57° CONGRESSO NAZIONALE SIGG

Milano Convention Center

21-24 novembre 2012

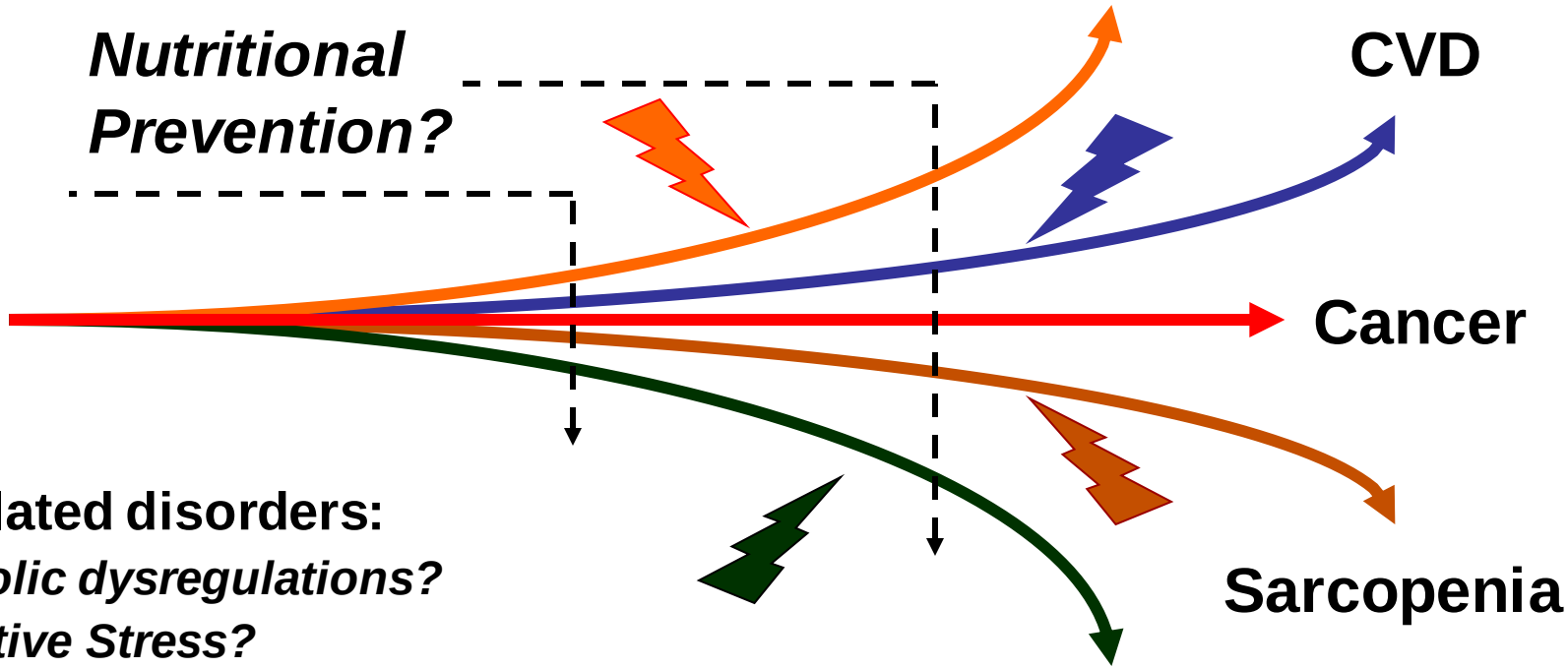
Nutrition: an essential strategy to fight Frailty

Pr. Yves Boirie

Human Nutrition Unit, Clinical Nutrition Department

University Hospital of Clermont-Ferrand, France

Role of preventive nutrition for a healthy aging

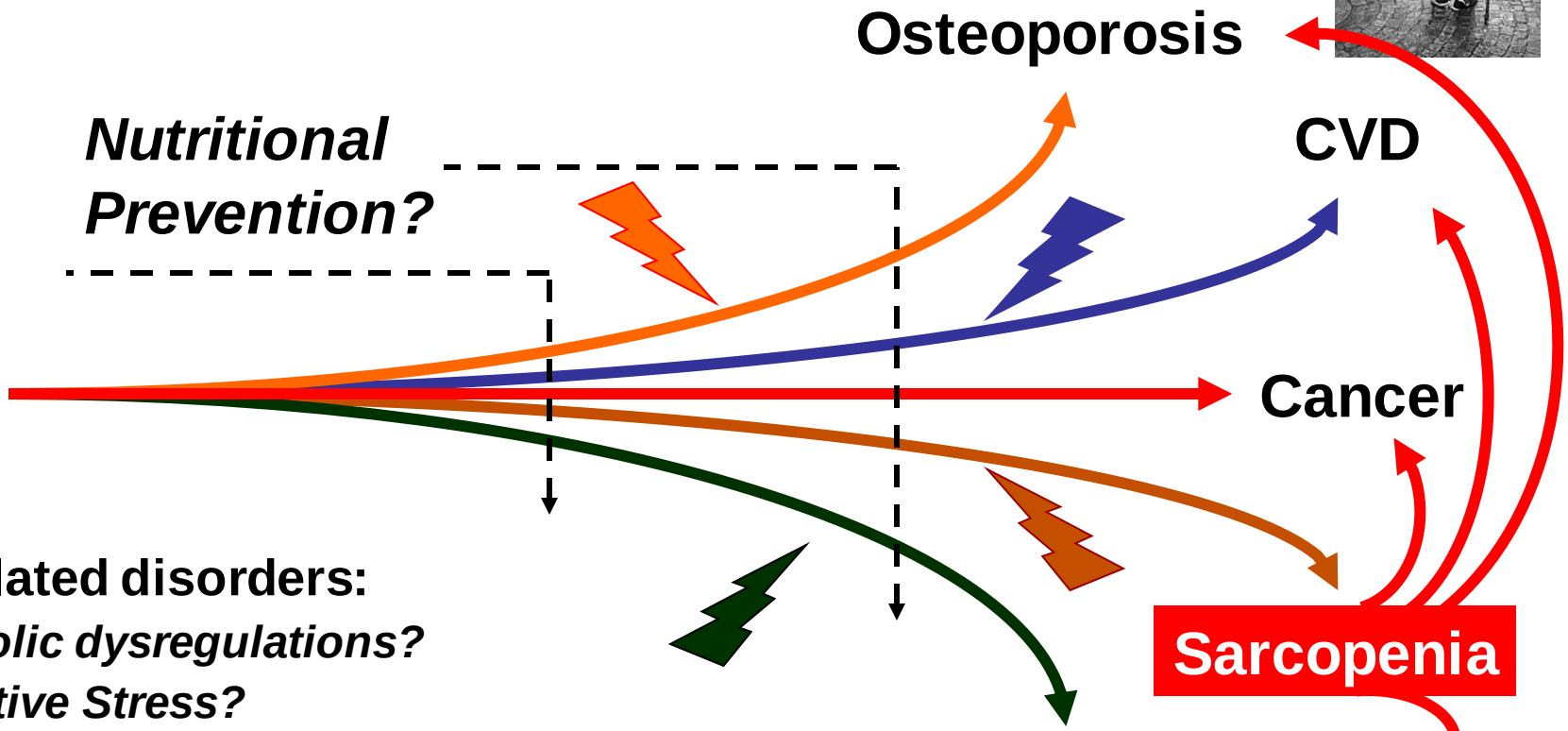


Age-related disorders:

- ***Metabolic dysregulations?***
- ***Oxydative Stress?***
- ***Inflammation?***
- ***Physical inactivity?***

Physiology ***Dysfunction*** ***Disease***

Role of preventive nutrition for a healthy aging



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Physiology ***Dysfunction*** ***Disease***

Nutrition and Frailty

- **Targeting muscle in elderly patients**
- **Anabolic resistance to nutrients**
- **Synergistical strategies**

Nutrition and Frailty

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- **Anabolic resistance to nutrients**
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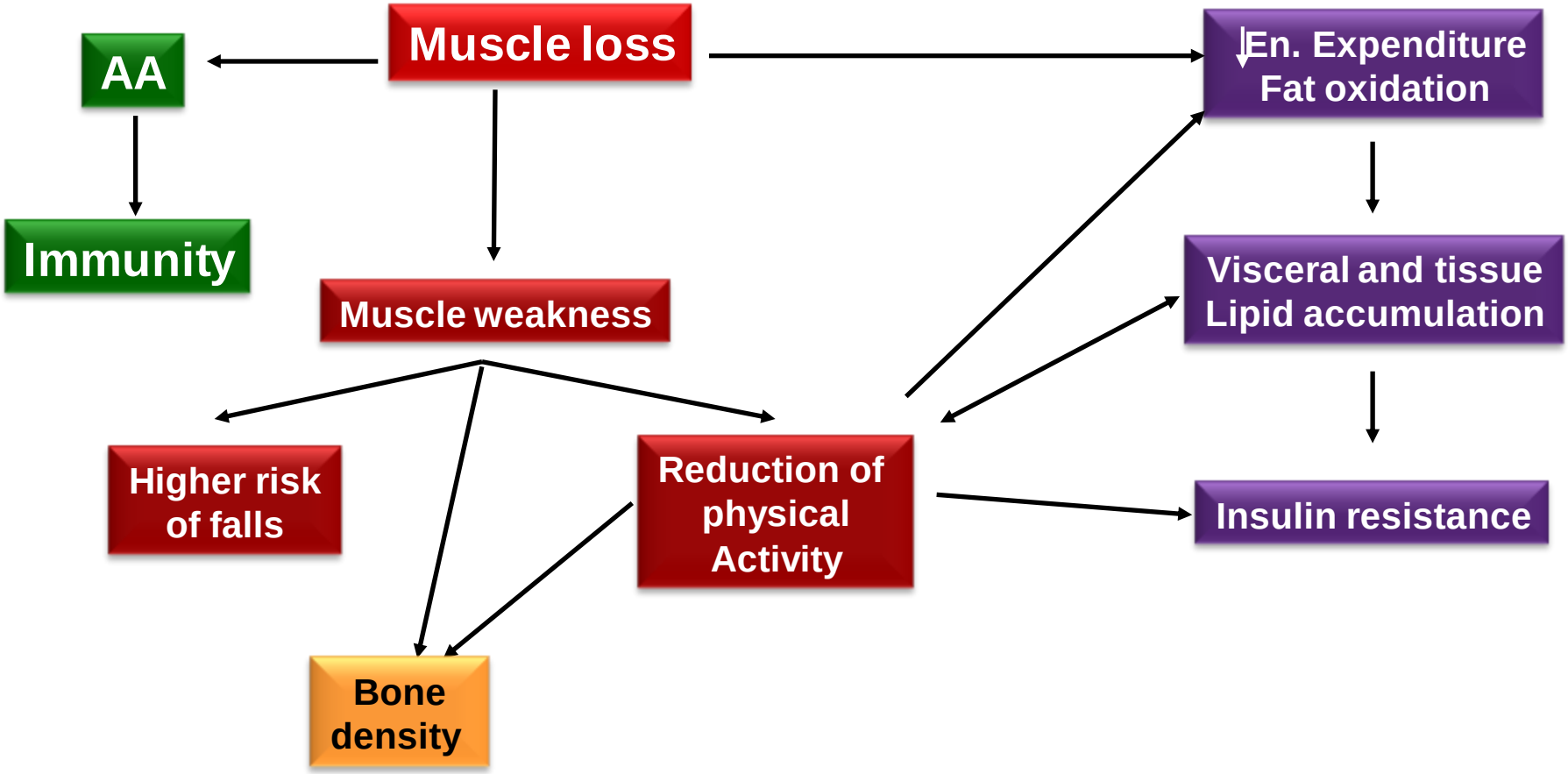
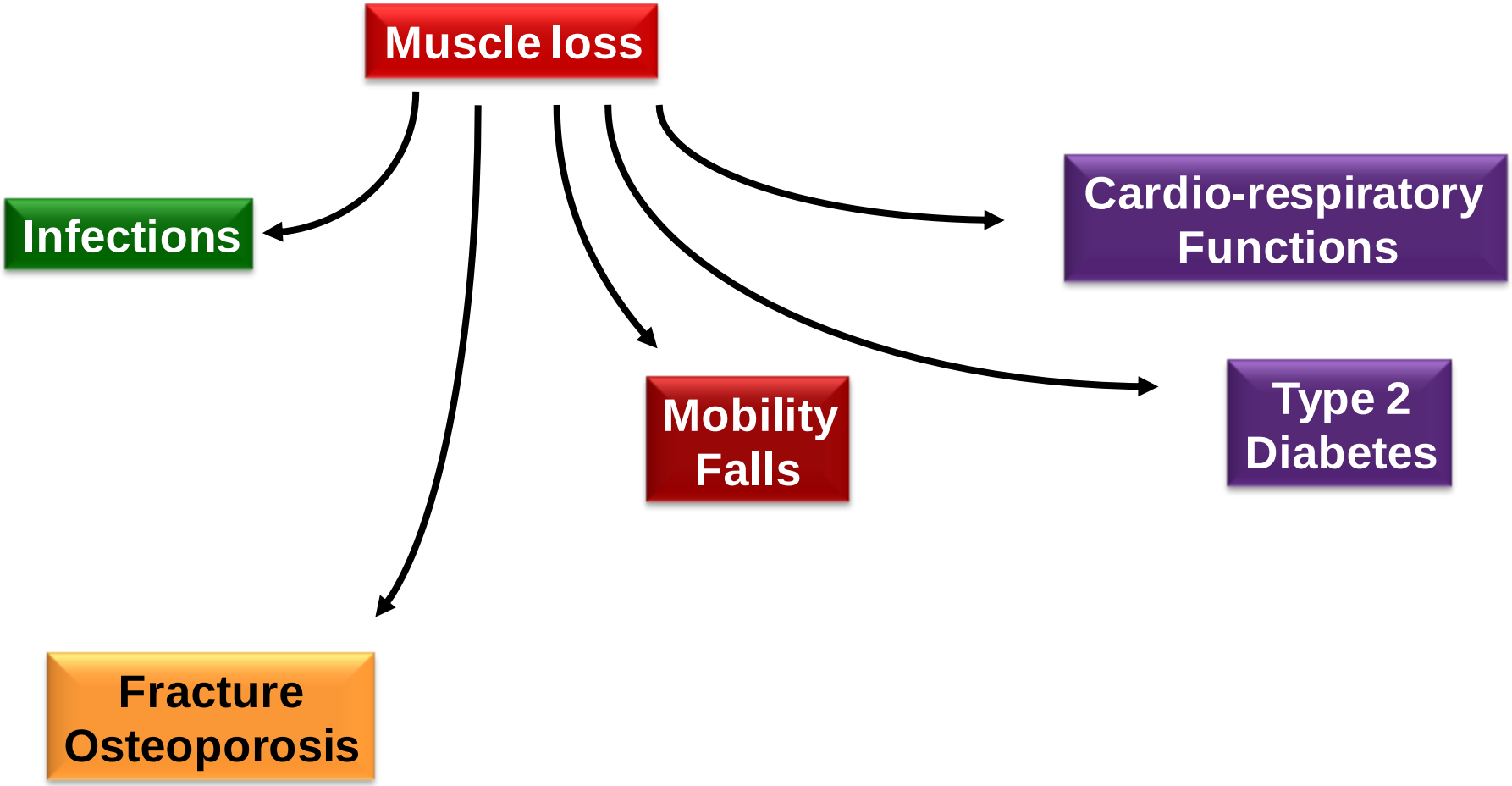
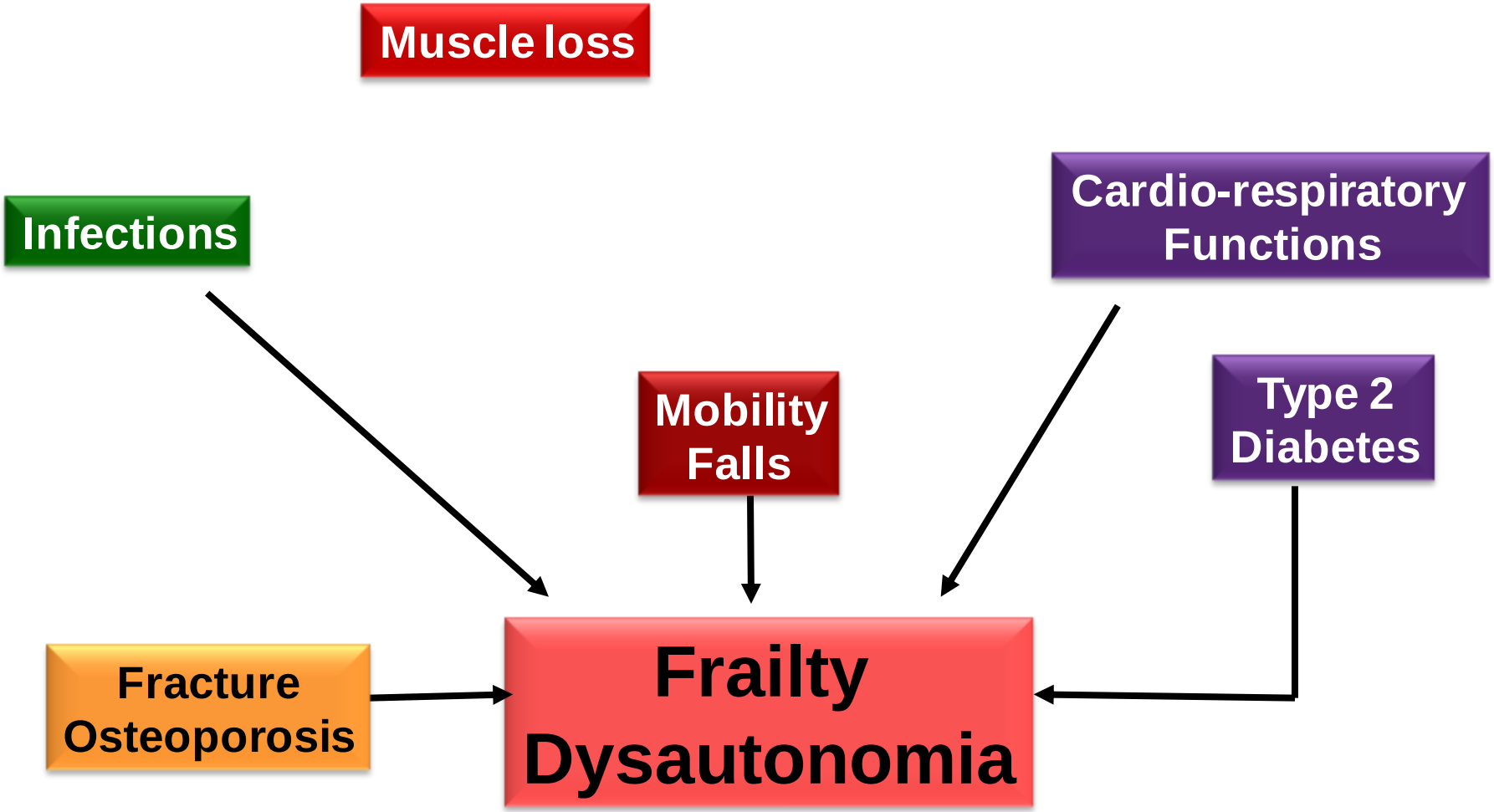
Impact of muscle loss in health and disease



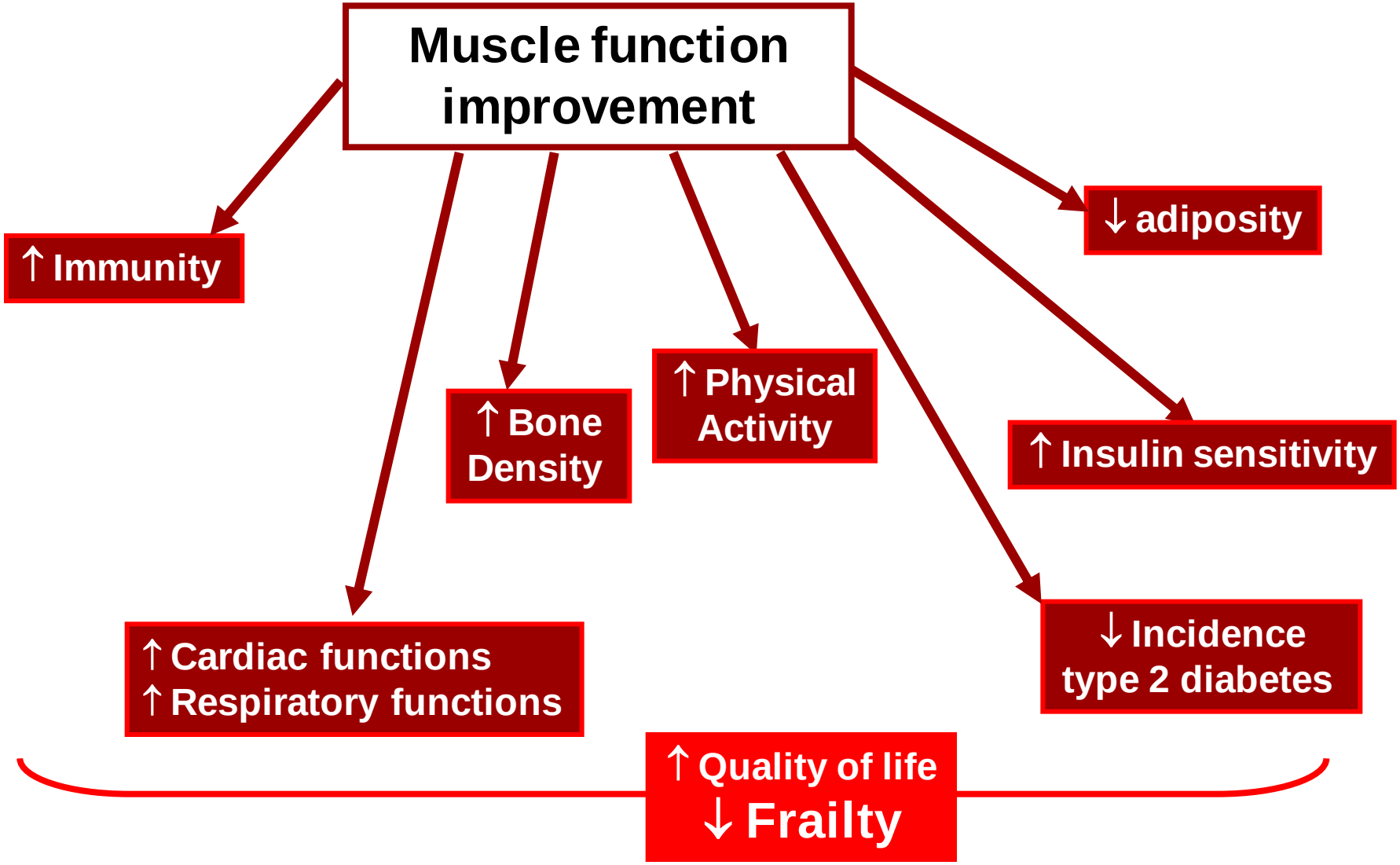
Impact of muscle loss in health and disease



Impact of muscle loss in health and disease



Impact of muscle improvement of global health



Impact of muscle improvement on mortality

- **A decline in walking speed of 0.1 m/s within 1 year increased the subsequent 5-year mortality rate**
  (Perera S, J Gerontol 2005)
- **Improvement in usual walking speed predicts a substantial reduction in mortality**
  (Hardy S, JAGS 2007)

➔ Physical performance (walking speed) is a strong predictor of morbidity and mortality like other predictive testing (blood pressure, glycemia, cholesterol)

ESPEN

THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

REPORT

Sarcopenia: European consensus on definition and diagnosis

Report of the European Working Group on Sarcopenia in Older People

ALFONSO J. CRUZ-JENTOFT[1], JEAN PIERRE BAEYENS[2], JÜRGEN M. BAUER[3], YVES BOIRIE[4], TOMMY CEDERHOLM[5], FRANCESCO LANDI[6], FINBARR C. MARTIN[7], JEAN-PIERRE MICHEL[8], YVES ROLLAND[9], STÉPHANE M. SCHNEIDER[10], EVA TOPINKOVÁ[11], MAURITS VANDEWOUDE[12], MAURO ZAMBONI[13]

– **Low muscle mass**

Geriatric Medicine
see more

+ one of the two components:

– **Low muscle strength**

– **Low physical performance**

International Academy Nutrition & Aging

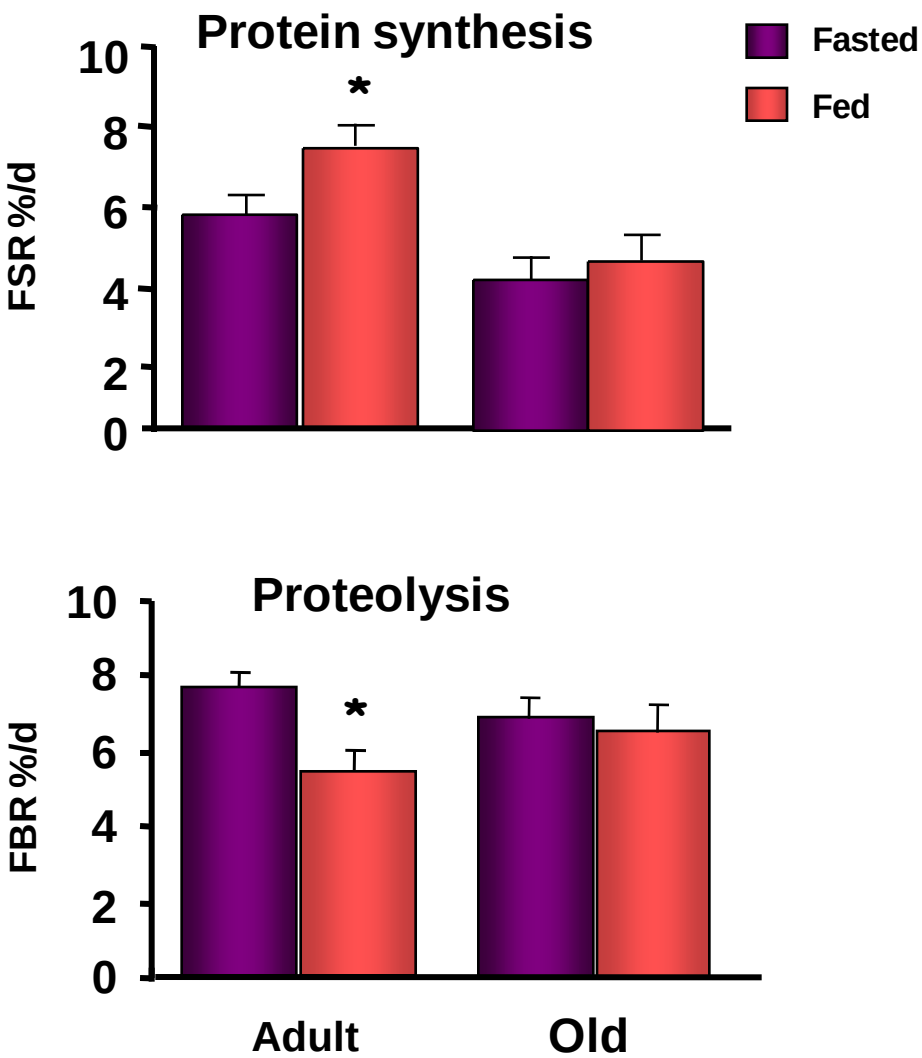
EUGMS
European Union Geriatric Medicine Society
Fostering geriatric medicine across Europe

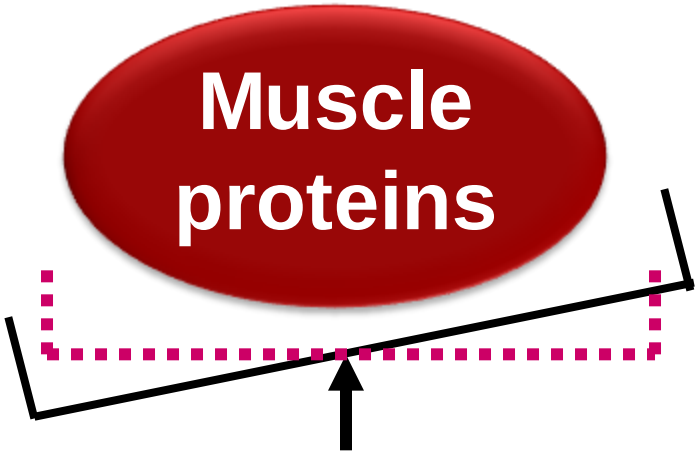
Cruz-Jentoft AJ, Report of the European Working Group on Sarcopenia in Older People, Age & Ageing 2010

Nutrition and Frailty

- Targeting muscle in elderly patients
- **Anabolic resistance to nutrients**
- Synergistical strategies

Impaired anabolic response to meal intake during aging (postprandial defect?) → **Anabolic resistance**





Impaired anabolic response to meal intake during aging

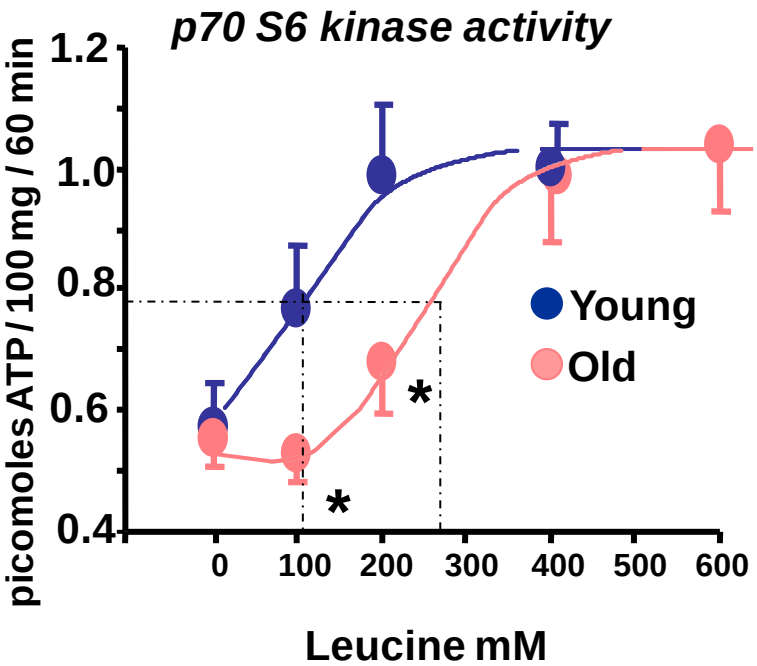
Anabolic resistance

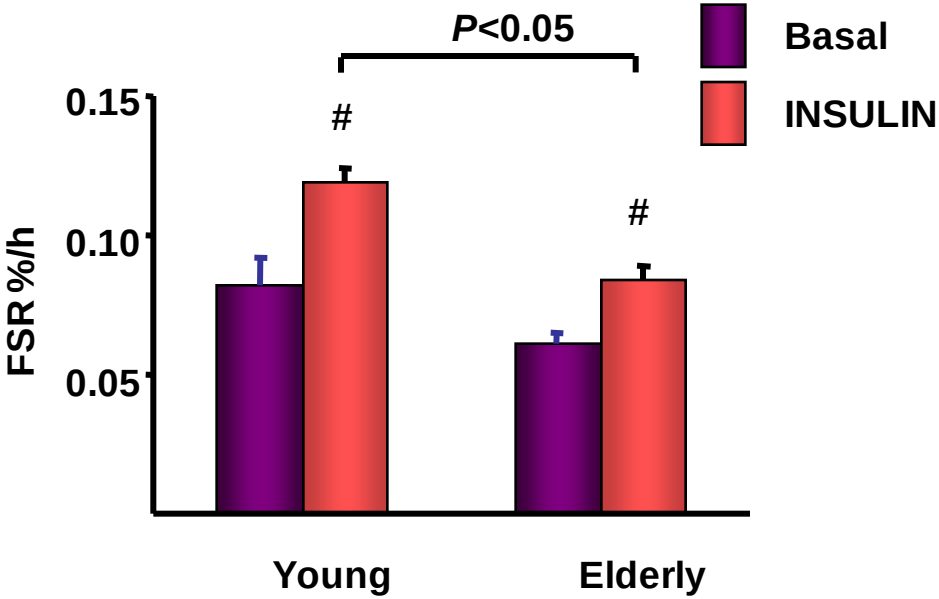
Defect in the regulation of mTOR signaling pathway by amino acids

Leucine resistance

Defect in the regulation of mTOR signaling pathway by insulin

Insulin resistance

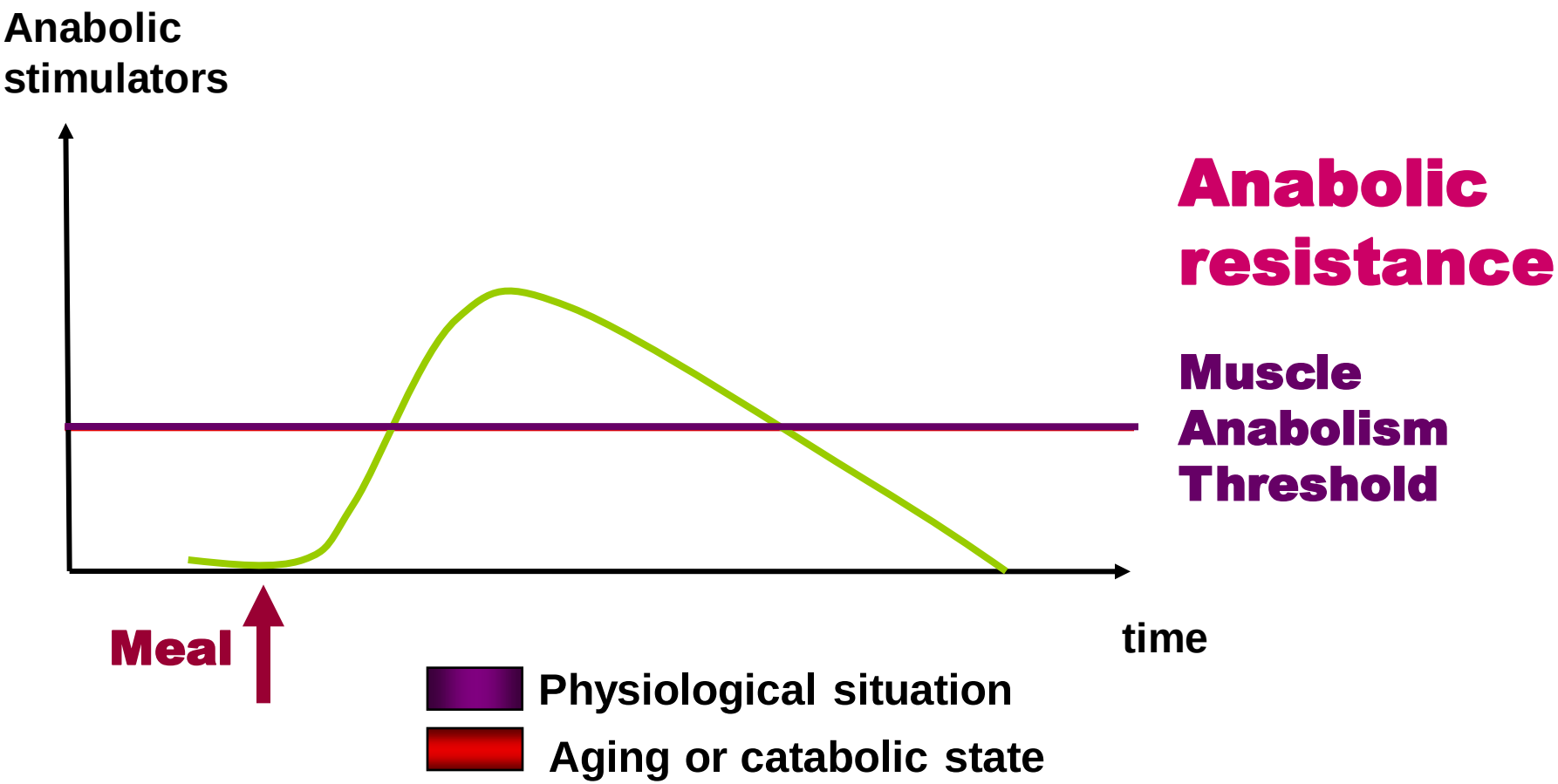


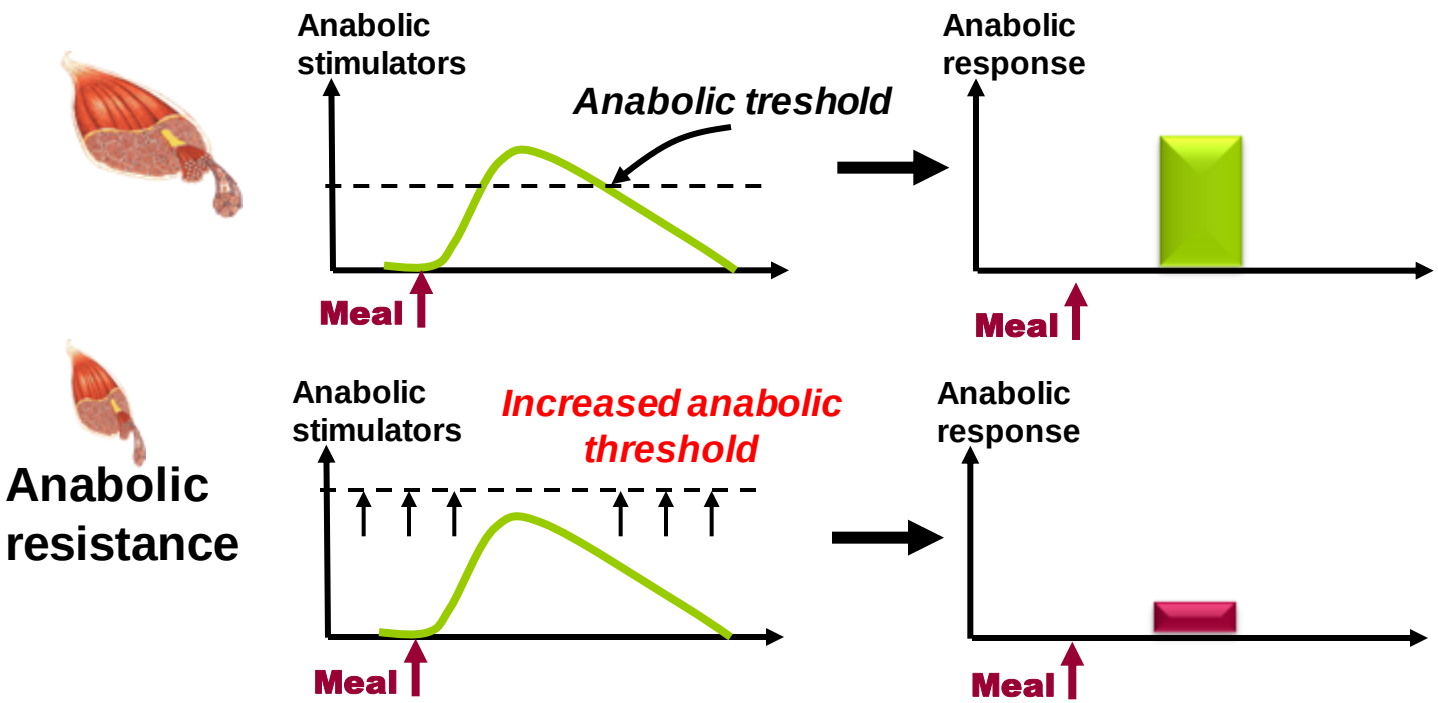


Dardevet, J Nutr 2000
Cuthberson, FASEB J 2005

Guillet, FASEB J 2004
Rasmussen, FASEB J 2006

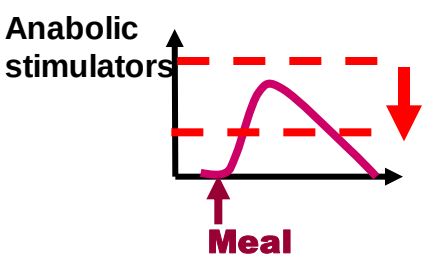
Muscle loss situations

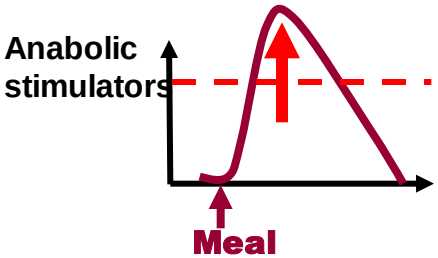




2 strategies

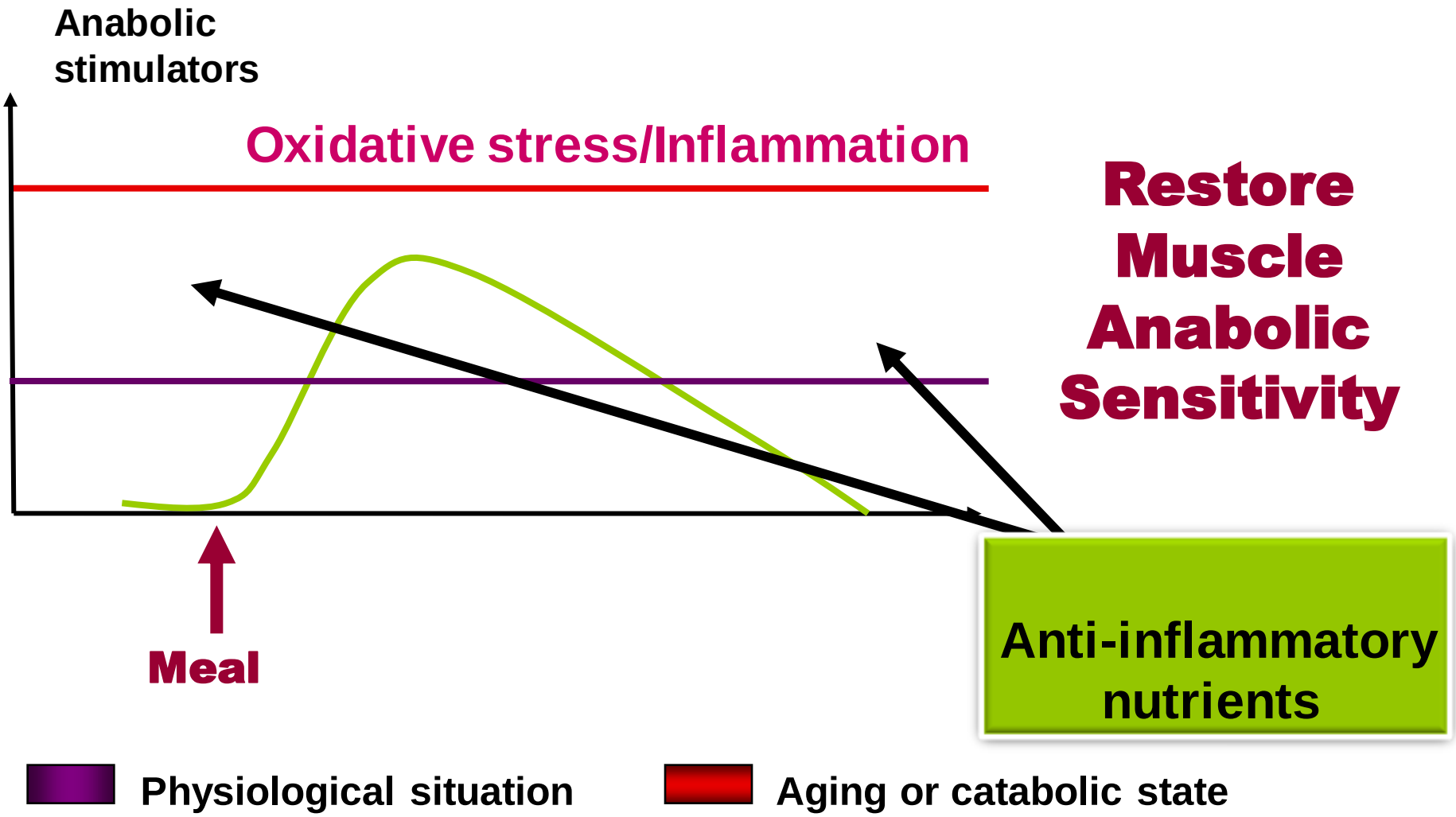
- to reduce muscle anabolic threshold
- to increase the availability of anabolic stimulators





Nutritional modulation of muscle anabolic threshold

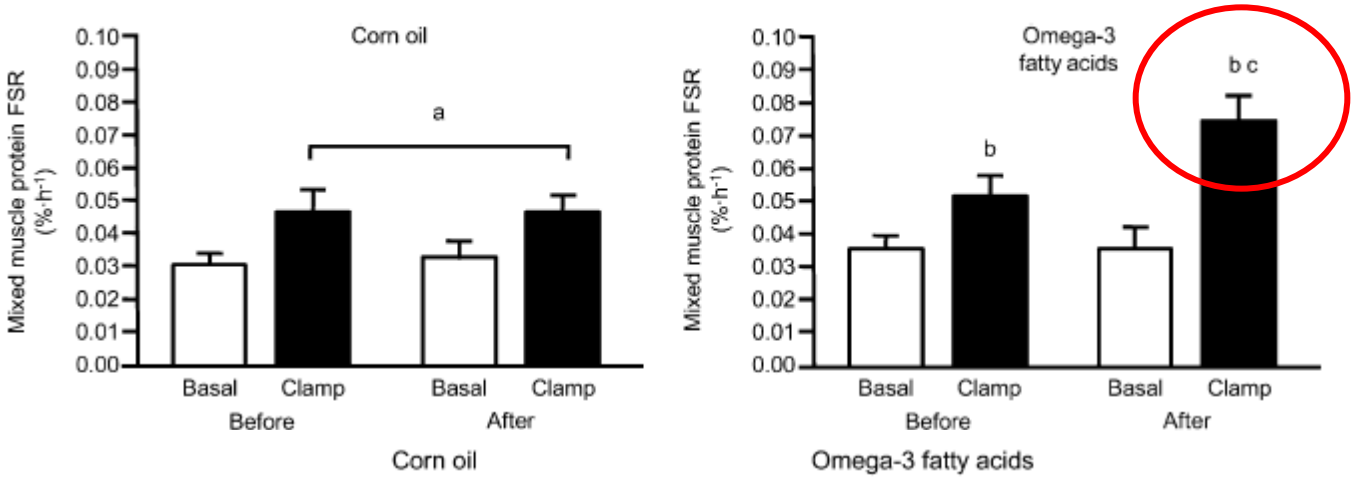
Improving muscle sensitivity to anabolic factors?



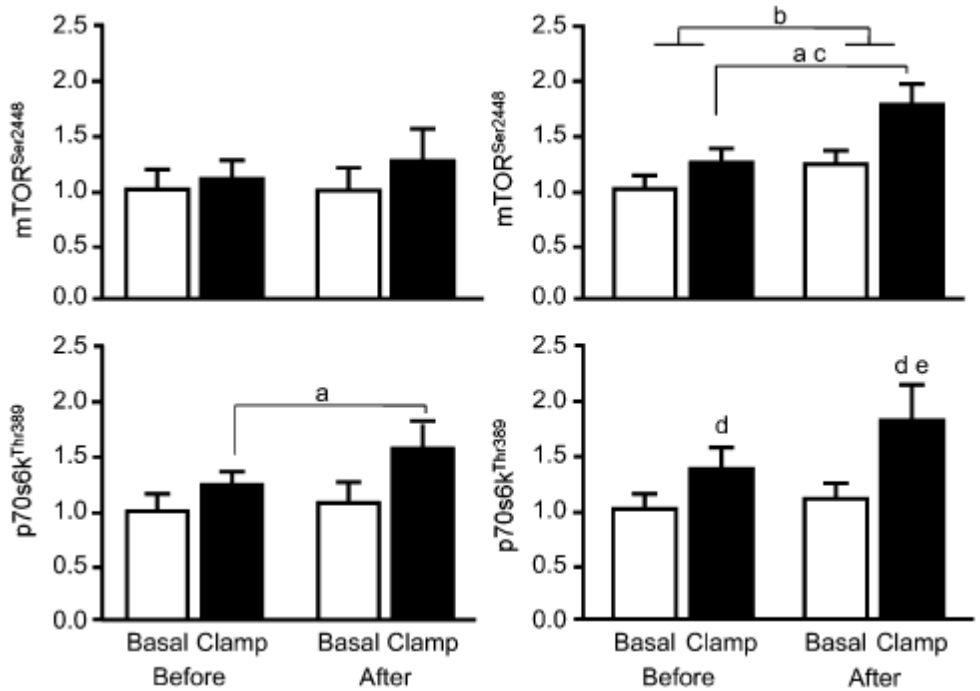
Physiological situation

Aging or catabolic state

Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial[1–3]



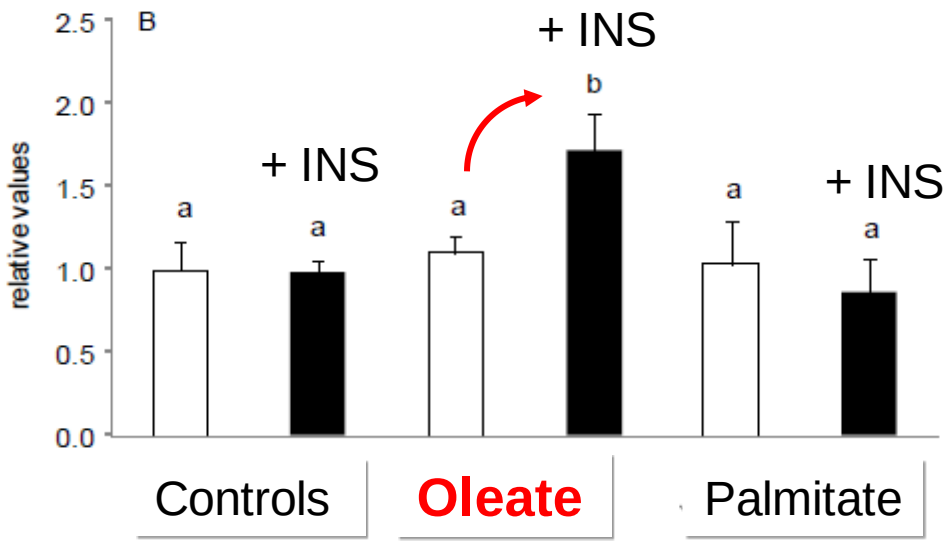
Muscle protein synthesis



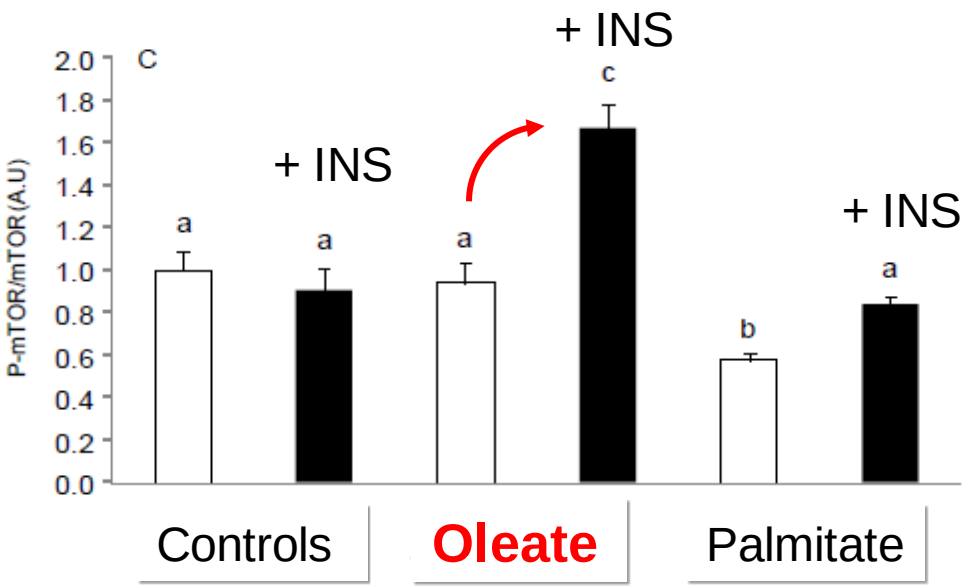
Signaling pathways for the initiation of Protein synthesis

Smith GI, Am J Clin Nutr 2011

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



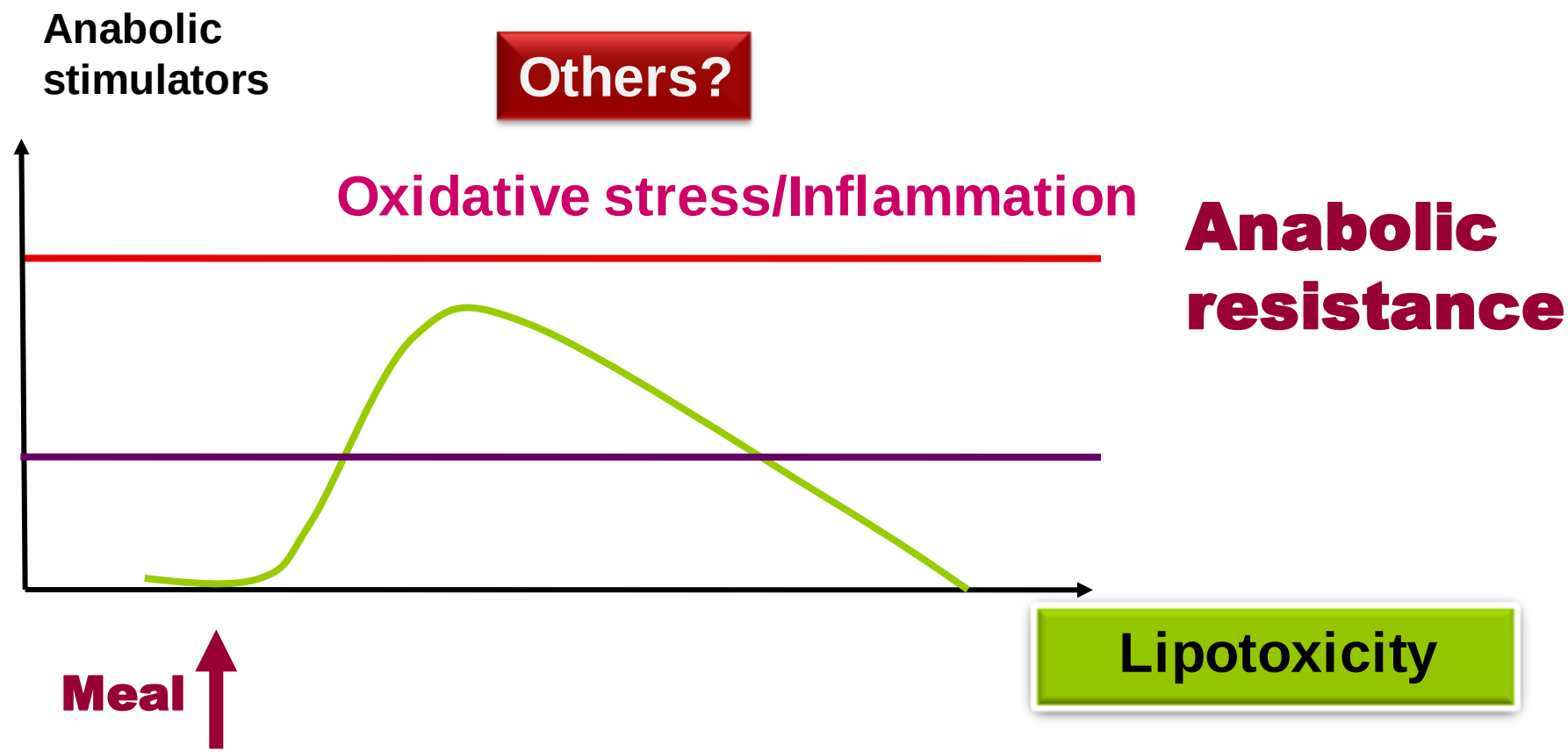
Muscle protein synthesis



Signaling pathways for the initiation of Protein synthesis

Tardif N, Clin Nutr 2011

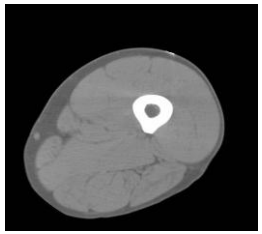
New mechanisms of muscle anabolic resistance?

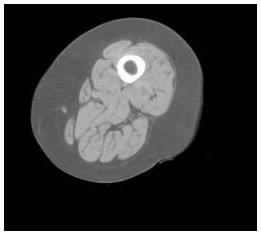


Physiological situation

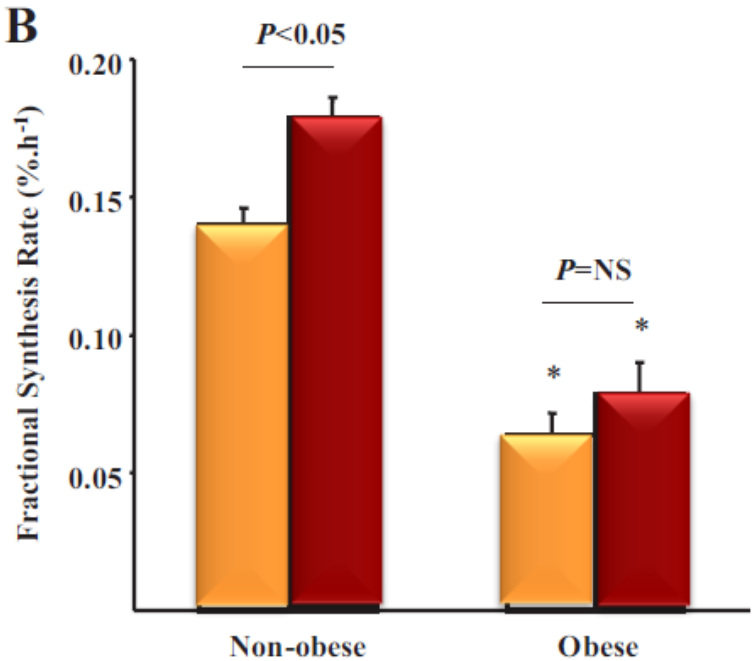
Aging or catabolic state

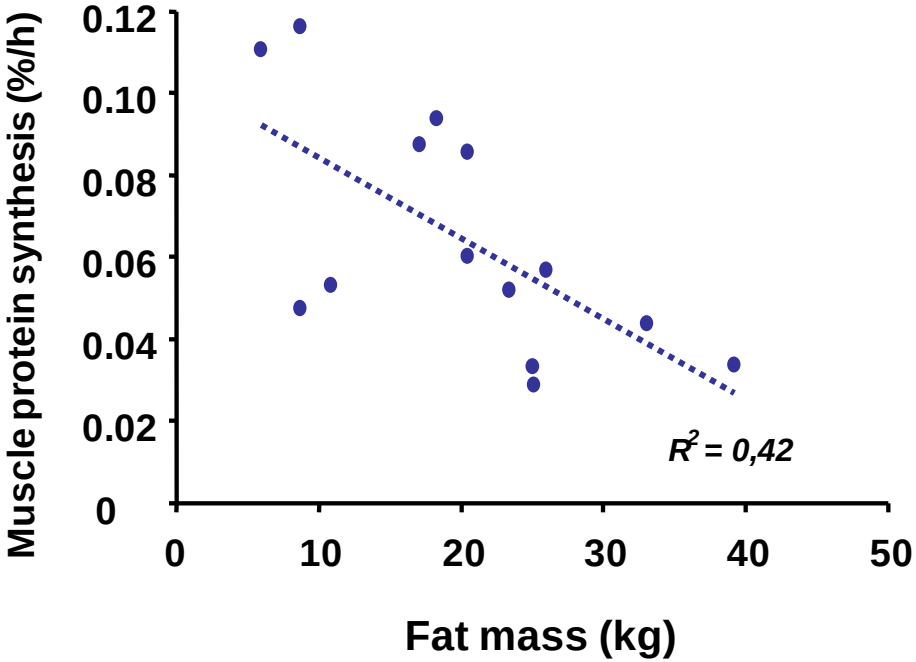
New mechanism of muscle anabolic resistance: lipotoxicity





Muscle Mitochondrial Protein synthesis (%/h)





Postabsorptive

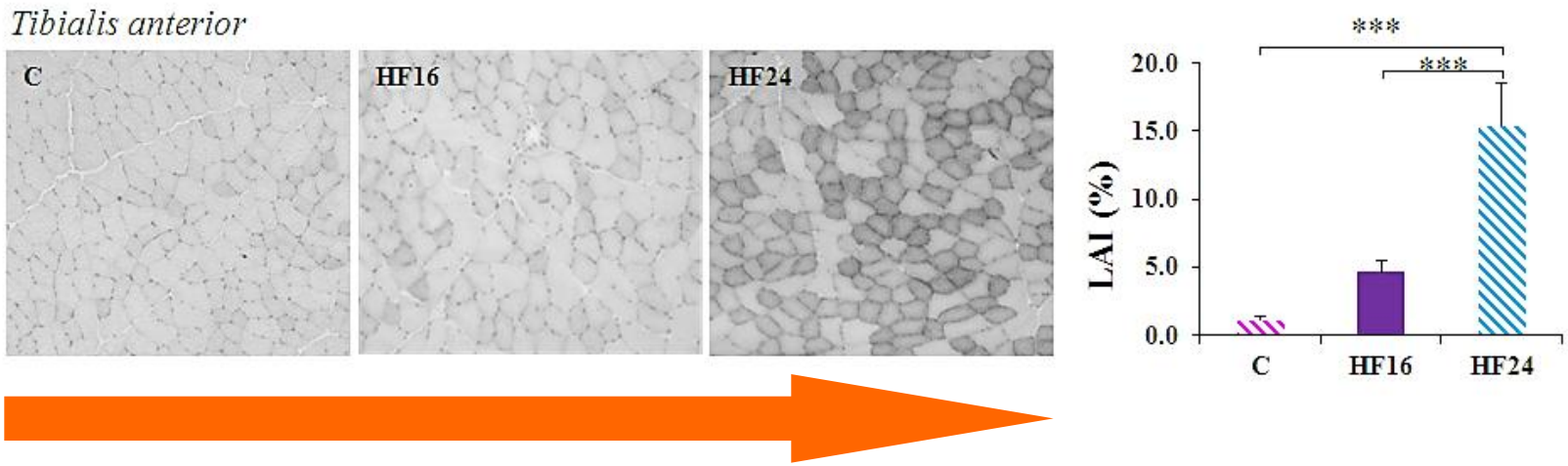
Insulin clamp

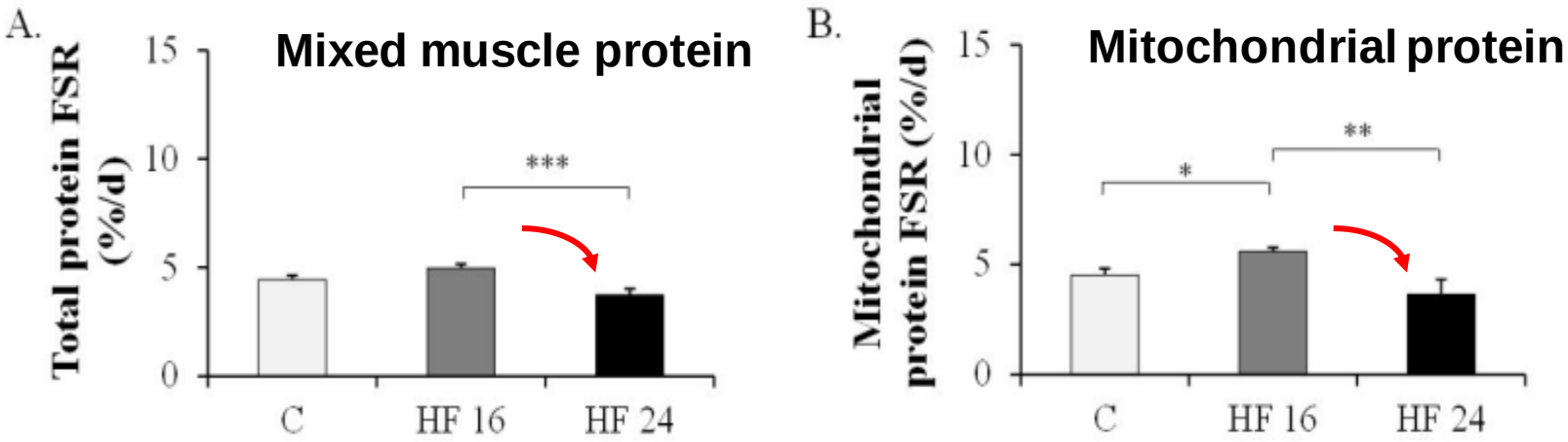
Fat mass could be deleterious for muscle protein synthesis?

Guillet C, JCEM 2009

Guillet C, Obes Rev 2012 (in press)

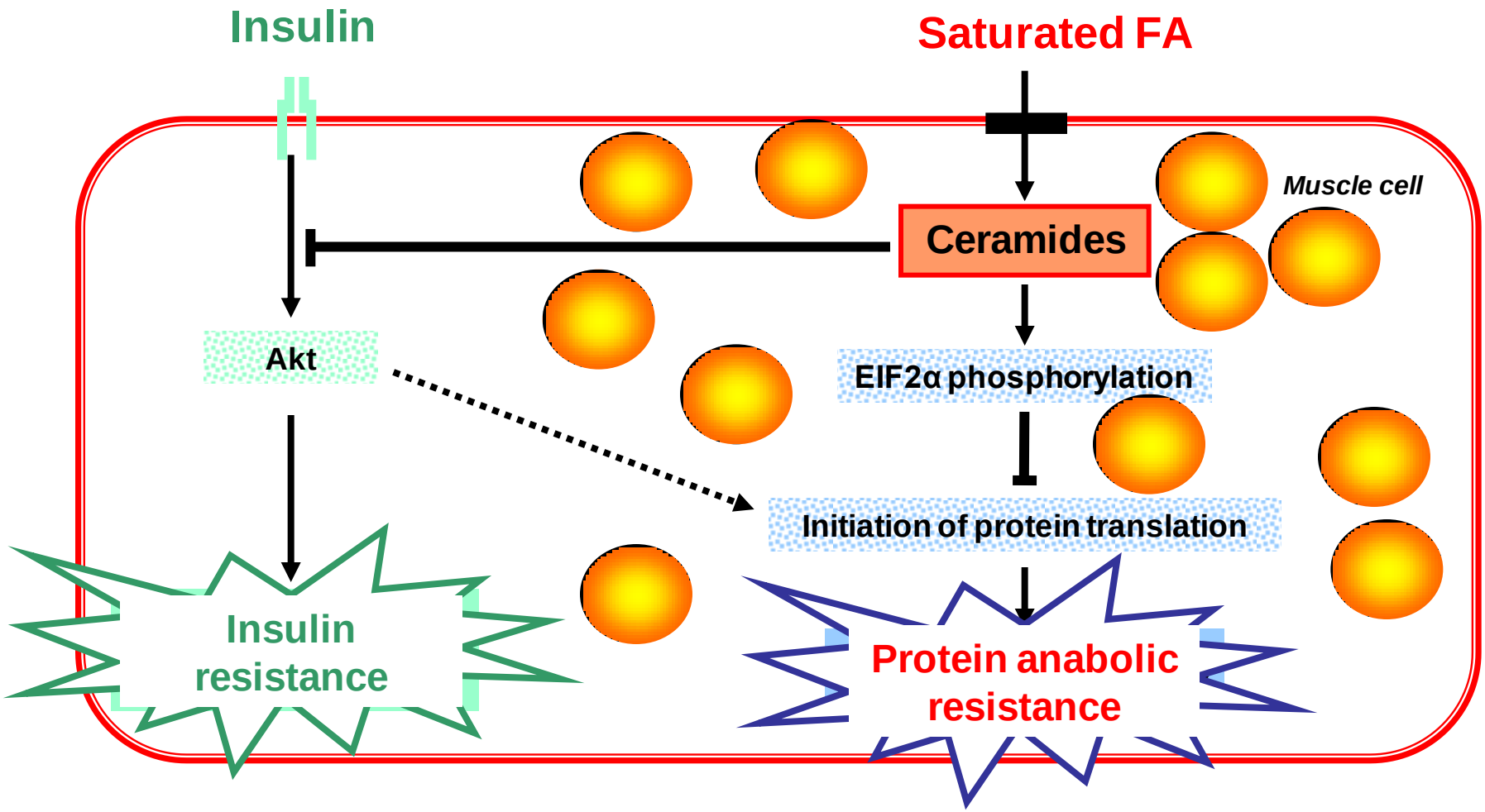
Response to high-fat feeding of muscle mixed and mitochondrial protein synthesis





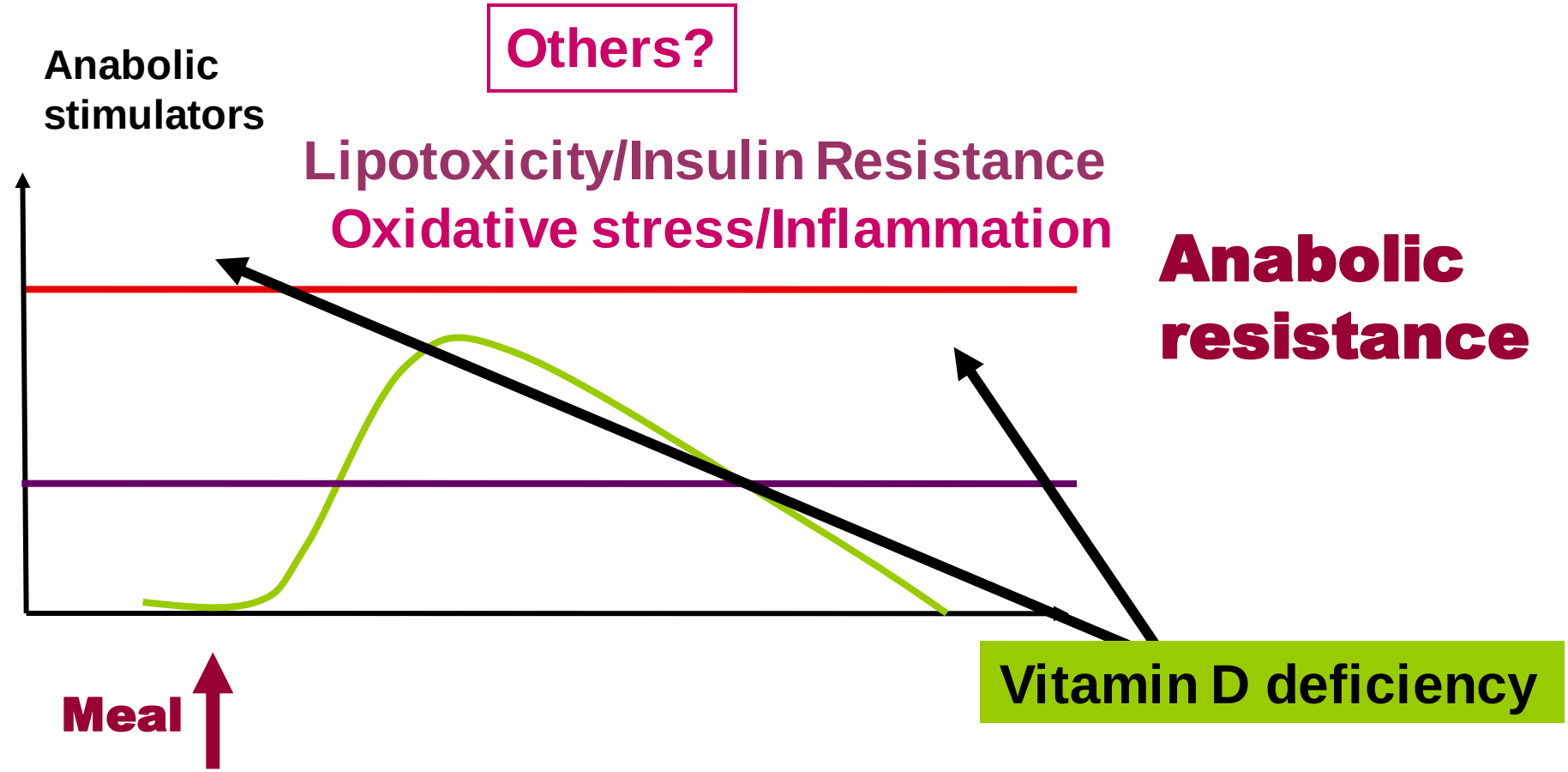
Masgrau A, J Physiol 2012

A double muscle anabolic resistance due to lipotoxicity



Tardif N, submitted

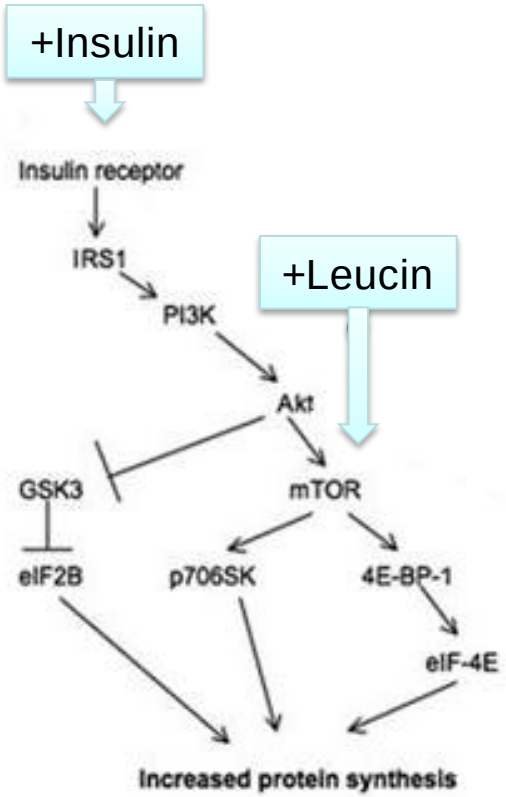
Modulators of muscle anabolic resistance



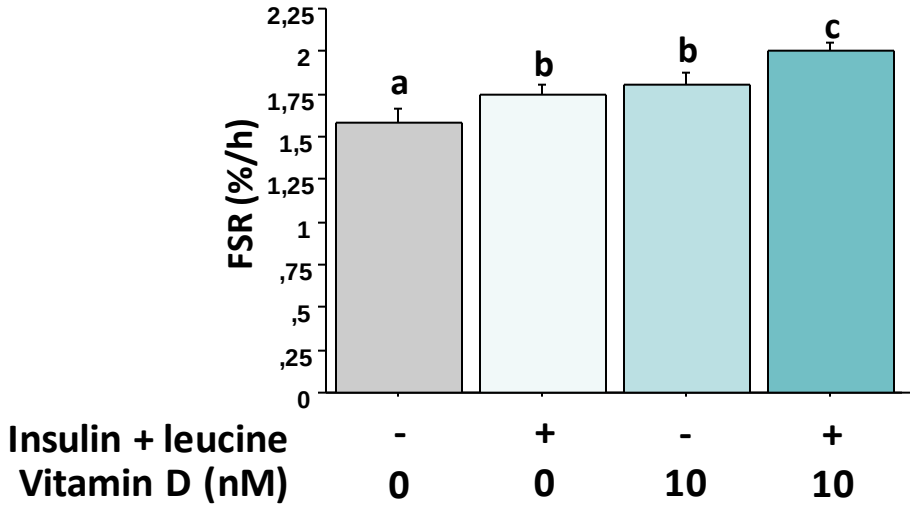
Physiological situation

Aging or catabolic state

1,25(OH)$_2$-vitamin D3 combined to anabolic factors increases protein synthesis and stimulates anabolic signals in differentiated C2C12 skeletal muscle cells



Muscle cells protein synthesis



Chanet A, submitted

Muscle loss situations

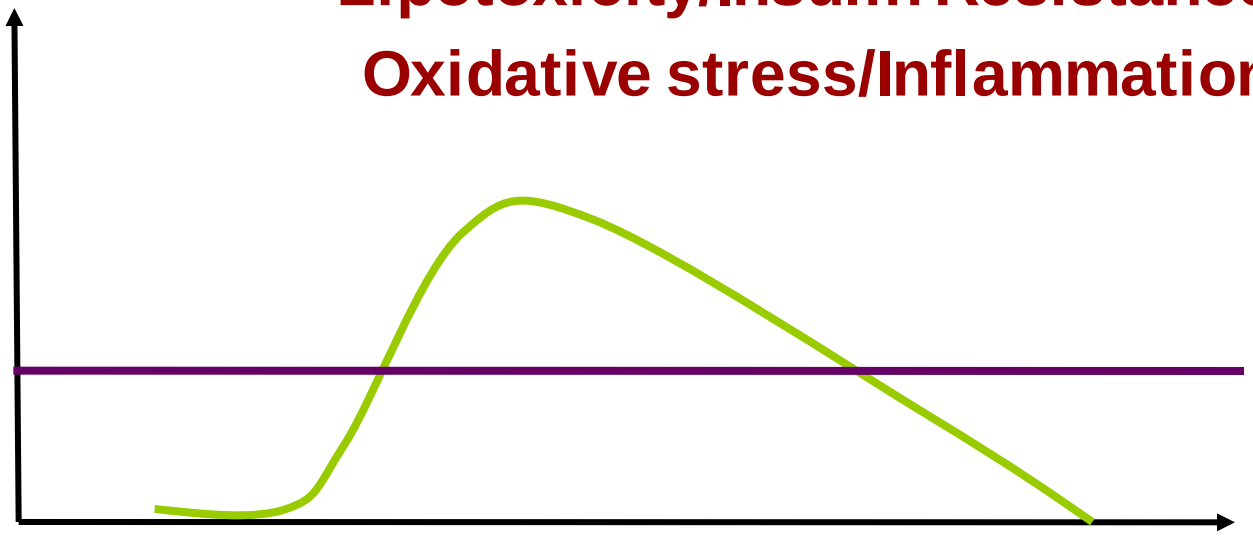
Other mechanisms?

Immobilization/Chronic Diseases

Lipotoxicity/Insulin Resistance

Oxidative stress/Inflammation

Anabolic resistance



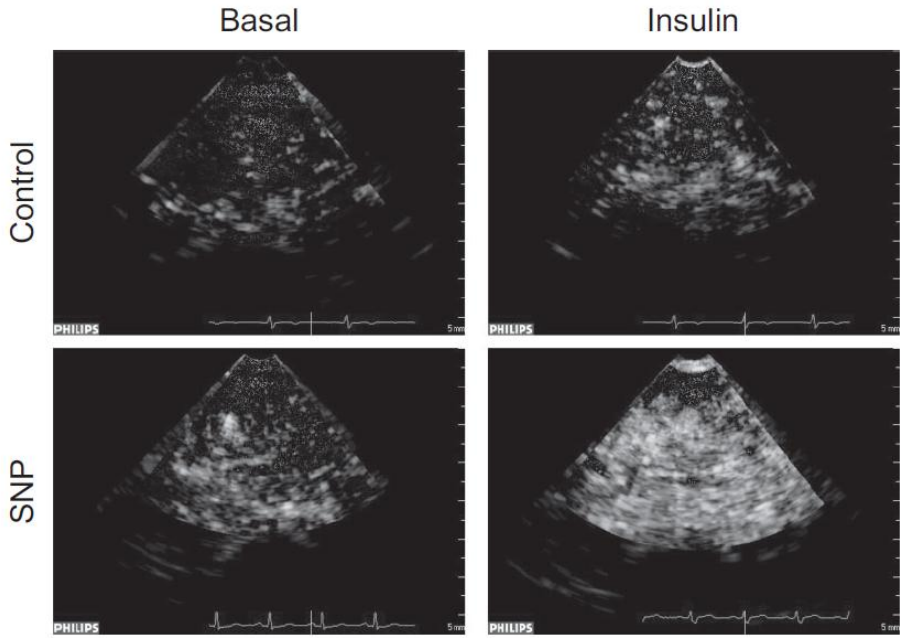
Meal

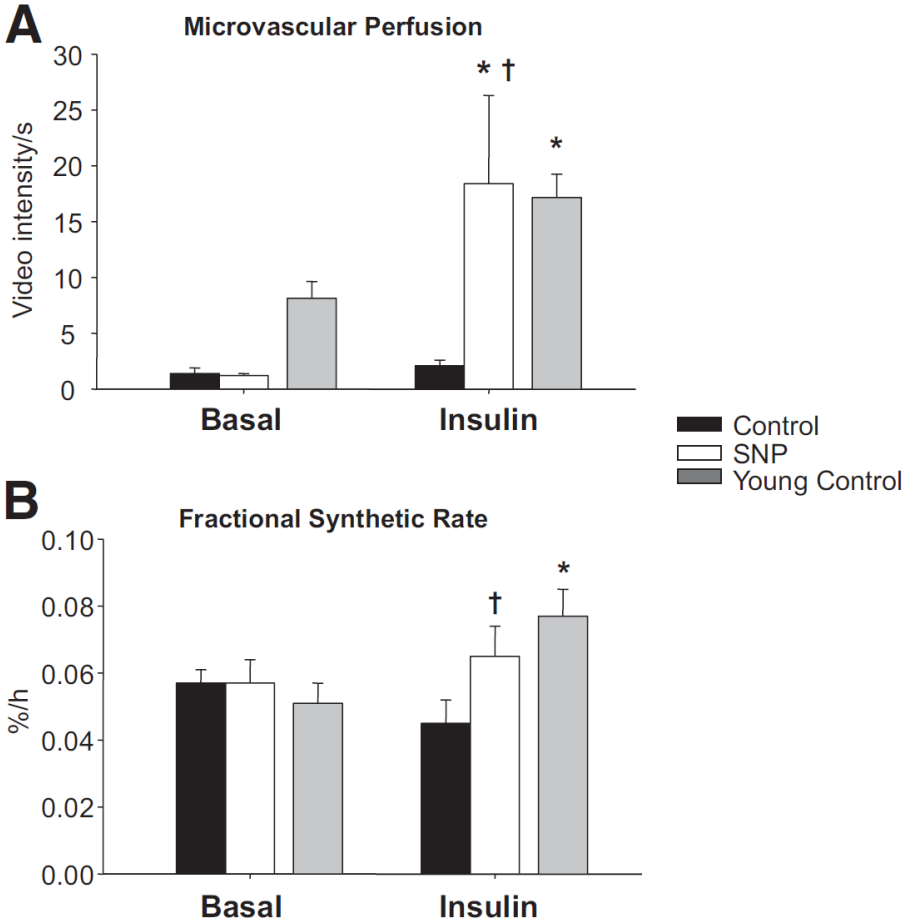
Physiological situation

Aging or catabolic state

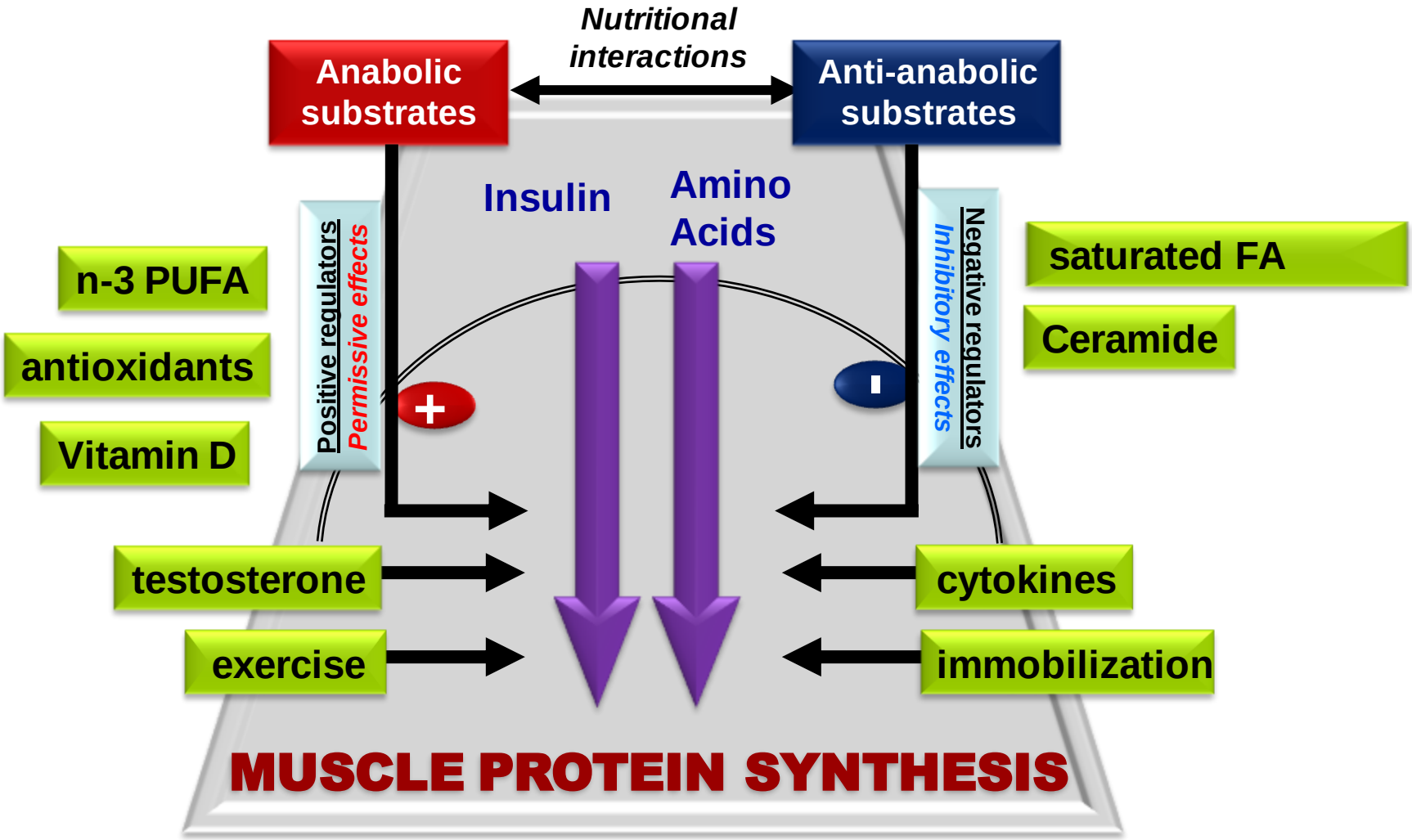
Pharmacological Vasodilation Improves Insulin-Stimulated Muscle Protein Anabolism but Not Glucose Utilization in Older Adults

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

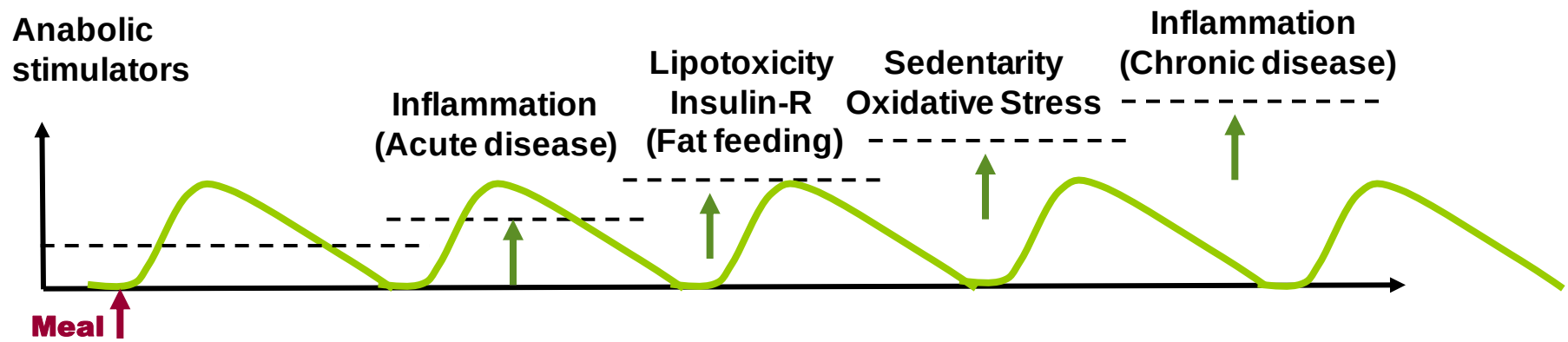


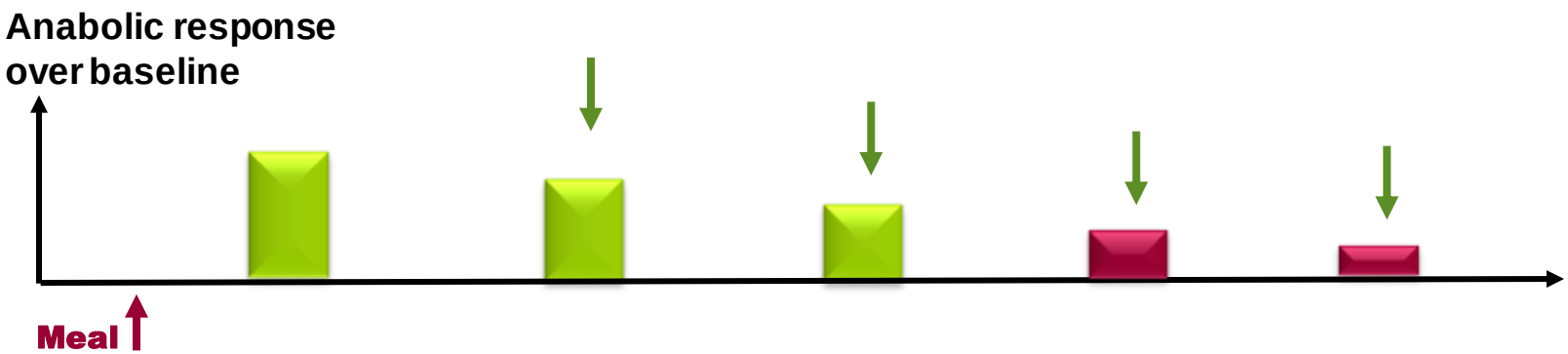


Timmerman KL, Diabetes 2010


Nutritional interactions
Anabolic substrates
Anti-anabolic substrates
Insulin
Amino Acids
Positive regulators
Permissive effects
Negative regulators
Inhibitory effects
n-3 PUFA
antioxidants
Vitamin D
saturated FA
Ceramide
testosterone
exercise
cytokines
immobilization
MUSCLE PROTEIN SYNTHESIS

Temporal changes in anabolic threshold?

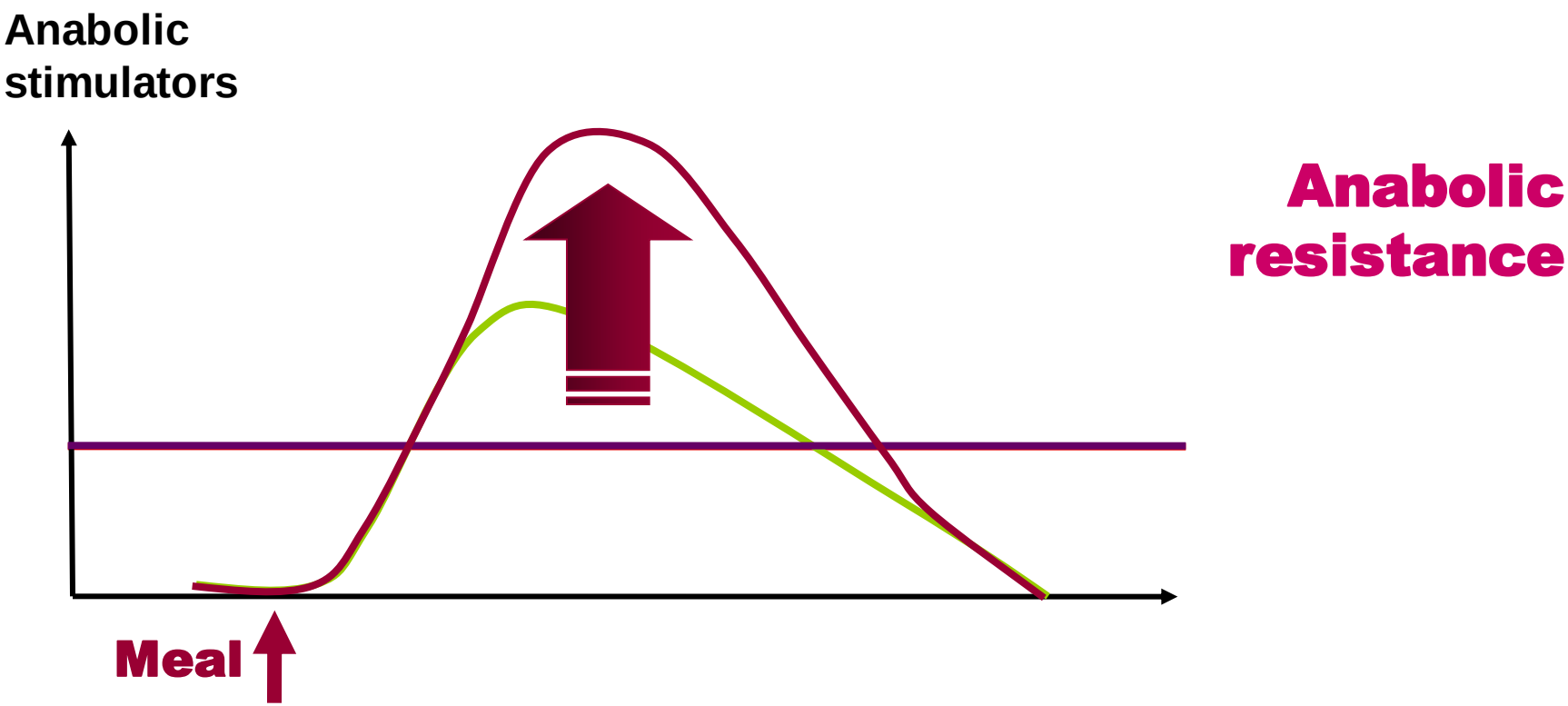




Boirie Y, J Am Med Dir Ass 2013 (in press)


MARCHE
BARBOT

- **Increased availability of anabolic stimulators**



How ?

- Acting on the diet and the determinants of digestion rate
- Modulating splanchnic metabolism in physiopathological situations

Acting on the diet and the determinants of postprandial protein utilization

- **Increase protein intake?**
- **Specific AA supplementation?**
- **Improve AA bioavailability:**
  - **Change the distribution of protein intake?**
  - **Use proteins of different digestion rate?**
- **Physical exercise?**

Acting on the diet and the determinants of postprandial protein utilization

- Increase protein intake?
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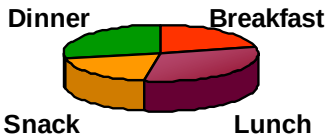
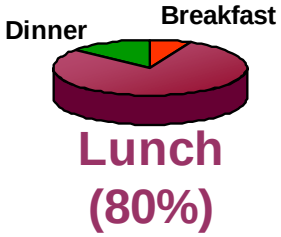
- **Improve AA bioavailability:**
  - Change the distribution of protein intake?
  - Use proteins of different digestion rate?
- Physical exercise?

Protein pulse-feeding ingestion pattern (chrononutrition)

Spread-feeding



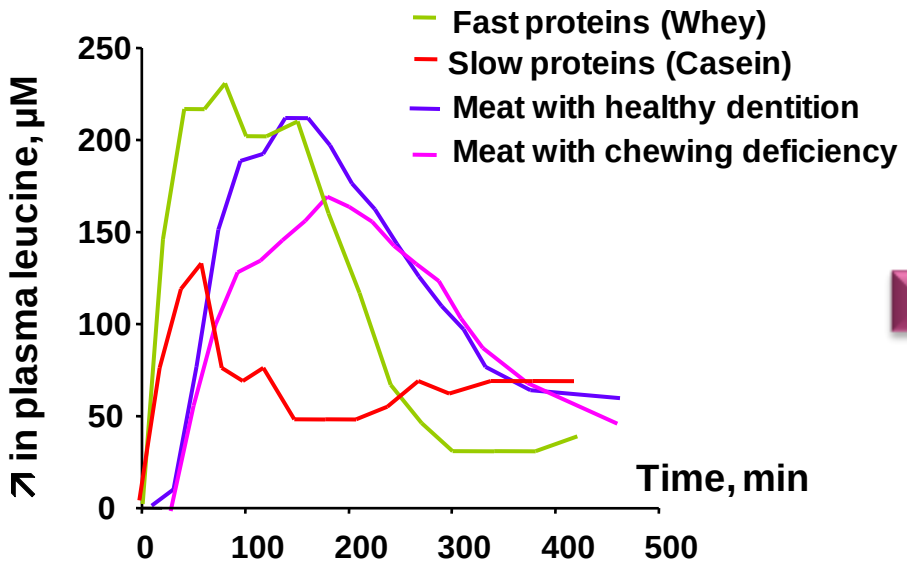
Pulse-feeding



Pulse feeding= ↗ nitrogen retention in the elderly

Arnal et al. AJCN 1999-2002

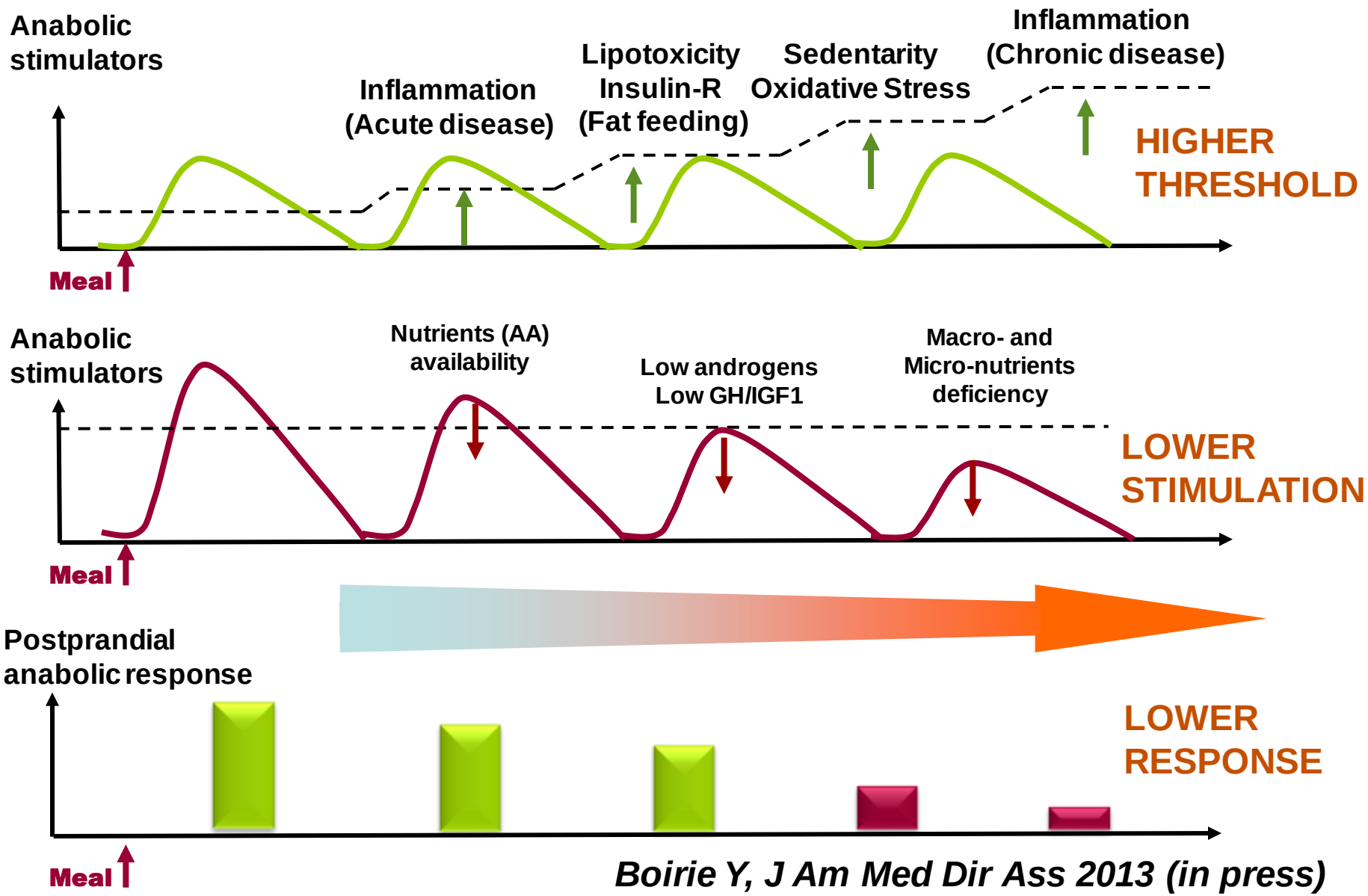
Protein digestion rate (fast/slow proteins concept)



Fast proteins= ↗ postprandial WB protein anabolism in the elderly

Boirie et al., PNAS 1997, Remond et al., Am. J. Clin. Nutr. 2007
Pennings B, Am J Clin Nutr 2011

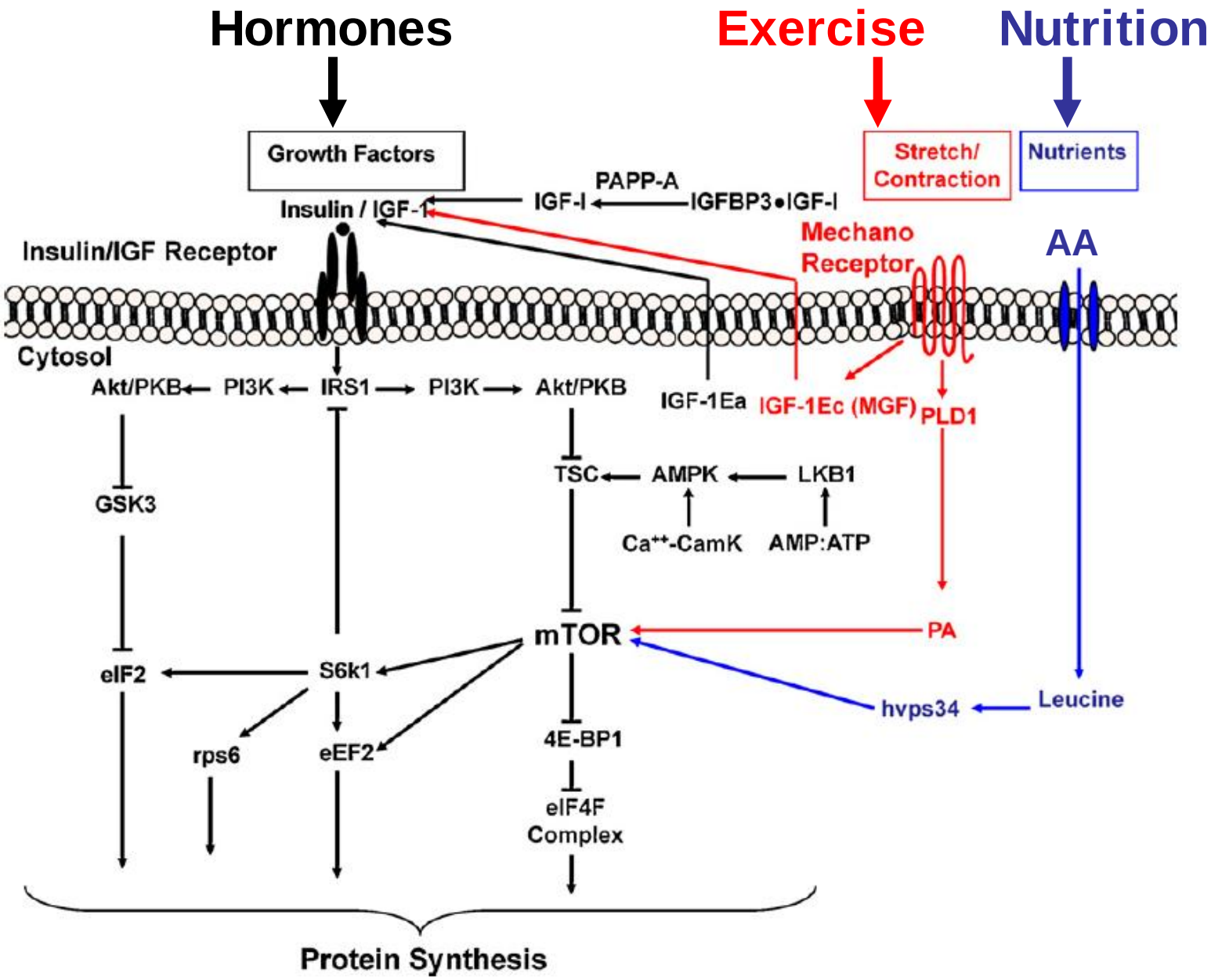
Temporal changes in postprandial muscle anabolic response to meal intake: reaching the threshold



Boirie Y, J Am Med Dir Ass 2013 (in press)

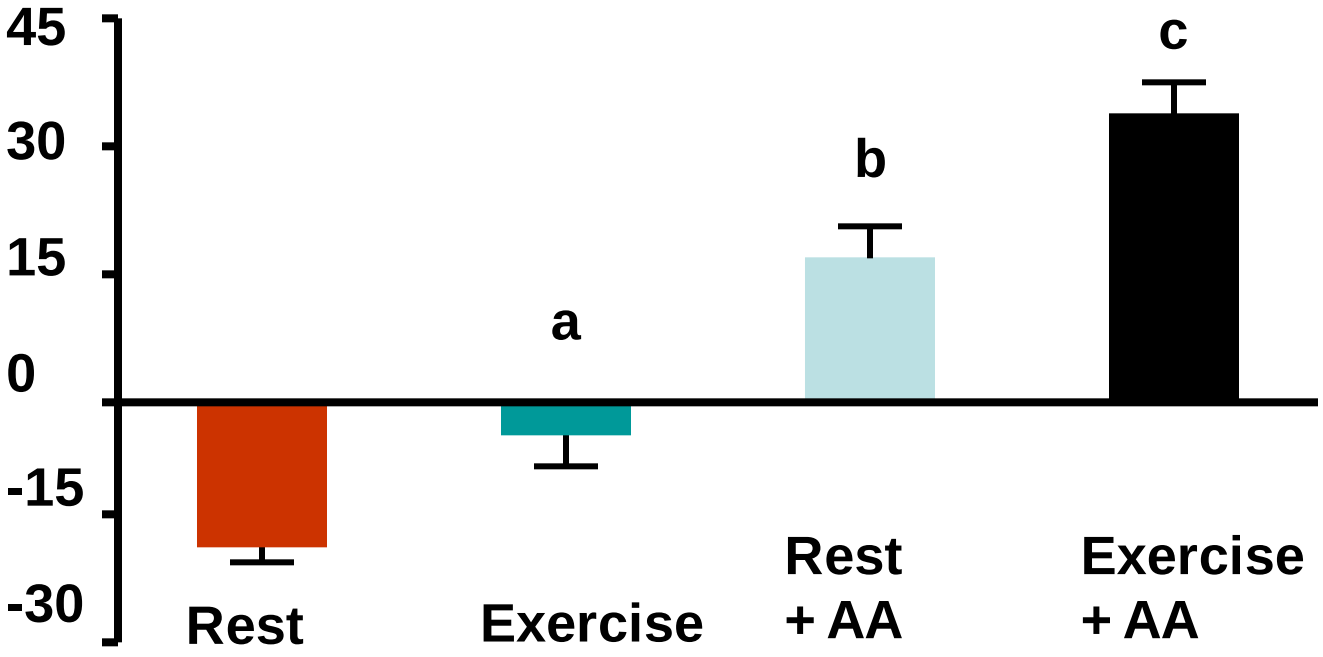
Nutrition and Frailty

- Targeting muscle in elderly patients
- Anabolic resistance to nutrients
- Synergistical strategies



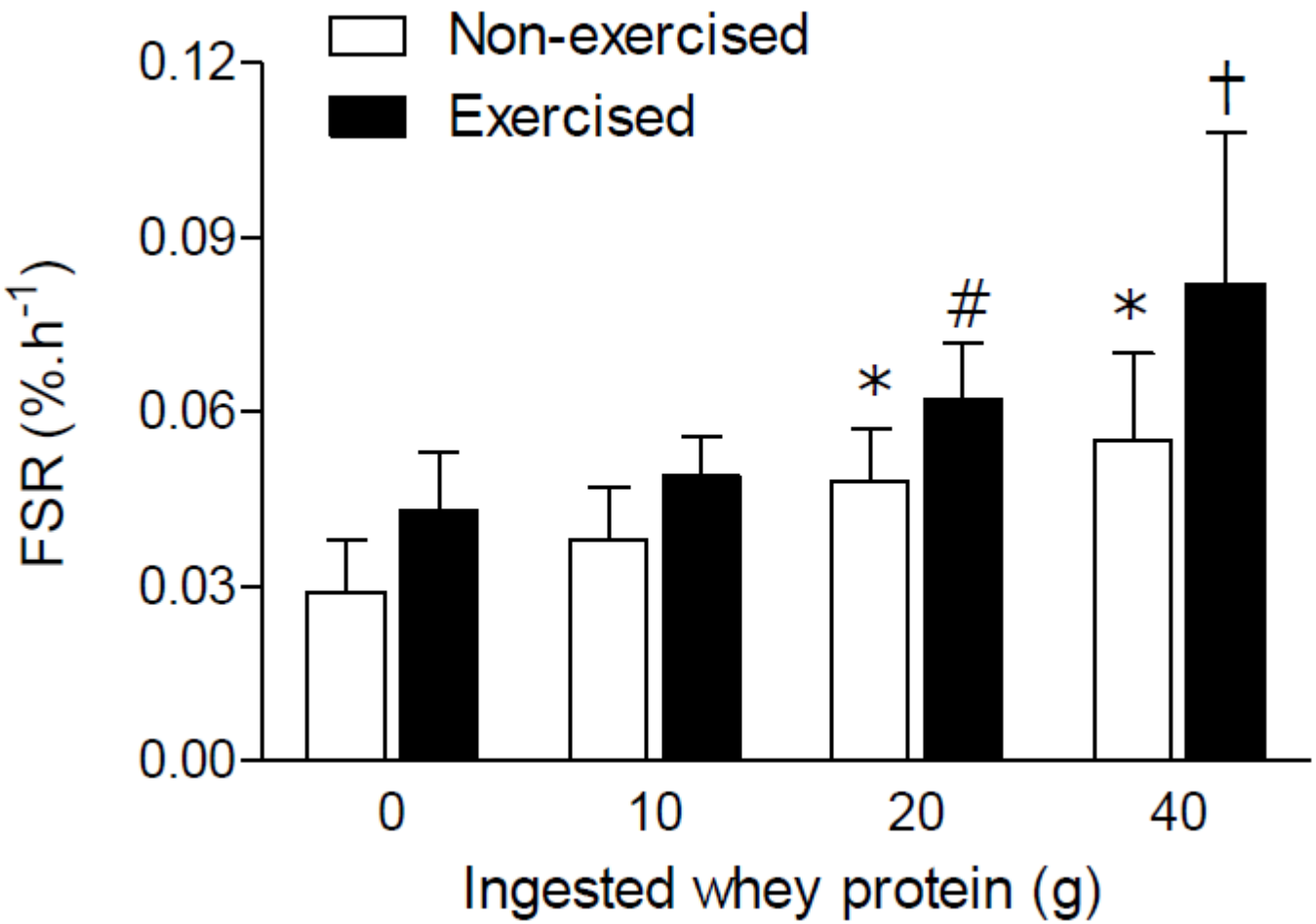
Irving BA, Aging Res Rev 2012

Physical exercise potentiates the anabolic impact of amino acid



Biolo G, J Clin Invest 1995

40g of protein maximally stimulate protein synthesis in elderly subjects after resistance exercise



Yang-Y, Phillips-SM et al. BJN 2012

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[‡]

Kim KH, JAGS 2012

Original Study

Protein Supplementation Improves Physical Performance in Frail Elderly People: A Randomized, Double-Blind, Placebo-Controlled Trial

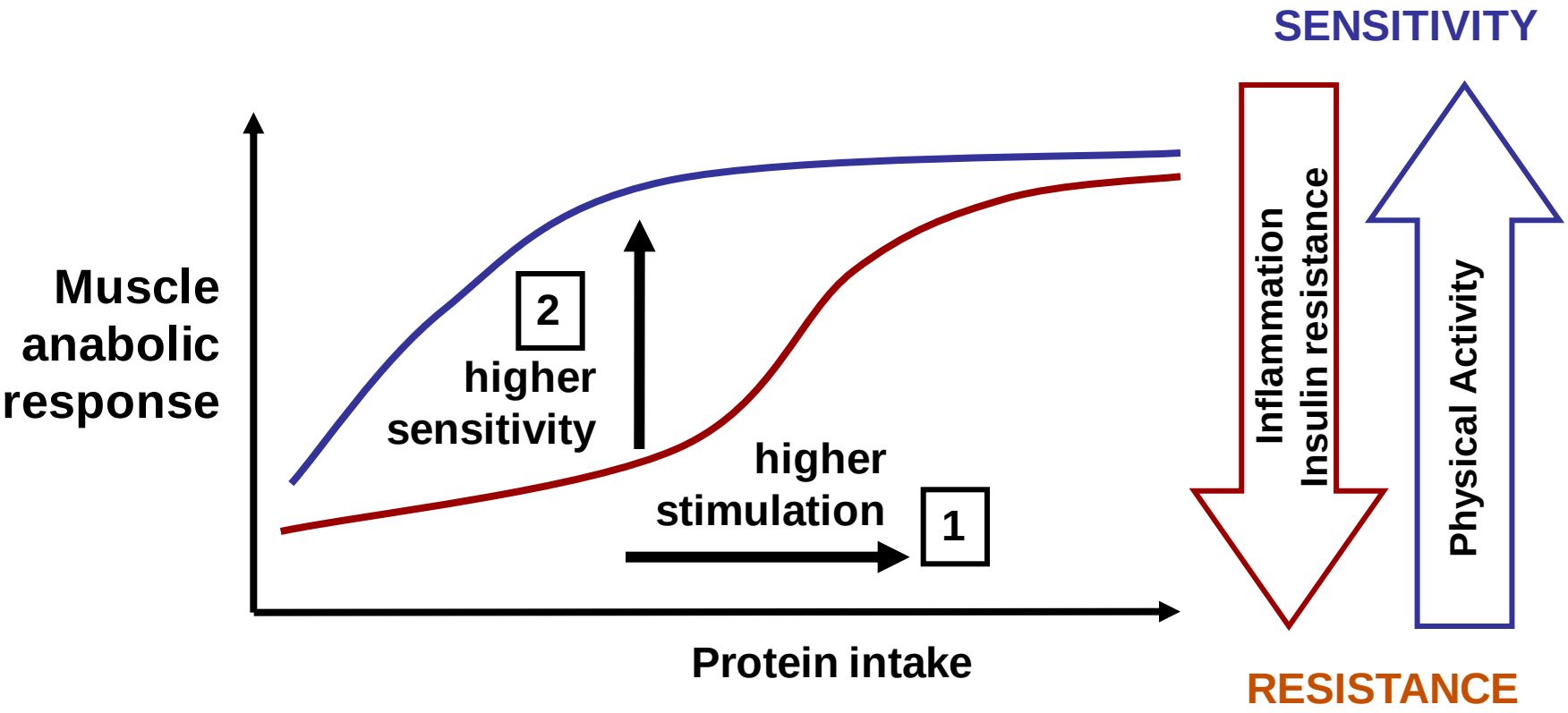
Original Study

Protein Supplementation Increases Muscle Mass Gain During Prolonged Resistance-Type Exercise Training in Frail Elderly People: A Randomized, Double-Blind, Placebo-Controlled Trial

Michael Tieland Msc[a,b,*], Marlou L. Dirks MSc[c], Nikita van der Zwaluw MSc[b], Lex B. Verdijk PhD[a,c], Ondine van de Rest PhD[b], Lisette C.P.G.M. de Groot PhD[a,b], Luc J.C. van Loon PhD[a,c]

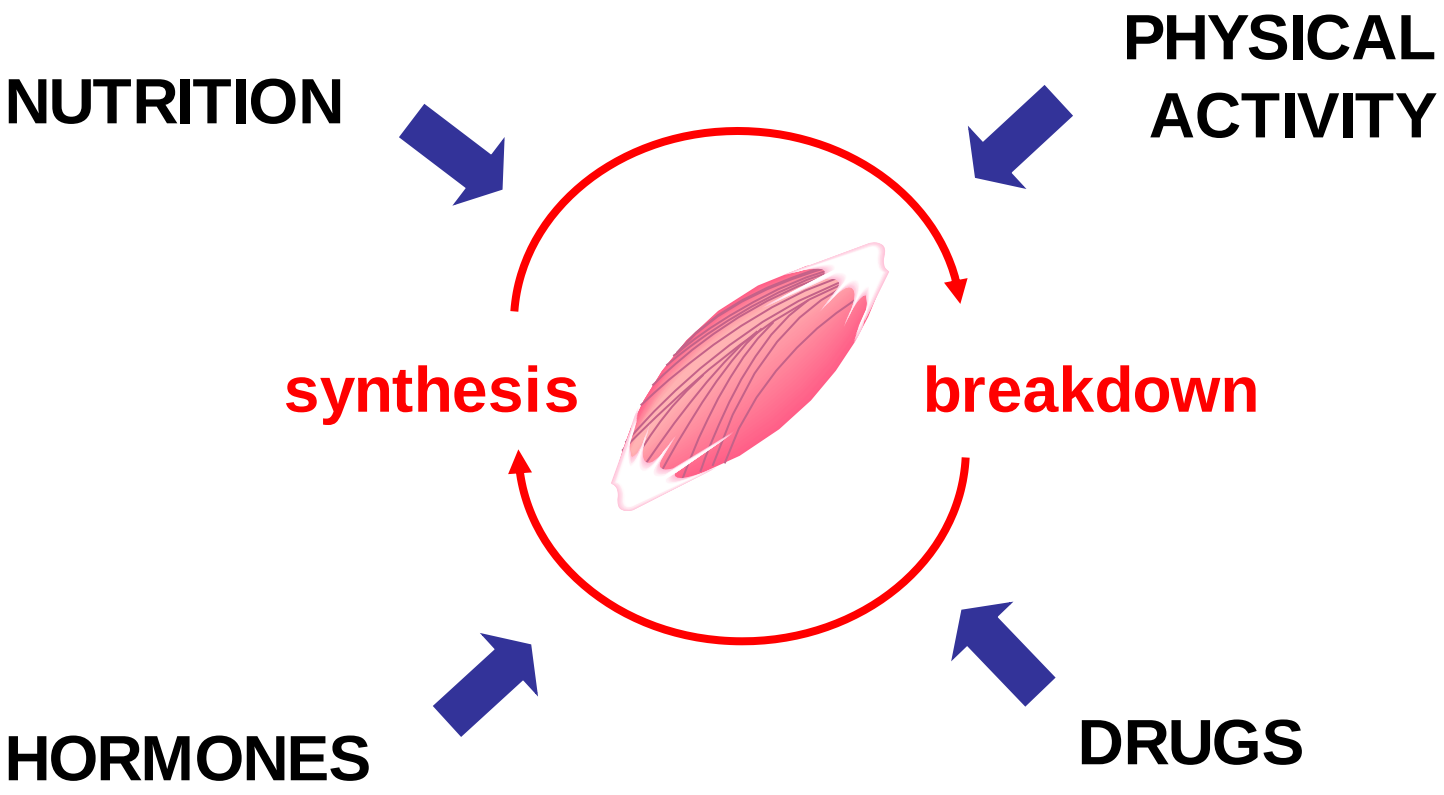
Tieland M, JAMDA 2012

Muscle anabolic response according to protein intake and exercise in older subjects



Boirie Y, J Am Med Dir Ass 2013 (in press)

Look for the best synergistical modulation of muscle protein anabolism



Thank you

UNH

Human Nutrition Unit

Metabolism & Health

INRA

UNIVERSITE D'AUVERGNE CLERMONT-FD1

CHU CLERMONT FERRAND

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