Cachexia Mechanisms

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- An integrated physiological response of substrate mobilization driven by inflammation
- Exacerbated by tumor progression, comorbid conditions, old age, deconditioning, nutritional deficiency, drugs and medical interventions

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Review

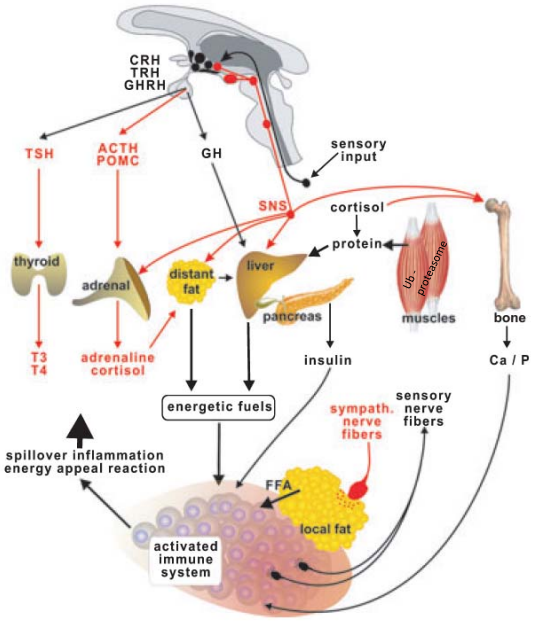
Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2010.02218.x

Energy regulation and neuroendocrine–immune control in chronic inflammatory diseases

R. H. Straub[1], M. Cutolo[2], F. Buttgereit[3] & G. Pongratz[1]

From the [1]Laboratory of Experimental Rheumatology and Neuroendocrino-Immunology, Division of Rheumatology, Department of Internal Medicine I, University Hospital, Regensburg, Germany, [2]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine and Medical Specialties, University of Genova, Genova, Italy, and [3]Department of Rheumatology and Clinical Immunology, Charité University Medicine Berlin, Berlin, Germany



An elegant choreographed response with the purpose of providing energetic fuels and amino acids to an activated immune system.

This response is paralleled by an energy storage response during periods without inflammation when nutrients are available .

Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic–pituitary–adrenal axis

Theodore P. Braun,[1,2] Xinxia Zhu,[1] Marek Szumowski,[1] Gregory D. Scott,[2,3] Aaron J. Grossberg,[1,2] Peter R. Levasseur,[1] Kathryn Graham,[4] Sheehan Khan,[5] Sambasivarao Damaraju,[6] William F. Colmers,[7] Vickie E. Baracos,[4] and Daniel L. Marks[1]

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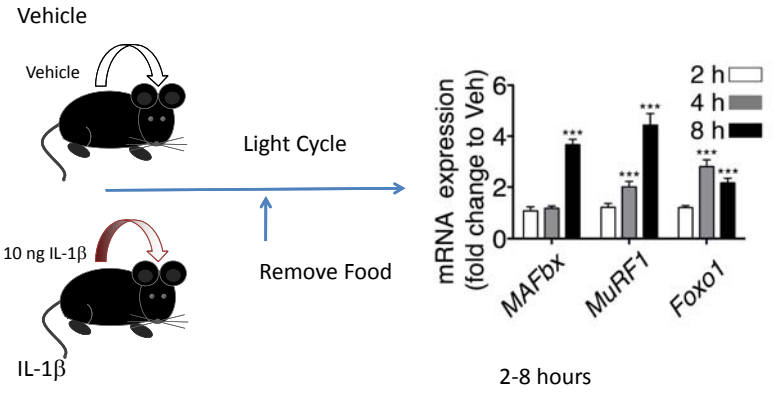
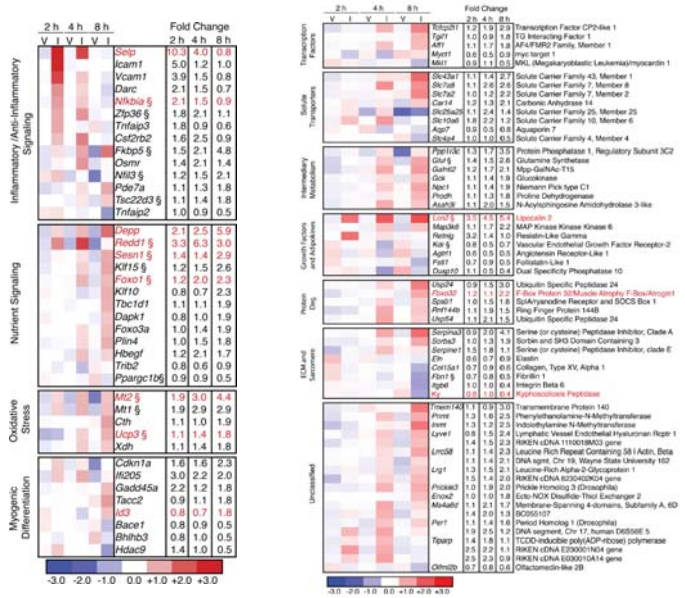
www.jem.org/cgi/doi/10.1084/jem.20111020

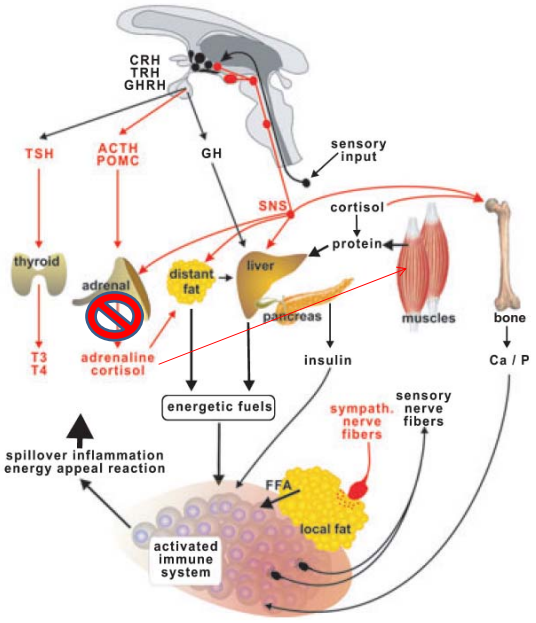
Central inflammation results in transcriptional changes of ubiquitin ligases consistent with atrophy



Central IL-1β treatment induces rapid and dynamic changes in skeletal muscle gene expression.



JEM



So brain does talk to muscle, but since adrenalectomy blocked the response, this is an HPA-mediated effect. There were many glucocorticoid responsive genes in the transcriptional profile.

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Inactivity / deconditioning / aging

RESEARCH LETTER

Effect of 10 Days of Bed Rest on Skeletal Muscle in Healthy Older Adults

1772 JAMA, April 25, 2007—Vol 297, No. 16 (Reprinted)

Table. Effects of 10 Days of Bed Rest in Older Adults

	No. of Participants (N = 12)*	Mean (95% Confidence Interval)			
		Bed Rest			
		Before	After	Change	*P* Value
Muscle fractional synthetic rate, % per h†	10	0.077 (0.059 to 0.095)	0.051 (0.035 to 0.067)	−0.027 (−0.007 to −0.047)	.02
% Change				−30.0 (−7.0 to −54.0)	
DEXA lean mass, kg‡	10				
Whole body		48.05 (40.61 to 55.49)	46.51 (39.57 to 53.45)	−1.50 (−0.62 to −2.48)	.004
% Change				−3.2 (−1.4 to −5.0)	
Lower Extremity		15.01 (12.41 to 17.61)	14.06 (11.85 to 16.27)	−0.95 (−0.42 to −1.48)	.003
% Change				−6.3 (−3.1 to −9.5)	
Isokinetic muscle strength, Nm per s§	11	120 (96 to 145)	101 (81 to 121)	−19 (−11 to −30)	.001
% Change				−15.6 (−8.0 to −23.1)	

Abbreviation: DEXA, dual-energy x-ray absorptiometry; Nm, Newton meter.
*One participant was excluded from all analyses because of insufficient protein intake.
†Because of a technical error, the muscle fractional synthesis rate measurement was excluded for 1 participant.
‡One participant was excluded from the DEXA analysis because the scan before bed rest was not administered.
§Isokinetic knee extension at 60° per second.

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The Journal of Clinical Endocrinology & Metabolism

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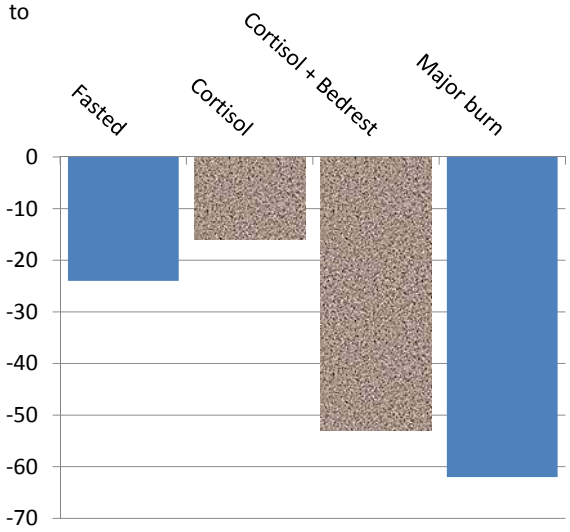
Inactivity Amplifies the Catabolic Response of Skeletal Muscle to Cortisol*

ARNY A. FERRANDO, CHARLES A. STUART, MELINDA SHEFFIELD-MOORE, AND ROBERT R. WOLFE

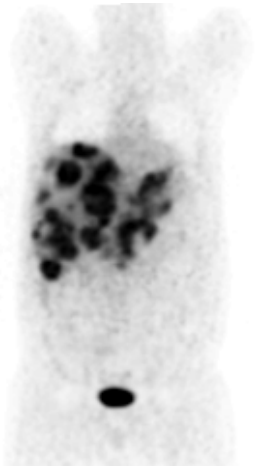
Departments of Surgery (A.A.F., M.S.-M., R.R.W.) and Internal Medicine (C.A.S.), University of Texas

Leg phenylalanine net balance (nmol/min/100mL leg)

- 26 y old men
- Cortisol infusion to 30 µg/dL
- 14 days bed rest

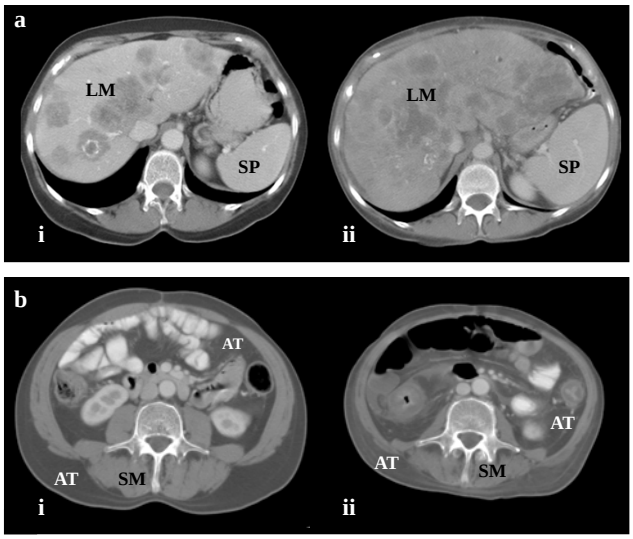


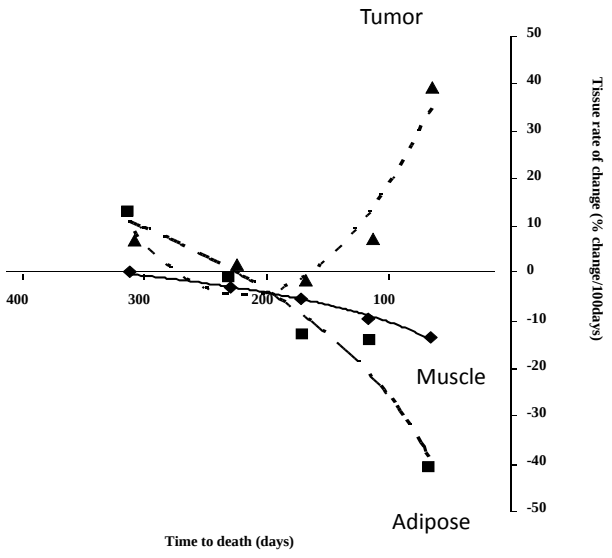
Tumor progression



Metabolic demand
Inflammatory mediators

Figure 1



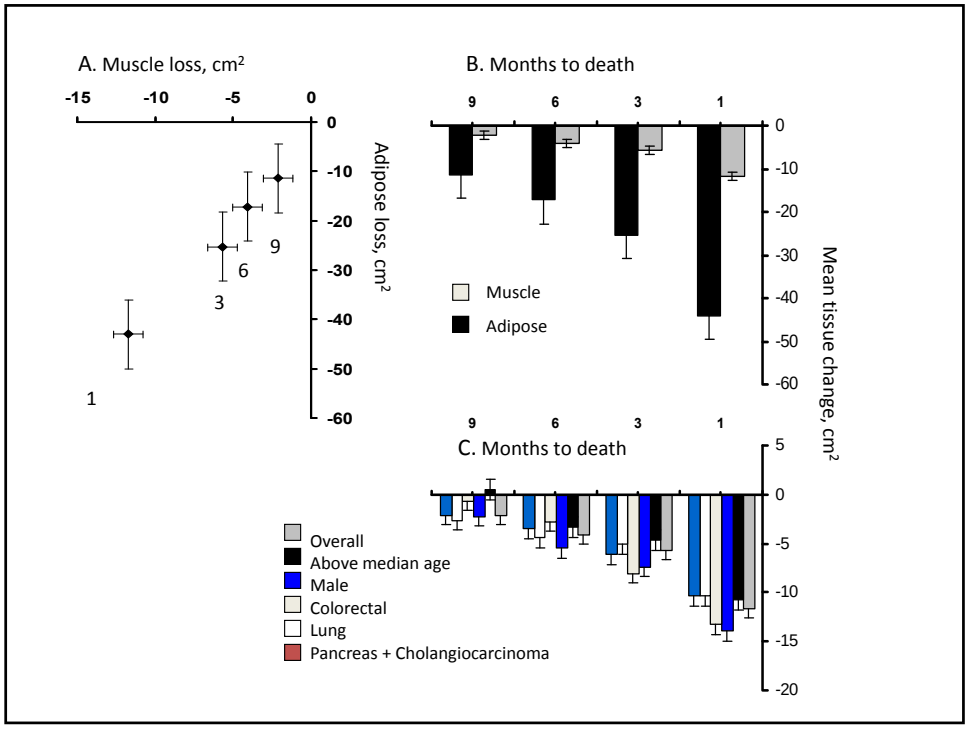


Colorectal cancer
Repeated measures
Tumor progression muscle and fat loss over time to death

Lieffers et al. AJCN 2009

Progression of tissue wasting in advanced malignancy

CT image analysis n= 1300



Comorbid conditions

- May also associated with cachexia or muscle wasting
- Organ failure (liver, heart, lung, kidney), obesity / hypertension / diabetes

Comorbidity in sarcopenic colorectal cancer patients	Normal (n=143)	Sarcopenic (n=91)	P value
Age, y	61 ± 11	66 ± 12	0.001
Cardiac Arrhythmias %	4.9	21.1	<0.001
Hypertension %	26.6	43.3	0.008
COPD %	2.1	8.9	0.025
Diabetes %	12.6	23.3	0.032
Hypothyroidism %	3.5	11.1	0.021
Deficiency Anemia %	2.1	8.9	0.025
Fluid & Electrolyte disorders %	3.5	8.9	0.081
Days in hospital in the last year	1.0 ± 2.5	2.8 ± 7.6	0.029
Cancer Stage II, III, IV			0.49
Bowel Obstruction %	7.7	18.7	0.012

Nutritional deficiency?

Original Article

Nutritional Intervention With Fish Oil Provides a Benefit Over Standard of Care for Weight and Skeletal Muscle Mass in Patients With Nonsmall Cell Lung Cancer Receiving Chemotherapy

Cancer 2011;117:1775–82.

Rachel A. Murphy, BSc[1]; Marina Mourtzakis, PhD[2]; Quincy S.C. Chu, MD[3]; Vickie E. Baracos, PhD[3]; Tony Reiman, MD, SM[4]; and Vera C. Mazurak, PhD[1]

Treatment effects

(head and neck cancer; Dechaphunkul & Baracos, unpublished)

- (6.3% muscle loss 10 days bed rest healthy elderly)
- 12.5% muscle loss oropharyngeal cancer resection with free flap reconstruction.
- 12.8% muscle loss oropharyngeal cancer course of radiotherapy + platinum – based chemotherapy.

Drug effects

Association of Skeletal Muscle Wasting With Treatment With Sorafenib in Patients With Advanced Renal Cell Carcinoma: Results From a Placebo-Controlled Study

Sami Antoun, Laura Birdsell, Michael B. Sawyer, Peter Venner, Bernard Escudier, and Vickie E. Baracos

VOLUME 28 · NUMBER 6 · FEBRUARY 20 2010

JOURNAL OF CLINICAL ONCOLOGY

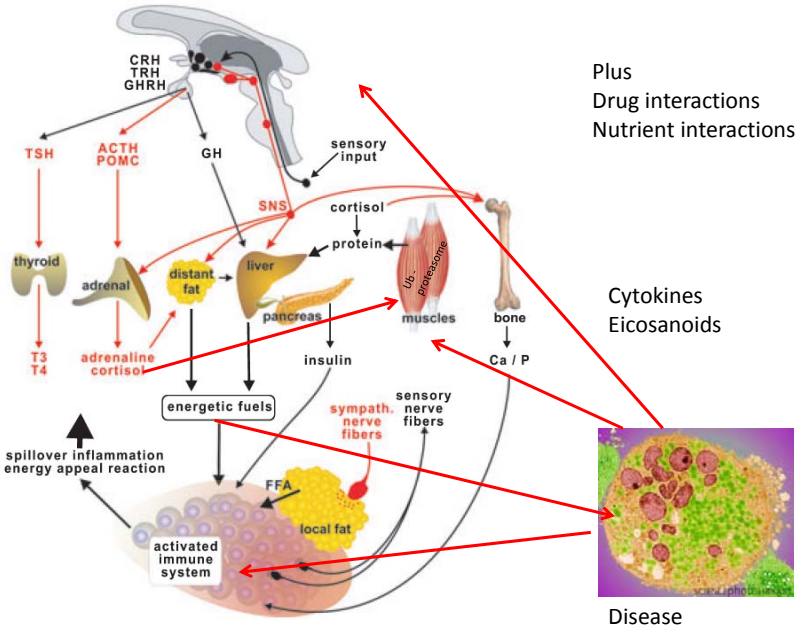
8.5% muscle loss in 12 months

Skeletal muscle anabolism is a side effect of therapy with the MEK inhibitor: selumetinib in patients with cholangiocarcinoma

CMM Prado[1], T Bekaii-Saab[2,3], LA Doyle[4], S Shrestha[1], S Ghosh[1], VE Baracos[1] and MB Sawyer[*,1]

British Journal of Cancer (2012), 1–4

9.8% muscle gain in 3 months



Plus
Drug interactions
Nutrient interactions

Cytokines
Eicosanoids

Disease