



# JDP

Montpellier 2012

Faculté de pharmacie

[www.journeesdeprintemps.com](http://www.journeesdeprintemps.com)

# Sarcopénie et cachexie : deux faces d'une même pièce ? mécanismes

*Pr. Yves Boirie*

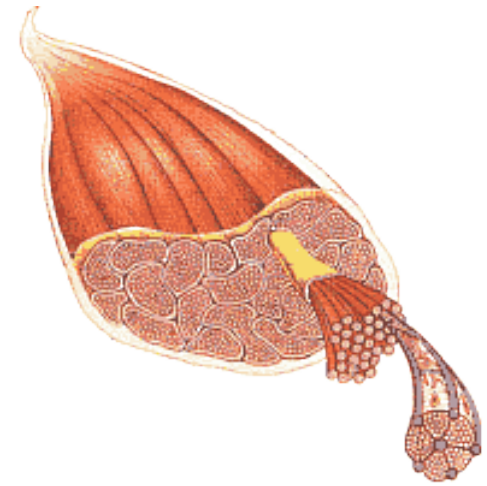
*Service de Nutrition Clinique*

*Unité de Nutrition Humaine (équipe NuTriM)*

*CRNH Auvergne, Clermont-Ferrand*

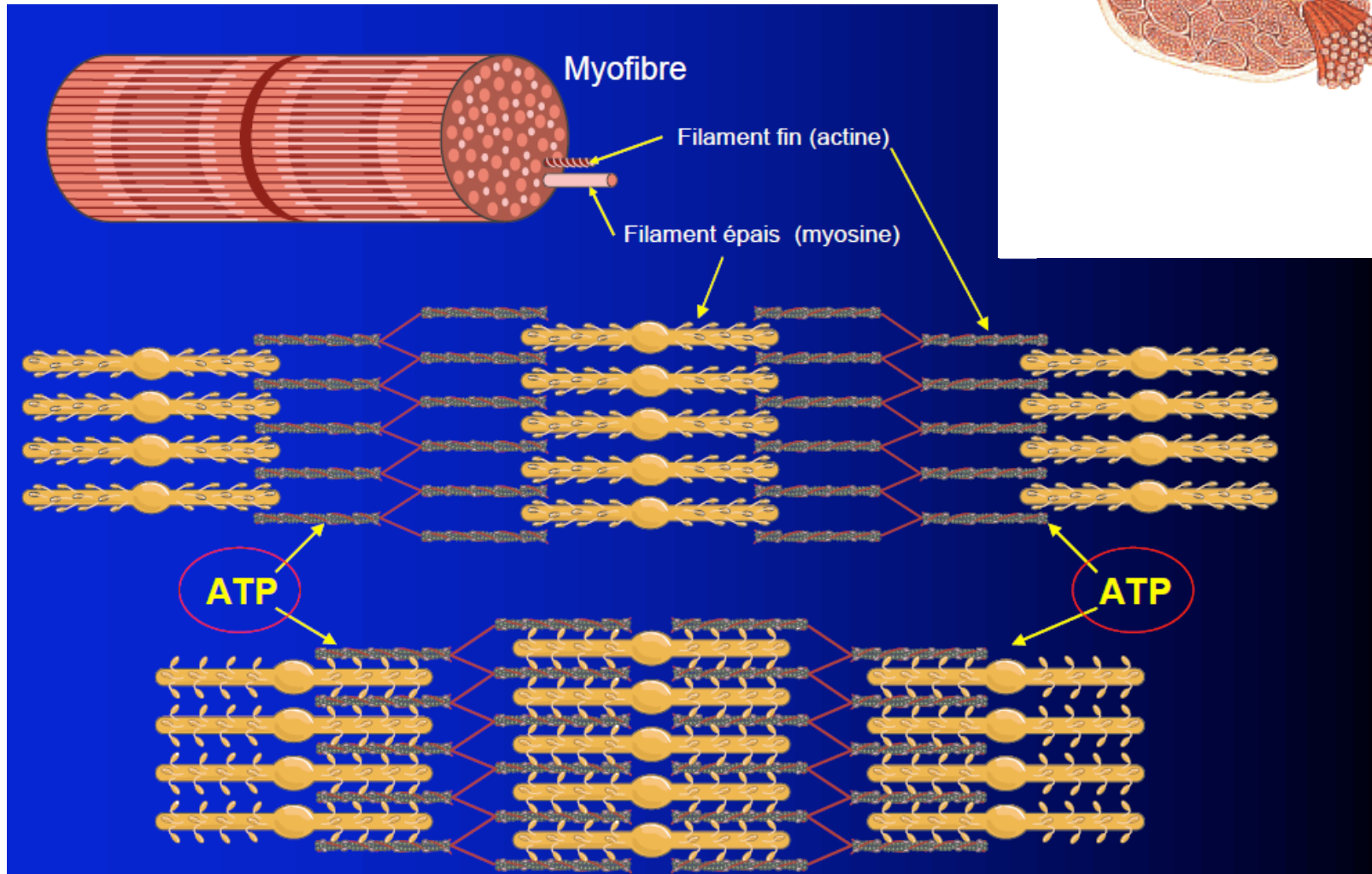
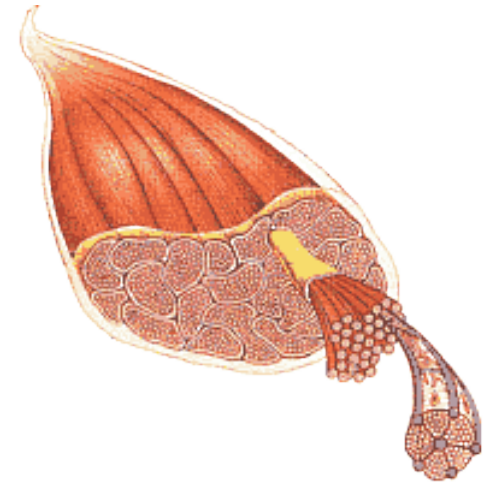


# Muscles squelettiques

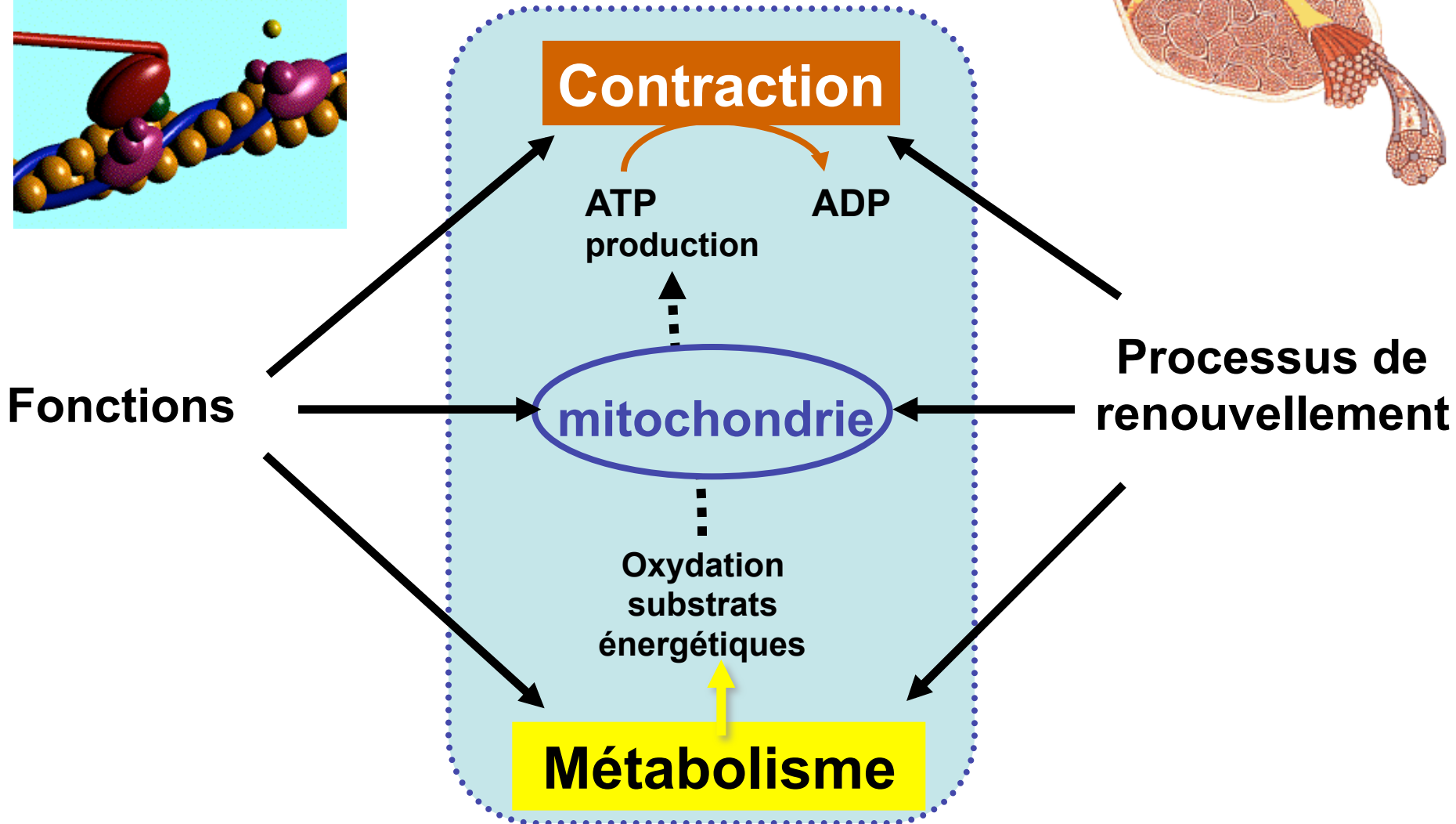
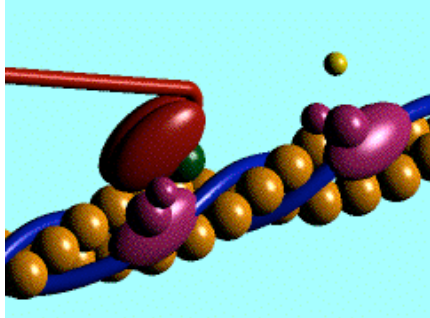
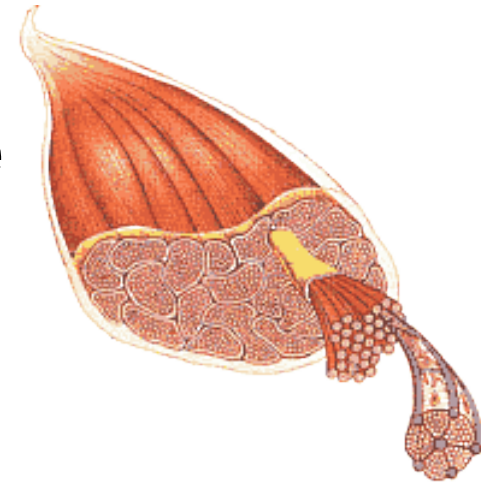


- **~ 600 muscles**
- **40% du poids corporel total**
- **55% dans les membres inférieurs**
- **50% des protéines corporelles totales**

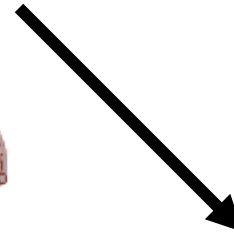
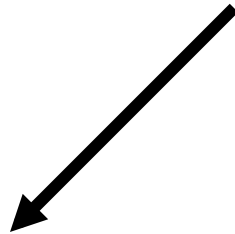
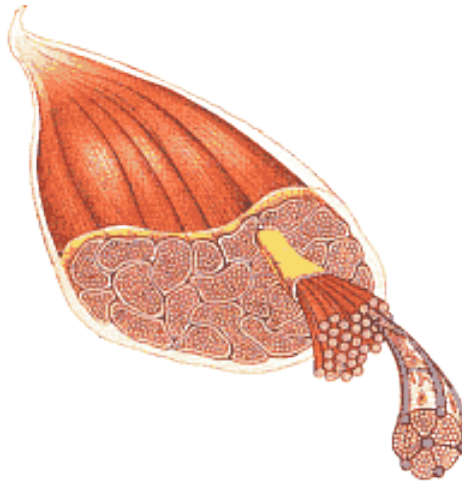
# Appareil contractile



# Approche intégrée de la fonction musculaire



# Rôle du muscle dans l'organisme



## **MOBILITE**

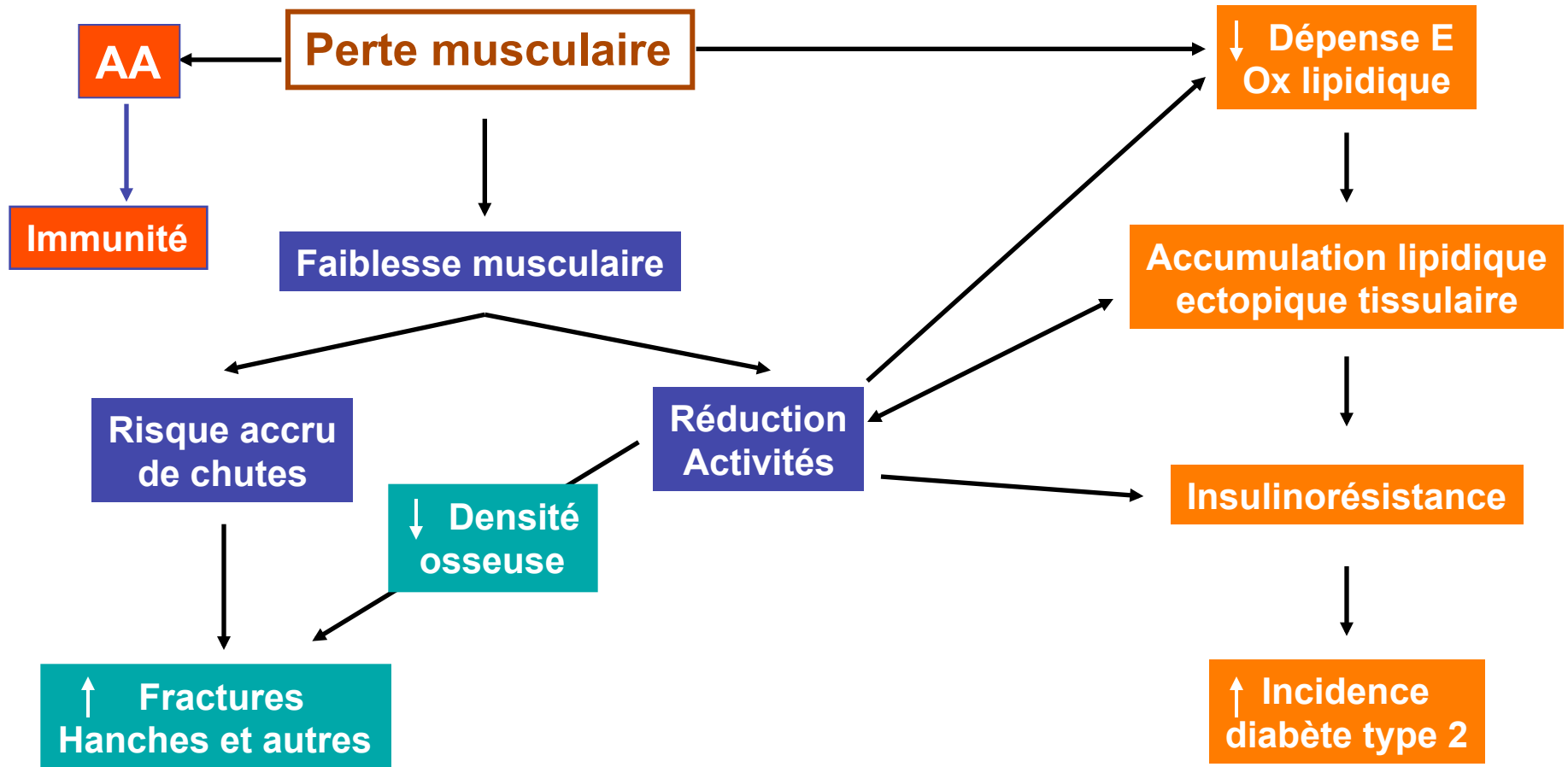
- fonction locomotrice
- force, endurance
- fatigabilité
- équilibre



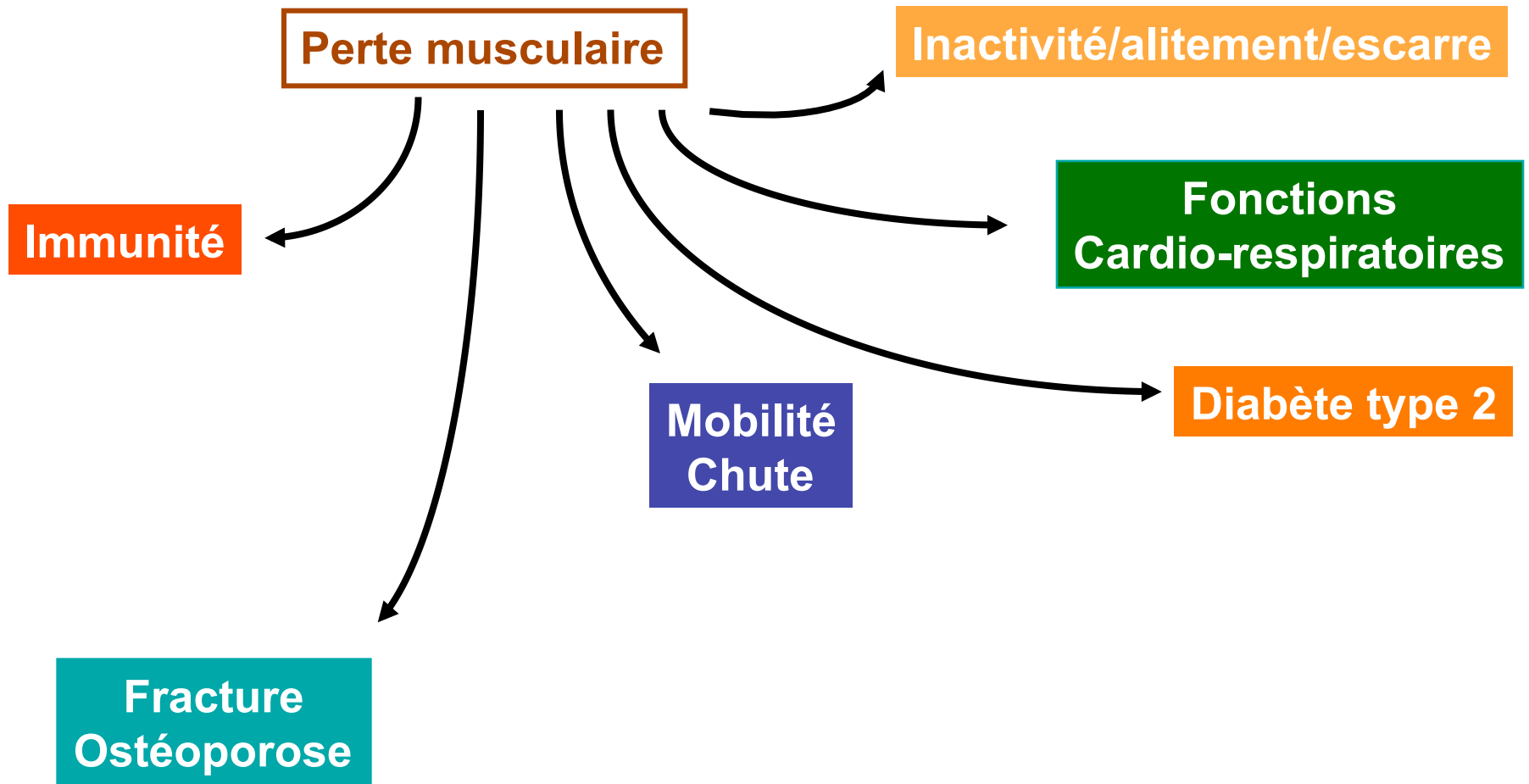
## **METABOLISME**

- captation du glucose
- oxydation lipidique
- production de chaleur

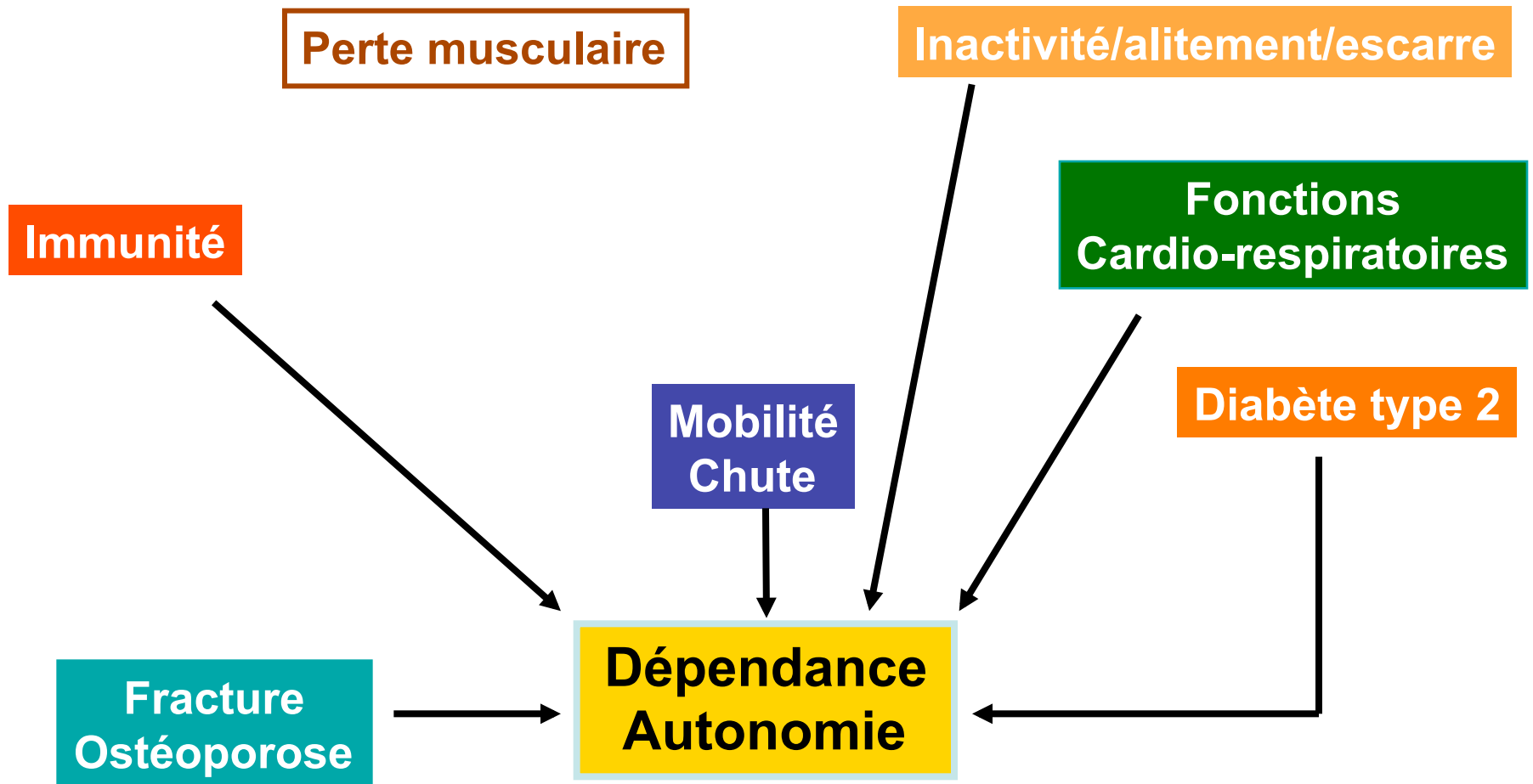
# Implication de la perte musculaire dans l'état de santé



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# **Sarcopénie et cachexie**

- **Évolution et involution musculaire**
- **Mécanismes de résistance ou de désadaptation anabolique**
- **Stratégies : l'union fait la force !**

# Sarcopénie et cachexie

- **Évolution et involution musculaire**
- Mécanismes de résistance ou de désadaptation anabolique
- Stratégies : l'union fait la force

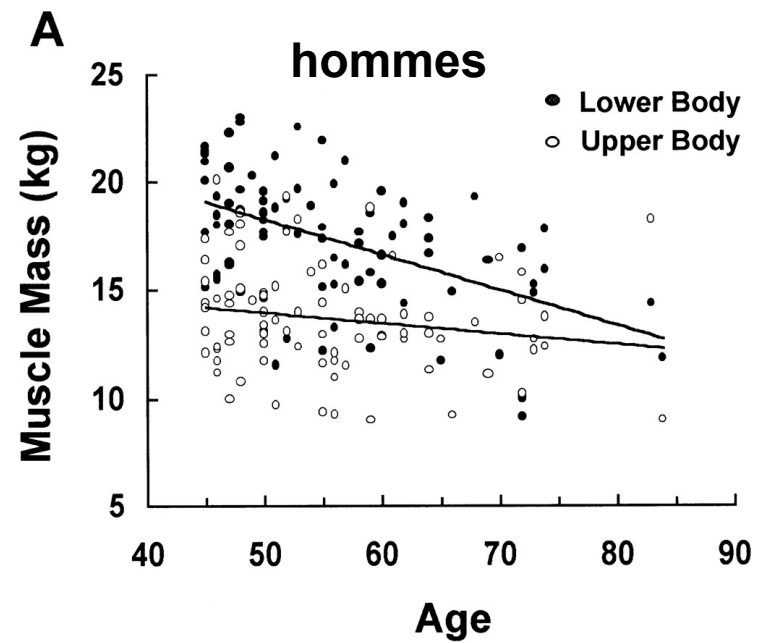
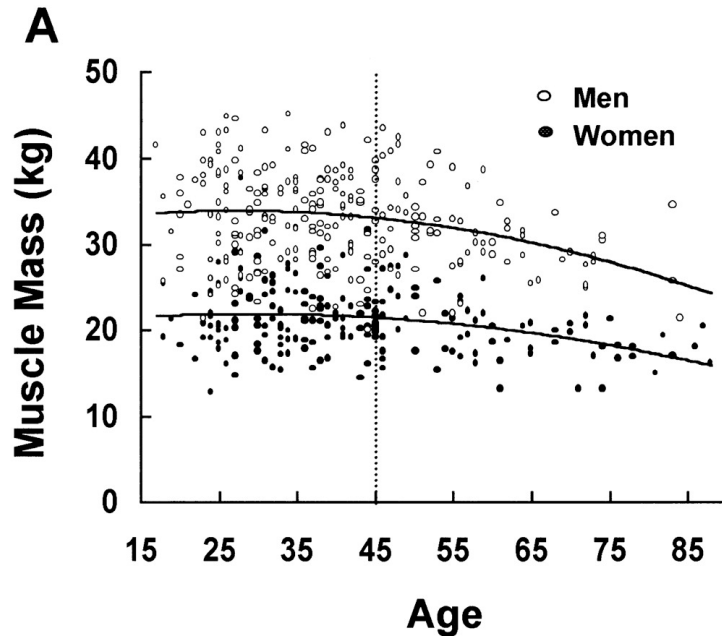
# Estimation de la masse musculaire : Il faut prendre des mesures...



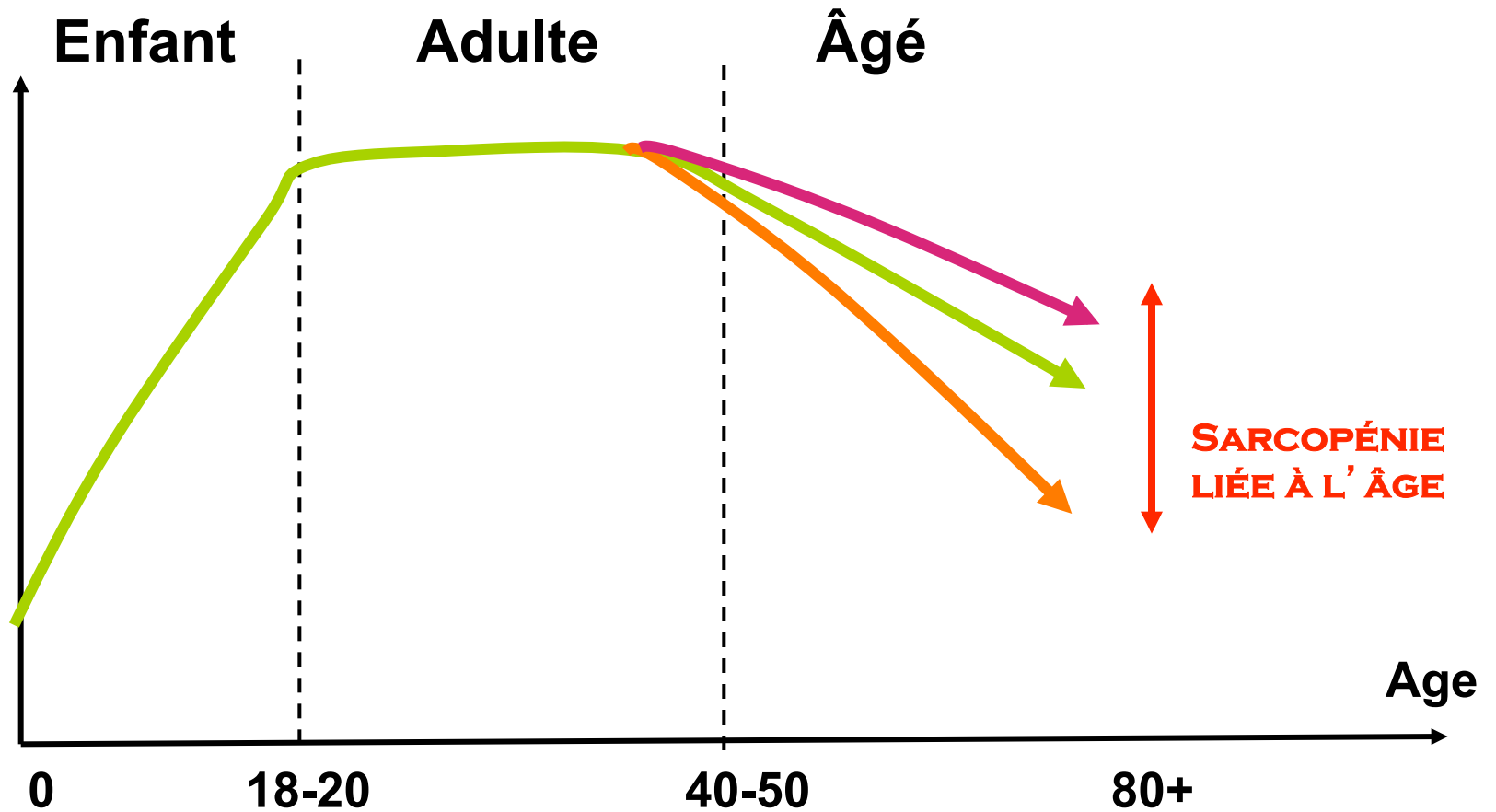
... mais lesquelles ? où ? et comment ?

# Une perte musculaire spécifique...

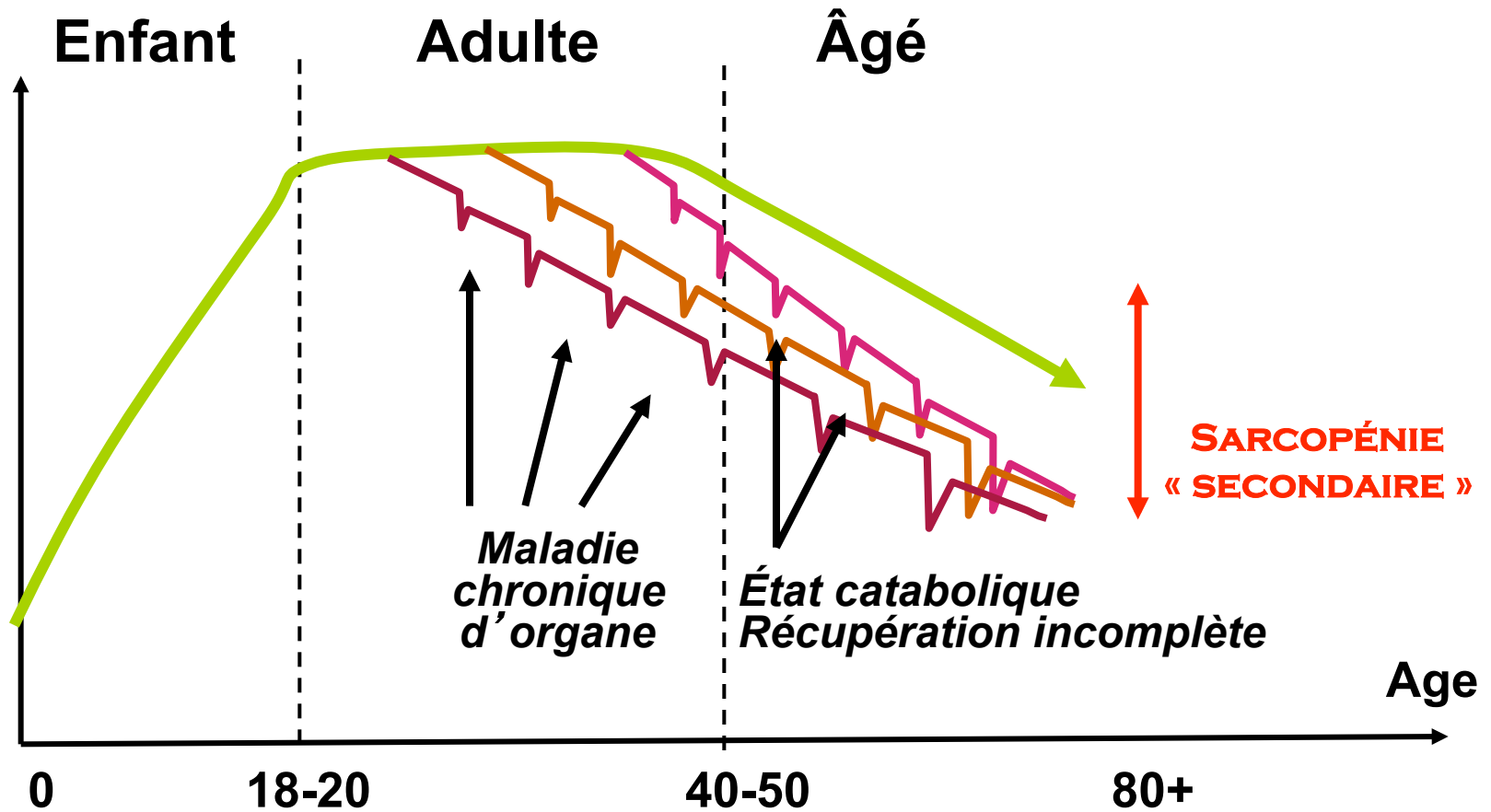
- *Hommes / Femmes*
- *Mbres inf / Mbres sup*



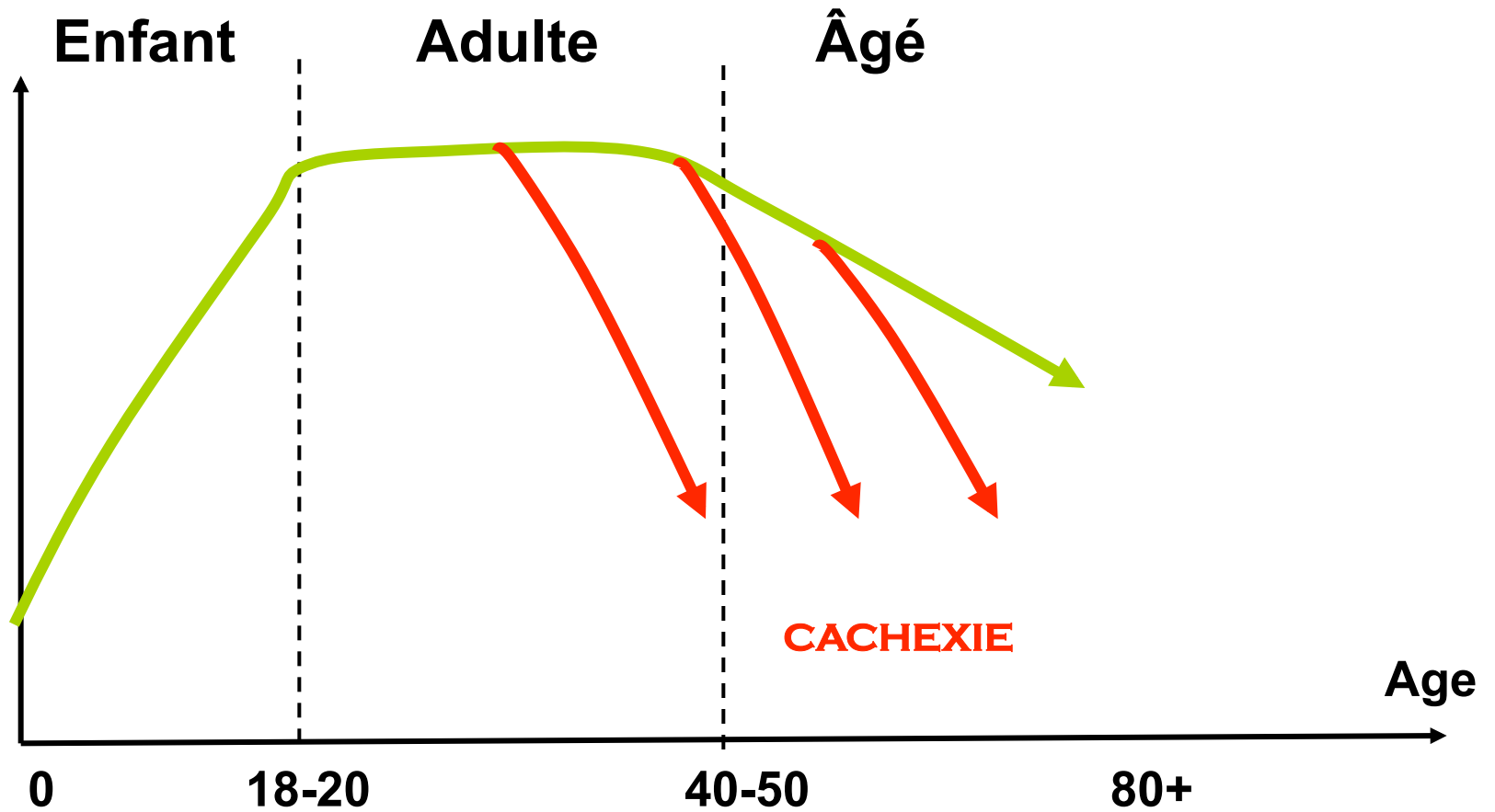
# Modèle d'évolution de la masse maigre



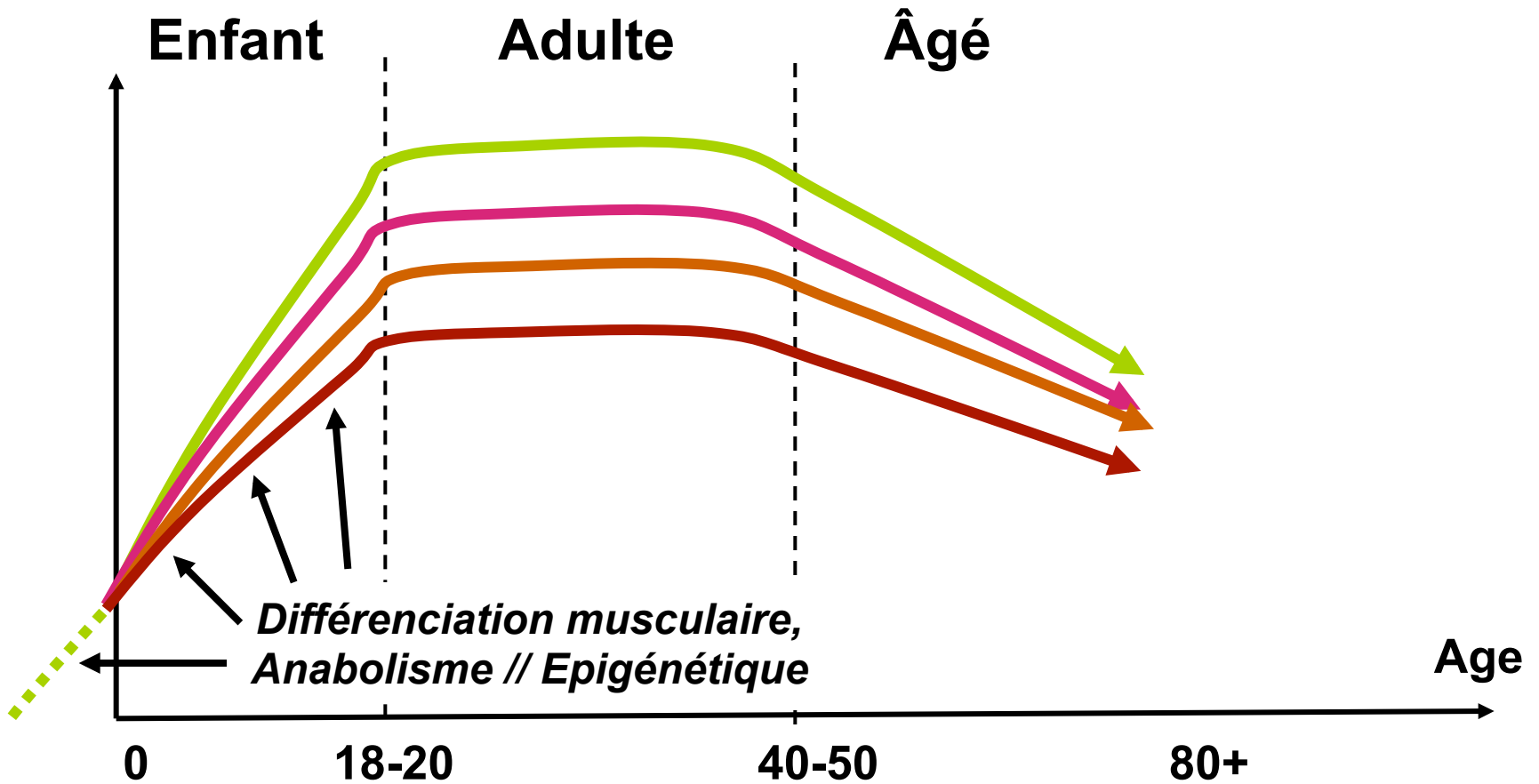
# Modèle d'évolution de la masse maigre



# Modèle d'évolution de la masse maigre

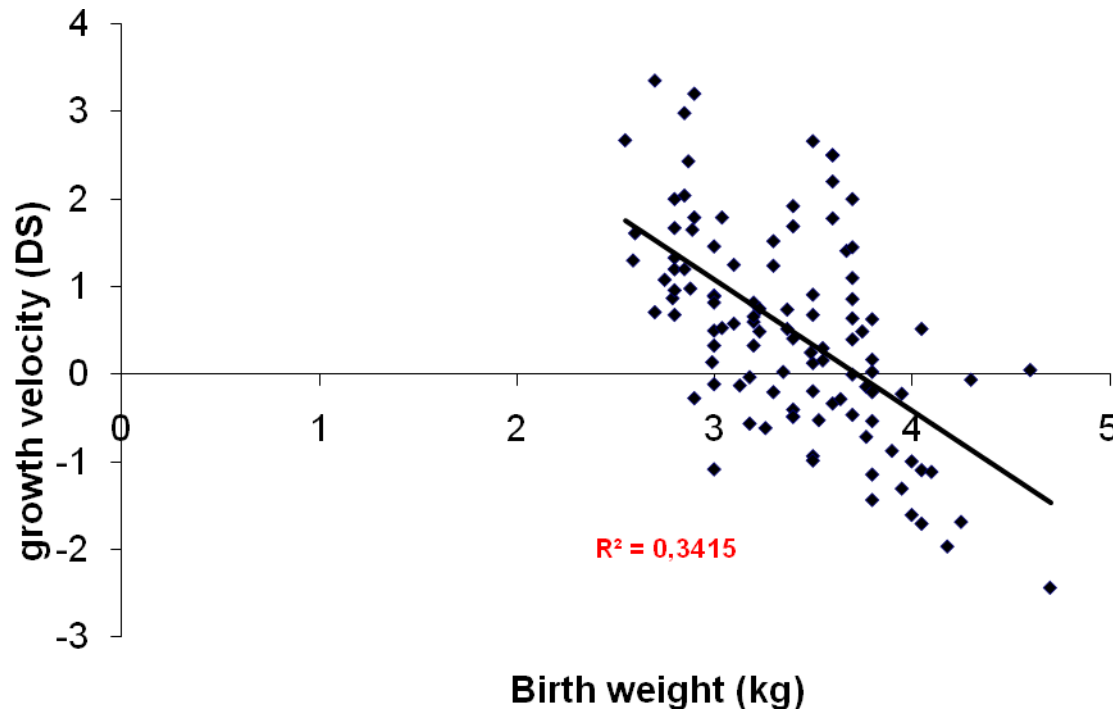


# Modèle d'évolution de la masse maigre





# Influence du poids de naissance sur la vélocité de croissance entre 0 et 2 ans



- **107** enfants
- PN (kg)  **$3.38 \pm 0.45$**
- Age (y)  **$12.8 \pm 0.8$**

----->  
**Composition  
Corporelle ?**  
----->

# La vélocité de croissance (0-2 ans) influence la masse maigre des adolescents obèses (12-14 ans) et leur dépense énergétique

	Normal growth	Rapid growth
<b>N</b>	<b>61</b>	<b>46</b>
<b>Birth Weight (kg)</b>	<b>3.60 ± 0.41</b>	<b>3.11 ± 0.36*</b>
<b>Weight (kg)</b>	<b>67.33 ± 13.06</b>	<b>75.29 ± 13.92*</b>
<b>Height (m)</b>	<b>1.57 ± 0.07</b>	<b>1.61 ± 0.08*</b>
<b>BMI (kg/m<sup>2</sup>)</b>	<b>27.25 ± 4.16</b>	<b>28.53 ± 4.10</b>
<b>FM (kg)</b>	<b>29.24 ± 8.50</b>	<b>32.63 ± 8.75*</b>
<b>FFM (kg)</b>	<b>38.09 ± 5.44</b>	<b>42.66 ± 6.18*</b>
<b>REE meas (kcal/d)</b>	<b>1586.23 ± 216.52</b>	<b>1765.43 ± 222.98*</b>
<b>REE/FFM</b>	<b>41.95 ± 5.14</b>	<b>41.67 ± 4.13</b>

# Body mass index during childhood and adult body composition in men and women aged 56–70 y<sup>1–3</sup>

Hilkka Ylihärsilä, Eero Kajantie, Clive Osmond, Tom Forsén, David JP Barker, and Johan G Eriksson

**Conclusions:** Rapid gain in BMI before the age of 2 y increased adult lean body mass without excess fat accumulation, whereas rapid gain in BMI in later childhood, despite the concurrent rise in lean mass, resulted in relatively larger increases in fat mass. *Am J Clin Nutr* 2008;87:1769–75.

## ORIGINAL ARTICLE

# Birth size, adult body composition and muscle strength in later life

H Ylihärsilä<sup>1</sup>, E Kajantie<sup>1</sup>, C Osmond<sup>2</sup>, T Forsén<sup>1</sup>, DJP Barker<sup>2</sup> and JG Eriksson<sup>1,3</sup>

**Conclusions:** Low birth weight is associated with lower lean mass in adult life and thus contributes to the risk of relative sarcopenia and the related functional inability at the other end of the lifespan. At a given level of adult BMI, low birth weight predicts higher body fat percentage.

*International Journal of Obesity* (2007) 31, 1392–1399; doi:10.1038/sj.ijo.0803612; published online 13 March 2007

# Sarcopénie et cachexie

- **Évolution et involution musculaire**
- **Mécanismes de résistance ou de désadaptation anabolique**
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# Causes de perte musculaire

Dysfonction  
mitochondriale

Réduction de  
l'activité physique

Altérations hormonales

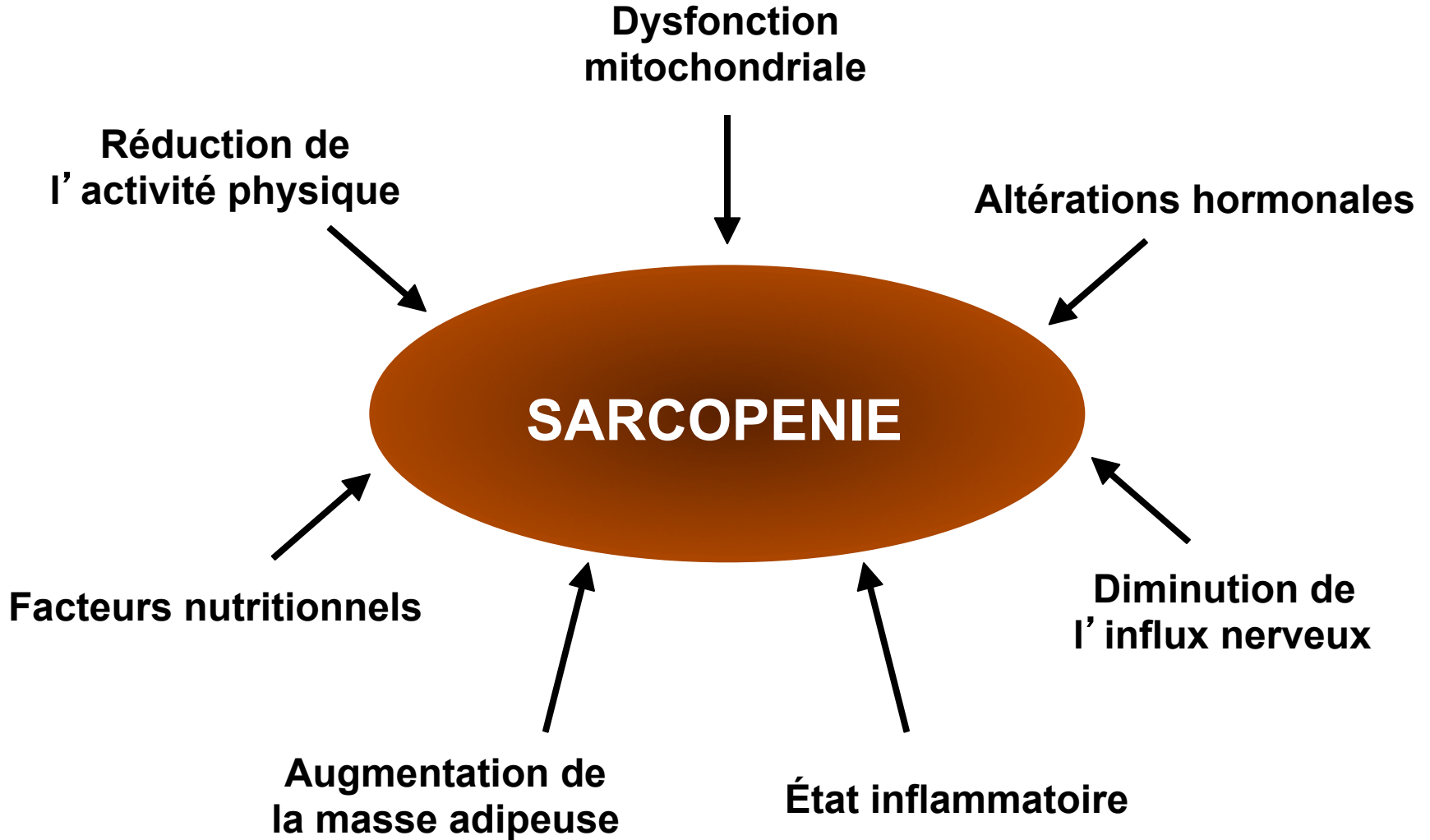
**SARCOPENIE**

Facteurs nutritionnels

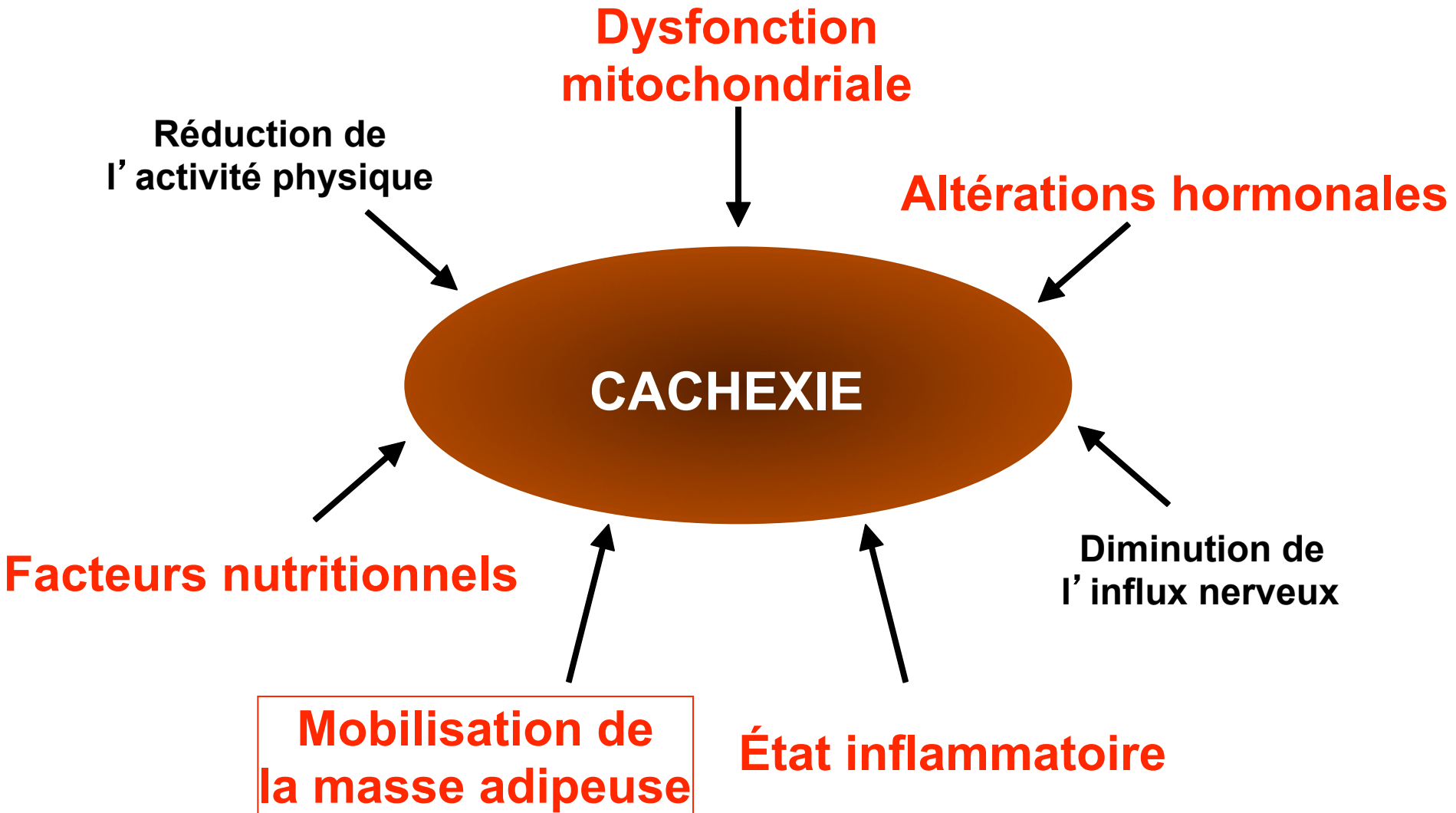
Diminution de  
l'influx nerveux

Augmentation de  
la masse adipeuse

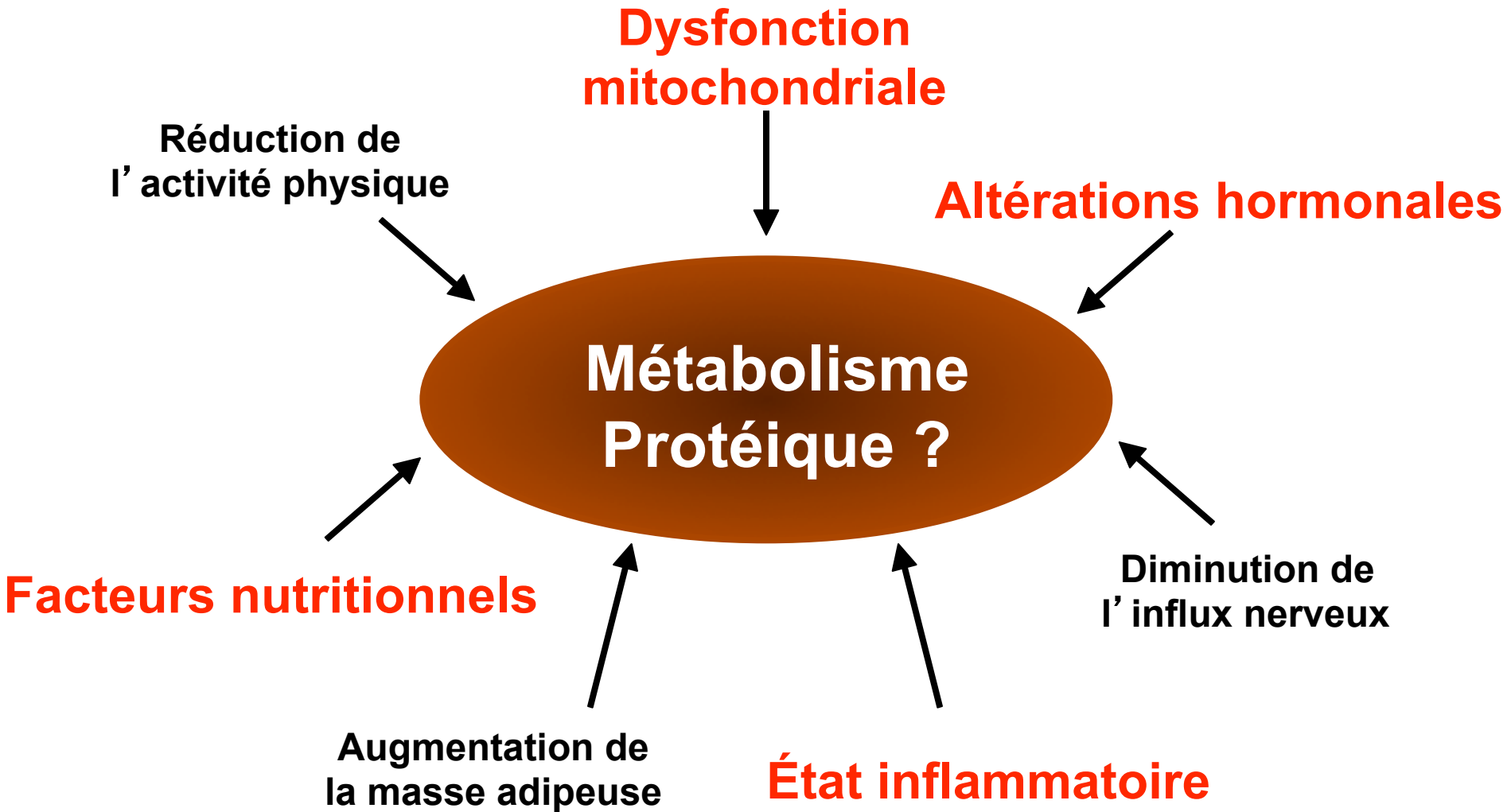
État inflammatoire



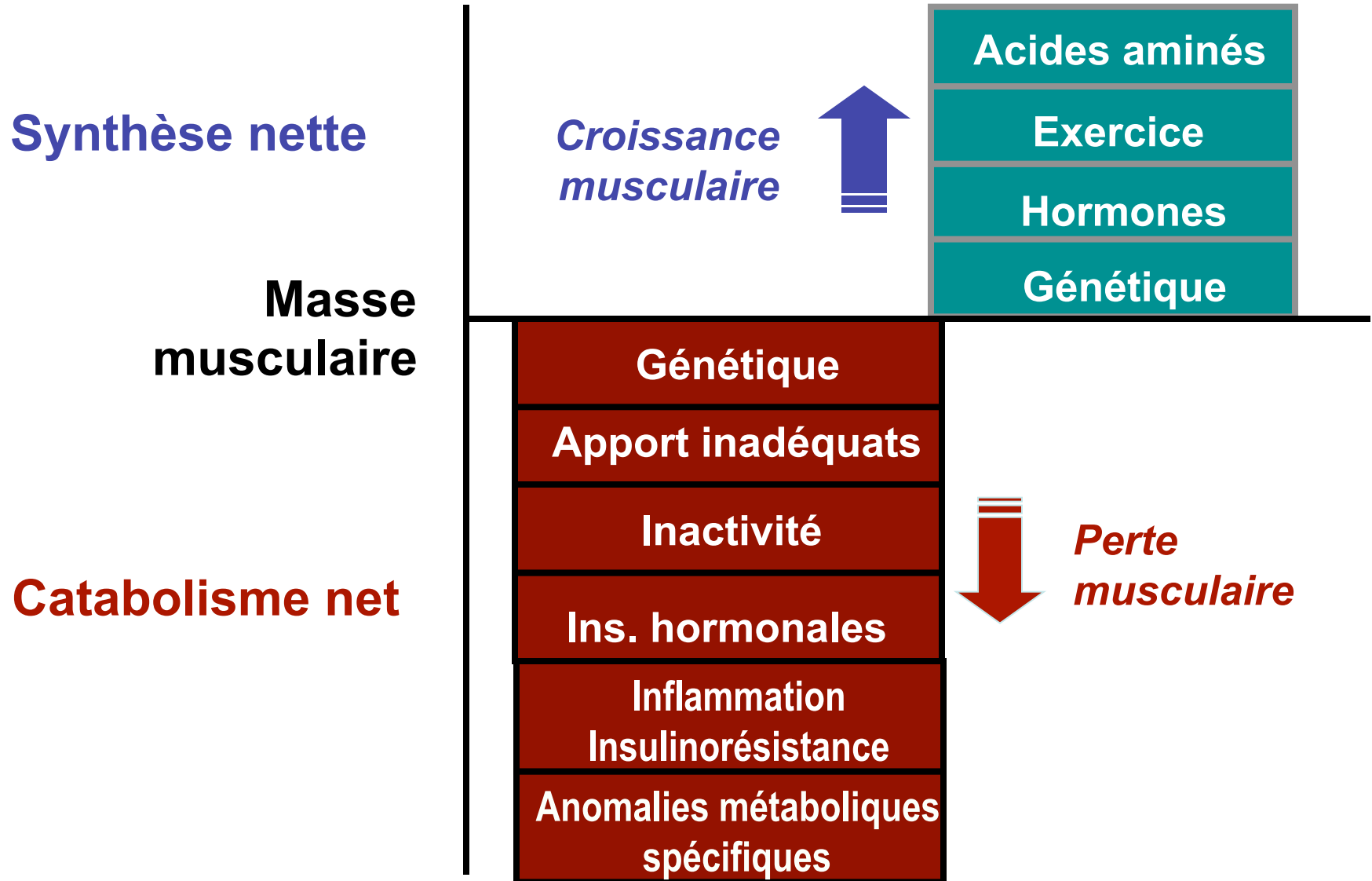
# Causes de perte musculaire



# Causes de perte musculaire

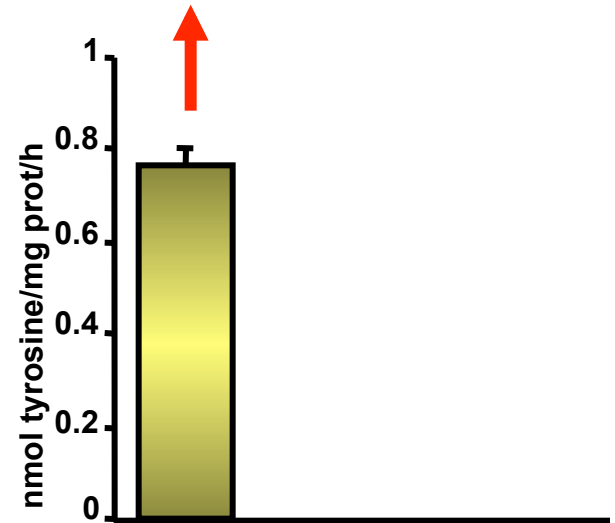
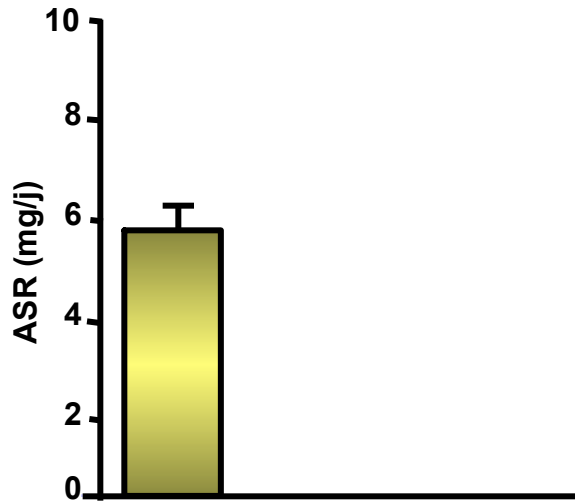


# Contrôle de la masse musculaire





# Postabsorptive protein balance in skeletal muscle



*Synthesis*

AA



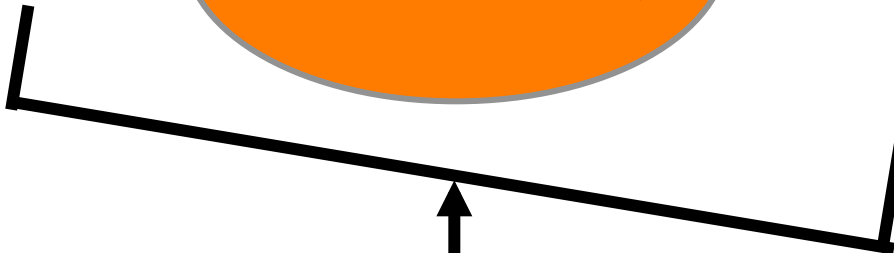
**Proteins** ↓



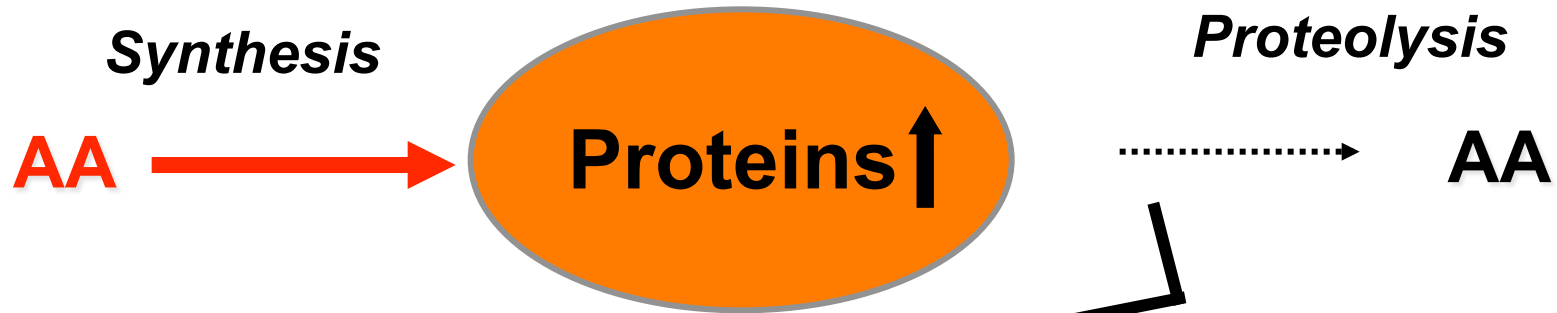
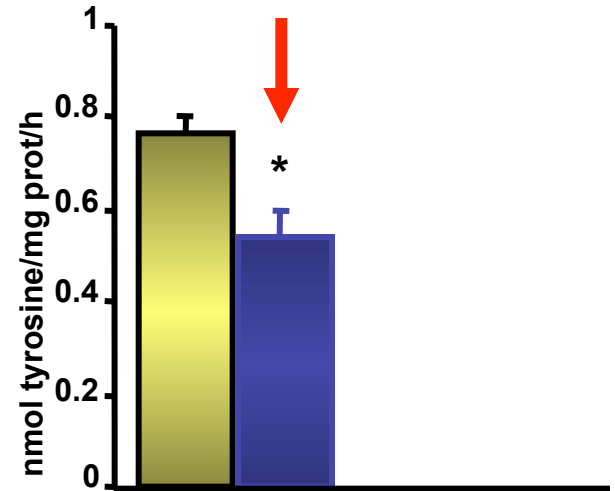
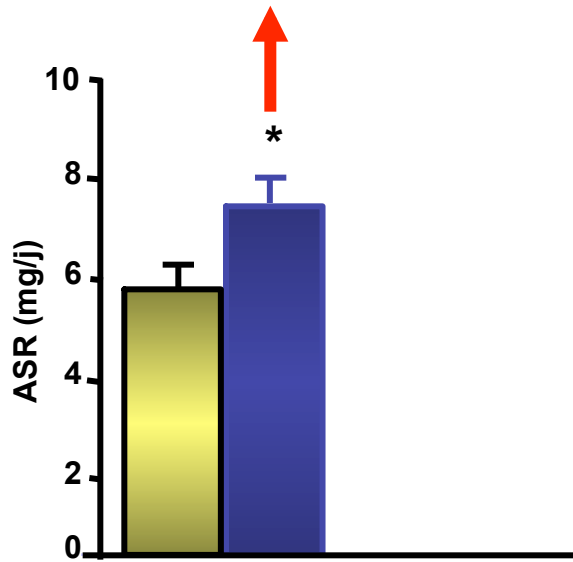
AA

*Proteolysis*

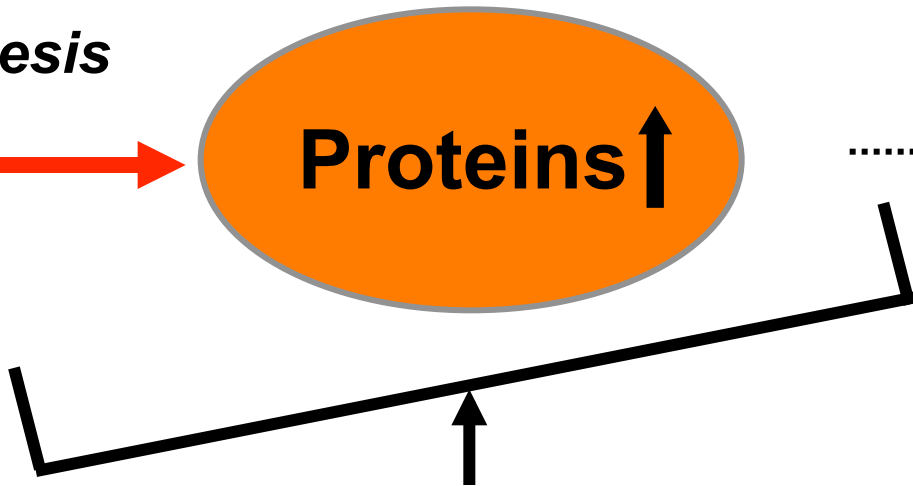
 Postabsorptive



# Postprandial protein balance in skeletal muscle



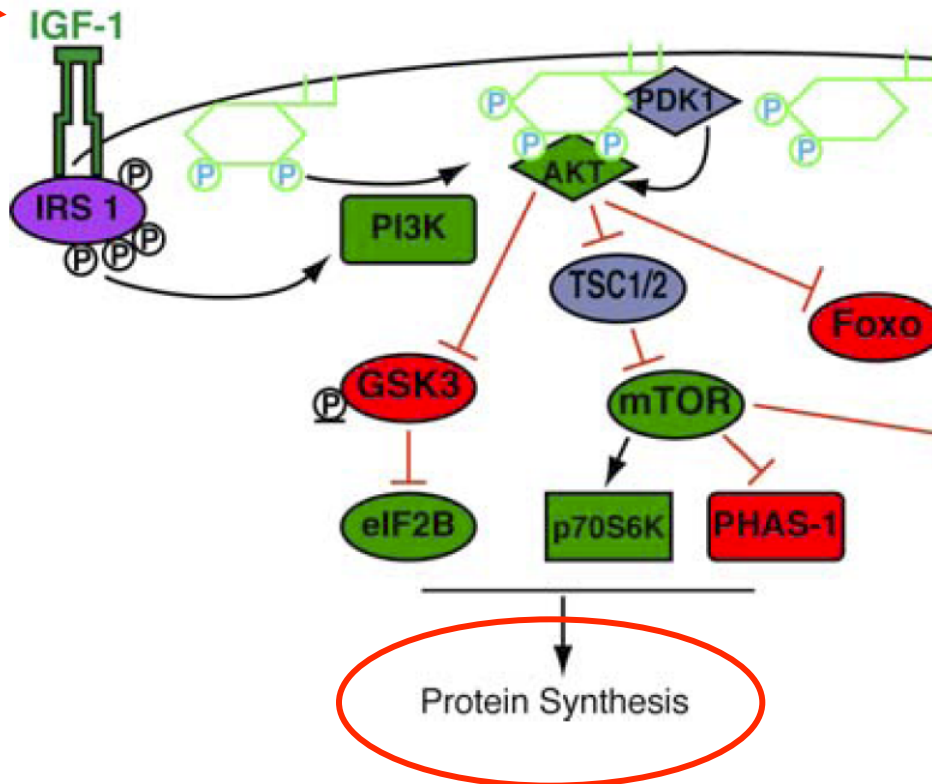
Postabsorptive  
Postprandial



# INSULIN

The IGF-1/PI3K/Akt pathway induces protein synthesis, and blocks atrophy pathways

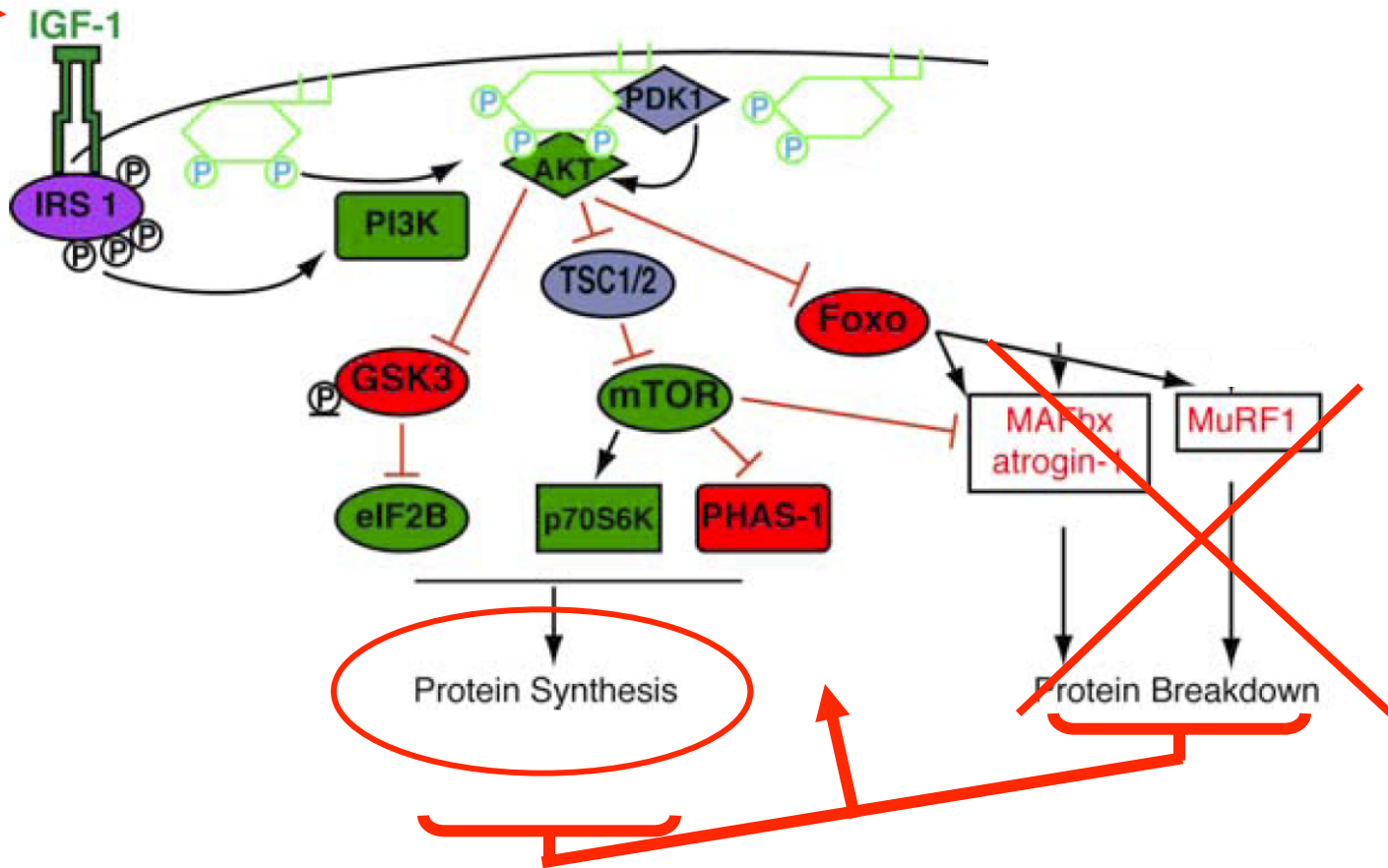
Hypertrophy Signaling



# INSULIN

The IGF-1/PI3K/Akt pathway induces protein synthesis, and blocks atrophy pathways

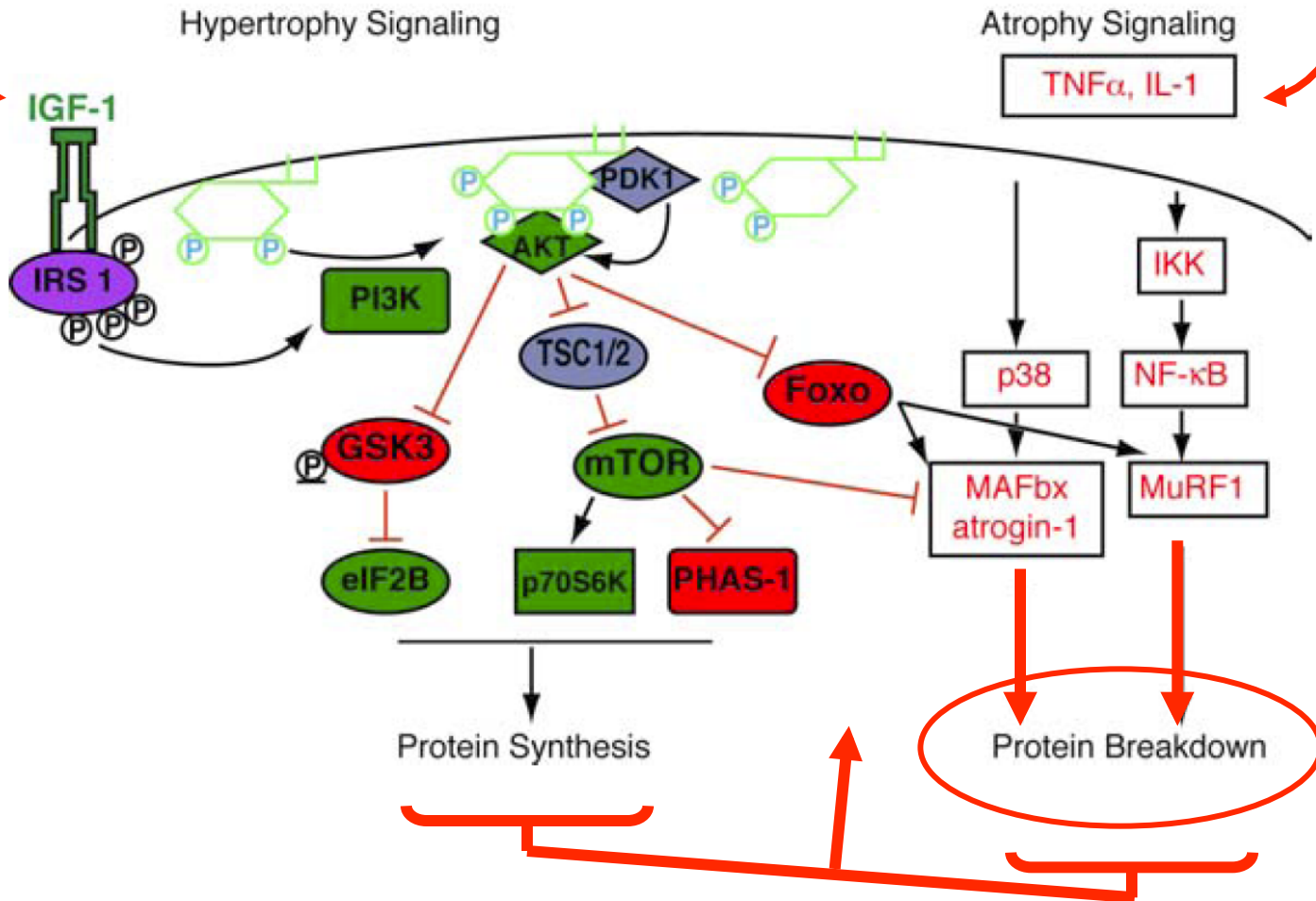
Hypertrophy Signaling



**INSULIN**

**CYTOKINES**

The IGF-1/PI3K/Akt pathway induces protein synthesis, and blocks atrophy pathways



# Impaired anabolic response to meal intake during aging

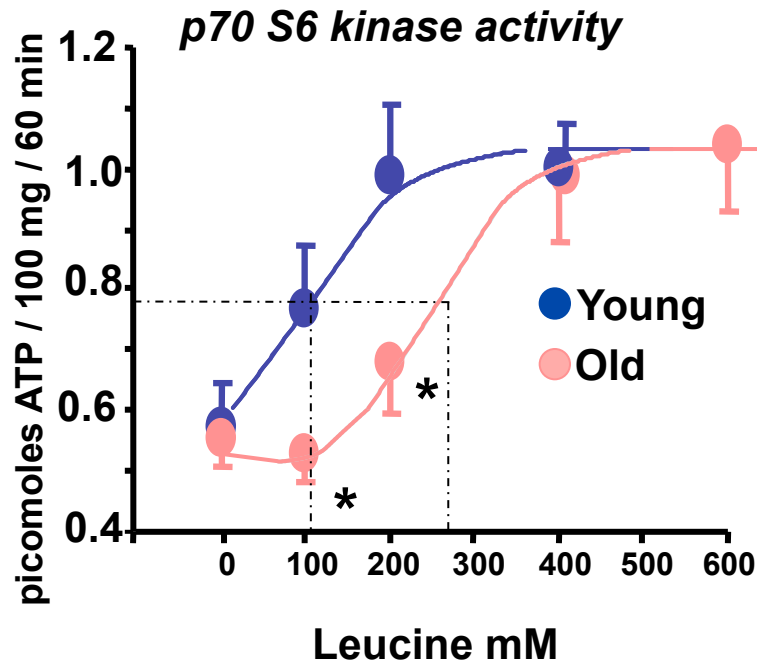


# Anabolic resistance

Defect in the regulation of mTOR signaling pathway by amino acids



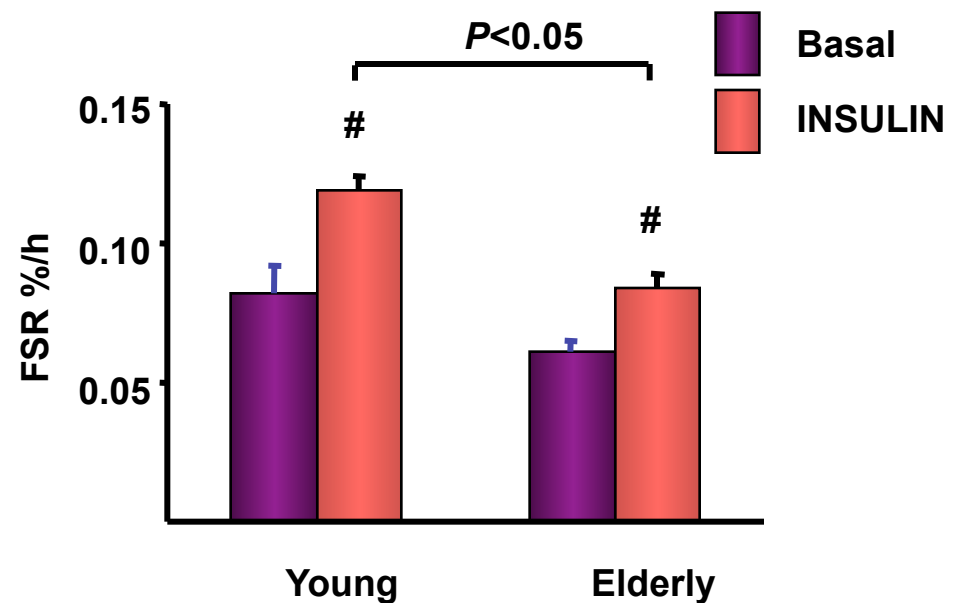
## Leucine resistance



Defect in the regulation of mTOR signaling pathway by insulin



## Insulin resistance

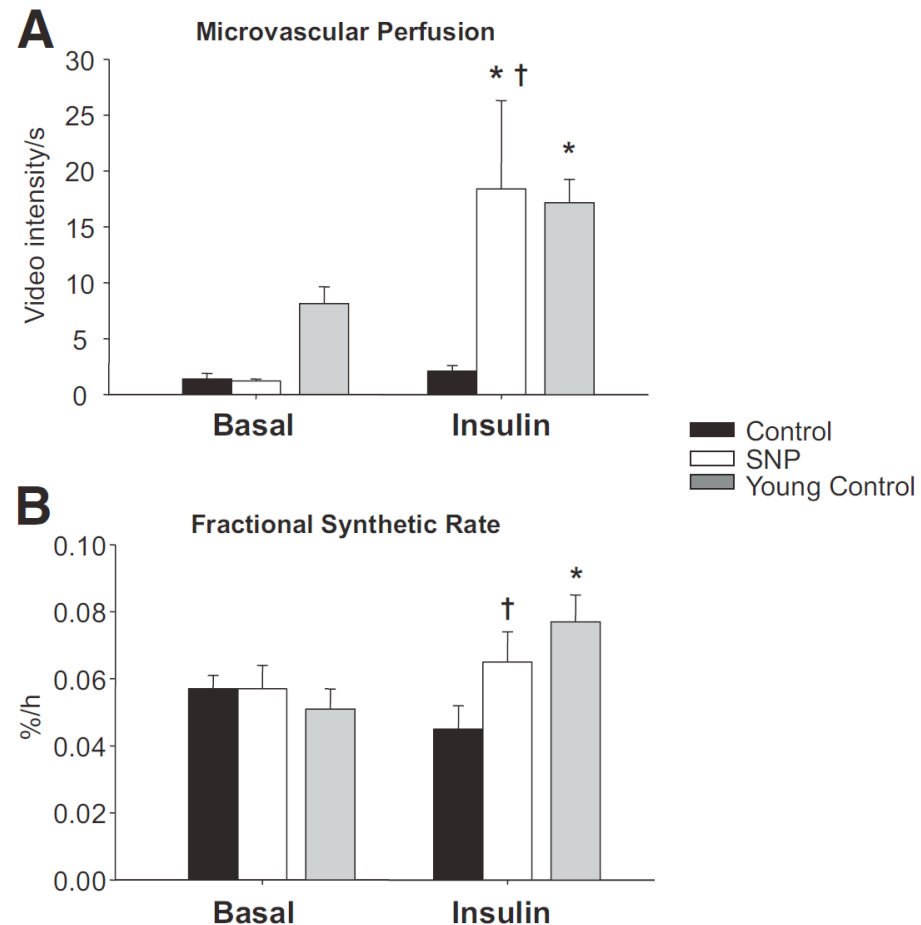
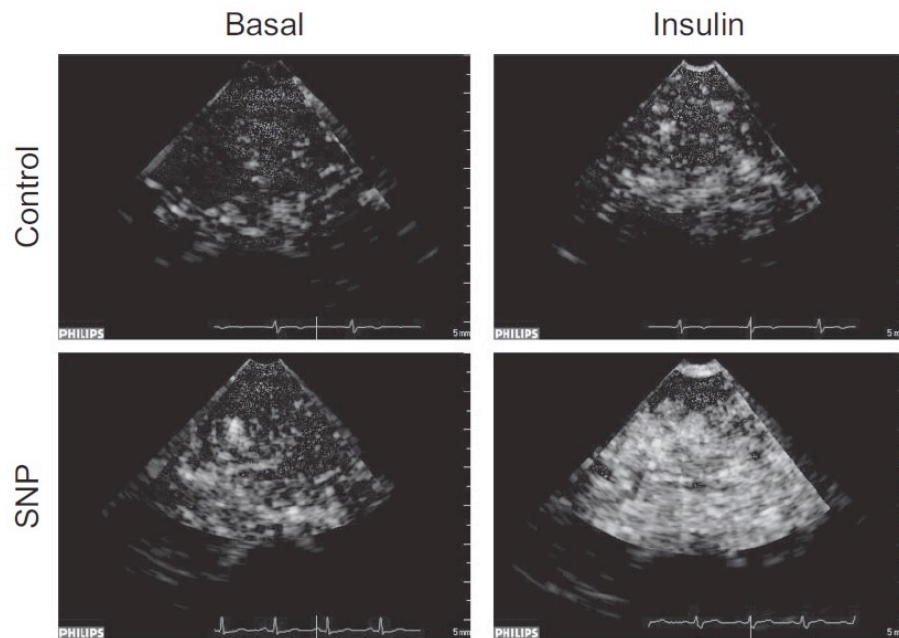


*Dardevet, J Nutr 2000*  
*Cuthbertson, FASEB J 2005*

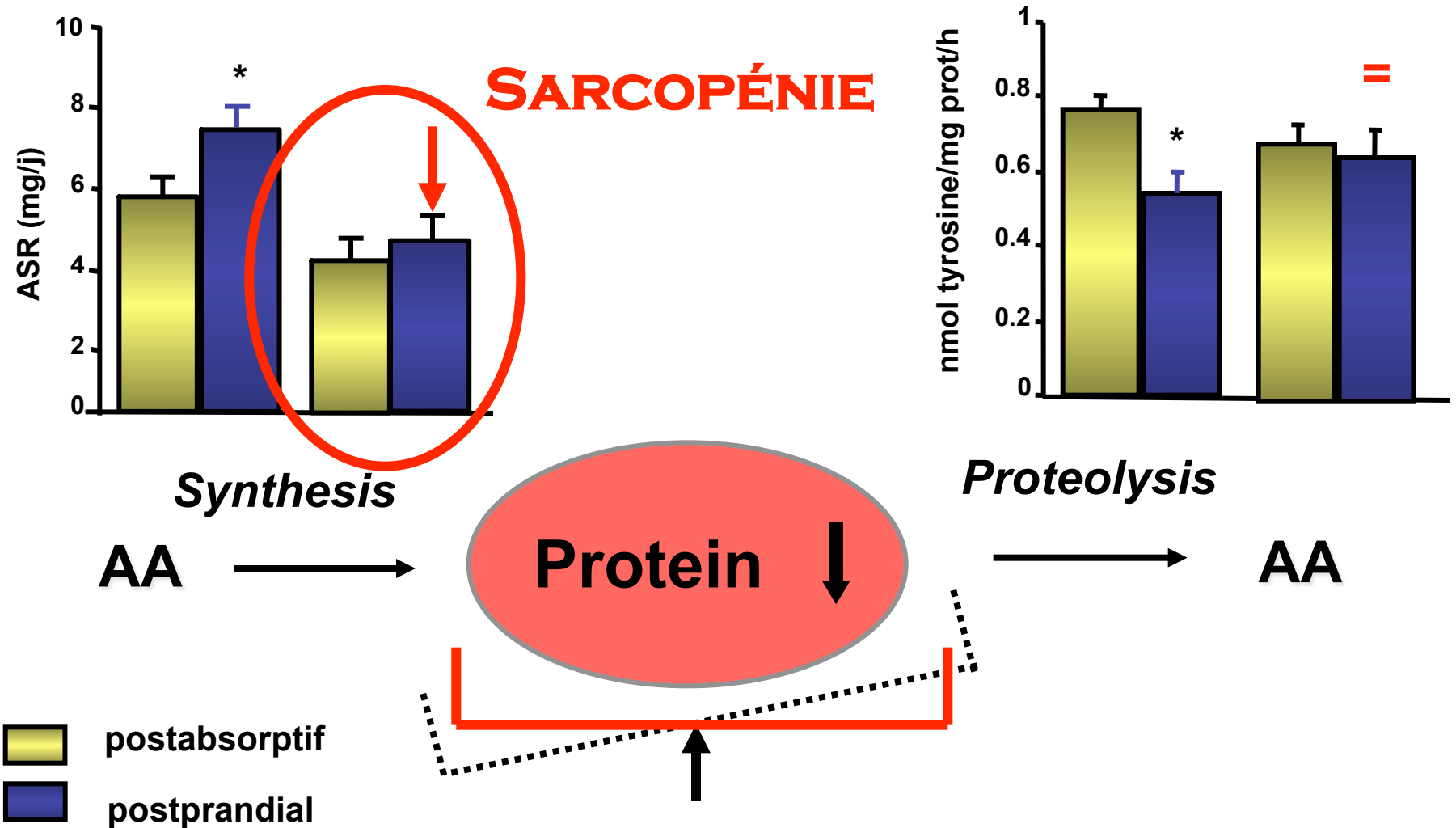
*Guillet, FASEB J 2004*  
*Rasmussen, FASEB J 2006*

# Pharmacological Vasodilation Improves Insulin-Stimulated Muscle Protein Anabolism but Not Glucose Utilization in Older Adults

Kyle L. Timmerman,<sup>1</sup> Jessica L. Lee,<sup>1</sup> Satoshi Fujita,<sup>1,2</sup> Shaheen Dhanani,<sup>1</sup> Hans C. Dreyer,<sup>3,4</sup> Christopher S. Fry,<sup>4</sup> Micah J. Drummond,<sup>4</sup> Melinda Sheffield-Moore,<sup>1,2</sup> Blake B. Rasmussen,<sup>1,3,4</sup> and Elena Volpi<sup>1,2</sup>



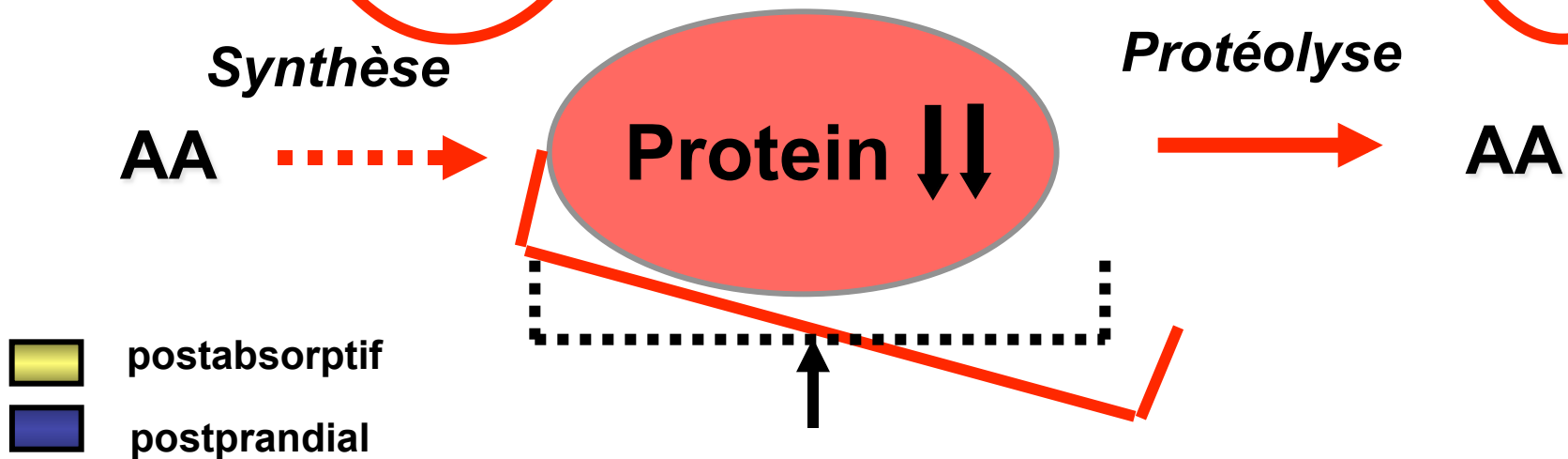
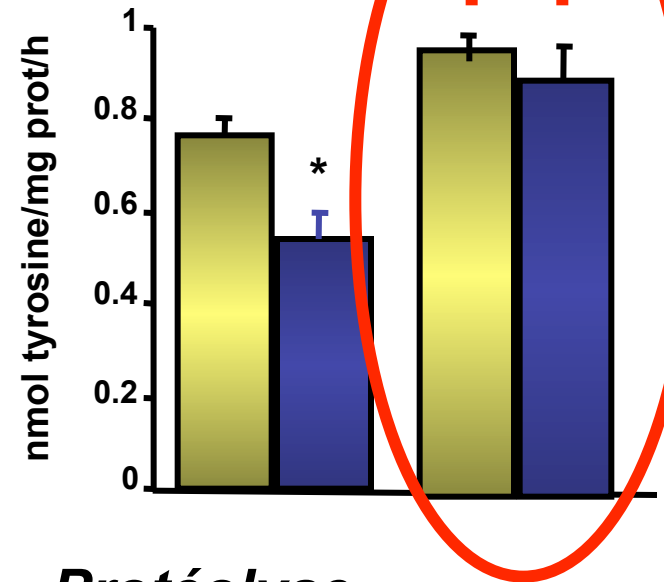
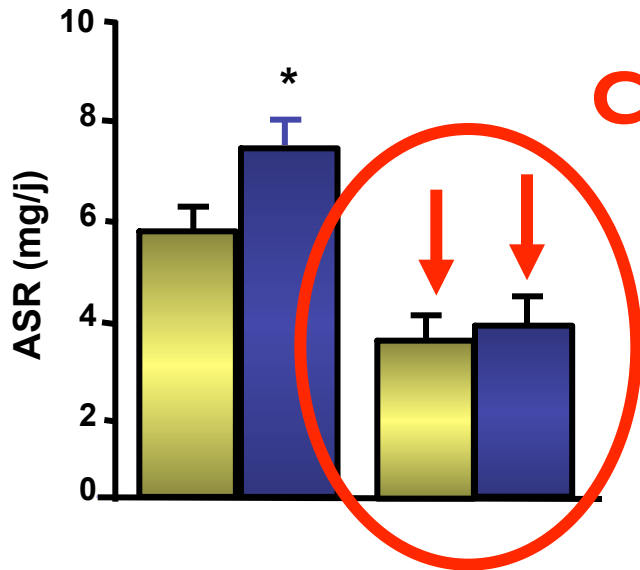
# Perte de l'effet anabolique du repas





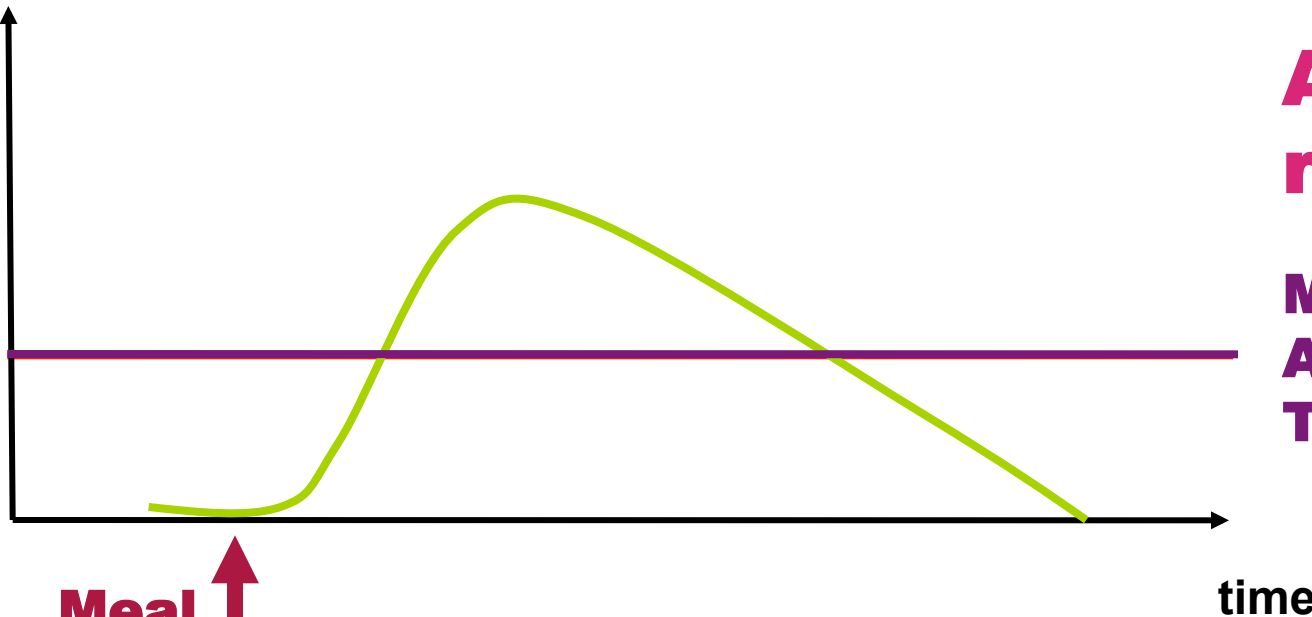
# Perte de l'effet anabolique et anticatabolique du repas

**CACHEXIE**



# Muscle loss situations

Anabolic stimulators



**Anabolic resistance**

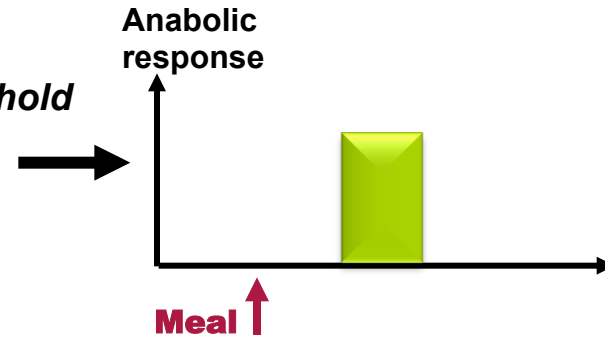
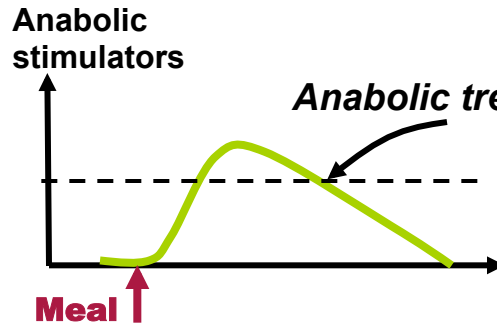
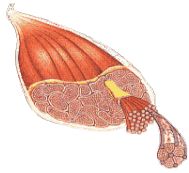
**Muscle Anabolism Threshold**

**Meal**

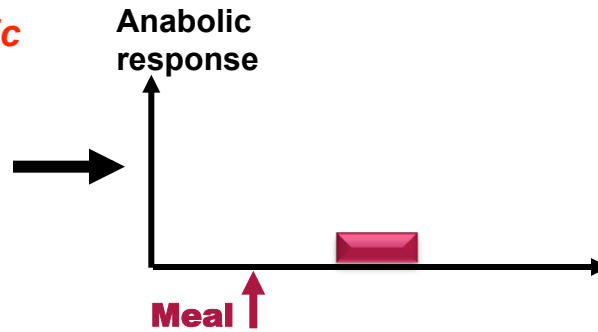
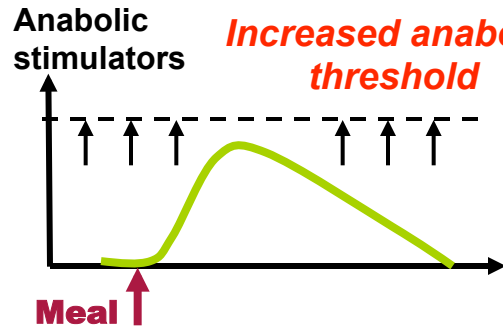


 Physiological situation

 Aging or catabolic state



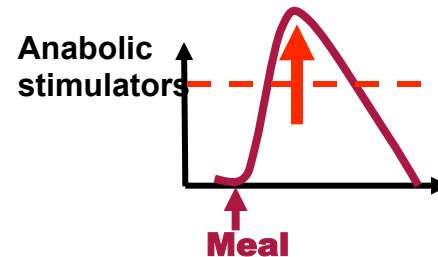
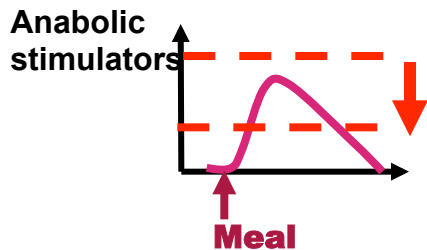
Anabolic resistance



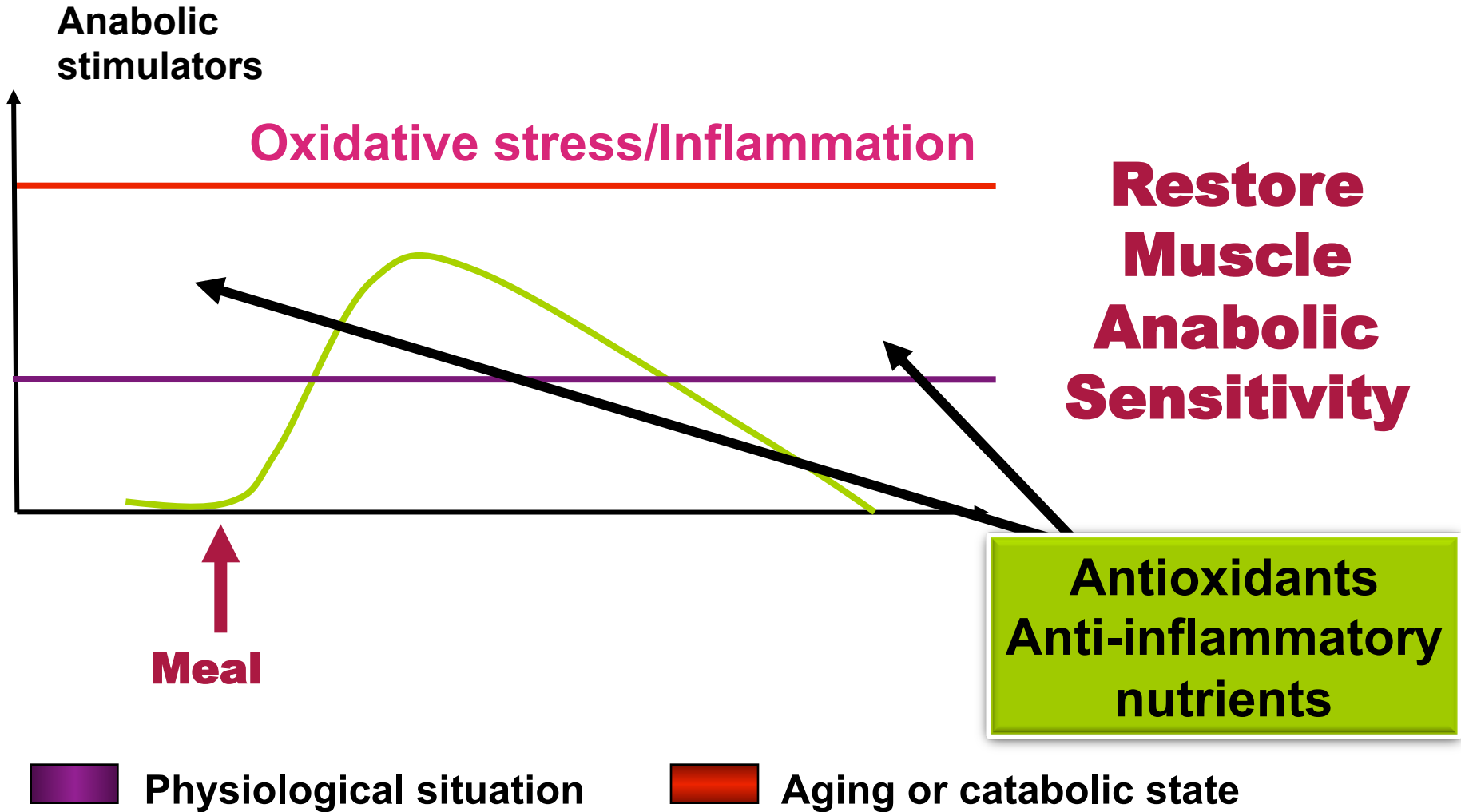
## 2 strategies

↳ to reduce muscle anabolic threshold

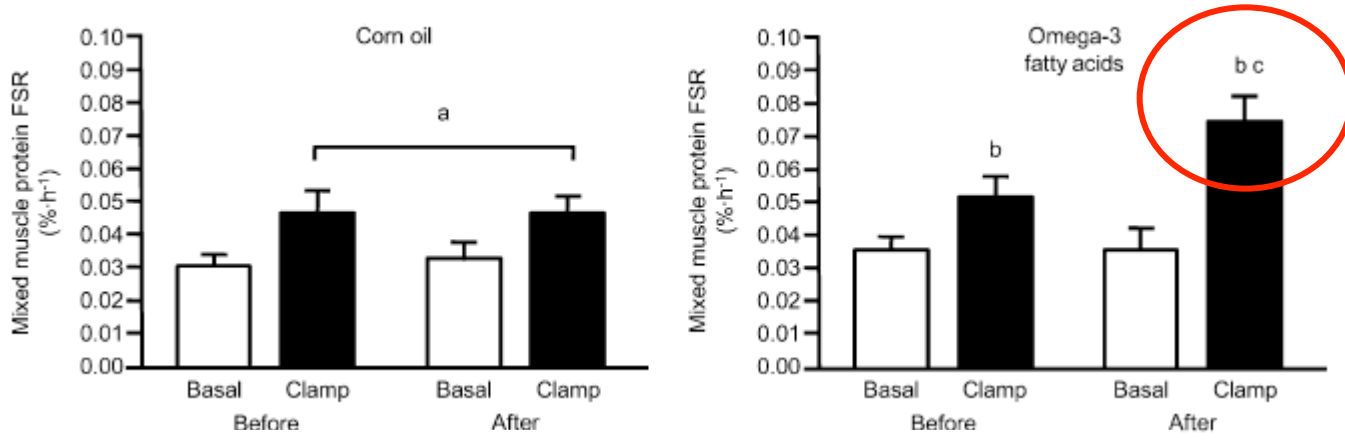
↳ to increase the availability of anabolic stimulators



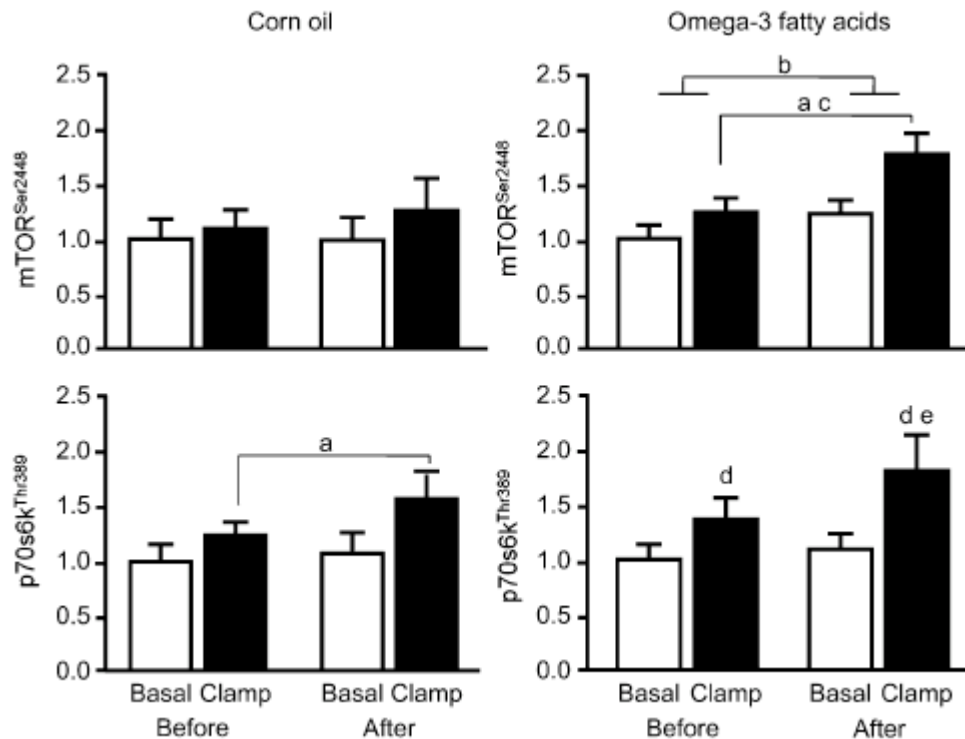
# Improving muscle sensitivity to anabolic factors?



# Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial<sup>1-3</sup>

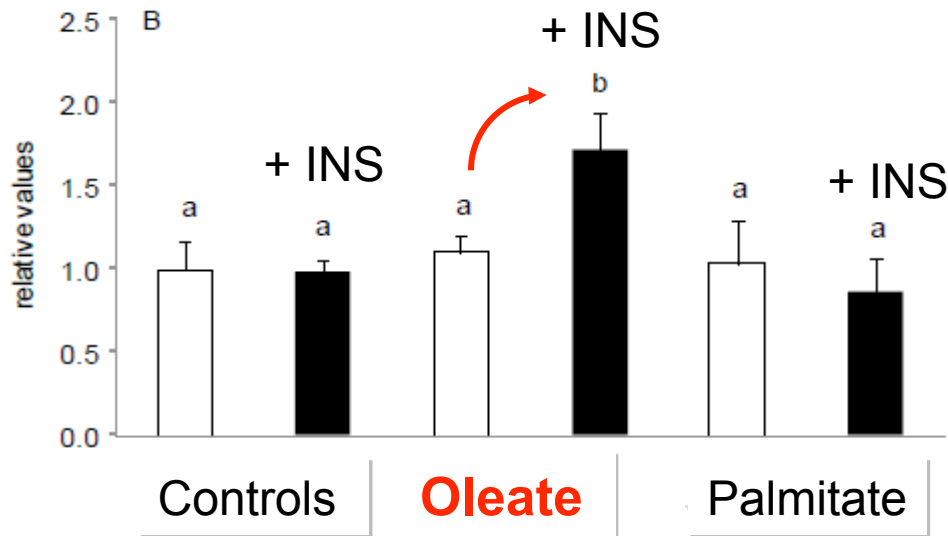


**Muscle protein synthesis**

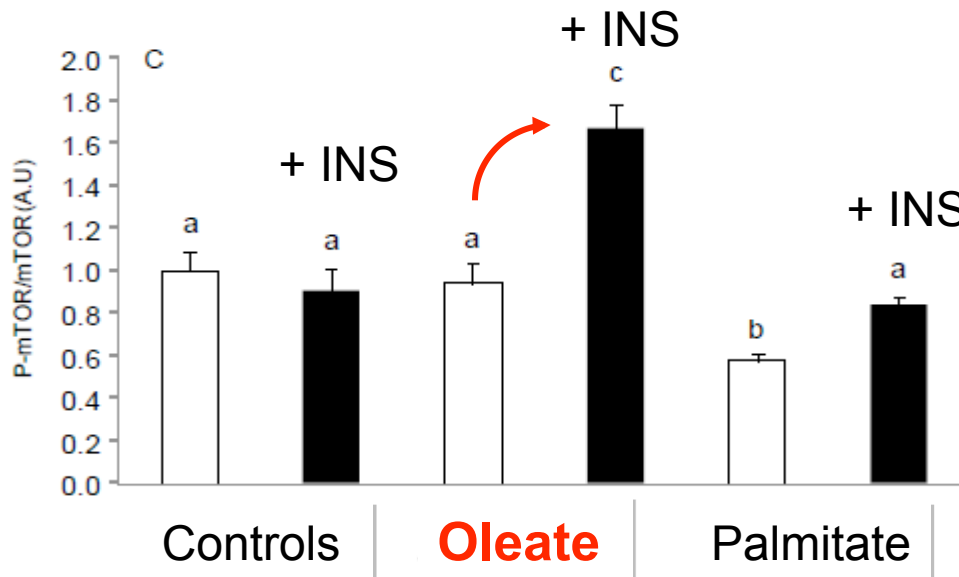


**Signaling pathways for the initiation of Protein synthesis**

# Muscle protein synthesis of old rats fed a control diet, a **high-oleate diet** or a high-palmitate diet

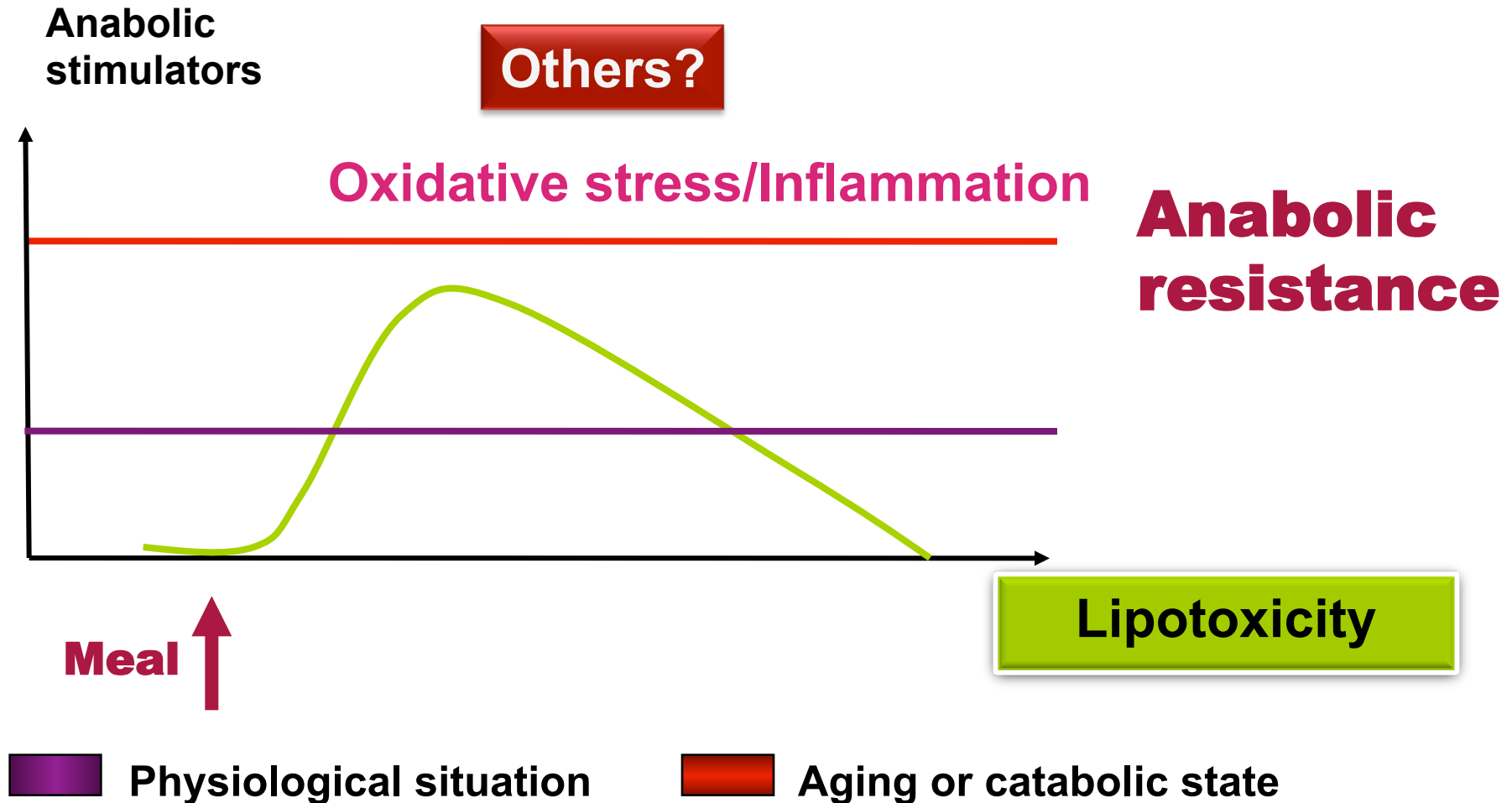


**Muscle protein synthesis**

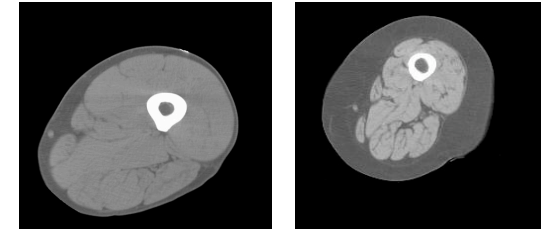


**Signaling pathways for the initiation of Protein synthesis**

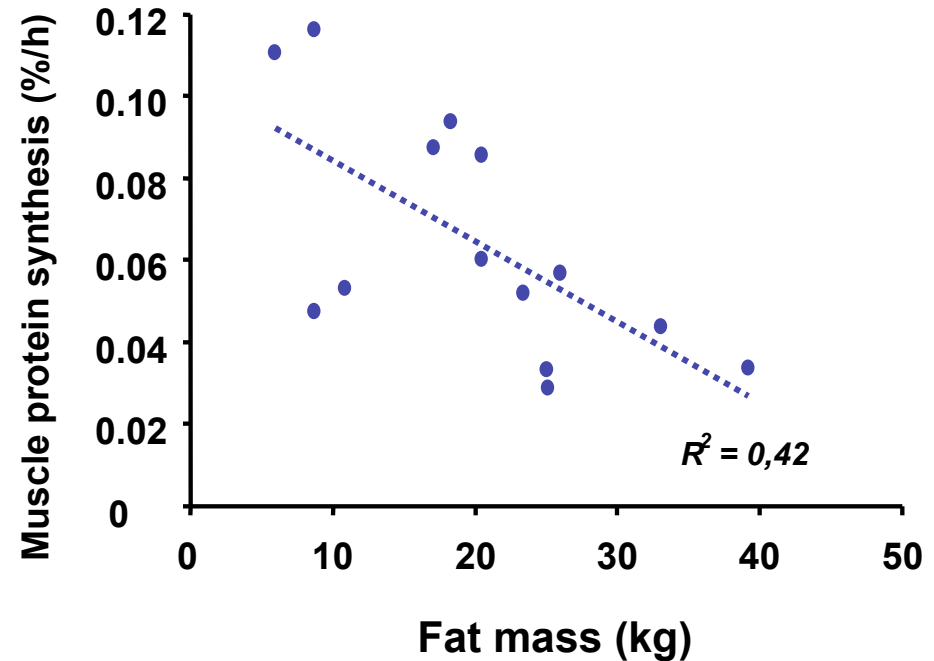
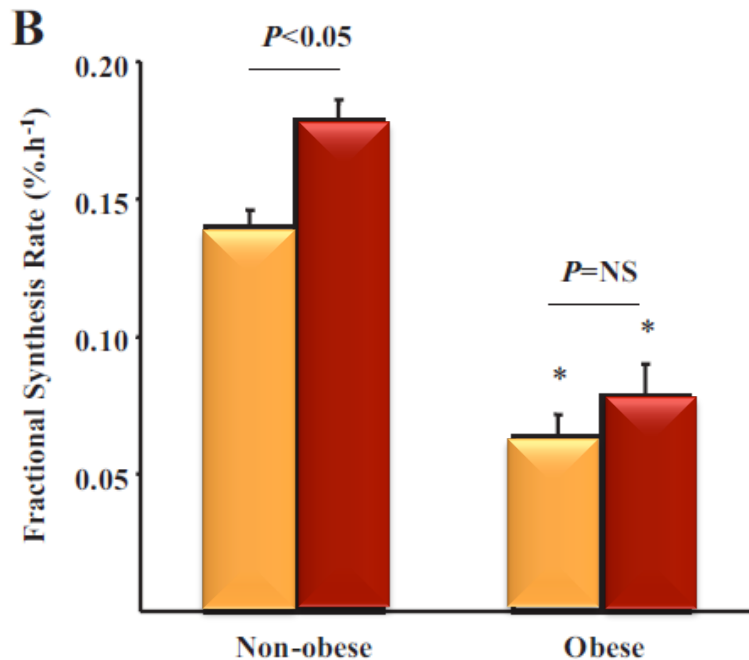
# New mechanisms of muscle anabolic resistance?



# New mechanism of muscle anabolic resistance: lipotoxicity



## Muscle Mitochondrial Protein synthesis (%/h)

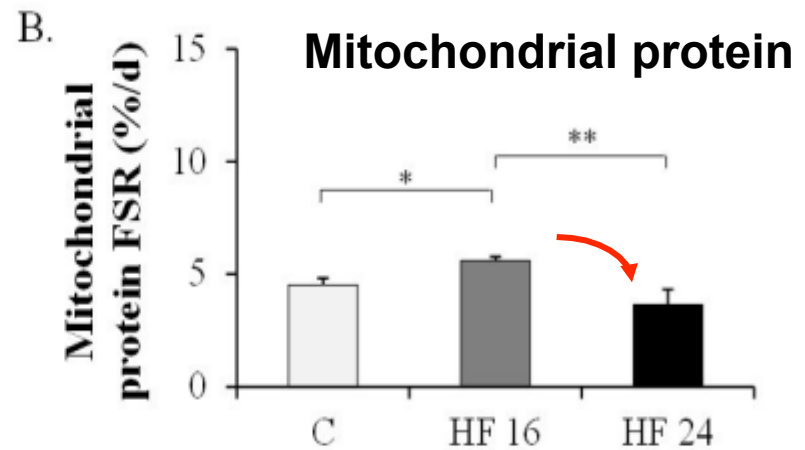
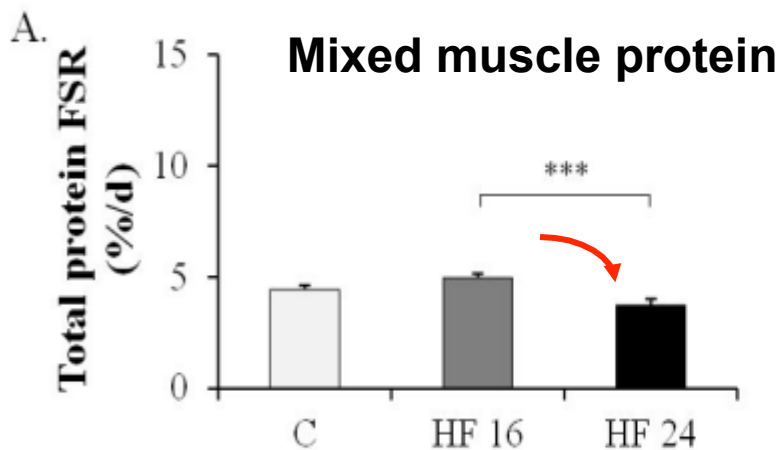
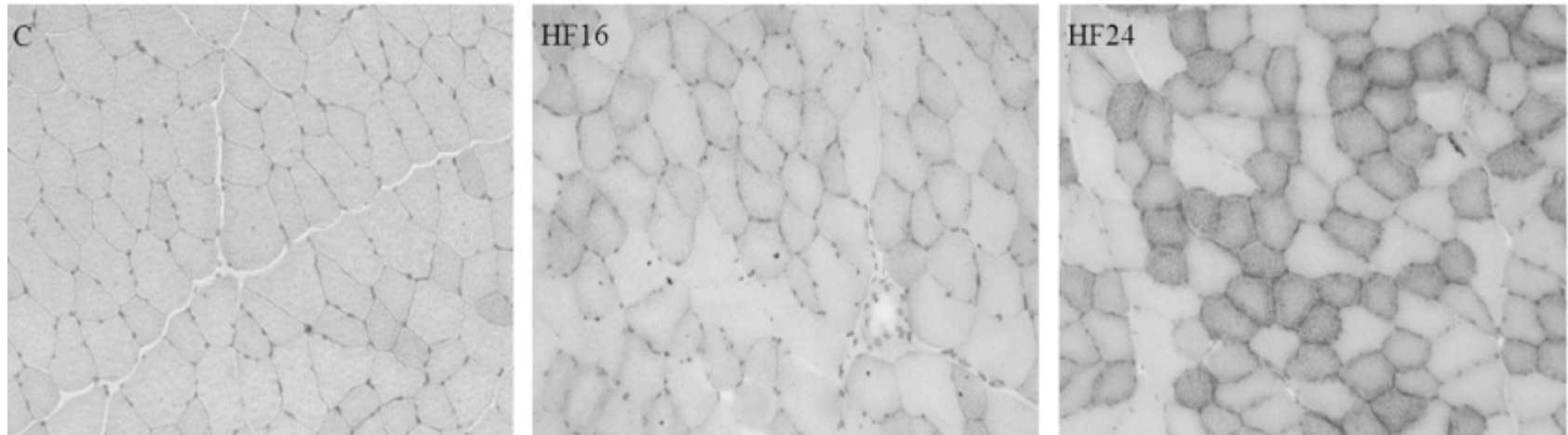


- Postabsorptive
- Insulin clamp

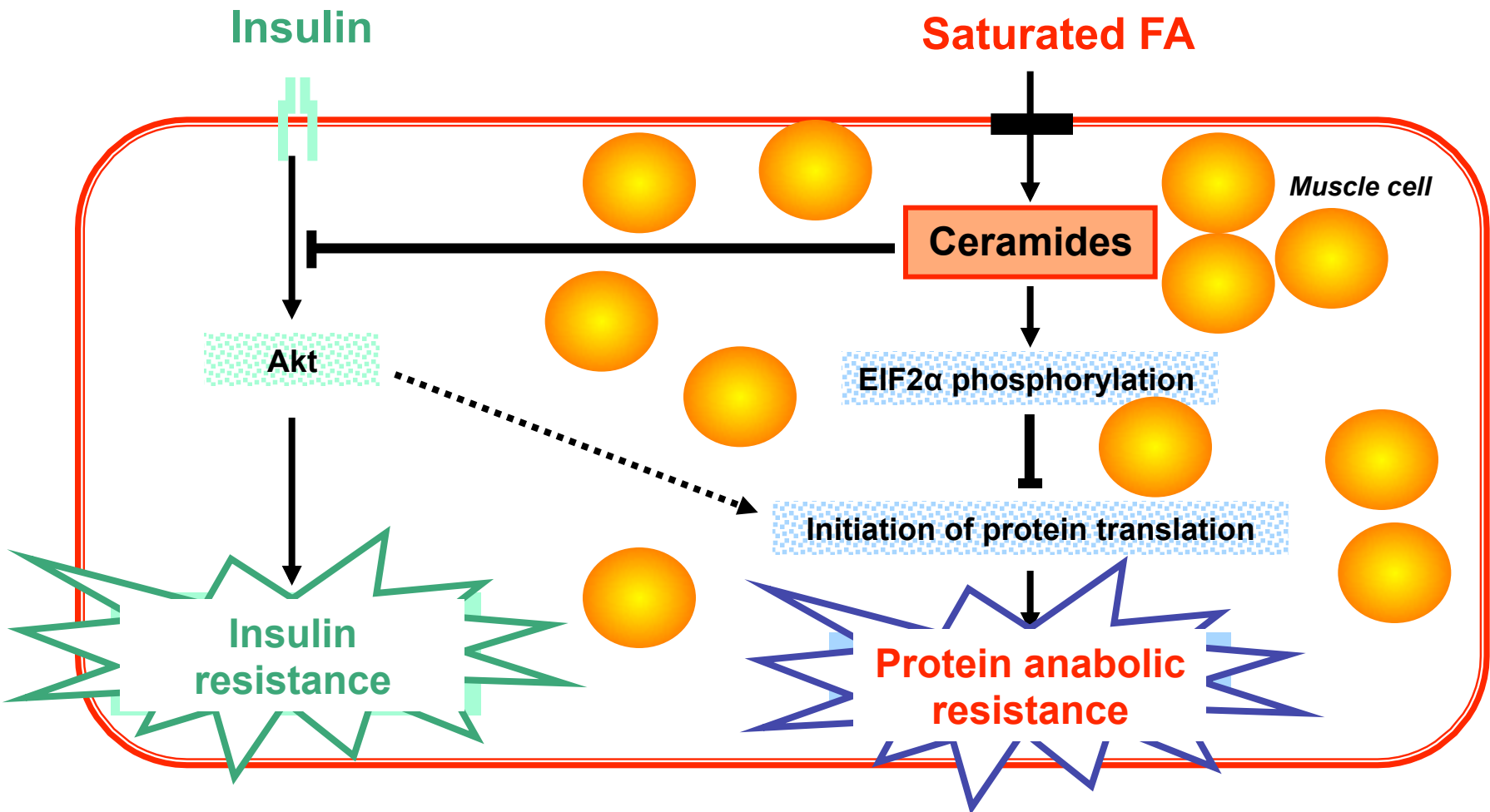
**Fat mass could be deleterious for muscle protein synthesis?**



# Response to high-fat feeding of total and mitochondrial protein synthesis

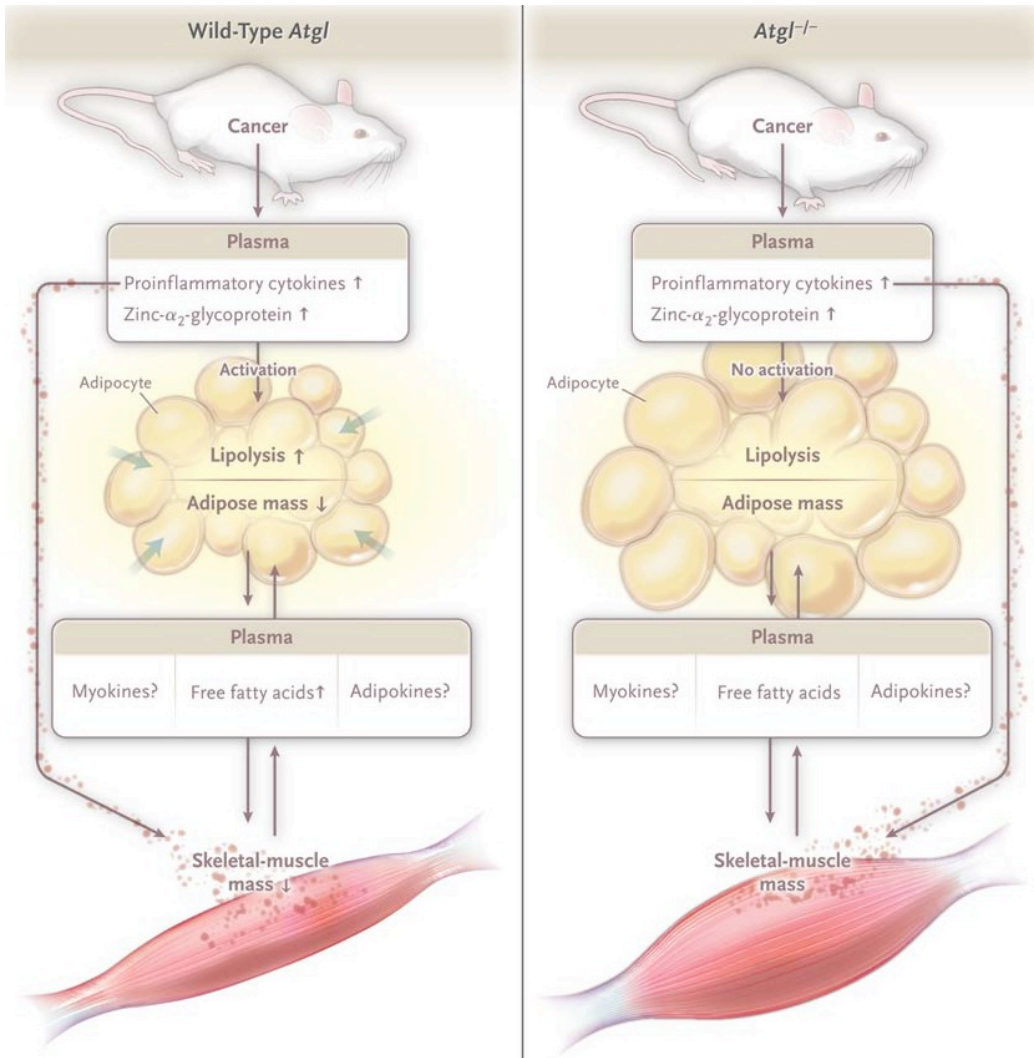


# New mechanism of muscle anabolic resistance: lipotoxicity



## Cancer Cachexia and Fat–Muscle Physiology

Kenneth C.H. Fearon, M.D.



**L' inactivation de la lipolyse chez l' animal porteur de tumeur empêche le développement de la cachexie !**

**Das SK, Science 2011  
Fearon K, NEJM 2011**

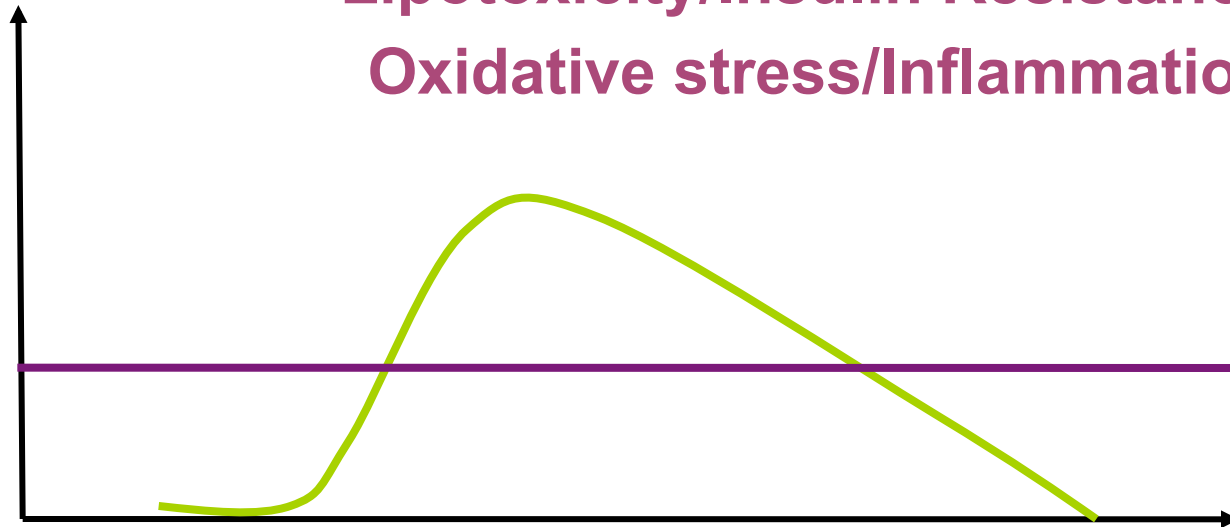
# Muscle loss situations

**Immobilization/Chronic Diseases**

Anabolic  
stimulators

Lipotoxicity/Insulin Resistance  
Oxidative stress/Inflammation

**Anabolic  
resistance**



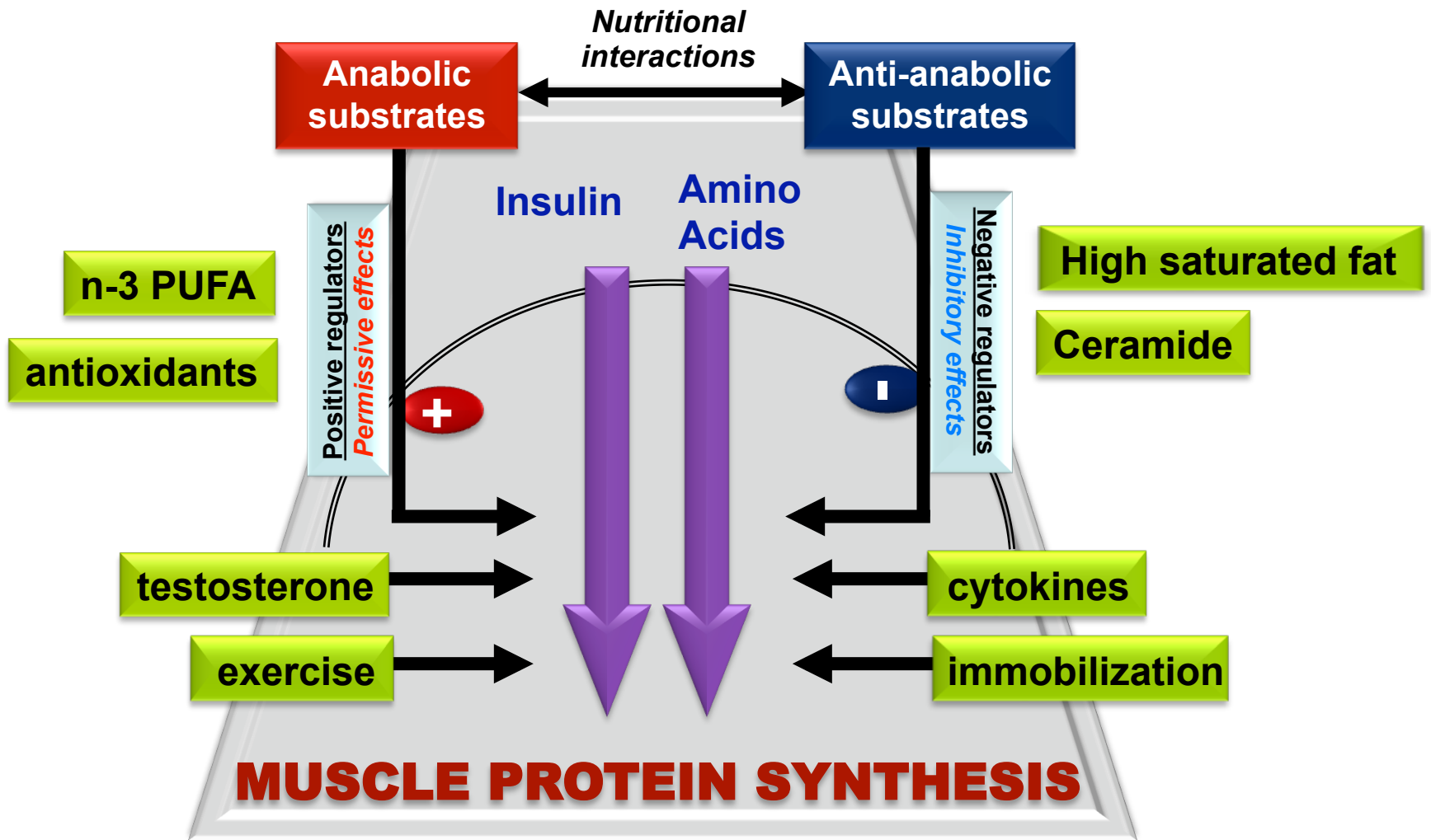
**Meal**



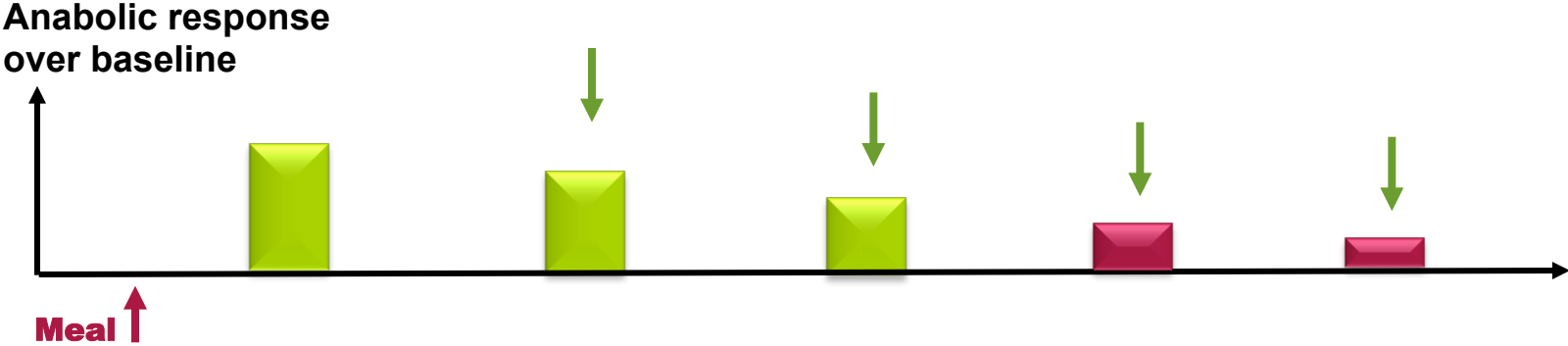
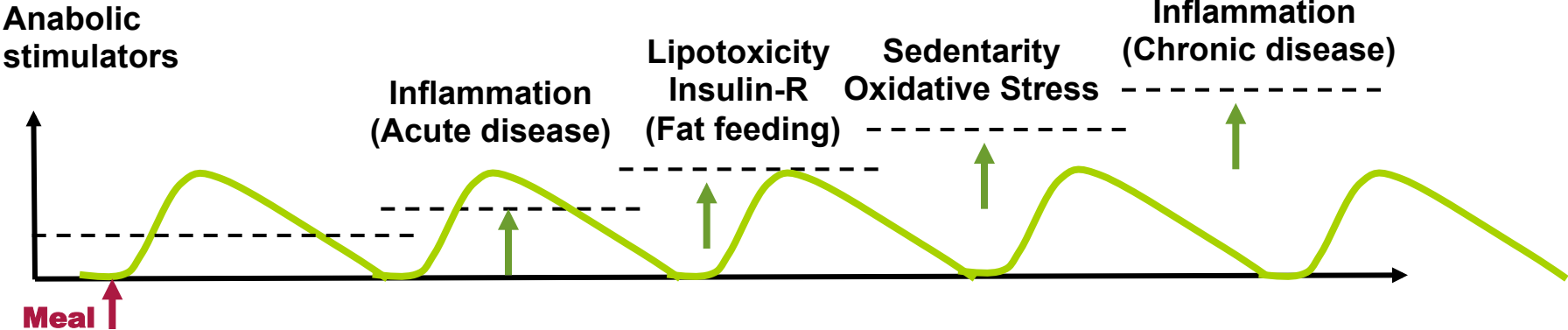
Physiological situation



Aging or catabolic state

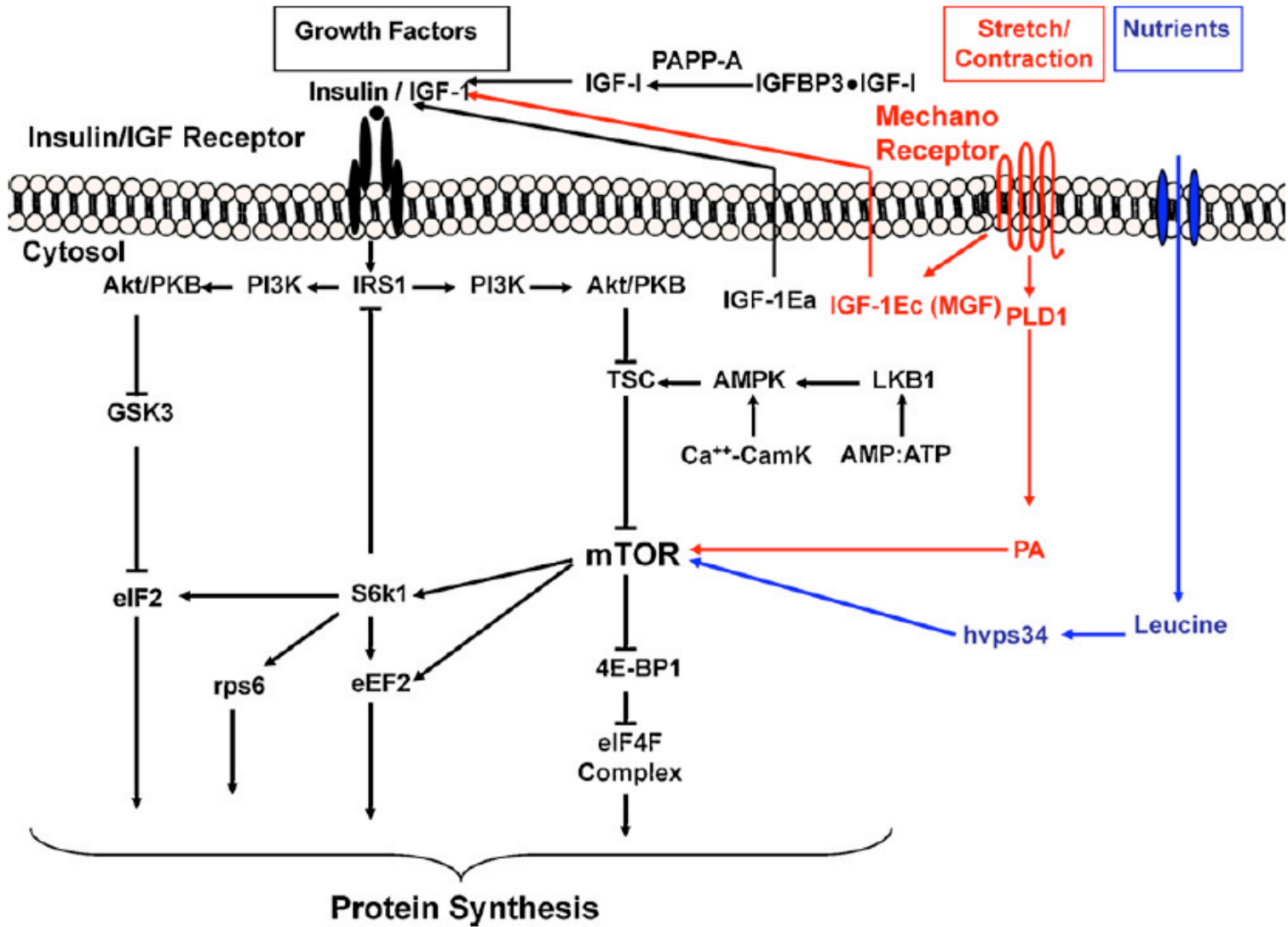


# Temporal changes in anabolic threshold?



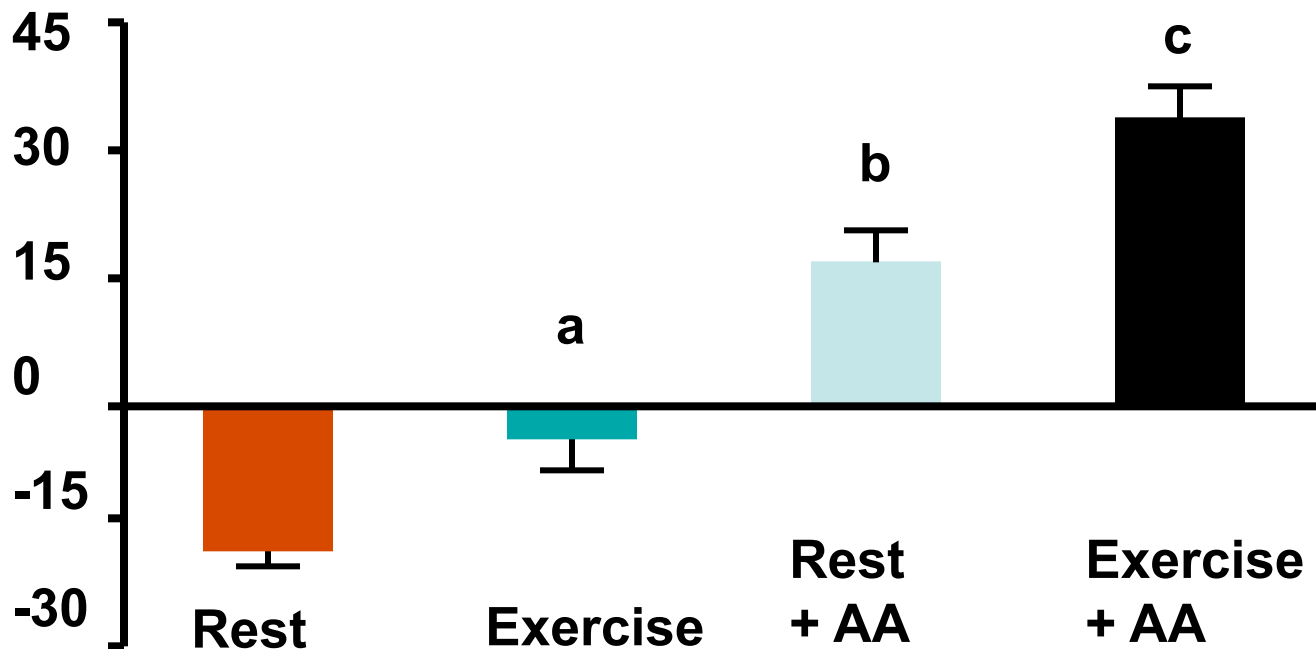
# Sarcopénie et cachexie

- Évolution et involution musculaire
- Mécanismes de résistance ou de désadaptation anabolique
- **Stratégies : l'union fait la force !**





# Physical exercise potentiates the anabolic impact of amino acid



# Effects of Exercise and Amino Acid Supplementation on Body Composition and Physical Function in Community-Dwelling Elderly Japanese Sarcopenic Women: A Randomized Controlled Trial

*Hun Kyung Kim, PhD,\* Takao Suzuki, MD, PhD,† Kyoko Saito, PhD,\* Hideyo Yoshida, MD, PhD,\* Hisamine Kobayashi, DVM,‡ Hiroyuki Kato, MS,‡ and Miwa Katayama, DVM‡*

**155 SARCOPENIC women  
age > 75y**

**4 groups:**

- exercise and AA supplementation (exercise + AAS; n = 38)
- exercise (n = 39)
- amino acid supplementation (AAS; n = 39)
- health education (HE; n = 39)

**Training program twice a week**

**AAS group : 3 g of a leucine-rich essential AA mixture twice a day**

**for 3 months**

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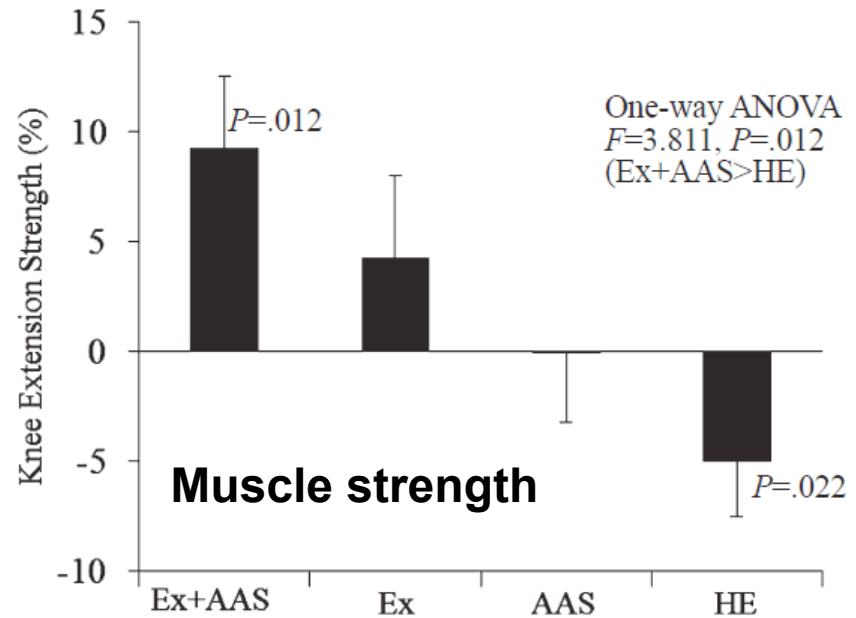
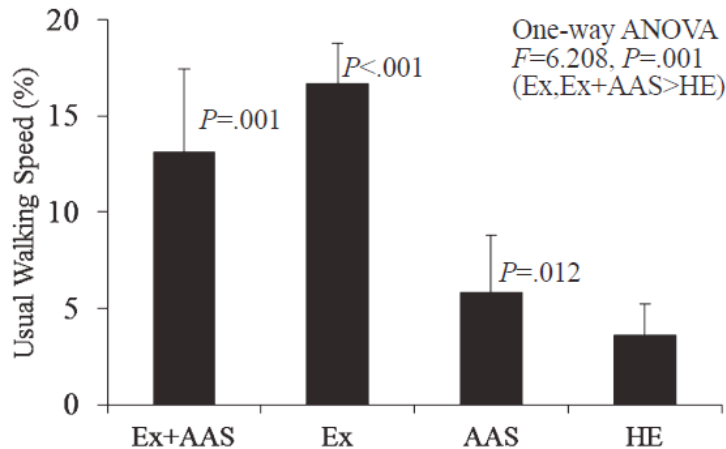
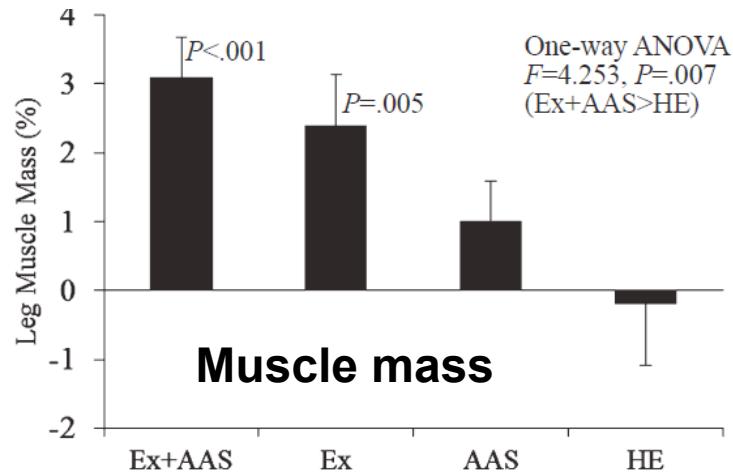


Figure 2. Mean percentage changes (standard errors) in leg muscle mass, usual walking speed, and knee extension strength after exercise (Ex), amino acid supplementation (AAS), both (Ex + AAS), or health education (HE). Bars indicate average changes from baseline to after the 3-month intervention. ANOVA = analysis of variance.

# Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial

French- IRAD2 : insuffisance respiratoire chronique

**Patients**                      60, 66.6 ± 9.6 ans, IMC 21.5 ± 3.8  
   62, 65.1 ± 9.6 ans, IMC 21.4 ± 4.0

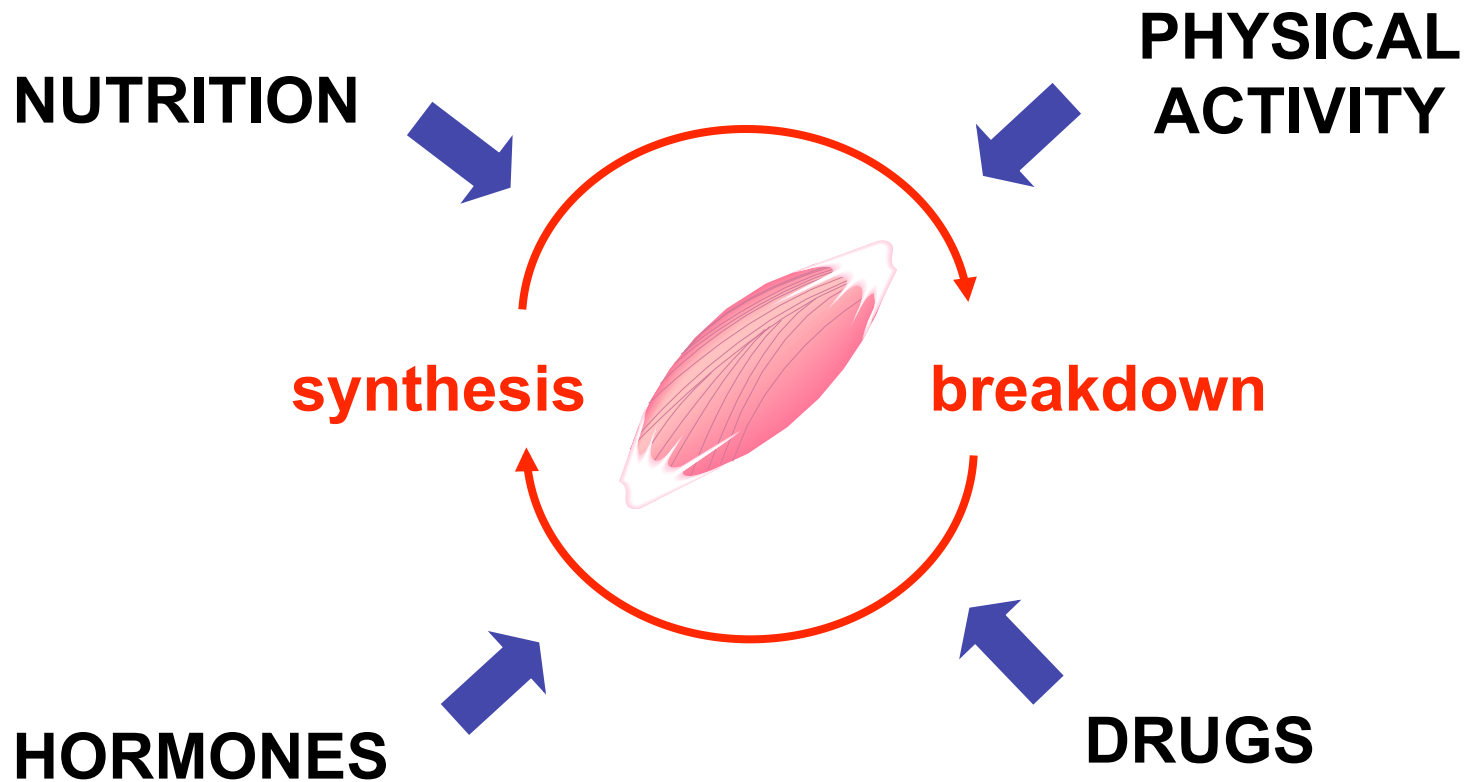
**Durée**                            12 semaines, 12 mois de suivi

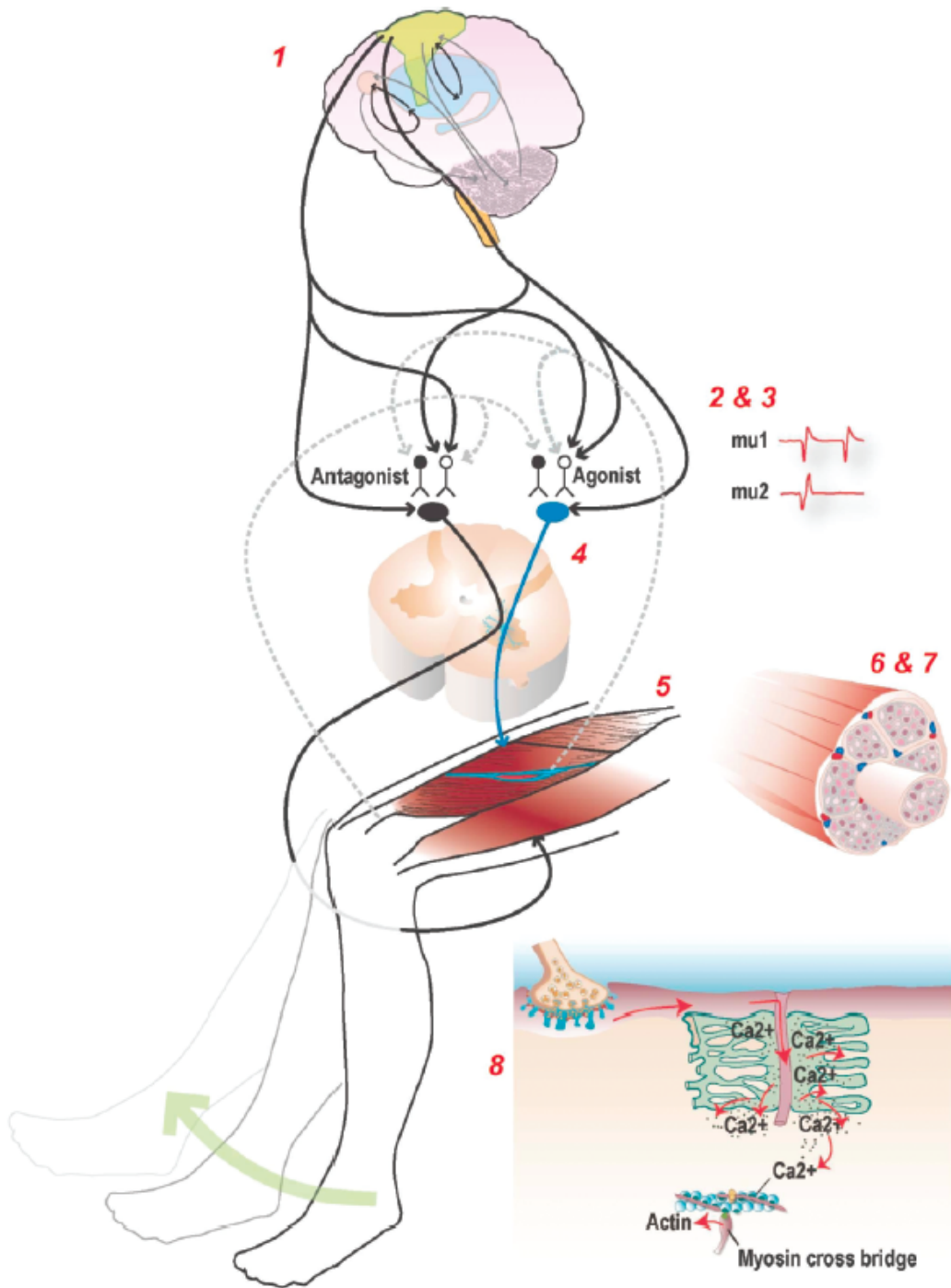
**Intervention**                - Éducation + **Exercice + ONS + testostérone orale**  
   - Éducation

## Résultats

- 3 mois : prise de poids, **augmentation de la masse musculaire** (quadriceps), de l'Hb, de l'endurance, de la Wmax, de la QdV
- 15 mois : **survie augmentée** (analyse per-protocole)

# Look for the best synergistical modulation of muscle protein anabolism





# Thank you

INRA



# UNH

**Human Nutrition Unit**  
*Metabolism & Health*