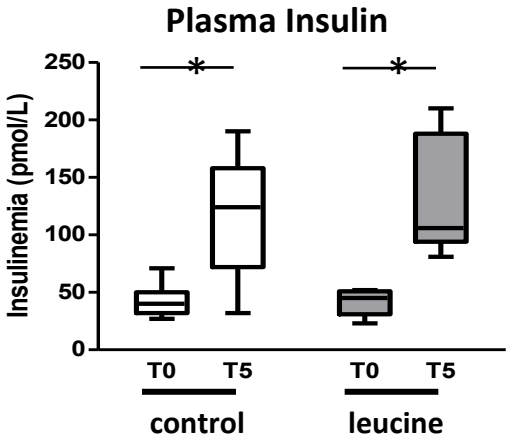
-**10 protéines dont l'état de phosphorylation était augmenté :**

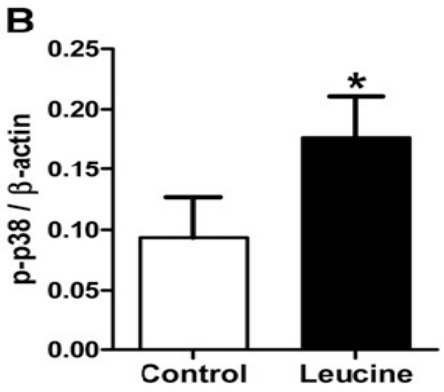
- **STAT6**
- **AMPKa1**
- **GSK3a/b**
- **JNK**
- **p38**

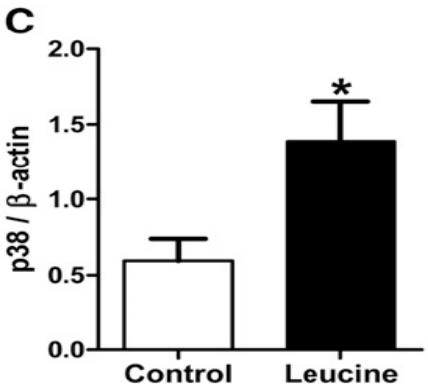
- **1 protéine dont l'expression était augmentée:**
  - **beta-catenin**

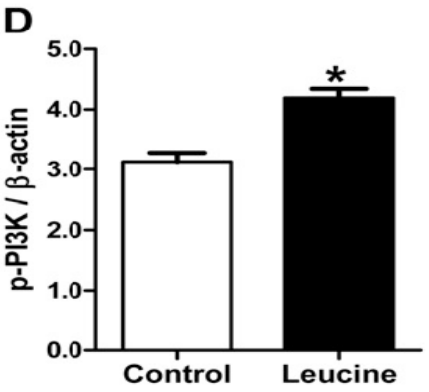
Coëffier et al, AJCN 2011



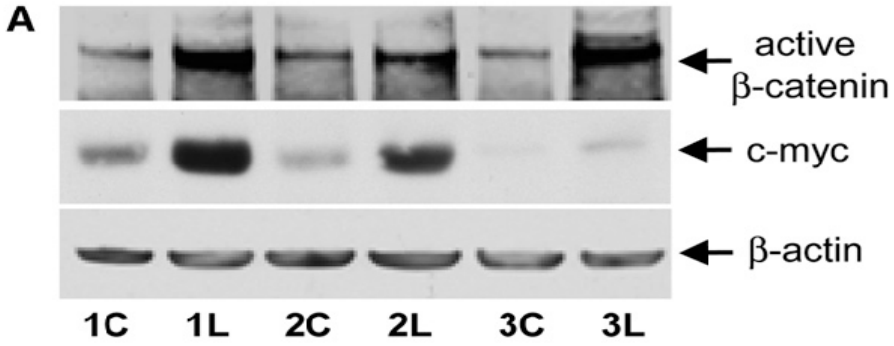


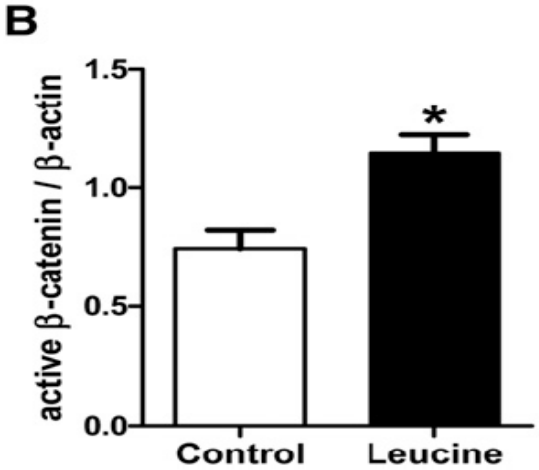




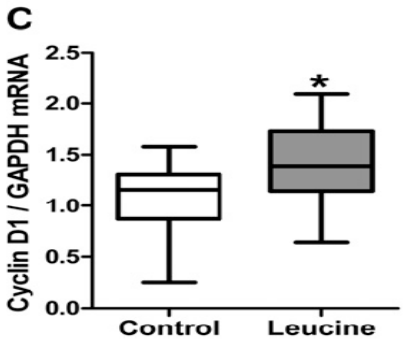


Coëffier et al, AJCN 2011



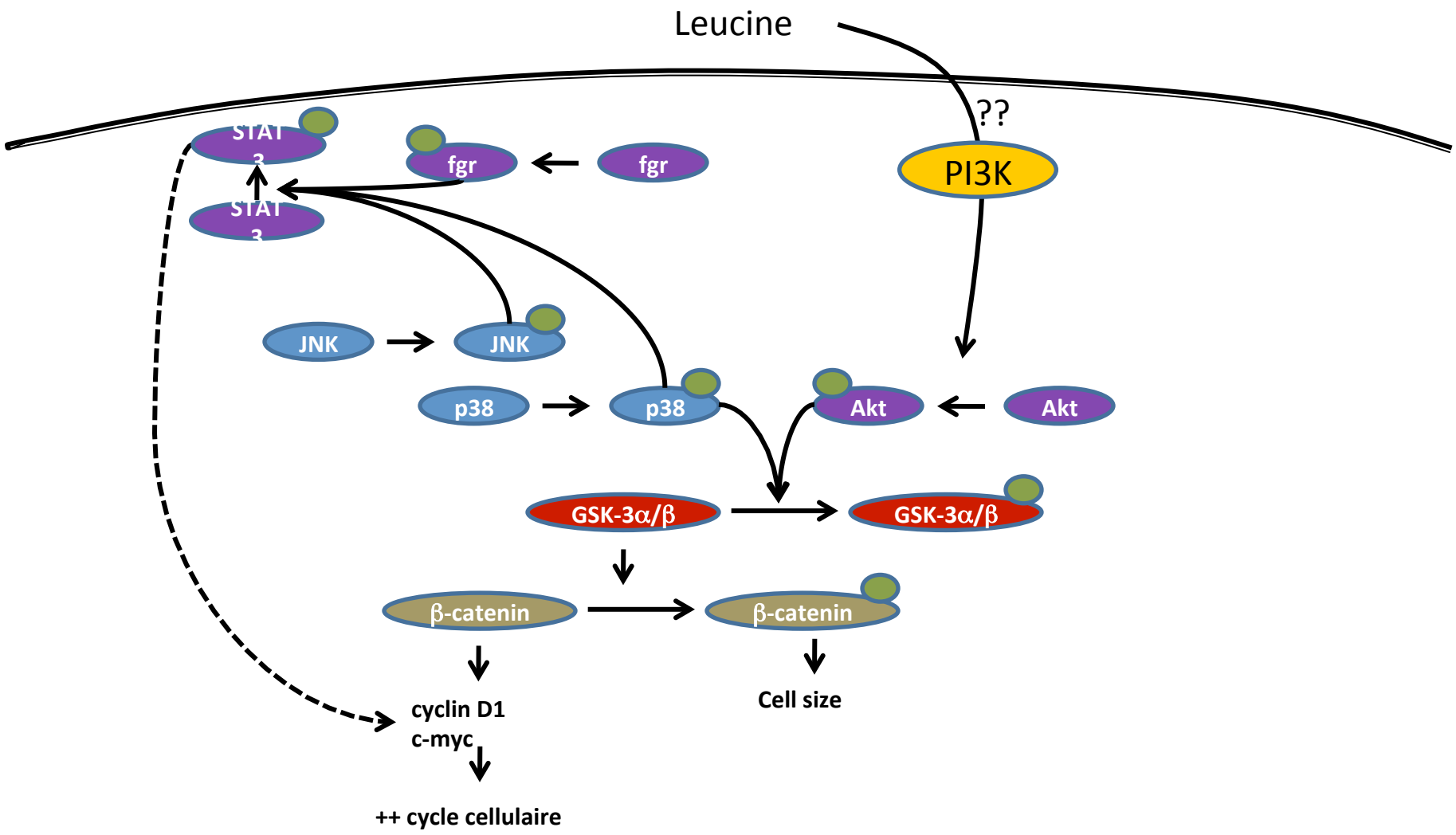


-**L'expression de la β-catenine non phosphorylée (forme active) est augmentée après l'épreuve Leucine.**



Augmentation du taux d'ARNm de la Cycline D1, marqueur de cycle cellulaire.

Coëffier et al, AJCN 2011


Leucine
??
PI3K
STAT 3
STAT 3
fgr
fgr
JNK
JNK
p38
p38
Akt
Akt
GSK-3α/β
GSK-3α/β
β-catenin
β-catenin
cyclin D1
c-myc
++ cycle cellulaire
Cell size

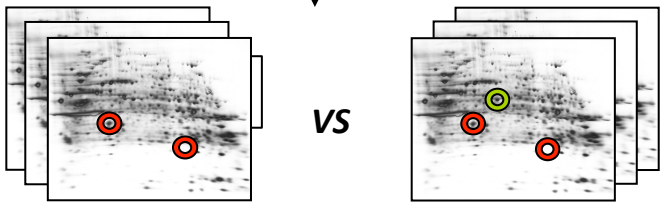
☞ approche protéomique sur des protéines totales

Biopsies duodénales

Extraction protéique total

Electrophorèse 2-D

Révélation des protéines : coloration au nitrate d'argent



Contrôle *VS* **Leucine**

Analyse différentielle des images 2D
(ImageMaster 2D Platinum^{Tm} v5.0)

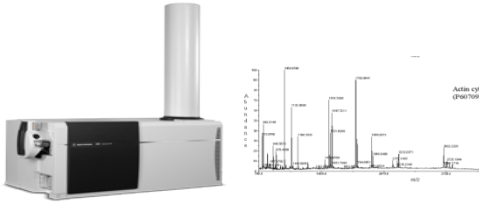
Ratio d'expression R ≥ 1,5

Test t de student (p<0,05)

Identification des spots d'intérêt

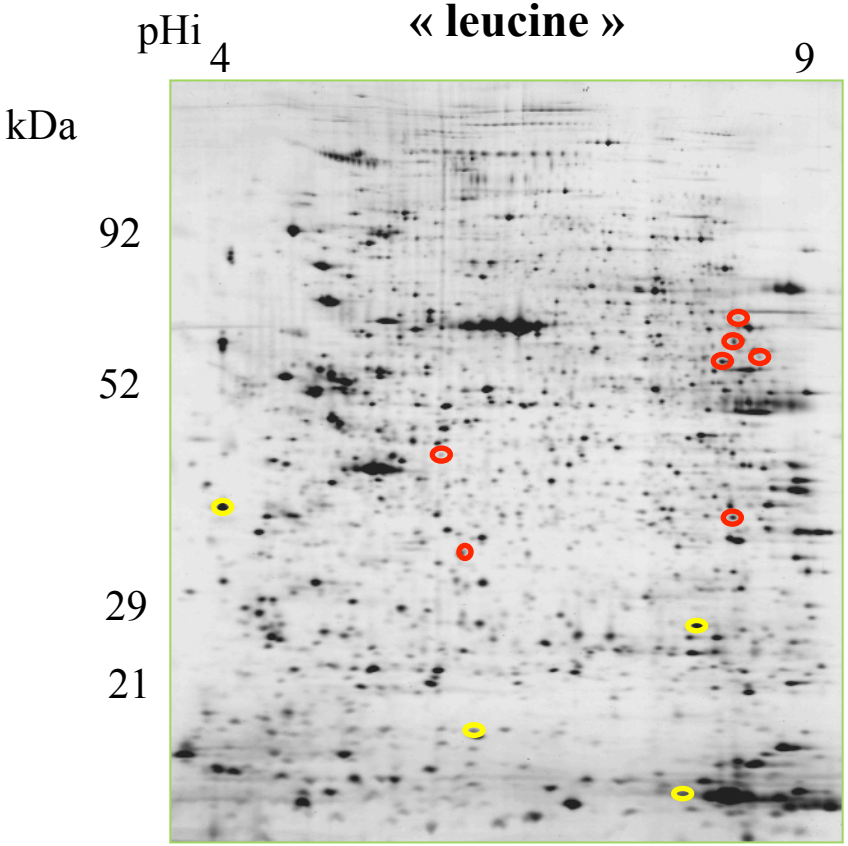
Découpe des spots sur gel

Digestion trypsique des protéines



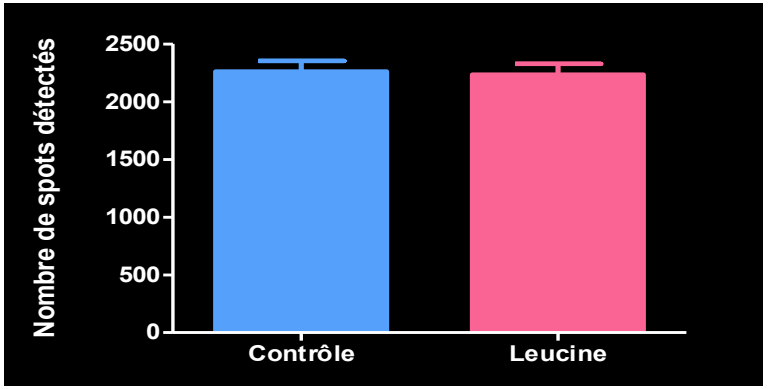
Identification des protéines par LC-chip-MS/MS et interrogation dans les banques de données

Profil protéique duodénal « leucine »

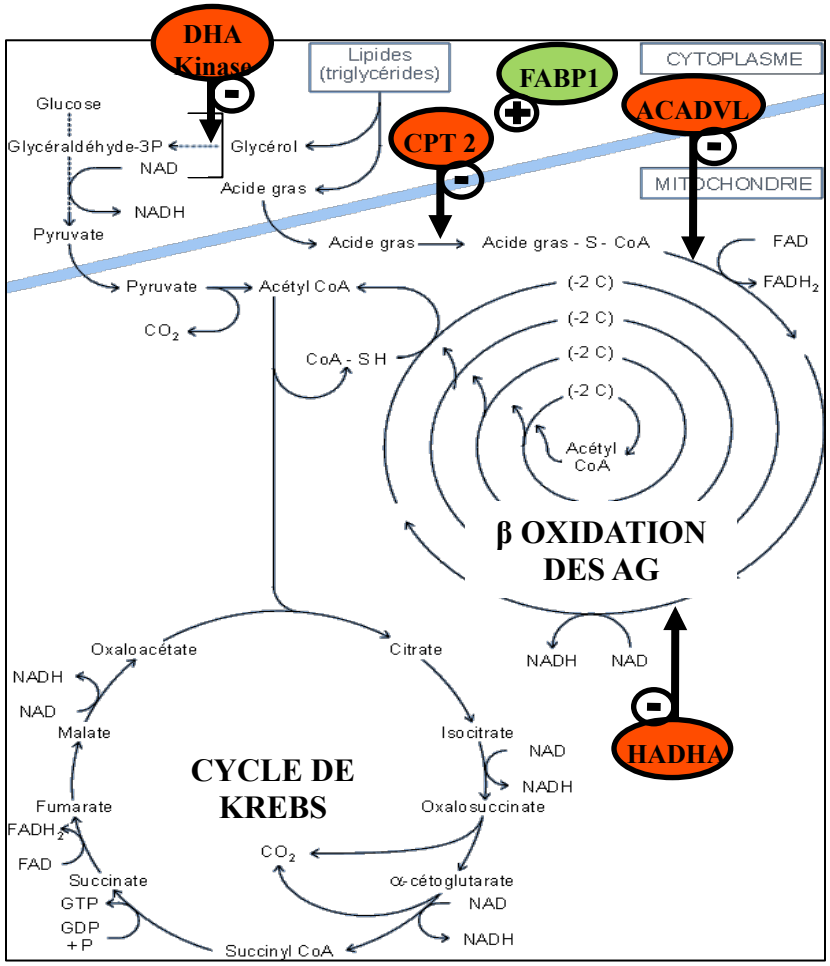


Résultats – Analyse différentielle des cartes protéomiques

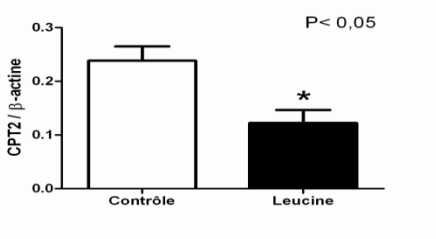
~ 2250 spots protéiques / gel

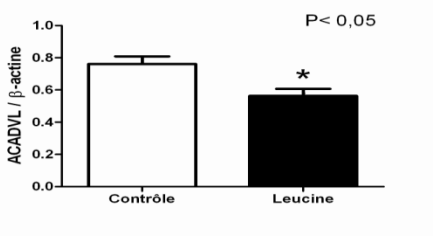


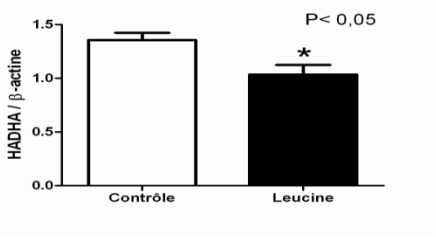
11 spots protéiques significativement modulés par la leucine :
7 spots sous-exprimés
4 spots sur-exprimés



Western blot



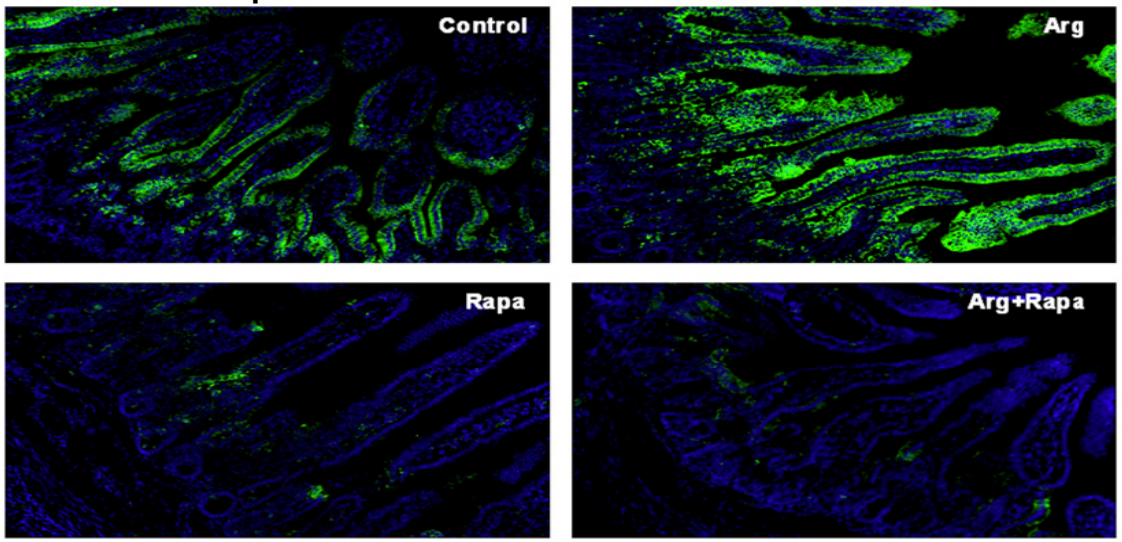




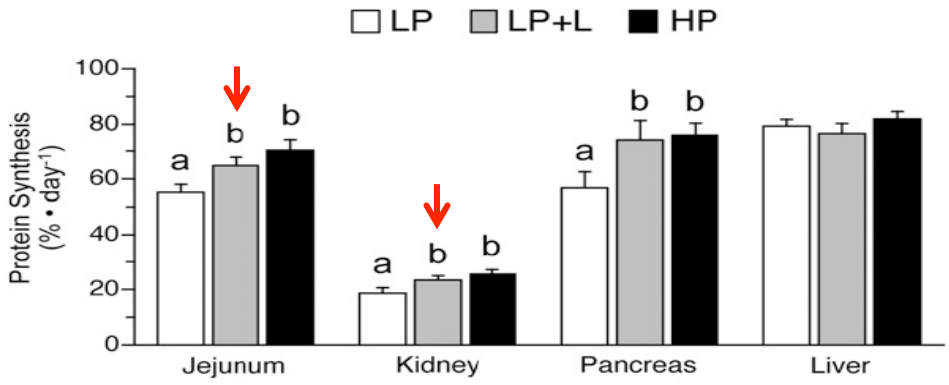
Ralentissement de la β-oxydation des acides gras

Goichon et al, J Proteomics 2013

A **en vert : p70S6K**

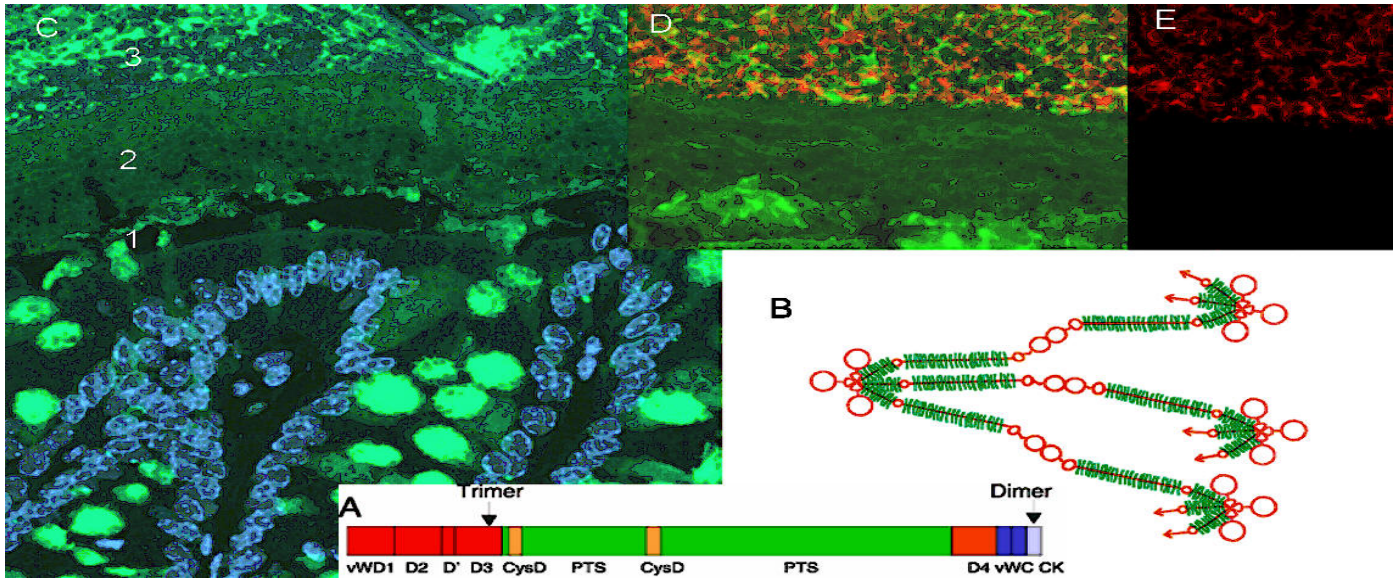


Corl et al, J Nutr 2008



Murgas et al, J Nutr 2010

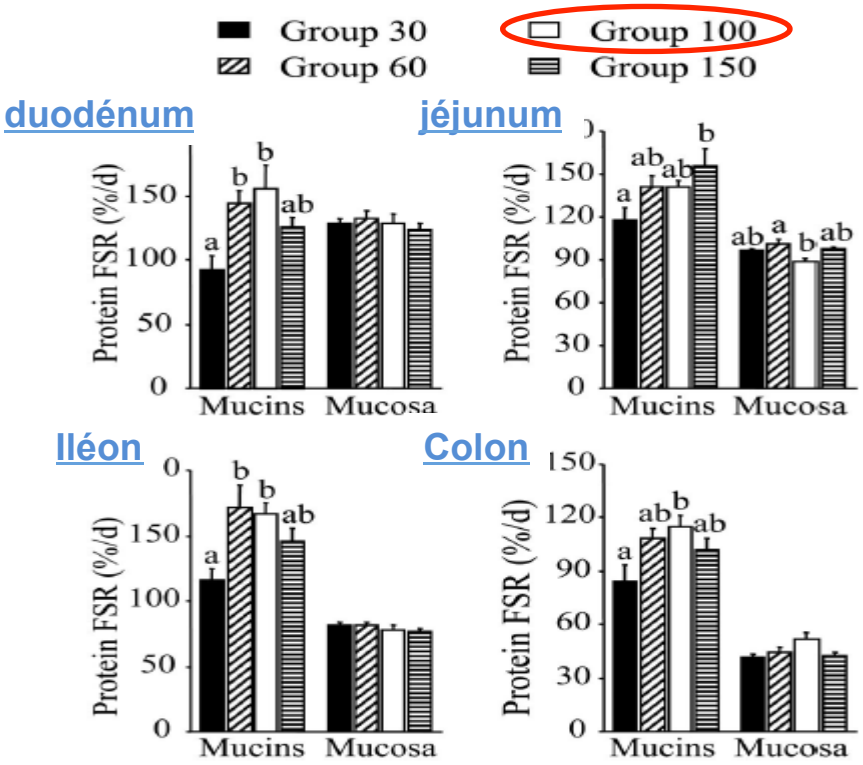
→Thréonine et synthèse de mucines



MUC2 (vert) et bactéries (rouge)

Dietary Threonine Restriction Specifically Reduces Intestinal Mucin Synthesis in Rats

Magali Faure,[1] Denis Moënnoz, Franck Montigon, Christine Mettraux, Denis Breuillé, and Olivier Ballèvre



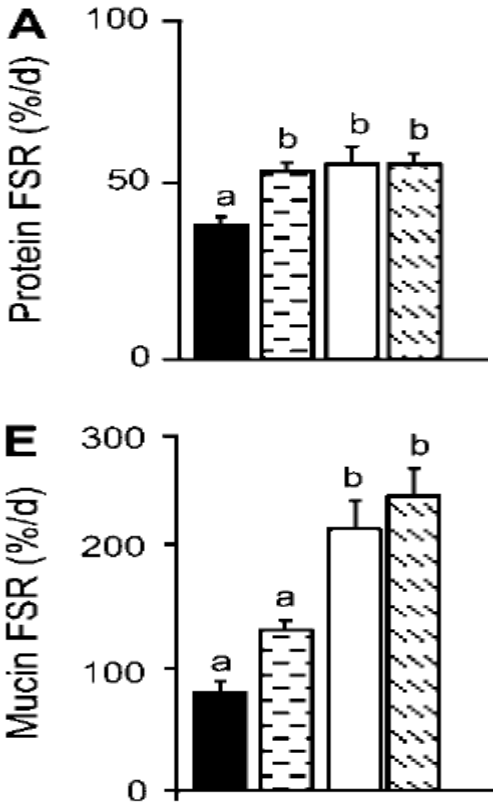
→ La thréonine n'affecte pas le taux de synthèse protéique des protéines de la muqueuse intestinale

→ Une restriction en thréonine diminue la synthèse des mucines

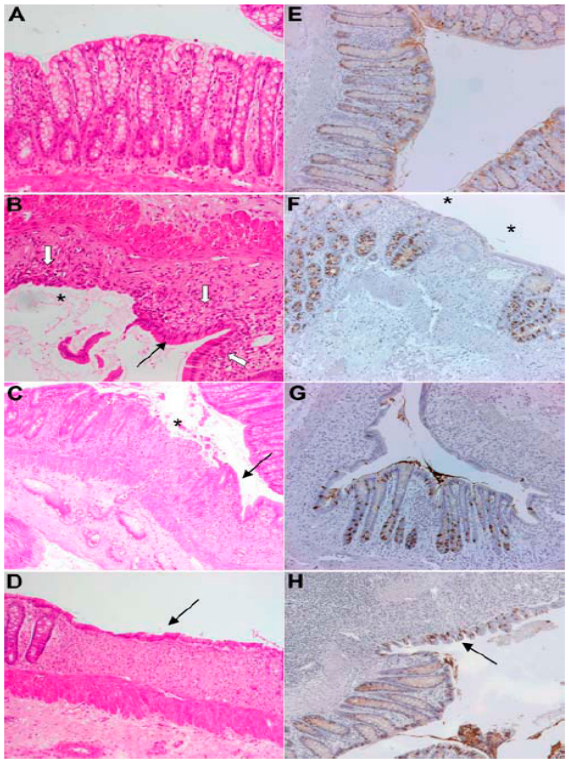
Faure et al, J Nutr 2005

Specific Amino Acids Increase Mucin Synthesis and Microbiota in Dextran Sulfate Sodium–Treated Rats

Magali Faure,*[1] Christine Mettraux,* Denis Moennoz,* Jean-Philippe Godin,* Jacques Vuichoud,* Florence Rochat,* Denis Breuillé,* Christiane Obled,[†] and Irène Corthésy-Theulaz*

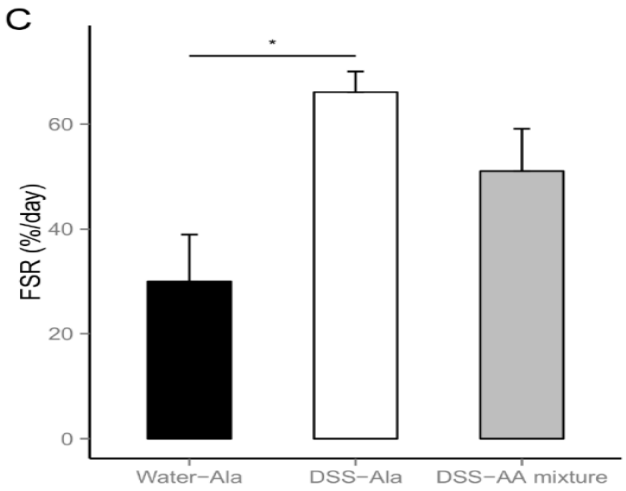


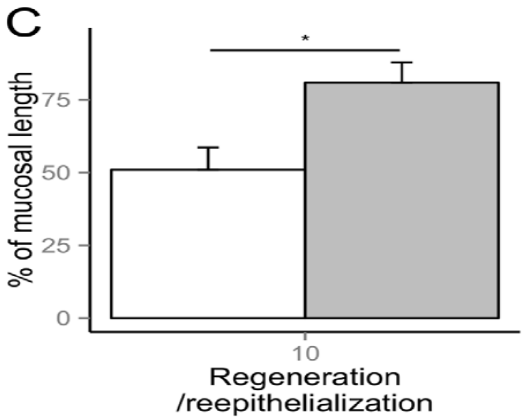
thréonine, cystéine
proline, sérine



Faure et al, J Nutr 2006

thréonine, cystéine
glutamate





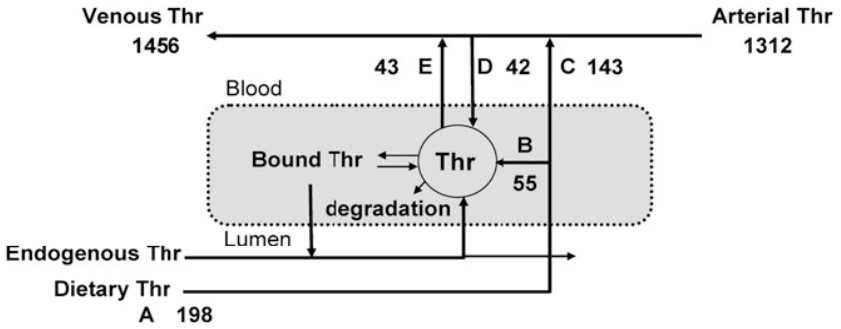
→ Pas d'effet sur les taux d'ARNm de Muc2

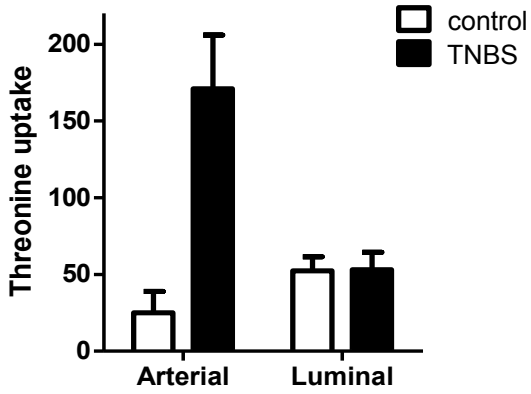
Liu et al, IBD 2013

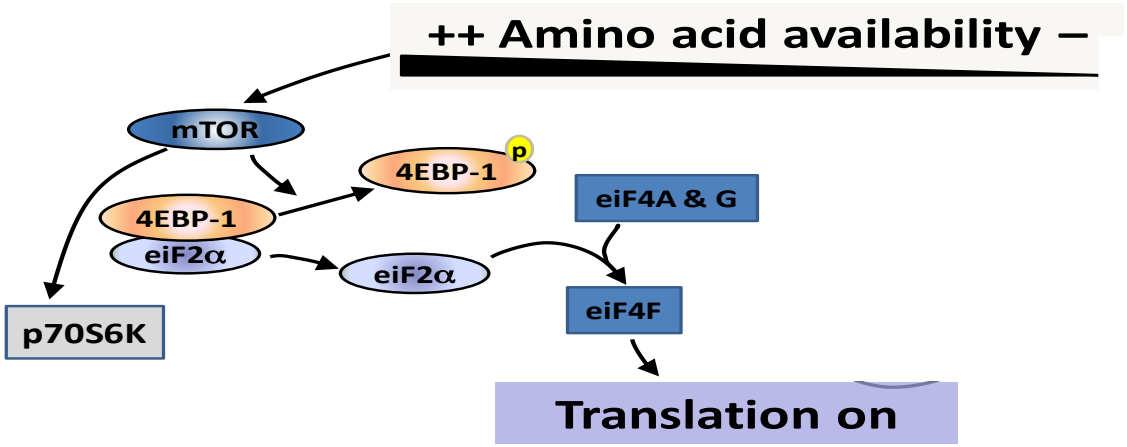
Intestinal Inflammation Increases Gastrointestinal Threonine Uptake and Mucin Synthesis in Enterally Fed Minipigs[1–3]

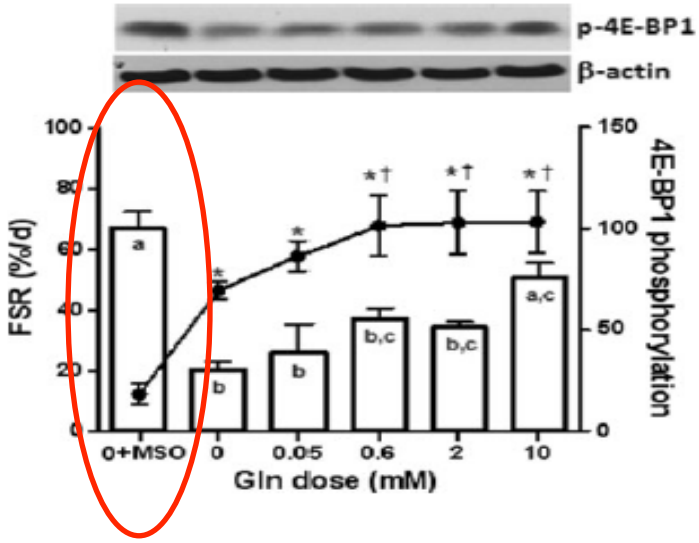
Didier Rémond,[4]* Caroline Buffière,[4] Jean-Philippe Godin,[5] Philippe Patureau Mirand,[4] Christiane Obled,[4] Isabelle Papet,[5] Dominique Dardevet,[4] Gary Williamson,[5] Denis Breuillé,[5] and Magali Faure[5]

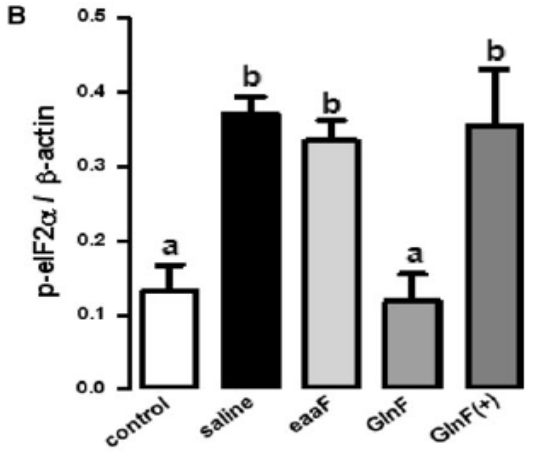
J Nutr 2009



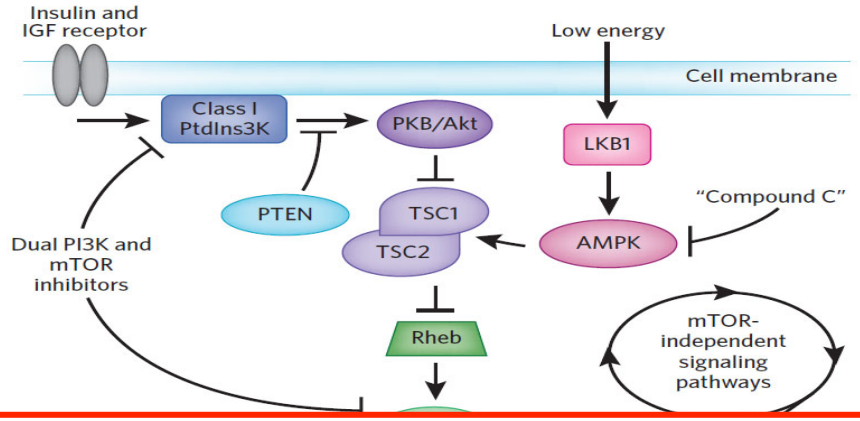


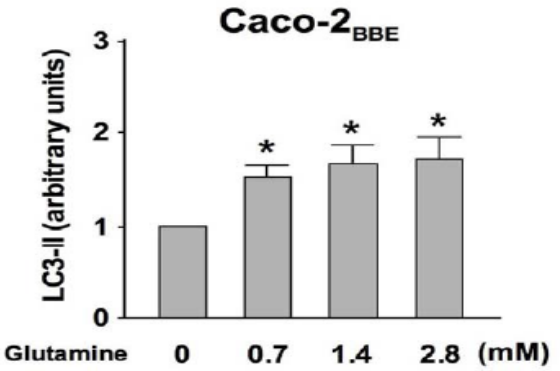




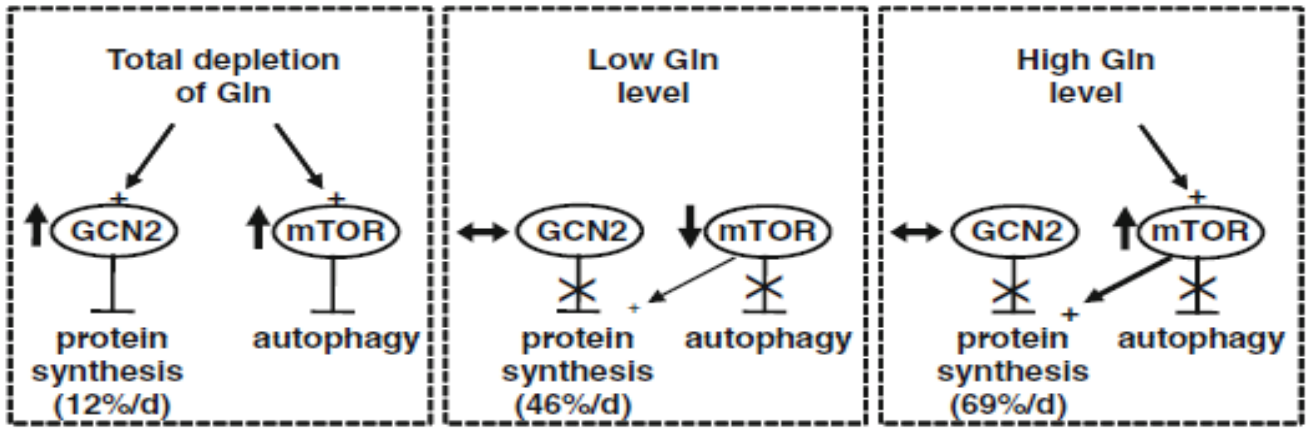


Boukhettala et al, Amino Acids 2012





Glutamine Increases Autophagy Under Basal and Stressed Conditions in Intestinal Epithelial Cells

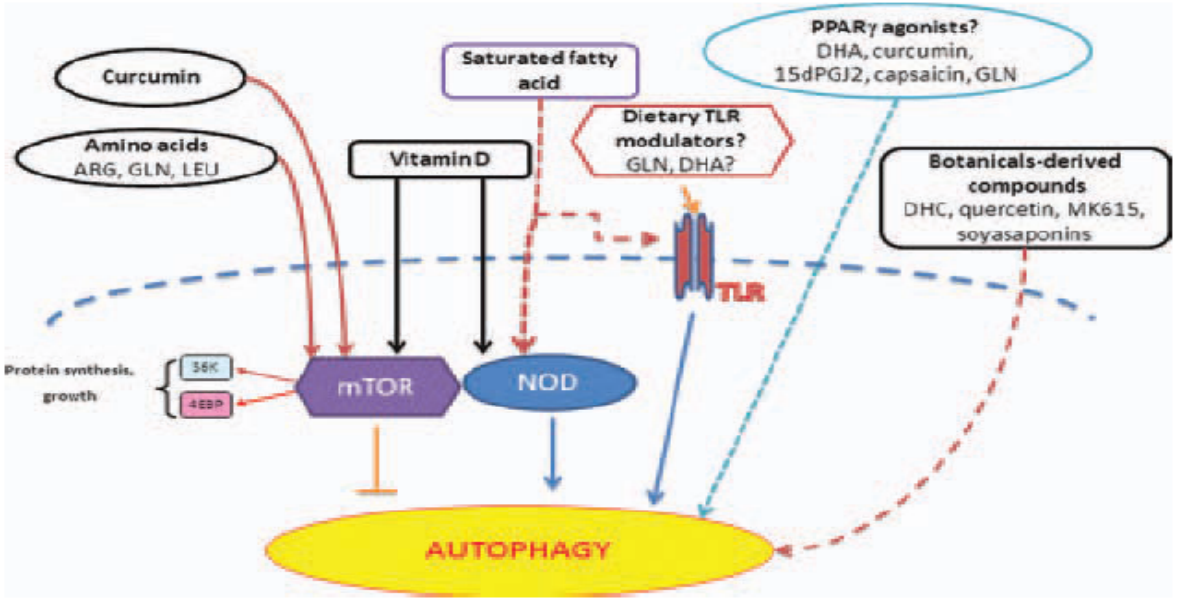


Boukhettala et al, Amino Acids 2012

Nutrient Modulation of Autophagy: Implications for Inflammatory Bowel Diseases

Rachel Marion-Letellier, PhD, Maitreyi Raman, MD,† Guillaume Savoye, MD,*,‡*
Pierre Déchelotte, MD, and Subrata Ghosh, MD†*

Inflammatory Bowel diseases 2012

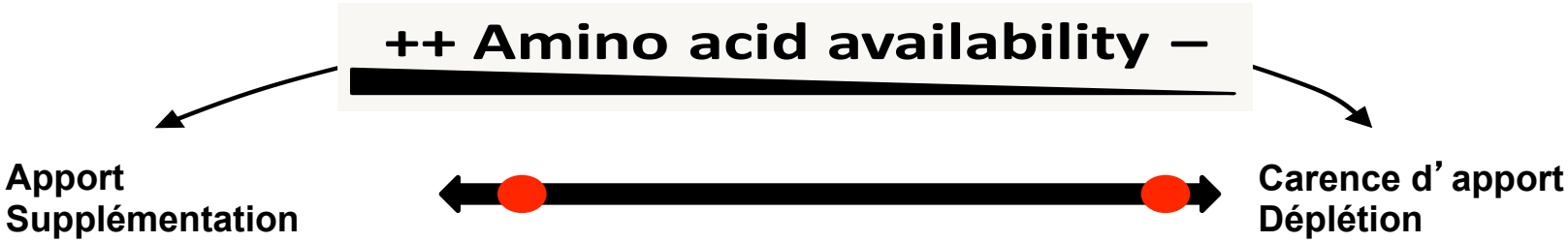


→Acides aminés et réponse inflammatoire intestinale

TABLE 1. Amino Acids That Have Shown Some Antiinflammatory Effects in Intestinal Epithelial Cells

Nutrient	Model	Main Results
Arginine	Co-culture model of Caco-2 cells with leukocytes and nonpathogenic bacteria	No effect on cytokine and NO production (31).
Arginine	HCT-8 treated with a cocktail of pro-inflammatory cytokines	Downregulation of the CXC-chemokine IL-8 through NO pathway (32).
Arginine	Newborn piglet jejunum IPEC-J2 cells Rat IEC-6	Upregulation of intestinal cell migration through a NO and a focal adhesion kinase (FAK) dependent mechanism (33).
Glutamine	IECs treated with a cocktail of pro-inflammatory cytokines	No effect on iNOS or NO production (34). Downregulation of CXC chemokines (35).
Glutamine	Caco-2 treated with TNFα	Inhibition of translocation of E. *coli* across Caco-2 monolayers (36).
Glutamine	Caco-2 treated with LPS	A decreased production and mRNA expression of IL-8 through STAT4 (37) and IκB/NFκB (38).
Glutamine	IEC-18, IEC-6	Induction of heat shock proteins (hsp25 (21), hsp70 (39-41)).
Glutamine/ Glycine	*In vitro* model of wound repair in HT-29	Glutamine significantly increased cell migration compared with controls whereas glycine incubation had no effect (42).
Histidine	Hydrogen peroxide and TNF-α induced Caco-2 and HT-29 cells	Inhibition of IL-8 production and mRNA expression (43)
Taurine	Co-culture model of Caco-2 with THP-1 cells	Inhibitory effect of TNFα-induced IL-8 mRNA expression and secretion from the Caco-2 cells (44). Downregulation of THP-1-induced LDH release (44)

Coëffier et al, IBD 2010

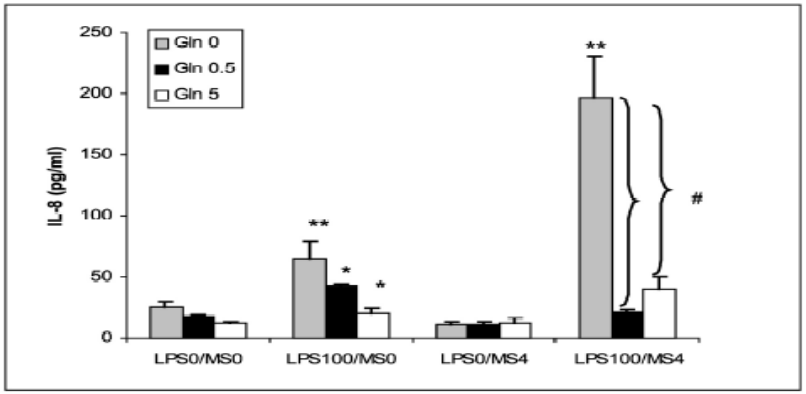


Supplémentation en glutamine

- ↓ Chimiokines (I-TAC, IP-10)
  Marion et al, Clin Nutr 2004
- ↓ cytokines pro-inflammatoires
  IL-6, TNFa
  Aosasa et al, JPEN 2003
- ↑ cytokine anti-inflammatoire
  IL-10
  Aosasa et al, JPEN 2003

« Privation » en glutamine

- ↑ IL-8
  Li et al, Cytokine 2000
  Liboni et al, J Nutr 2005



LETTER

doi:10.1038/nature11228

ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation

Tatsuo Hashimoto[1,2]*, Thomas Perlot[1]*, Ateequr Rehman[3]†, Jean Trichereau[1], Hiroaki Ishiguro[2], Magdalena Paolino[1], Verena Sigl[1], Toshikatsu Hanada[1], Reiko Hanada[1], Simone Lipinski[3], Birgit Wild[4], Simone M. R. Camargo[5], Dustin Singer[5], Andreas Richter[4], Keiji Kuba[6], Akiyoshi Fukamizu[7], Stefan Schreiber[3], Hans Clevers[8], Francois Verrey[5], Philip Rosenstiel[3] & Josef M. Penninger[1]

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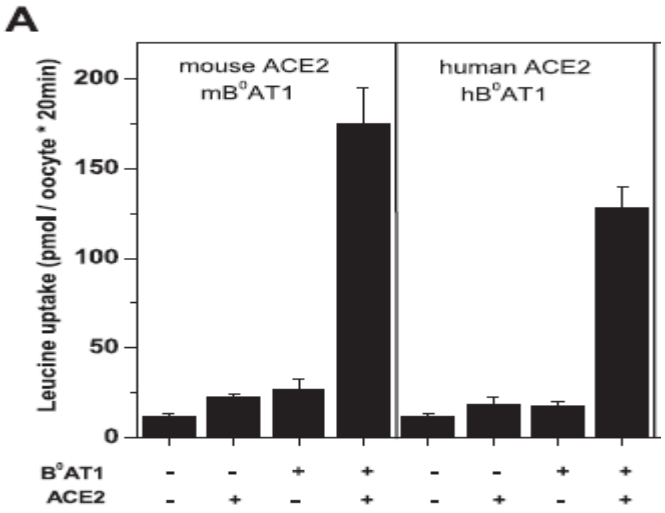
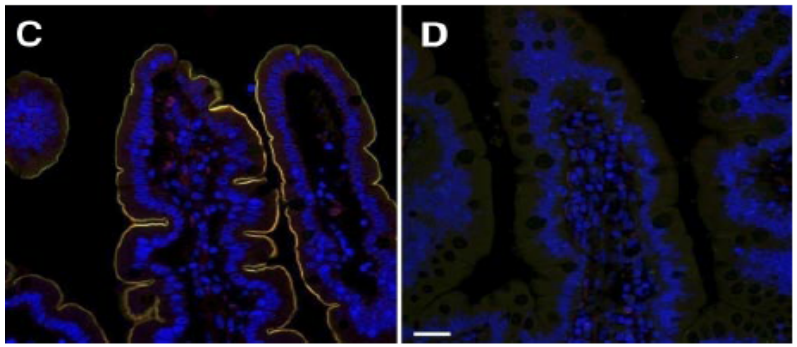
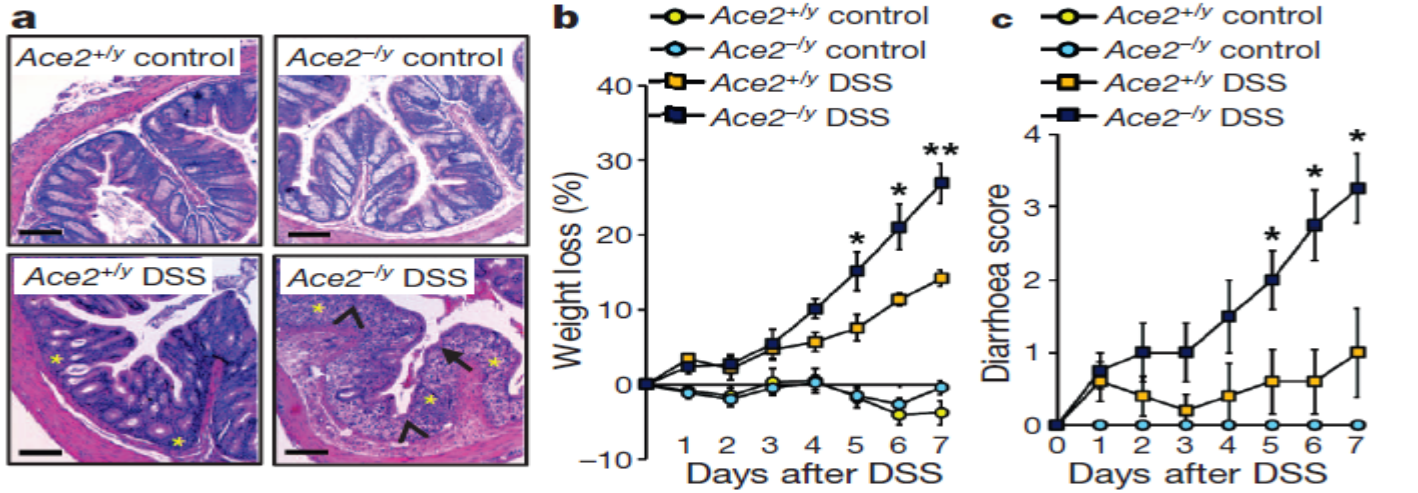
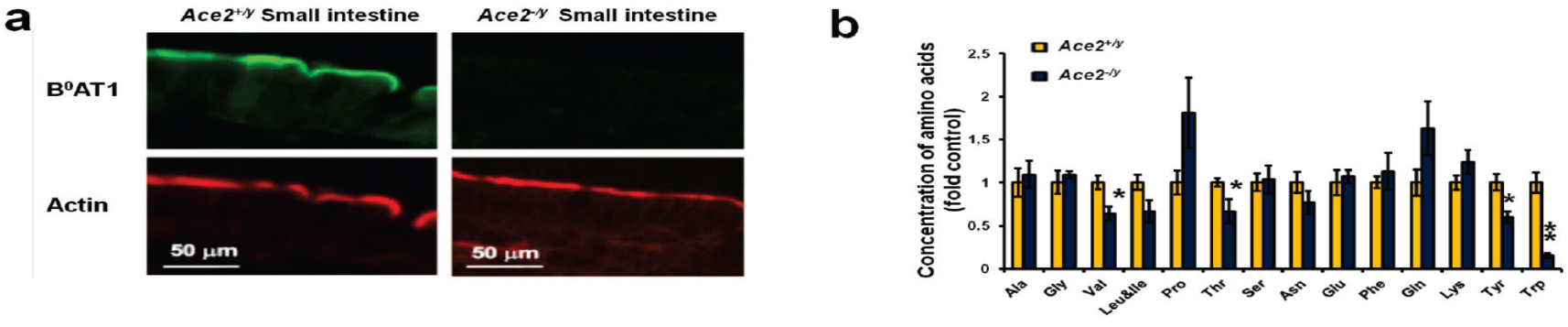


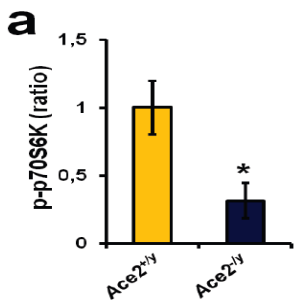


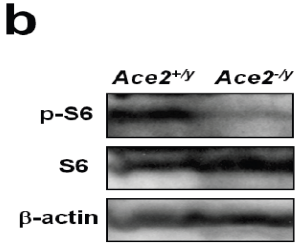
Kowalczuk et al, FASEB J 2008

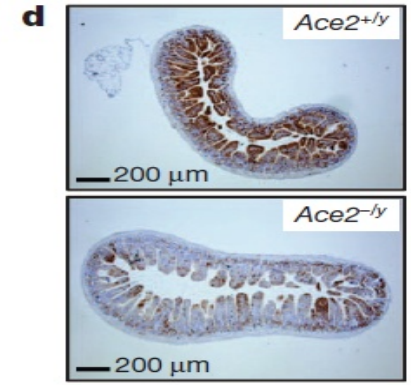


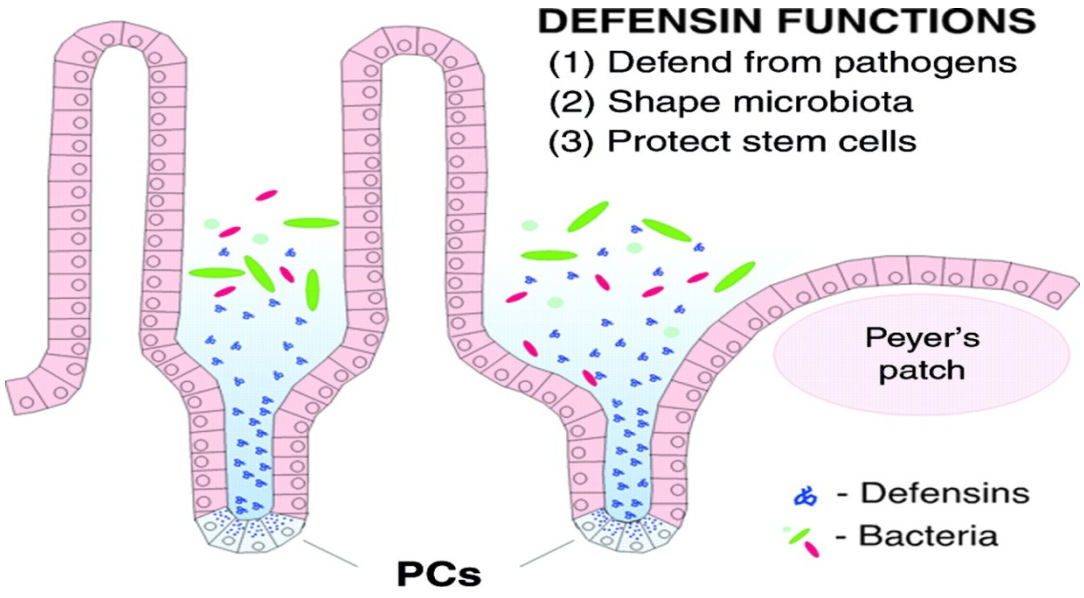


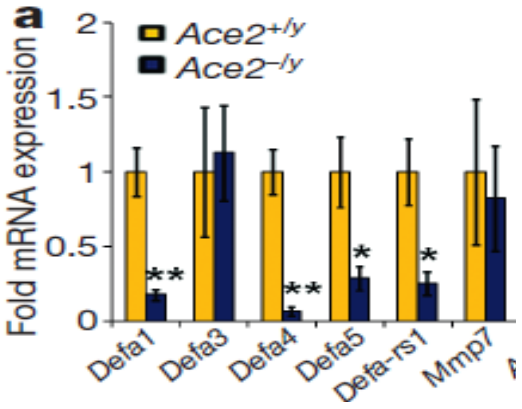
Hashimoto et al, Nature 2012



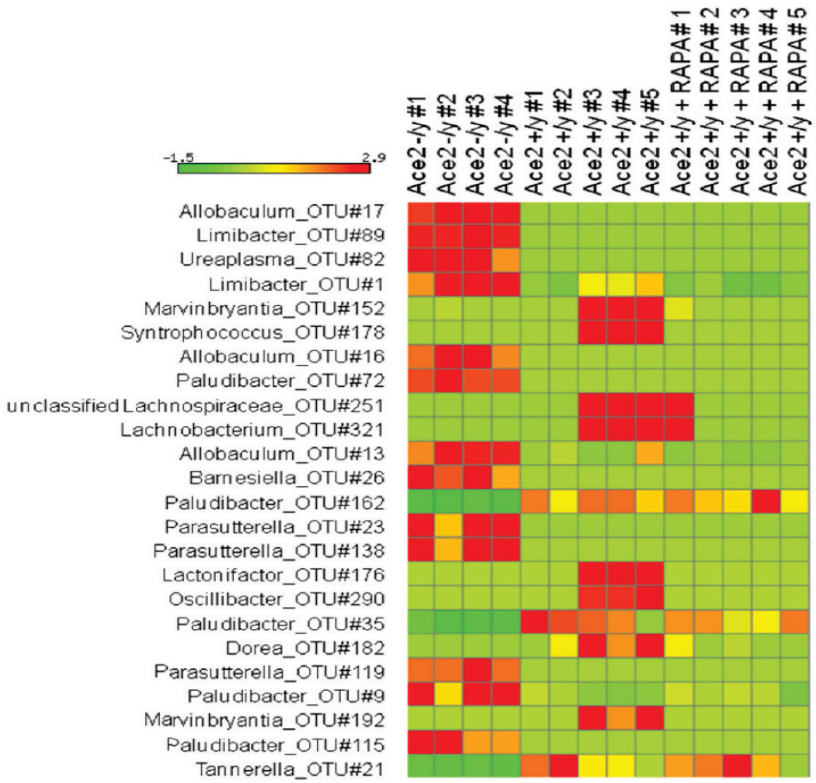


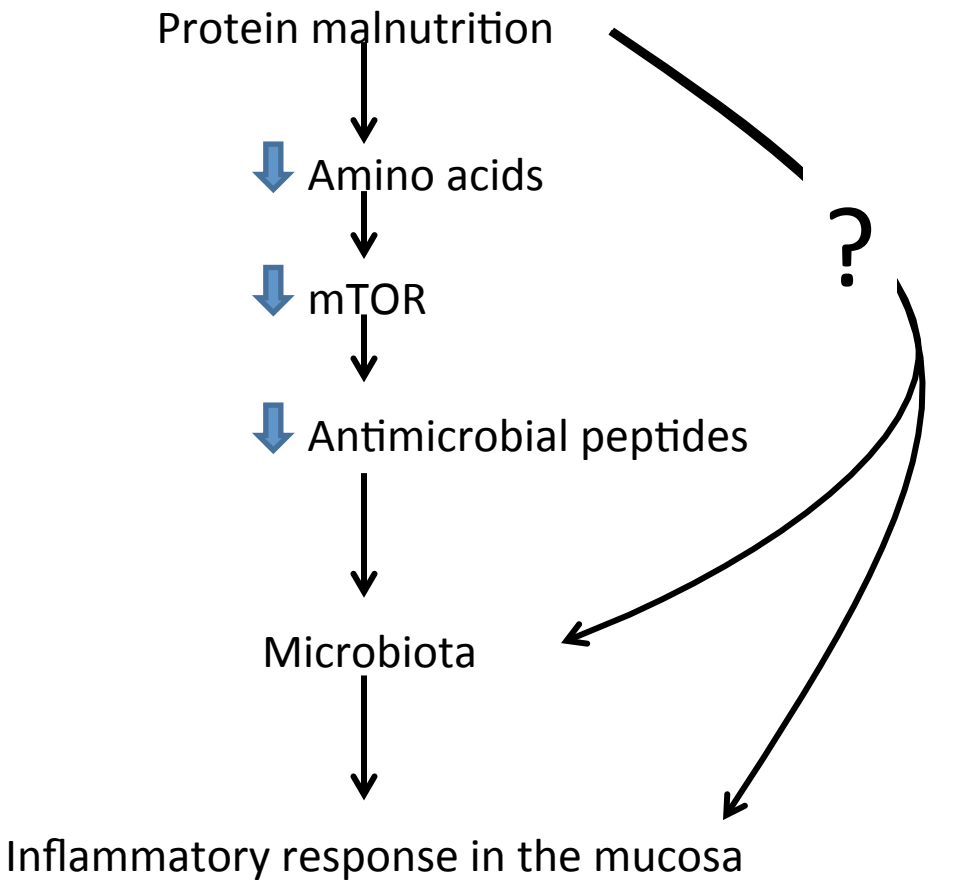




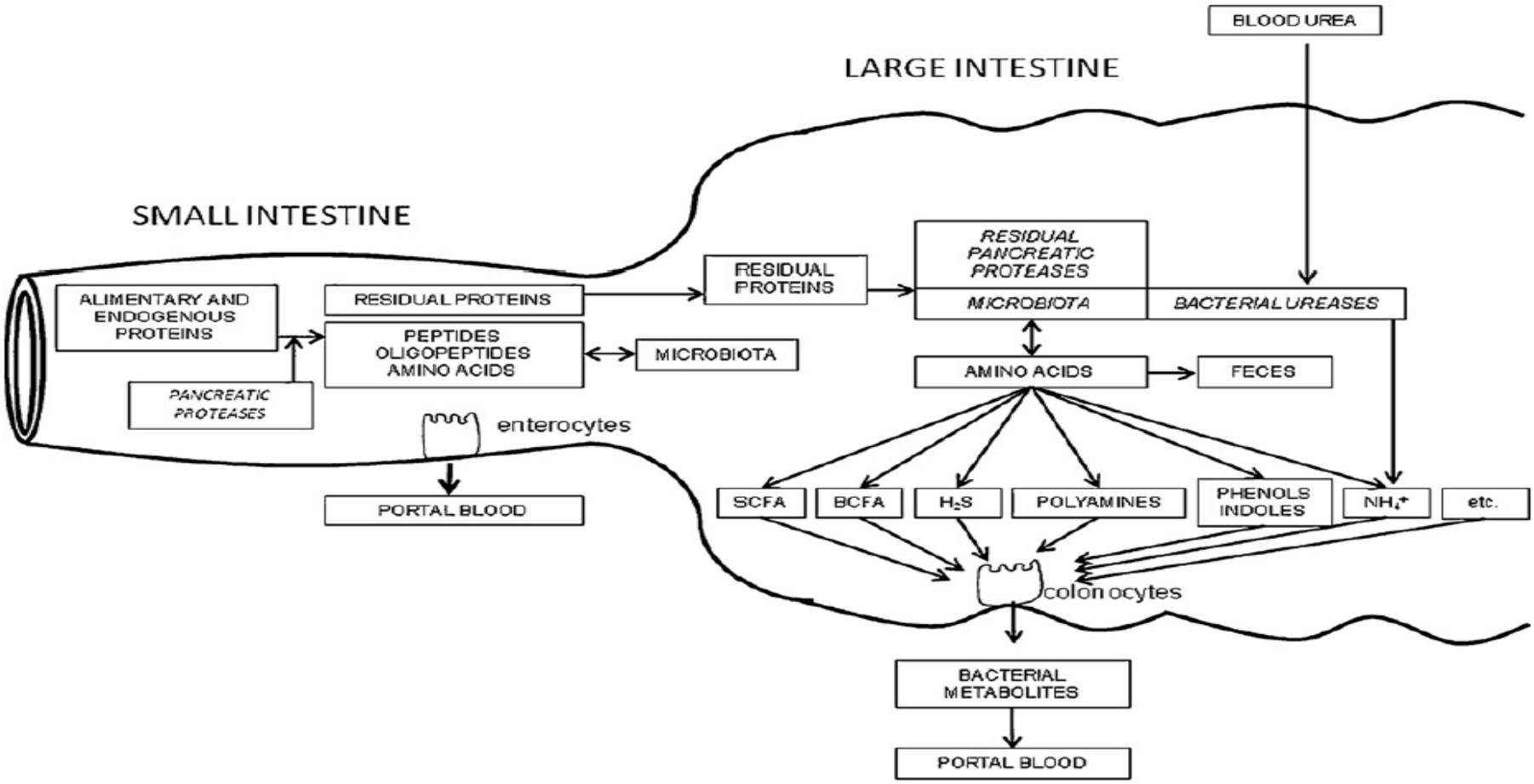


Hashimoto et al, Nature 2012





Hashimoto et al, Nature 2012



Davilla et al, Pharmacological Research 2013

Amino Acids (2012) 43:233–244
DOI 10.1007/s00726-011-1067-z

ORIGINAL ARTICLE

Regulatory role for L-arginine in the utilization of amino acids by pig small-intestinal bacteria

Zhao-Lai Dai · Xi-Long Li · Peng-Bin Xi · Jing Zhang · Guoyao Wu · Wei-Yun Zhu

Amino Acids
DOI 10.1007/s00726-012-1264-4

ORIGINAL ARTICLE

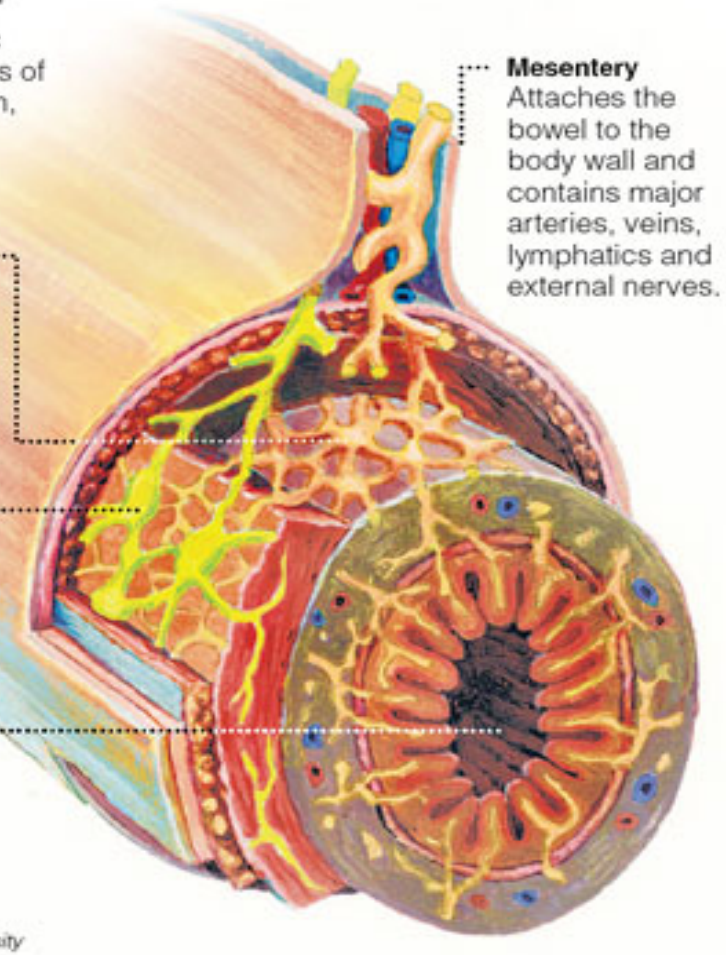
L-Glutamine regulates amino acid utilization by intestinal bacteria

Zhao-Lai Dai · Xi-Long Li · Peng-Bin Xi · Jing Zhang · Guoyao Wu · Wei-Yun Zhu

The Brain in Your Gut

The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.

SMALL INTESTINE CROSS SECTION



Mesentery Attaches the bowel to the body wall and contains major arteries, veins, lymphatics and external nerves.

Submucosal plexus Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.

Myenteric plexus Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.

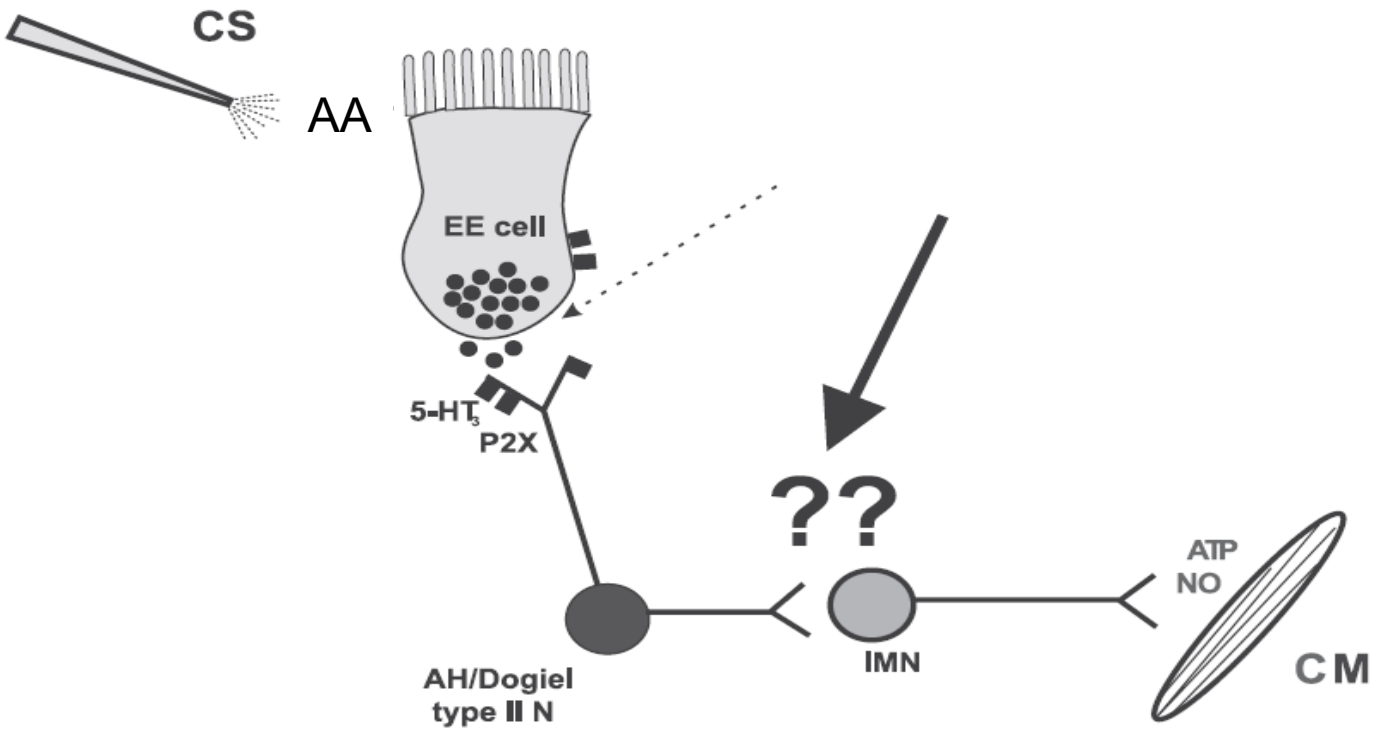
Lumen No nerves actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.

Source: Dr. Michael D. Gershon, Columbia University

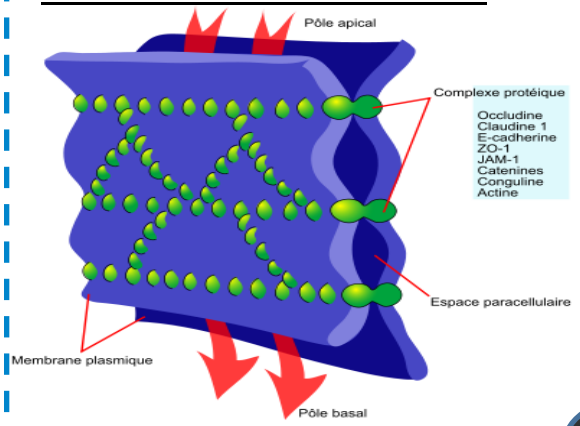
Local inhibitory reflexes excited by mucosal application of nutrient amino acids in guinea pig jejunum

R. M. Gwynne and J. C. Bornstein

Am J Physiol Gastro Liver Physiol 2007

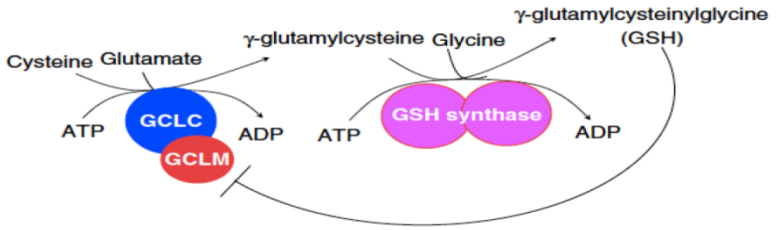


Barrière intestinale



Glutamine
Glutamate
Arginine
Méthionine
Leucine ?
…

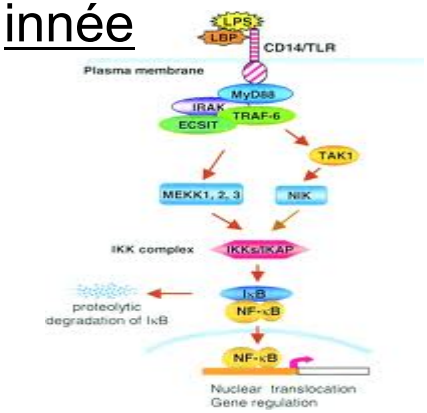
Stress oxydant/ HSP



Glutamine
Glutamate
Cystéine – Méthionine - Taurine

Acides aminés

Réponse immunitaire innée



Glutamine
Arginine
Cystéine

Glutamate ?
…

Merci pour votre attention