



Journées  
Francophones  
de Nutrition

REIMS

7 - 9 décembre 2011

***SYMPOSIUM CRNH :  
APPORTS DES TRACEURS  
AU COURS DES ÉTUDES MÉTABOLIQUES***

# Traceurs et étude de la synthèse des protéines musculaires

***Yves Boirie***

***Service de Nutrition Clinique, CHU Clermont-Ferrand***

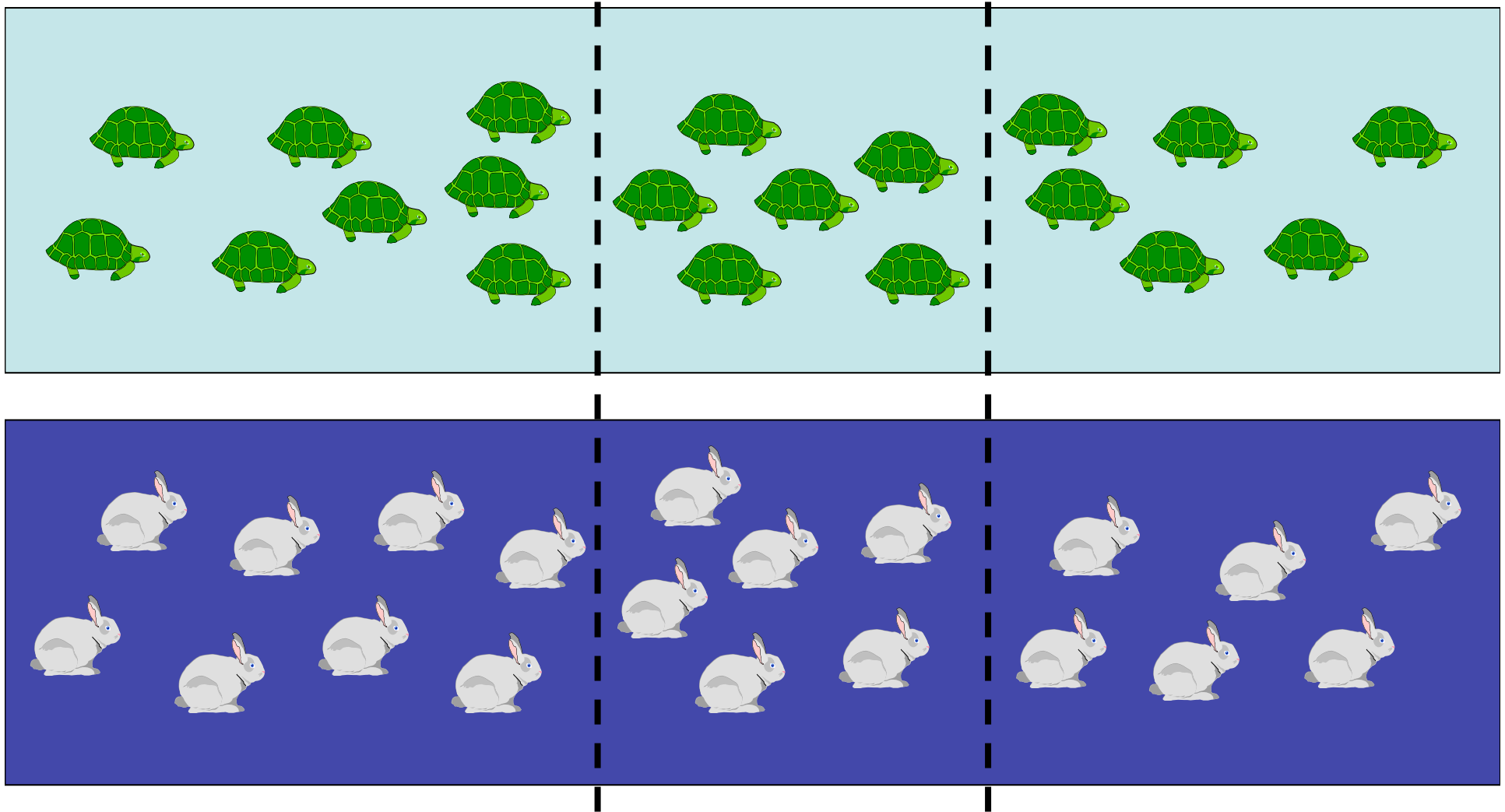
***Unité de Nutrition Humaine, CRNH Auvergne***



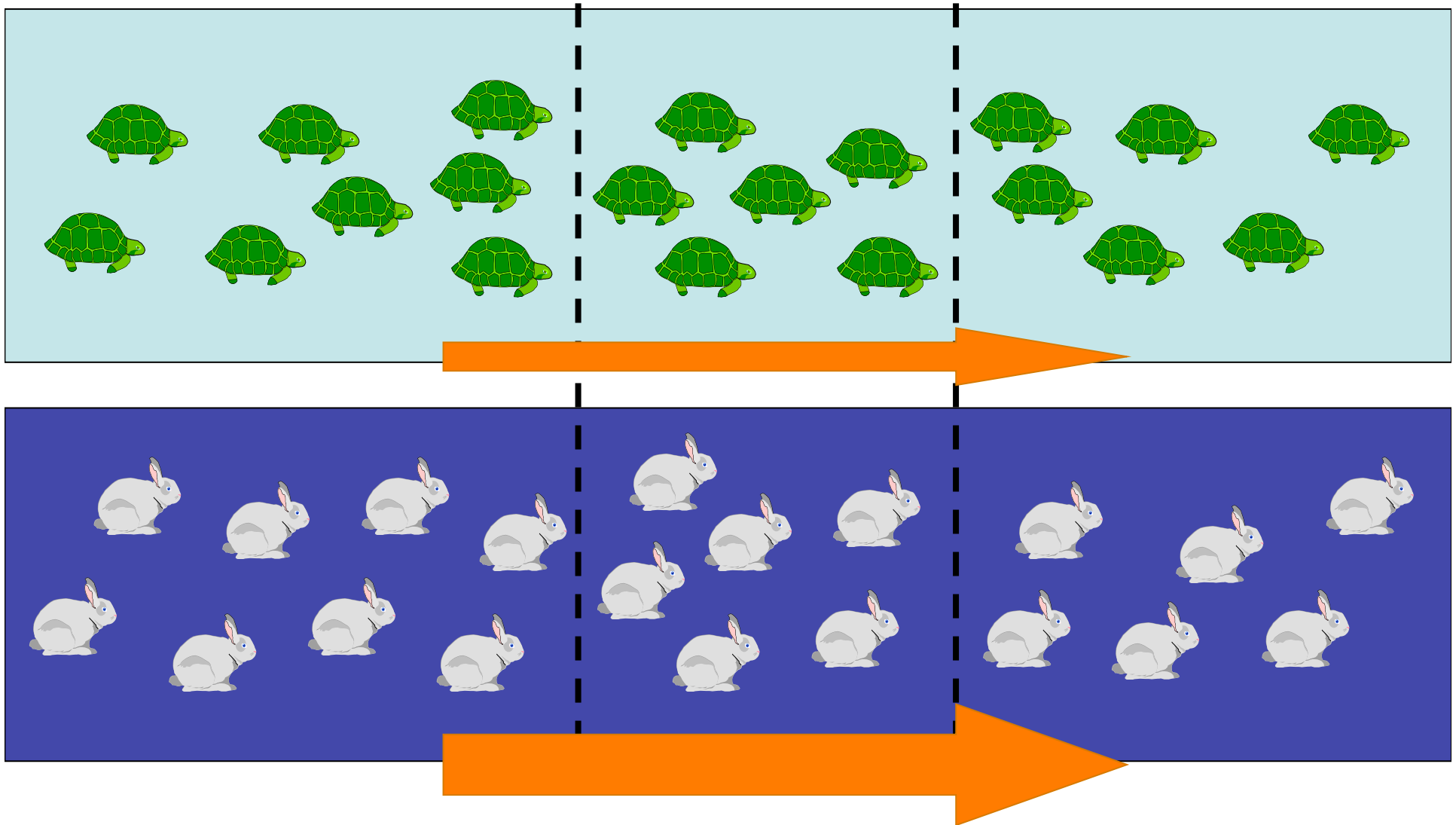
# **En préambule...**

- **La plupart des concepts en médecine reposent sur des mesures ponctuelles de substrats, sans considération de leurs débits et généralement à jeun**
- **Les protéines corporelles notamment musculaires, ont une masse constante chez l'adulte sain malgré leur renouvellement permanent**

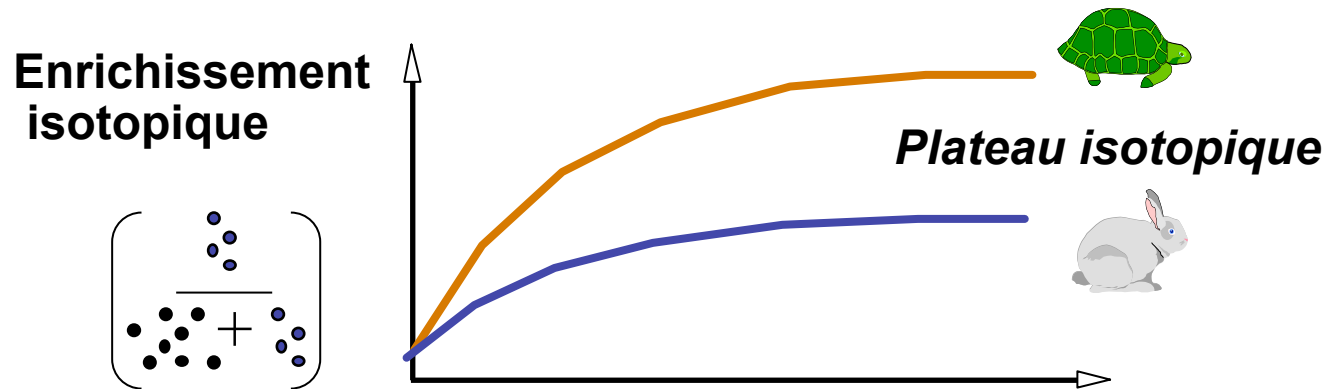
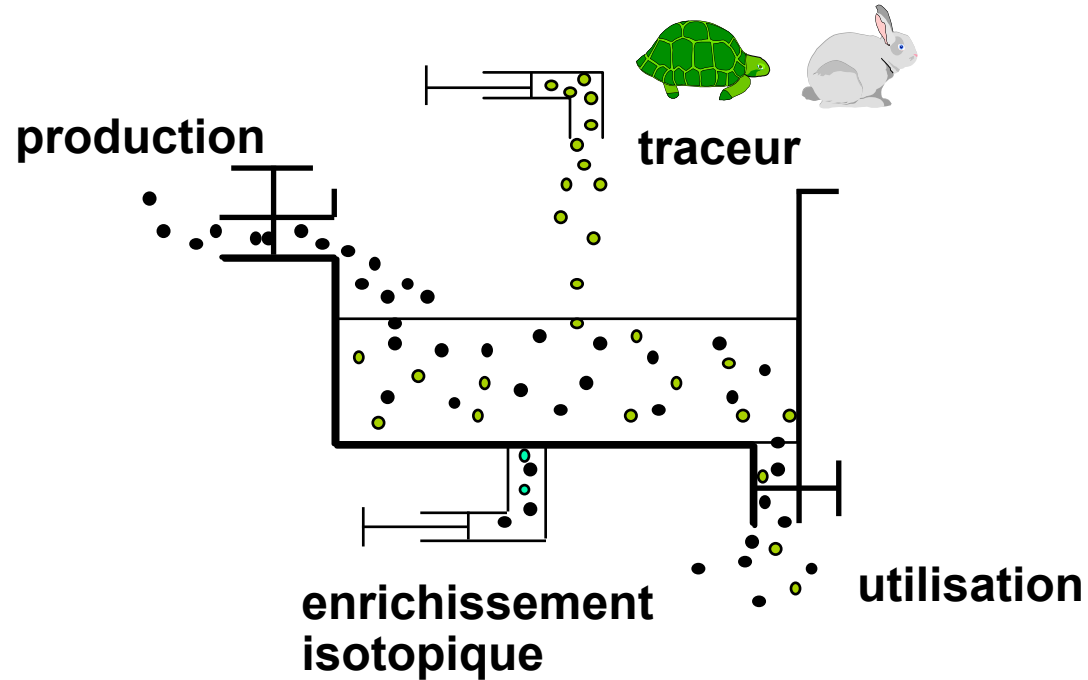
# Flux - Concentration



# Flux - Concentration

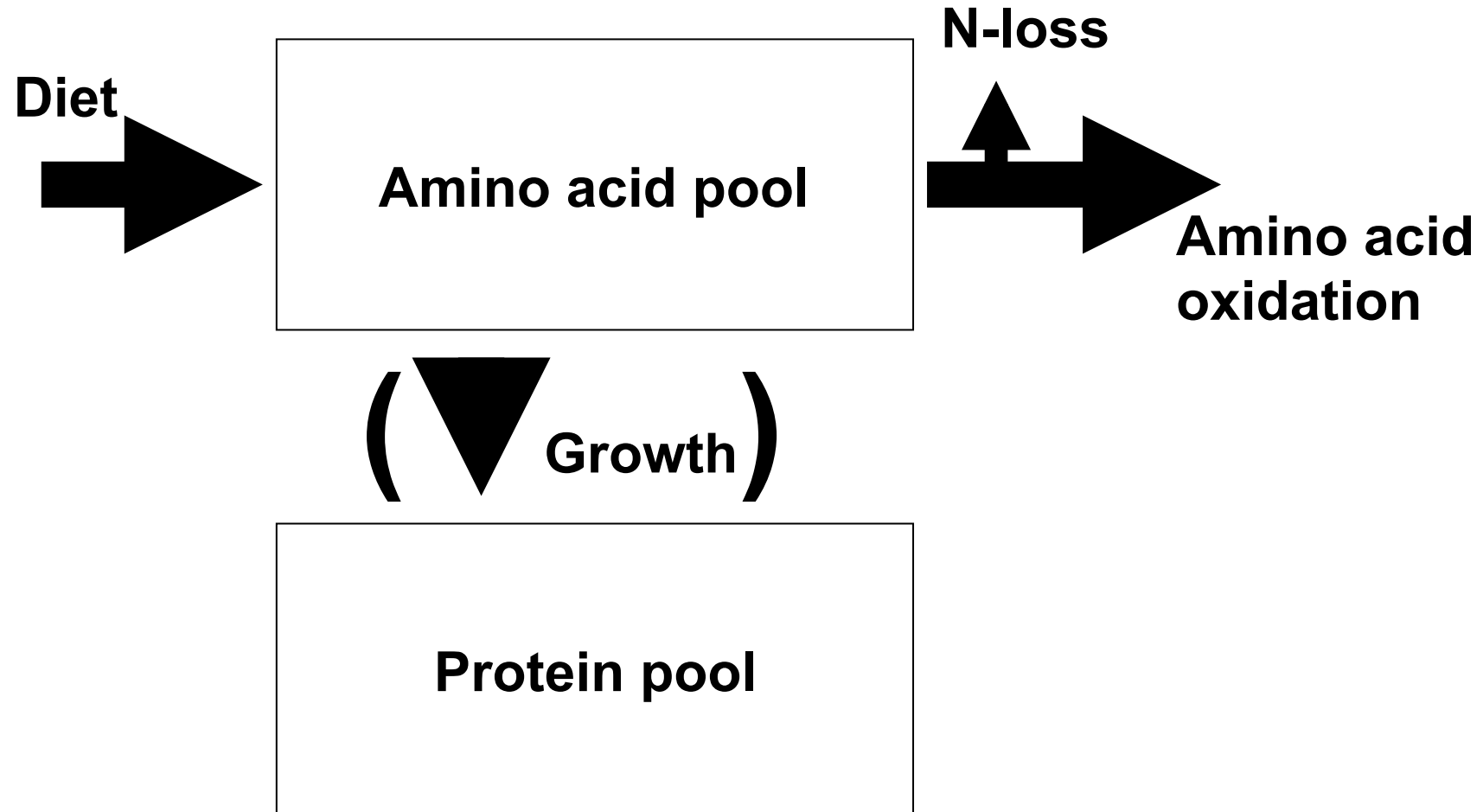


# Dilution isotopique continue

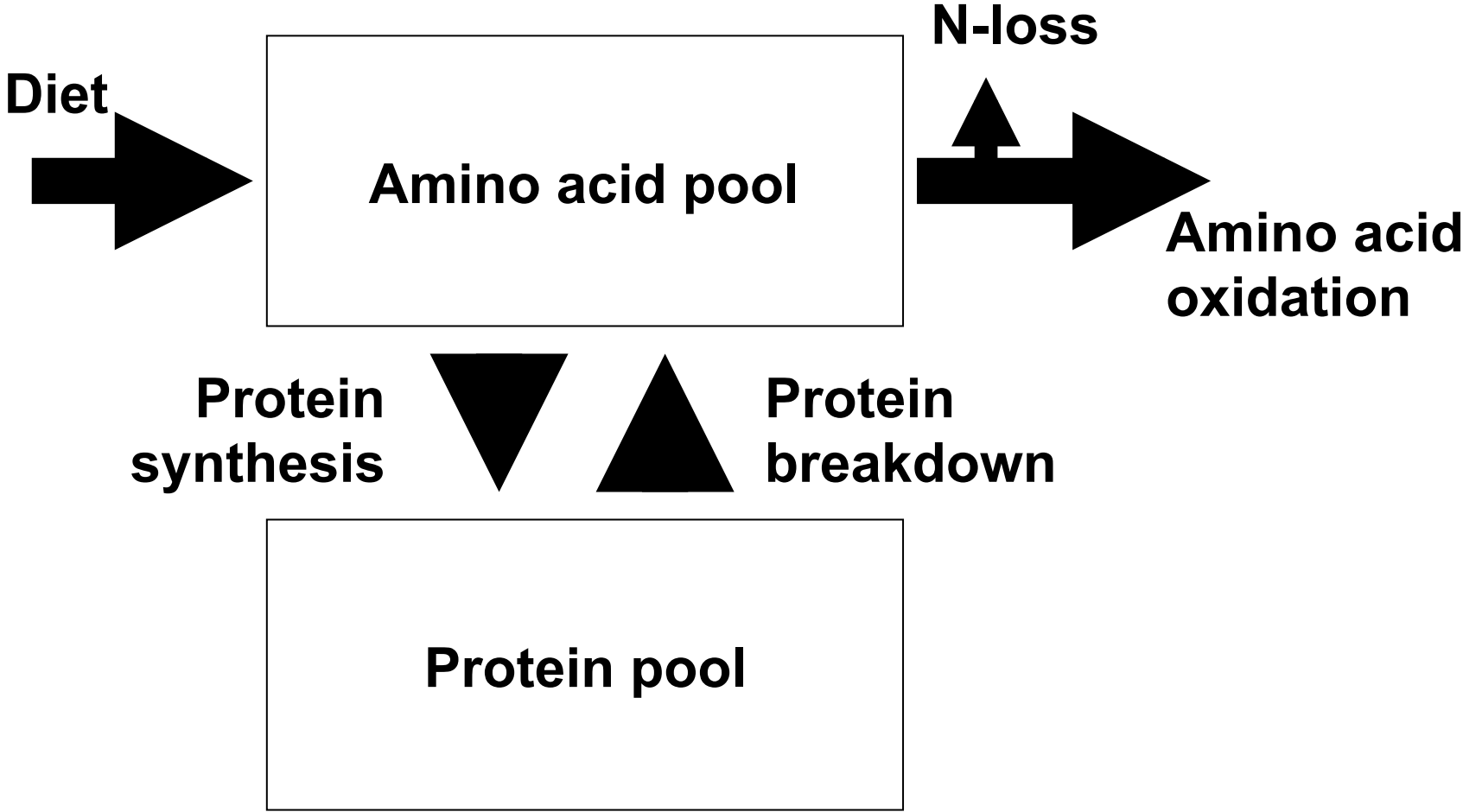


# Before 1930

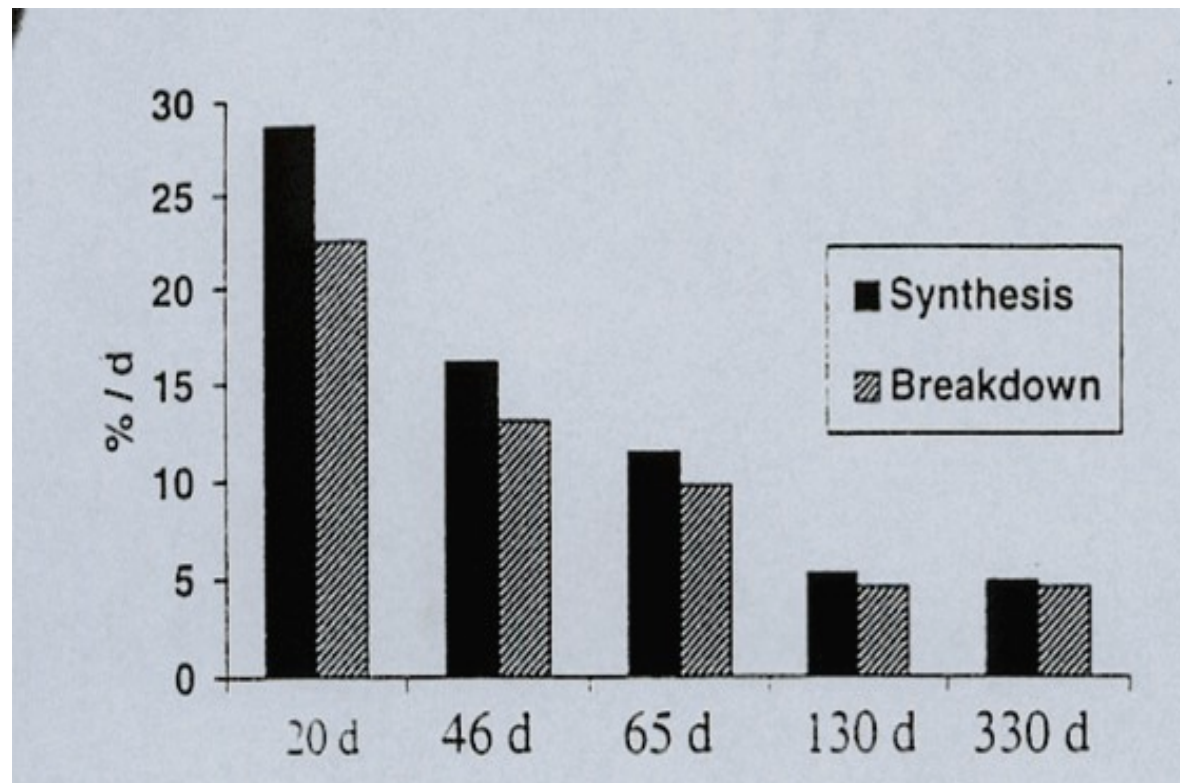
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# After 1930



# Whole body protein synthesis and breakdown in relation with age

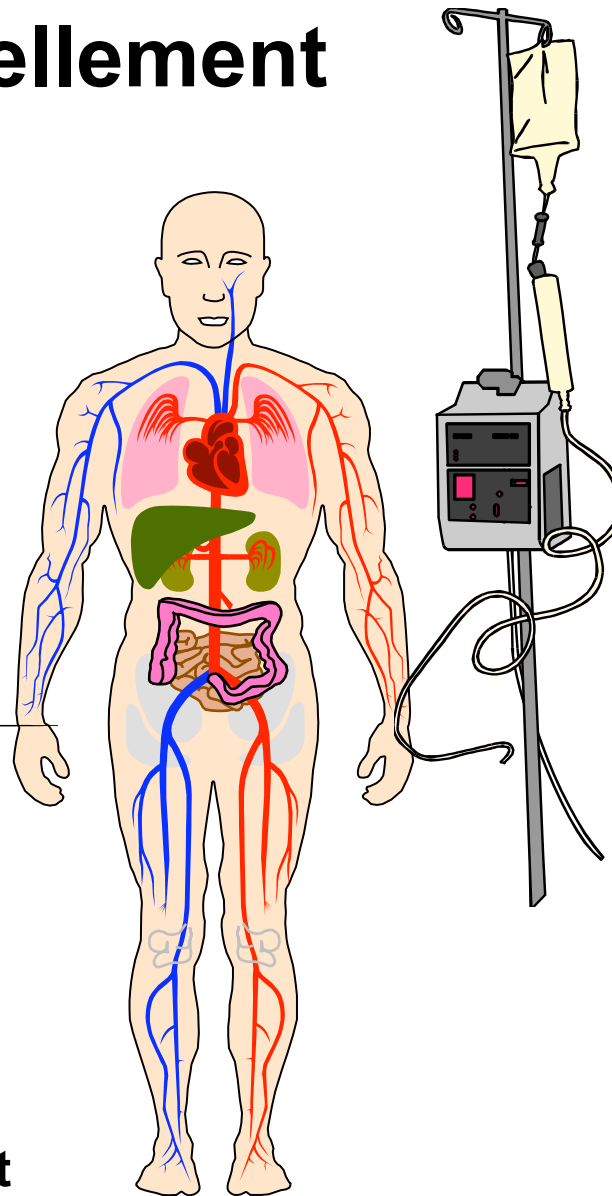


Waterlow JC, Nature 1975

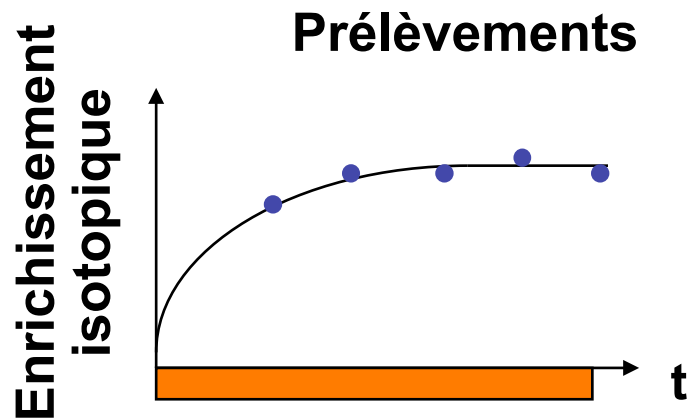


# Étude du renouvellement

- Traceurs (AA\*)
- Modèles
- Analyses (SM)

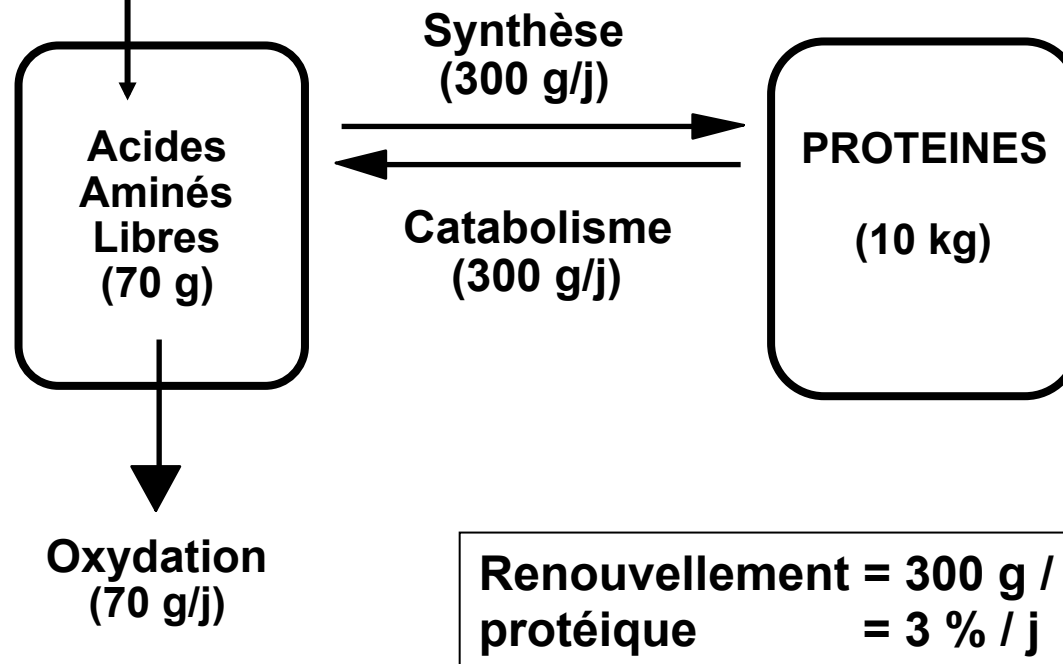


Traceur :  
AA marqué  
par isotopes  
stables  
( $^{13}\text{C}$ ,  $^2\text{H}$ ,  $^{18}\text{O}$ )

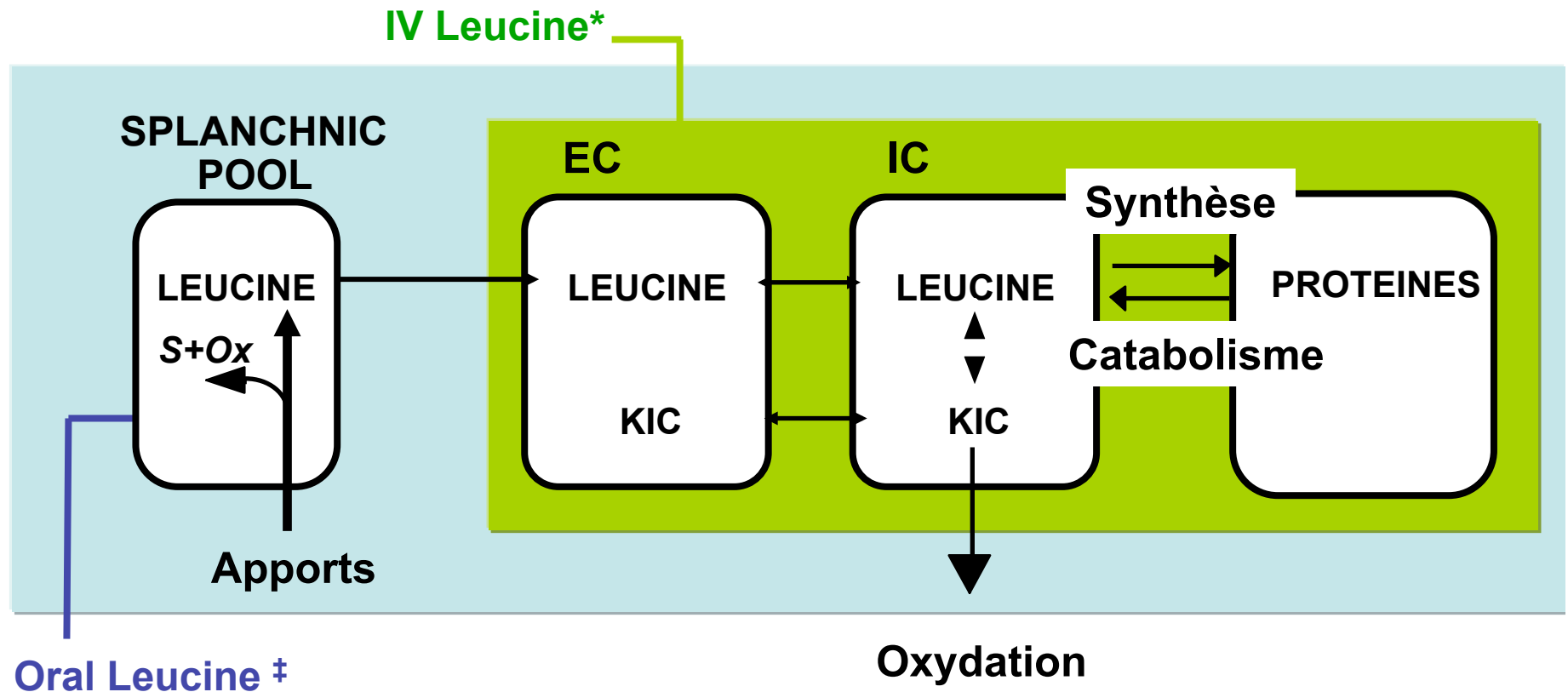


# Modèles d'étude du métabolisme protéique (modèle des précurseurs)

Traceur :  
Acide aminé  
marqué

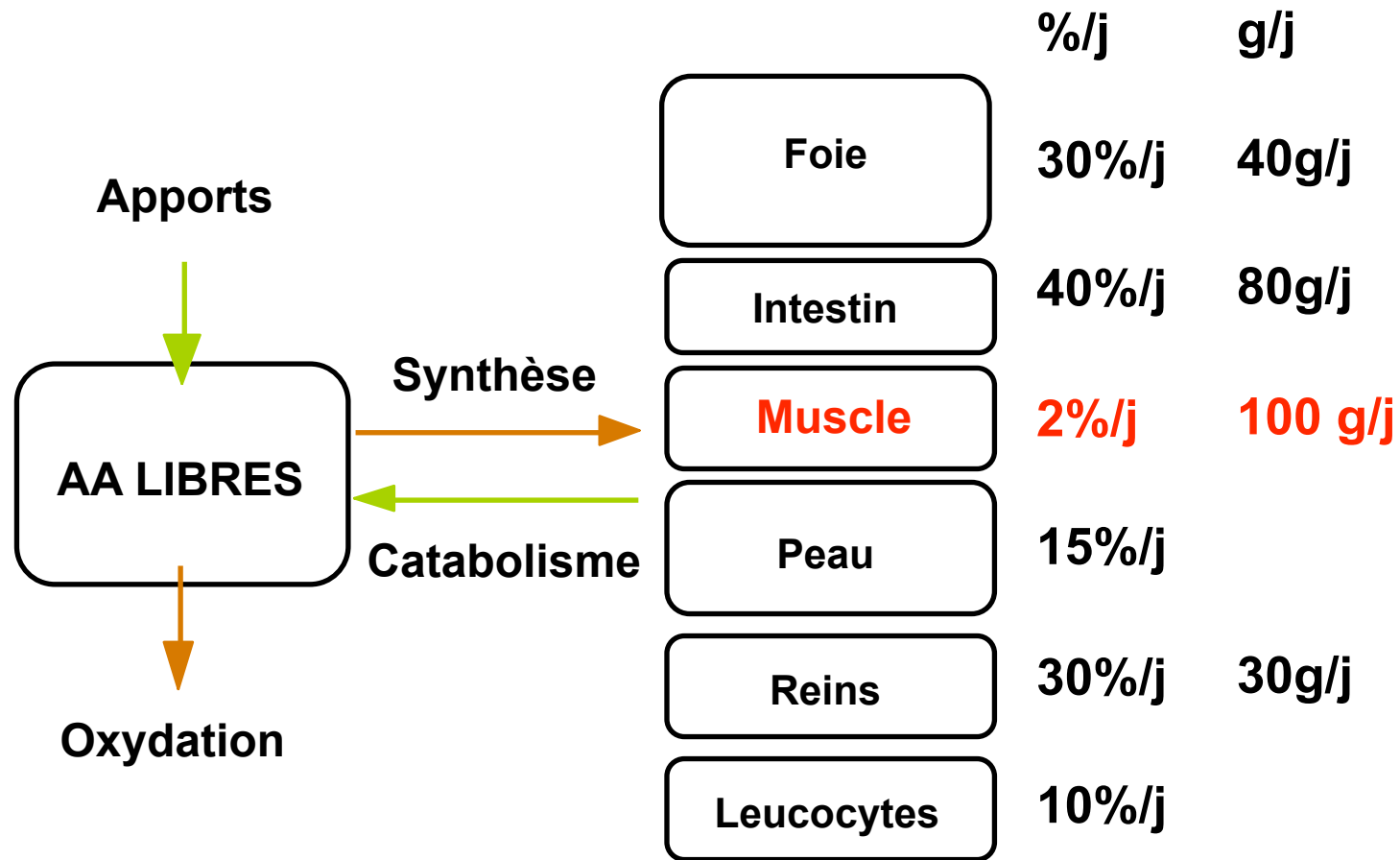


# Modèle d'étude de l'état nourri



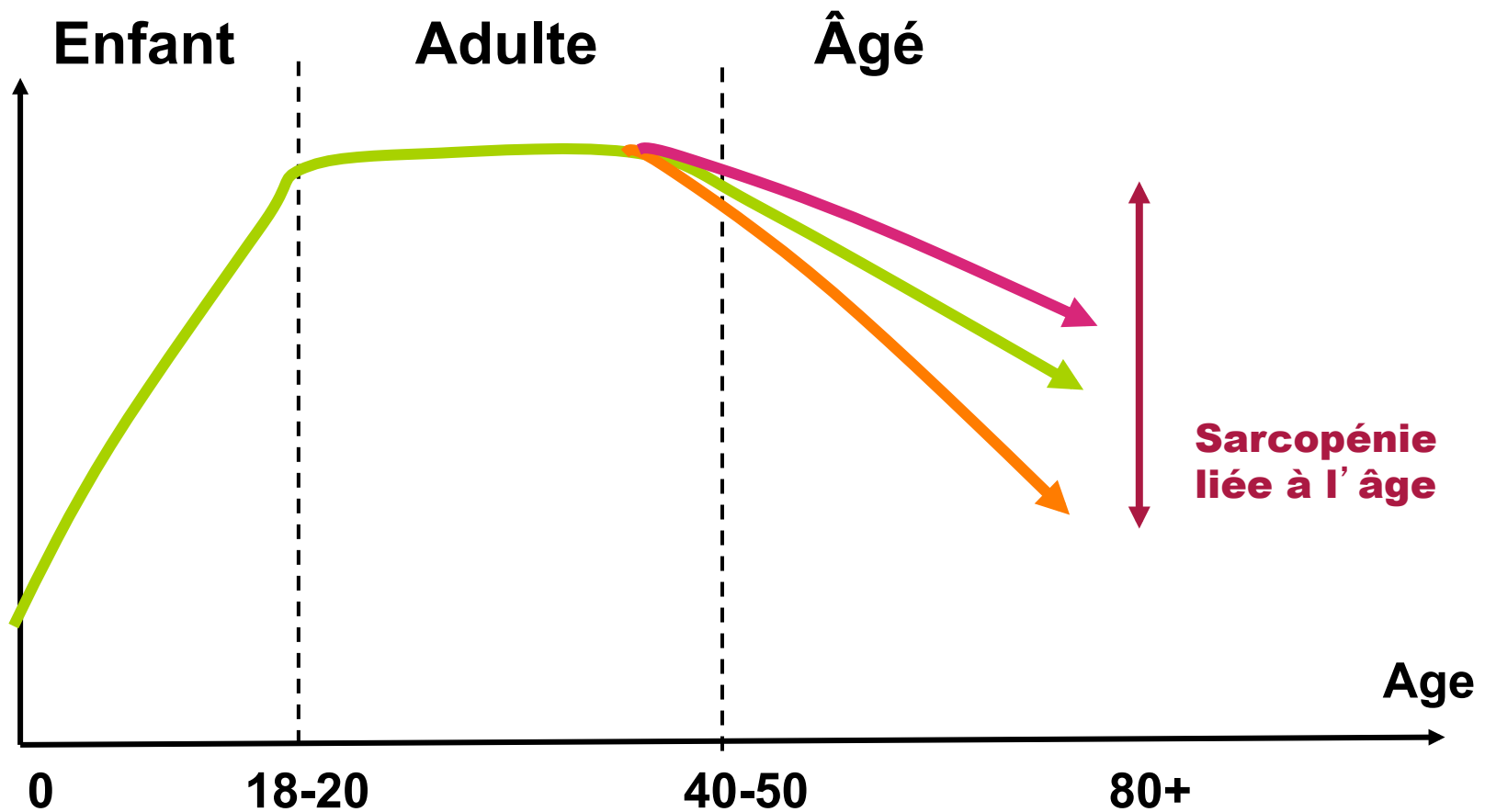
$$\text{Extraction Splanchnique} = 1 - (\text{IV Leu flux} / \text{Oral Leu flux})$$

# Renouvellement protéique corporel = sommation du renouvellement individuel de toutes les protéines

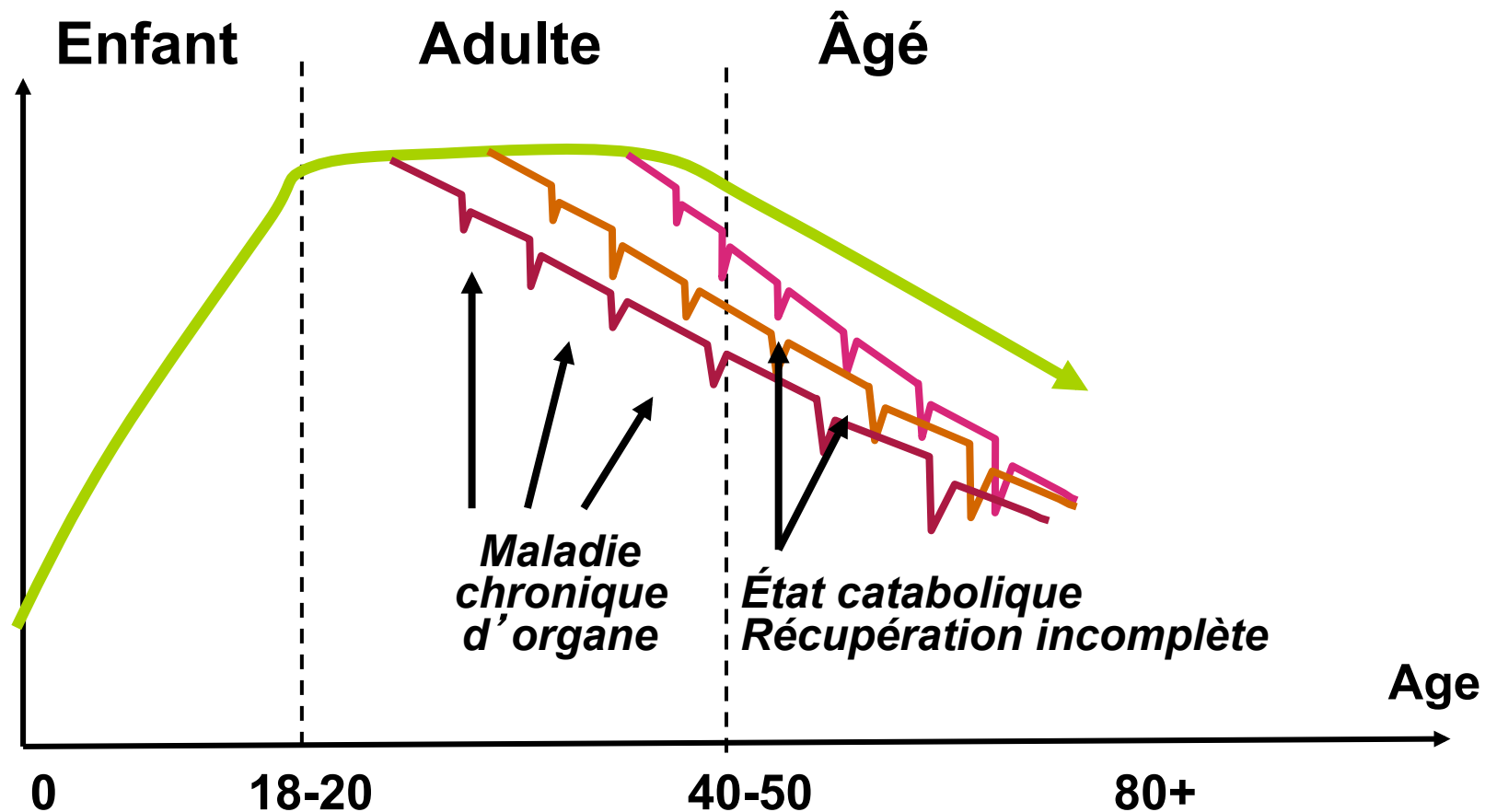


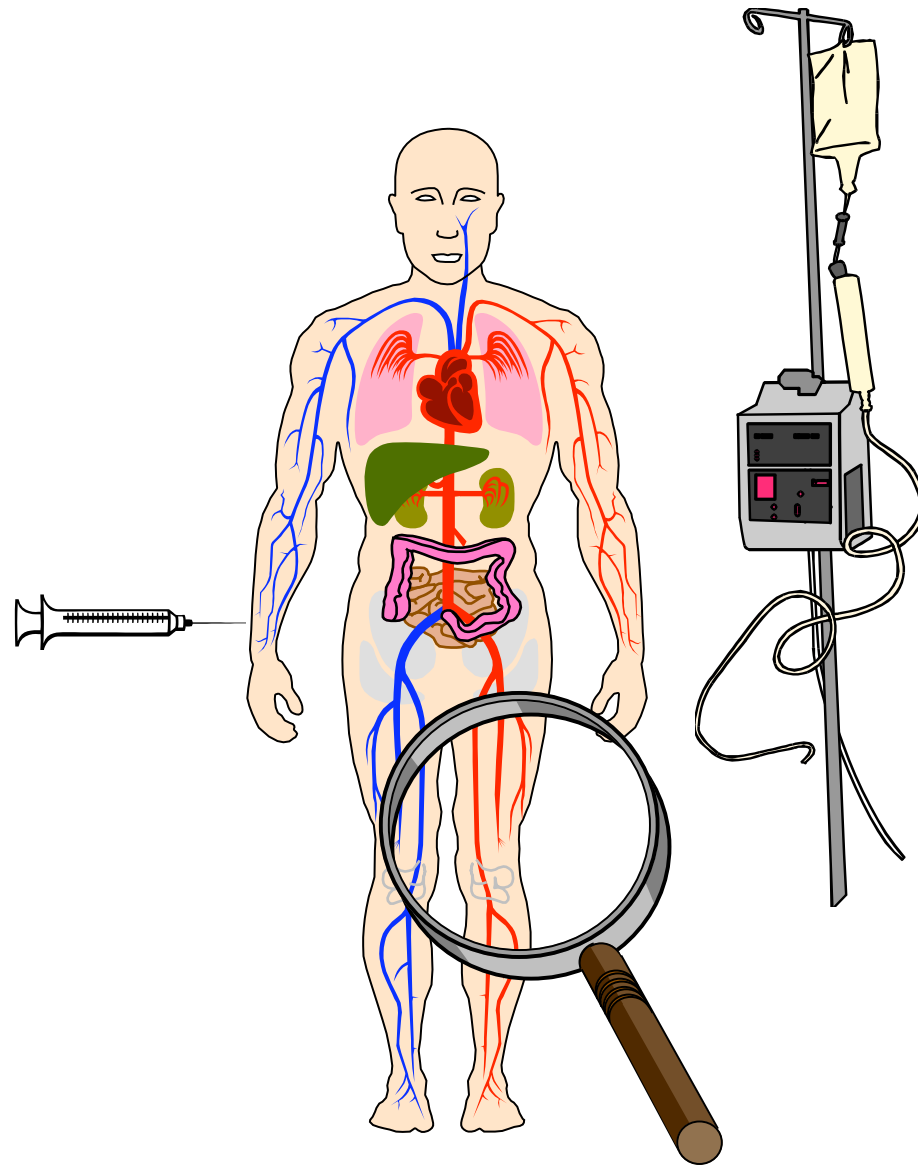
→ niveau corps entier  
↳ tissu (muscle, foie, intestin)

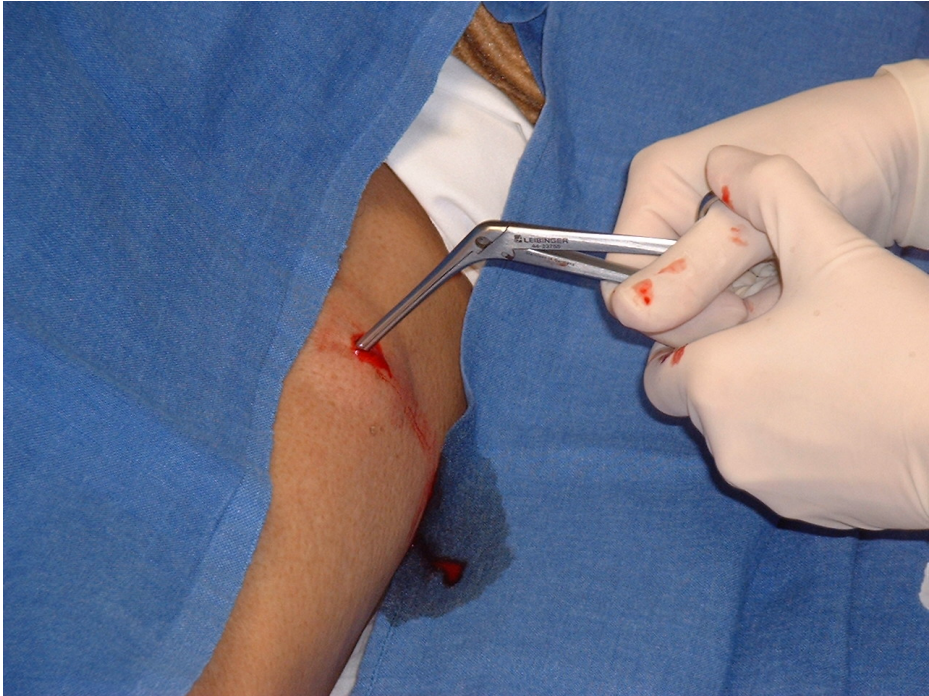
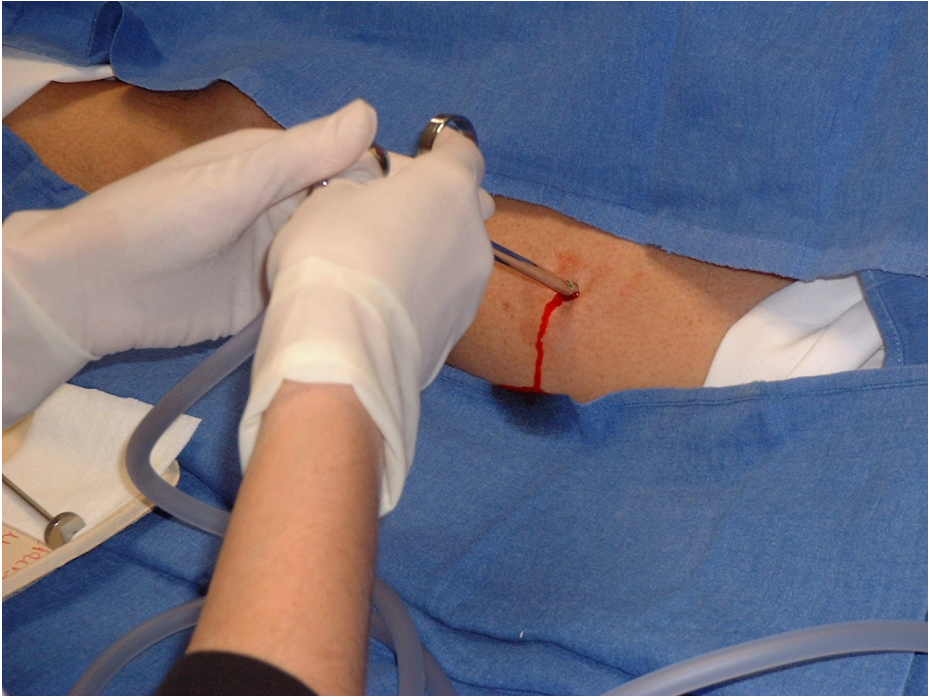
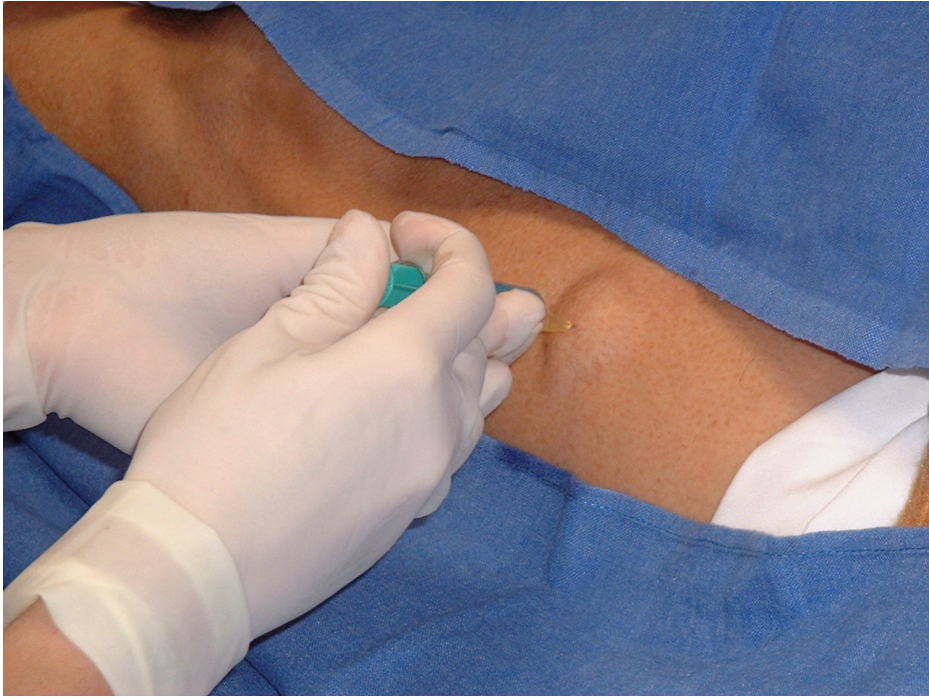
# Modèle d'évolution de la masse musculaire



# Modèle d'évolution de la masse musculaire



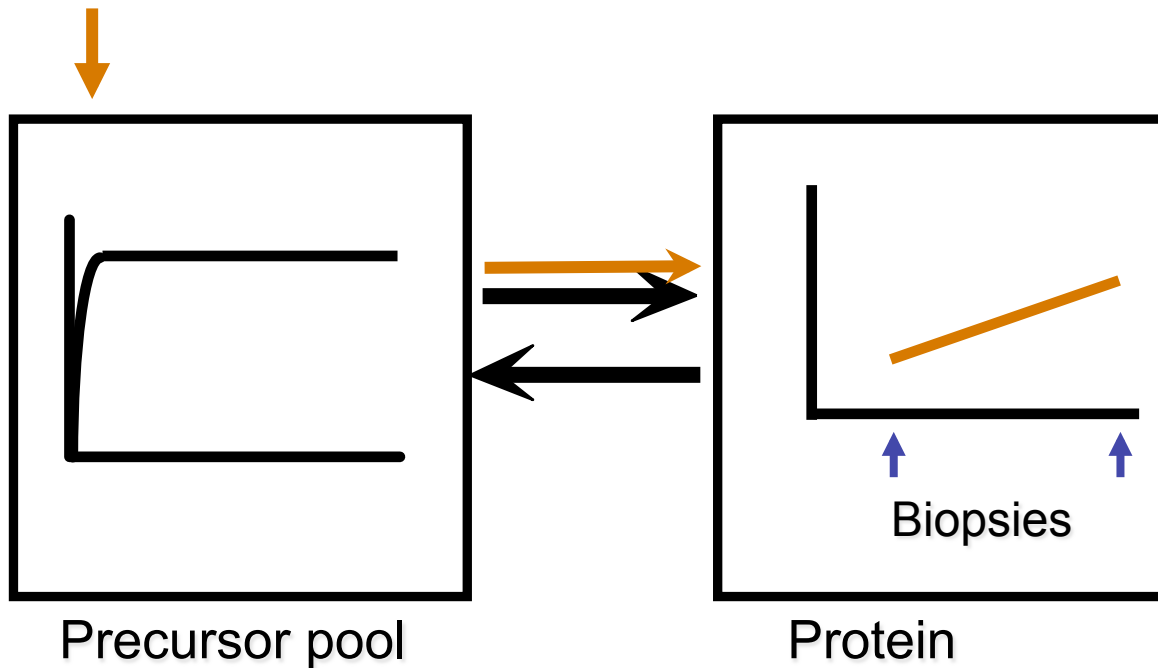






# Protein synthesis rate measurement (tracer incorporation)

Tracer (Leucine-1-<sup>13</sup>C)



**Fractional synthesis rate (FSR)**

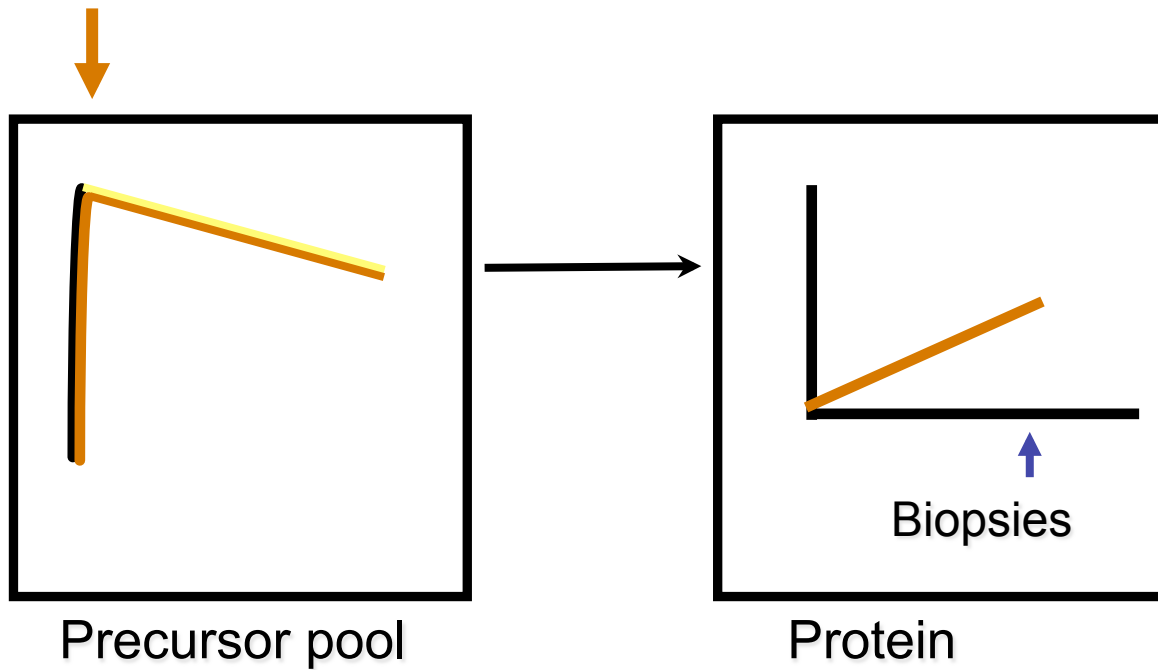
$$= (E_{p2} - E_{p1}) \cdot 100 / E_{prec} \quad [\%/h]$$

# **FSR – suppositions...**

- **Incorporation linéaire du traceur ds protéine**
- **Pas de réapparition du traceur**
- **Compartiment protéique constant**
- **Pureté de la protéine**
- **Vrai pool précurseur**
- **Equilibre isotopique dans le pool précurseur**

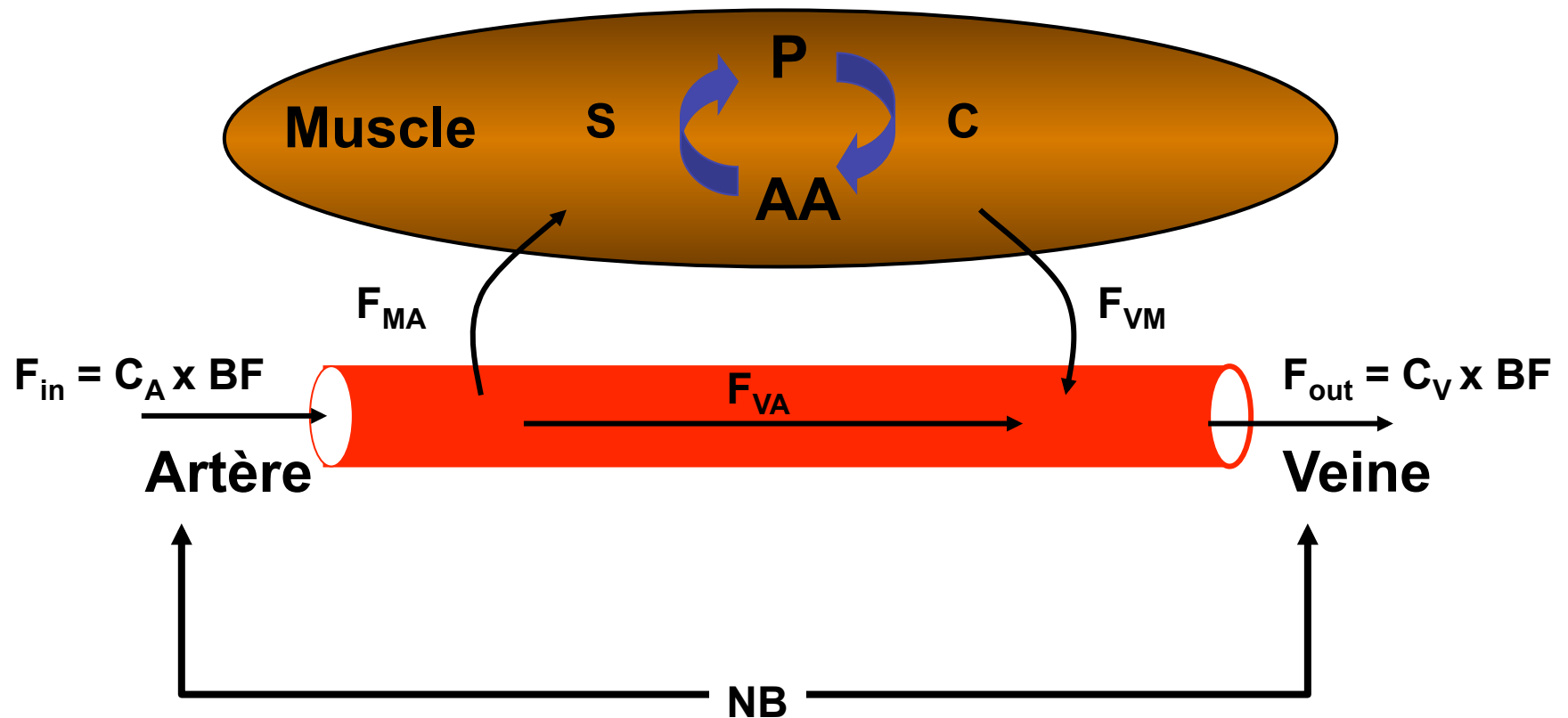
# Flooding dose

“Tracer” (Phe-ring-D5 + Large dose Phe)



$$\text{Fractional synthesis rate} = E_b(t_2) / \int E_{\text{prec}}(t) \cdot dt$$

# Bilan artérioveineux d'un territoire musculaire



# Human muscle protein turnover—why is it so variable?

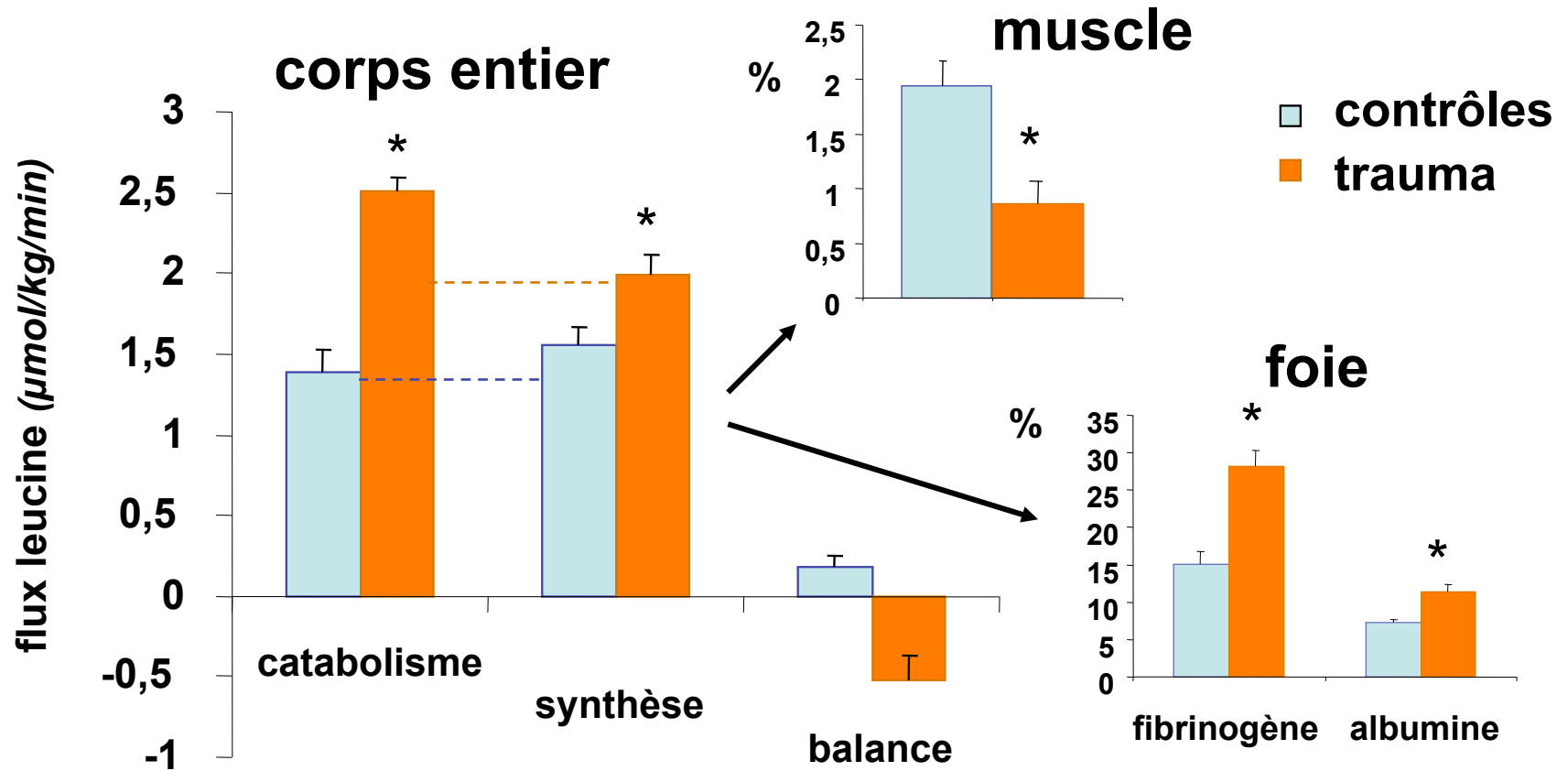
Gordon I. Smith, Bruce W. Patterson, and Bettina Mittendorfer

Washington University School of Medicine, St. Louis, Missouri

Table 3. Descriptive statistics for muscle protein FSR in the vastus lateralis portion of the quadriceps femoris in healthy, young adults in the postabsorptive state at rest

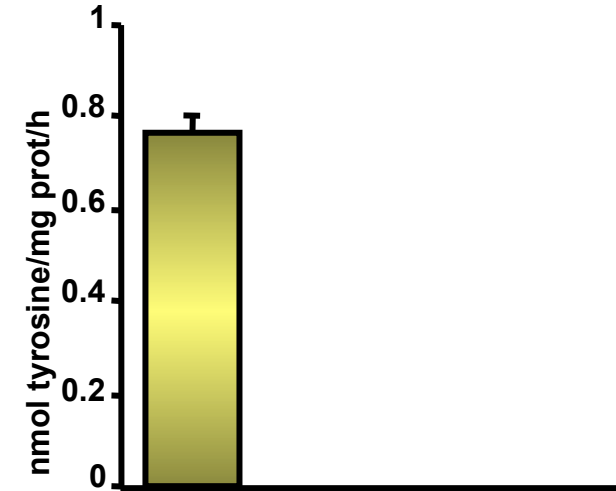
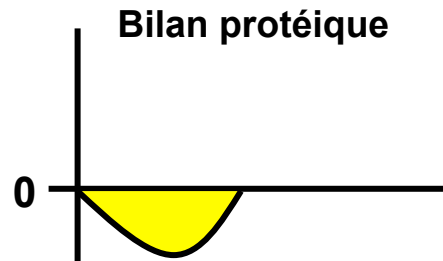
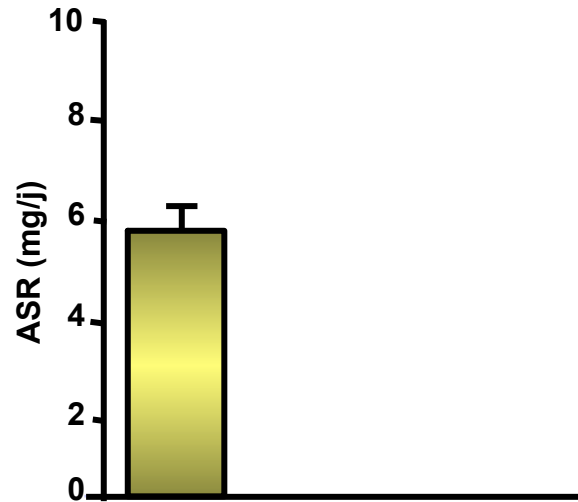
Tracer	Method Precursor/protein analysis	n	Time Between Biopsies, min	FSR, %·h <sup>-1</sup>		Population Variance, %	
				Median [quartiles]	Range	Median [quartiles]	Range
<i>Mixed muscle protein</i>							
KIC	Plasma or mean of arterial and muscle free leucine/GCMS and IRMS	2	150, 180	0.076, 0.094	0.076-0.094	N/A	12-26
Leucine	Plasma KIC/IRMS	18	483 ± 192 <sup>a</sup>	0.048 [0.046, 0.049]	0.037-0.059	21 [18, 33] <sup>a</sup>	14-50
Leucine	Muscle free leucine/IRMS	5 <sup>d</sup>	366 ± 183 <sup>a,b</sup>	0.060 [0.057, 0.060]	0.035-0.086	28 [23, 32]	22-44
Phenylalanine	Plasma phenylalanine/GCMS and IRMS	9	193 ± 40 <sup>b,c</sup>	0.036 [0.031, 0.046]	0.021-0.055	29 [17, 31]	14-39
	IRMS only	3	180	0.030, 0.035, 0.046	0.030-0.046	14, 17, 20	14-20
	GCMS only	6	156 ± 53 <sup>c</sup>	0.039 [0.032, 0.046]	0.0210-0.055	31 [30, 33]	15-39
Phenylalanine	Muscle free phenylalanine/GCMS and IRMS	44	160 ± 49 <sup>c</sup>	0.062 [0.056, 0.068]	0.038-0.086	29 [22, 39]	9-70
	IRMS only	7	180	0.054 [0.046, 0.066]	0.040-0.074	35 [30, 39]	26-43
	GCMS only	37	156 ± 53 <sup>c</sup>	0.063 [0.057, 0.069]	0.038-0.086	27 [21, 38]	9-70
<i>Myofibrillar and myosin heavy chain</i>							
Leucine	Plasma KIC/IRMS	11	273 ± 155 <sup>b</sup>	0.036 [0.034, 0.047]	0.030-0.061	19 [12, 28] <sup>a</sup>	8-41
Leucine	Muscle free leucine/IRMS	4	398 ± 195 <sup>a,b</sup>	0.047 [0.046, 0.052]	0.044-0.066	31 [21, 43]	21-48
Phenylalanine	Muscle free phenylalanine/IRMS	1	150	0.037	N/A	27	N/A

# Métabolisme protéique lors de la renutrition chez le traumatisé crânien



Mansoor O, PNAS & AJP 1997

# Bilan protéique postprandial dans le muscle



*Synthèse*

AA



*Protéolyse*

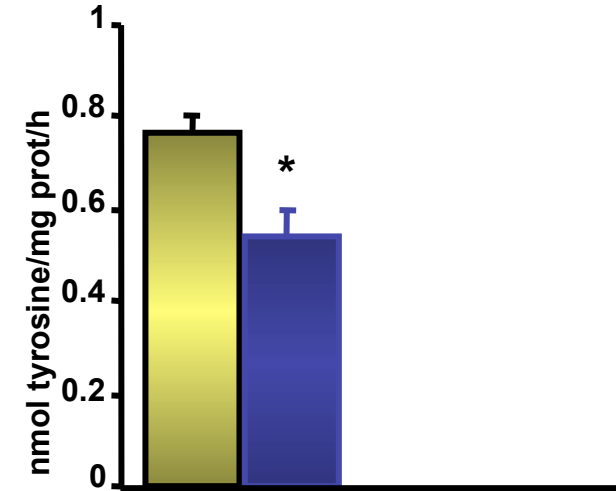
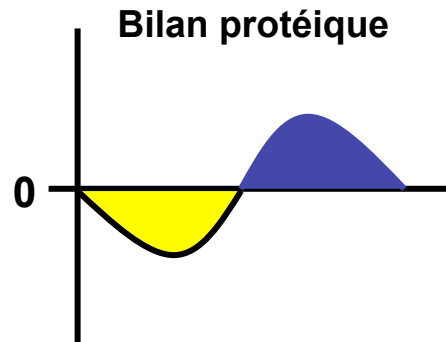
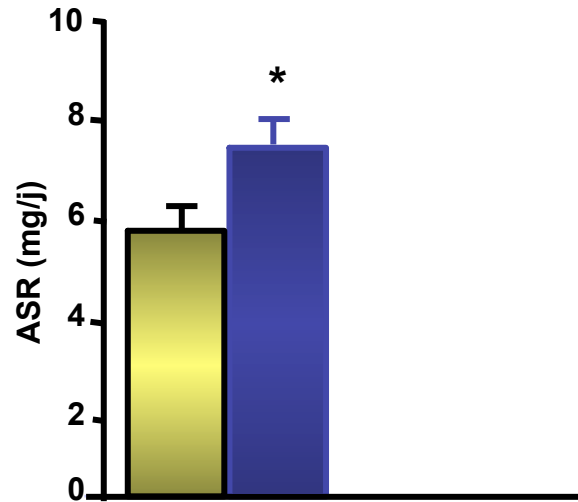


AA

 Postabsorptive



# Bilan protéique postprandial dans le muscle



*Synthèse*

AA

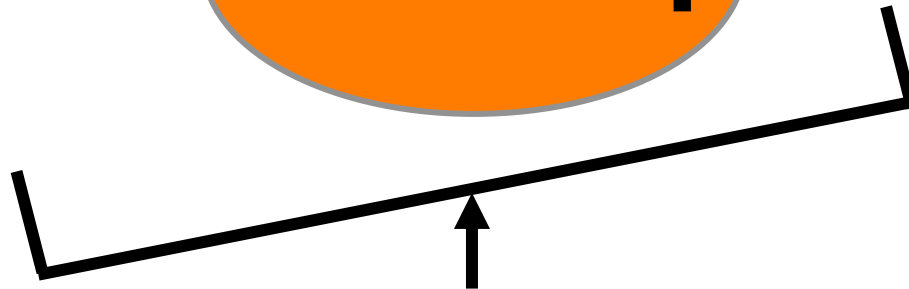


*Protéolyse*



AA

-  Postabsorptive
-  Postprandial

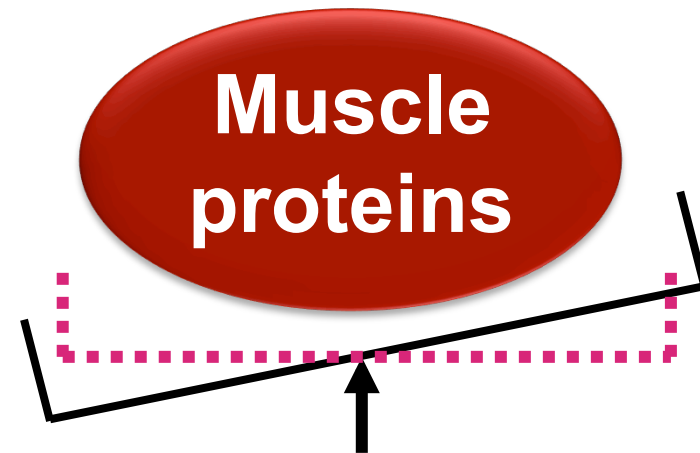
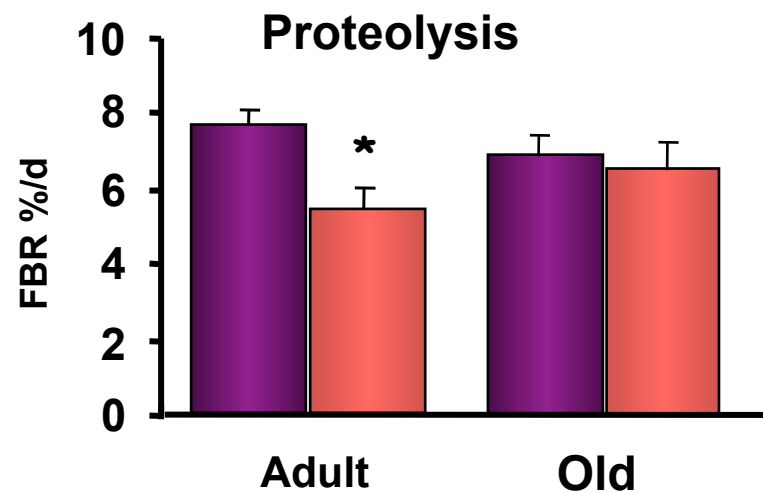
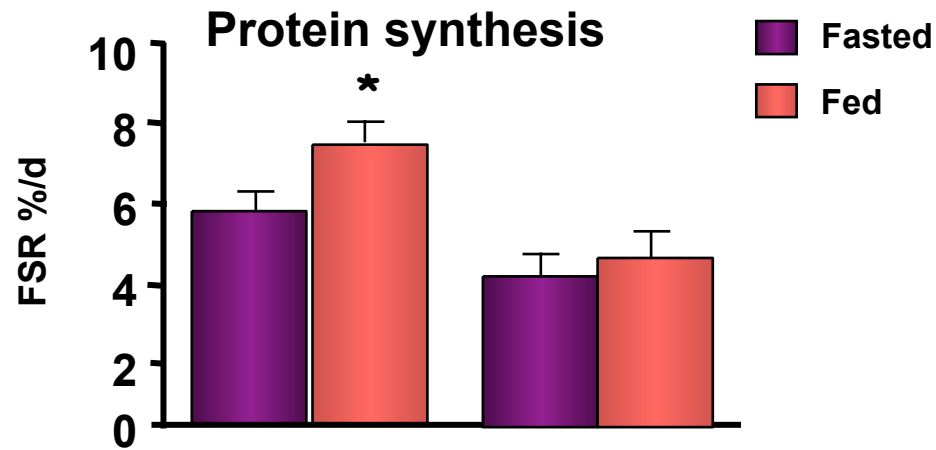




Impaired anabolic response to meal intake during aging



Anabolic resistance



Impaired anabolic response to meal intake during aging



Anabolic resistance

Defect in the regulation of mTOR signaling pathway by amino acids

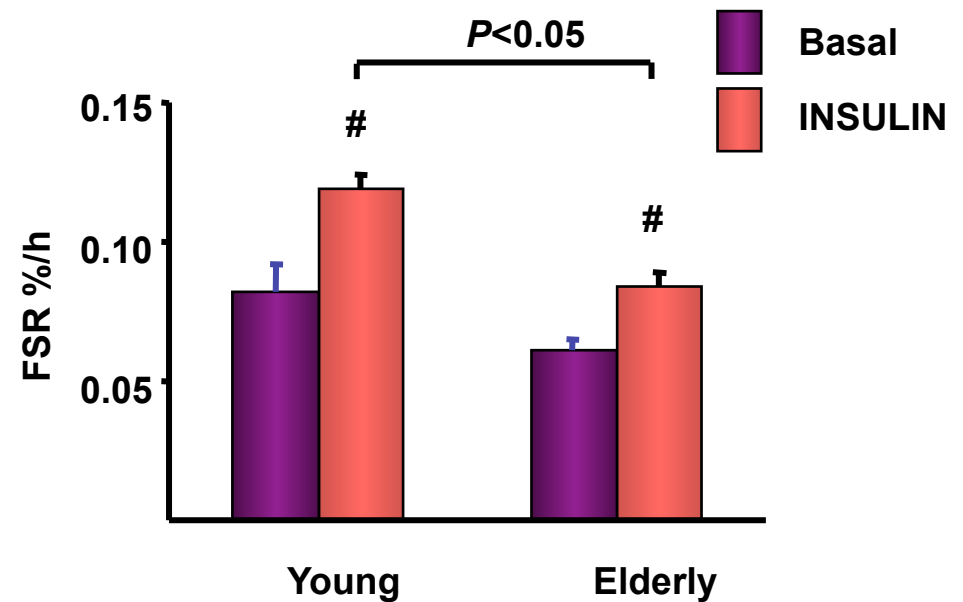
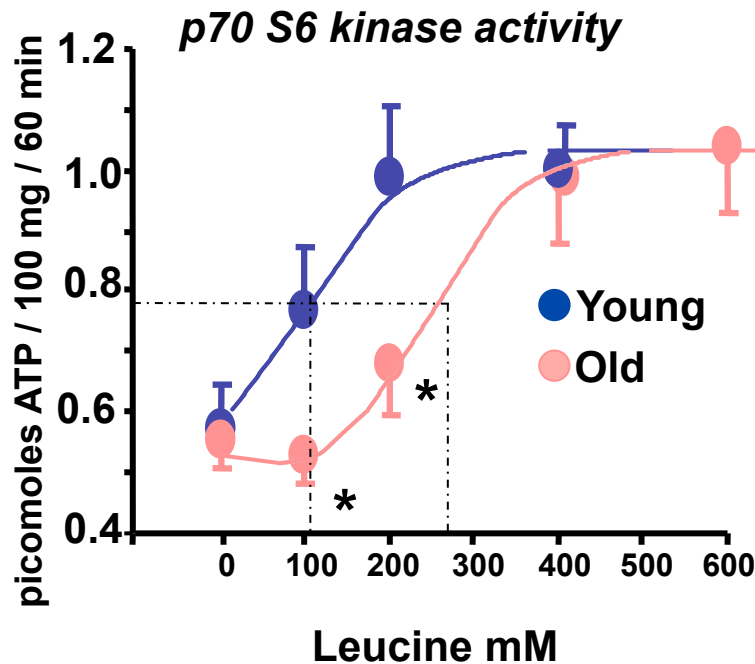


Leucine resistance

Defect in the regulation of mTOR signaling pathway by insulin



Insulin resistance

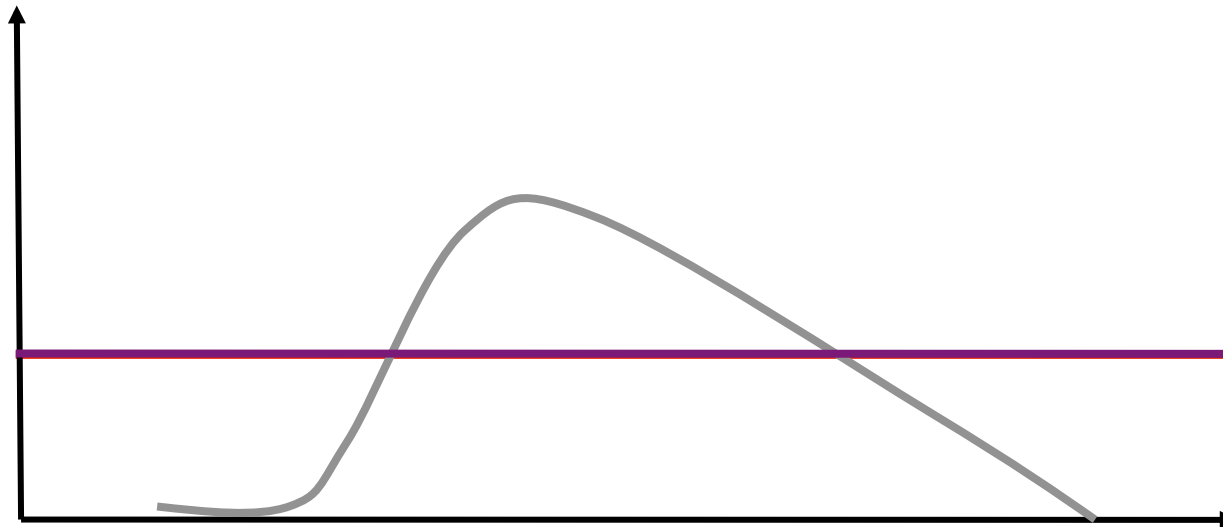


Dardevet, *J Nutr* 2000  
Cuthbertson, *FASEB J* 2005

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

# Déclenchement postprandial de l'anabolisme et perte de masse maigre

Stimuli  
anaboliques



**Résistance  
Anabolique**

**Seuil de  
Réponse  
Anabolique**

repas



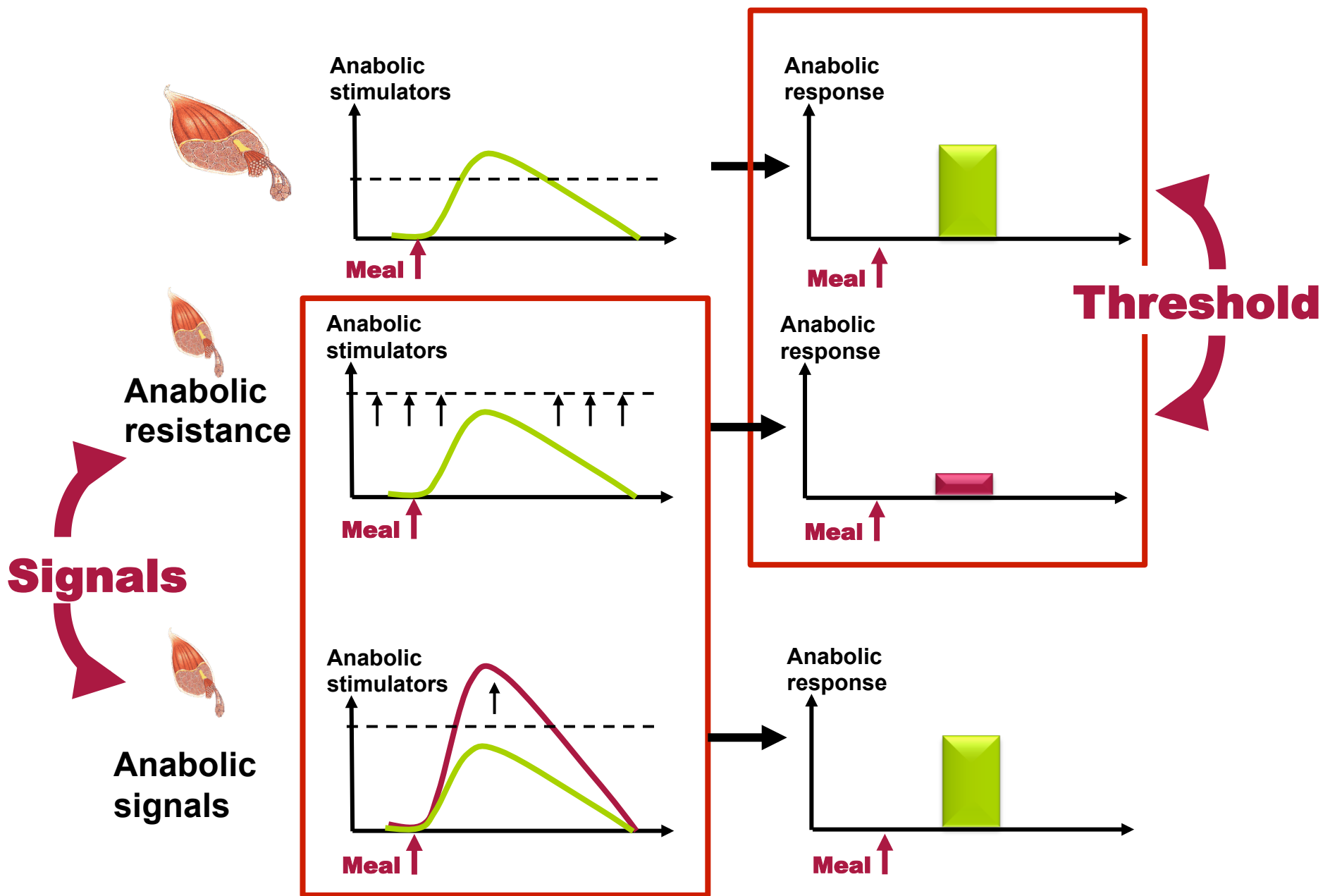
temps



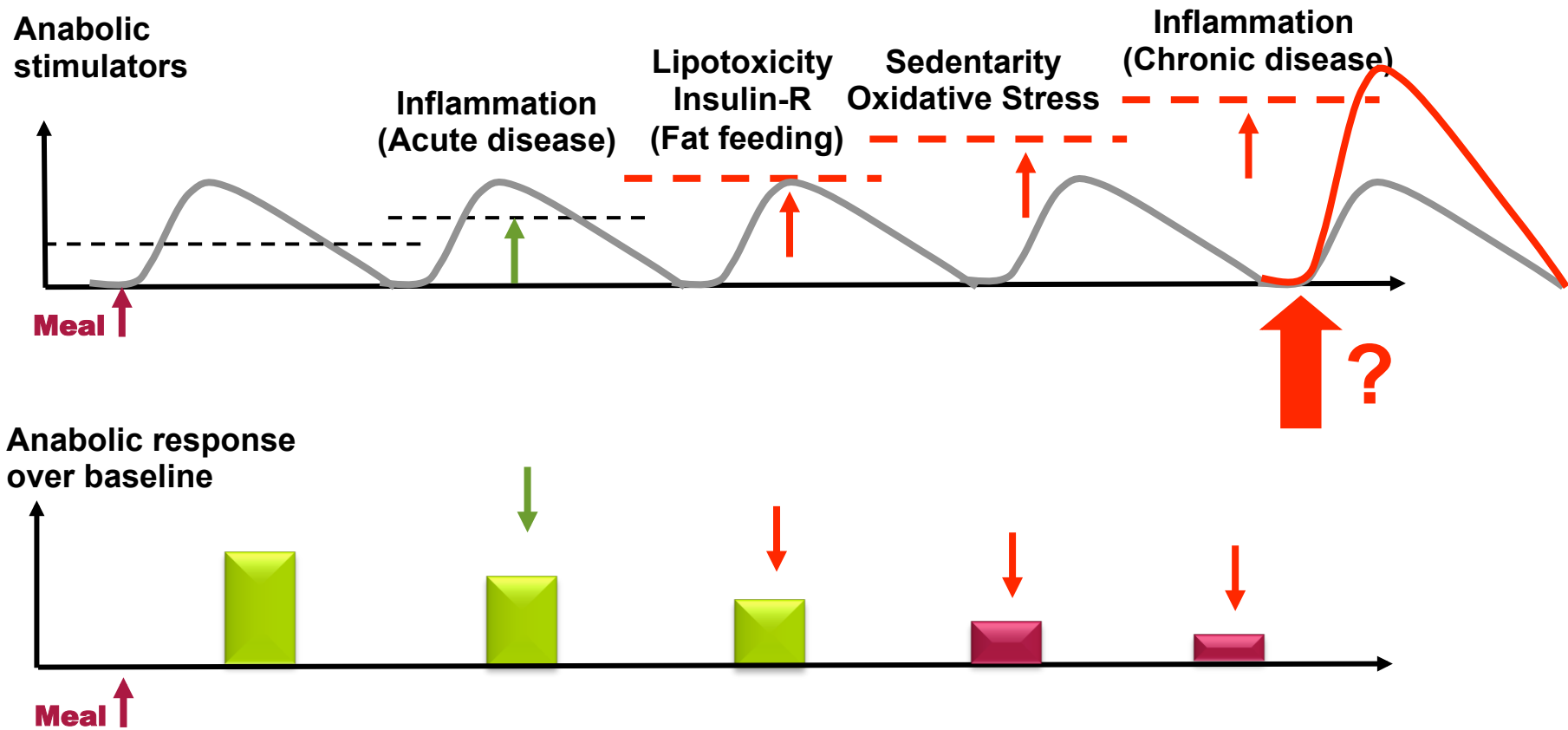
situation physiologique



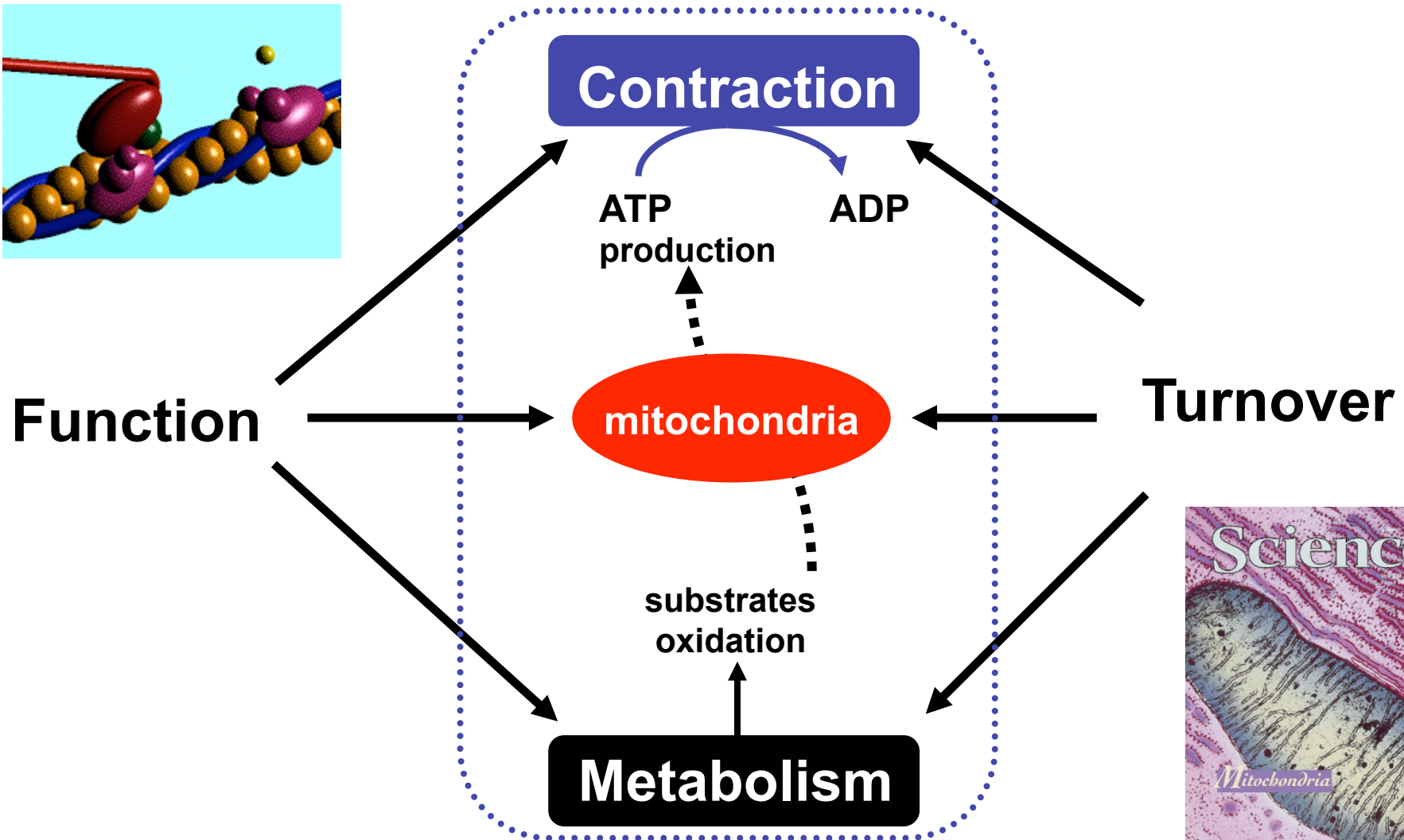
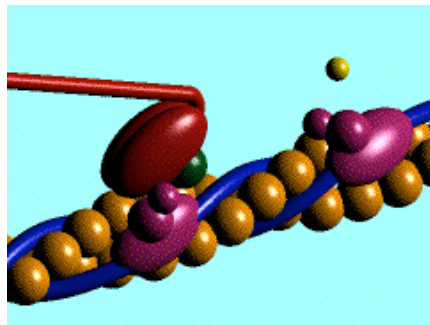
Vieillesse ou état catabolique



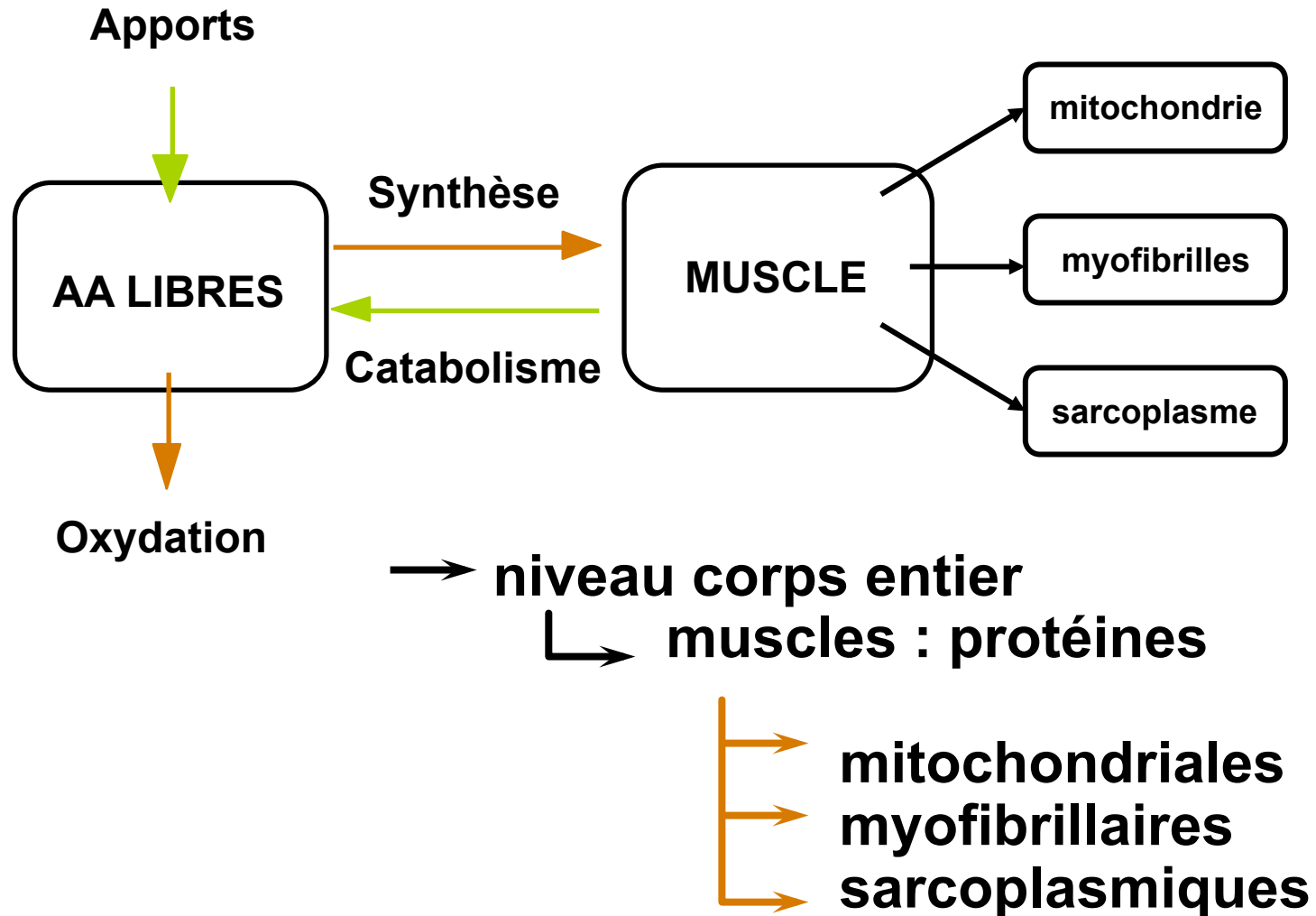
# Temporal changes in anabolic threshold?



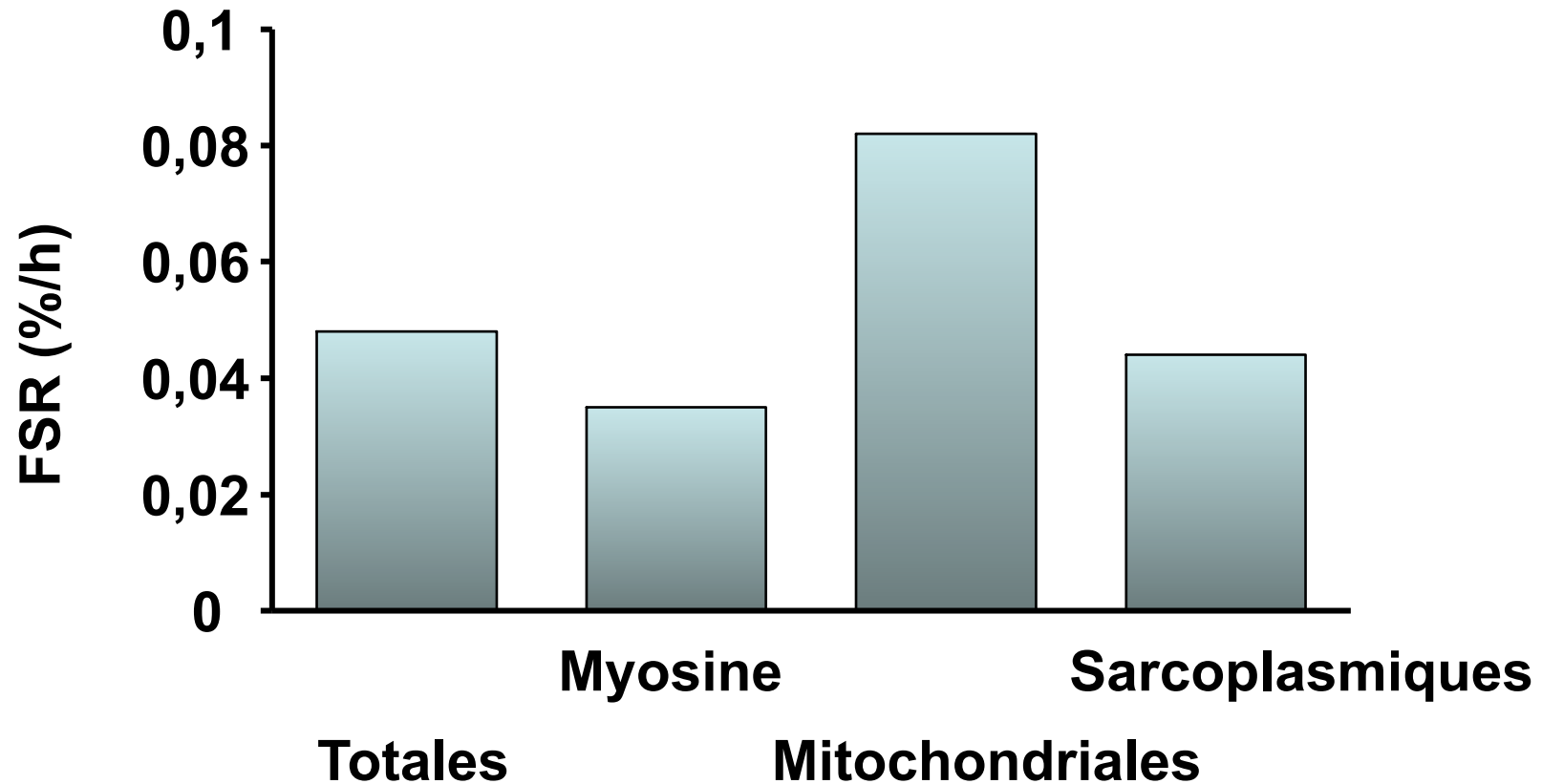
# Integrative approach of muscle protein function



# Renouvellement protéique musculaire = sommation du renouvellement individuel des protéines



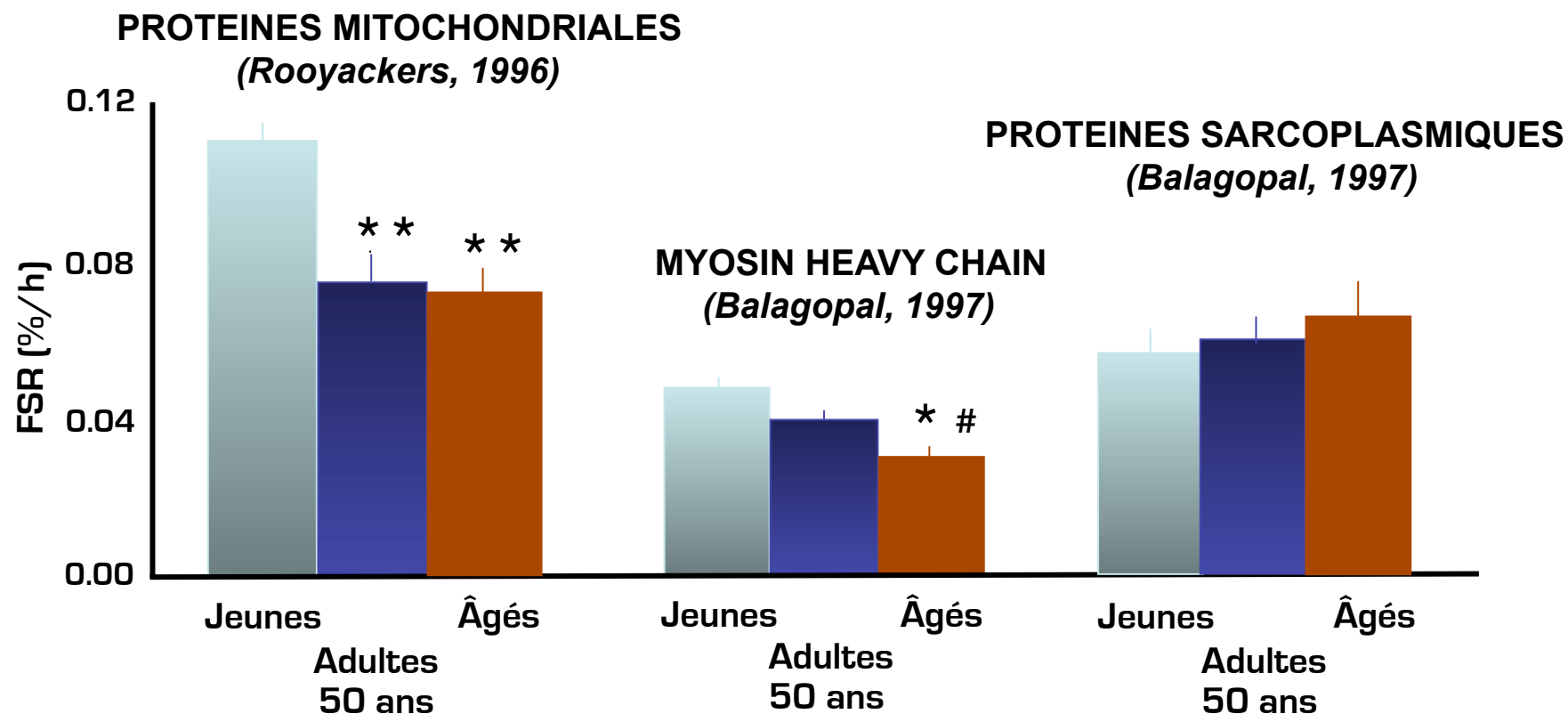
# Vitesse de synthèse des protéines musculaires spécifiques



*Rooyackers OE, Muscle & Nerve 1997*



# Synthèse des protéines spécifiques musculaires selon l'âge

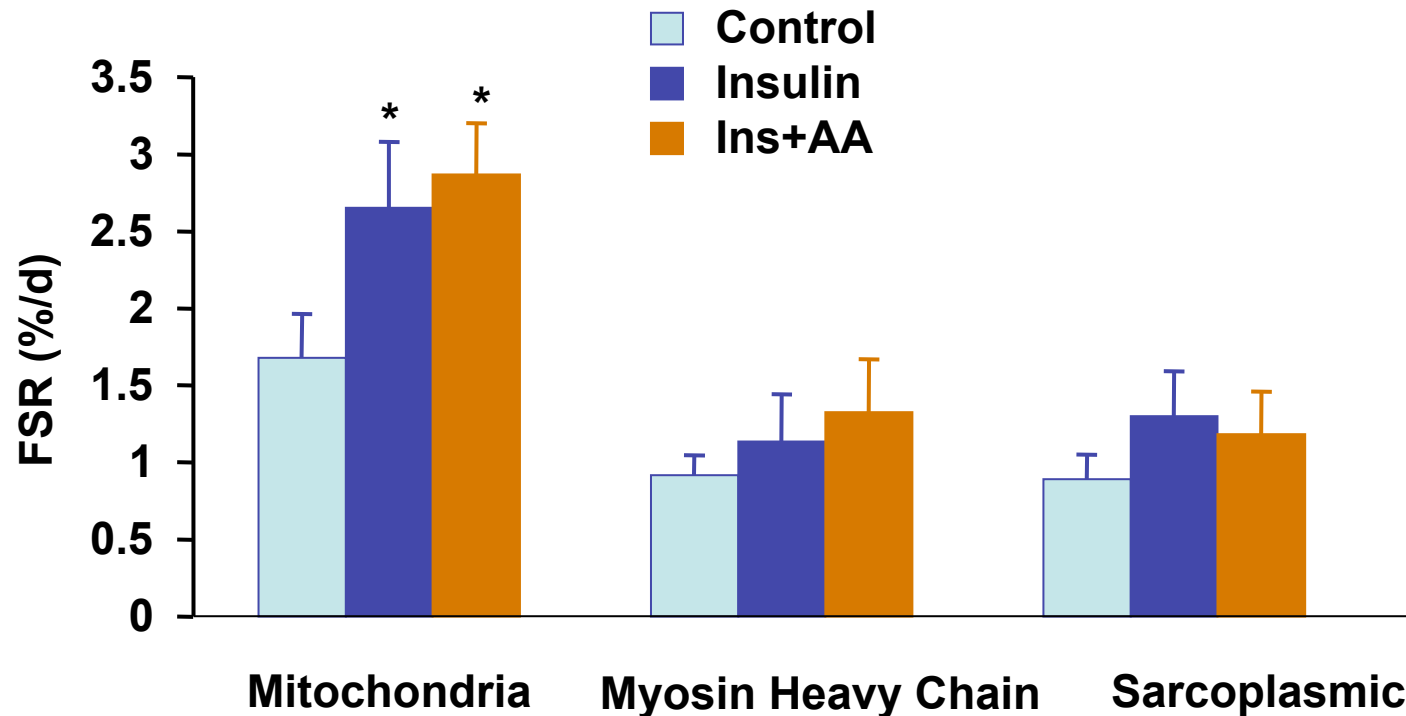


\*  $p < 0.05$  versus jeunes

\*\*  $p < 0.01$  versus jeunes

#  $p < 0.05$  versus adultes

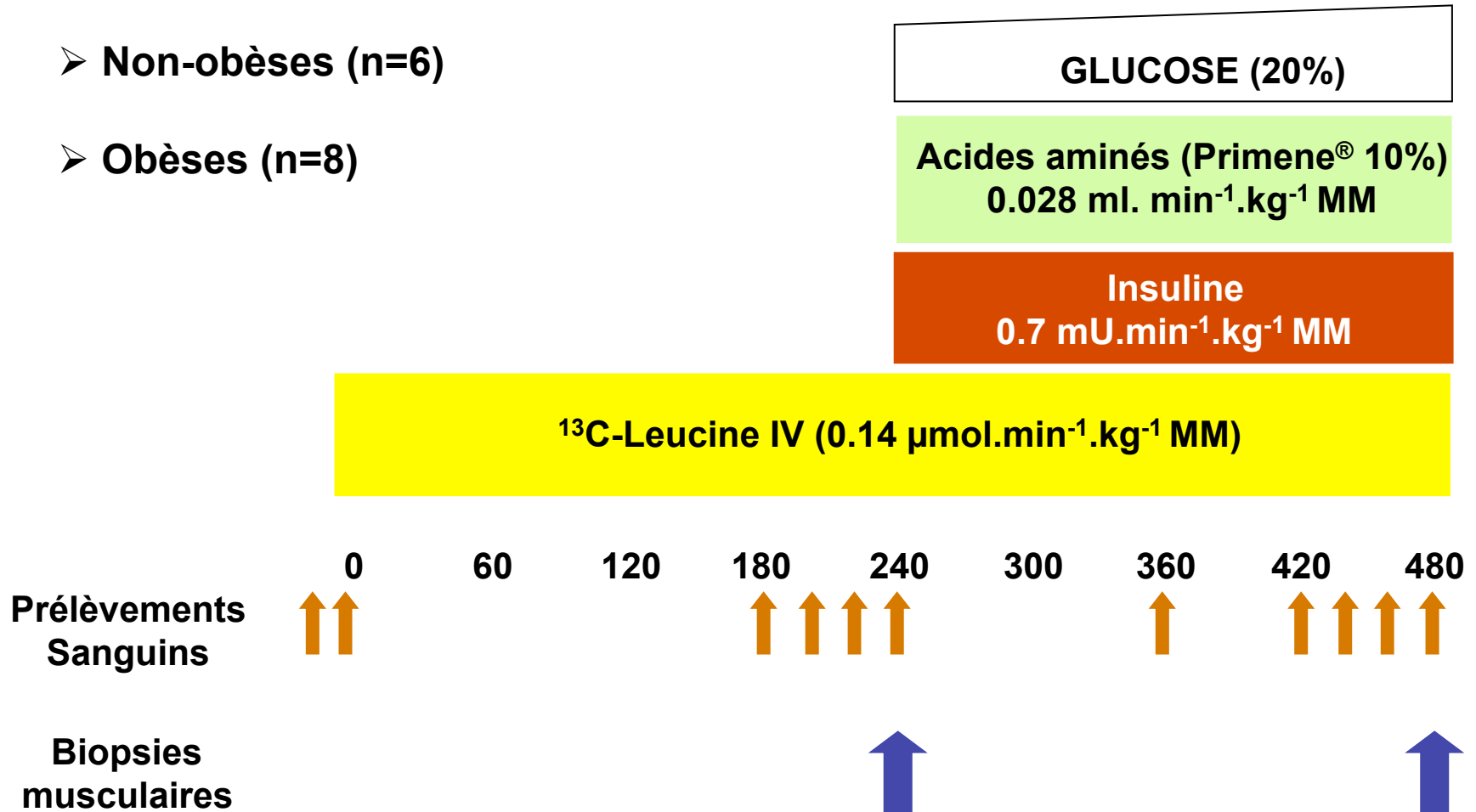
## In muscle, insulin stimulates the synthesis of mitochondrial proteins but not of myosin or sarcoplasmic proteins



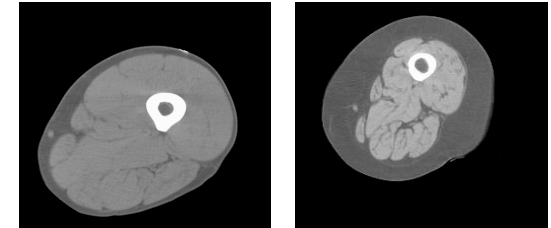
\*  $p < 0.05$  vs control

*Boirie, Diabetes 2001*

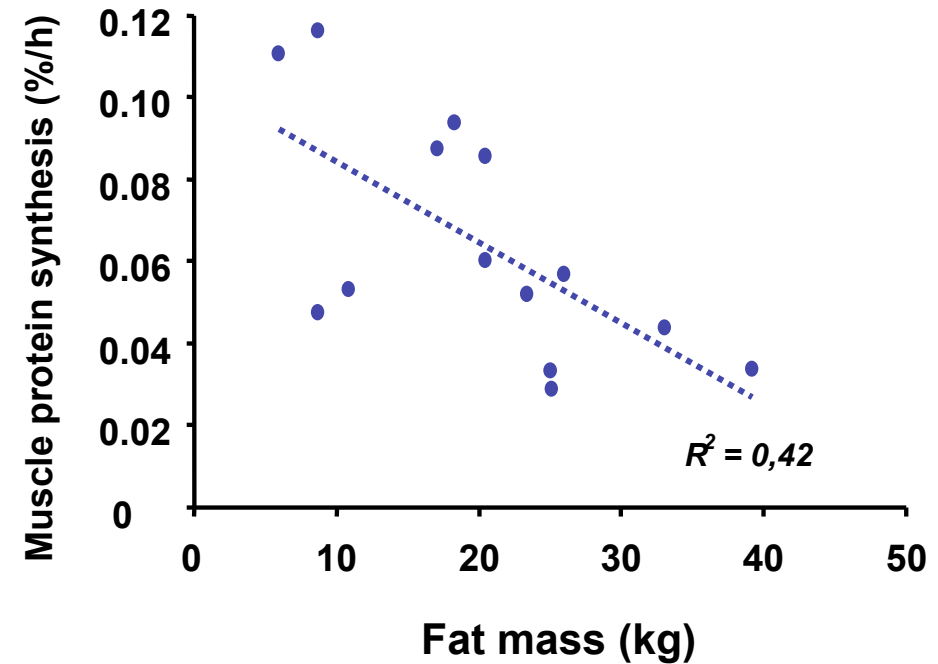
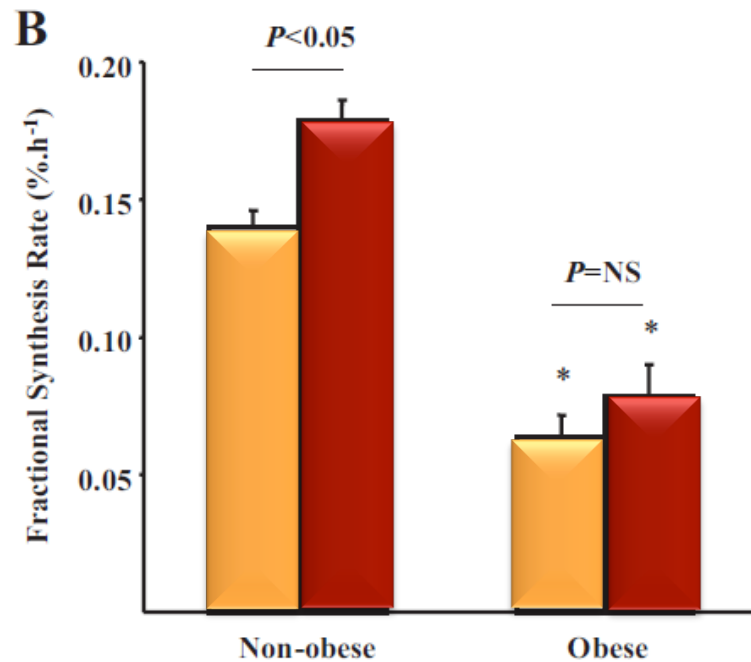
# Protocole expérimental



# L'obésité perturbe la vitesse de synthèse des protéines mitochondriales

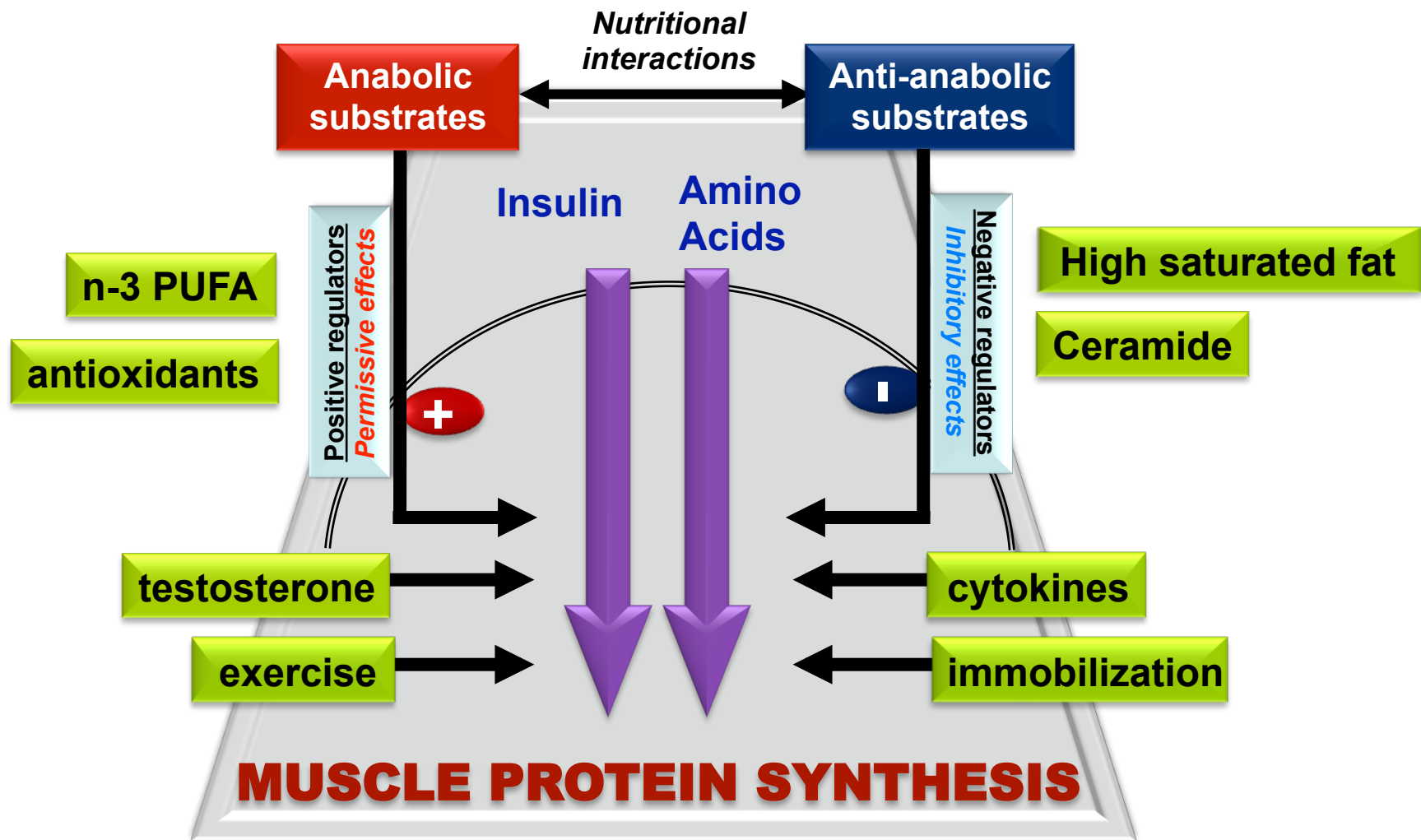


## Muscle Mitochondrial Protein synthesis (%/h)

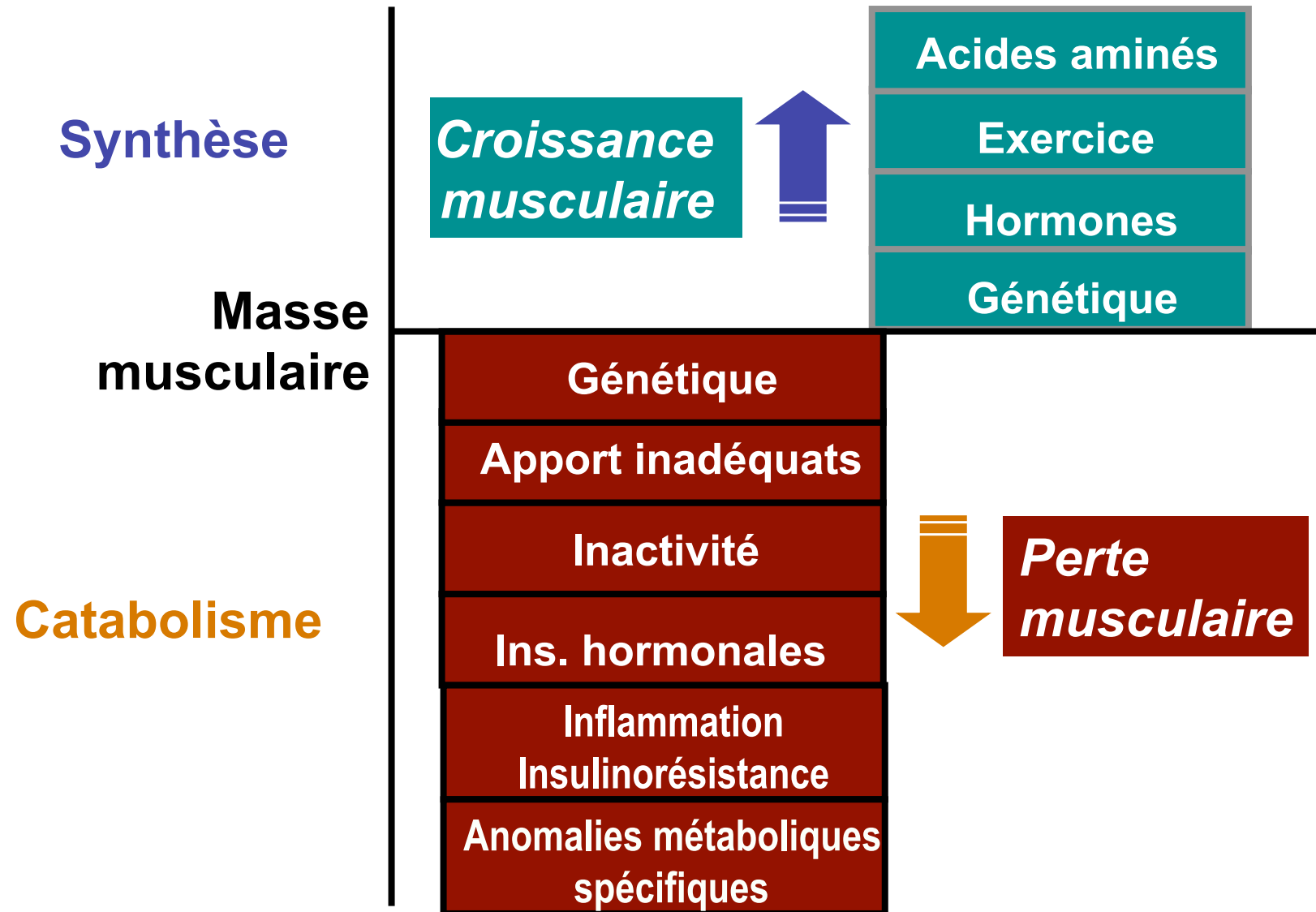


- Postabsorptive
- Insulin clamp

Guillet C, JCEM 2009

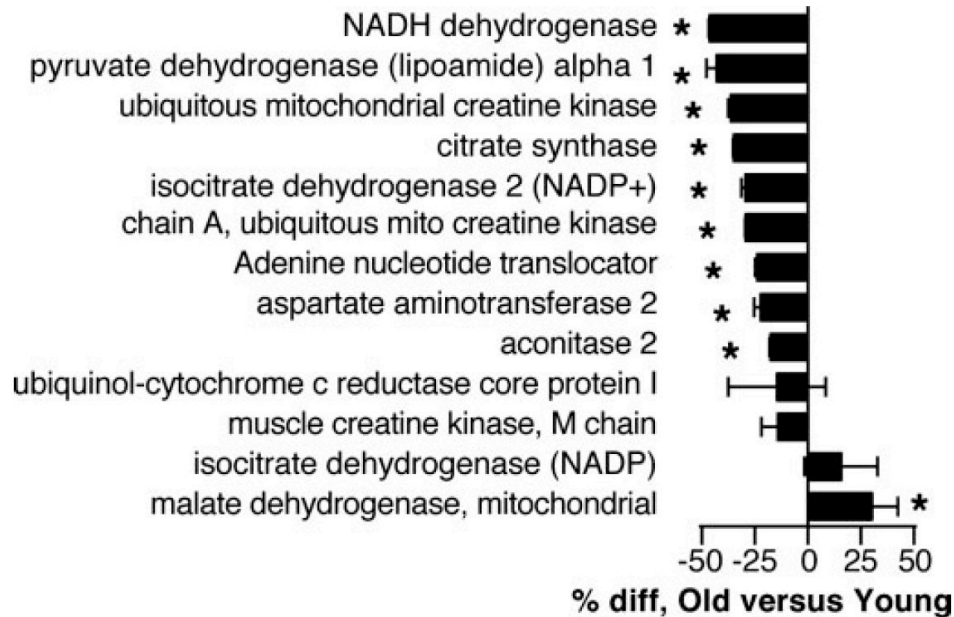


# Contrôle de la masse musculaire

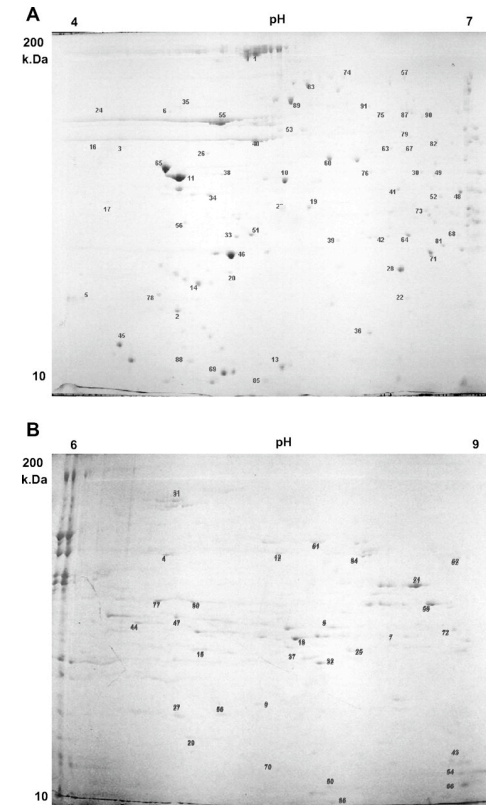


# Decline in skeletal muscle mitochondrial function with aging in humans

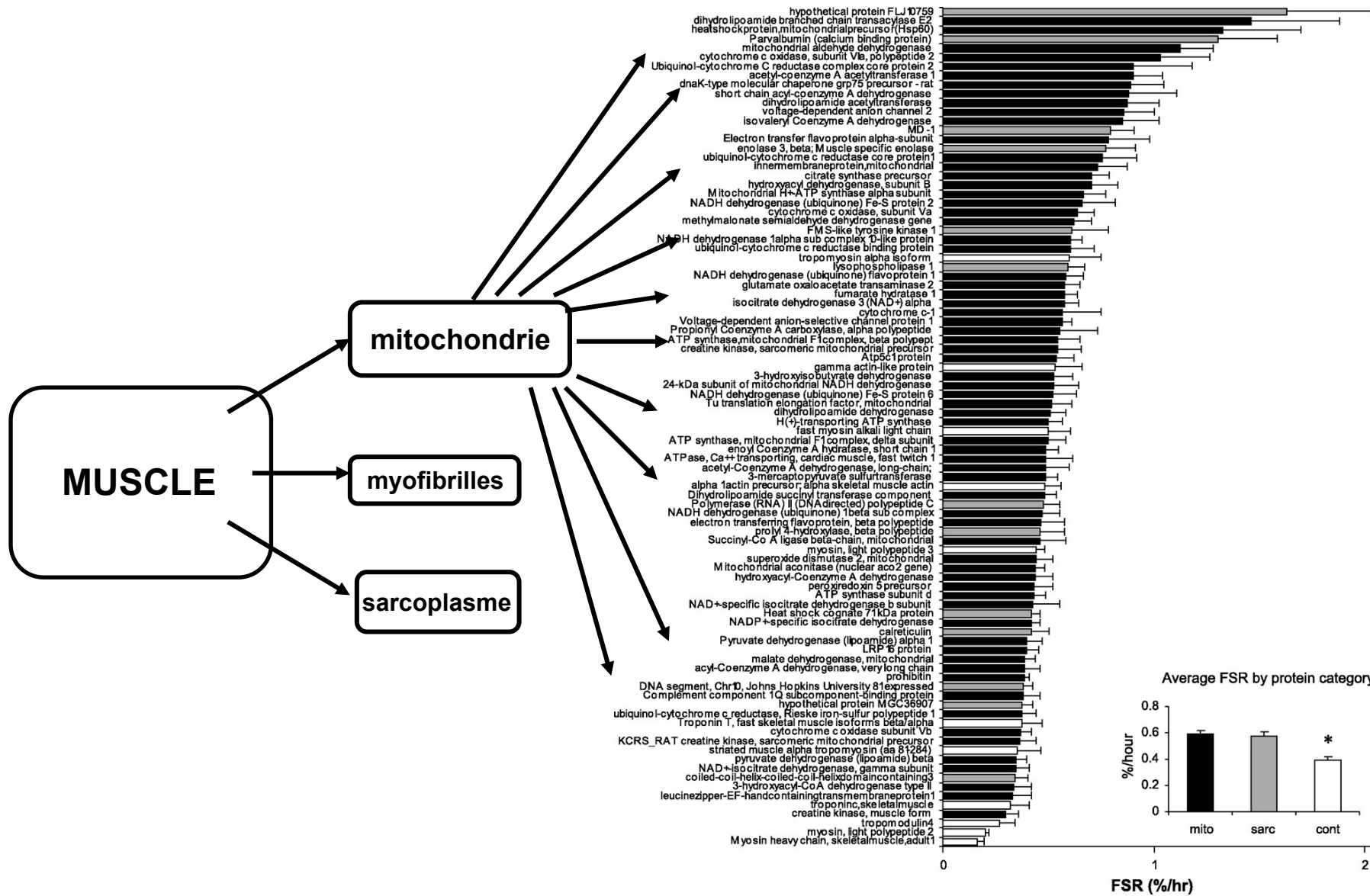
Kevin R. Short\*, Maureen L. Bigelow\*, Jane Kahl\*, Ravinder Singh†, Jill Coenen-Schimke\*, Sreekumar Raghavakaimal\*, and K. Sreekumaran Nair\*\*‡



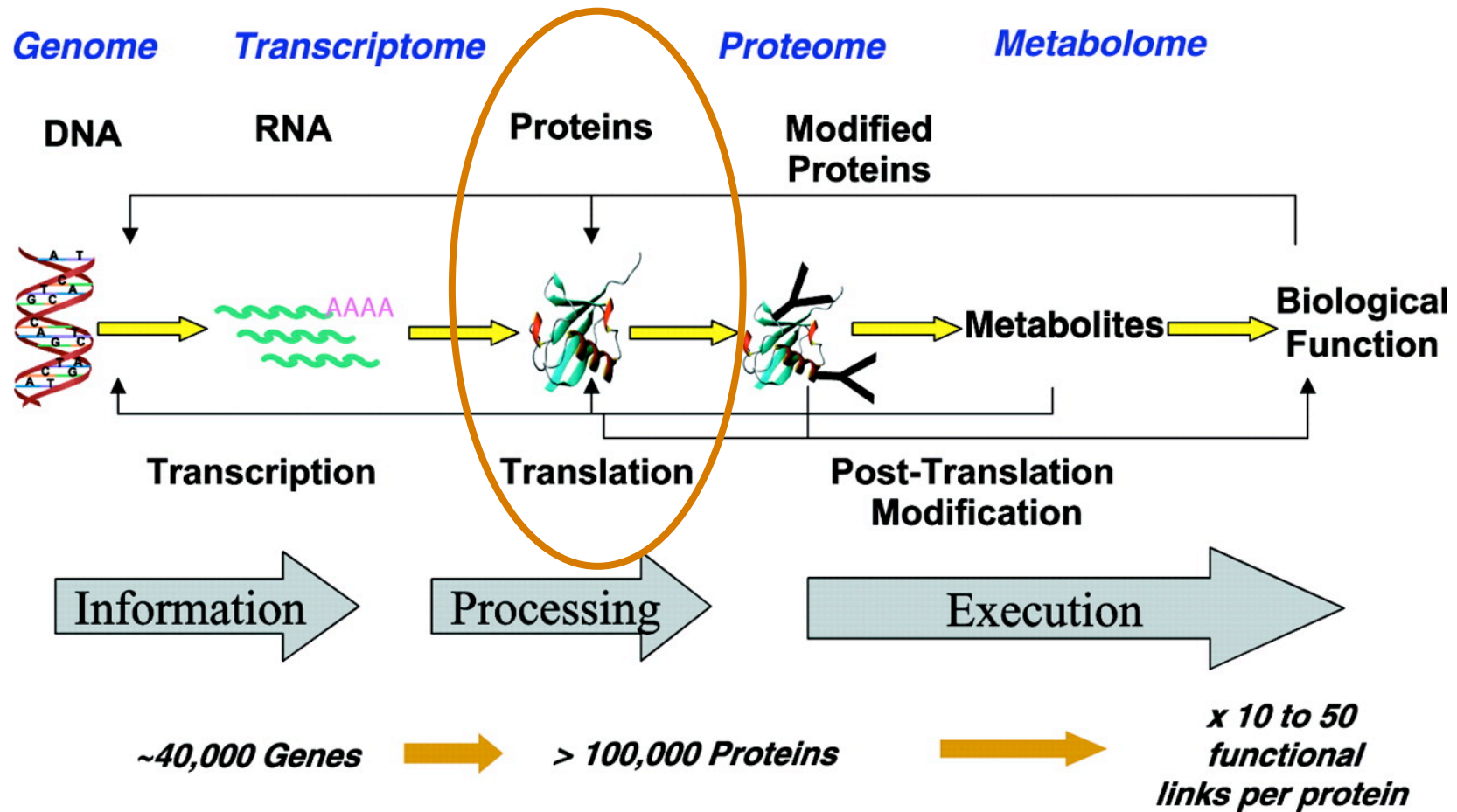
Short K, PNAS 2005



Jaleel A, Am J Physiol Endocrinol Metab 2008







Nair K S et al. Am J Physiol Endocrinol Metab  
2004;286:E863-E874

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Endocrinology and Metabolism



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**UMR 1019, Unité de Nutrition Humaine**

