



## The Muscle Anabolic Threshold Concept for an Adapted and Efficient Nutrition during Catabolic States

Dominique Dardevet, Didier Remond, Marie-Agnès Peyron, Isabelle I. Papet,  
Isabelle Savary-Auzeloux, Laurent Mosoni

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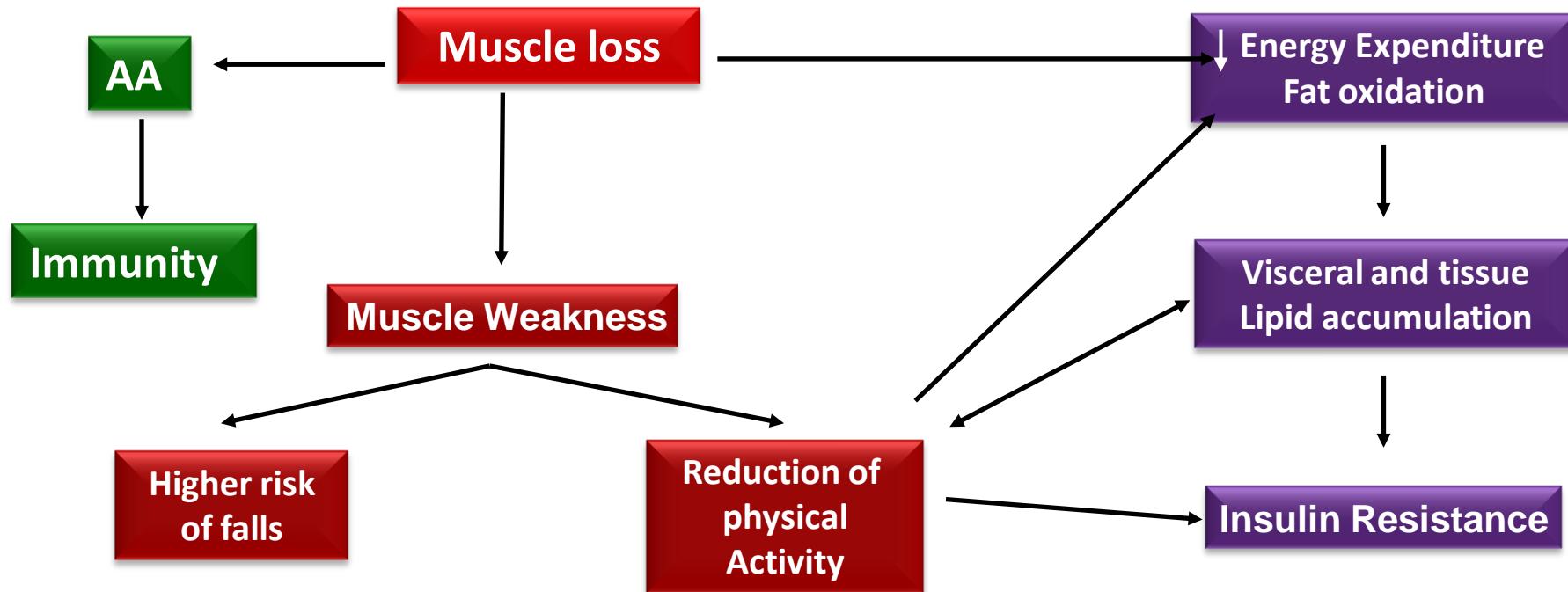
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# The Muscle Anabolic Threshold Concept for an Adapted and Efficient Nutrition during Catabolic States

Dardevet Dominique, Rémond Didier, Peyron Marie-Agnès, Papet Isabelle,  
Savary-Auzeloux Isabelle and Mosoni Laurent.



# **Impact of muscle loss in health and diseases**



**Frailty, Loss of Autonomy**

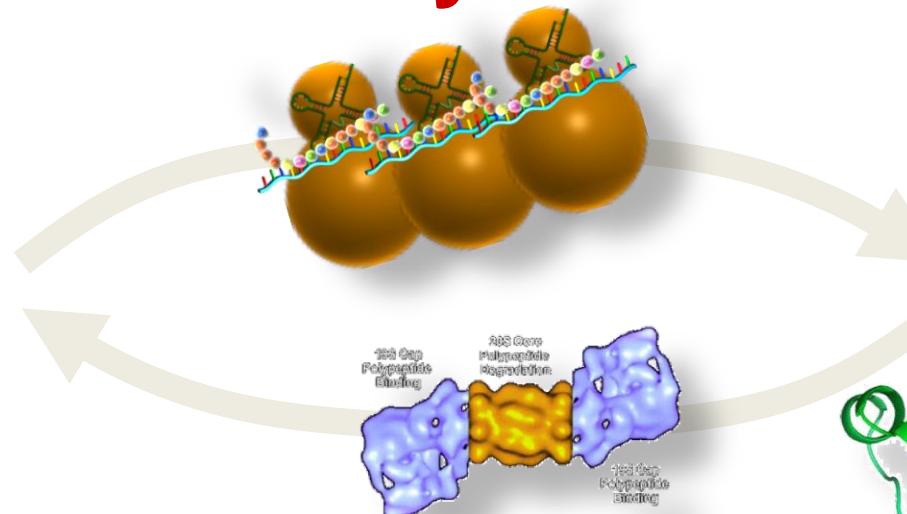
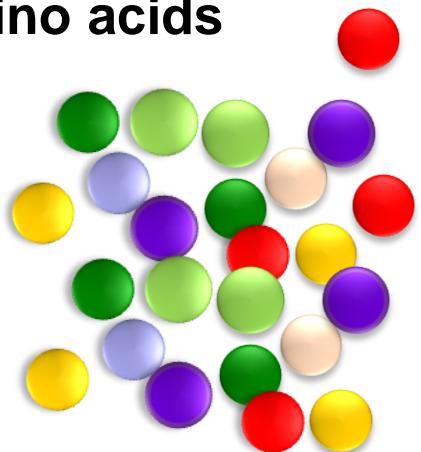
↗ **Morbidity, ↗ Mortality**



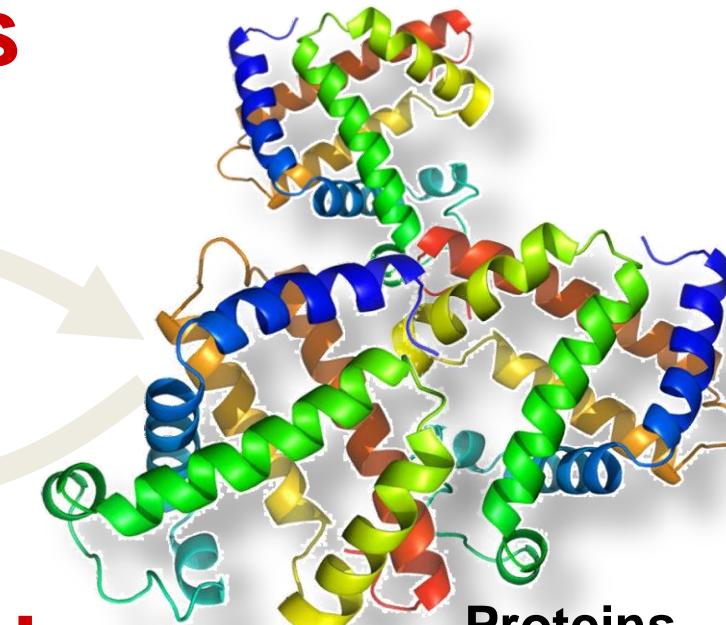
# Protein metabolism

## Protein Synthesis

Amino acids



## Proteolysis



Proteins

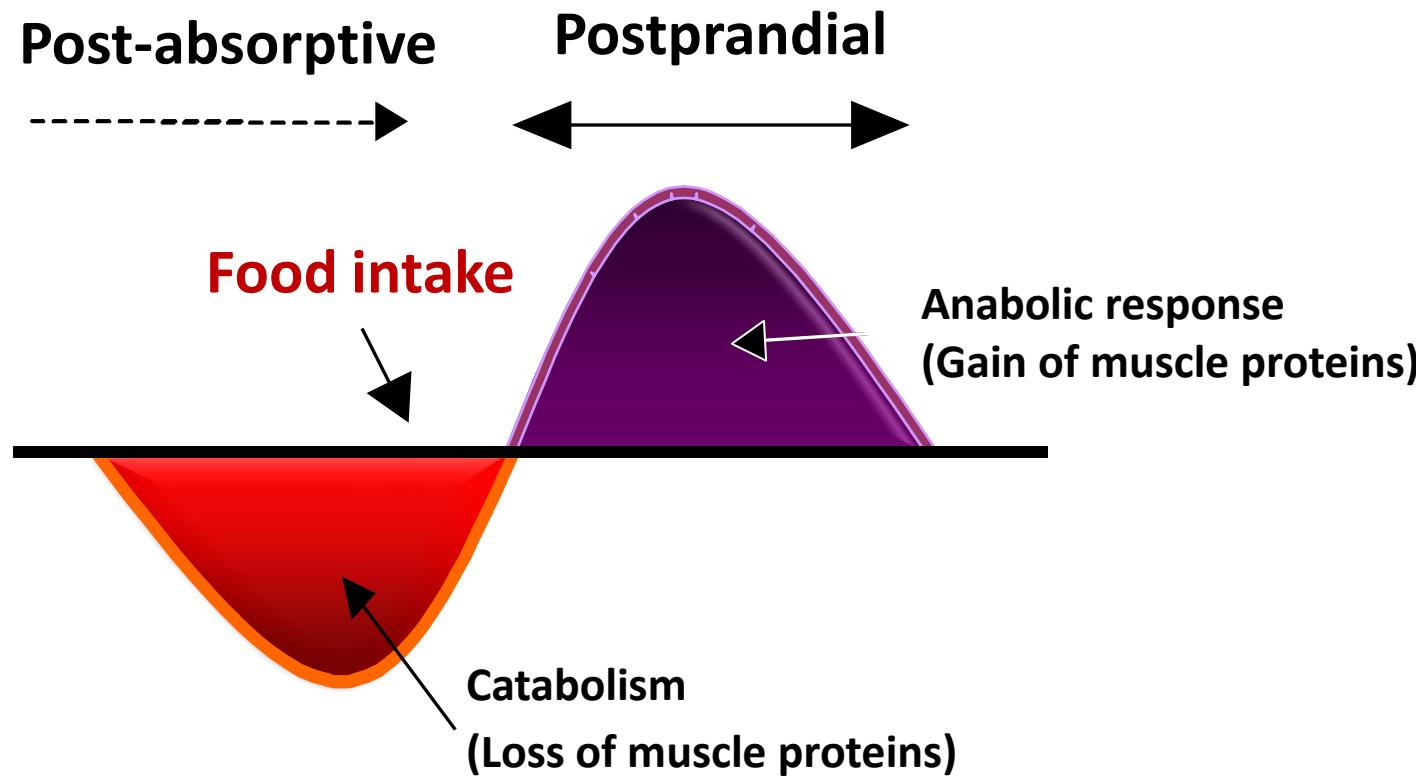
Bioavailability of dietary  
amino acids



Anabolic factors  
(Insulin)



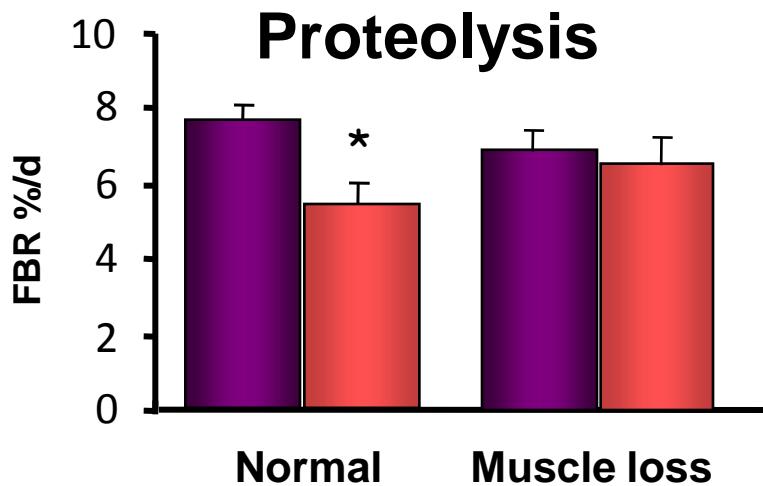
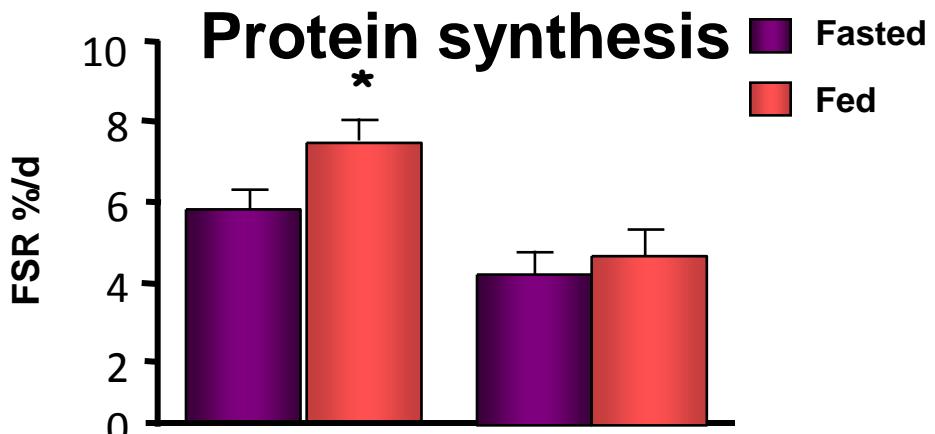
# Protein metabolism



**Post prandial protein gain should compensate the post absorptive loss of proteins**

# Post prandial Protein metabolism

In situations of muscle mass loss



Impaired anabolic response  
to food intake (with the RDA)

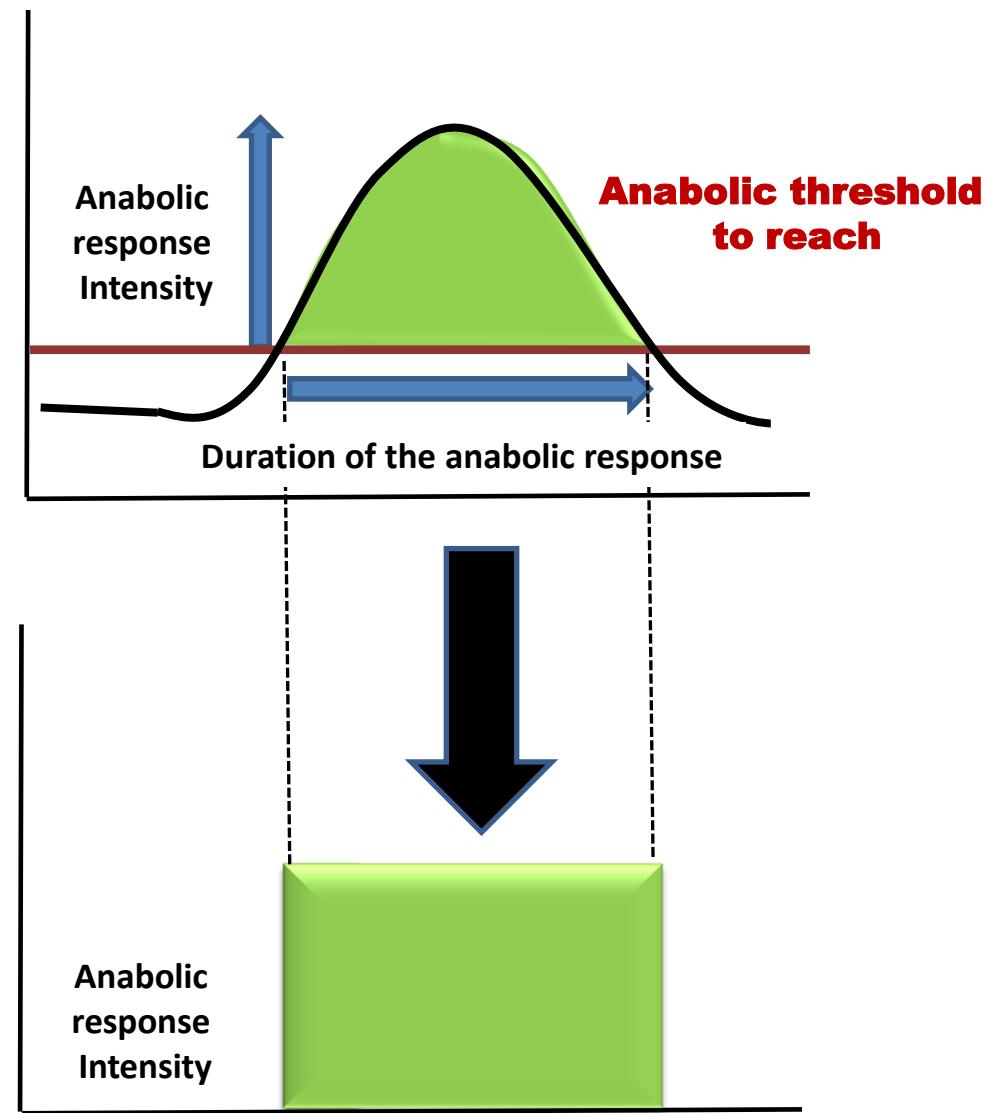
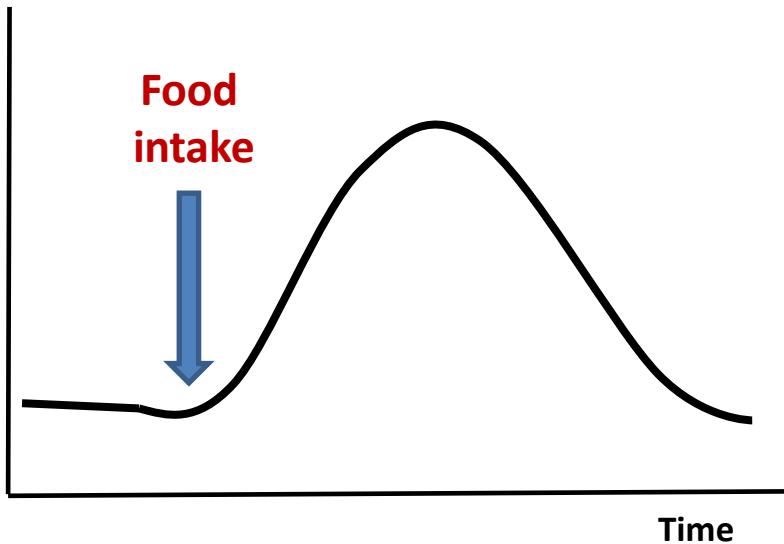


**Anabolic  
resistance**

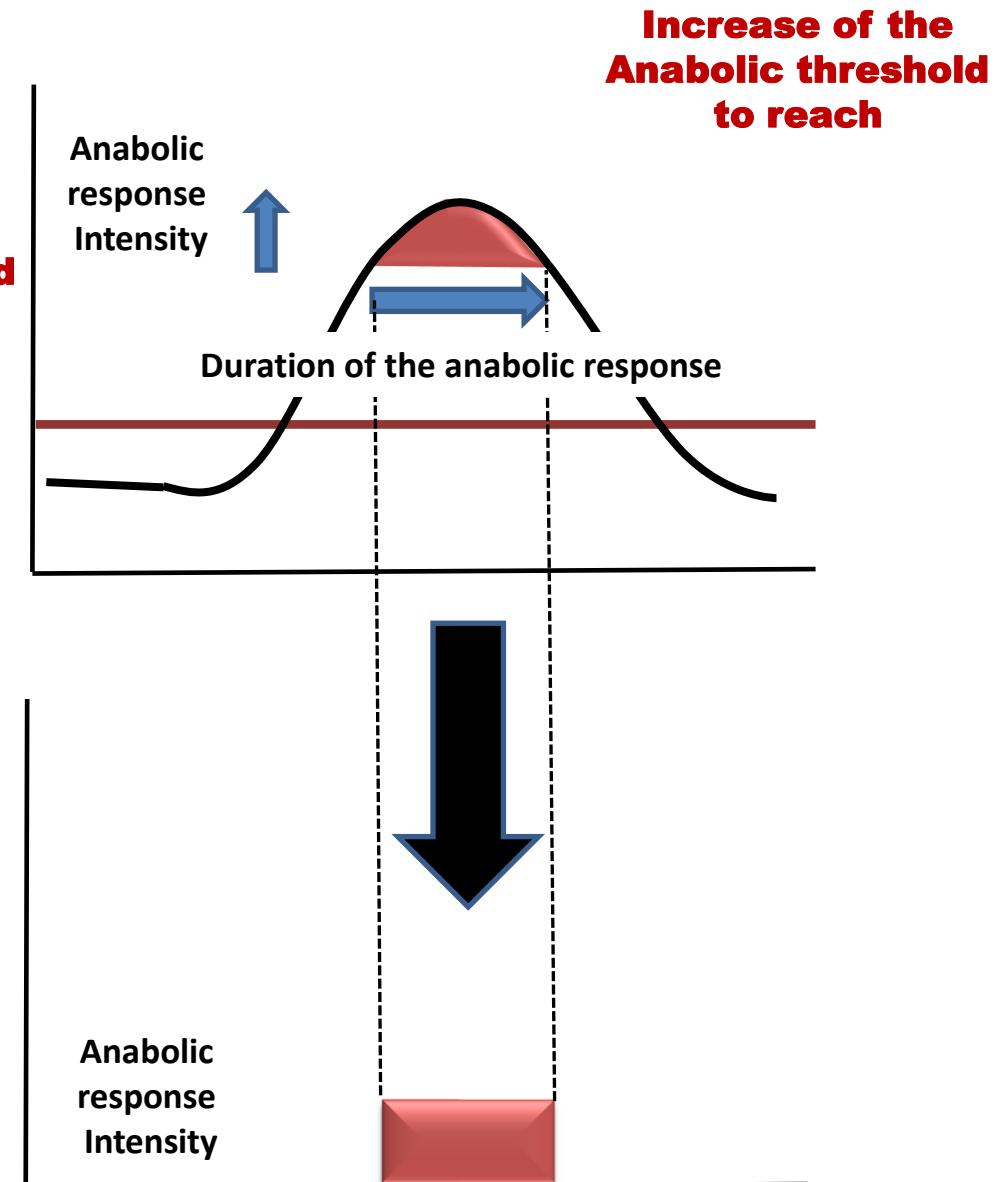
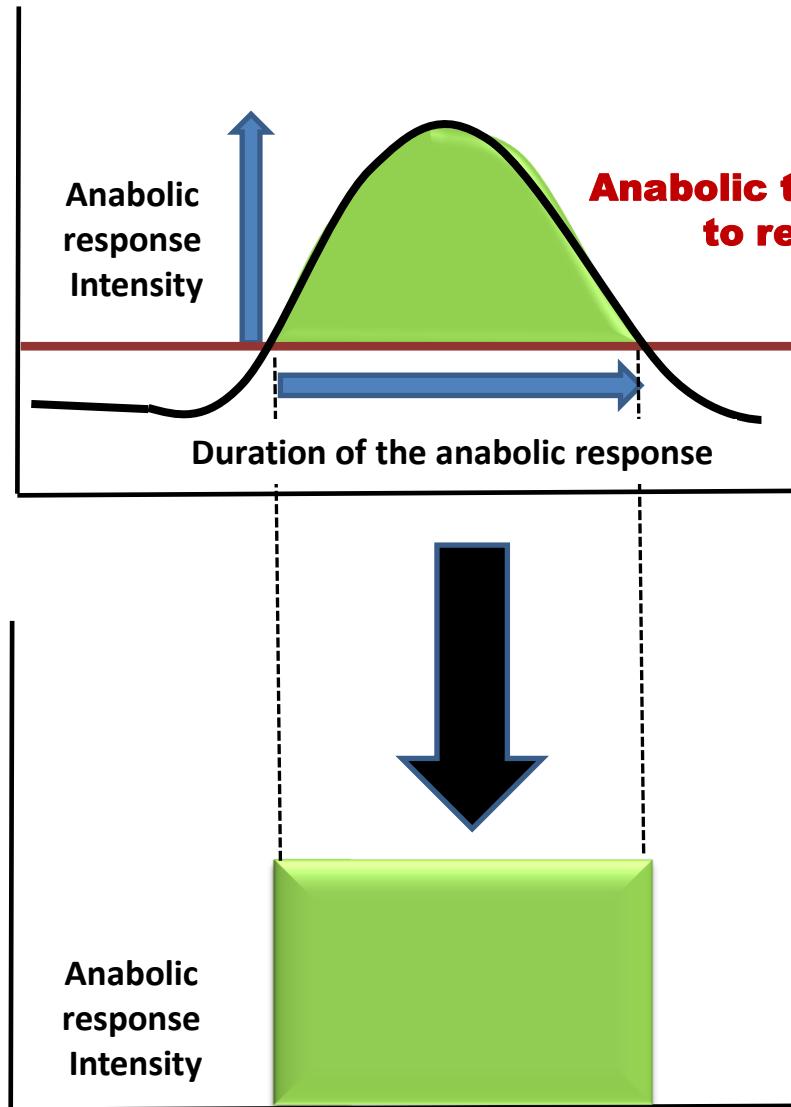
# The Anabolic Threshold Concept

Dardevet et al. Scientific World Journal, 2012

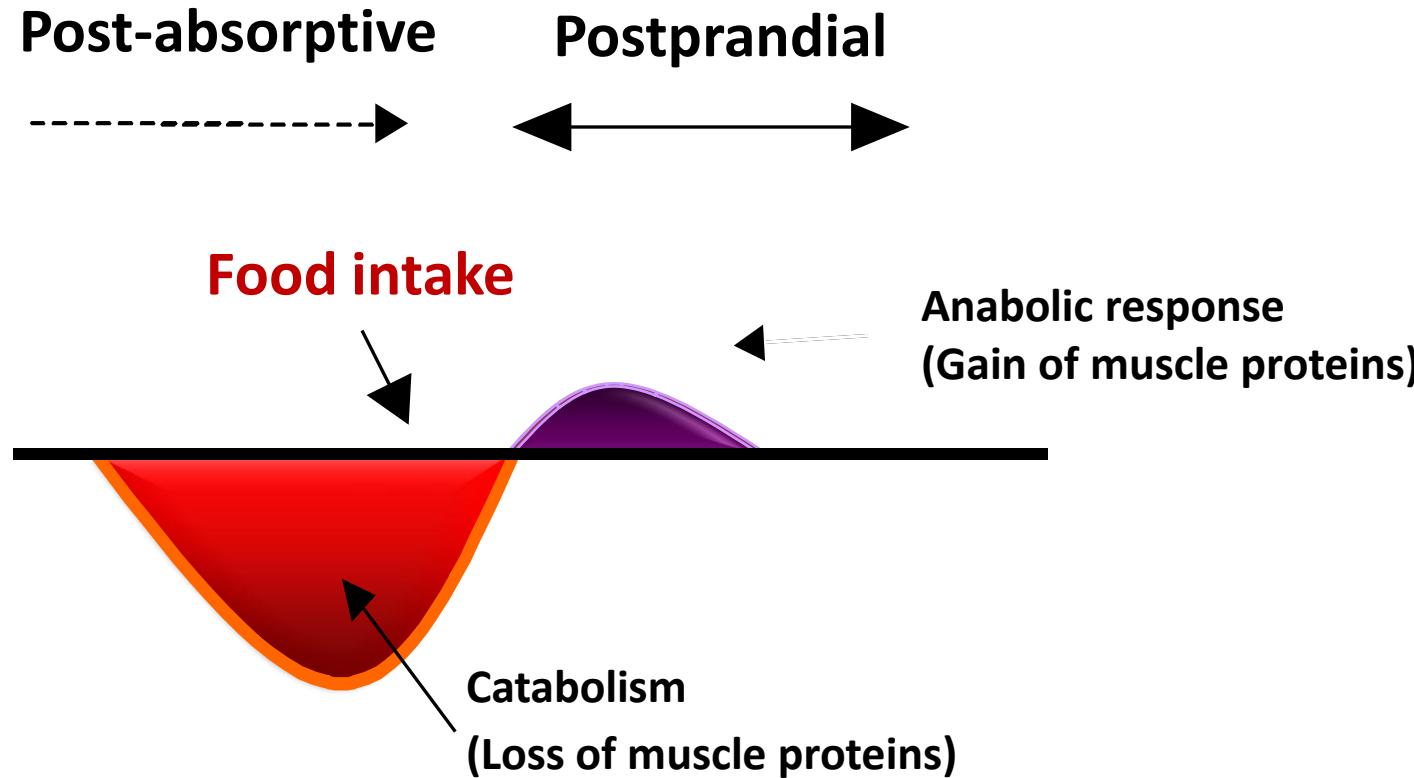
Anabolic factors  
(Amino acids)



# The Anabolic Threshold Concept



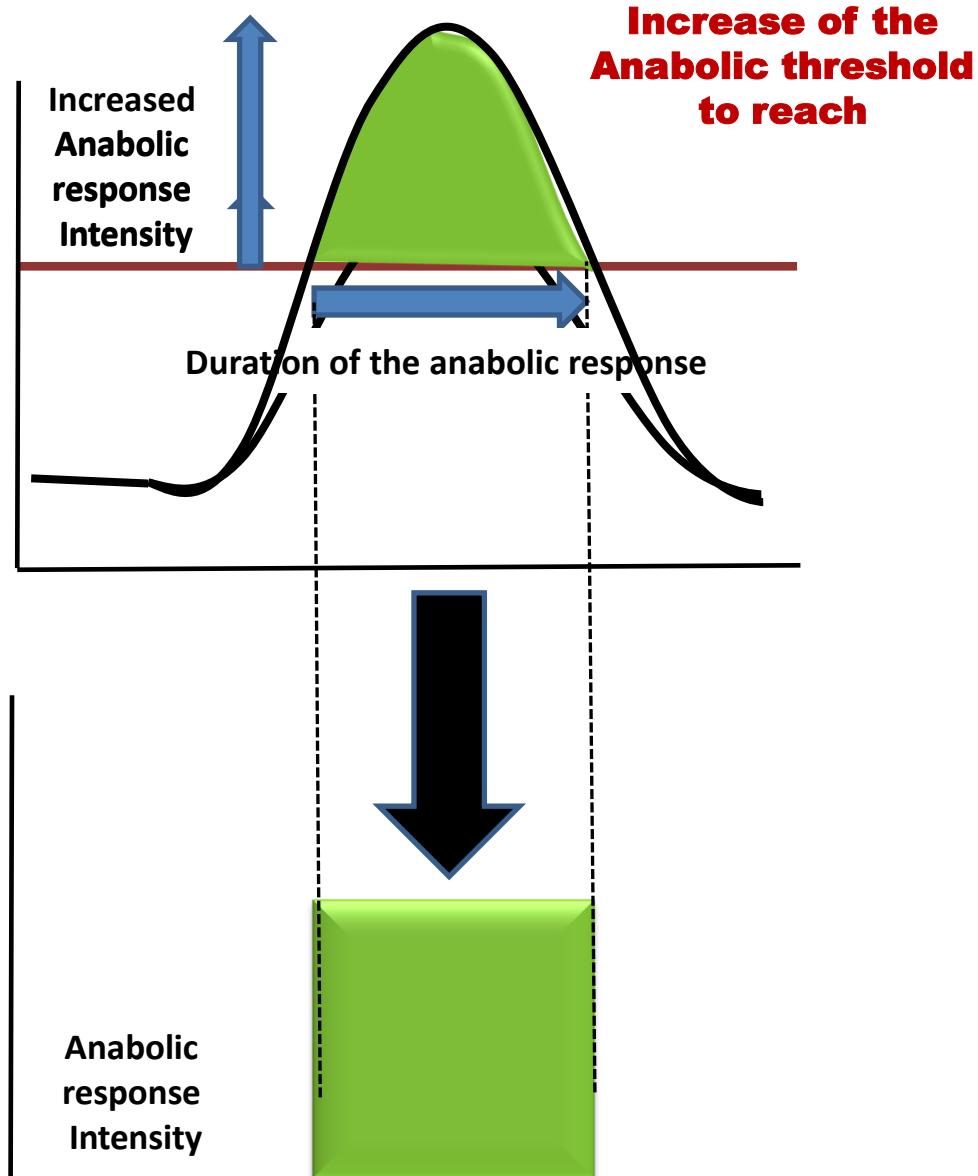
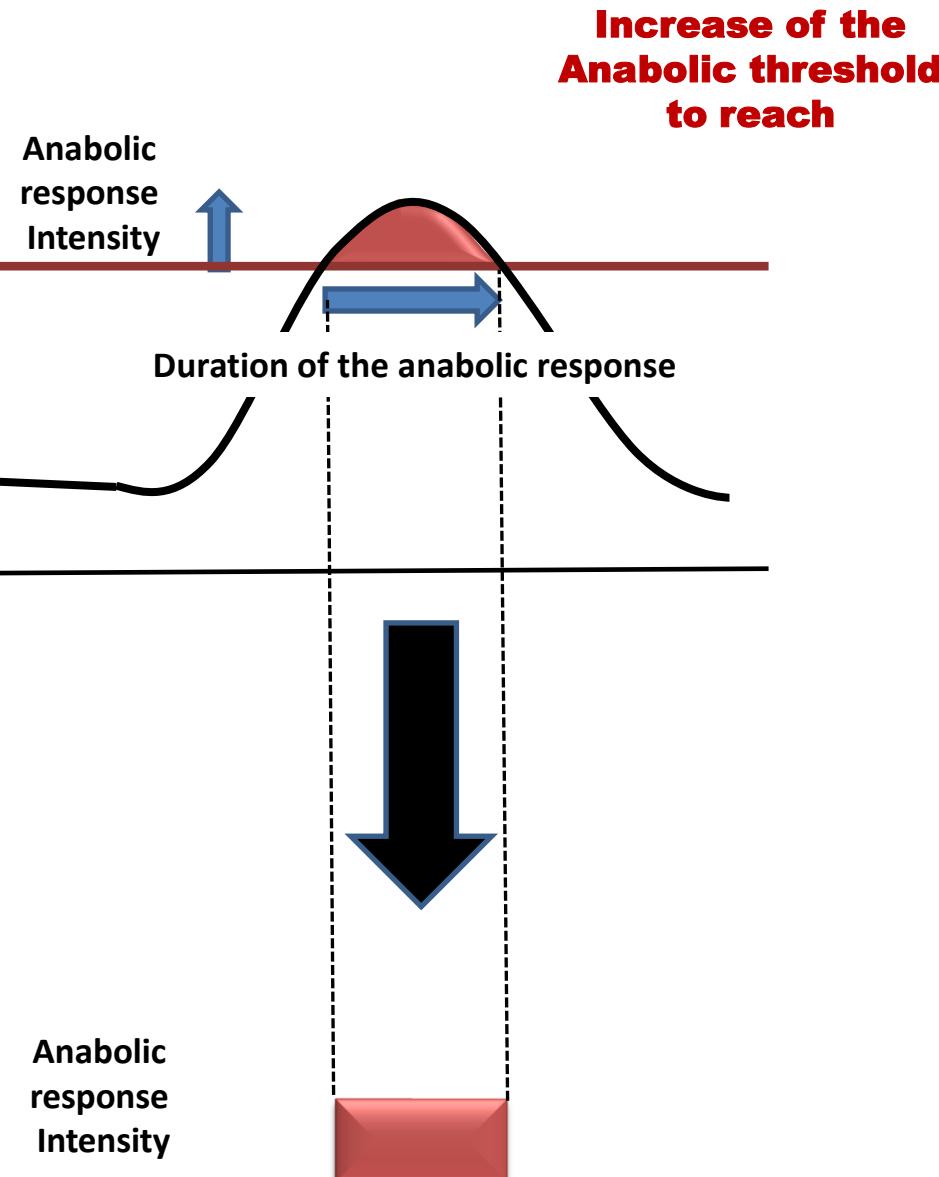
# Protein metabolism in anabolic resistance situations

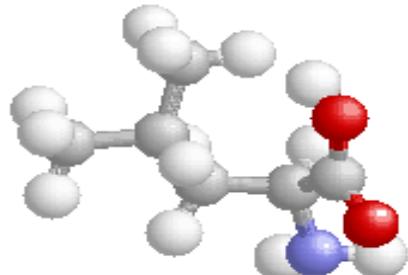


**Post prandial protein gain does not compensate the post absorptive loss of proteins = Muscle Atrophy**

# The Anabolic Threshold Concept

Dardevet et al. Scientific World Journal, 2012





# The Anabolic Threshold Concept

Dardevet et al. World Scientific Journal, 2012

In situations of muscle loss and anabolic resistance:

**Is Leucine capable to overcome the increase of muscle anabolic threshold?**

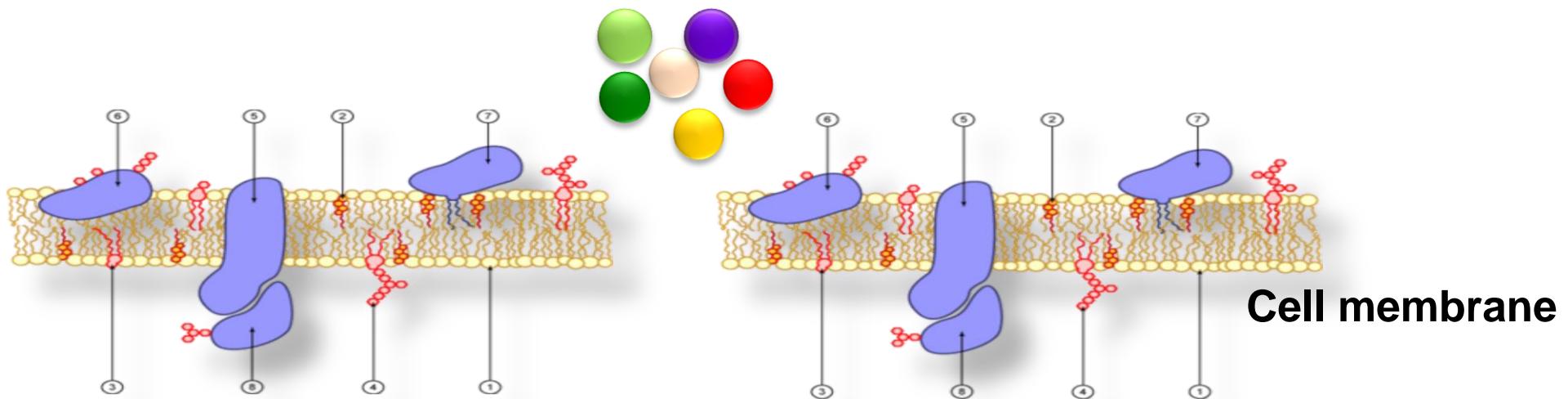
**3 contrasted situations**

Cancer cachexia

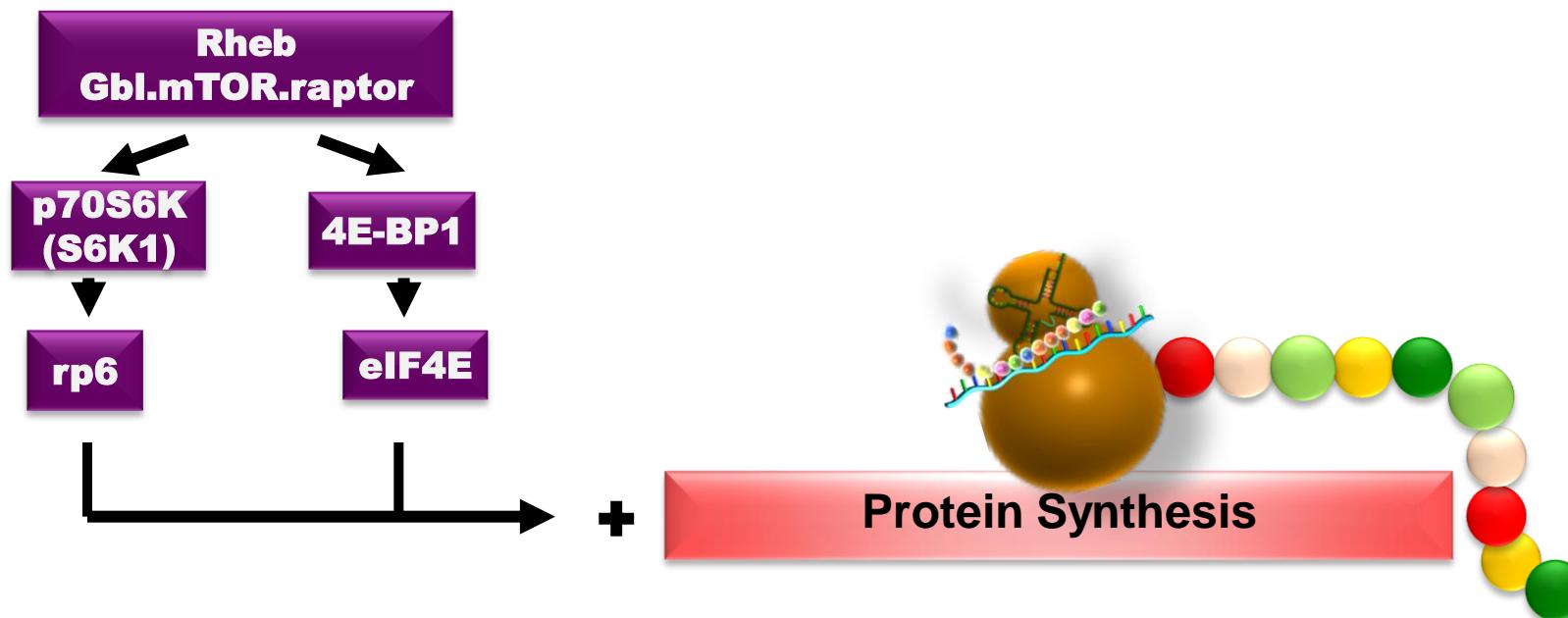
Sarcopenia (aging)

Immobilization/bedrest

# Leucine= a signal nutrient



Leucine



## Free Leucine supplementation

**Improvement of nitrogen balance**

Daily et al. 1983

**Improvement of body weight**

Tayek et al. 1986

**4 g of leucine 29 months**

**Improvement of muscle strength**

Poon et al. 2004

**8,7g to 14,6g leucine/kg dietary proteins in the diet**

**Improvement of muscle mass**

Peters et al. 2011

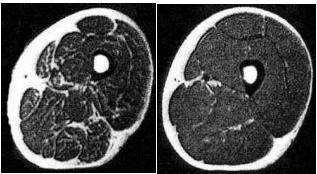
**1g /kg body weight**

**Improve muscle protein synthesis**

**Improvement of muscle mass**

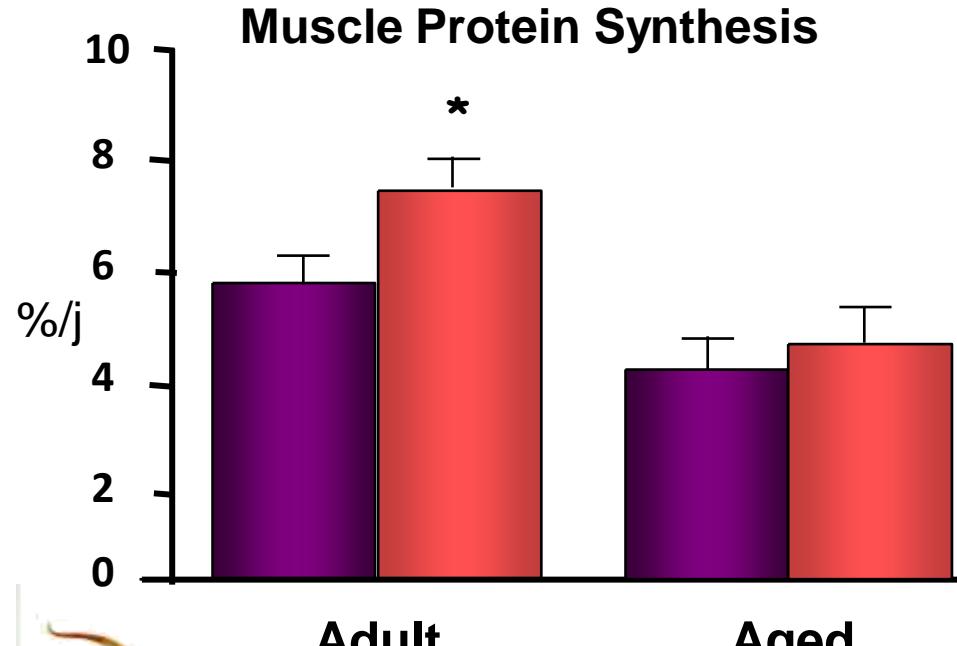
Eley et al. 2007

# Free Leucine supplementation in a meal



## Sarcopenia and aging

Fasted      Fed



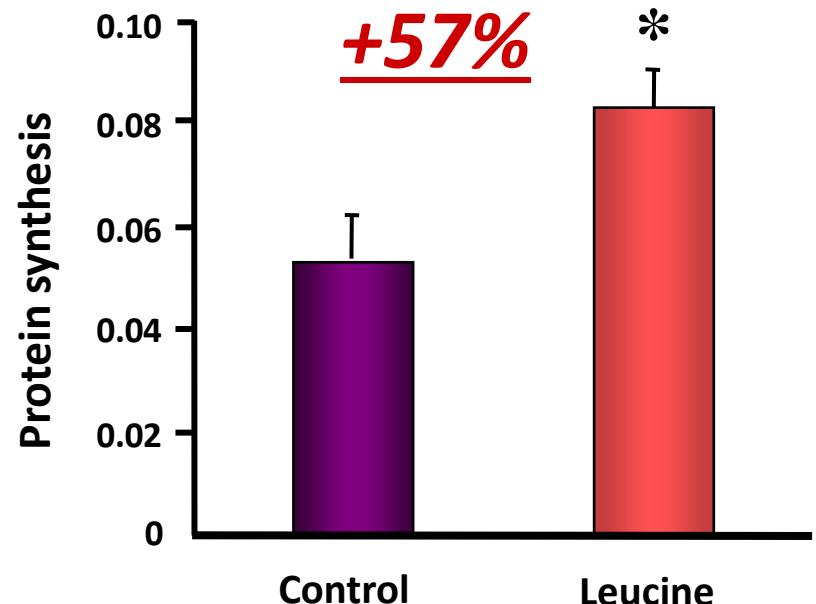
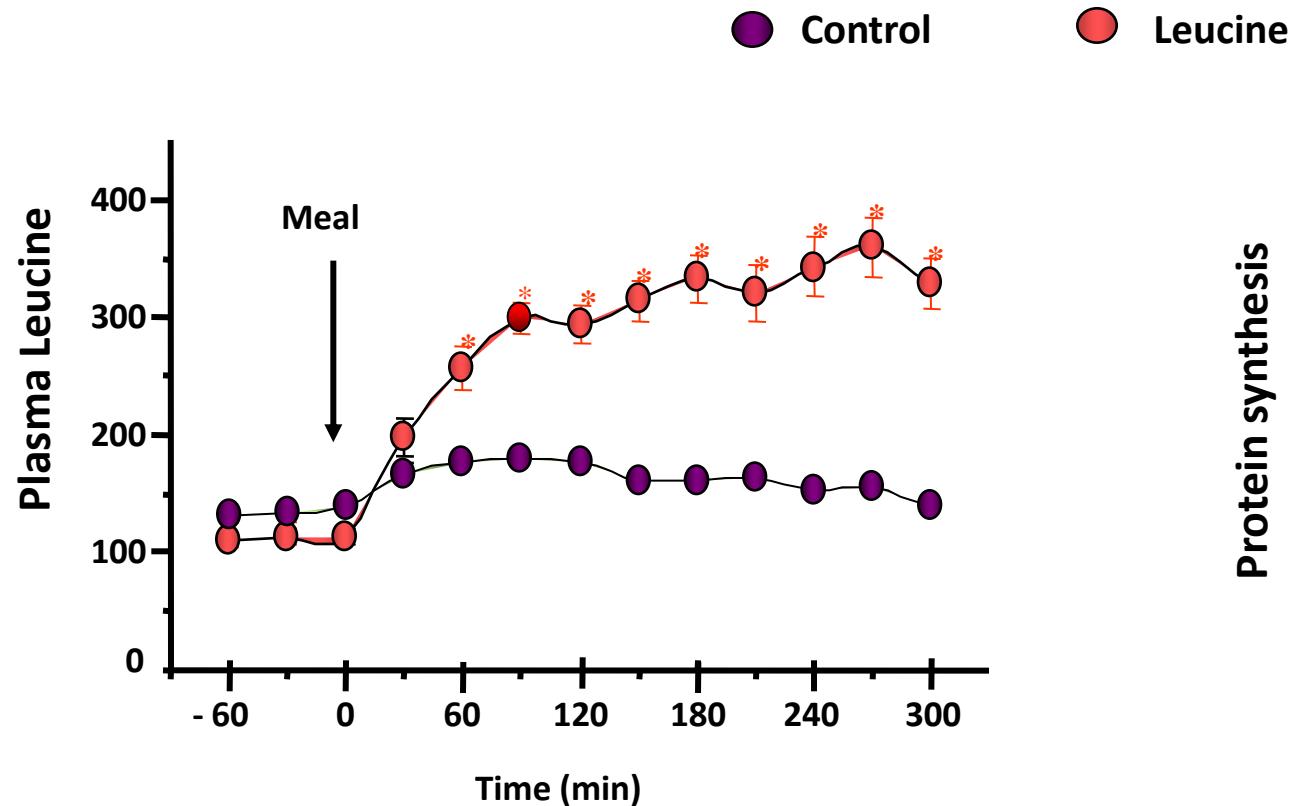
(Mosoni et al, 1995)

**Anabolic  
resistance**



# Leucine , Sarcopenia and Aging

Rieu et al, 2006  
Katsanos et al. 2006



# Leucine , Sarcopenia and Aging



**6 -10 months  
4.5% leucine in the  
diet**

**Negative on muscle mass**  
(Zeanandin et al. 2012)  
Vianna et al. 2011



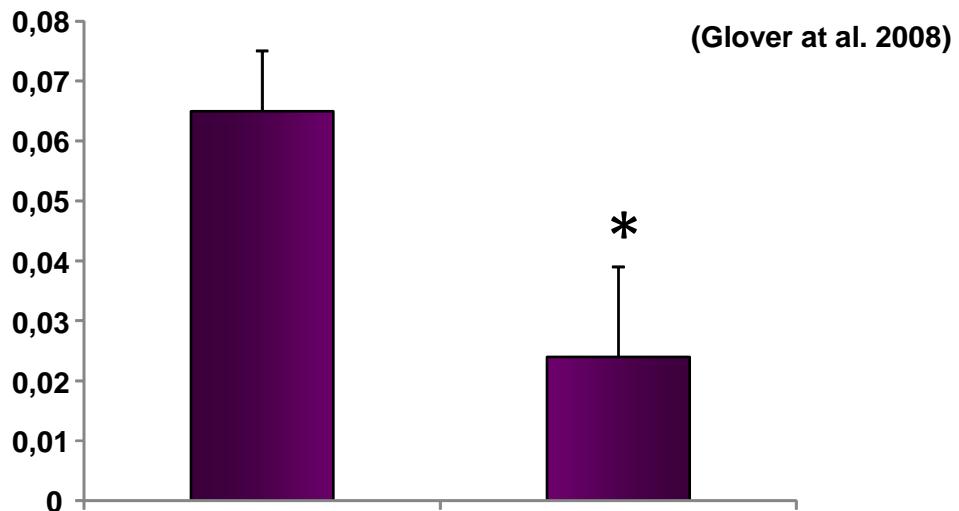
**3 months  
7.5 g leucine / day**

**Negative on muscle mass and  
strength**  
(Verhoven et al. 2009):

# Leucine, Muscle loss and Bed rest/Immobilization



## Post-prandial Stimulation of Muscle Protein Synthesis (% /h)



## Free Leucine supplementation

**3.1g leucine , 28 days:**  
Improvement of post prandial muscle protein synthesis  
No change in muscle mas loss

Paddon-Jones et al. 2004

**3.6g leucine , 60 days:**  
No change in muscle mas loss

Trappe et al. 2007

**3.6g leucine , 60 days:**  
No change in muscle strength

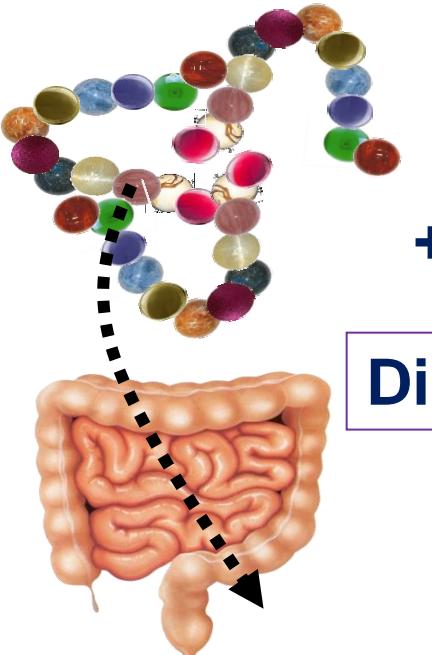
Trappe et al. 2008

**4,5% leucine in the diet**  
No change in muscle mass recovery

Magne et al. 2012



# Why free leucine can be disappointing?



+ Leucine

Digestion time

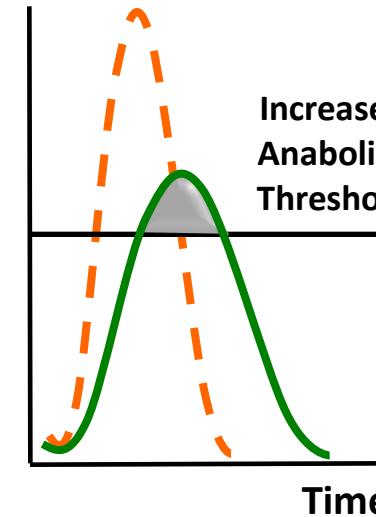


20 amino acids

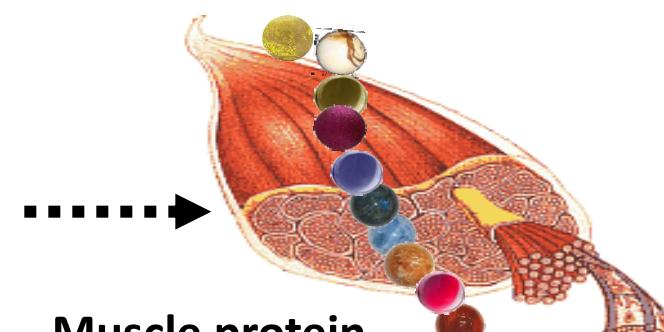


Leucine

Increased Anabolic Threshold



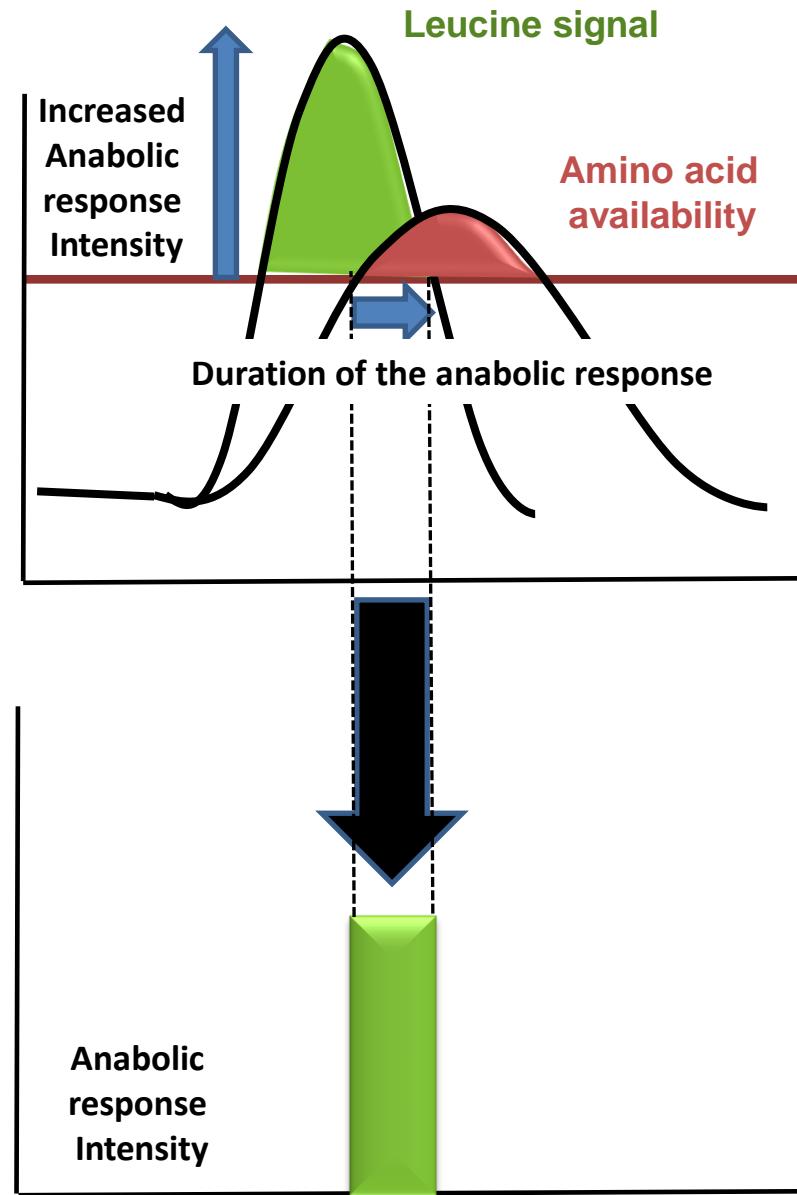
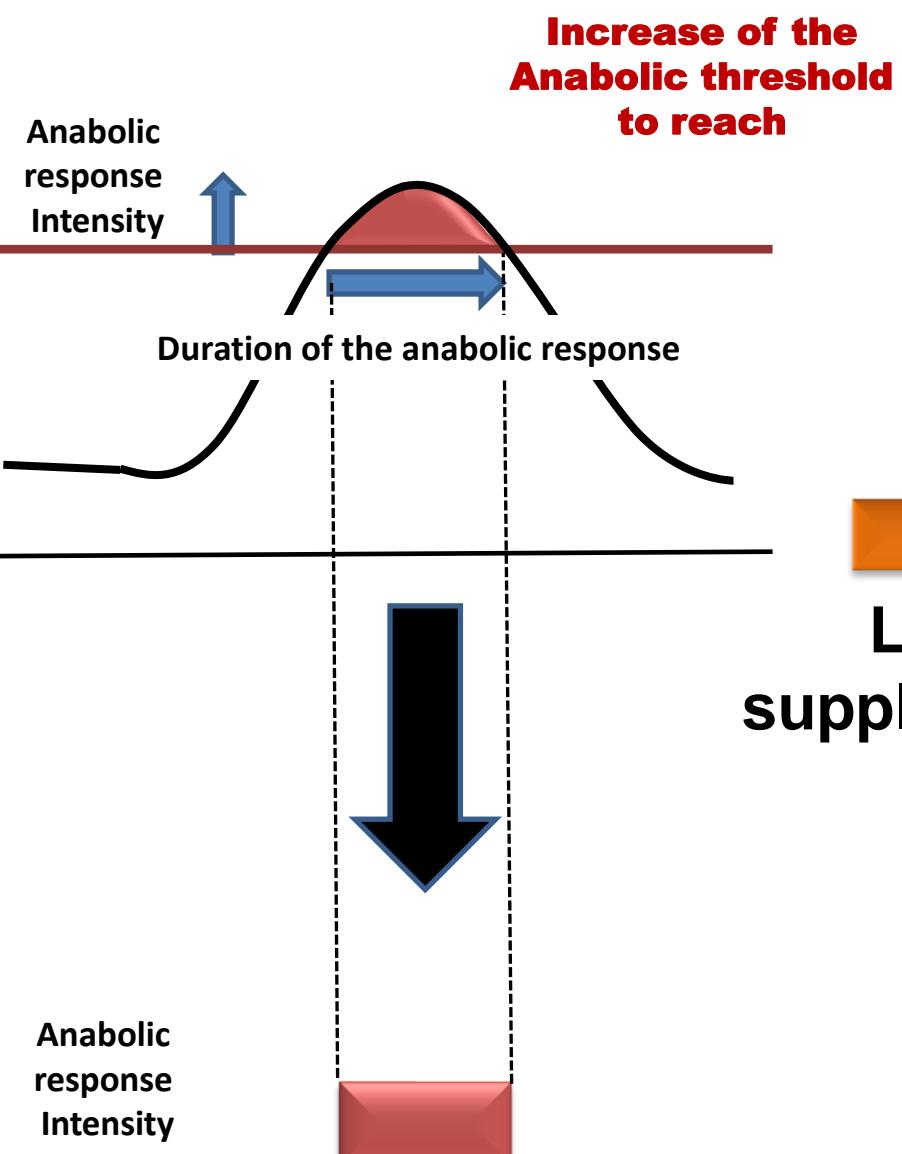
Other Amino acids



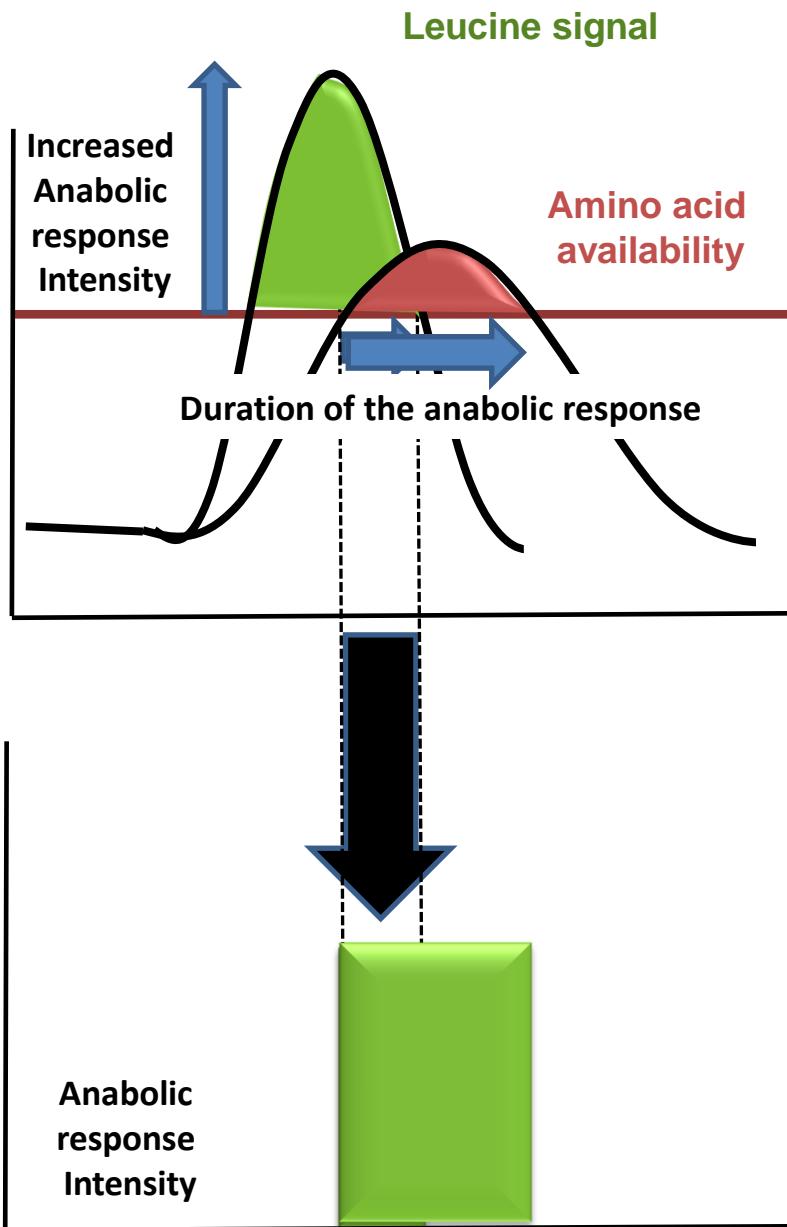
Muscle protein synthesis

# Why free leucine supplementation disappointing?

Dardevet et al. Scientific World Journal, 2012



# Resynchronisation leucine signal/amino acids



Synchronization  
possible with leucine  
rich proteins rapidly  
digested

Whey Proteins

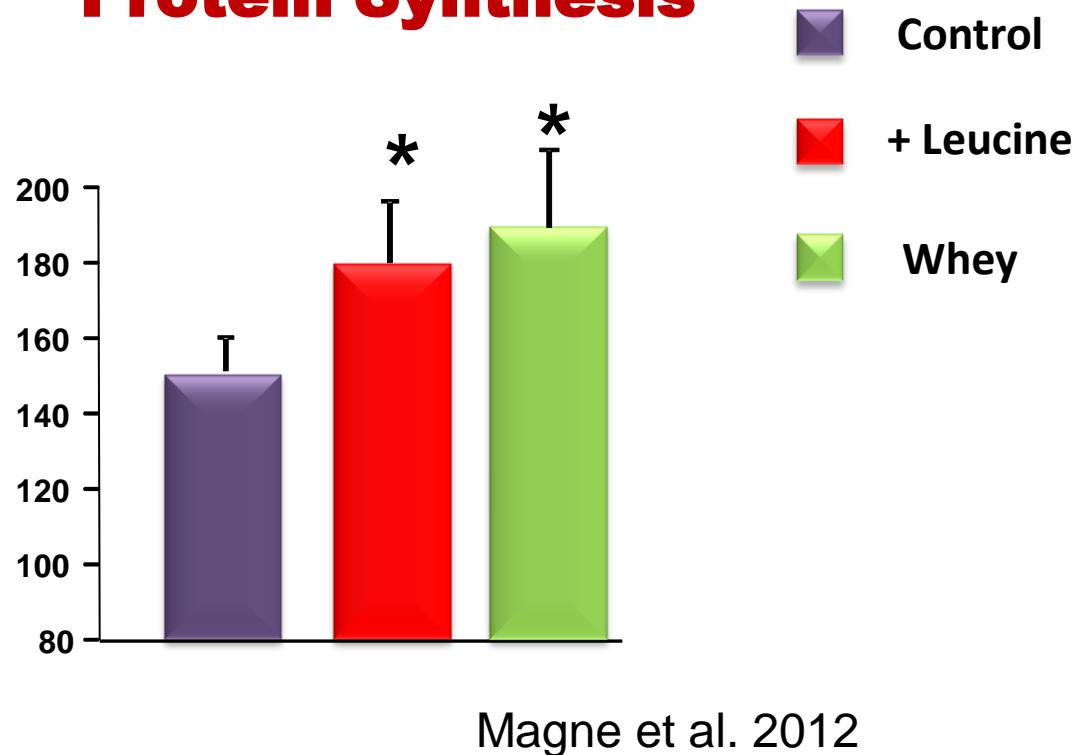


# Leucine supplementation with whey

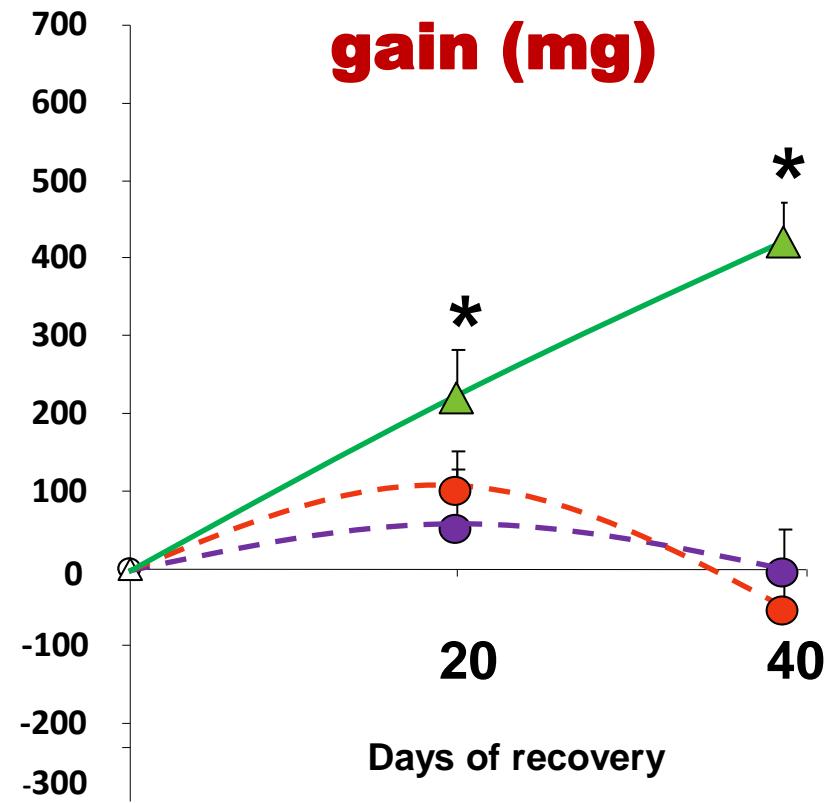
## Muscle Recovery Post-immobilization

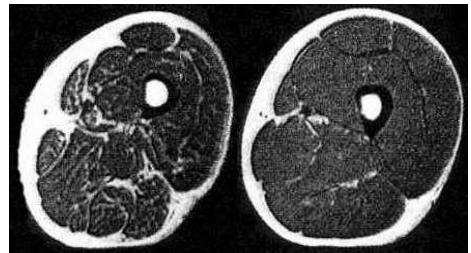


### Post prandial Protein Synthesis



### Muscle mass gain (mg)



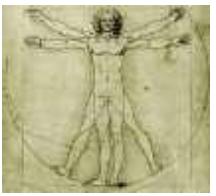


# Leucine supplementation with whey

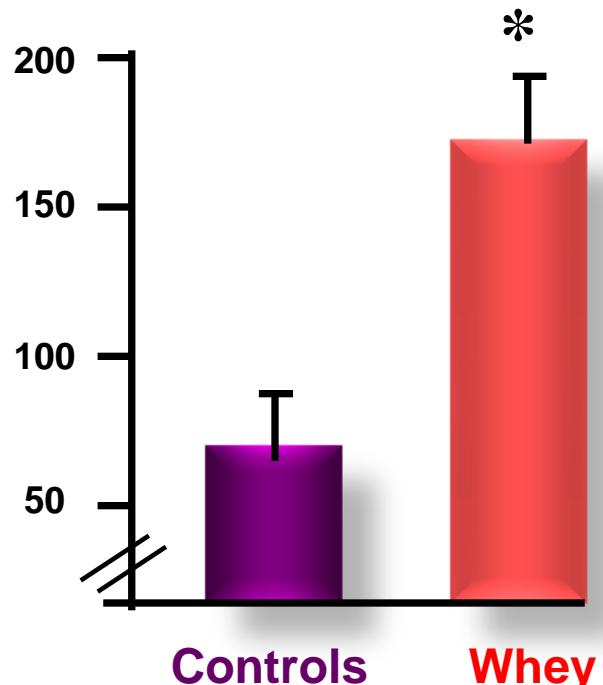
## Sarcopenia and Aging



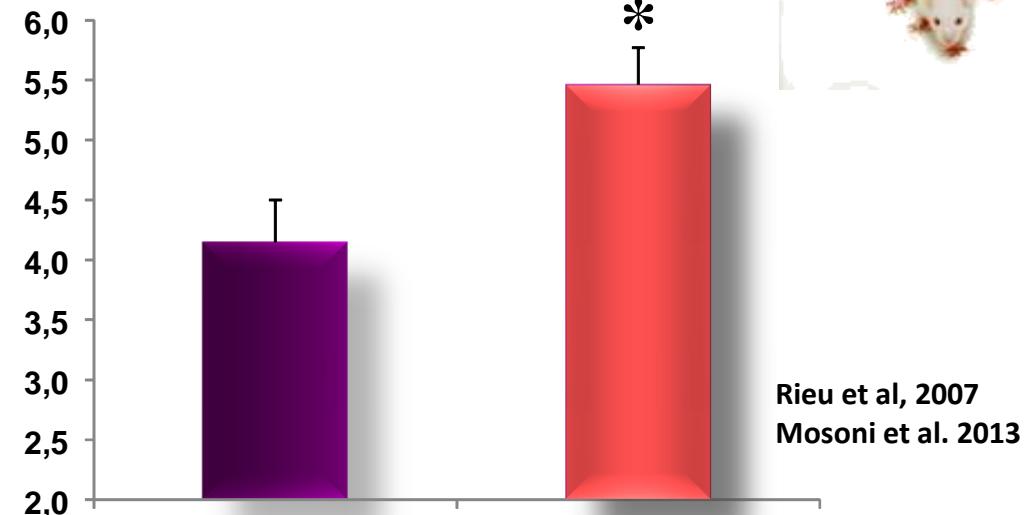
### Protein Synthesis



### Protein Synthesis



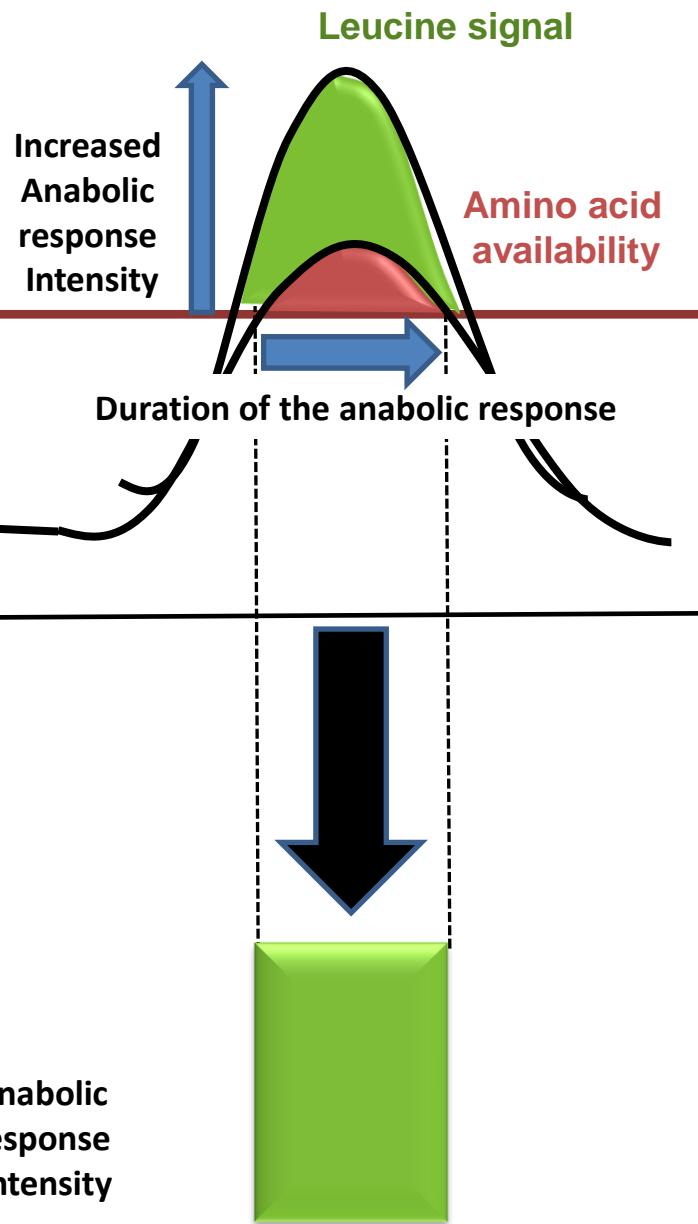
Dangin et al., 2002, 2003; Boirie et al, 1997



### Muscle mass (10 d or 6 months)



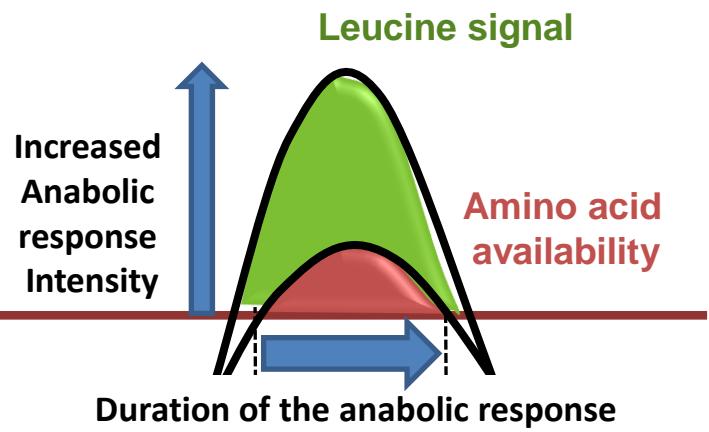
# When Resynchronisation remained inefficient?



## Duration of the anabolic response?

- Decrease of the anabolic threshold
- Increase more the protein intake
- Interaction between protein and energy intake

# When Resynchronisation is inefficient?

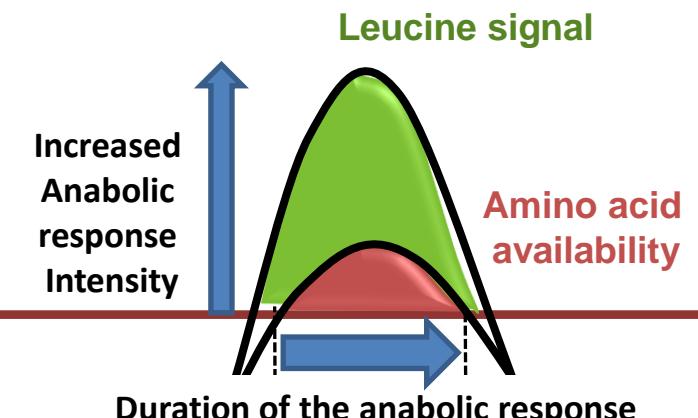


Duration of the anabolic response

**Duration of the  
anabolic  
response?**

Anabolic  
response  
Intensity

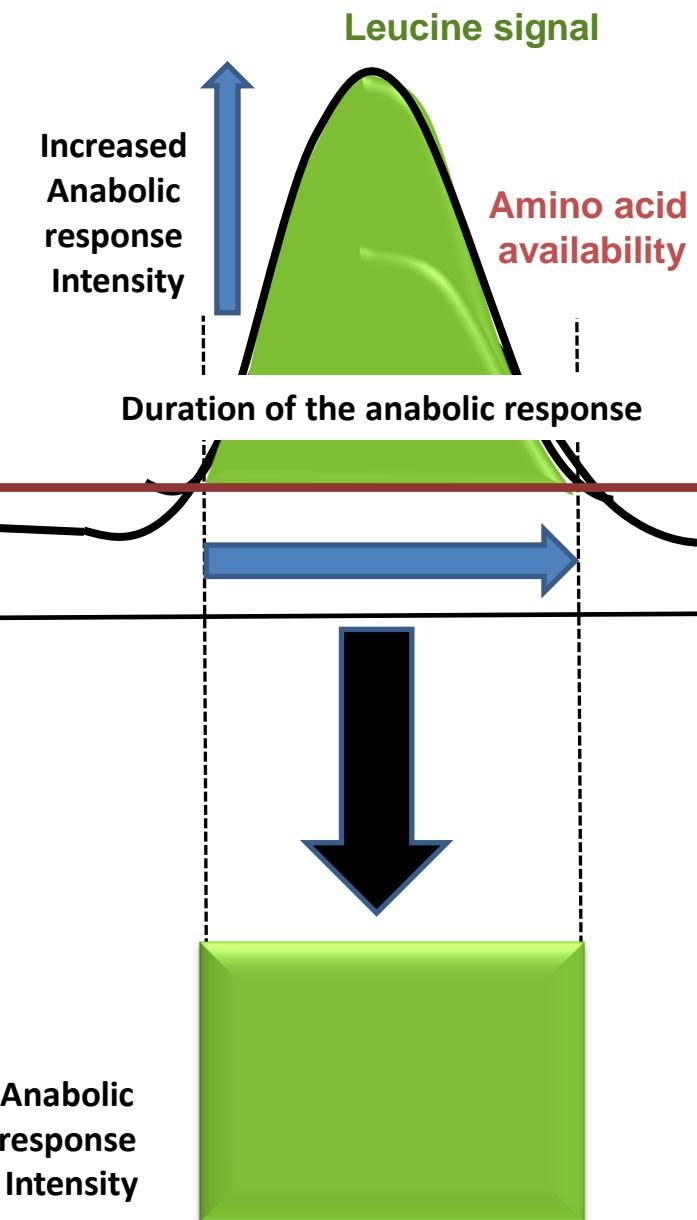
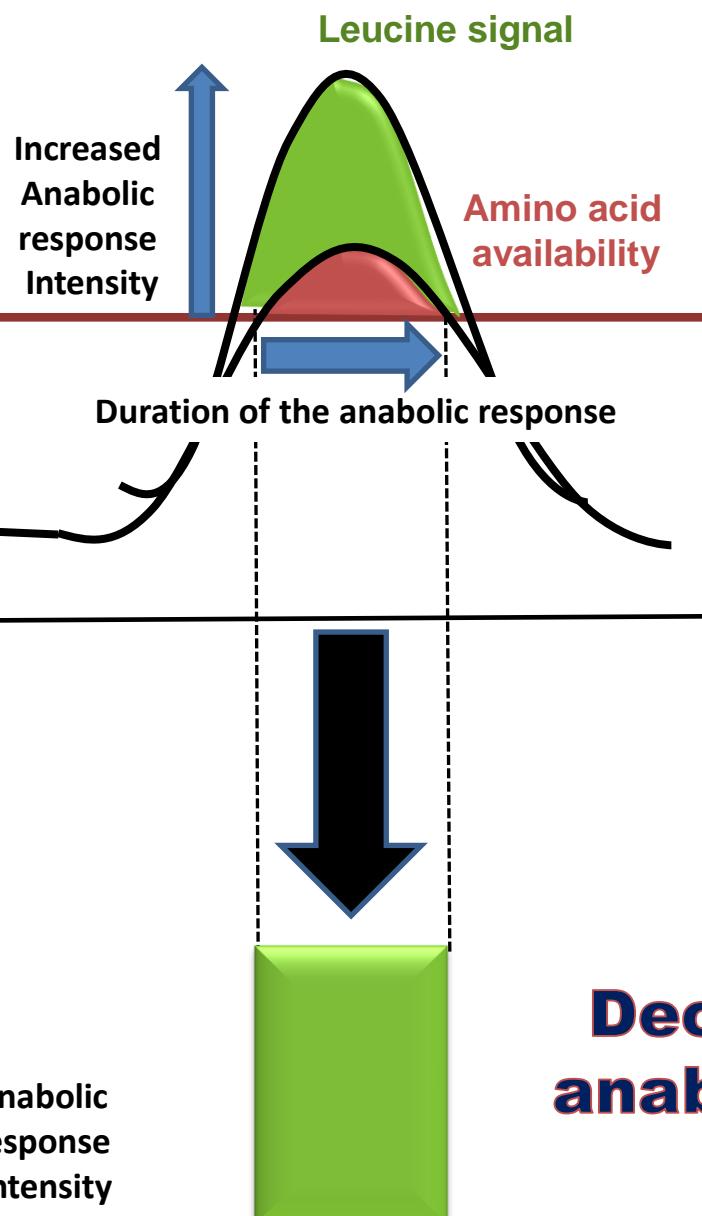
**Decrease the  
anabolic threshold**



Duration of the anabolic response

Anabolic  
response  
Intensity

# When Resynchronisation is inefficient?



**Decrease of the anabolic threshold**

# How to decrease the anabolic threshold?

Most of the situations of muscle loss are associated with an increase of :

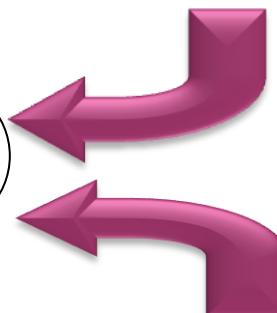
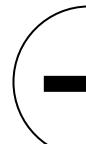
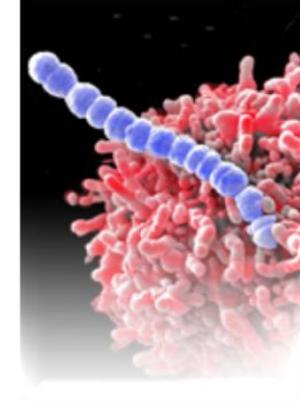
## Inflammation and Oxidative Stress

Muscle Anabolism

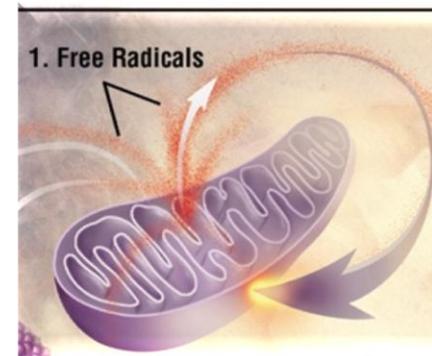


Cytokines  $\text{TNF}\alpha$ ,  $\text{IL}_1$ ,  $\text{IL}_6$

Inflammation



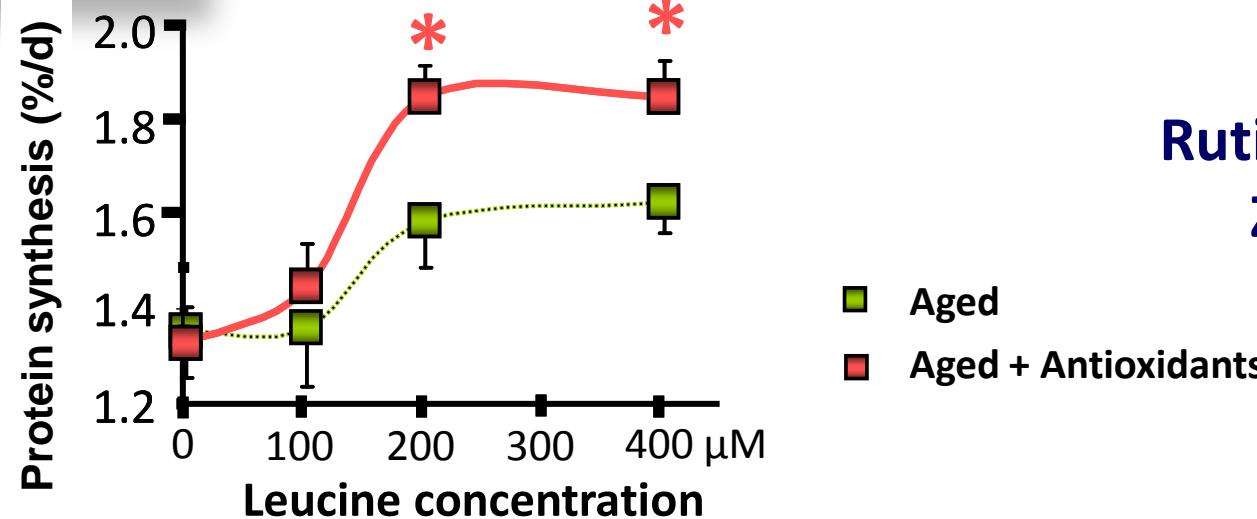
$\text{O}_2^-$



Oxidative Stress

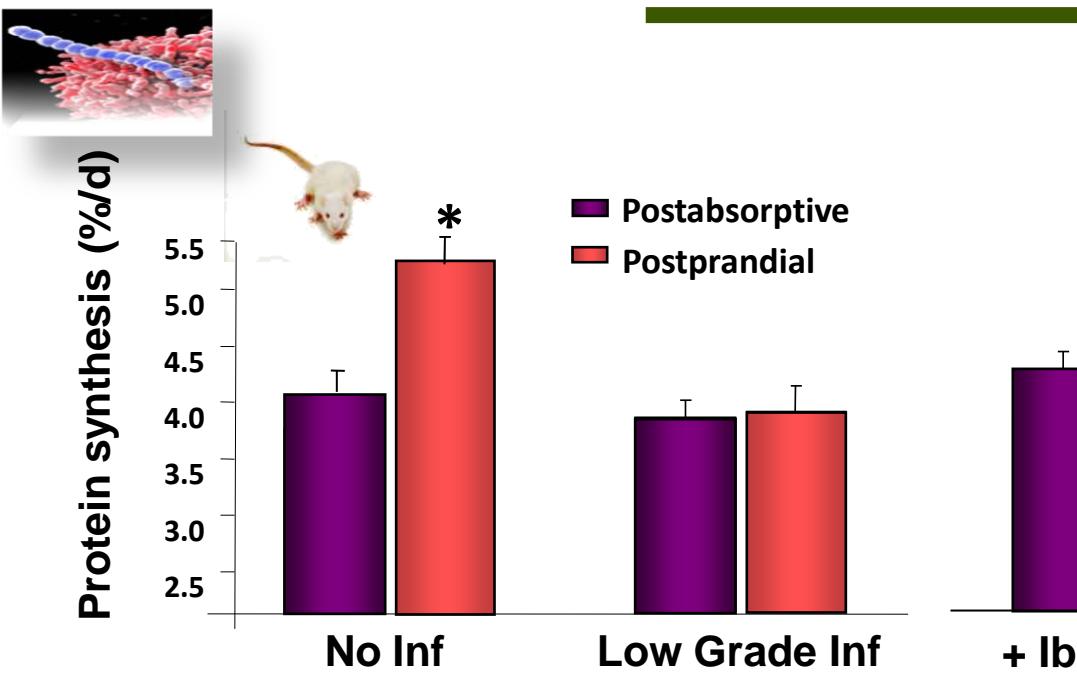


# How to decrease the anabolic threshold?

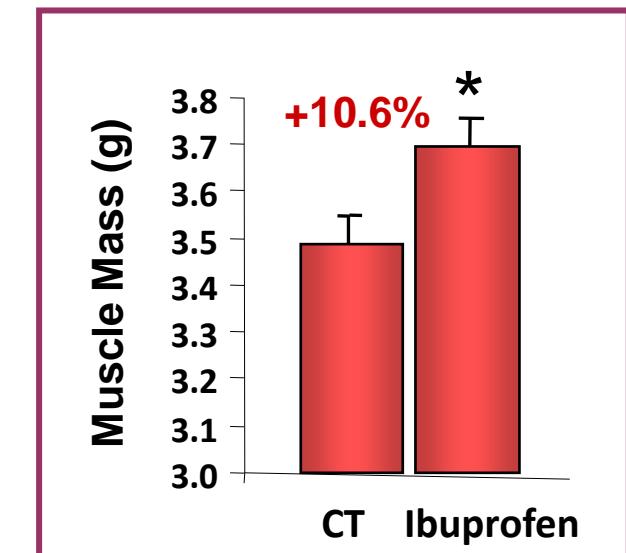


Marzani et al. J Nutr 2008  
Mosoni et al. Nutrition, 2010

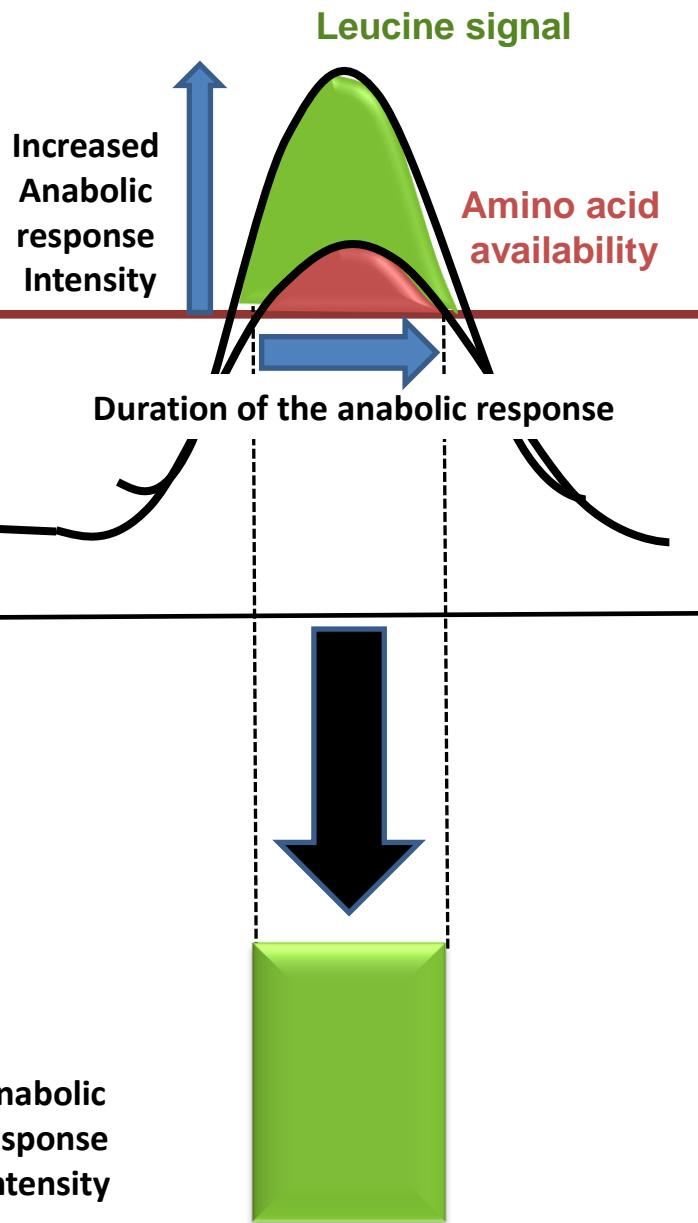
Rutin, vitamin E, vitamin A,  
Zn et Se for 7 weeks



Rieu I, J Physiol 2009  
Balage et al. JNB, 2010



# When Resynchronisation is inefficient?

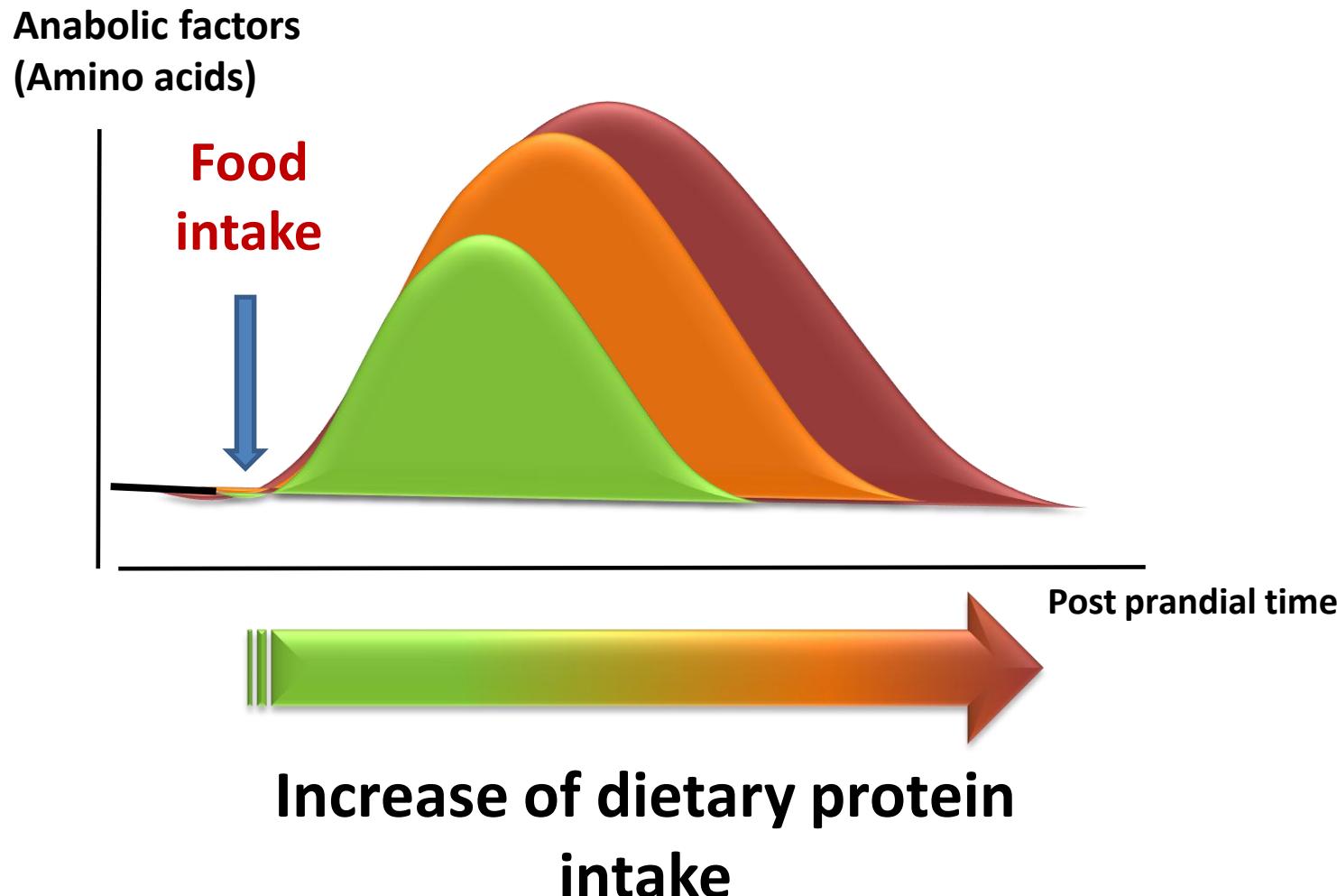


**Duration of the anabolic response?**

➡ **Increase more the protein intake?**

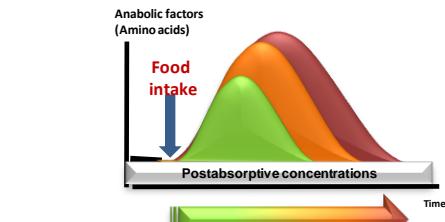
# High protein diet: The protein pulse feeding?

(Arnal et Mosoni 1999, 2000, 2002)



# The protein pulse feeding?

Dardevet et al. Scientific World Journal, 2012



Anabolic response Intensity

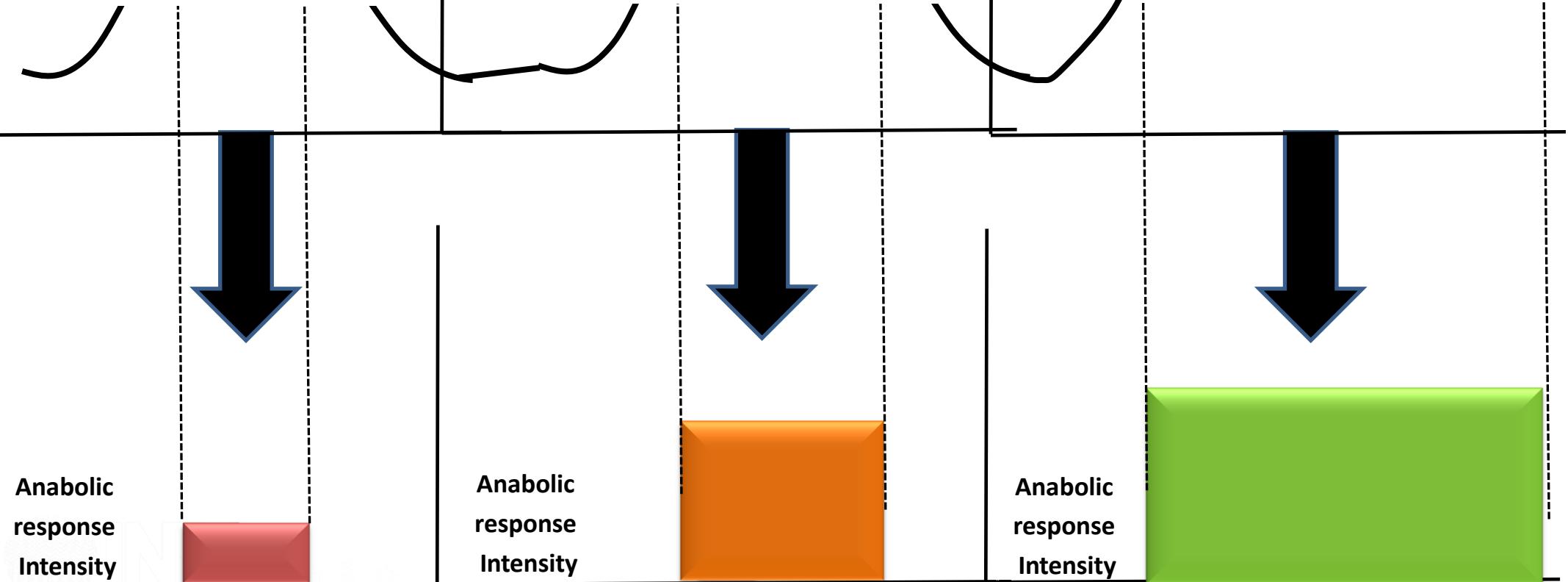
Anabolic response Intensity

Anabolic response Intensity

Duration of the anabolic response

Duration of the anabolic response

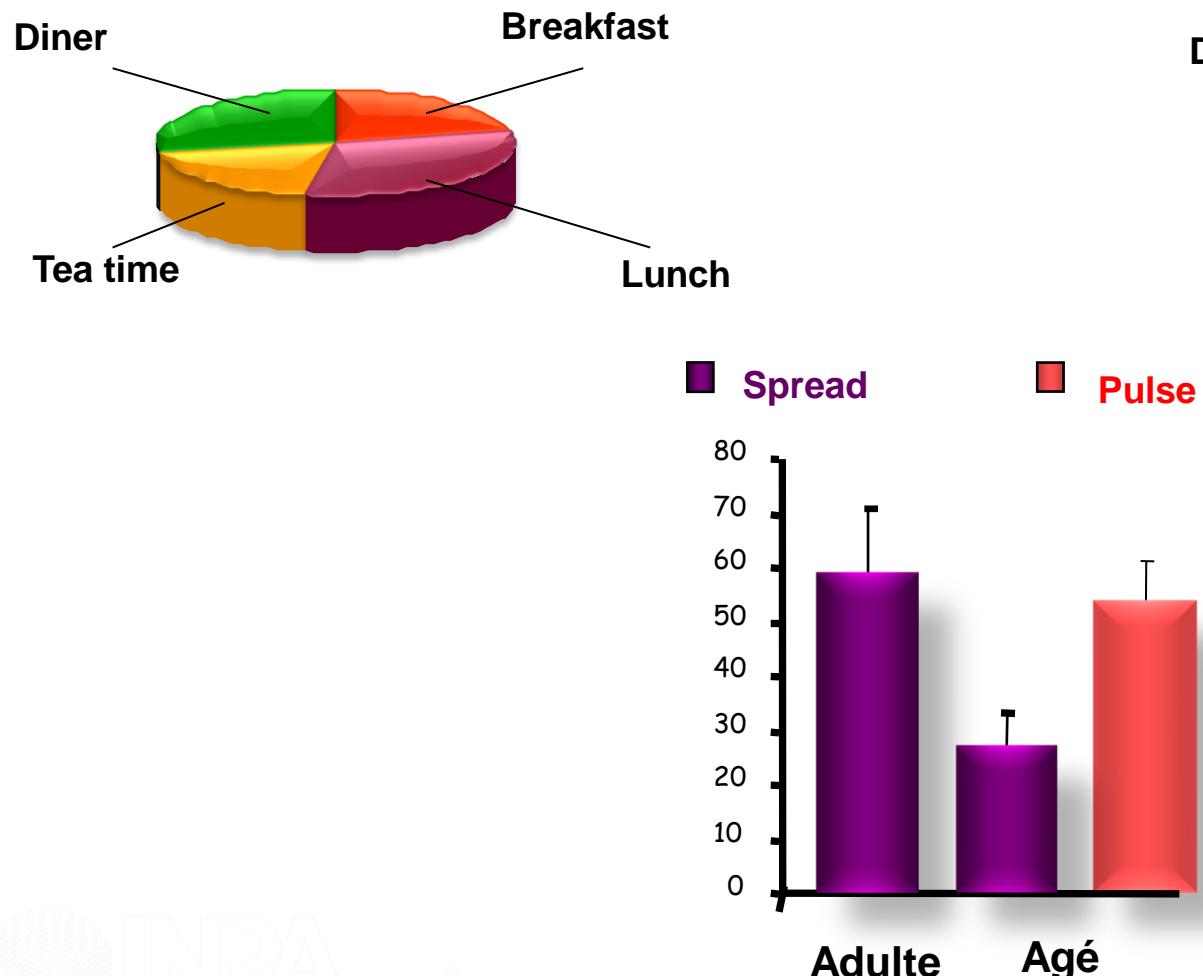
Duration of the anabolic response



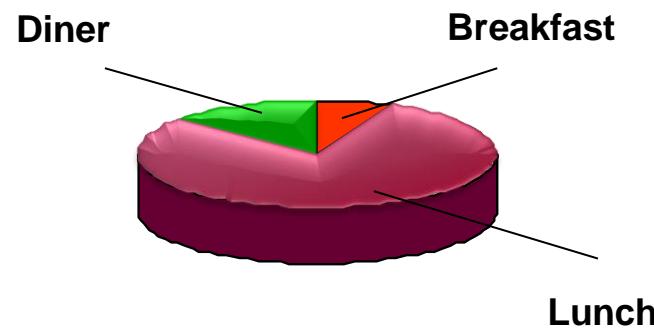
# The protein pulse feeding?

## Increase of the dietary protein intake

### Spread protein diet

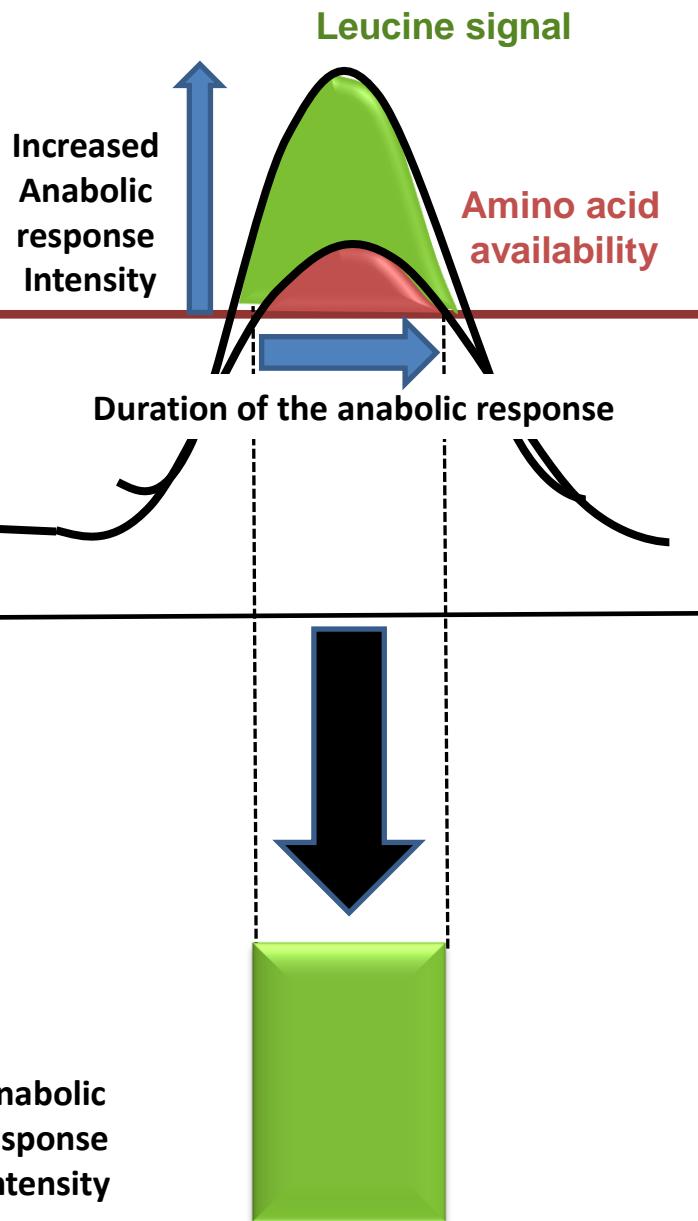


### Pulse protein diet



(Arnal et al. 1999,2002  
Bouillanne et al. 2013)

# When Resynchronisation is inefficient?



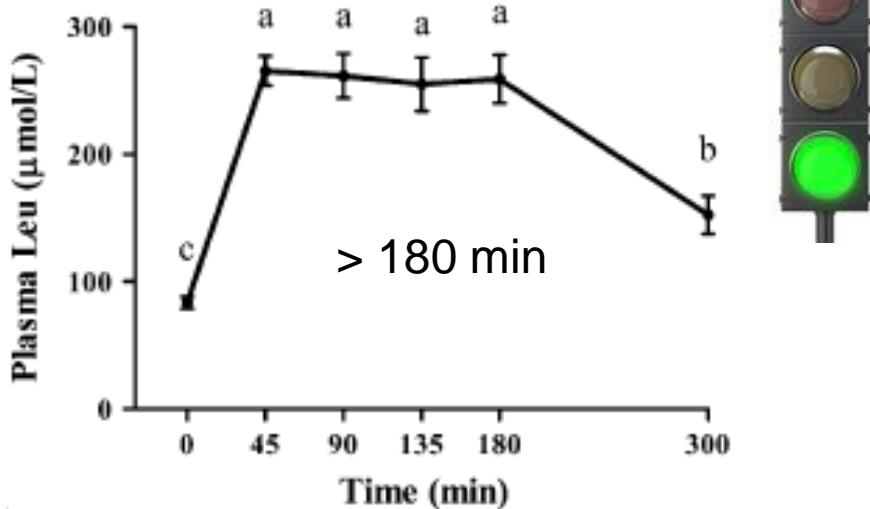
**Duration of the anabolic response?**

■ **Interaction with protein and energy intake?**

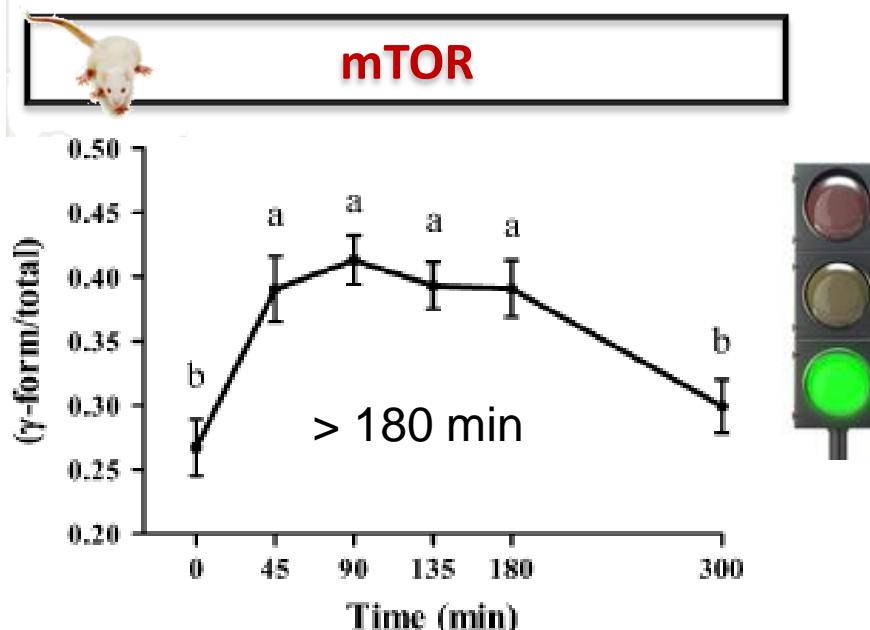
# When Resynchronisation is inefficient? Whey too fast?



Amino acids



Muscle protein synthesis

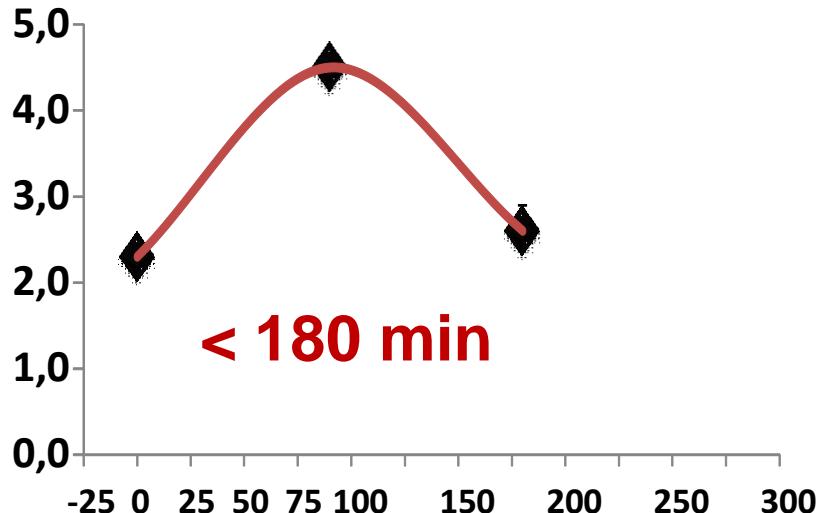


Existence of « Stop Signals »  
stronger than the anabolic  
signals !!

Wilson et al. 2010; Atherton et al. 2010

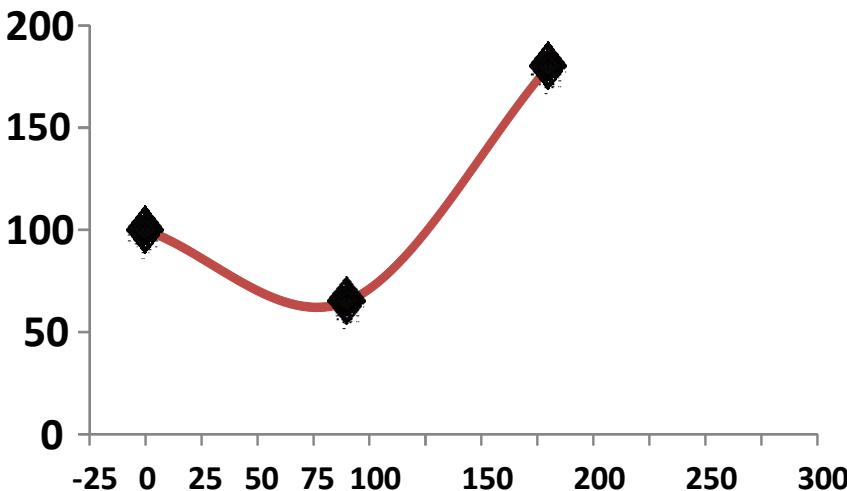
# What is the “Stop signal”?

Muscle protein synthesis



< 180 min

AMPK activity



AMPK



Activity increases when ATP decreases

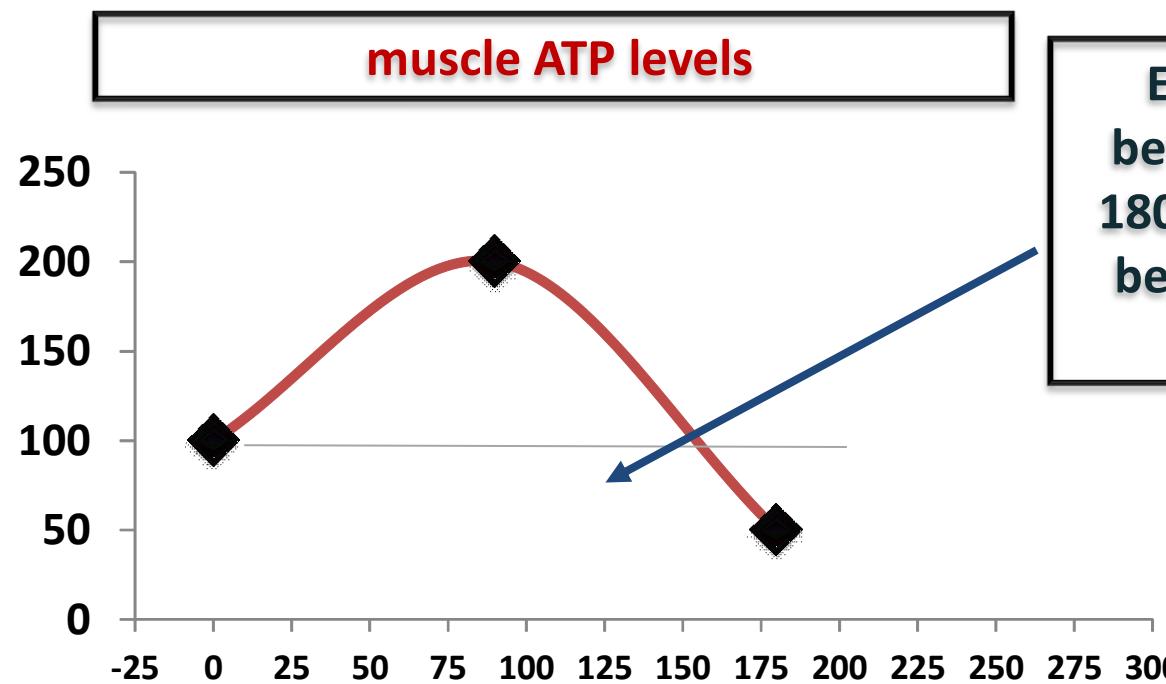
Protein synthesis has a high energetic cost

Protection mechanism?

# Nutritional strategy to take into account AMPK?

**Prevent the AMPK activity to increase**

**Maintain the muscle ATP levels as long as possible during the post prandial period**

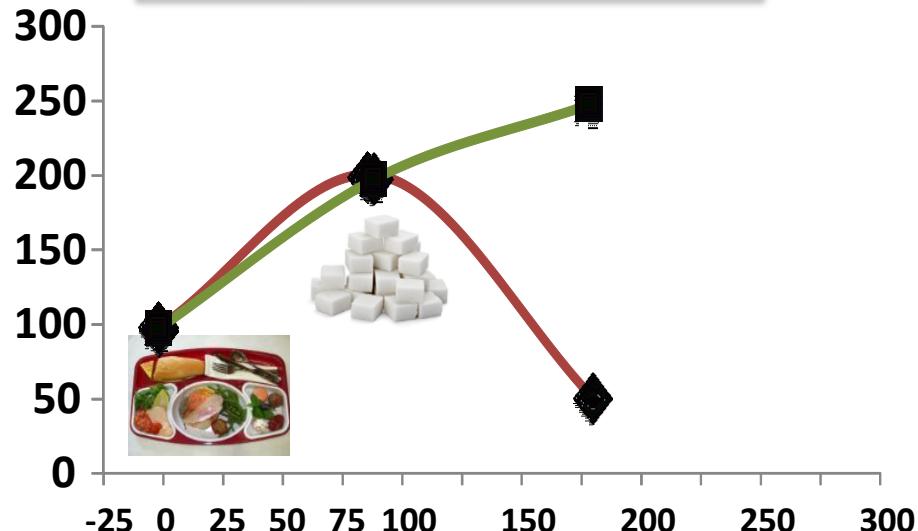


**Energy intake  
between 90 and  
180 min after the  
beginning of the  
meal**

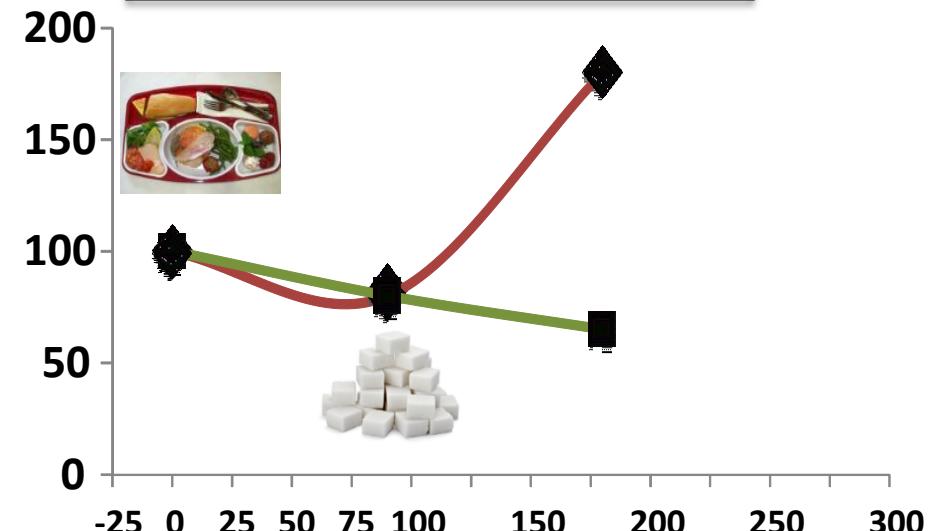


# Energetic chrononutrition?

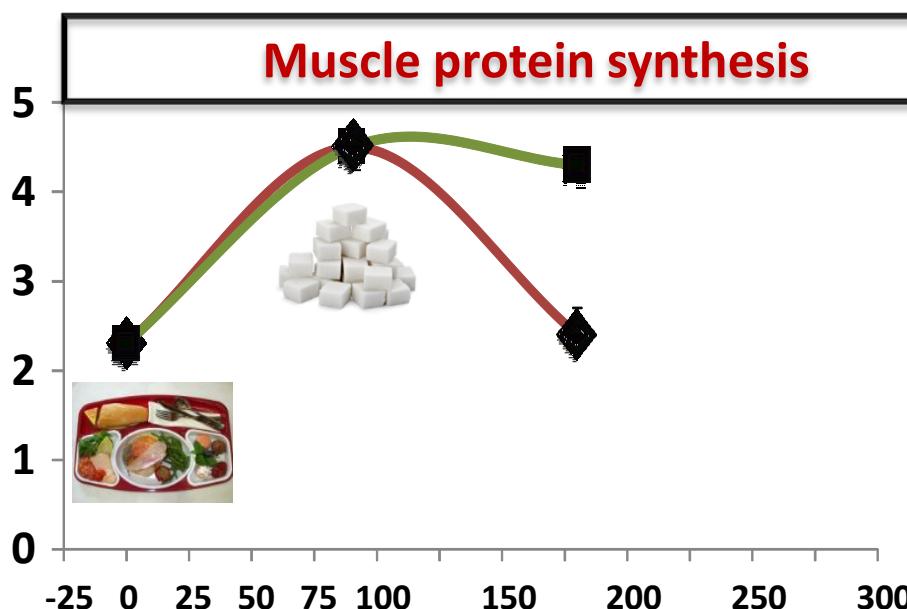
Muscle ATP



AMPK



Muscle protein synthesis



■ Meal with whey proteins

■ Meal with whey proteins and energetic bolus 90 min later

- A nutritional strategy efficient in one situation of muscle wasting may not be efficient in an another one

Intensity of the anabolic resistance

Duration of this anabolic resistance

---

- Leucine is indeed a very good stimulator muscle protein synthesis
- 

- If leucine given as a free amino acid over a normal protein diet

May be inefficient in several situations

Desynchronization with the other amino acids

---

- Synchronization of leucine with the other amino acids is possible with leucine rich proteins

Whey

---

# Dietary Whey supplementation: Matrix effect?

## Process of the milk protein sources

Milk



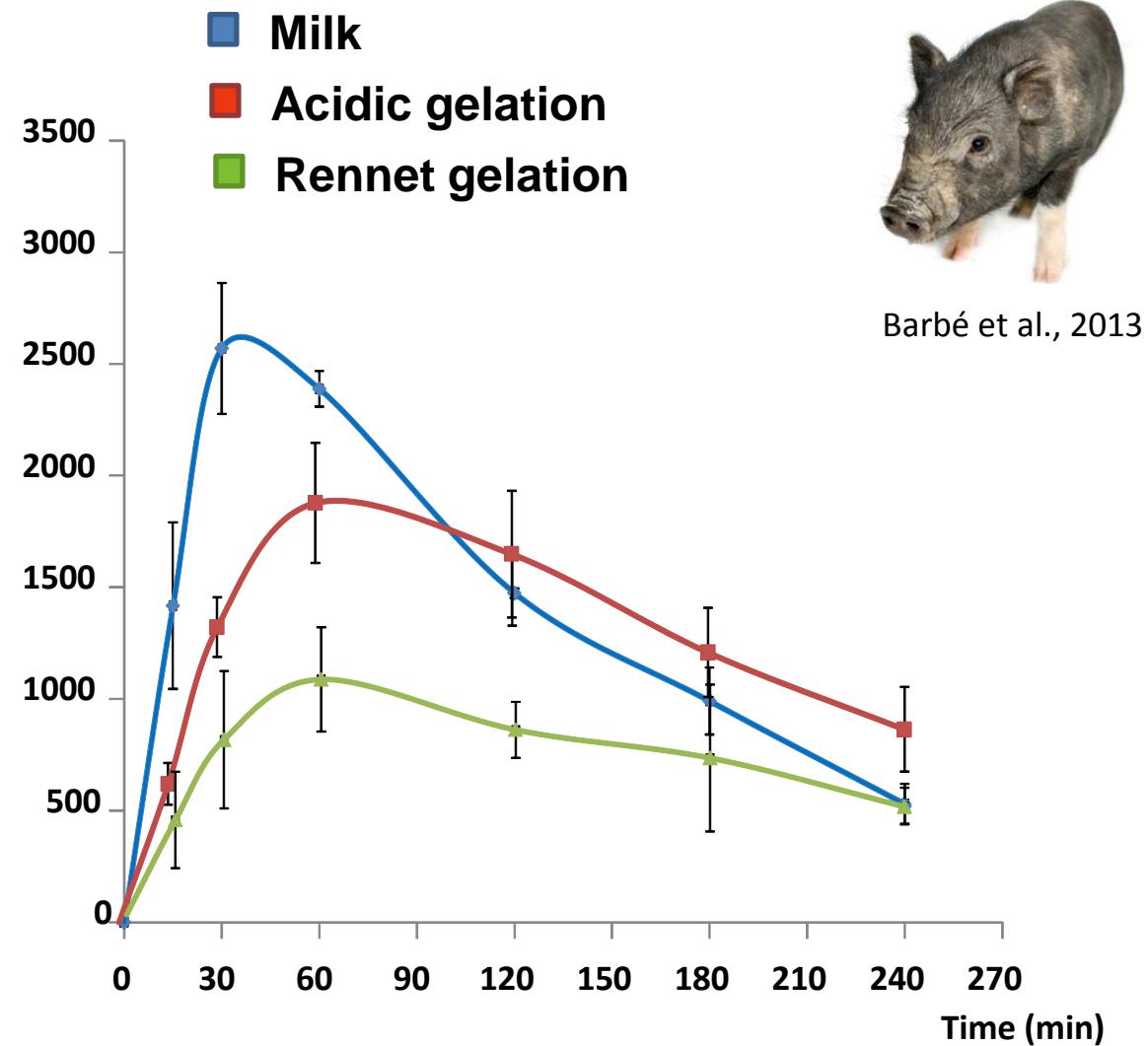
Milk  
Gelation



Gelation



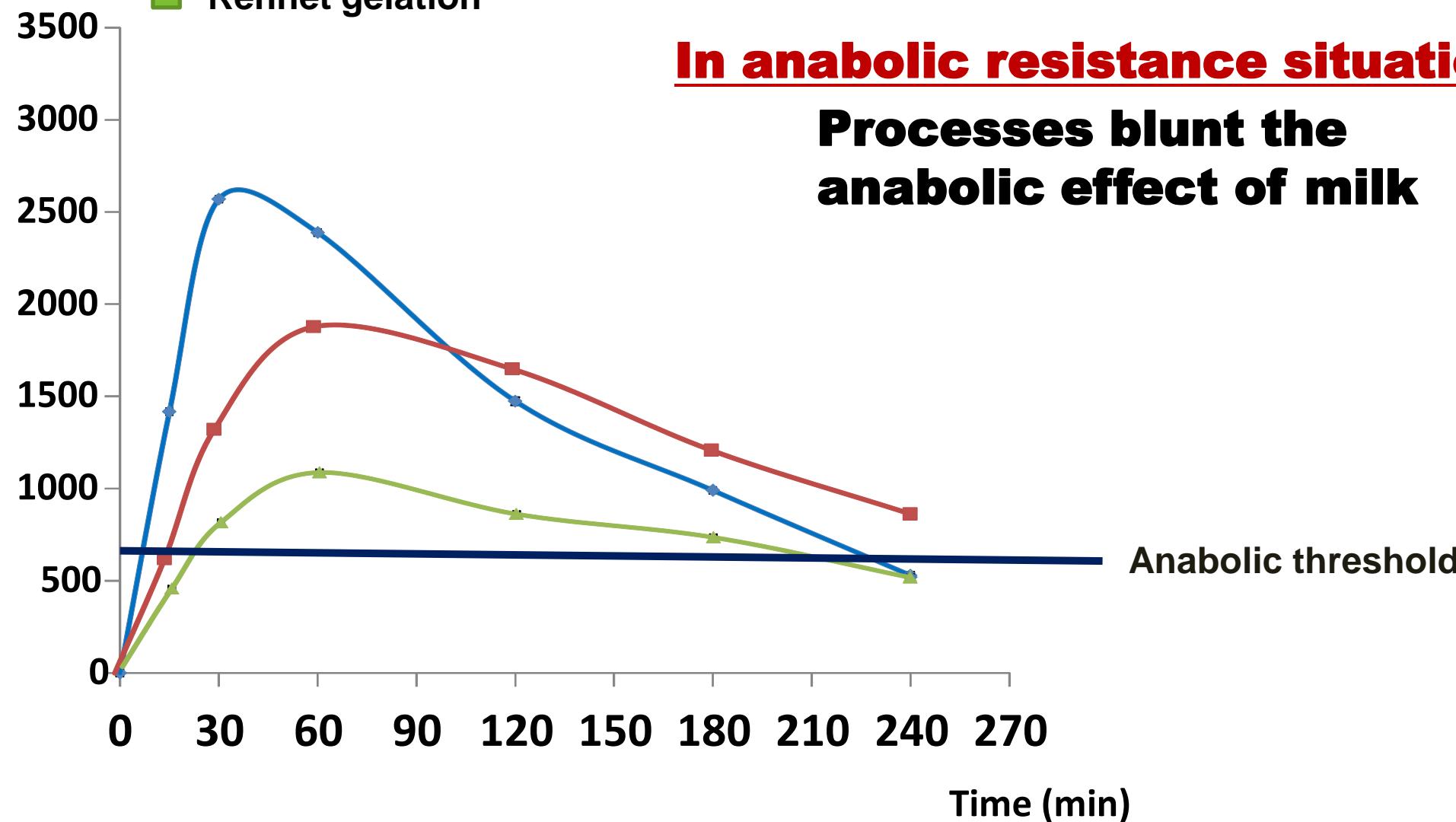
Decreased digestion speed  
Decreased of amino acid bioavailability



Barbé et al., 2013

# Matrix effect: Which consequences ?

- Milk
- Acidic gelation
- Rennet gelation



**In normal healthy situations**

**Processes has limited impact**

**In anabolic resistance situations**

**Processes blunt the anabolic effect of milk**

Anabolic threshold

- Prolonged and better efficiency of whey proteins if the anabolic threshold is also controlled

## Combination whey and anti-inflammatory and antioxidants

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- So far, only the pulse protein feeding is efficient during aging

Feasibility? In other muscle loss situations?

Long term effect ?

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- An energetic chrononutrition has to be tested in combination with whey proteins in (a) real muscle wasting situation(s)

Could the « Stop signal » be a target?

Presence of insulin resistance? (prevention of ATP to increase?)

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- Unknown is the effet of dietary chronic leucine bioavailability

Pro diabetic? Insulin resistance?

# UNH

# Unité de Nutrition Humaine

## *Métabolismes & Santé*

# Thank you

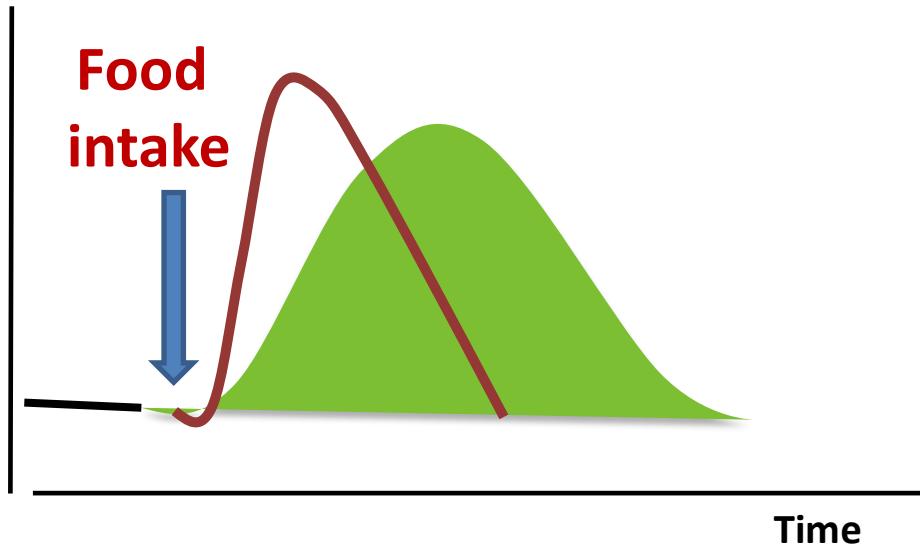


UNH 1019



# Measurement of post prandial protein synthesis in steady state

Anabolic factors  
(Amino acids)



With free leucine into the diet

