

VI Congresso Nazionale **B&M** Nutrizione e Neurodegenerazione

SESSIONE I: RELATORI



- *Ghrelin: from orexigenic signal to metabolic master regulator?*

- **Prof. Rocco Barazzoni**

Professore associato di Medicina Interna Università degli Studi di Trieste

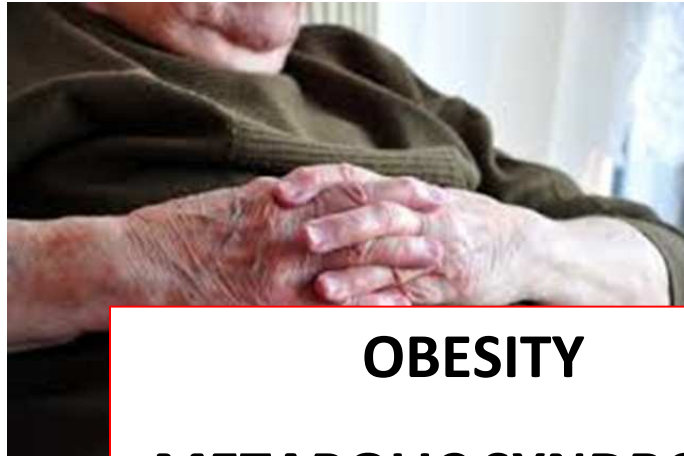
Ghrelin: da segnale oressizzante a regolatore del metabolismo intermedio

Rocco Barazzoni



Dept of Medical, Surgical and Health
Sciences
University of Trieste - Italy





OBESITY
METABOLIC SYNDROME

Nutritional

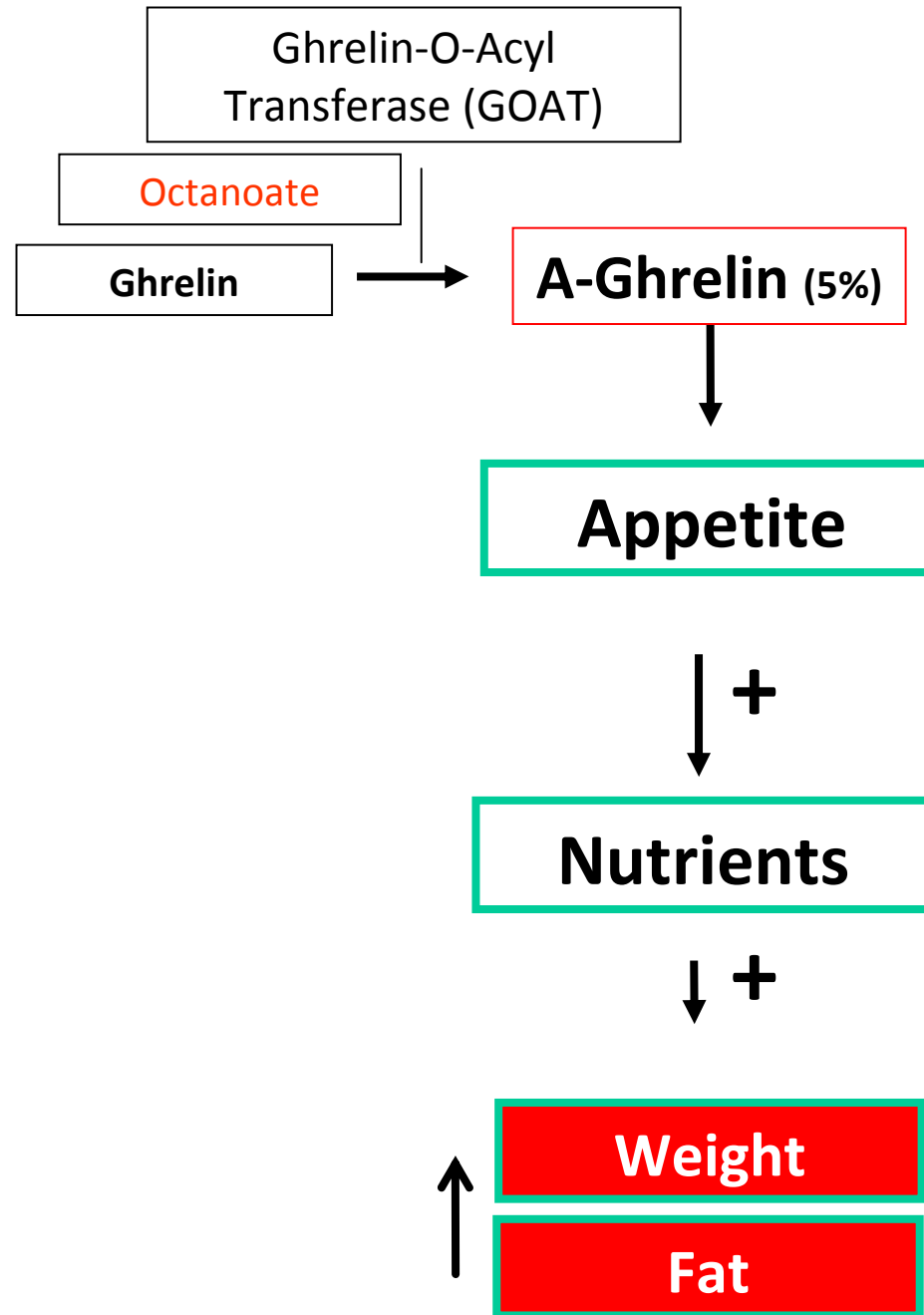
Metabolic

Vascular

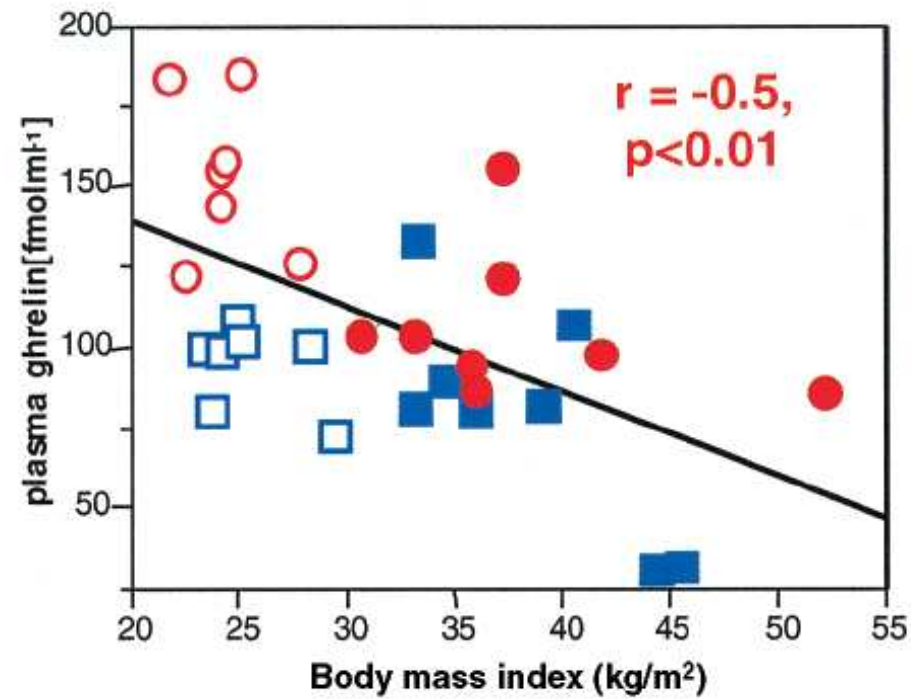
Hormonal

**Neurodegenerative
DISEASES**





Low total ghrelin in human obesity



Tschop et al, Diabetes 2001



Ghrelin-O-Acyl
Transferase (GOAT)

Octanoate

Ghrelin

A-Ghrelin (5%)

Appetite

Nutrients

Weight

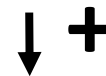
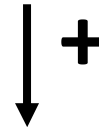
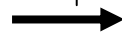
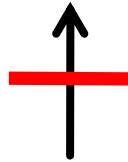
Fat

Leptin

Barazzoni et al,
Gastroenterology 2003

Insulin

Saad et al, JCEM 2002





A-Ghrelin

Appetite

Skeletal Muscle

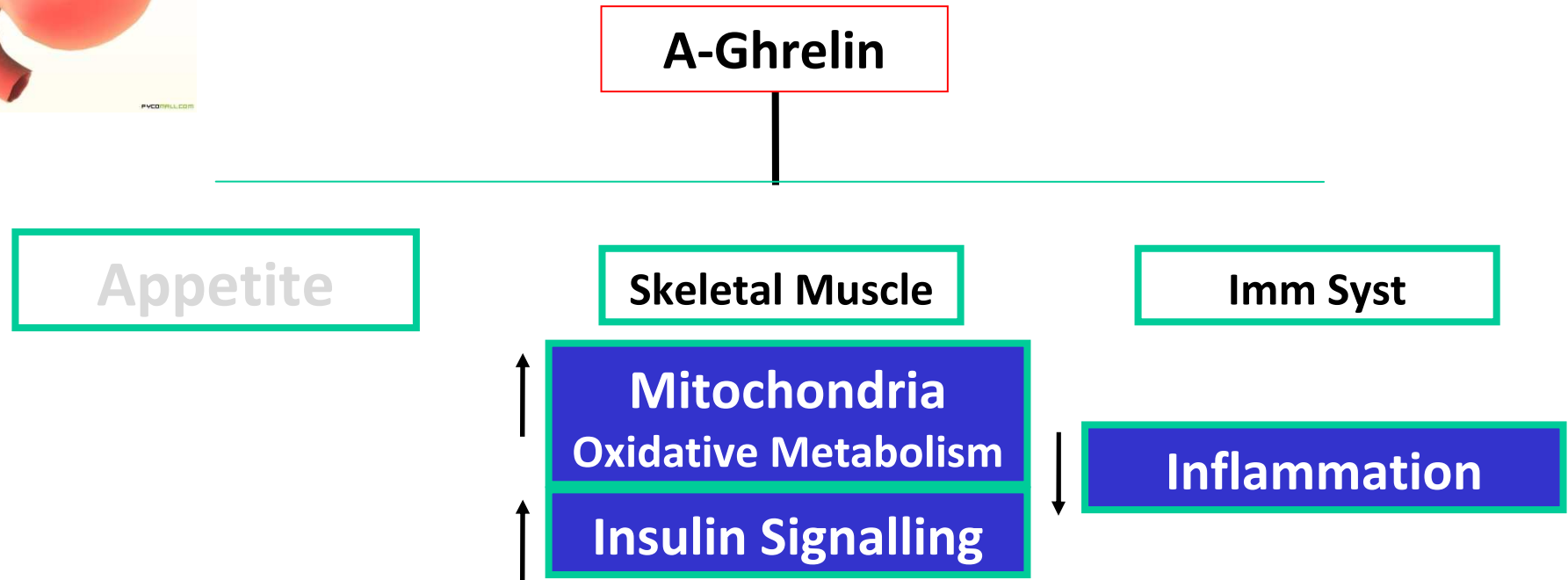
Immune

**Mitochondria
Oxidative Metabolism**

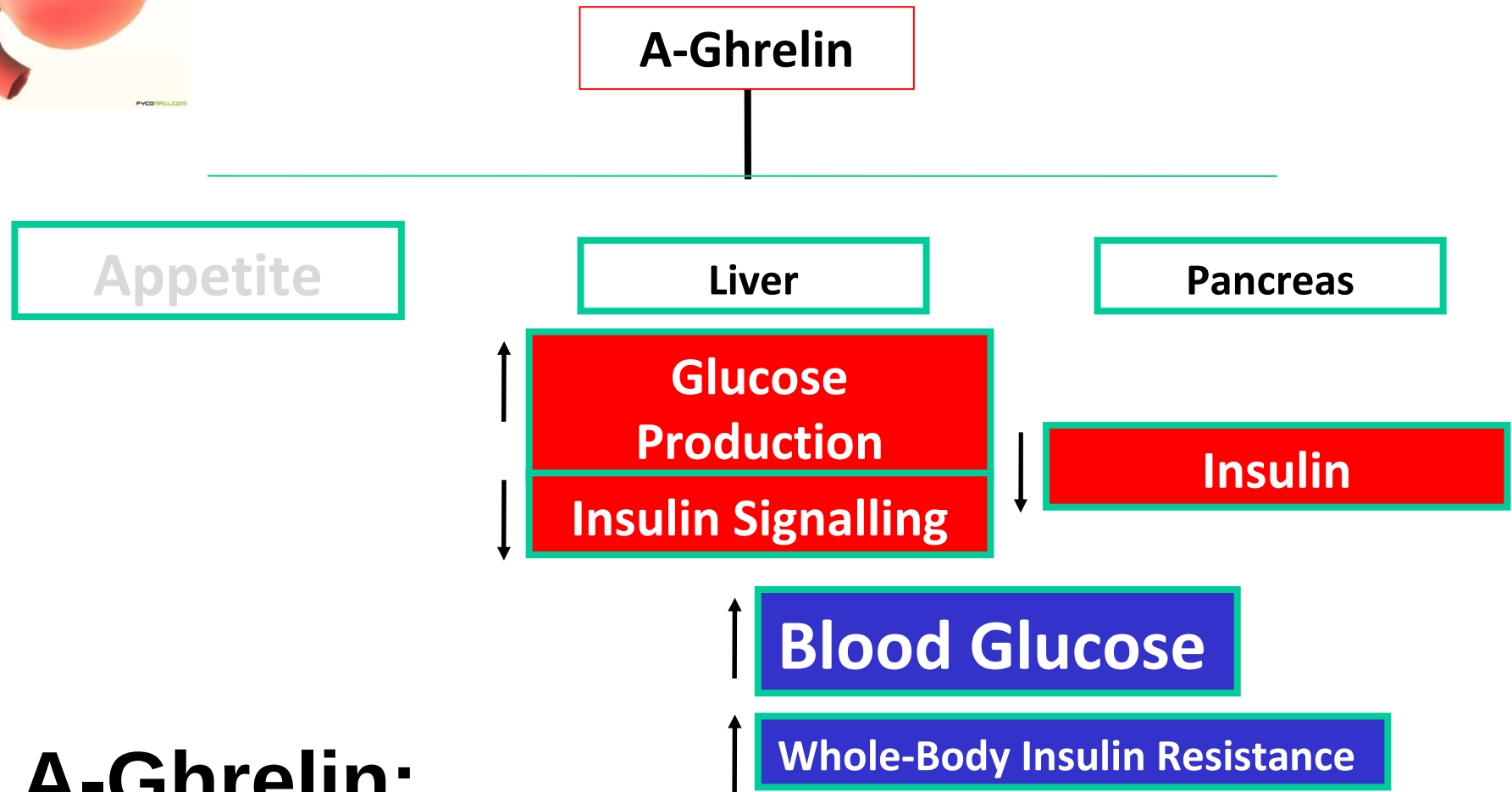
Insulin Signalling

Inflammation





**A-Ghrelin:
a FASTING - CALORIE RESTRICTION
hormone?**



**A-Ghrelin:
a FASTING - CALORIE RESTRICTION
hormone?**

Chronic Kidney Disease

Clinical Science

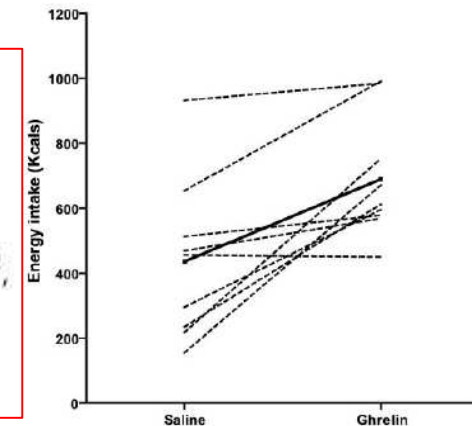
Subcutaneous Ghrelin Enhances Acute Food Intake in Malnourished Patients Who Receive Maintenance Peritoneal Dialysis: A Randomized, Placebo-Controlled Trial

Wynne et al, J Am Soc Nephrol 2005

Sustained appetite improvement in malnourished dialysis patients by daily ghrelin treatment

Damien R. Ashby^{1,2}, Heather E. Ford¹, Katie J. Wynne¹, Alison M. Wren¹, Kevin G. Murphy¹, Mark Busbridge¹, Edwina A. Brown², David H. Taube², Mohammad A. Ghatei¹, Frederick W.K. Tam², Stephen R. Bloom¹ and Peter Choi²
Ashby et al, Kidney Int 2009

¹Department of Investigative Medicine, Imperial College London, London, UK and ²West London Renal and Transplant Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK



<http://www.kidney-international.org>

© 2010 International Society of Nephrology

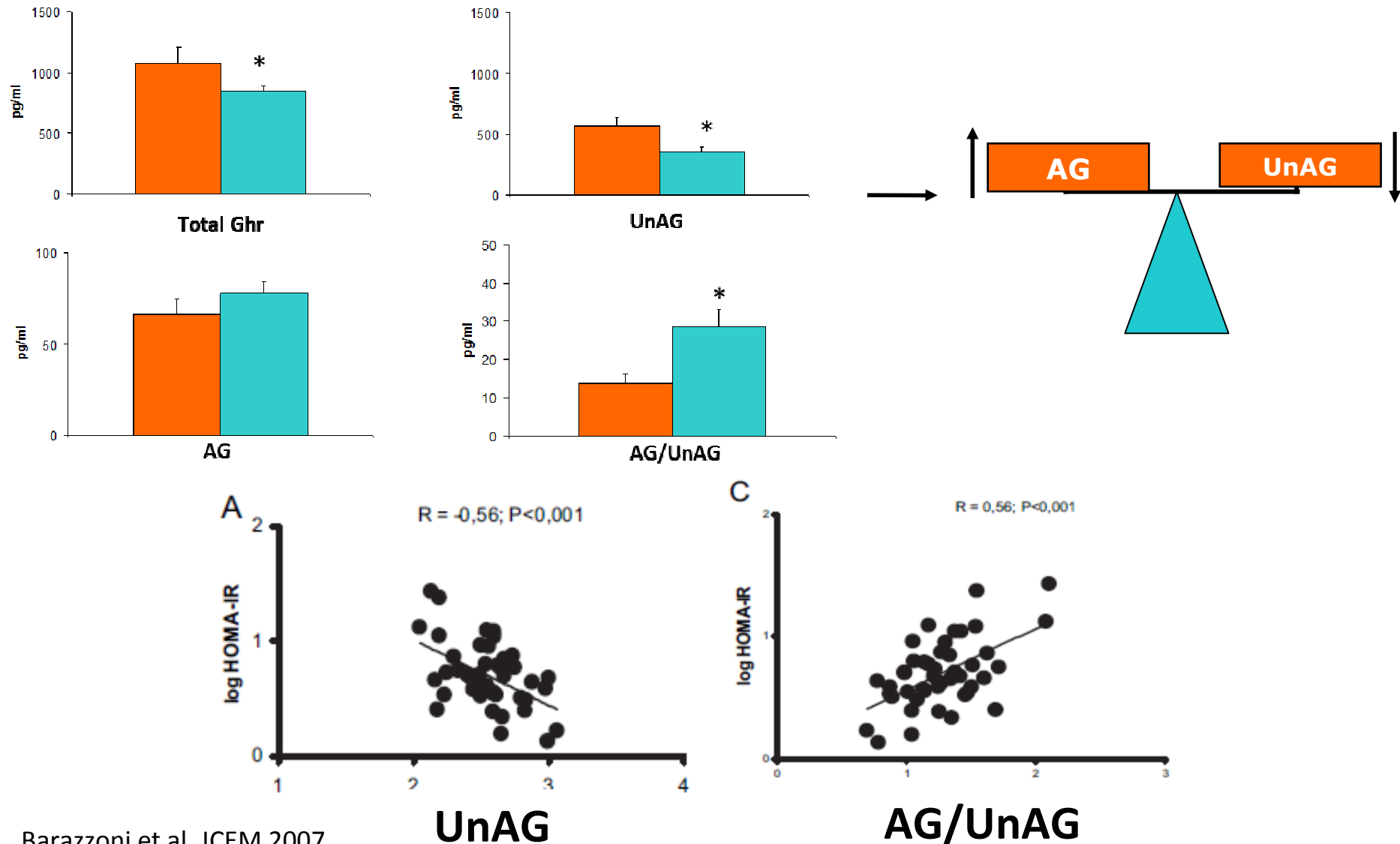
original article

Combined effects of ghrelin and higher food intake enhance skeletal muscle mitochondrial oxidative capacity and AKT phosphorylation in rats with chronic kidney disease

Rocco Barazzoni¹, XinXia Zhu², Mark DeBoer², Rakesh Datta³, Michael D. Culler³, Michela Zanetti¹, Gianfranco Guarnieri¹ and Daniel L. Marks²

OBESITY and METABOLIC SYNDROME:

altered PLASMA ghrelin profile and associations with insulin resistance

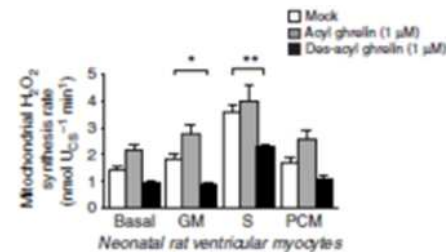


Is UnAG an independent (and potentially beneficial) hormone?

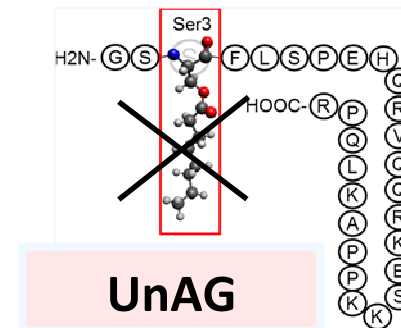


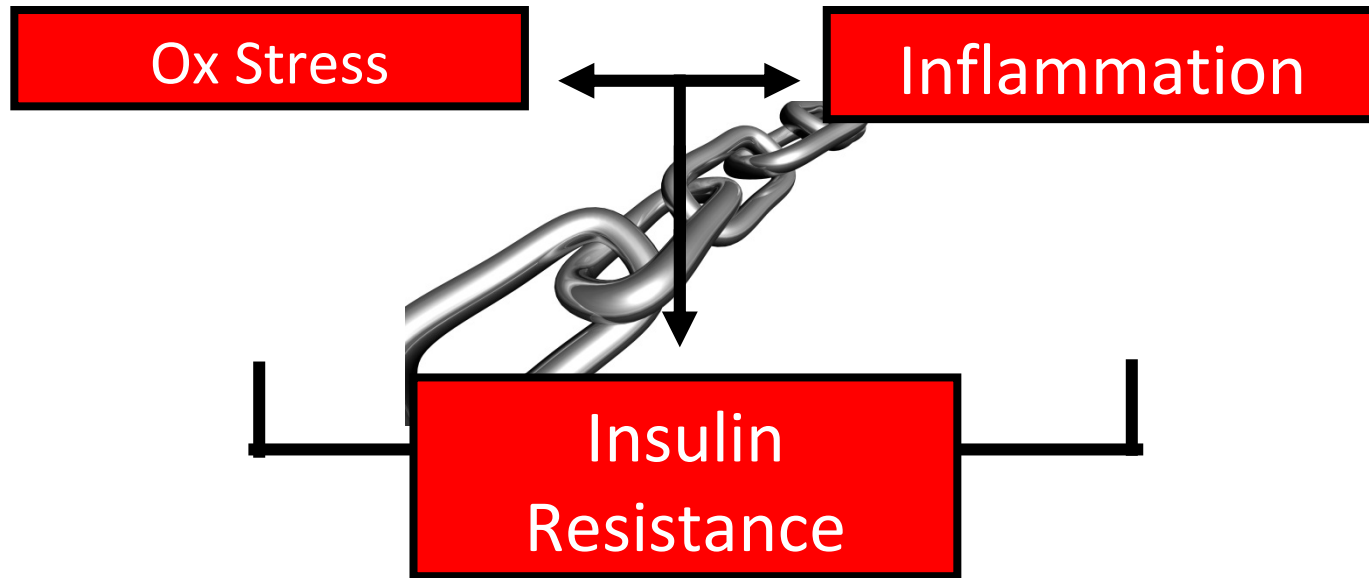
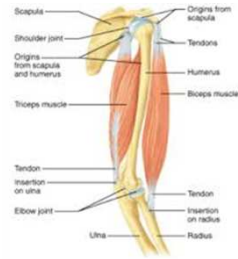
AAV-mediated *in vivo* functional selection of tissue-protective factors against ischaemia

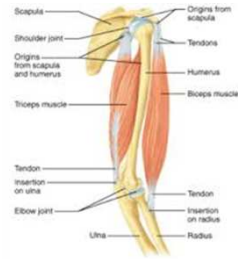
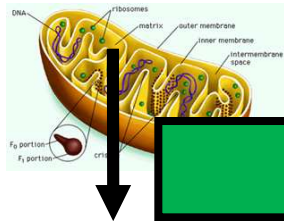
Giulia Ruozzi¹, Francesca Bortolotti¹, Antonella Falcione¹, Matteo Dal Ferro^{1,2}, Laura Ukovich¹, Antero Macedo¹, Lorena Zentilin¹, Nicoletta Filigheddu³, Gianluca Gortan Cappellani², Giovanna Baldini², Marina Zweyer², Rocco Barazzoni², Andrea Graziani³, Serena Zacchigna^{1,2} & Mauro Giacca^{1,2}



UnAG reduces ROS production in cardiomyocytes *in vitro*







Ox Stress

Inflammation

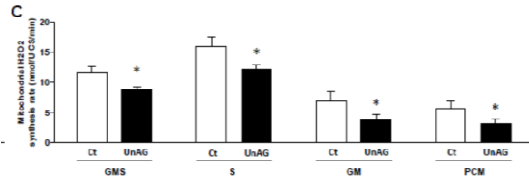


UnAG

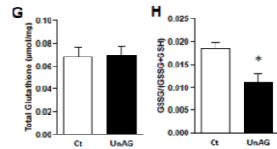
Insulin Resistance

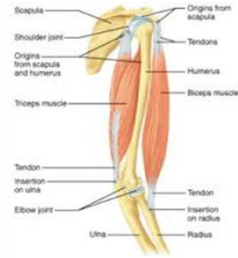
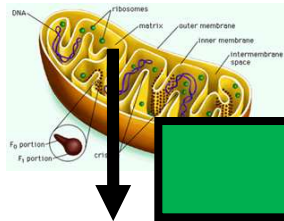


Mitochondrial H₂O₂ Production



GSSG:Total Glutathione



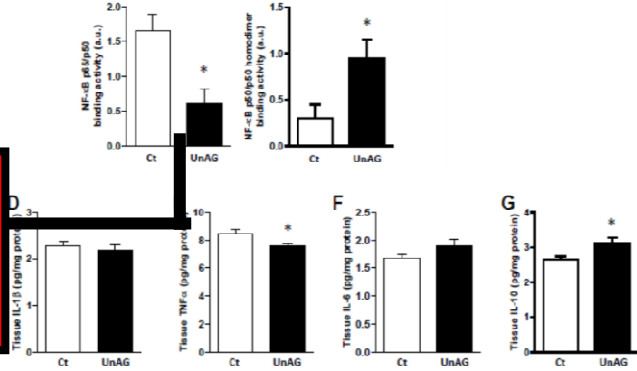


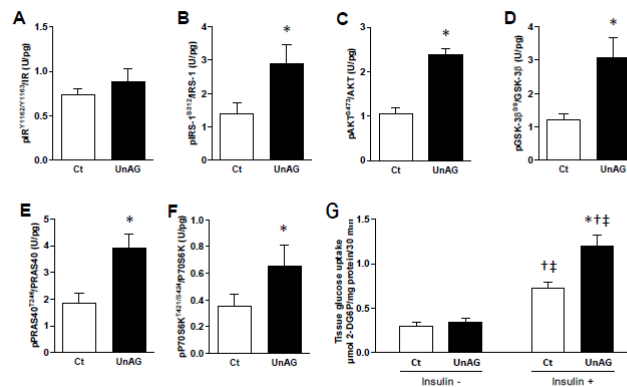
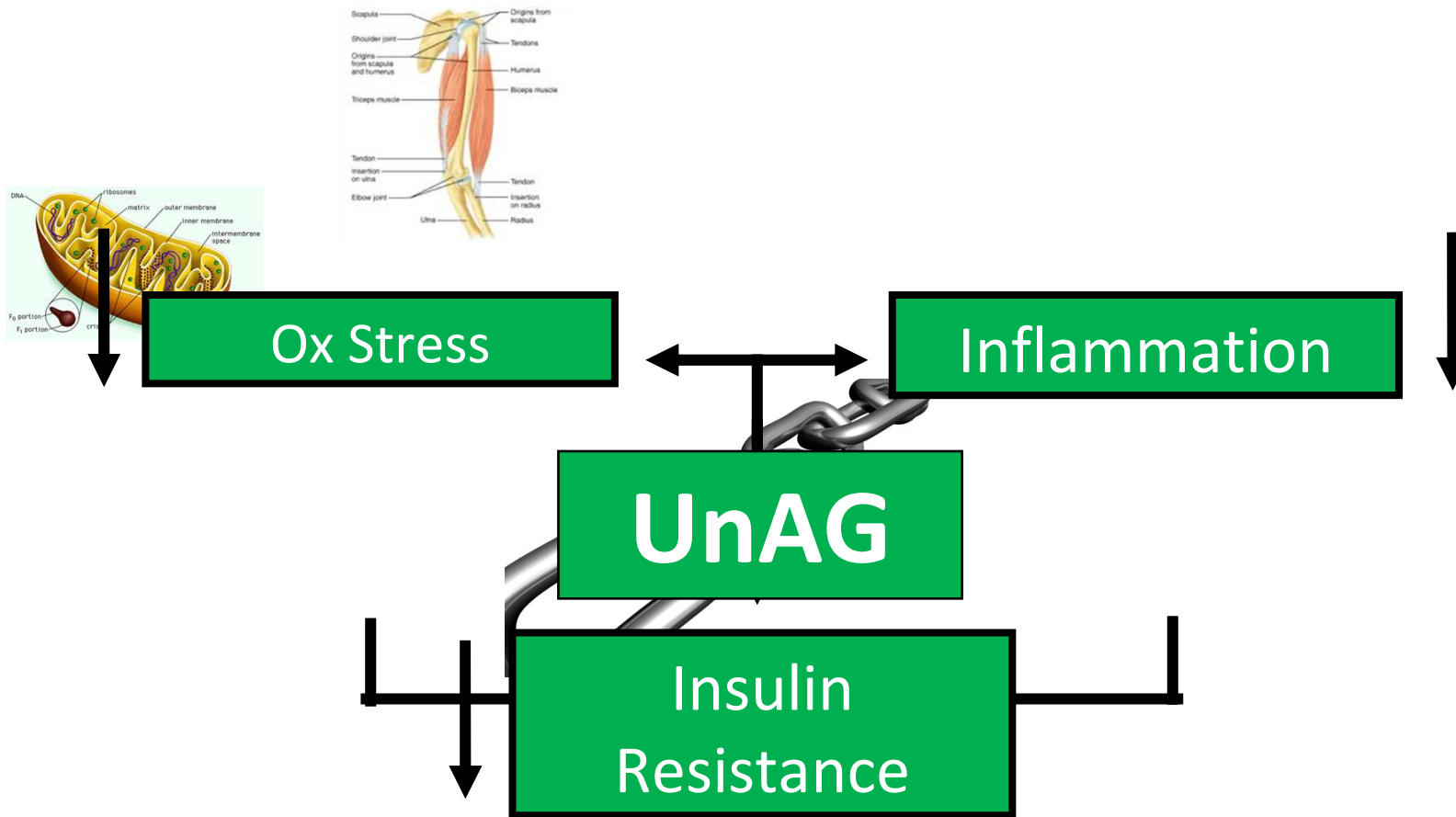
Ox Stress

Inflammation

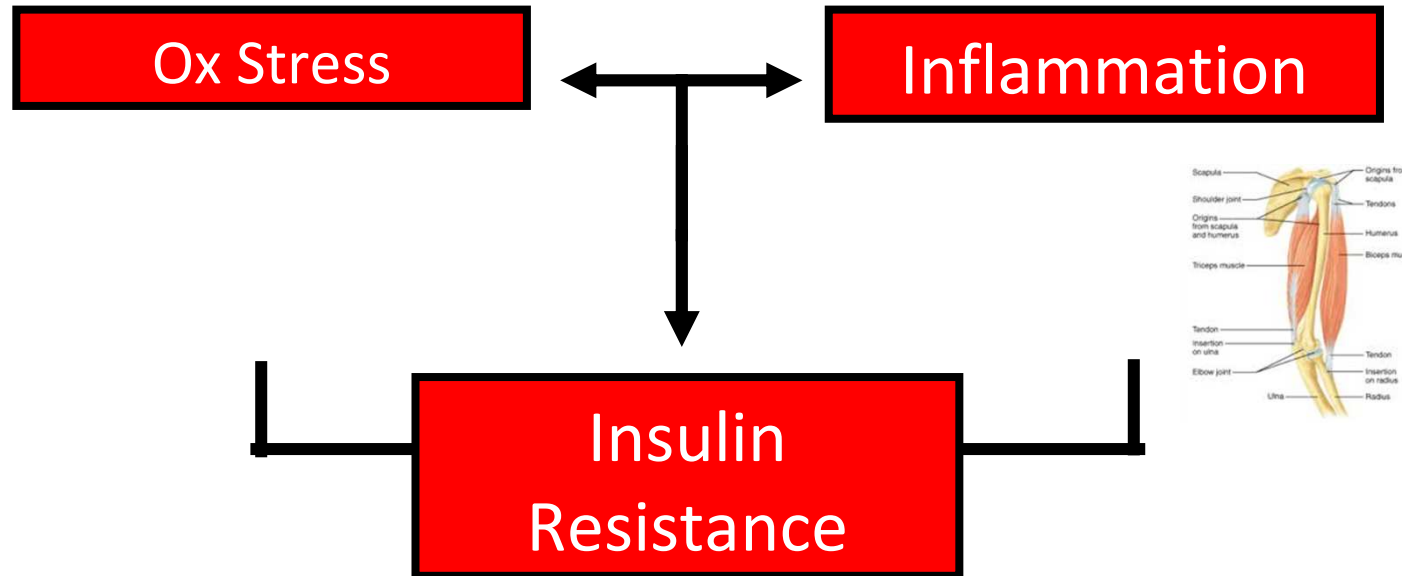
UnAG

Insulin Resistance

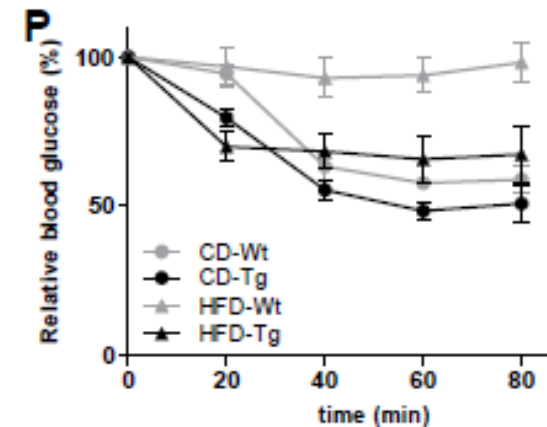
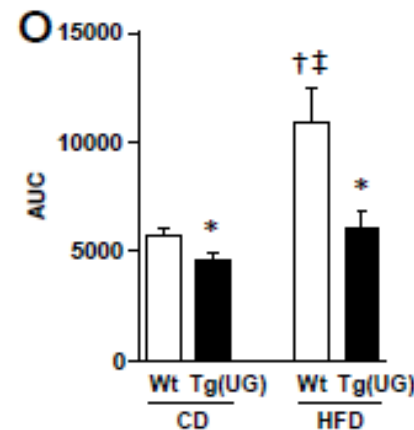
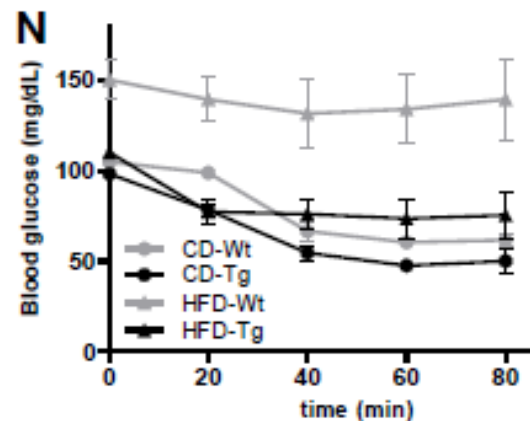
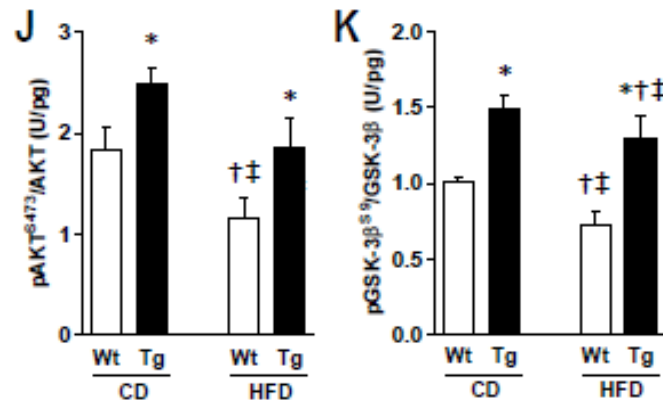




OBESITY ?

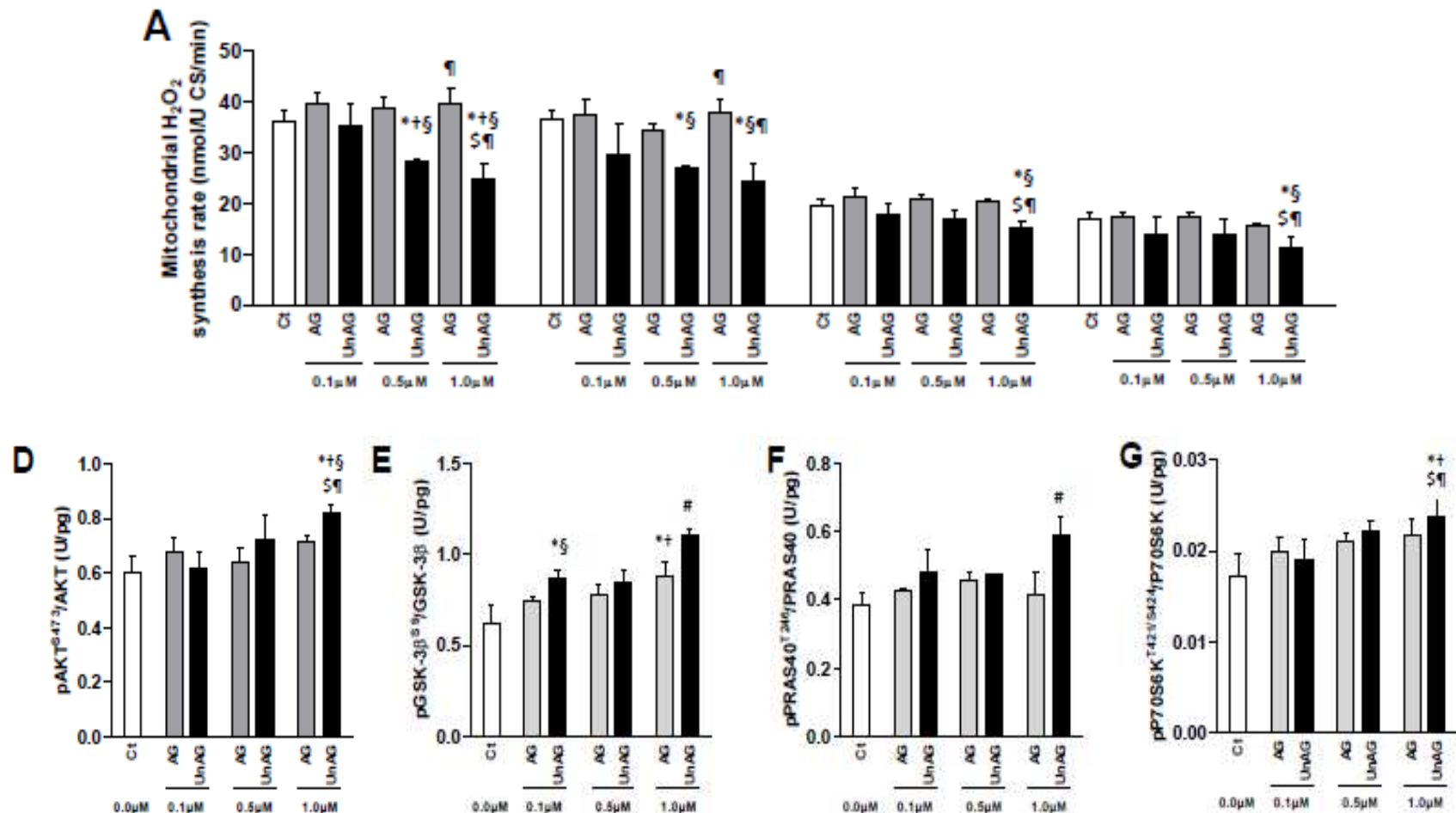


Genetically-induced chronic UnAG elevation prevents obesity-associated insulin resistance and hyperglycemia



Are UnAG activities direct and independent of AG?

Myotubes in vitro: AG vs UnAG

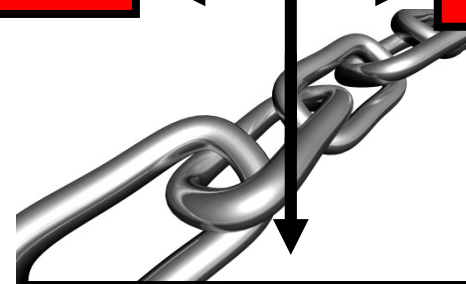




**CHRONIC
Disease**

Ox Stress

Inflammation



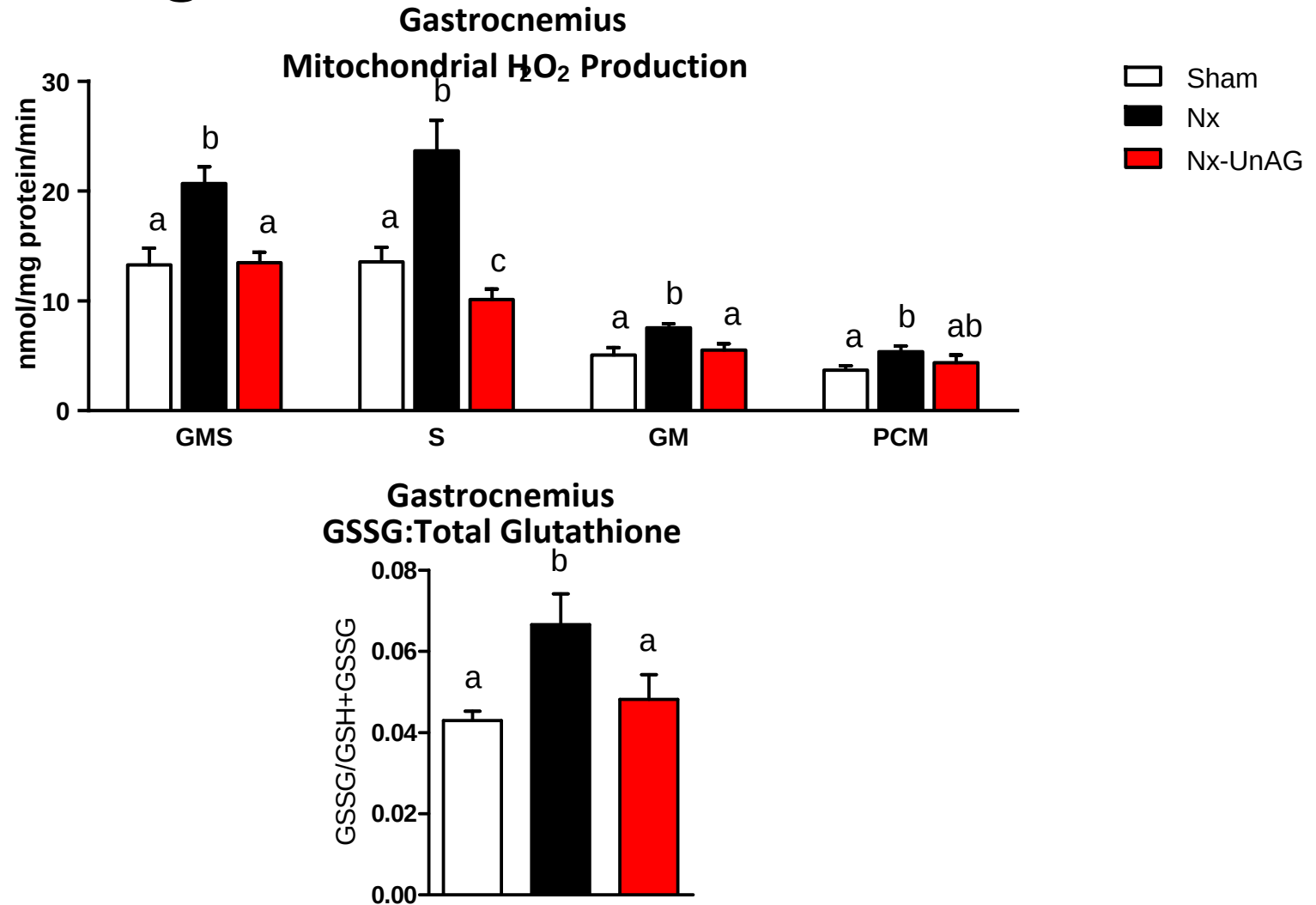
**Insulin
Resistance**

WASTING

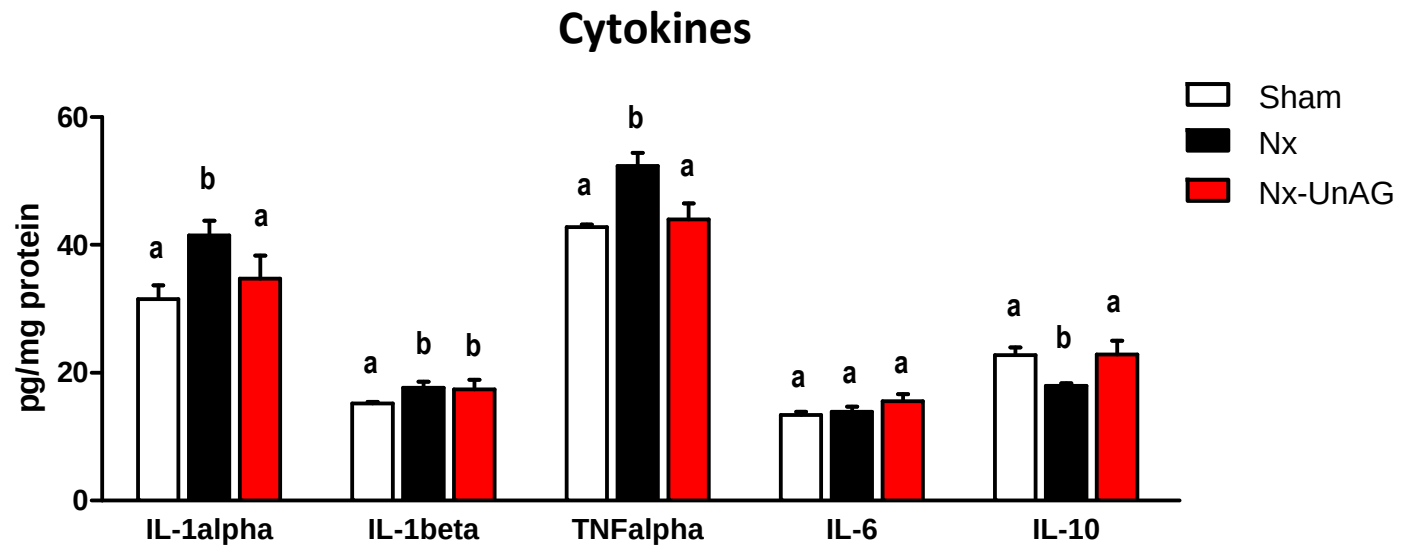
Is UnAG a potential treatment
for chronic disease-associated
muscle metabolic alterations?

Experimental CKD

ROS generation and redox state



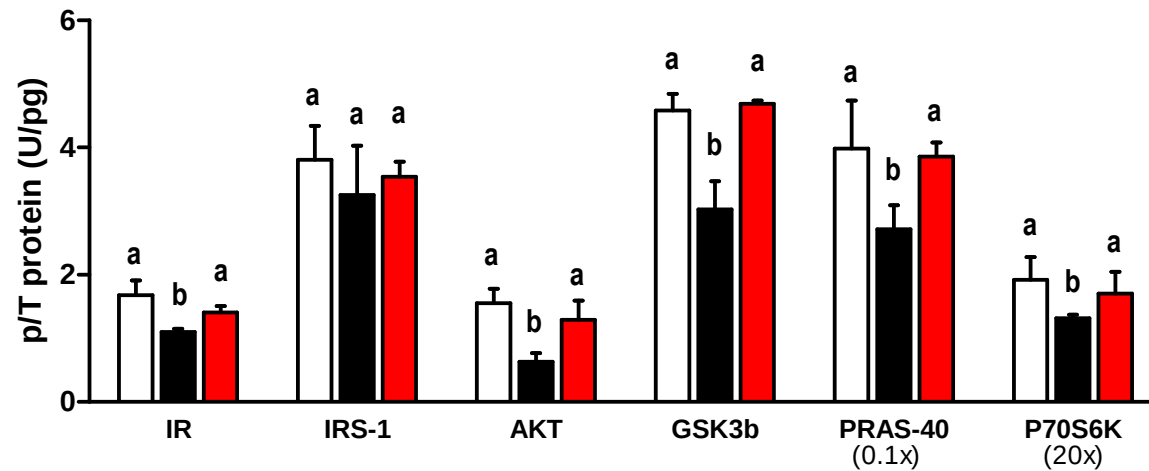
Experimental CKD Inflammation



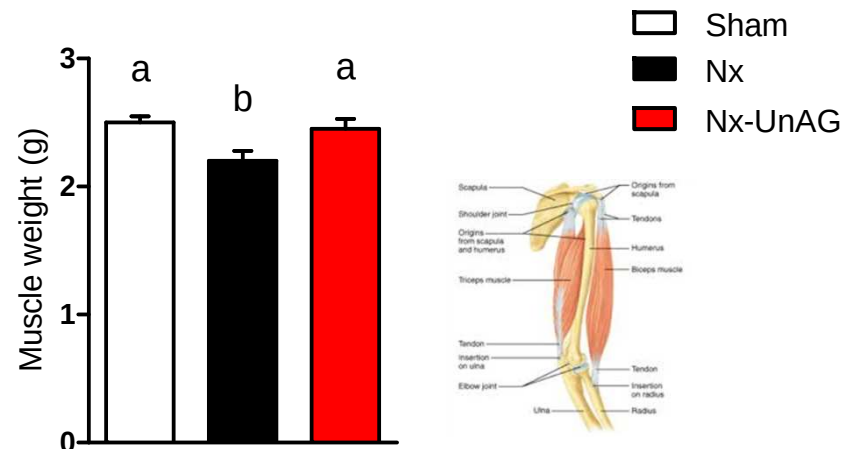
Experimental CKD

Insulin signalling and MUSCLE MASS

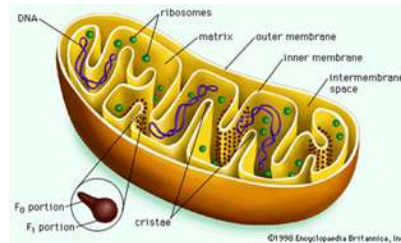
Insulin signalling



Muscle weight

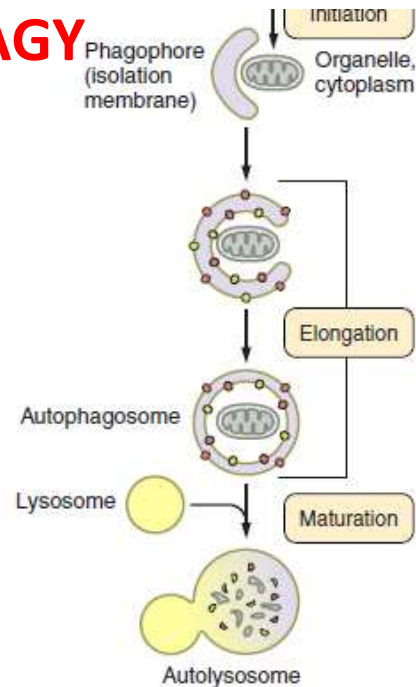


What are the mechanisms of muscle UnAG activities?



AUTOPHAGY: complex catabolic process contributing to disposal of DAMAGED tissue organelles (MITOCHONDRIA)

AUTOPHAGY

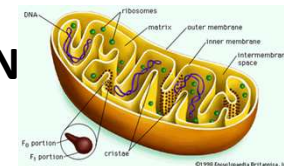


↑↑↑
EXCESS

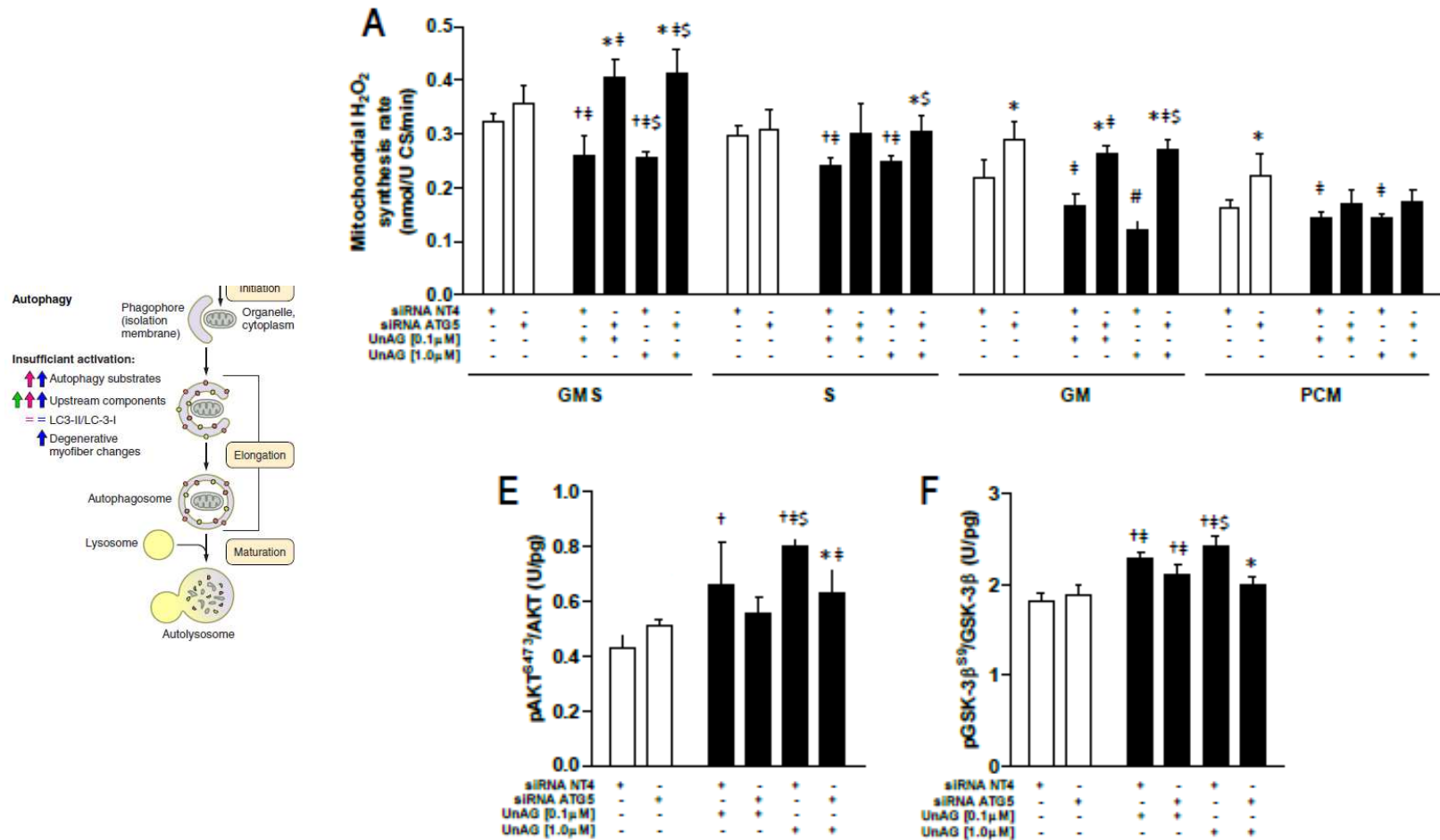
↓↓↓
DEFECT

DEATH

**DAMAGE
ACCUMULATION
DYSFUNCTION**

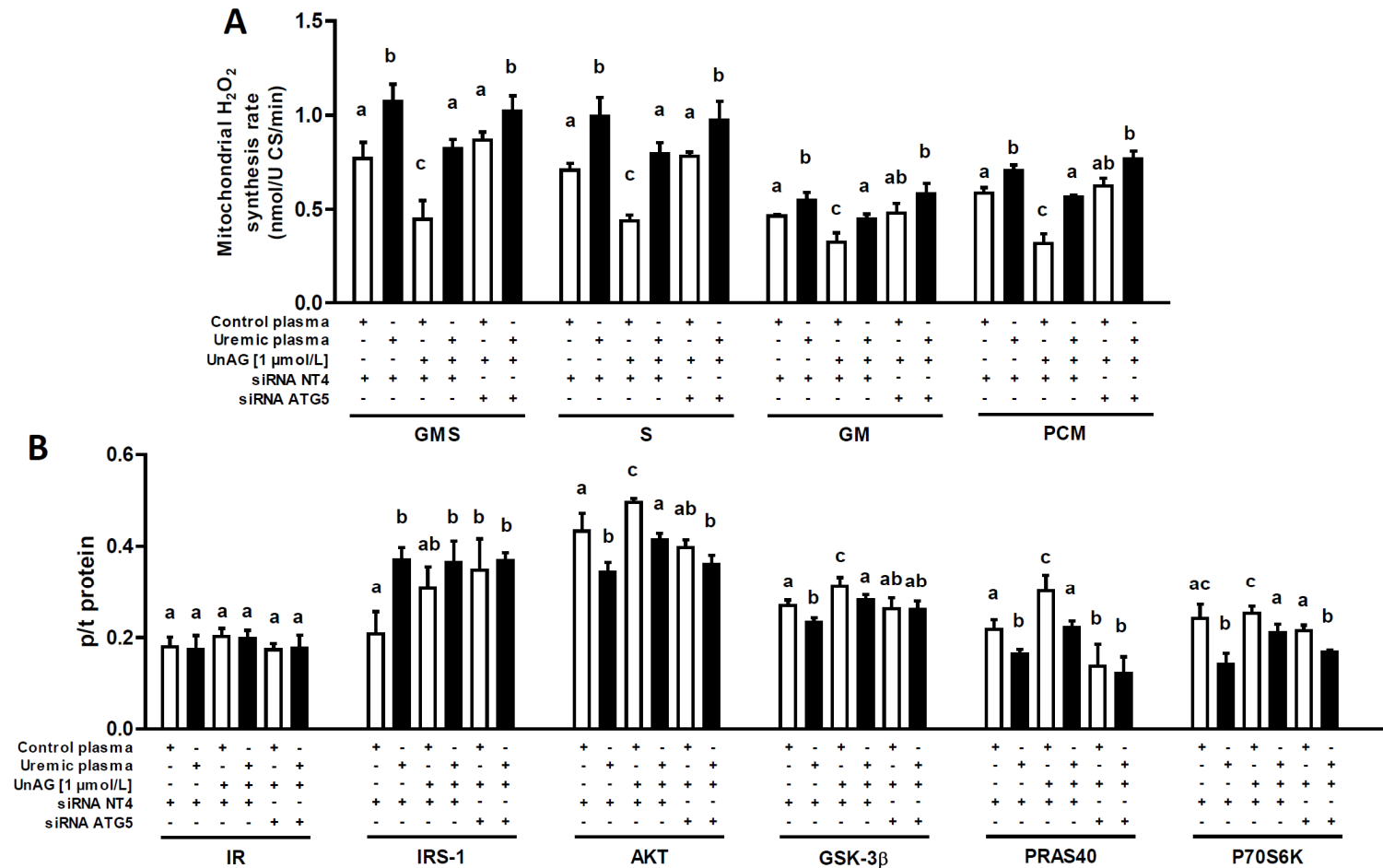


UnAG antioxidant and insulin-sensitizing effects are mediated by AUTOPHAGY in myotubes

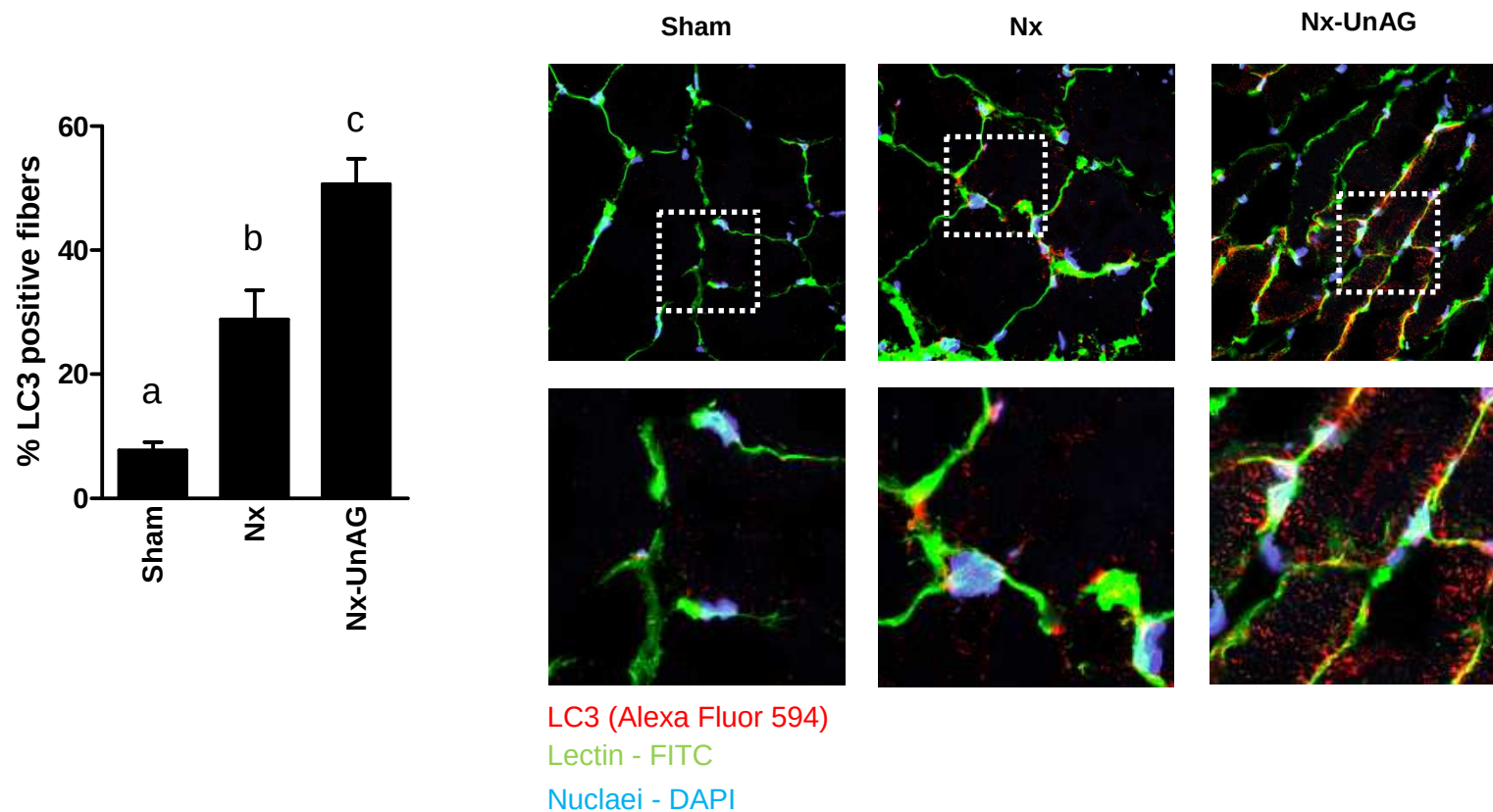


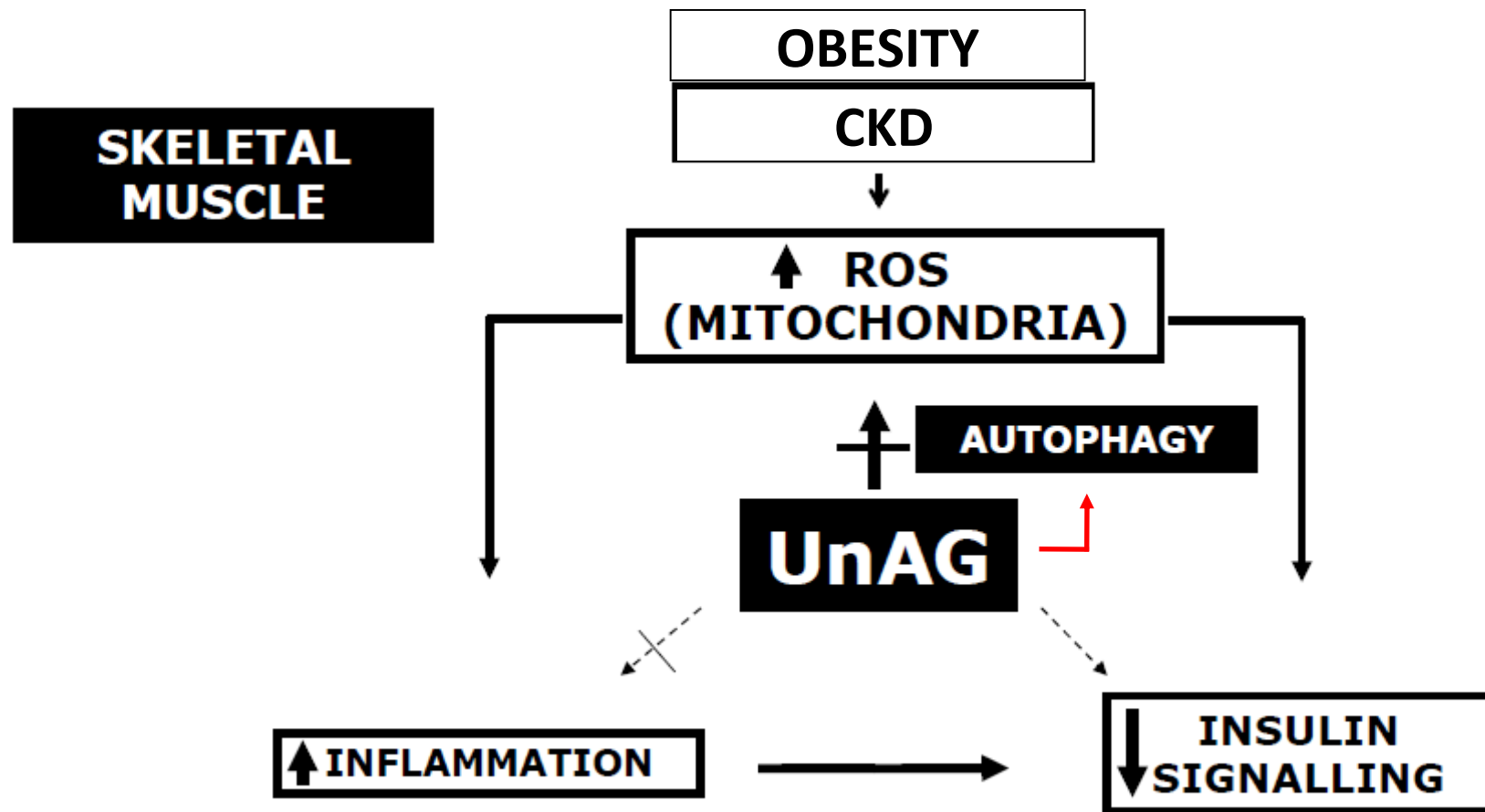
UnAG antioxidant and insulin-sensitizing effects are mediated by AUTOPHAGY in myotubes

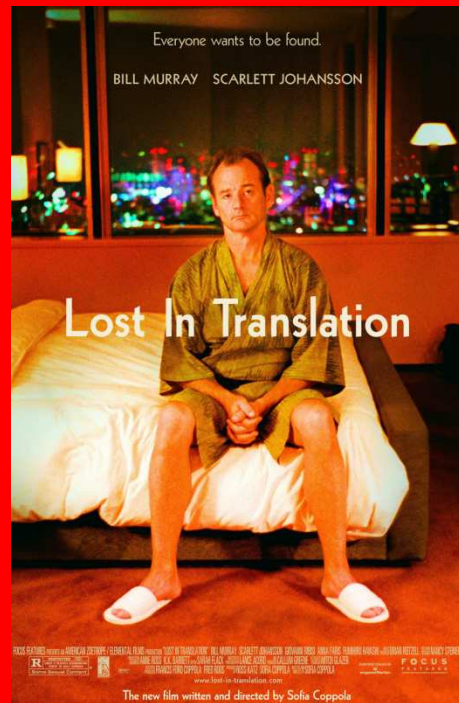
In vitro uremic model



Autophagy activation in Skeletal Muscle - CKD



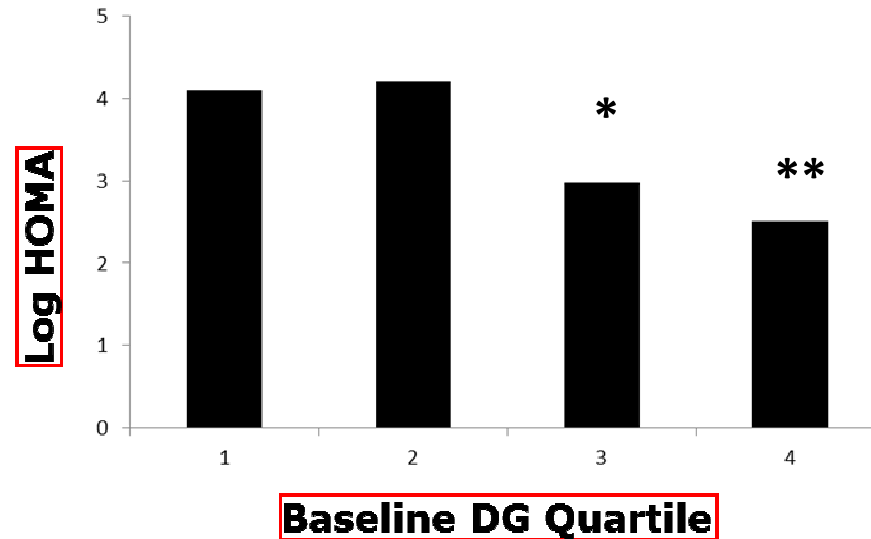




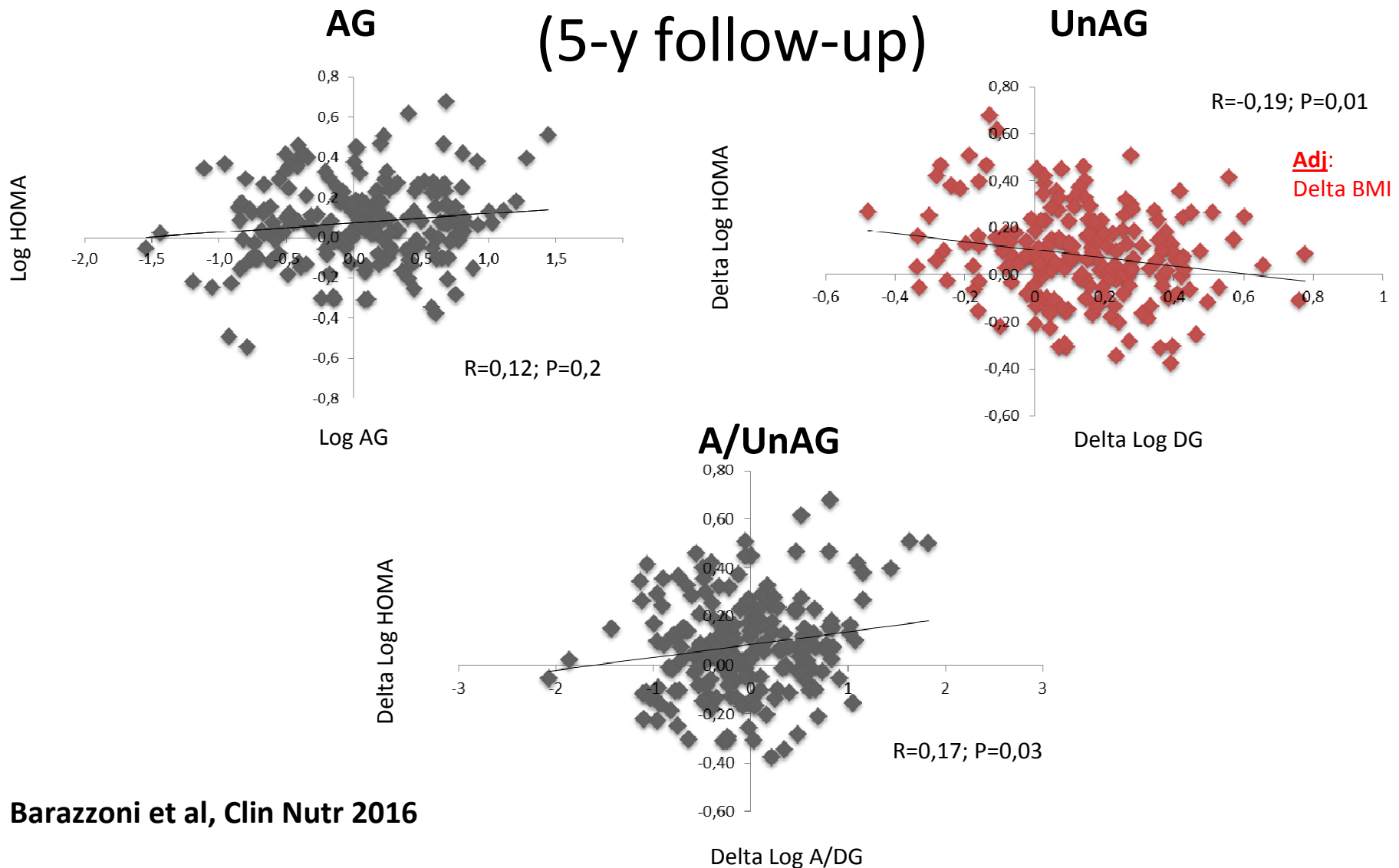
UnAG – HUMAN RELEVANCE?

Baseline plasma UnAG predicts insulin sensitivity

(n=250; general population cohort; 5-y follow-up)

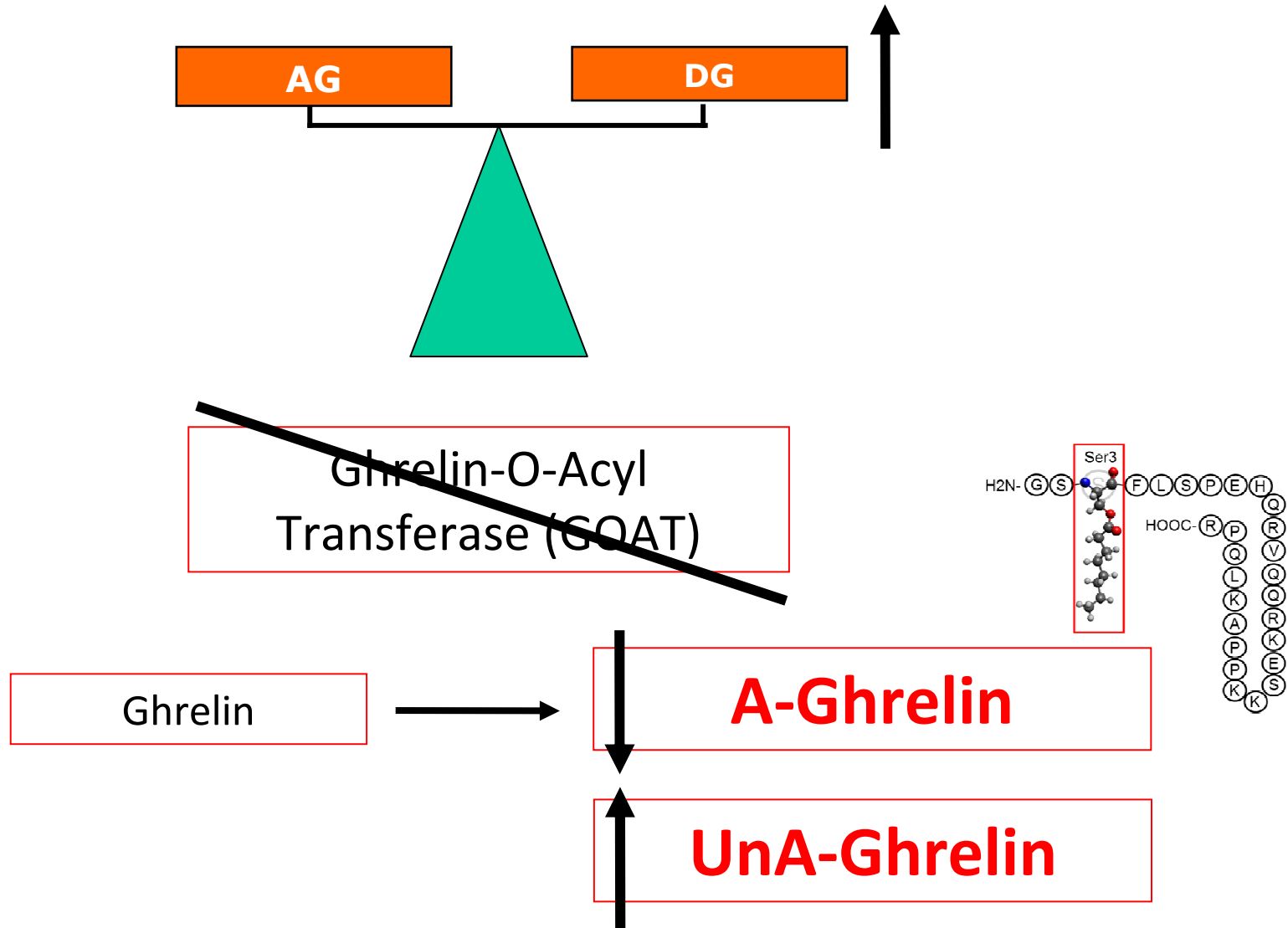


Changes in plasma ghrelin profile predict changes in insulin sensitivity (5-y follow-up)



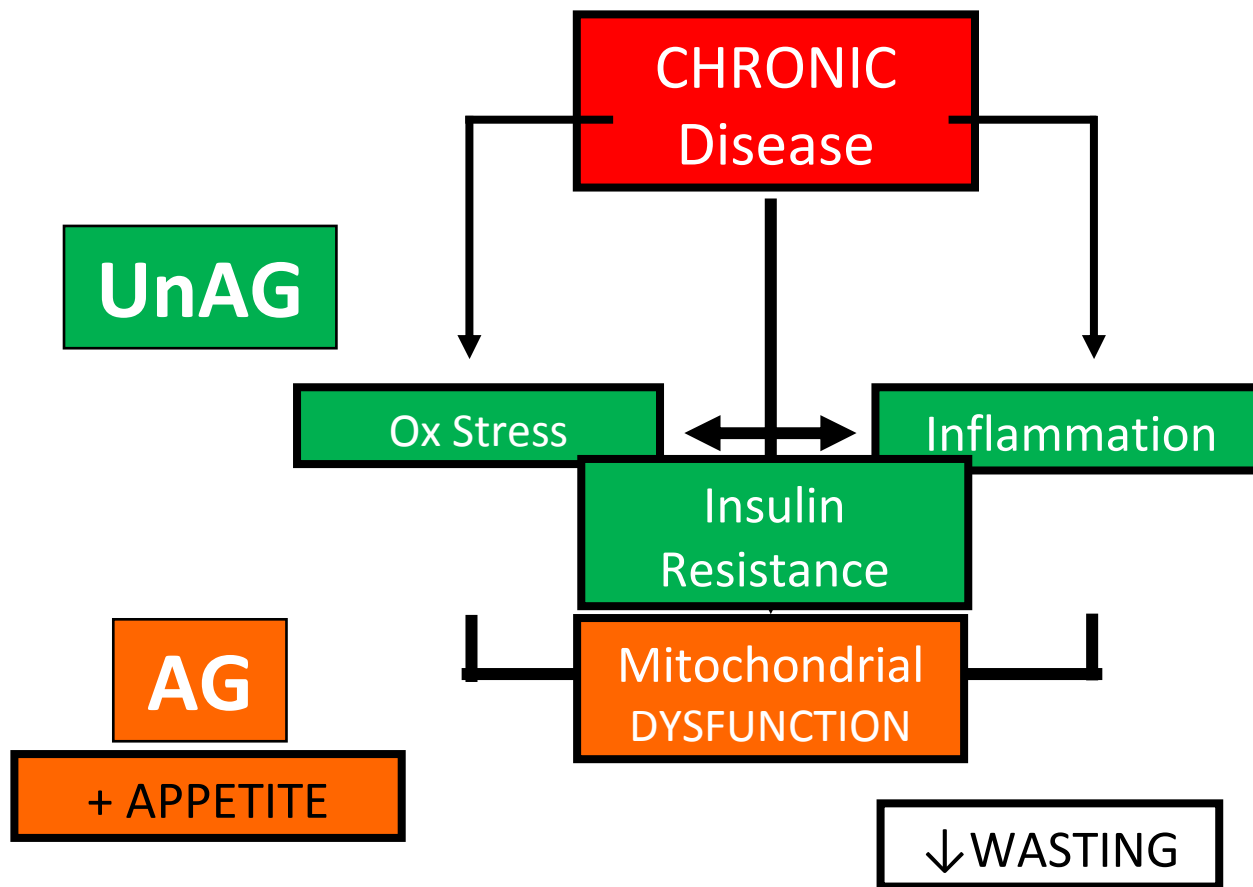
THERAPEUTIC PERSPECTIVE

Obesity and Metabolic Syndrome



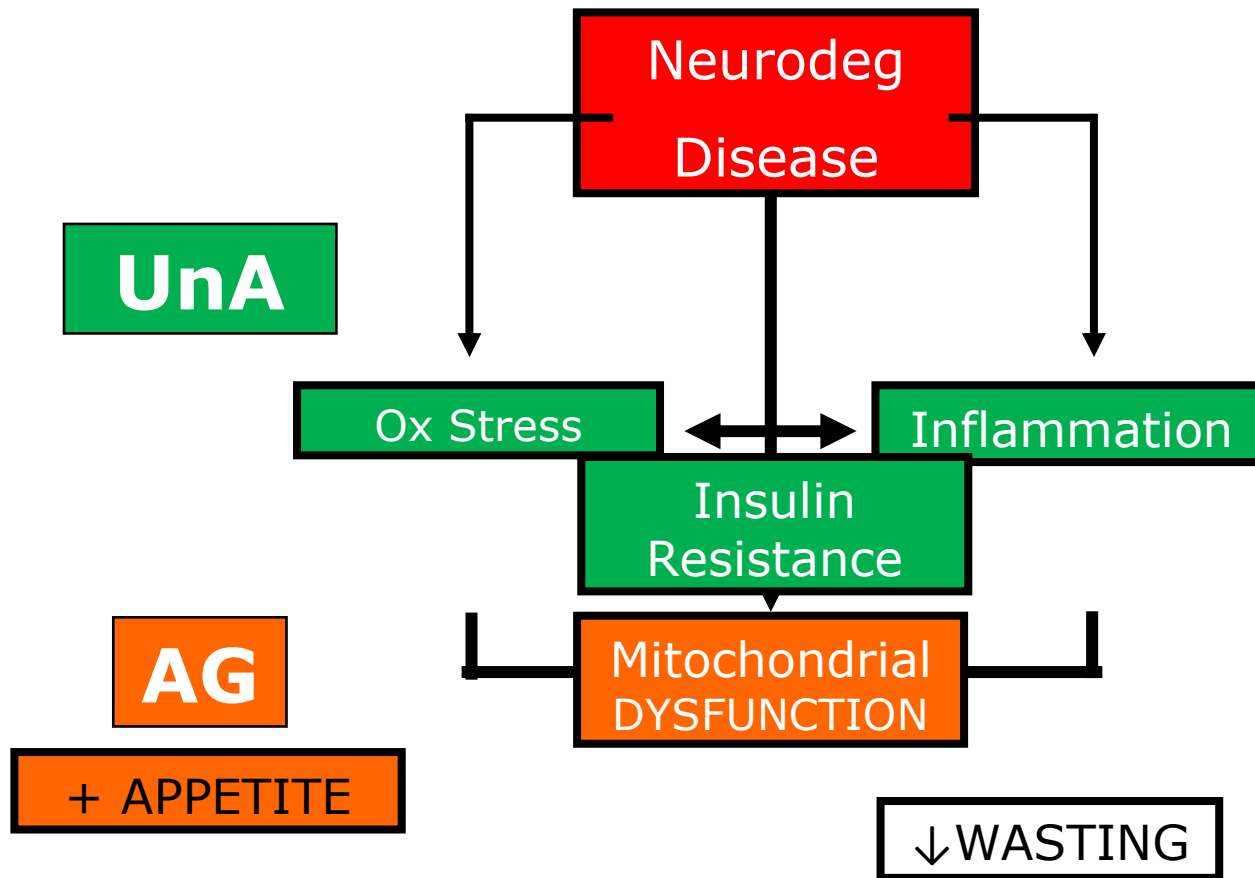
THERAPEUTIC PERSPECTIVE

Chronic Disease-Induced Malnutrition



THERAPEUTIC PERSPECTIVE

Neurodegenerative Disease-Induced Malnutrition



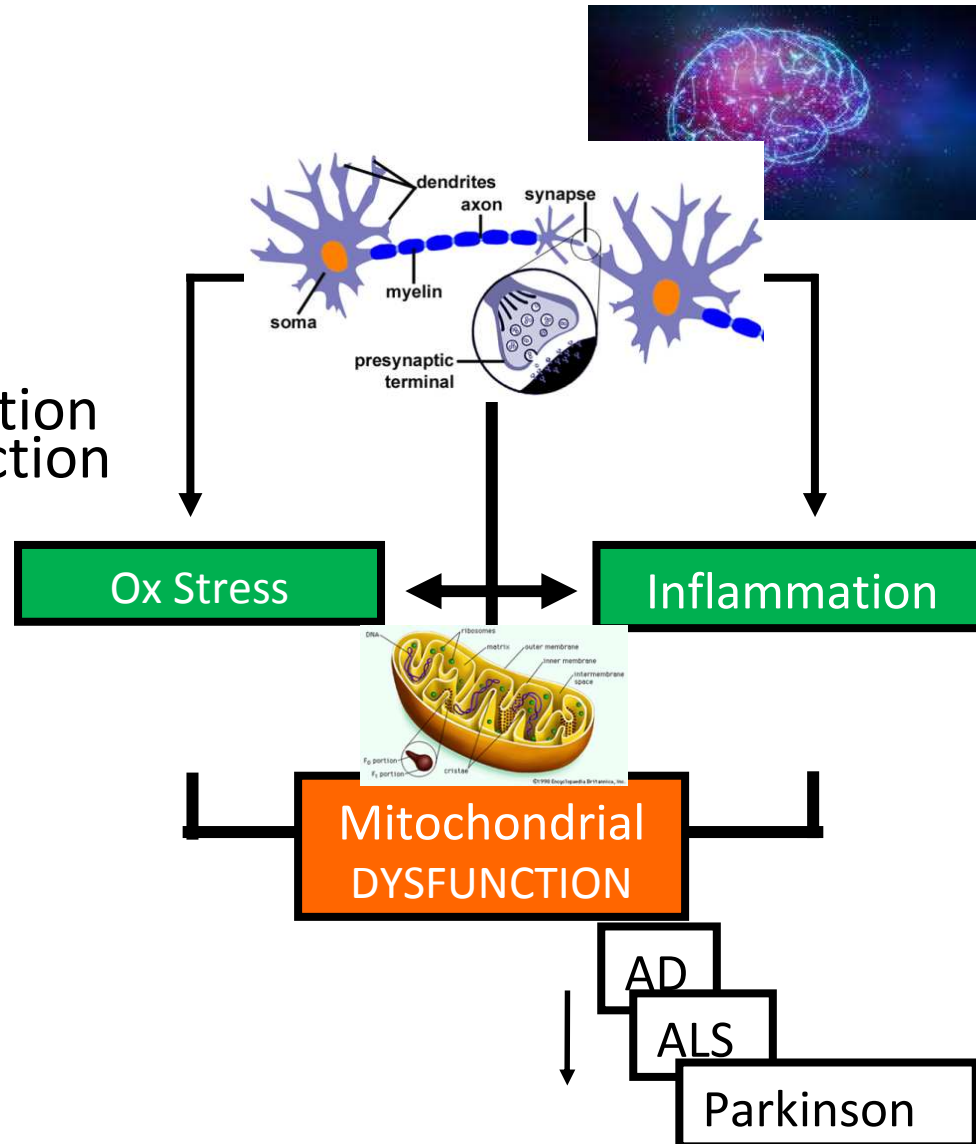
THERAPEUTIC PERSPECTIVE

Neurodegenerative Disease-Pathophysiology

AG

UnAG?

Neuroprotection
Synaptic function





THERAPEUTIC PERSPECTIVE

Neurodegenerative Disease - Pathophysiology

Journal of Neuroendocrinology

Journal of Neuroendocrinology, 2014, 26, 176–185

© 2014 British Society for Neuroendocrinology

ORIGINAL ARTICLE

Protective Effect of Leptin and Ghrelin against Toxicity Induced by Amyloid- β Oligomers in a Hypothalamic cell Line

S. Gomes*, I. Martins*, A. C. R. G. Fonseca†, C. R. Oliveira†‡, R. Resende† and C. M. F. Pereira†‡

Ghrelin-AMPK Signaling Mediates the Neuroprotective Effects of Calorie Restriction in Parkinson's Disease

Jacqueline A. Bayliss,¹ Moyra B. Lemus,¹ Romana Stark,¹ Vanessa V. Santos,¹ Aiysha Thompson,² Daniel J. Rees,² Sandra Galic,³ John D. Elsworth,⁴ Bruce E. Kemp,³  Jeffrey S. Davies,² and  Zane B. Andrews¹

J Neurosci 2016

Review

Ghrelin: A link between ageing, metabolism and neurodegenerative disorders

I.I. Stoyanova*

protective effect. All these make ghrelin an attractive target for development of biomarkers or therapeutics for prevention or treatment of disorders, in which cell protection and recruitment of new neurons or synapses are needed.

Neurobiol Dis 2014

• Summary

- Ghrelin is a gastric orexigenic hormone circulating in acylated and unacylated forms (UnAG)
- AG has orexigenic effects and may enhance muscle mitochondrial function with potential anticatabolic effects
- UnAG has independent metabolic effects that include reduction of muscle oxidative stress, inflammation and insulin resistance
- UnAG may normalize metabolic alterations causing muscle wasting and hyperglycemia in chronic disease or in diet-induced obesity
- UnAG activities appear to be mediated by autophagy and removal of dysfunctional organelles (mitochondria)

These combined observations indicate potential for combined utilization of UnAG (direct administration, downregulation of ghrelin acylating systems) and-or AG as therapeutic strategies for chronic disease-related malnutrition as well as obesity-associated neurodegenerative complications

Acknowledgements

Trieste team:

G Gortan

A Semolic

P Vinci

M. Zanetti

Collaborations:

D. Marks

M. Giacca

A. Graziani

