

Ernährung 2006

International Cachexia Workshop

Berlin, June 2006

Antiproteolytic strategies

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Hippocrates of Kos:

(460-370 BC)

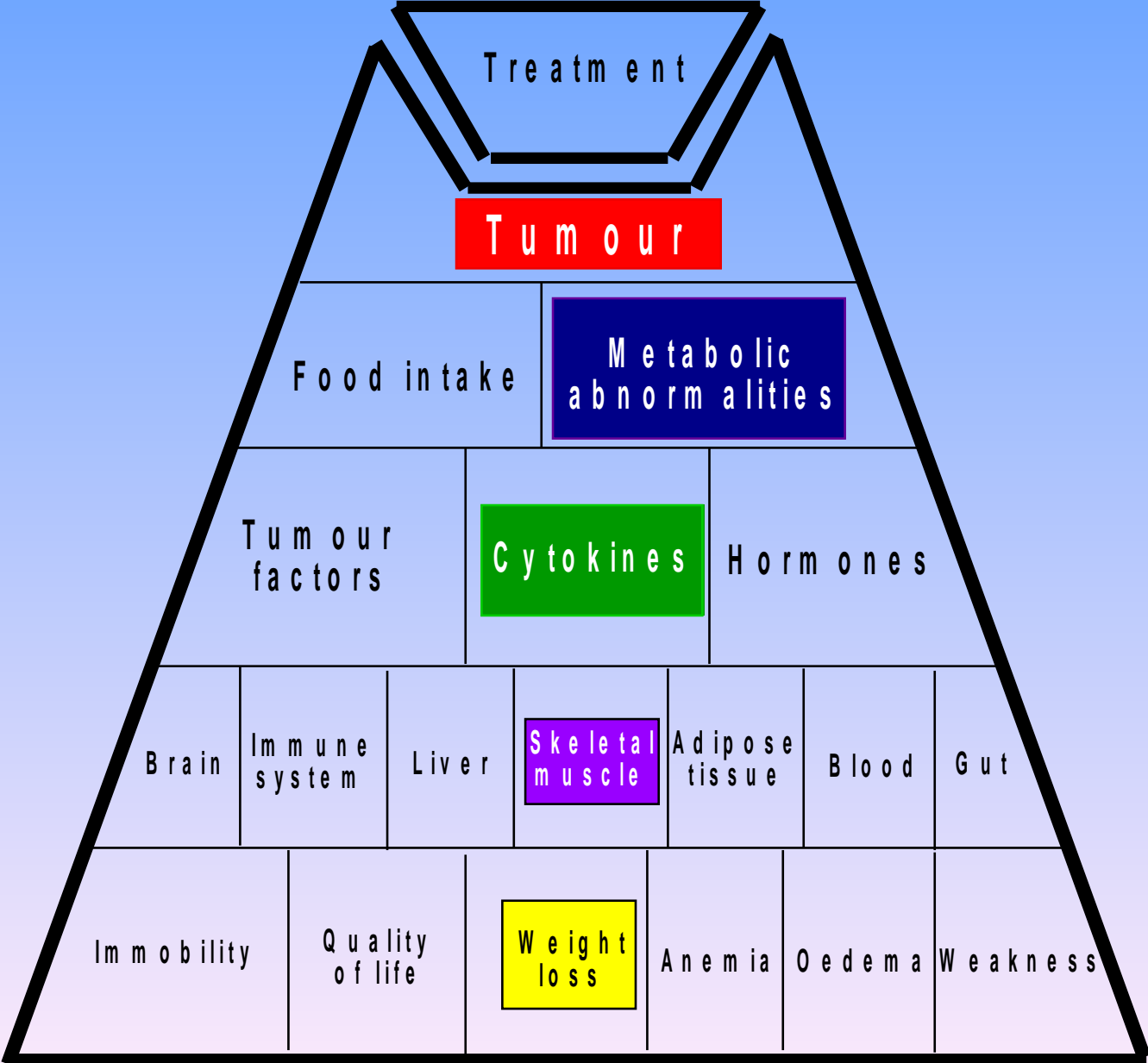
**“The flesh is
consumed and
becomes water,...
, the shoulders,
clavicles, chest
and thighs melt
away. The illness
is fatal”**



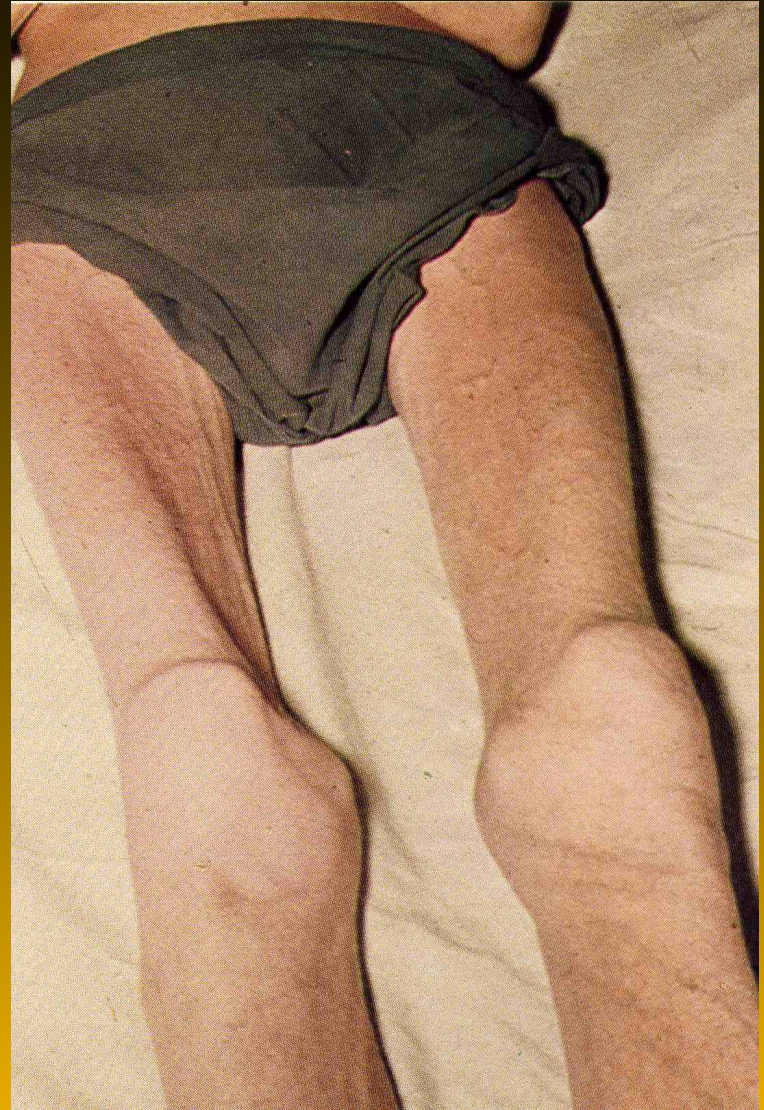
Multiorgan syndrome

Systemic disorder

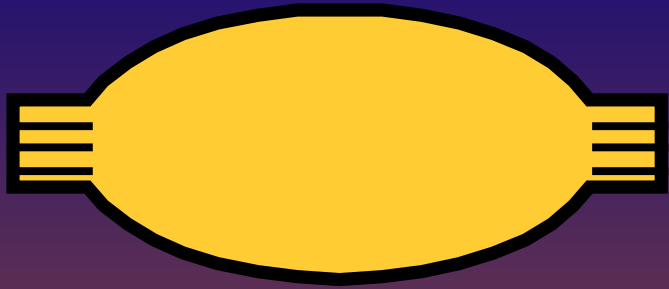
The Cachexia Pyramid



Skeletal muscle



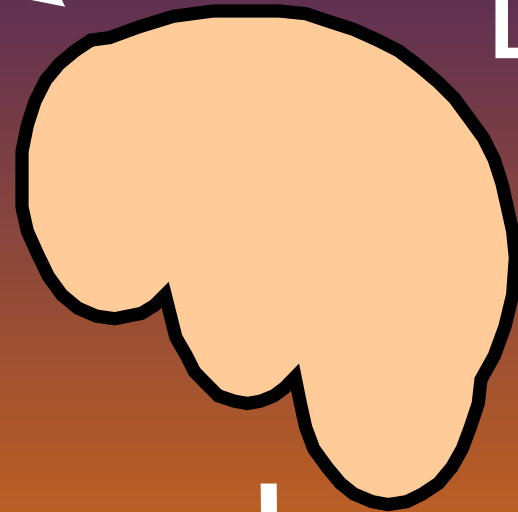
MUSCLES



AA



LIVER



**Acute-phase
proteins**



Gluconeogenesis

Skeletal muscle

- Decreased AA uptake
- Increased AA oxidation
- Decreased glucose transport
- Alterations in mitochondrial function (uncoupling)
- Apoptosis
- Alterations in satellite cell proliferation/differentiation
- ***Increased proteolysis***

ESTIMATION OF PROTEIN TURNOVER *IN VIVO*

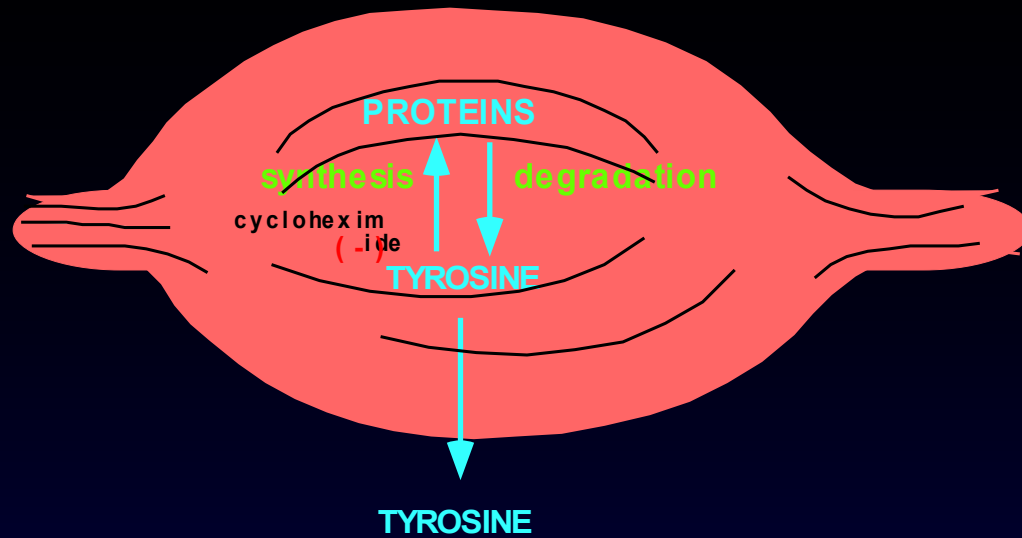
^{14}C -PROTEIN LOADING

400mCi/kg body weight $\text{NaH}^{14}\text{CO}_3$

SKELETAL MUSCLE (GASTROCNEMIUS)

	Ks	Kd	Ka
Control	11.6	5.63	5.14
AH-130	12.0	13.9	-1.97

Costelli et al., J Clin Invest. 1993;92(6):2783-9.



TOTAL PROTEOLYSIS = DEGRADATION
NET PROTEOLYSIS = DEGRADATION - SYNTHESIS

Tyrosine released by isolated *soleus* rat muscles

(nmoles/g.hr)

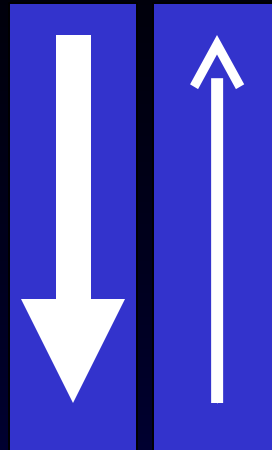
PAIR-FED	TUMOUR
194	251 ***

(Martínez et al, 1994)

CANCER CACHEXIA

PROTEIN

K_d



K_s

AMINO ACIDS

Proteolytic systems in muscle

```
graph TD; A[Proteolytic systems in muscle] --> B[Lysosomal]; A --> C[Non-lysosomal]; B --- D[Cathepsins]; C --- E["Ca++ -dependent Calpains"]; C --- F["ATP-dependent Ubiquitin"];
```

Lysosomal

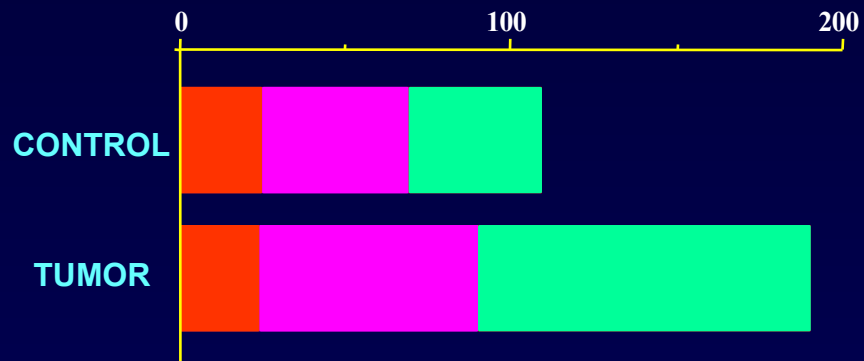
Cathepsins

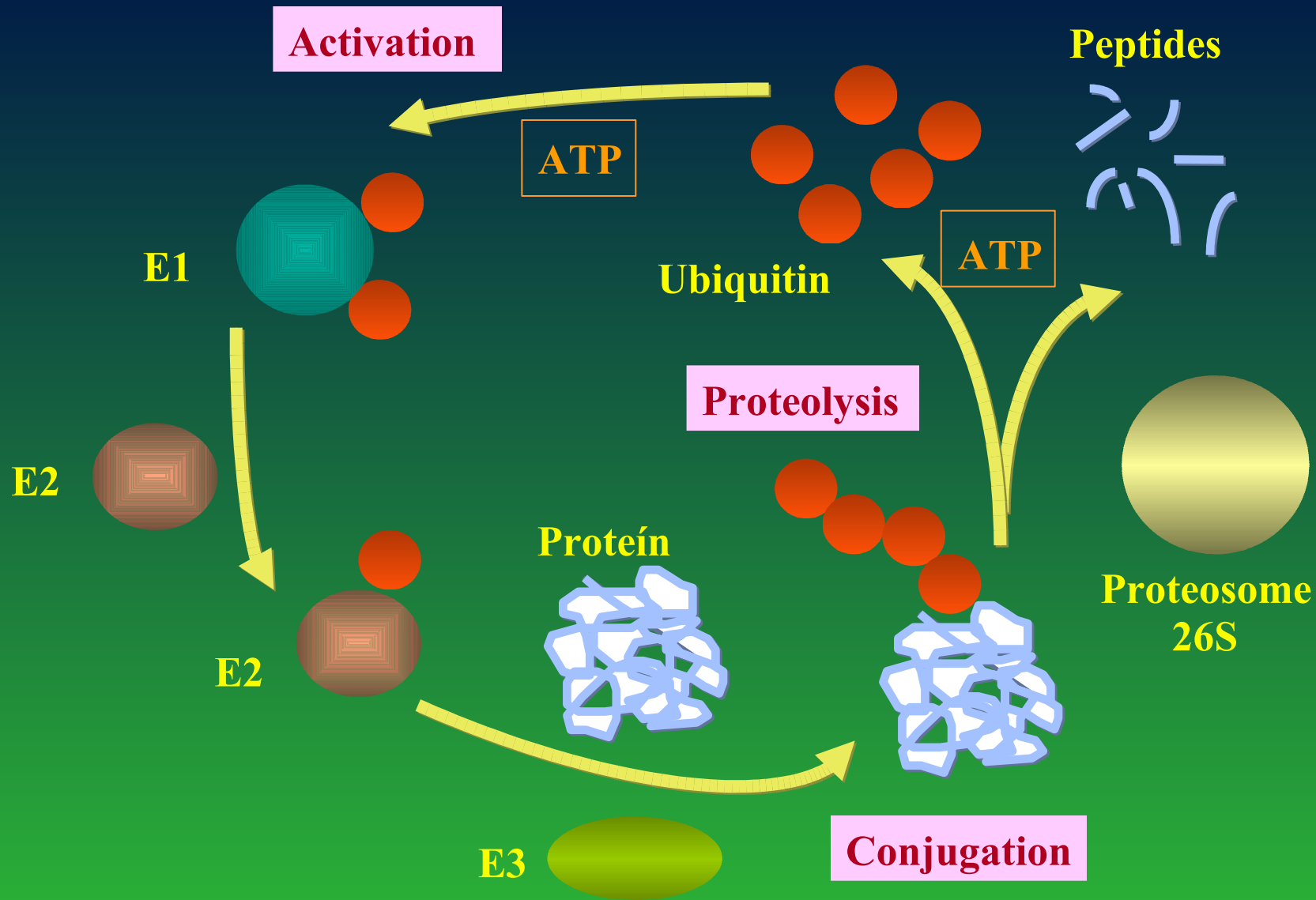
Non-lysosomal

**Ca⁺⁺ -dependent
Calpains**

**ATP-dependent
Ubiquitin**

In vitro proteolysis
(nmol Tyr released/g/h)



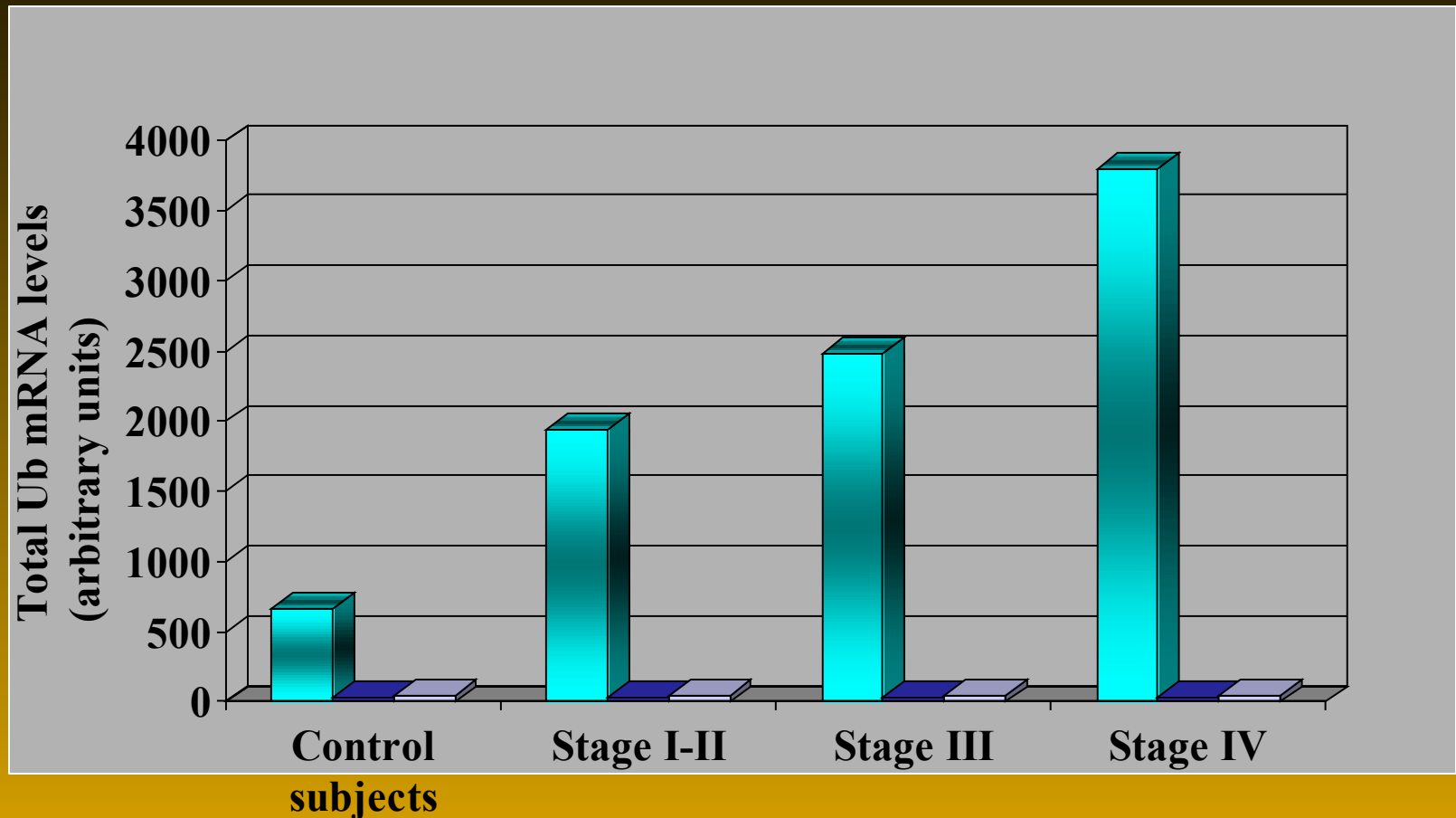


Muscle-specific ubiquitin ligases

MAFbx (atrogenin-5)

MURF-1

Ubiquitin mRNA levels in skeletal muscle of gastric cancer patients



Patients lost 5.57% of body weight (n= 20)

Cytokine network

Wasting

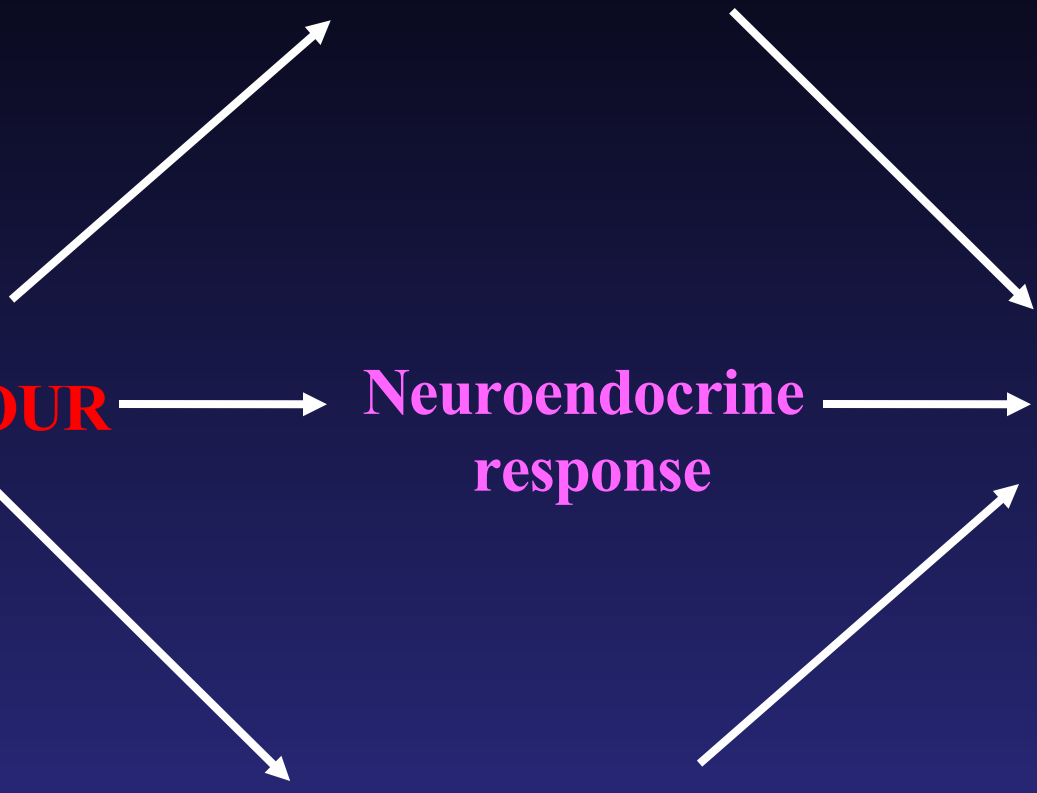
TUMOUR

**Neuroendocrine
response**

**Muscle
proteolysis**

Tumour-specific products

Treatment



Therapeutic approaches

Pharmacological strategies



MUSCLE WASTING



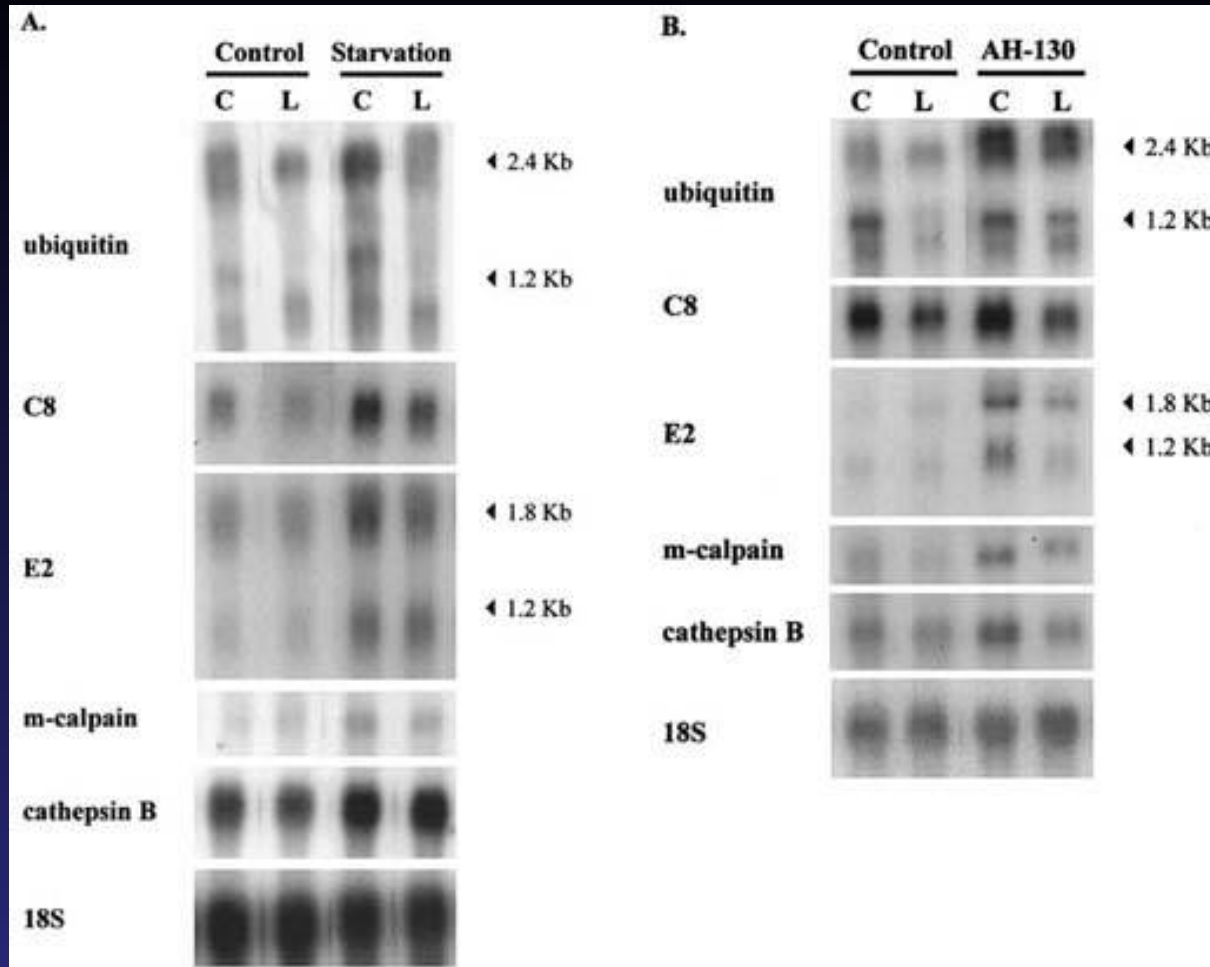
Nutritional approaches

Anticatabolic
+ *Anabolic*

Using nutrition

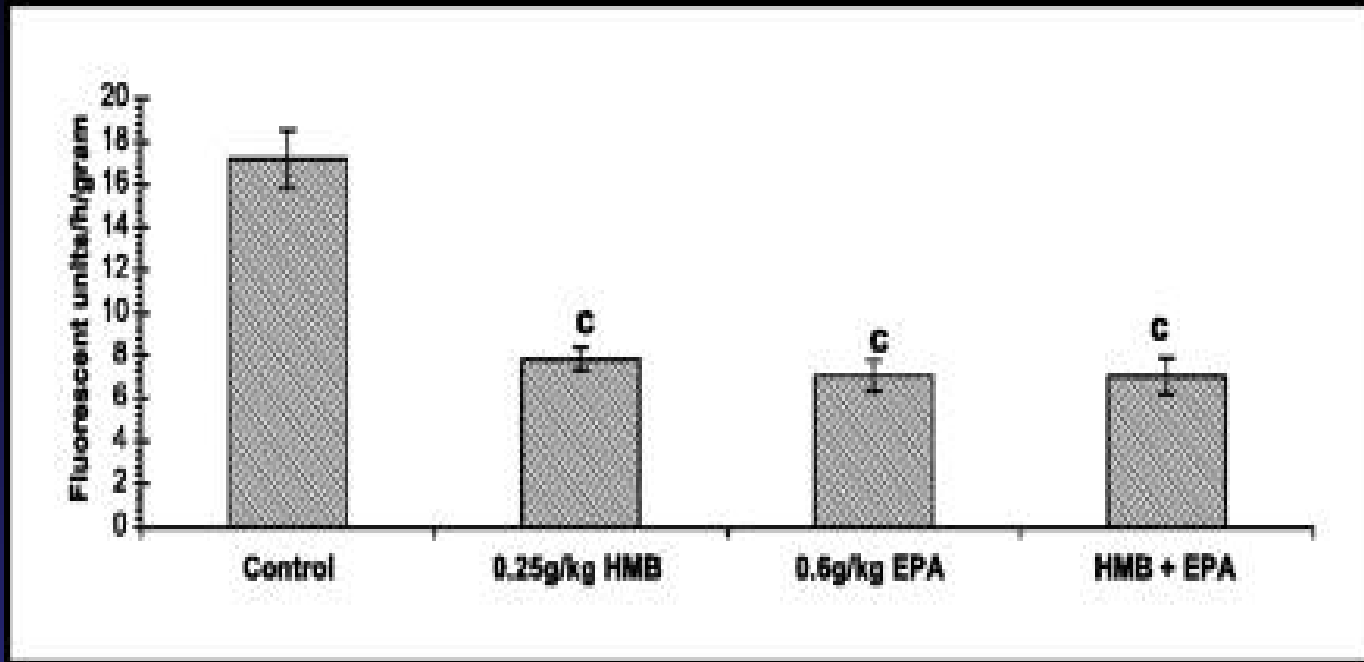
Leu

β -hydroxy- β -methylbutyrate



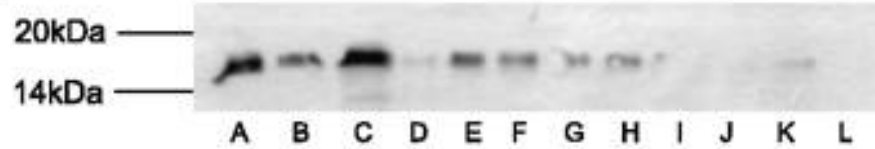
Busquets et al., J Cell Physiol. 2002 191(3):283-9.

Chymotrypsin-like activity in proteasome

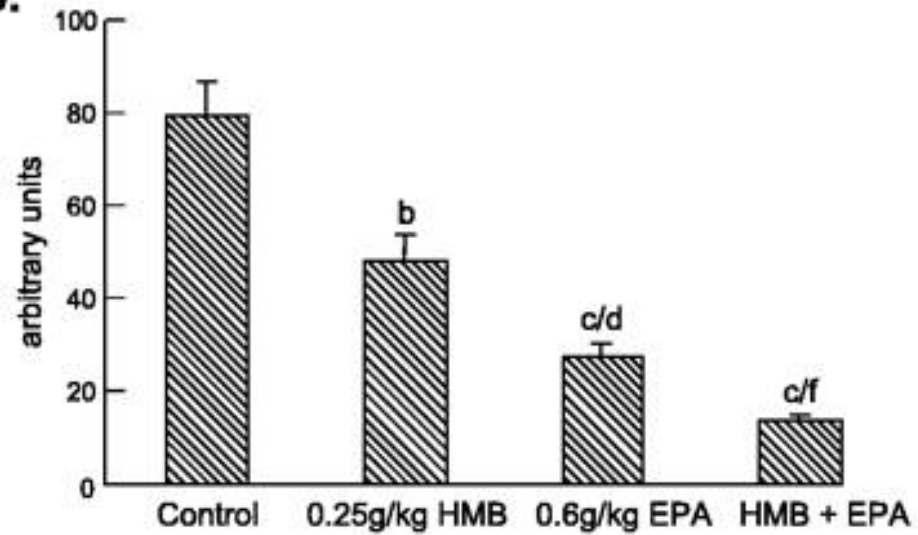


Smith et al., Cancer Res. 2005;65(1):277-83

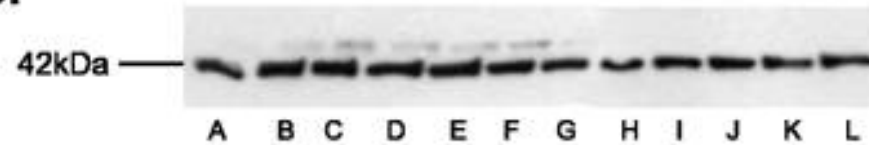
A.



B.



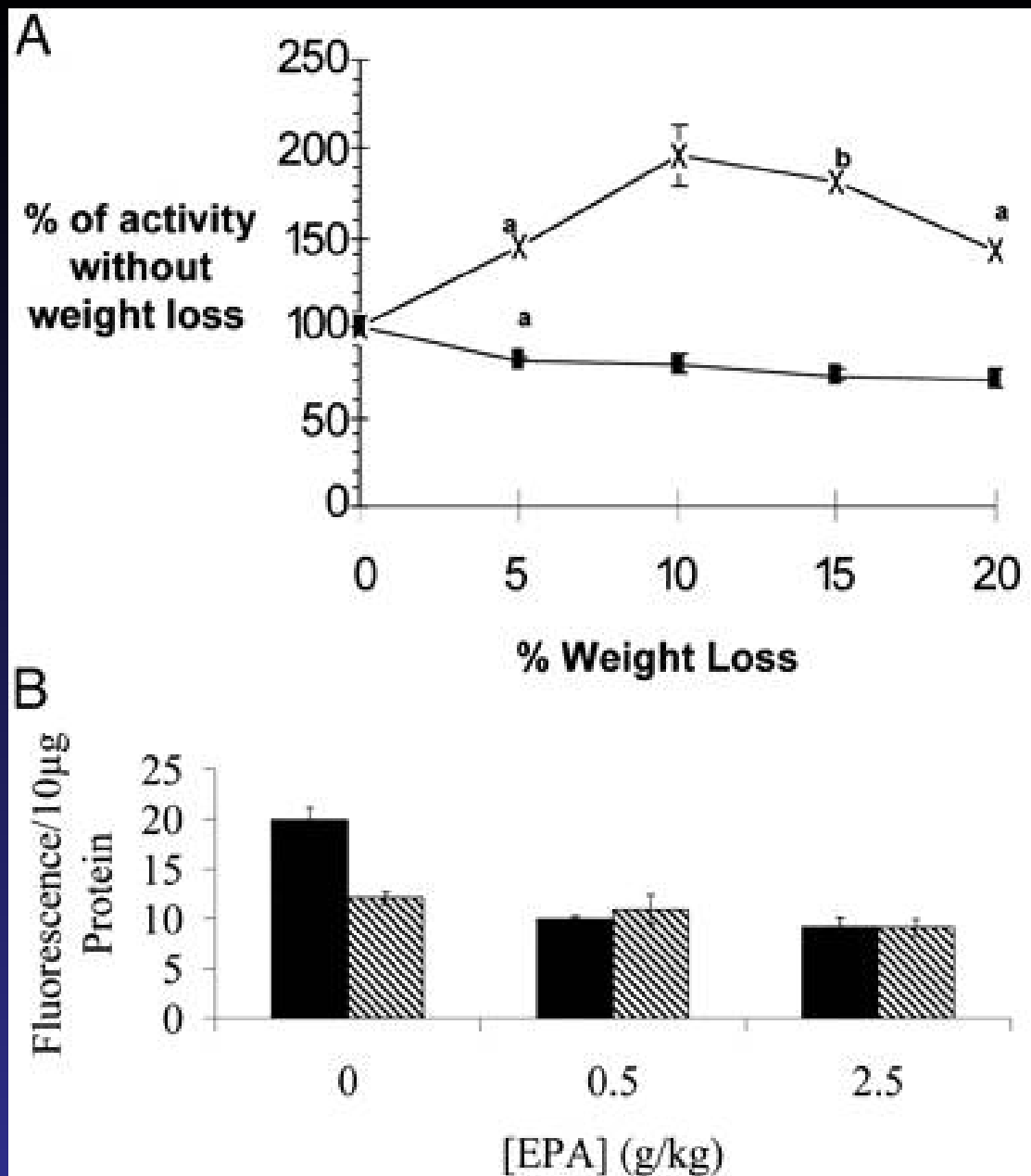
C.



Using nutraceuticals

EPA

Resveratrol



Whitehouse et al., Cancer Res. 2001;61(9):3604-9.

ω -3 FATTY ACIDS

Wigmore et al., 1996

Treated a group of pancreatic cancer patients with fish oil capsules (containing 18% EPA and 12% DHA) for three months and observed an increase in body weight, a reduction of acute-phase proteins (C-reactive protein) and a stabilization of the resting energy expenditure.

Fearon et al., 2003

A randomized double blind trial in pancreatic cancer patients using a protein and energy dense supplement enriched with ω -3 fatty acids and antioxidants. The trial demonstrates weight and LBM gain and improved quality of life. Gut. 52(10):1479-86 2003

Resveratrol

Diphenol found in grapes,
peanuts

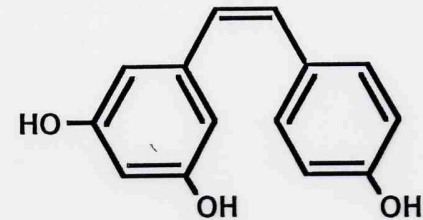
nF- κ B inhibitor

COX-2 inhibitor

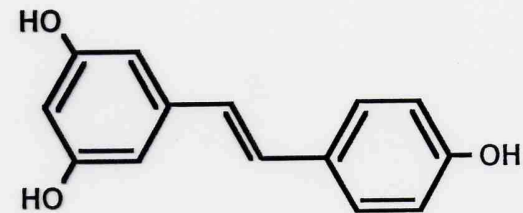
Br J Cancer. 2004 91(9):1742-50.

Wyke SM, Russell ST, Tisdale MJ.

***Induction of proteasome
expression in skeletal muscle is
attenuated by inhibitors of NF-
kappaB activation.***



cis-RESVERATROL



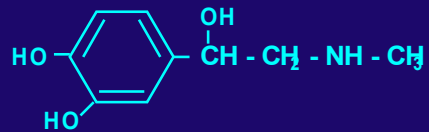
trans-RESVERATROL

Using drugs

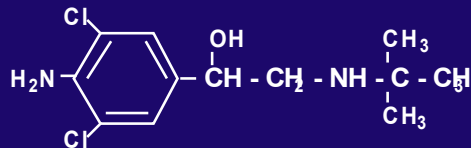
β2 agonists

Anticachectic cytokines

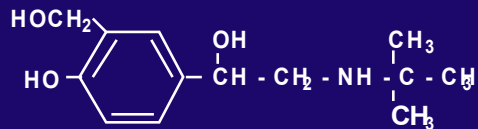
BETA-2 ADRENERGIC AGONISTS



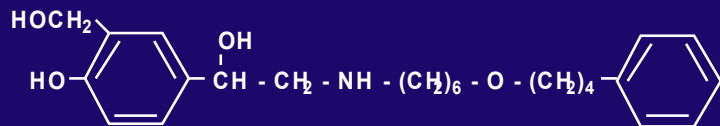
ADRENALINE
(EPINEPHRINE)



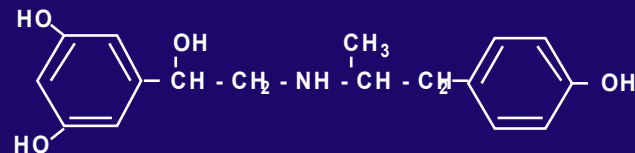
CLENBUTEROL



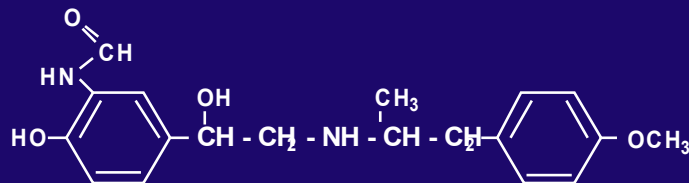
SALBUTAMOL



SALMETEROL

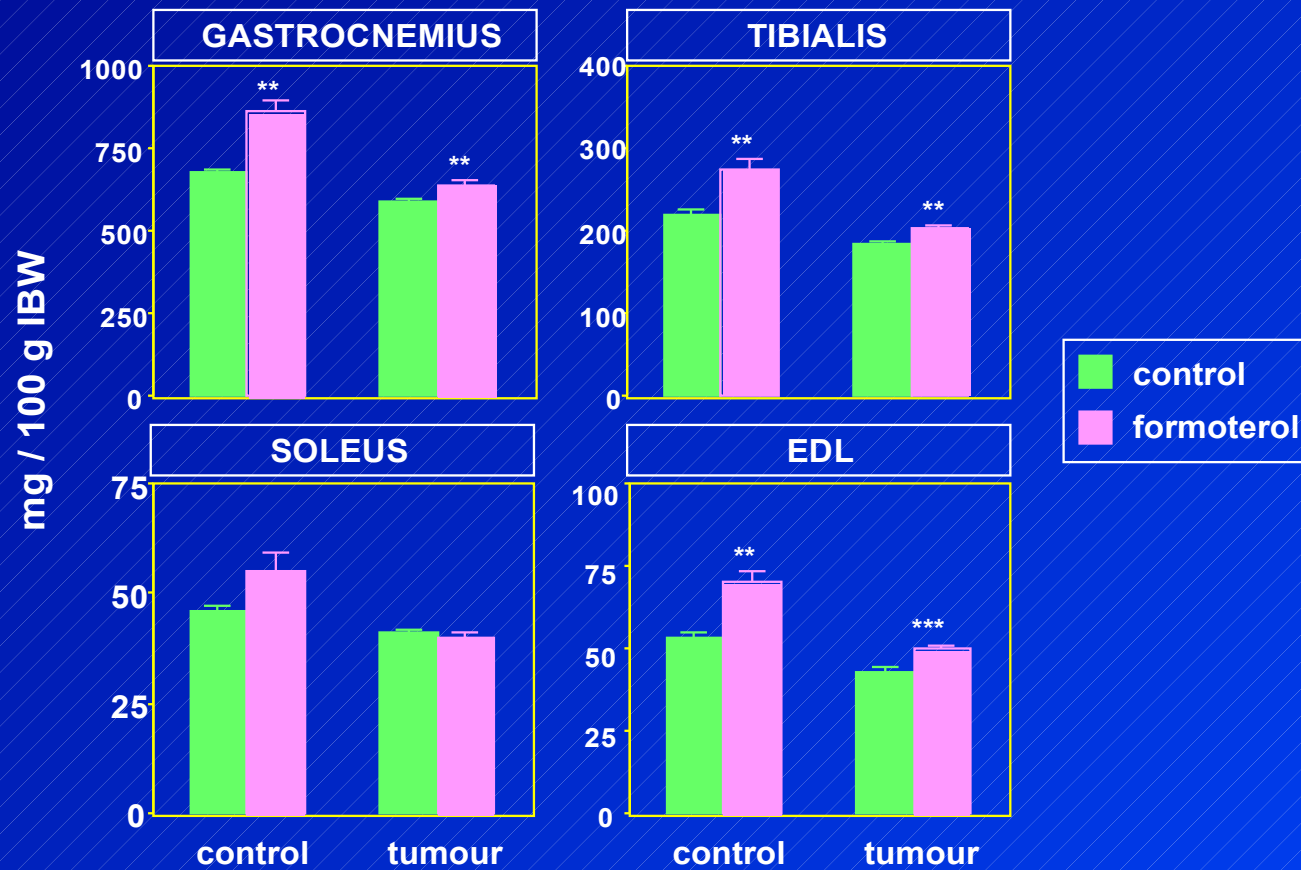


FENOTEROL

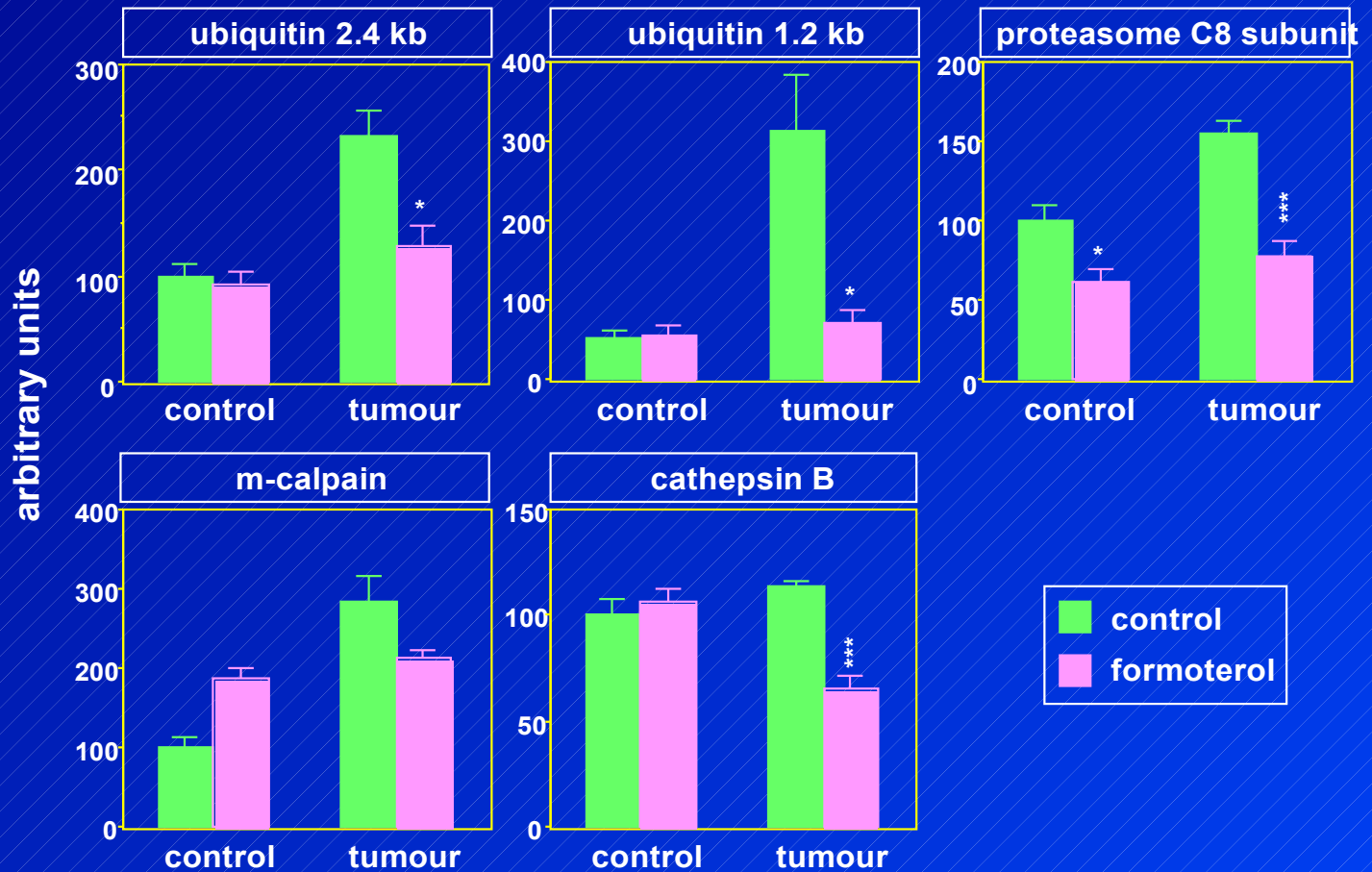


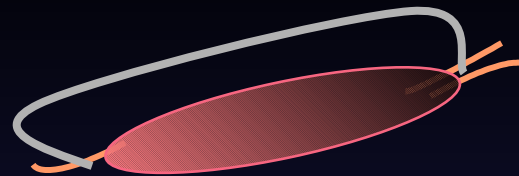
FORMOTEROL

EFFECT OF FORMOTEROL TREATMENT ON SKELETAL MUSCLE WEIGHTS OF TUMOUR-BEARING RATS

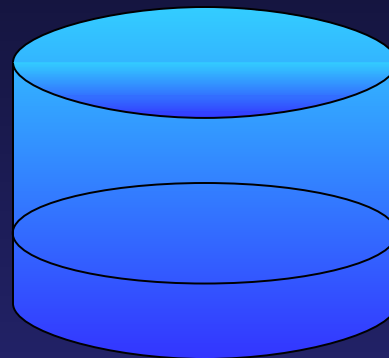


EFFECT OF FORMOTEROL TREATMENT ON GENE EXPRESSION OF PROTEOLYTIC SYSTEMS IN RAT GASTROCNEMIUS

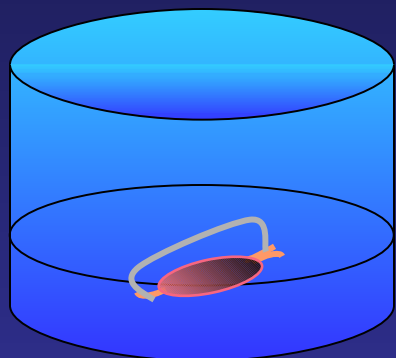




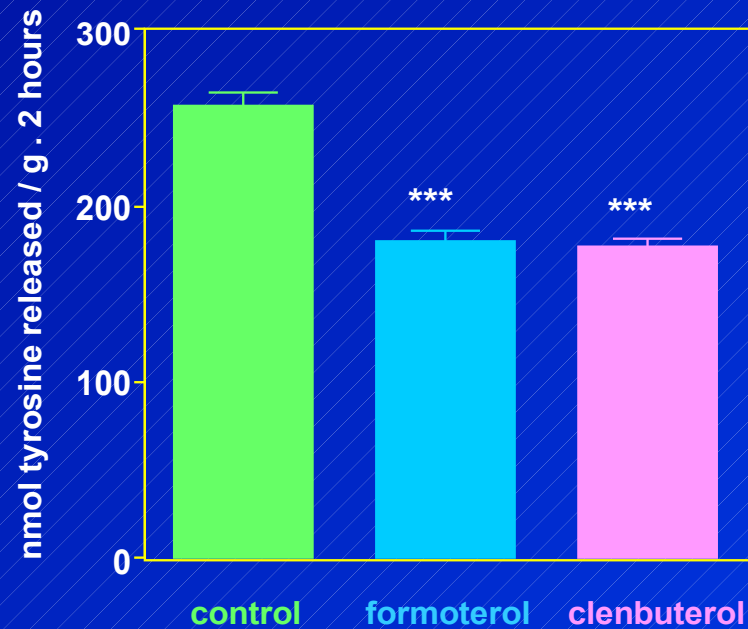
EDL or Soleus



Krebs-Henseleit buffer 35°C

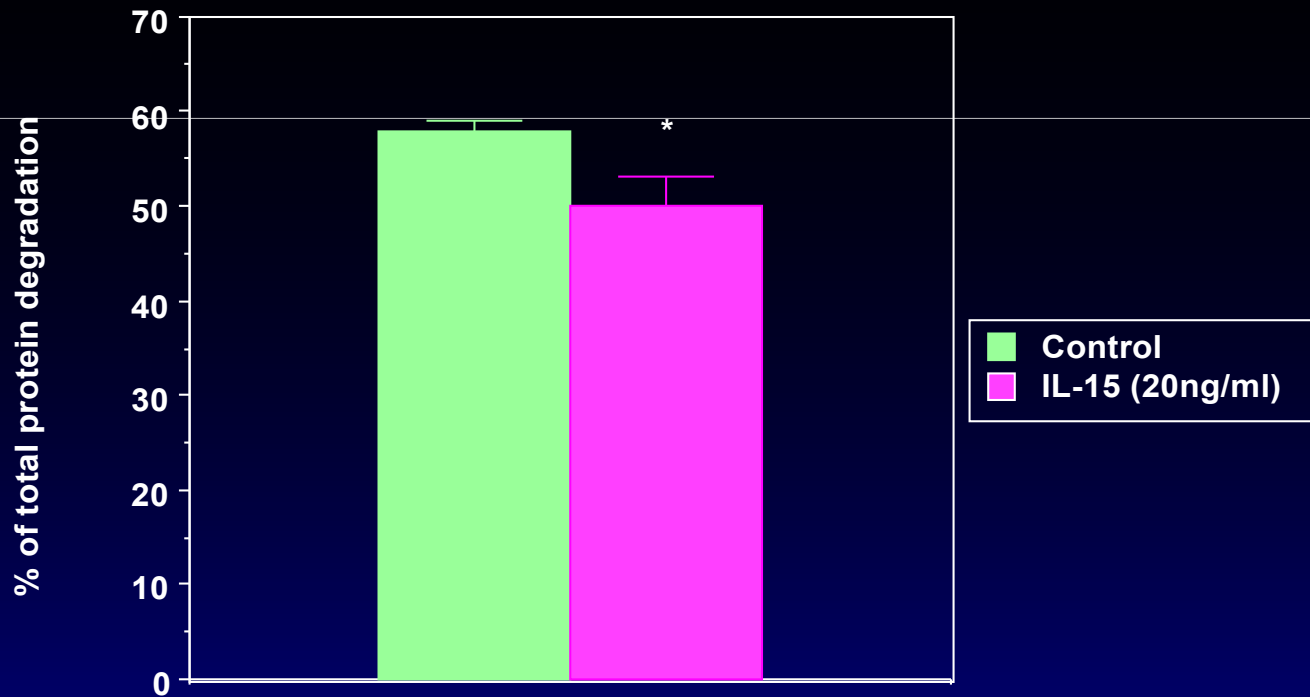


**EFFECTS OF BETA-AGONISTS ON IN VITRO
PROTEOLYTIC RATE IN ISOLATED EDL MUSCLES**



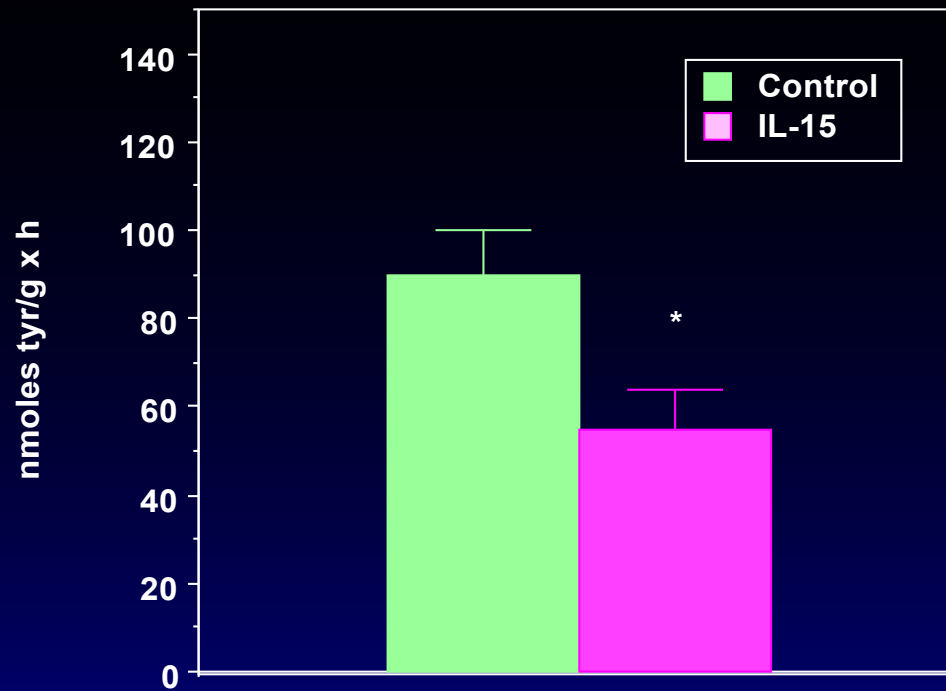
Anticachectic cytokines: IL-15

Protein degradation in C2 myotubes



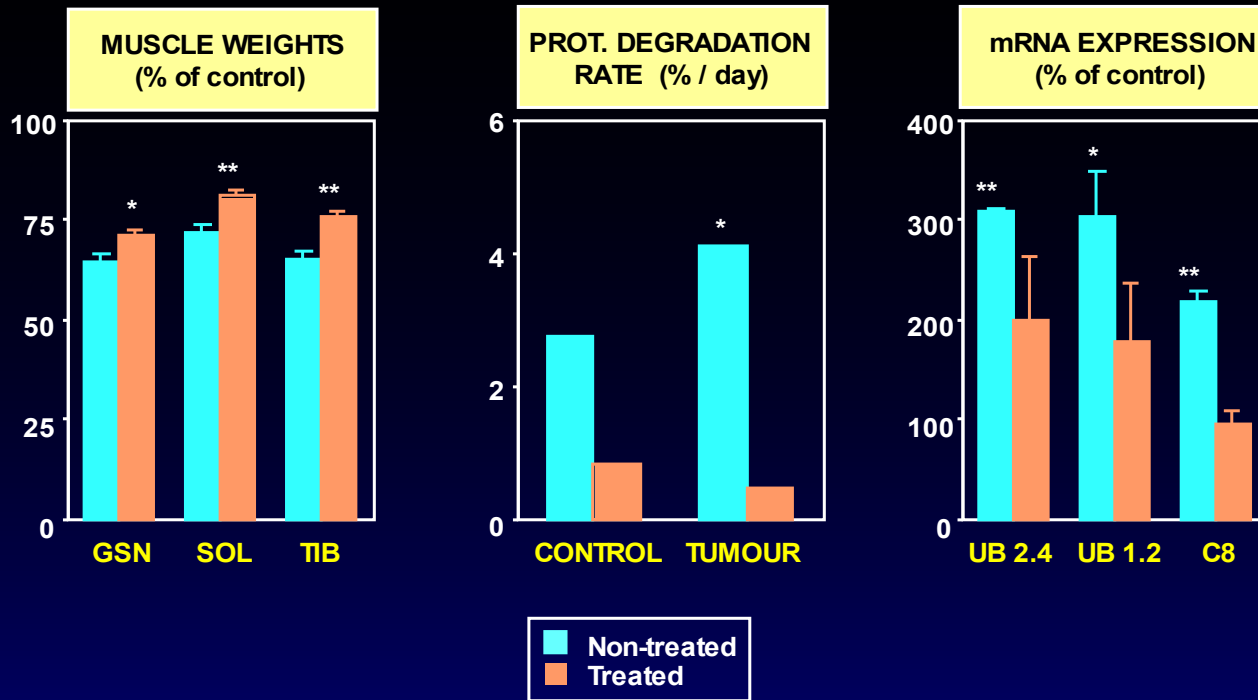
Busquets et al., 2005

Proteolytic rate in isolated EDL rat muscles



Busquets et al., 2005

EFFECTS OF IL-15 TREATMENT ON SKELETAL MUSCLE FROM TUMOUR-BEARING RATS



Using proteolytic inhibitors

Proteasome inhibitors

Lactacystin

Bortezomib (PS-341)

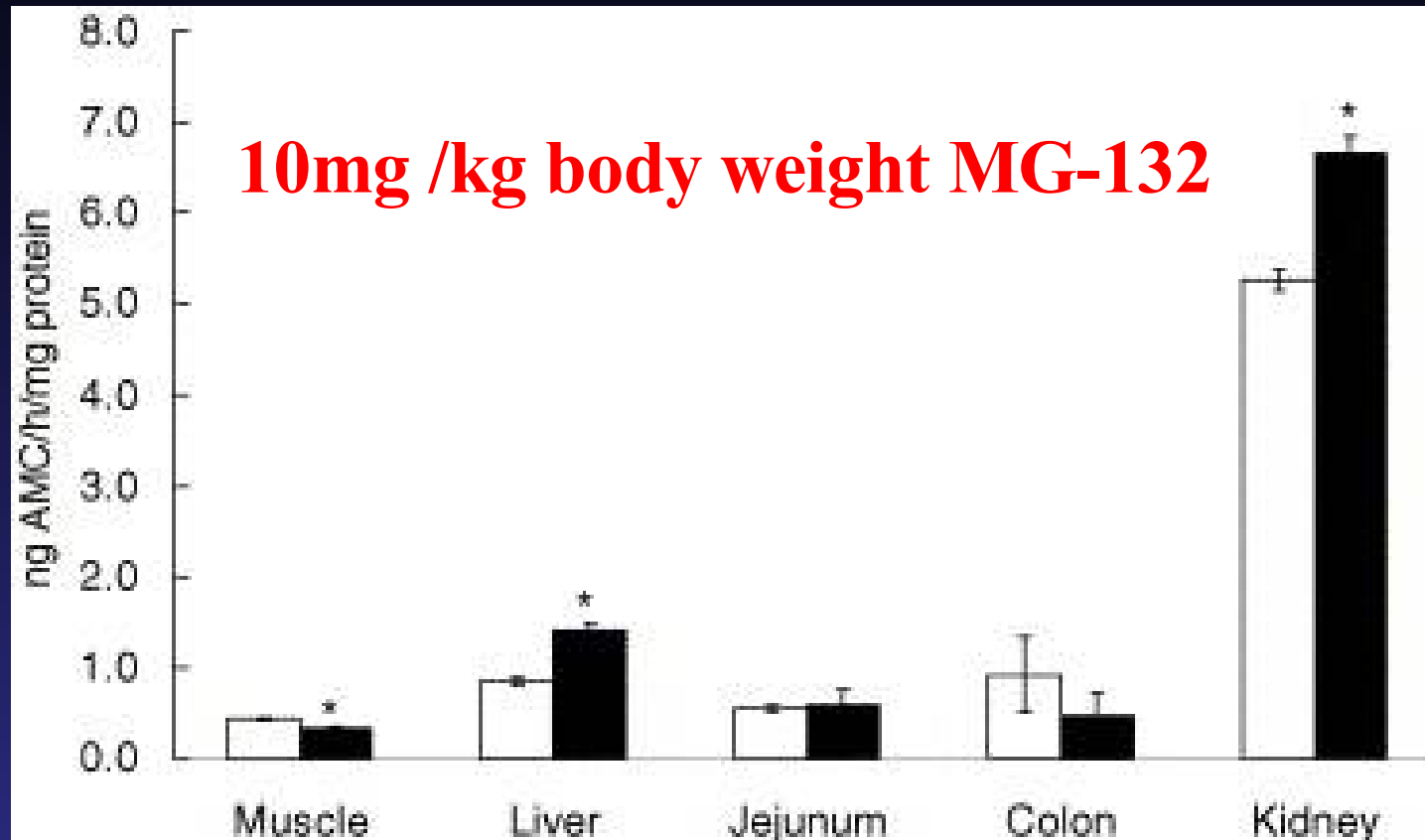
MG-132

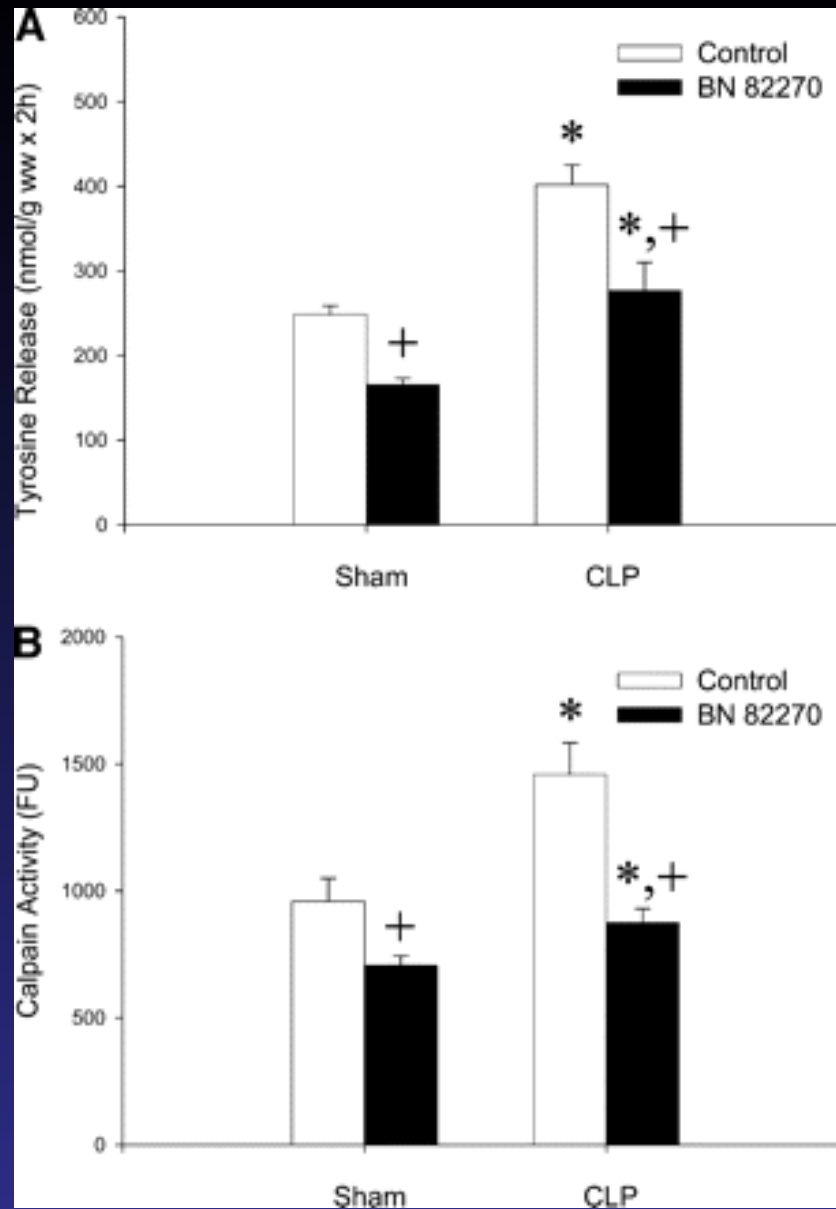
Calpain inhibitors

Calpeptin

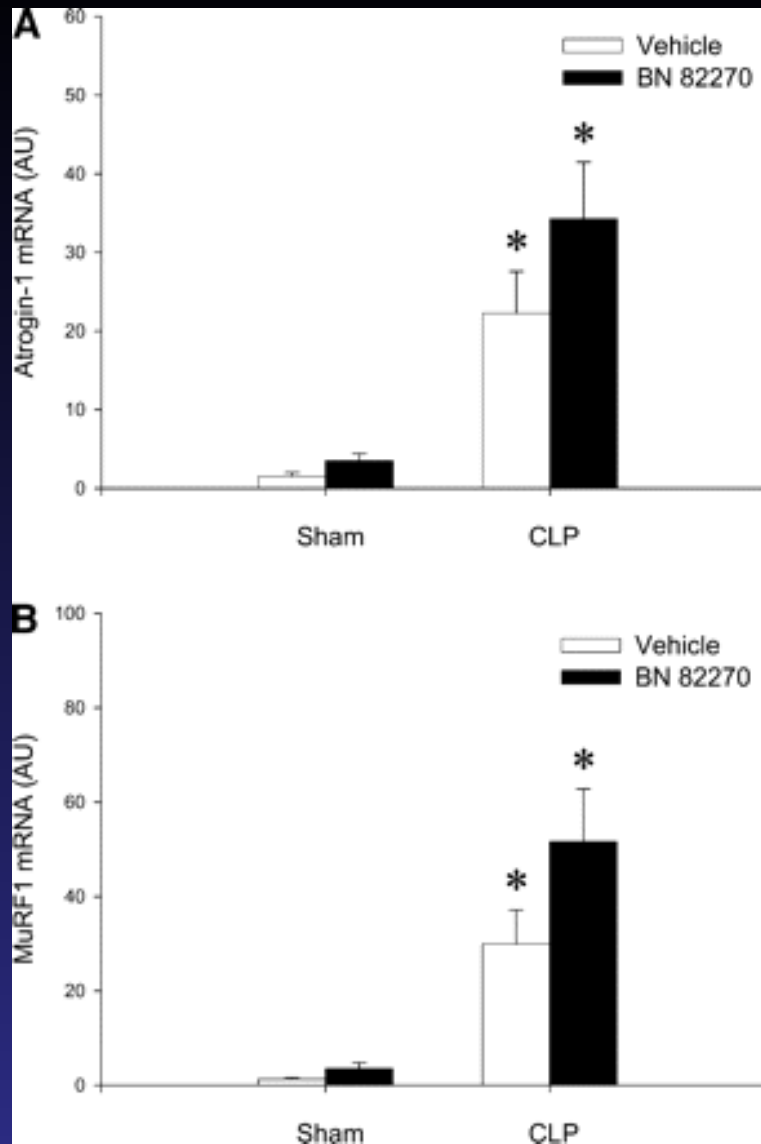
BN82270

Chymotrypsin-like activity in proteasome





Fareed et al., Am. J. Physiol. 290: R1589-97, 2006



Fareed et al., Am. J. Physiol. 290: R1589-97, 2006

**Molecular mechanisms
potentially involved in muscle wasting**

Preproteasomal

Paraproteasomal

Proteasomal

Postproteasomal

Cancer

Myofibrils

Ca⁺⁺/Calpain
dependent release of
myofilaments



Reincorporation

Myofilaments

Substrate modification



Ub/proteasome
dependent proteolysis

COP9 signalosome
CHIP



VCP

Peptides

TPP, aminopeptidases
other exopeptidases



Amino acids

CACHEXIA TREATMENT

ANTIPROTEOLYTIC STRATEGIES

Nutrition + Nutraceuticals + Drugs

Anabolic +Anticatabolic



Thank you.



Danke.