Kalorische Restriktion: der Schlüssel zum ewigen Leben im Erwachsenenalter?

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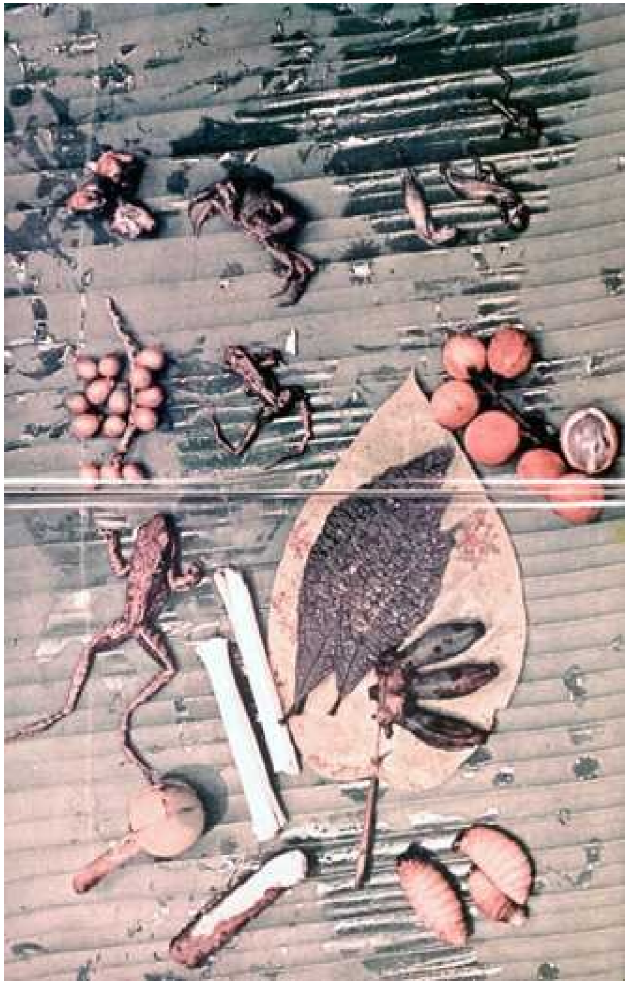
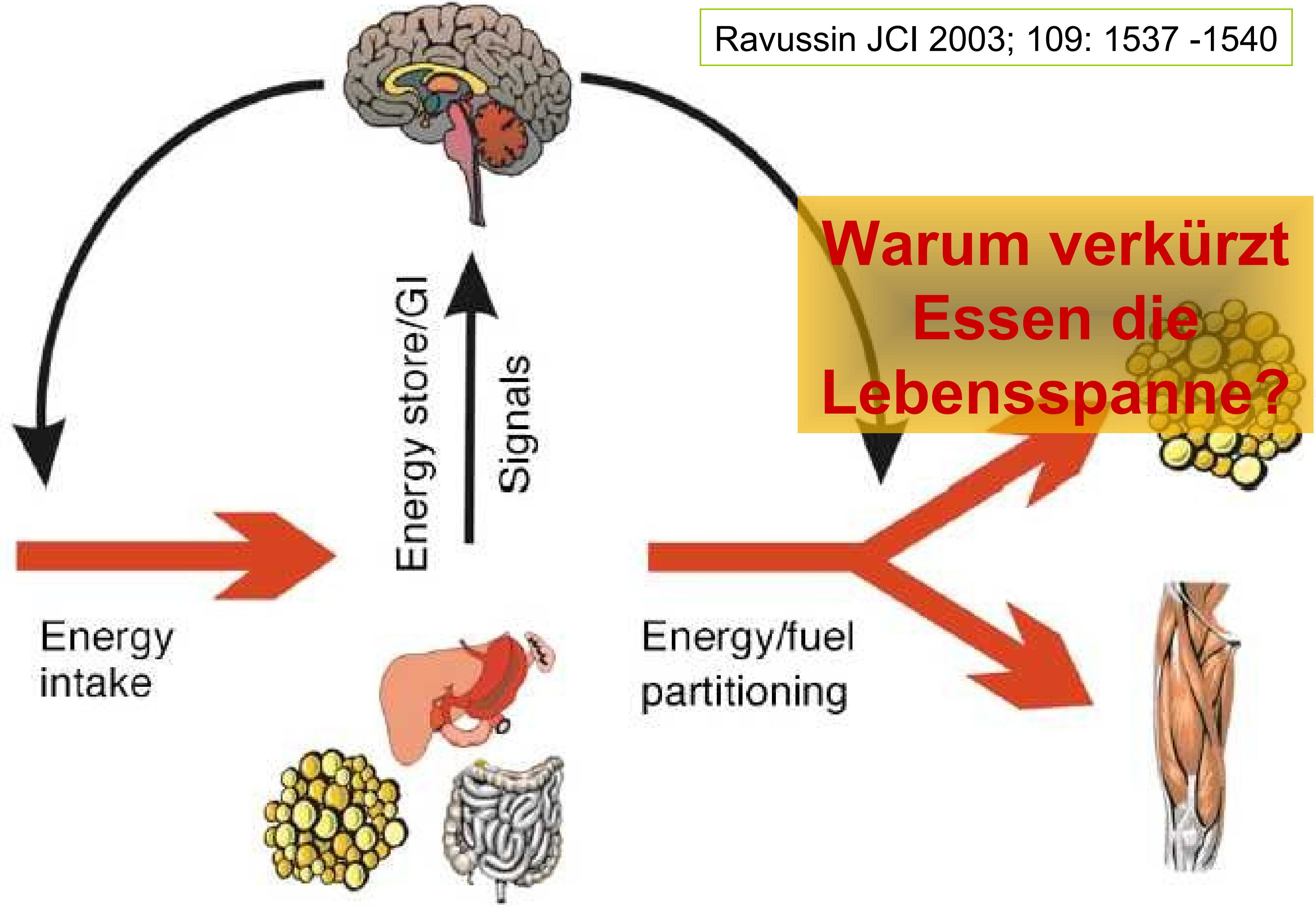
Speiseplan und BMI einer Steinzeitkultur auf Mindanao



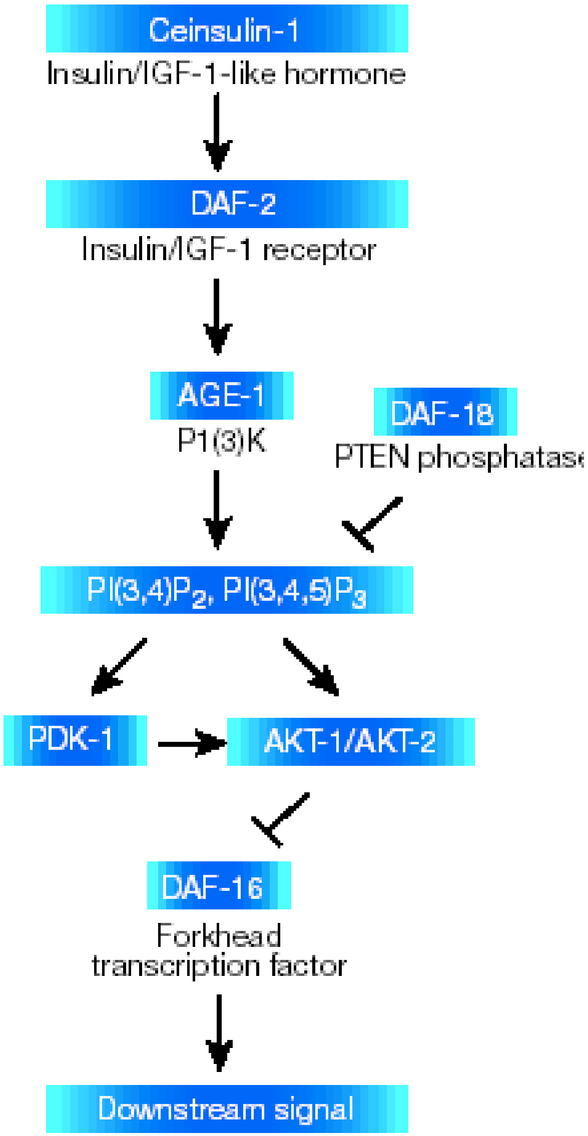
Nahrungsaufnahme wird kompliziert gesteuert

Ravussin JCI 2003; 109: 1537 -1540



Warum verkürzt Essen die Lebensspanne?

Weniger Nahrung verlängert die Lebensspanne des Fadenwurmes C.elegans.
Hemmung des Insulinsignals hat denselben Effekt.


Ceinsulin-1
Insulin/IGF-1-like hormone

DAF-2
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$PI(3,4)P_2$, $PI(3,4,5)P_3$

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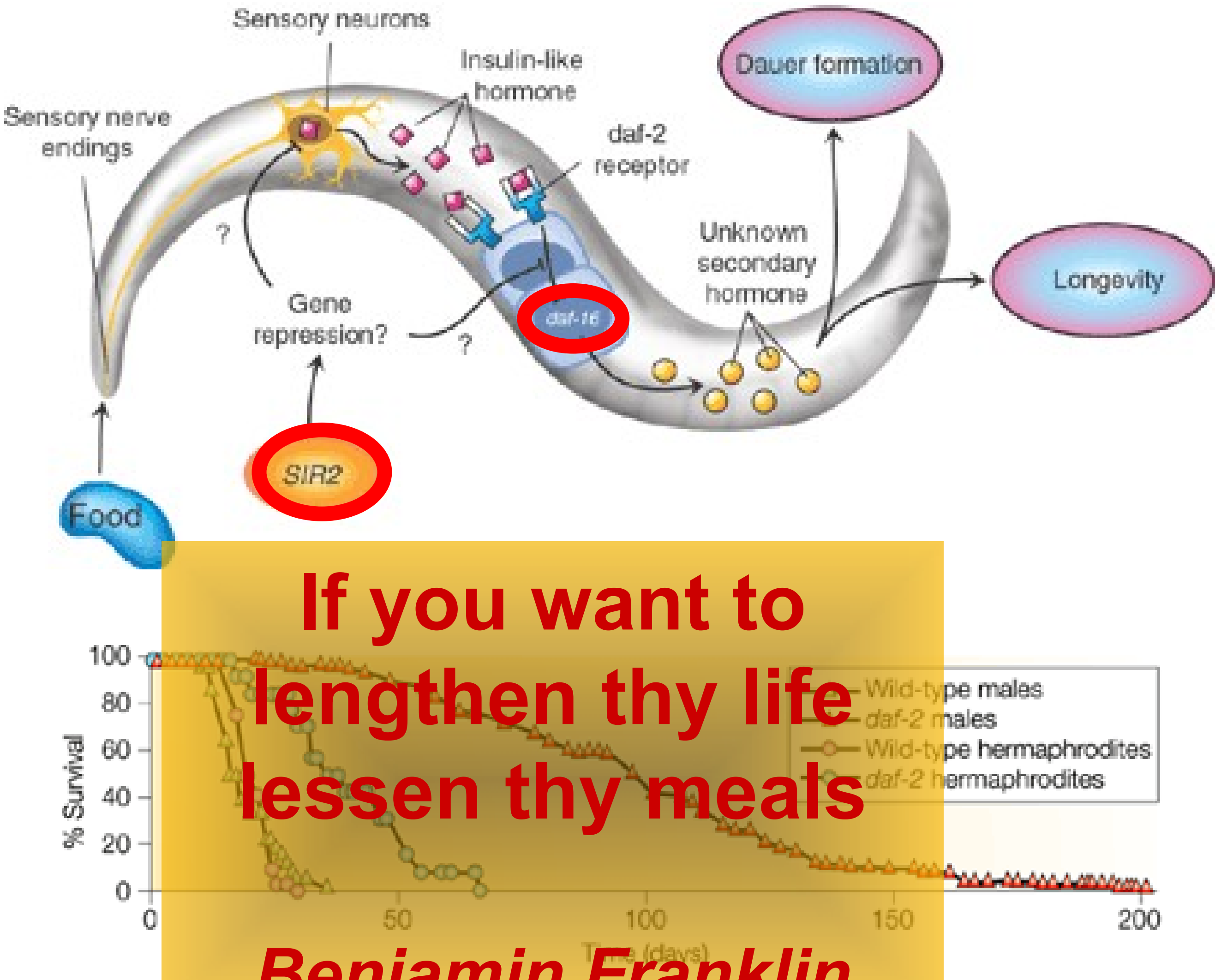
Downstream signal



If you want to lengthen thy life lessen thy meals

Benjamin Franklin

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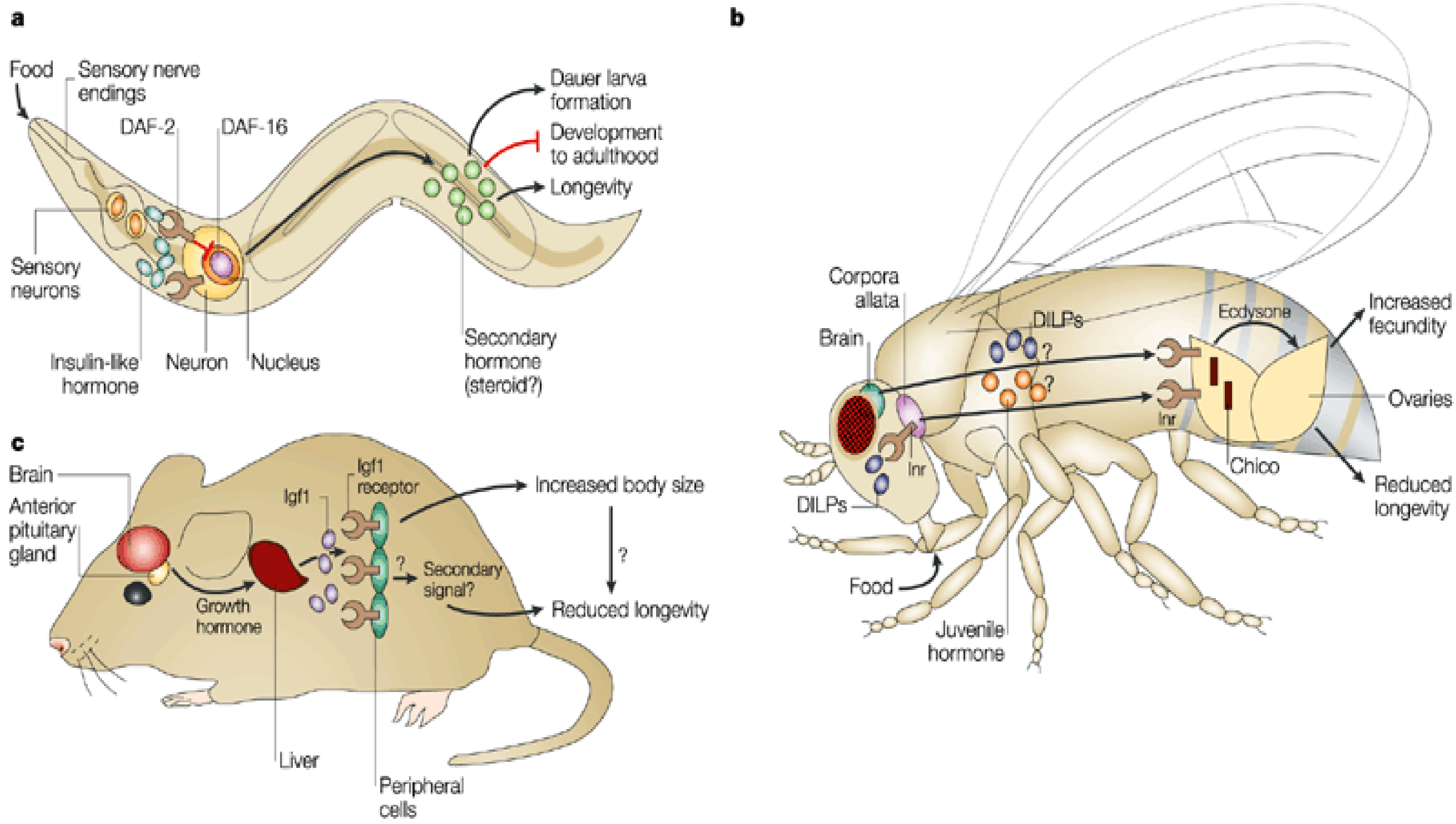
Kalorienrestriktion = wenig Essen verlängert die Lebensspanne aller Spezies durch Verminderung des Insulinsignals



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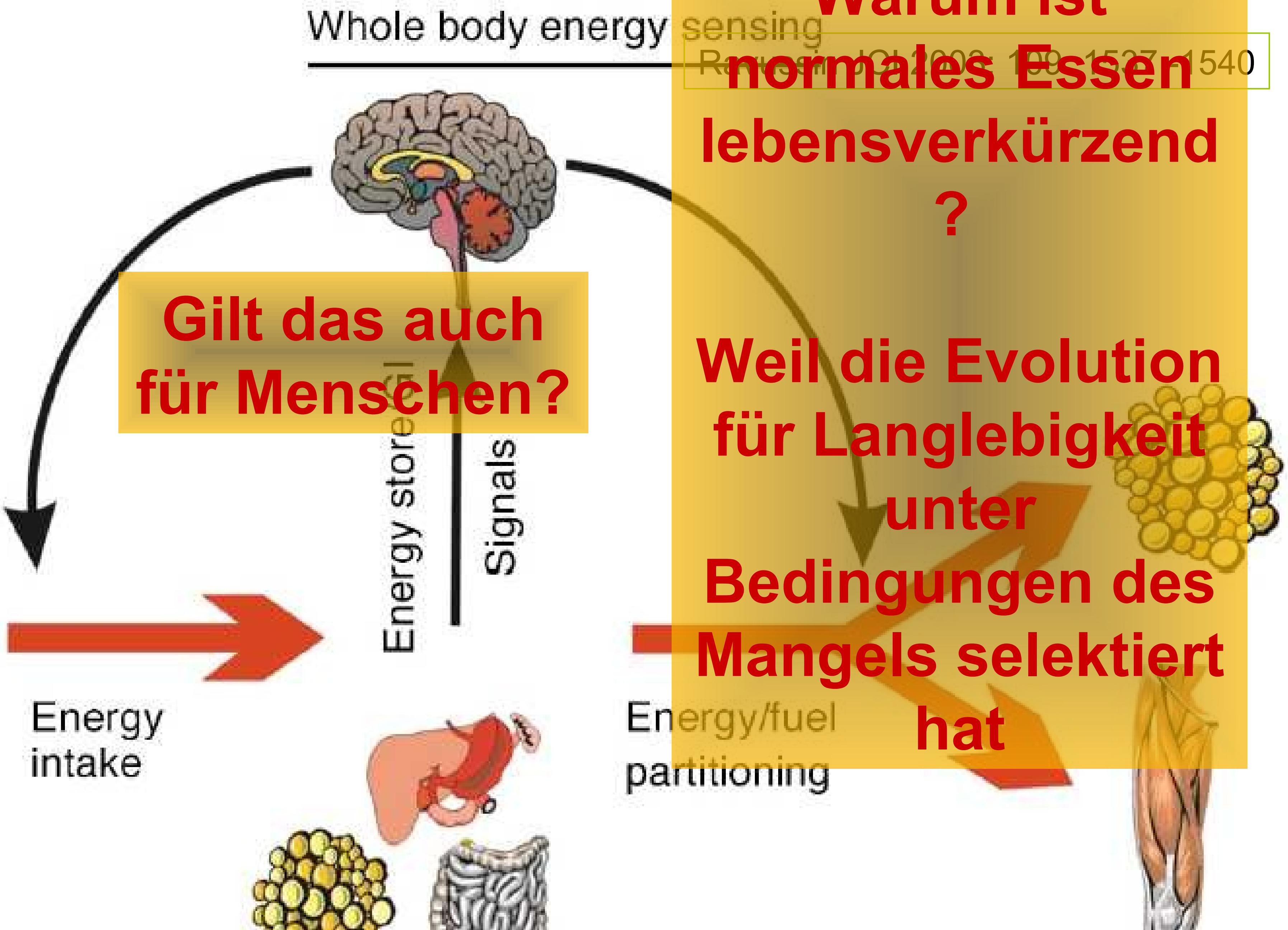
Warum ist normales Essen lebensverkürzend ?

Ra[illegible] JCI 2009; 119: 1537-1540



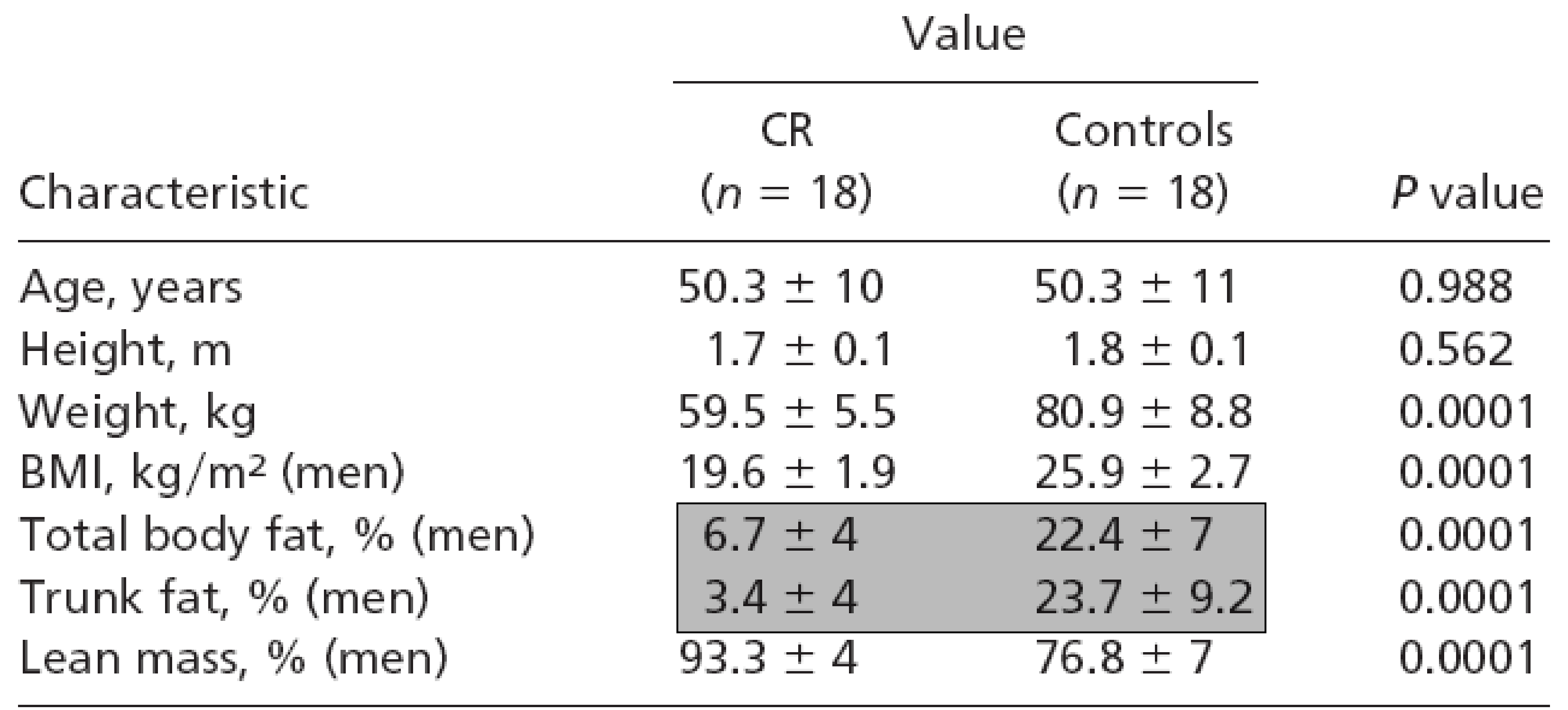
Gilt das auch für Menschen?

Weil die Evolution für Langlebigkeit unter Bedingungen des Mangels selektiert hat

Beste Ernährung für gesunde Energiebilanz, Zellpflege, Antiaging, Antidiseasing…..

Kalorienrestriktion ohne Nährstoffmangel

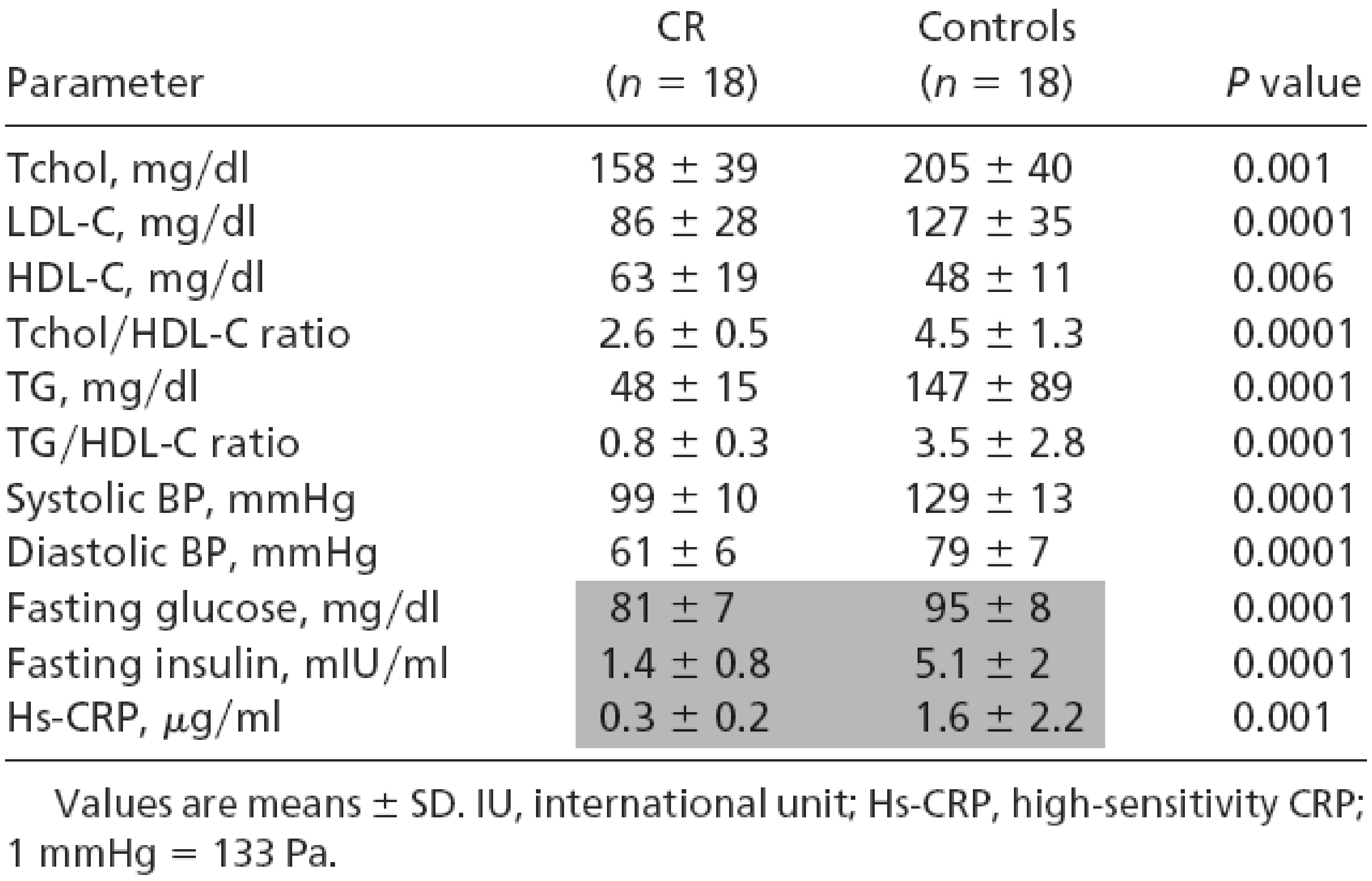
6 Jahre caloric restriction: anthropometrische Parameter



Characteristic	Value CR (*n* = 18)	 Controls (*n* = 18)	*P* value
Age, years	50.3 ± 10	50.3 ± 11	0.988
Height, m	1.7 ± 0.1	1.8 ± 0.1	0.562
Weight, kg	59.5 ± 5.5	80.9 ± 8.8	0.0001
BMI, kg/m² (men)	19.6 ± 1.9	25.9 ± 2.7	0.0001
Total body fat, % (men)	6.7 ± 4	22.4 ± 7	0.0001
Trunk fat, % (men)	3.4 ± 4	23.7 ± 9.2	0.0001
Lean mass, % (men)	93.3 ± 4	76.8 ± 7	0.0001

Caloric intake (kcal/d)	**1112 – 1958**	**1976 – 3537**
Protein %	**26**	**18**
Fat %	**28**	**32**
Carbohydrate %	**46**	**50**

6 Jahre caloric restriction: erhebliche Verbesserung aller Surrogatparameter



Parameter	CR (*n* = 18)	Controls (*n* = 18)	*P* value
Tchol, mg/dl	158 ± 39	205 ± 40	0.001
LDL-C, mg/dl	86 ± 28	127 ± 35	0.0001
HDL-C, mg/dl	63 ± 19	48 ± 11	0.006
Tchol/HDL-C ratio	2.6 ± 0.5	4.5 ± 1.3	0.0001
TG, mg/dl	48 ± 15	147 ± 89	0.0001
TG/HDL-C ratio	0.8 ± 0.3	3.5 ± 2.8	0.0001
Systolic BP, mmHg	99 ± 10	129 ± 13	0.0001
Diastolic BP, mmHg	61 ± 6	79 ± 7	0.0001
Fasting glucose, mg/dl	81 ± 7	95 ± 8	0.0001
Fasting insulin, mIU/ml	1.4 ± 0.8	5.1 ± 2	0.0001
Hs-CRP, μg/ml	0.3 ± 0.2	1.6 ± 2.2	0.001

Values are means ± SD. IU, international unit; Hs-CRP, high-sensitivity CRP; 1 mmHg = 133 Pa.

Aging, Adiposity, and Calorie Restriction

Fontana & Klein; *JAMA. 2007;297:986-994*

„Available data support the notion that calorie restriction with adequate nutrient intake in humans causes many of the same metabolic adaptations and reduction of multiple chronic disease risk factors that occur in calorie-restricted animal models, even when restriction is started in midlife, ……including decreased metabolic, hormonal, and inflammatory risk factors for diabetes, cardiovascular disease, and possibly cancer“

Aging, Adiposity, and Calorie Restriction

Wenig Insulin bei hoher Insulinempfindlichkeit fördert offenbar langlebigen Zellstoffwechsel

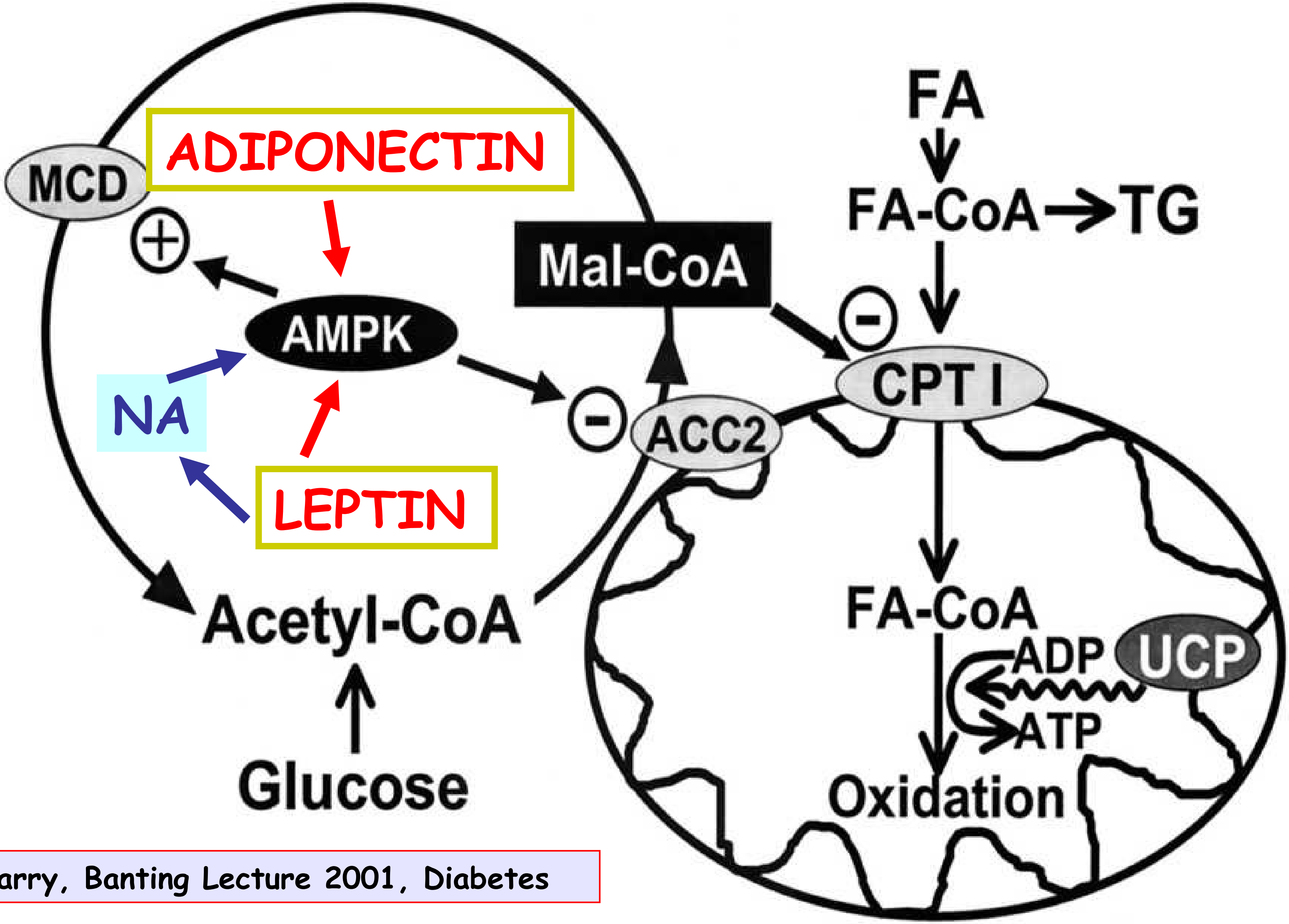
Hohes Insulin bei geringerer Insulinempfindlichkeit scheint ungünstig zu sein

Zelluläre Energiebilanz ist eng mit hormonellen Signalwegen verknüpft

- **Sensoren der Energiebalance**
  - AMP/ATP – **AMPK – Energiezustand** Malonyl CoA – **ACC2**
  - NAD/NADH – Sir2 (yeast) or **Sirt1-Sirt7 (mammals) Redoxstatus**
  - Glucose + metabolites of PPP - **ChREBP + LXR - Glucosespiegel**
- Hormonal pathways
  - **Insulin** – IGF signaling
  - **FoxO** – DAF16
  - mTOR - Aminosäuren

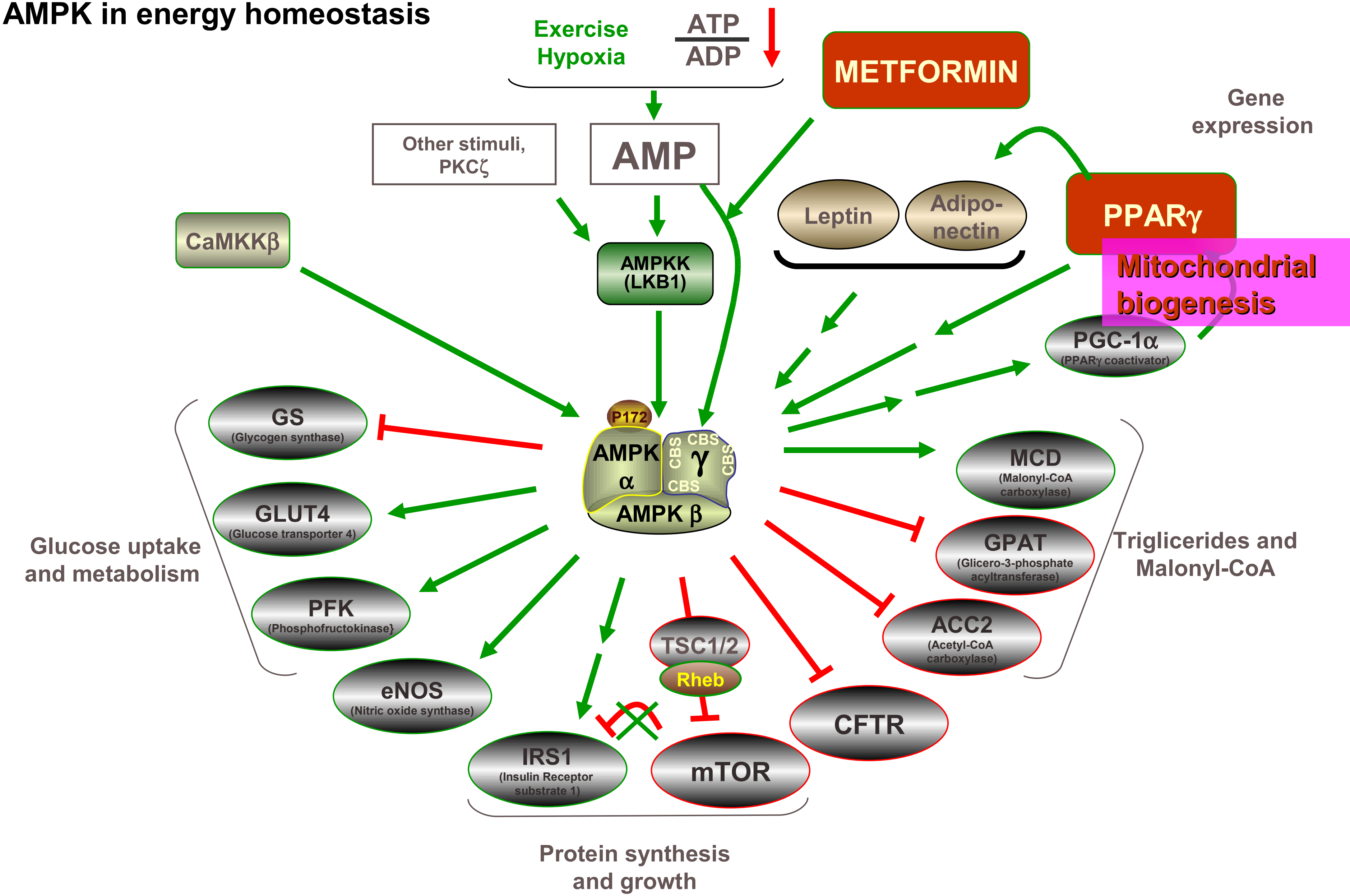
Energiedefizit stimuliert Fettoxidation in Leber/Muskel via 5‘AMPK

(Minokoshi et al., 2002; Nature 415: 339; Yamauchi et al., 2002 Nature Med 8: 1288)



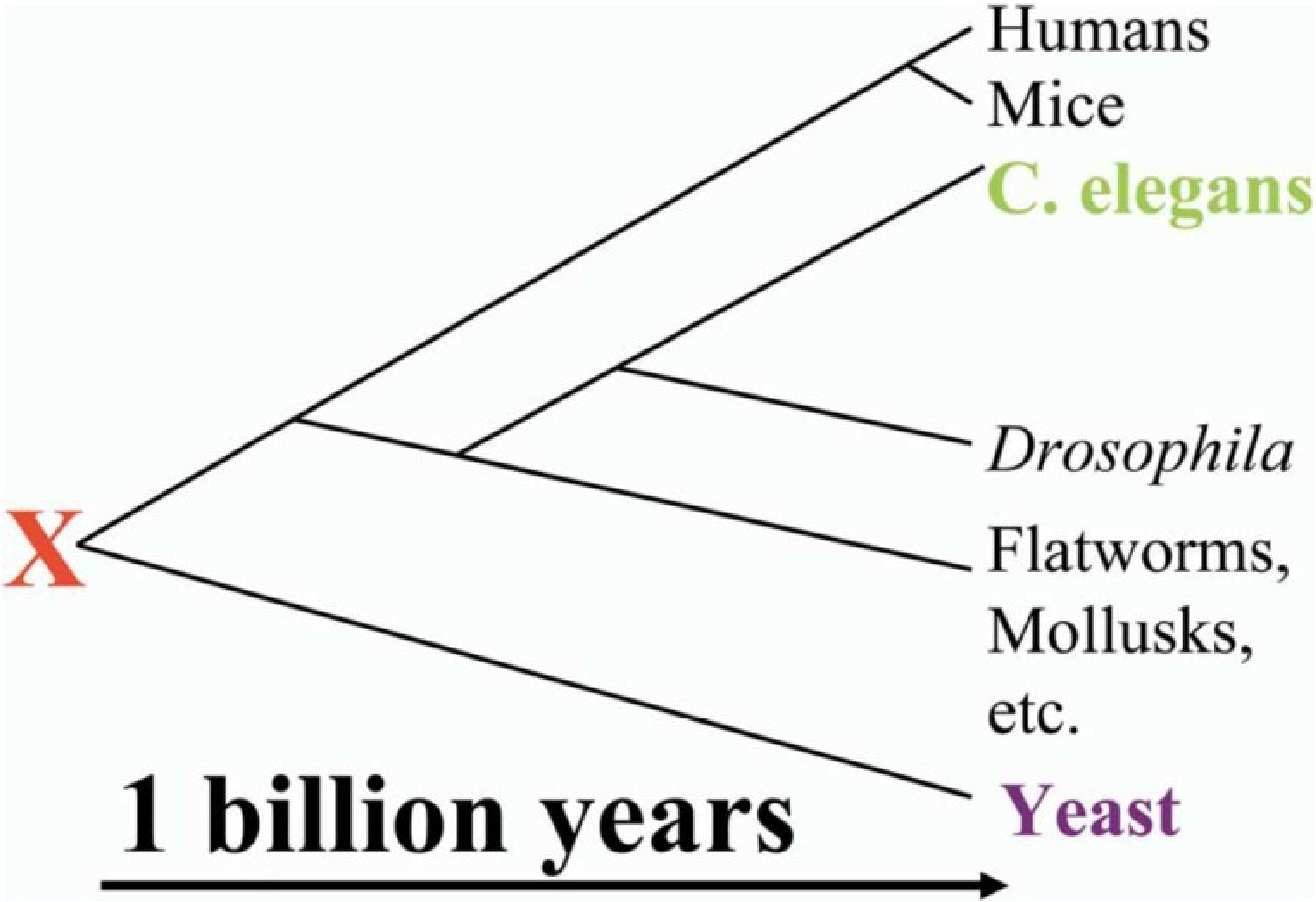
McGarry, Banting Lecture 2001, Diabetes

AMPK in energy homeostasis



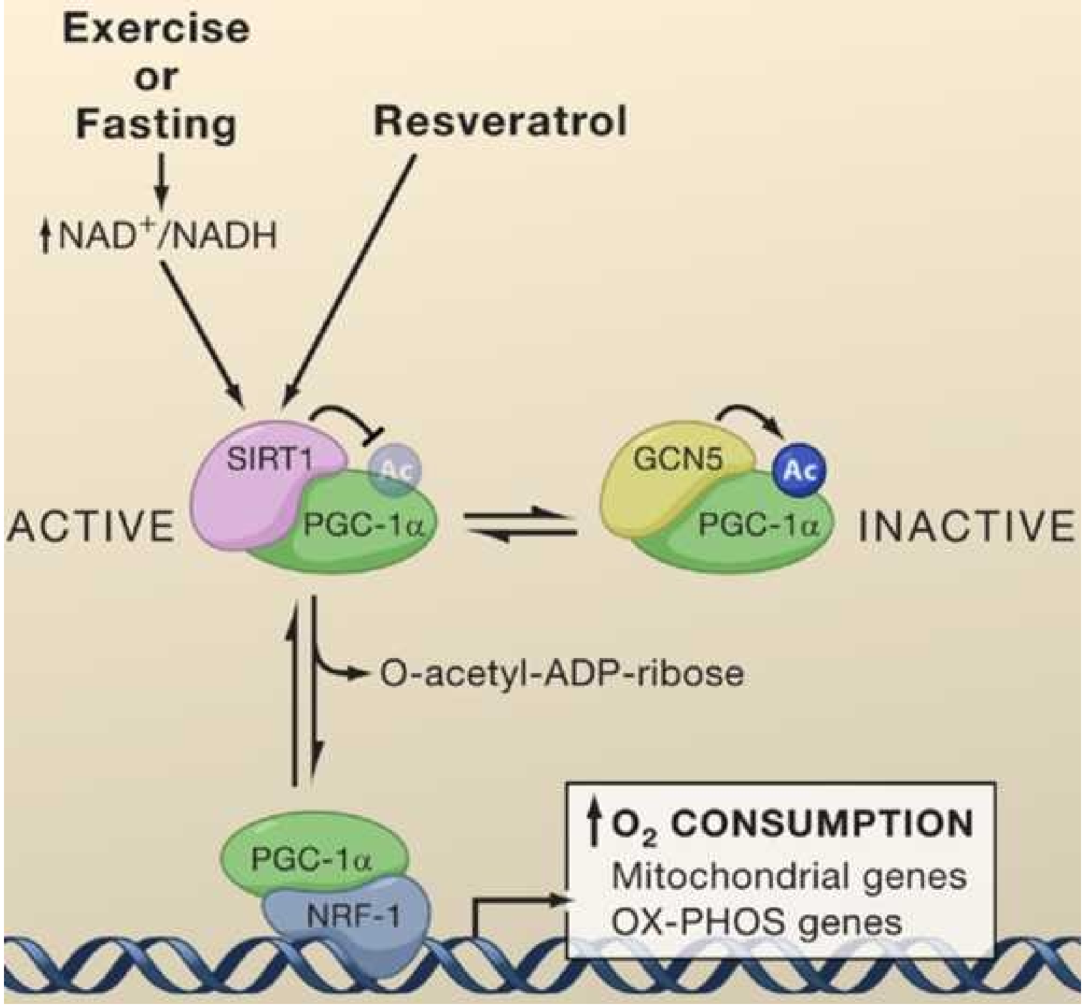
Evolutionäre Konservierung: Hefen und Fadenwürmer (C. elegans) haben sich evolutionär vor 1 Milliarde Jahre getrennt. Gene, wie Sir2, die in beiden vorkommen sollten weithin konserviert sein

Guarente & Picard., Cell 2006



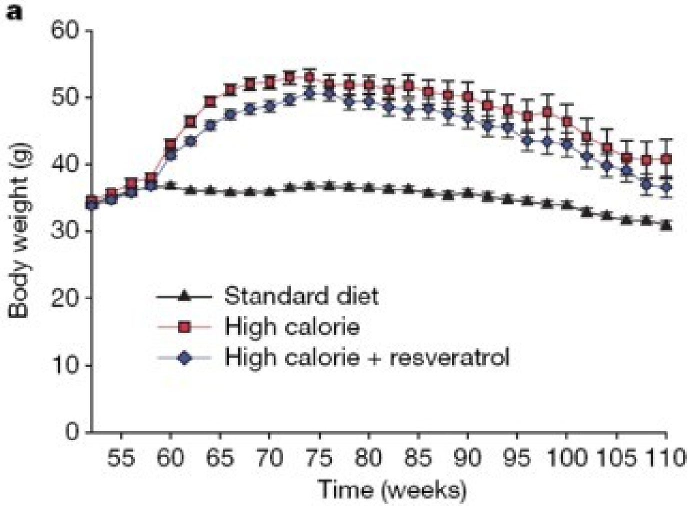
Sirt1 activates PGC-1α by deacetylation which induces mitochondrial biogenesis as cofactor of nuclear respiratory factor 1 (NRF-1) and increases insulin sensitivity

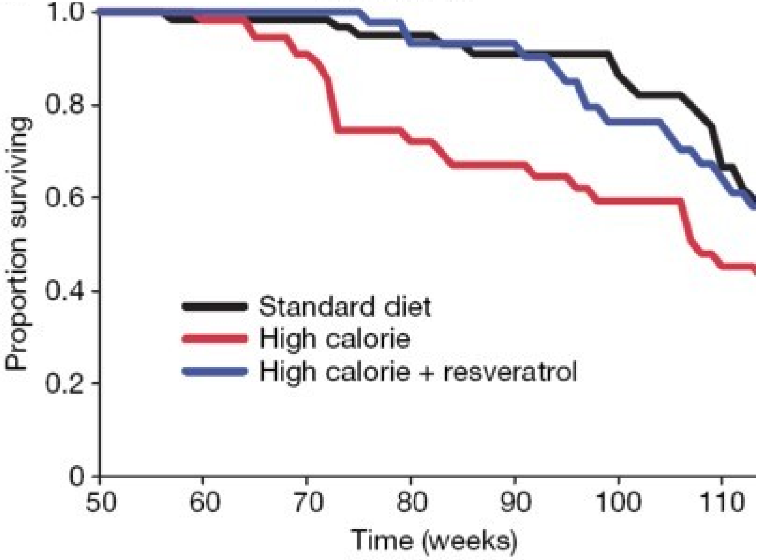
Koo & Montminy., Cell 2006

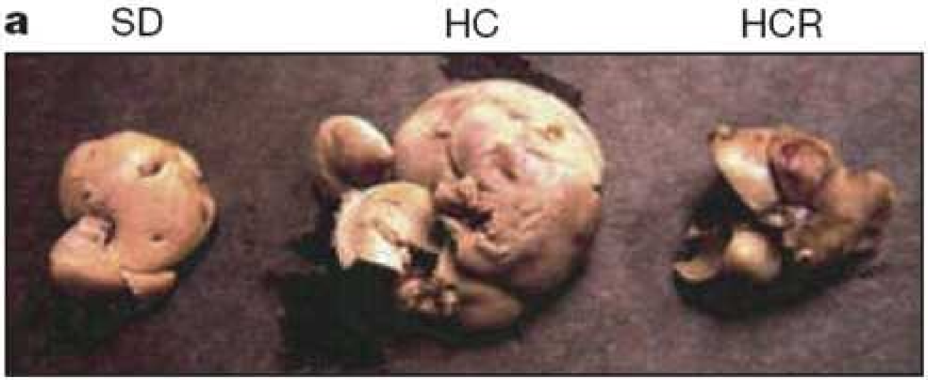


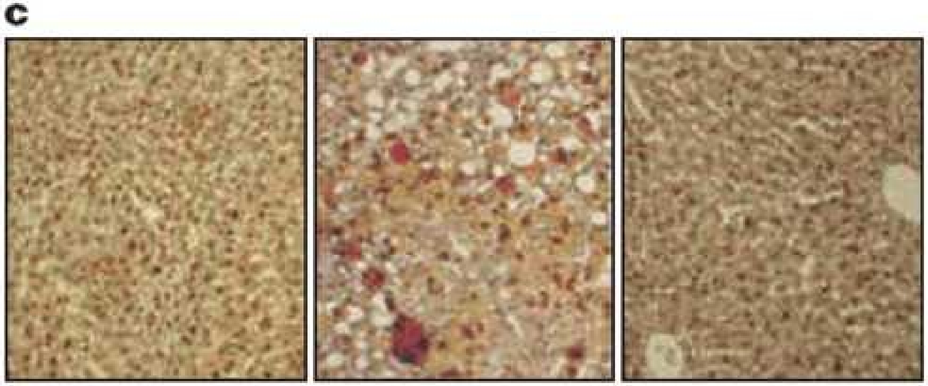
Activation of SirT1 by resveratrol in mice improves survival in high calorie diet fed mice and reduces fatty liver without changing body weight

Baur et al., Nature 2006



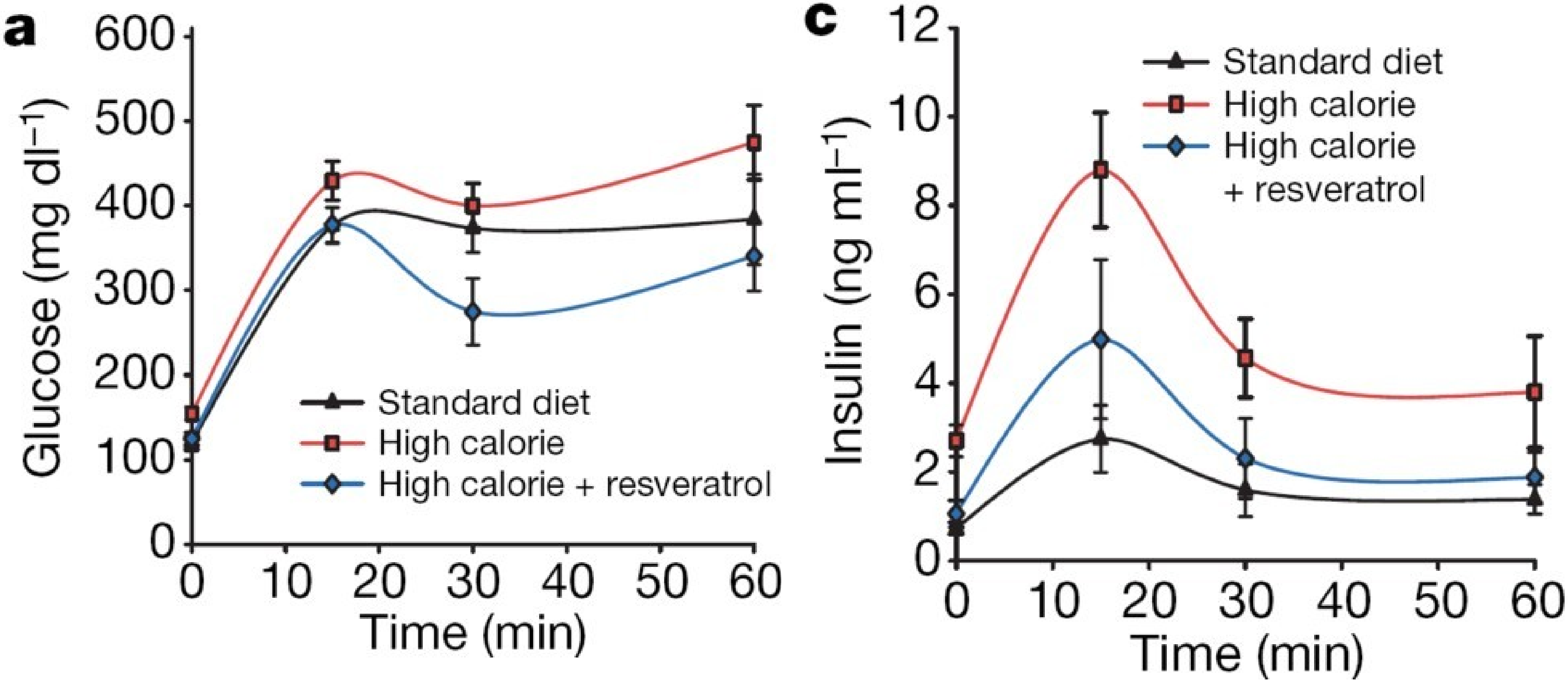






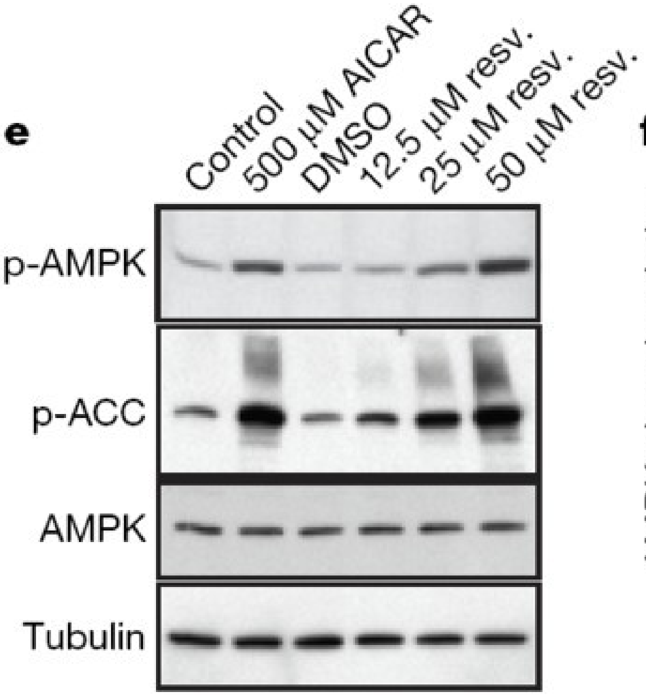
High insulin sensitivity in high calorie diet fed in mice upon activation of SirT1 by resveratrol

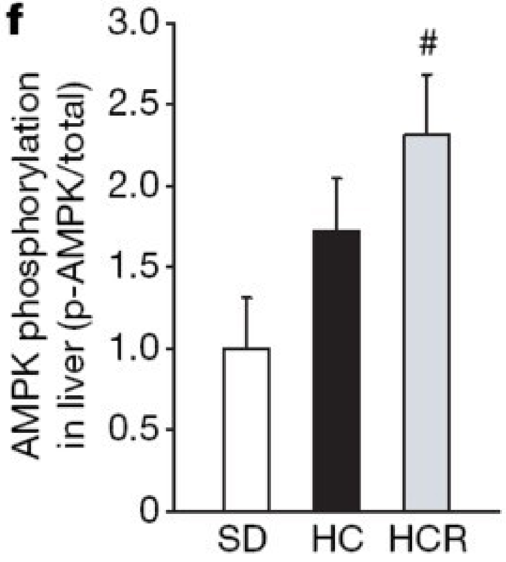
Baur et al., Nature 2006

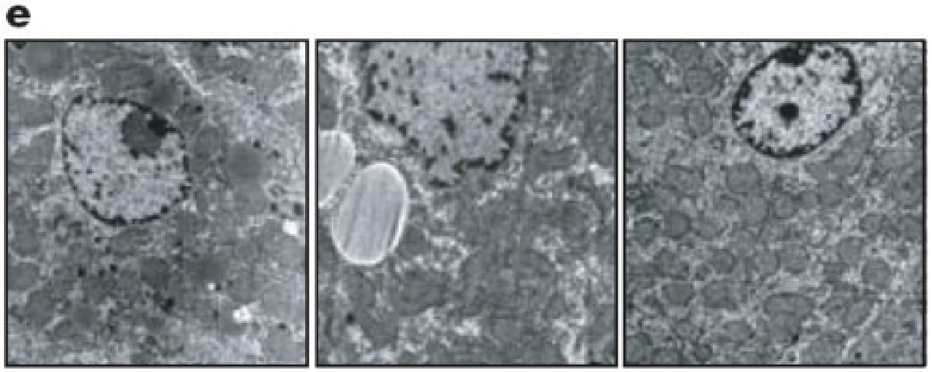


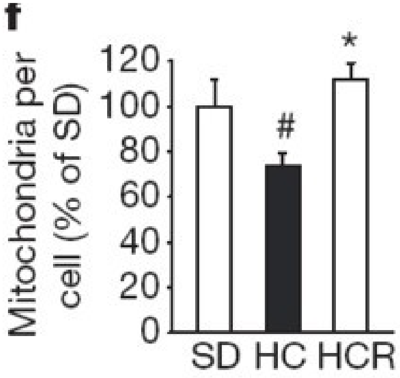
Phosphorylation of AMPK and its substrate ACC upon activation of SirT1 by resveratrol and increased mitochondrial density in mice

Baur et al., Nature 2006



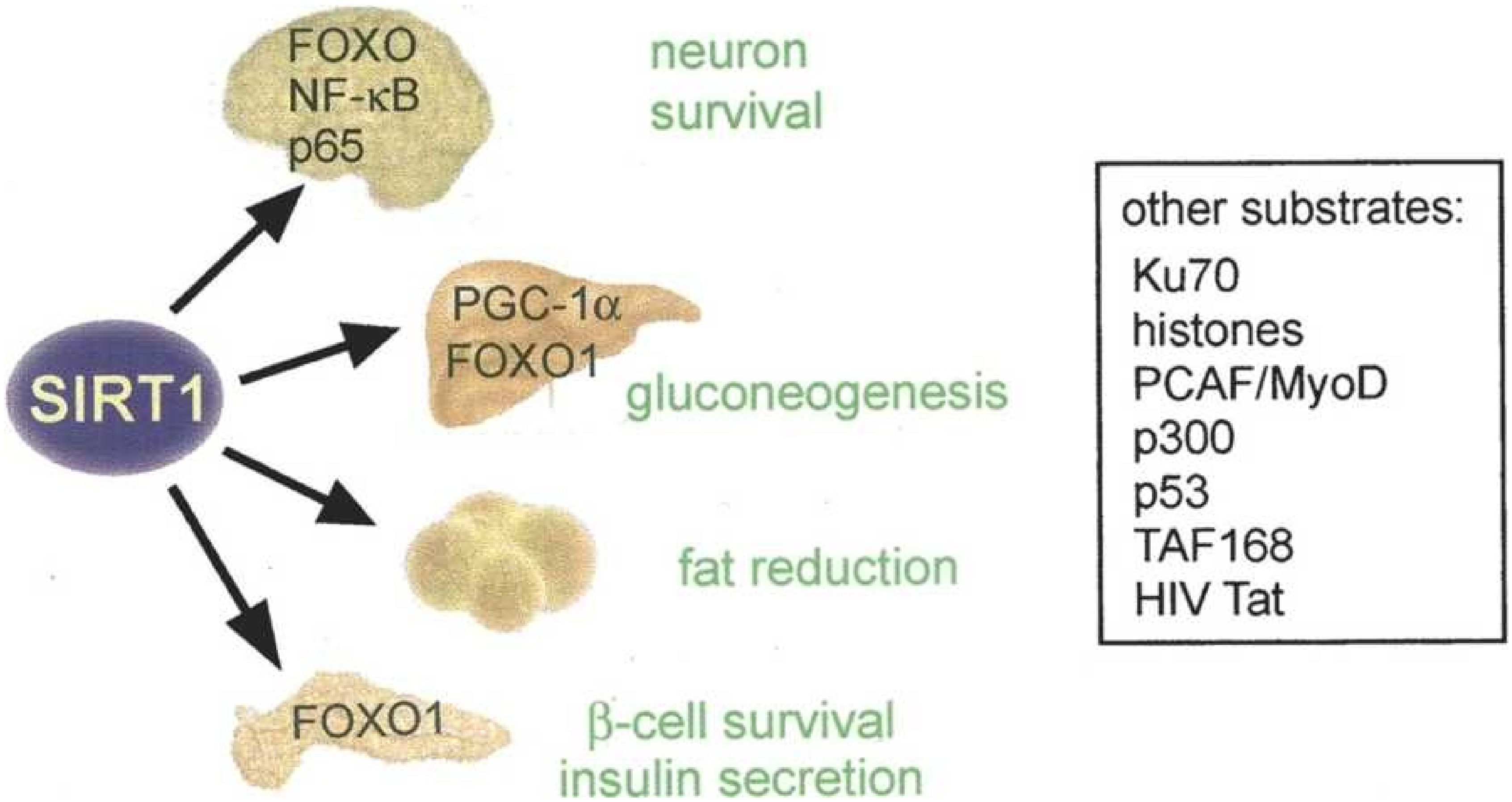






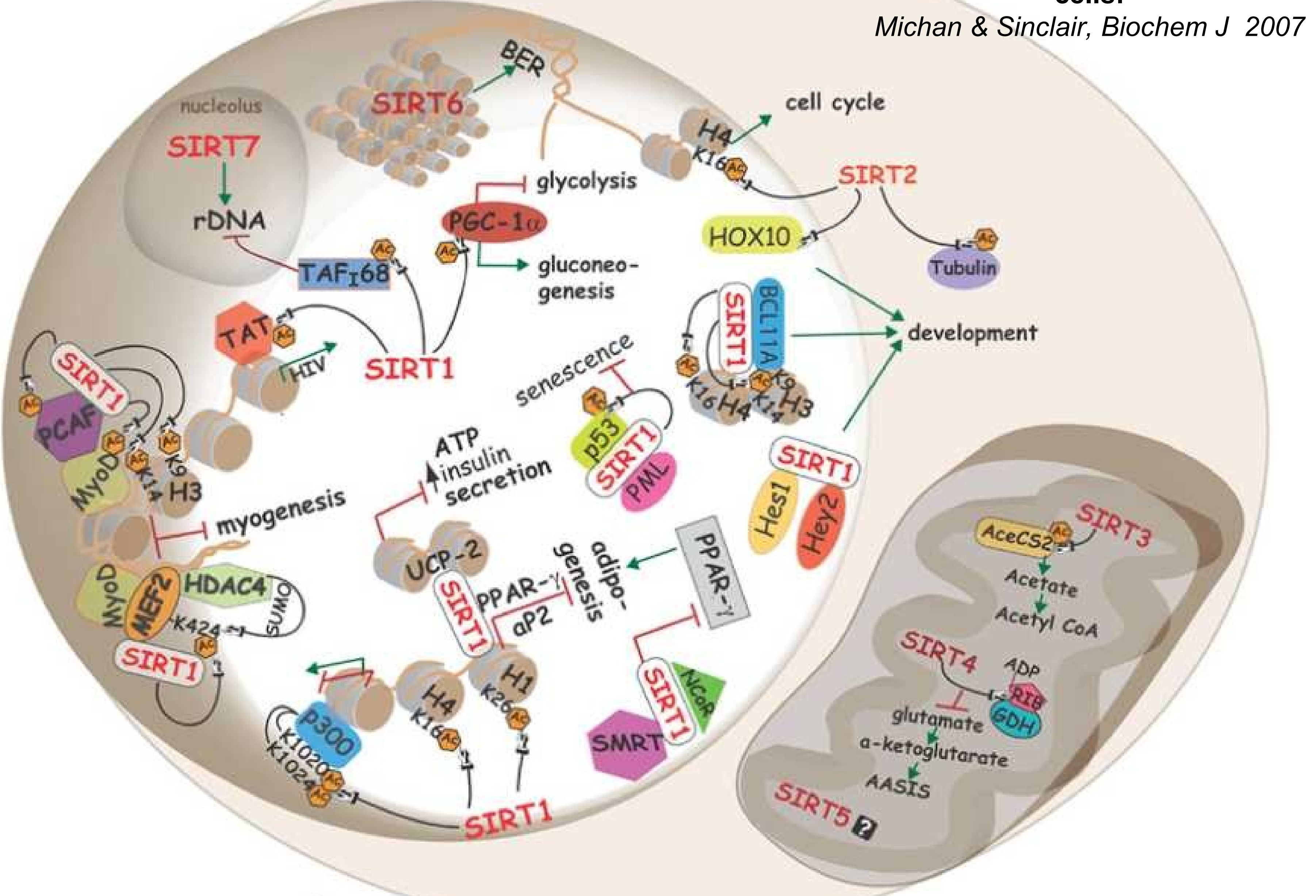
Sirt1 is induced by CR and regulates many substrates related to energy metabolism in mammalian cells by deacetylation

Haigis & Guarente, Genes Dev 2006



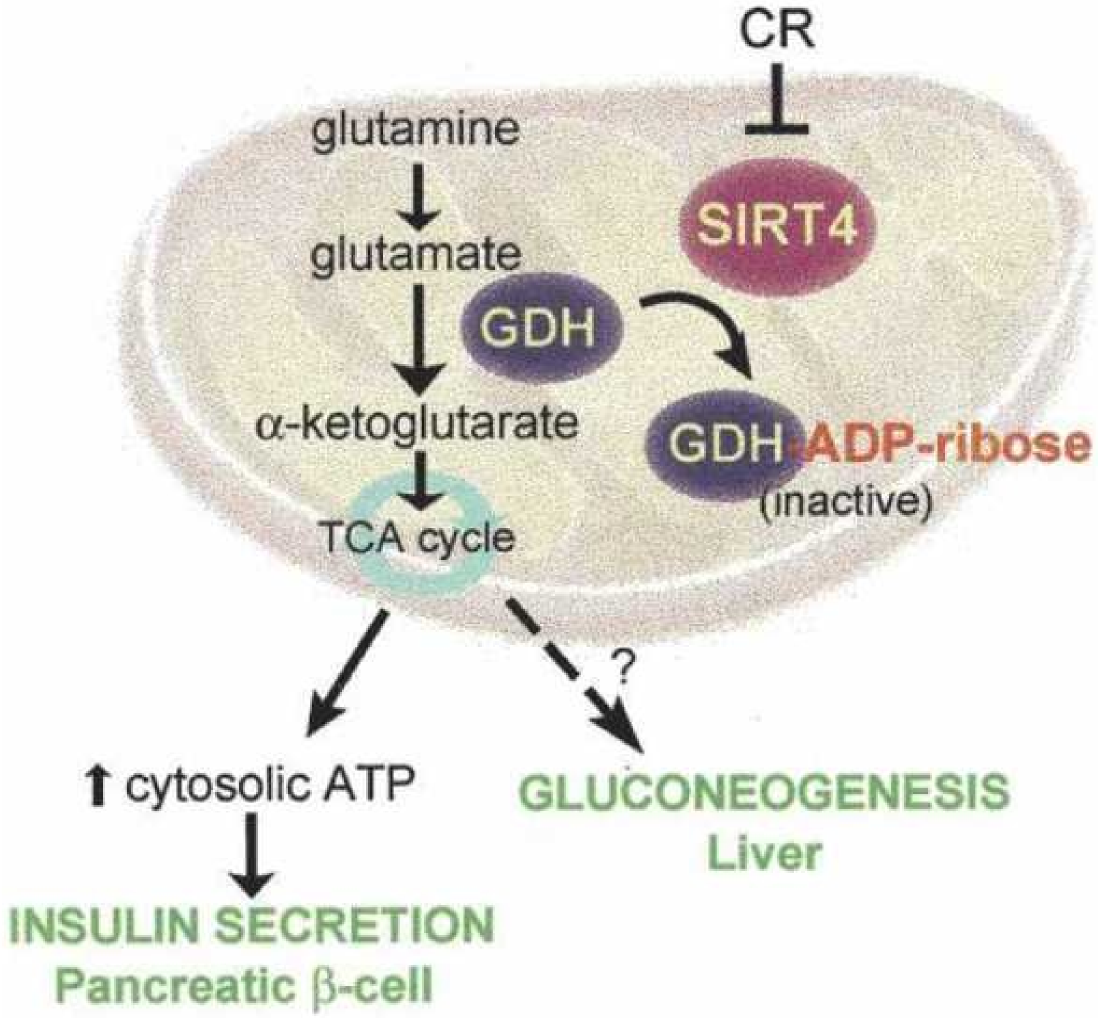
Sirtuin activities in mammalian cells:

Michan & Sinclair, Biochem J 2007



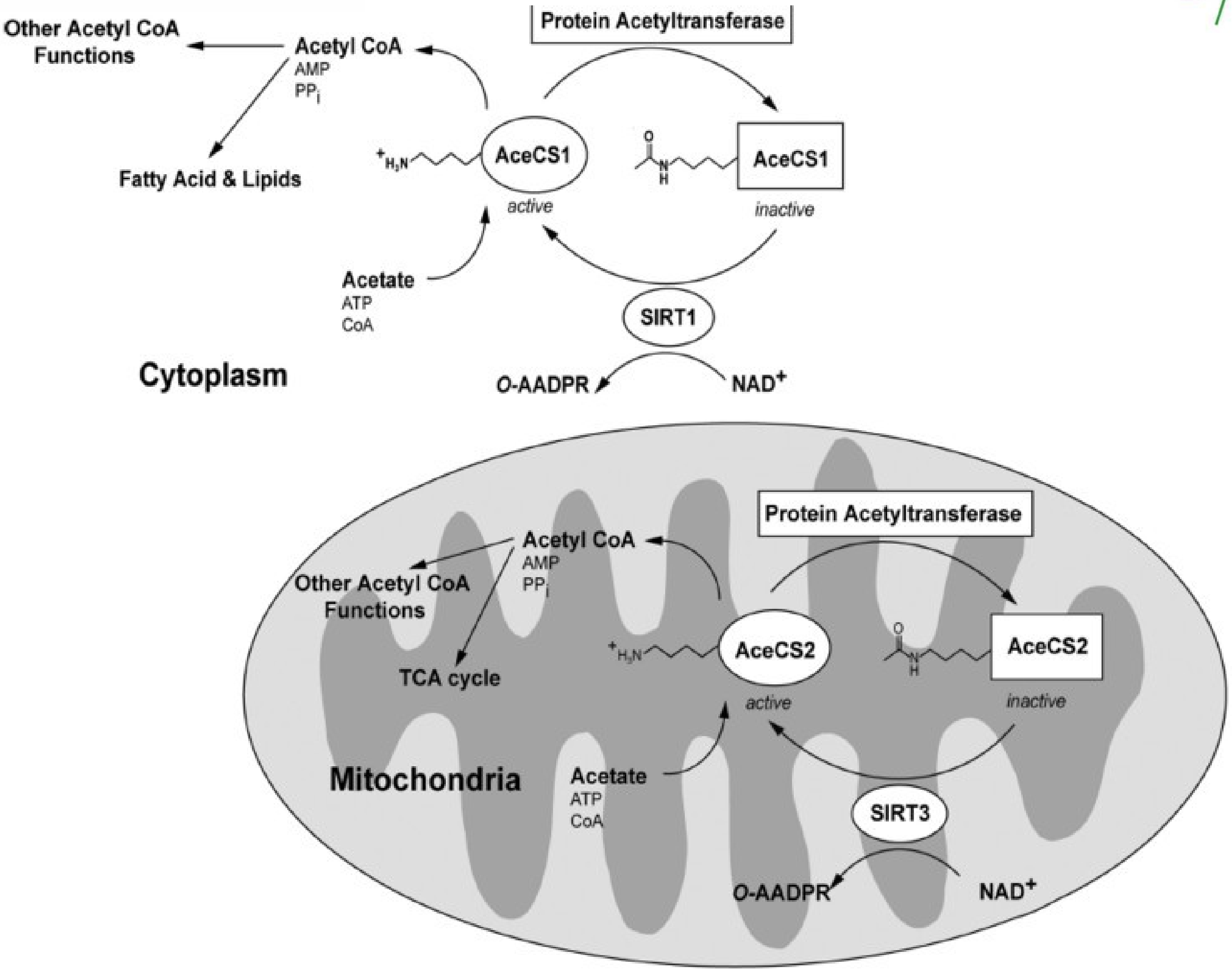
Sirt4 is involved in amino acid induced insulin secretion and hepatic gluconeogenesis via regulation of glutamate dehydrogenase

Haigis & Guarente, Genes Dev 2006



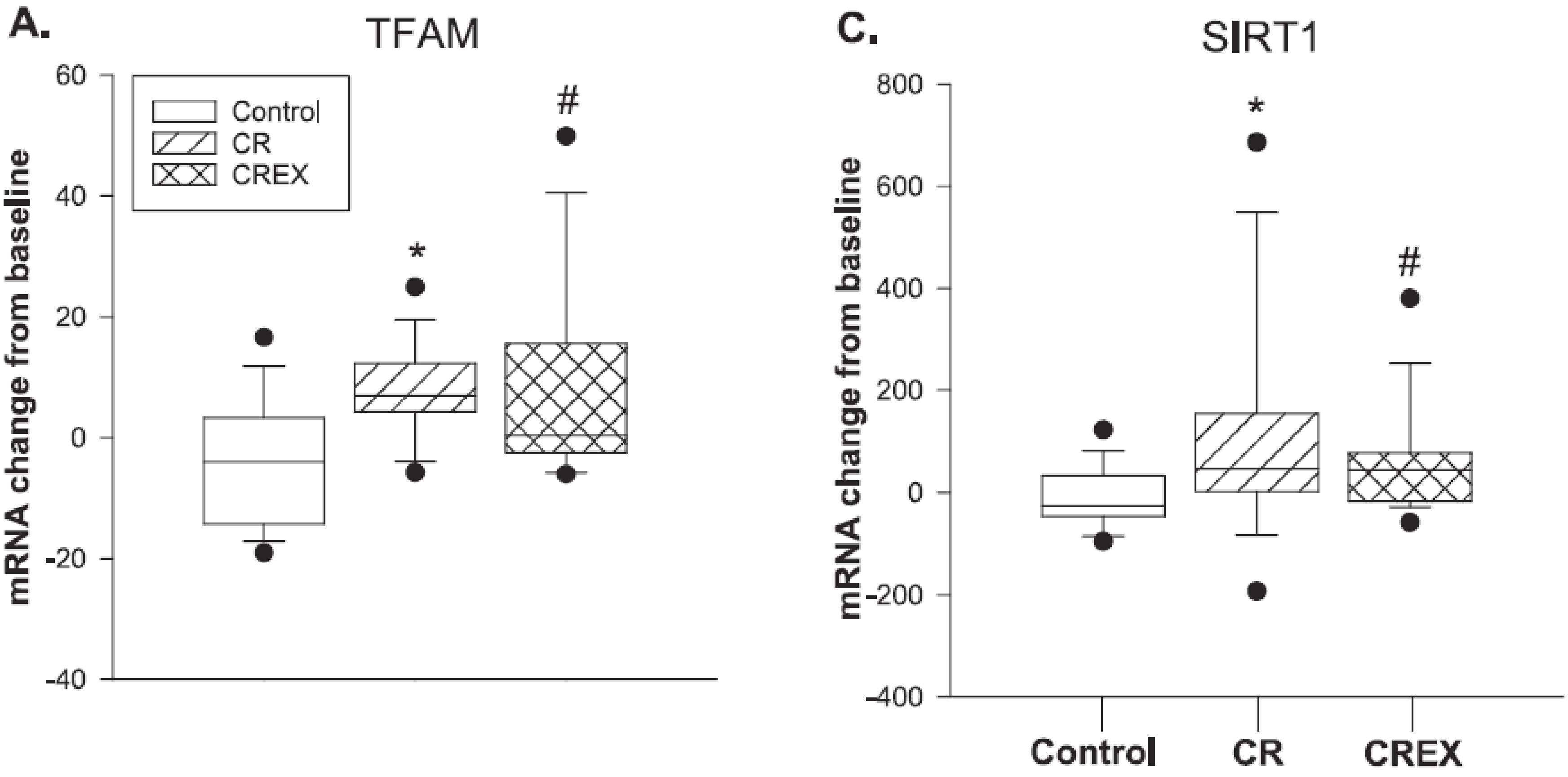
Acetyl-CoA-Synthetase (AceCS2) is deacetylated and activated by Sirt1 and Sirt3, a function conserved from procaryotes to mammals

Hollows et al, PNAS 2006



CALERIE-Studie: Anstieg der muskulären SIRT1 und TFAM- mRNA nach Gewichtsabnahme (10% Körpergewicht) durch CR oder CR+Sport

Civitarese et al., PLOS Medicine 2007



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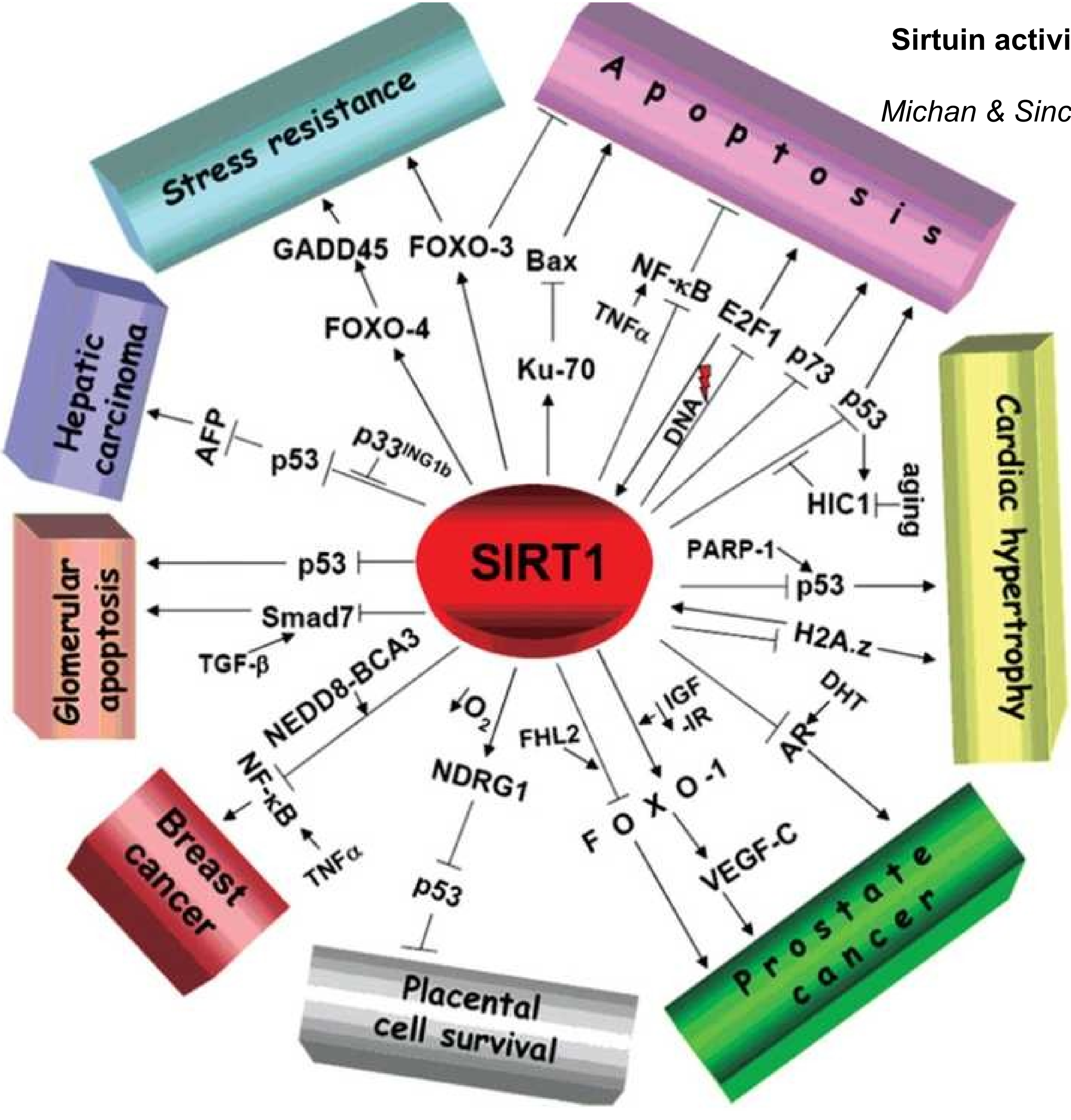
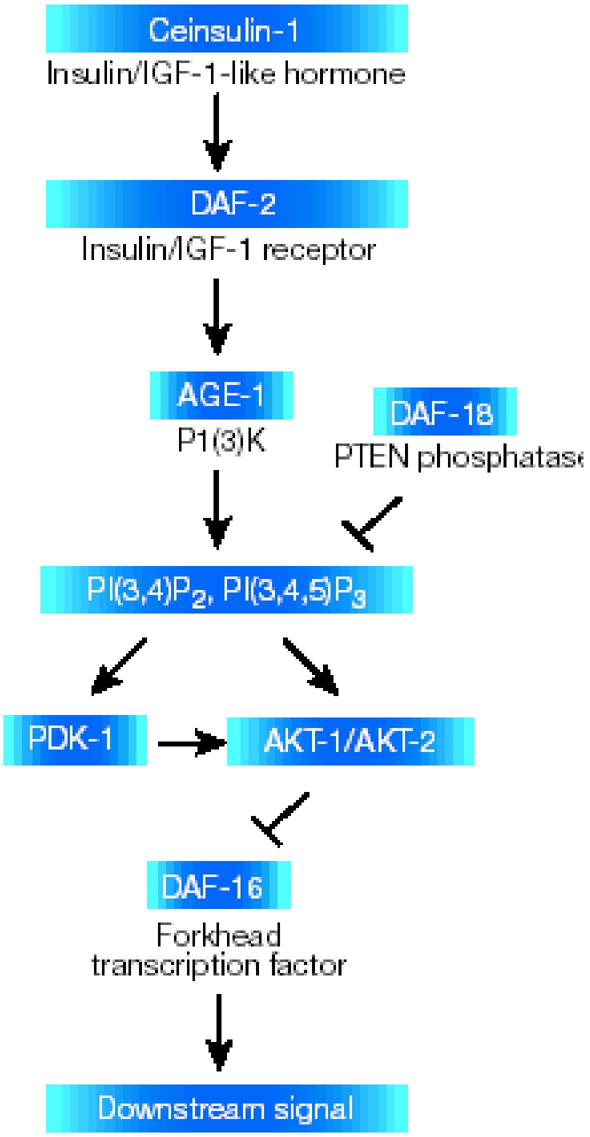


SIR2 is required together with daf16/FoxO to prolong life in C-elegans



Ceinsulin-1
Insulin/IGF-1-like hormone

DAF-2
Insulin/IGF-1 receptor

AGE-1
P1(3)K

DAF-18
PTEN phosphatas

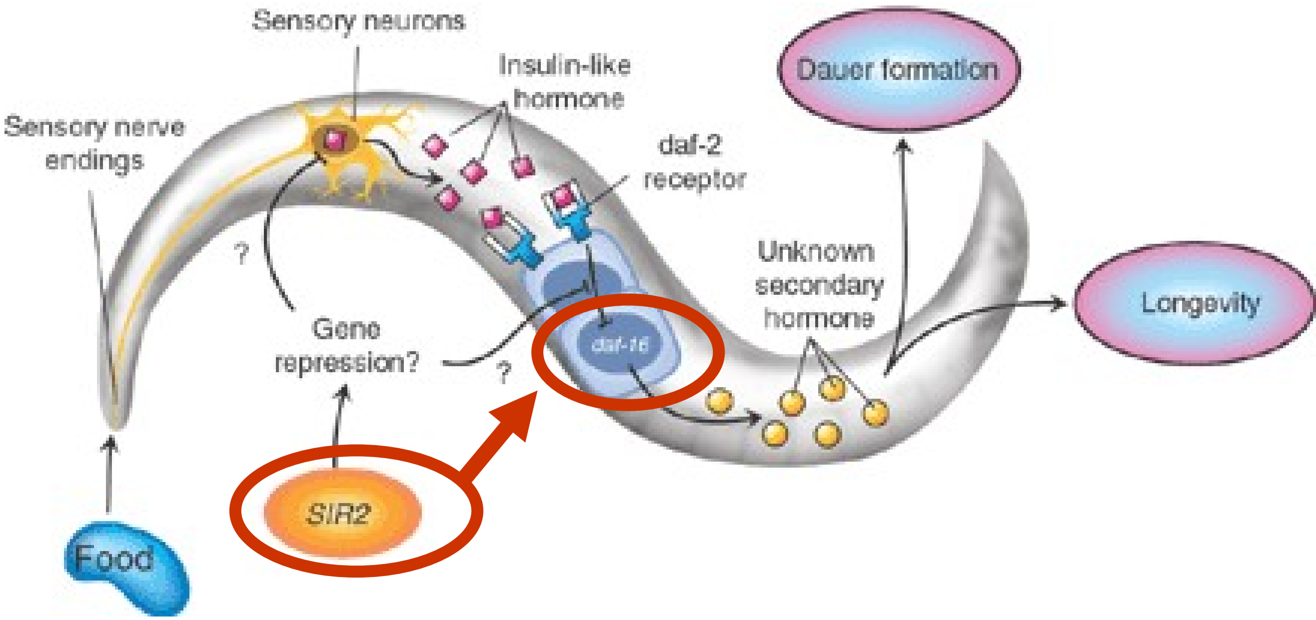
$PI(3,4)P_2$, $PI(3,4,5)P_3$

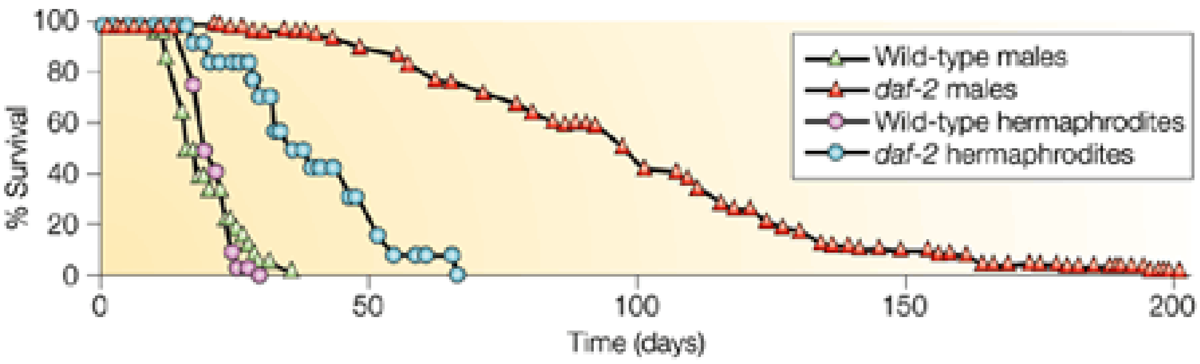
PDK-1

AKT-1/AKT-2

DAF-16
Forkhead transcription factor

Downstream signal





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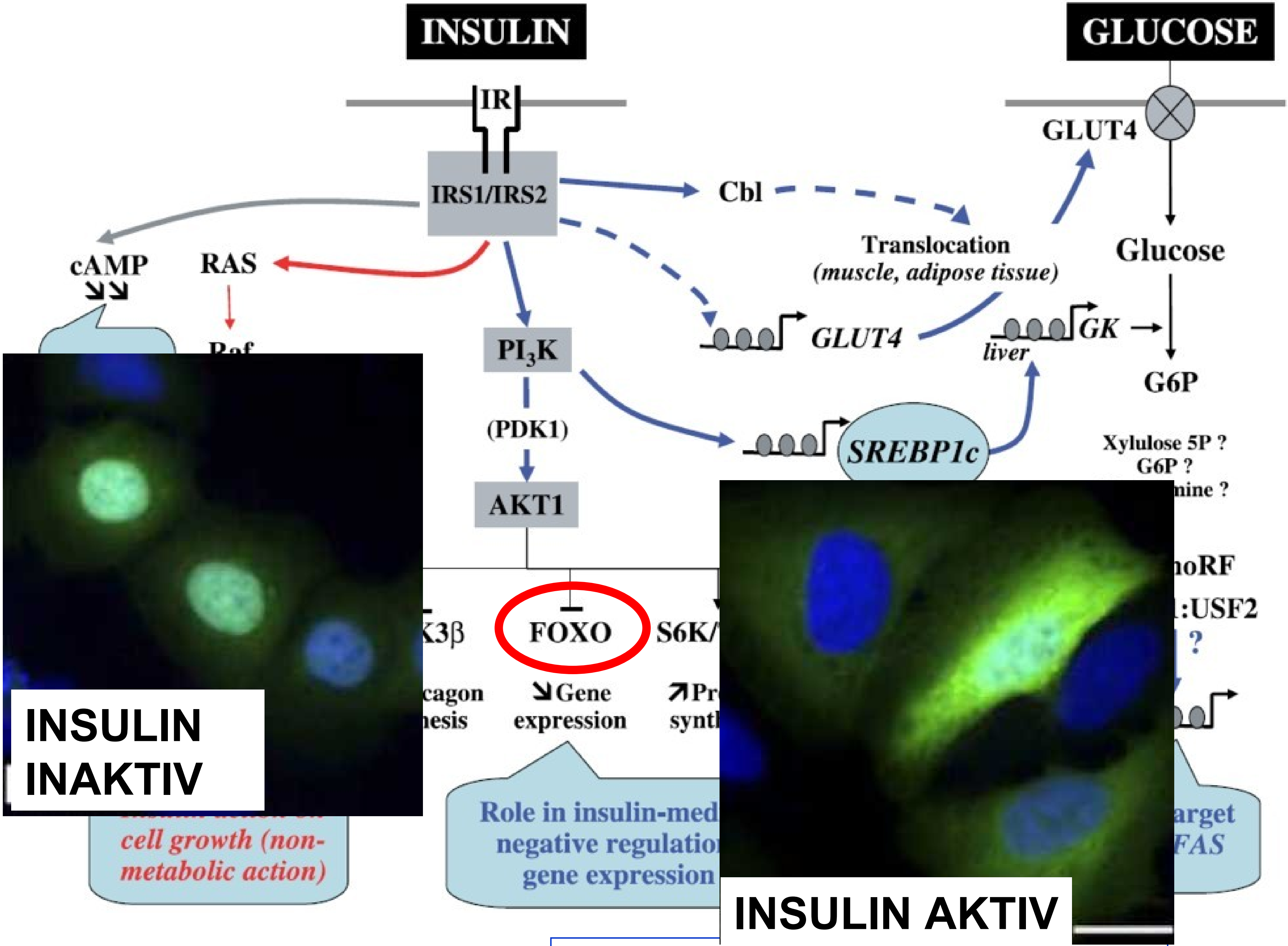


INSULIN INAKTIV

INSULIN AKTIV

Desvergne, Michalik & Wahli, 2006; Physiol Rev

Viel / wenig Insulin ± Glucose steuern die Genexpression für Zuckerproduktion und Fettsynthese

Signal pathway

GLUCOSE

PPP
X5P

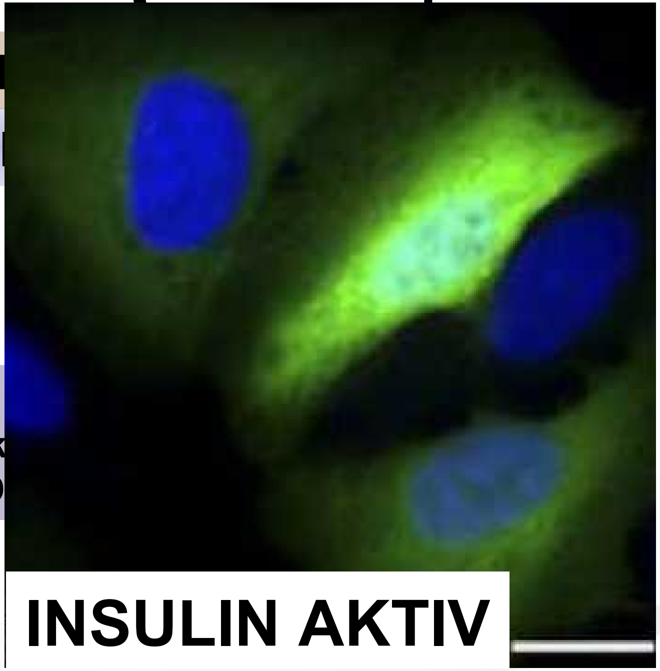
Transcrip-tion factor

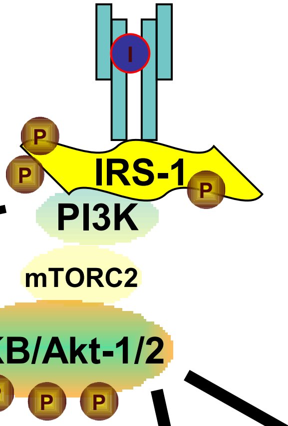
LX

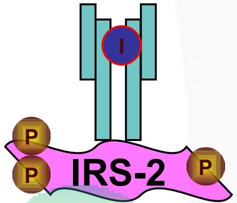
C

Gene ex-pression

FFA
Fruk
SCD


INSULIN AKTIV





FOXO1

GNG:
G6Pase
PEPCK


INSULIN
INAKTIV

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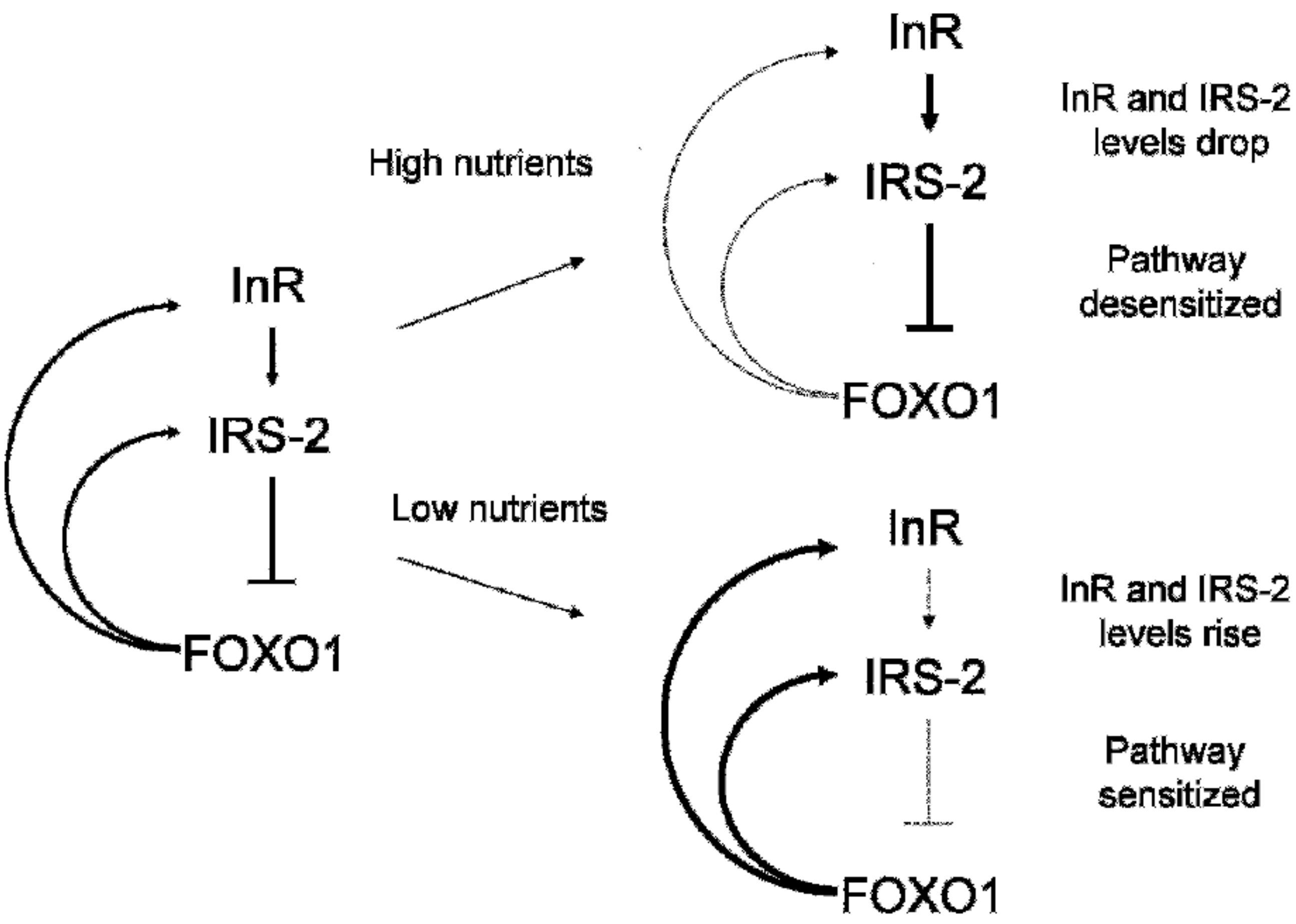
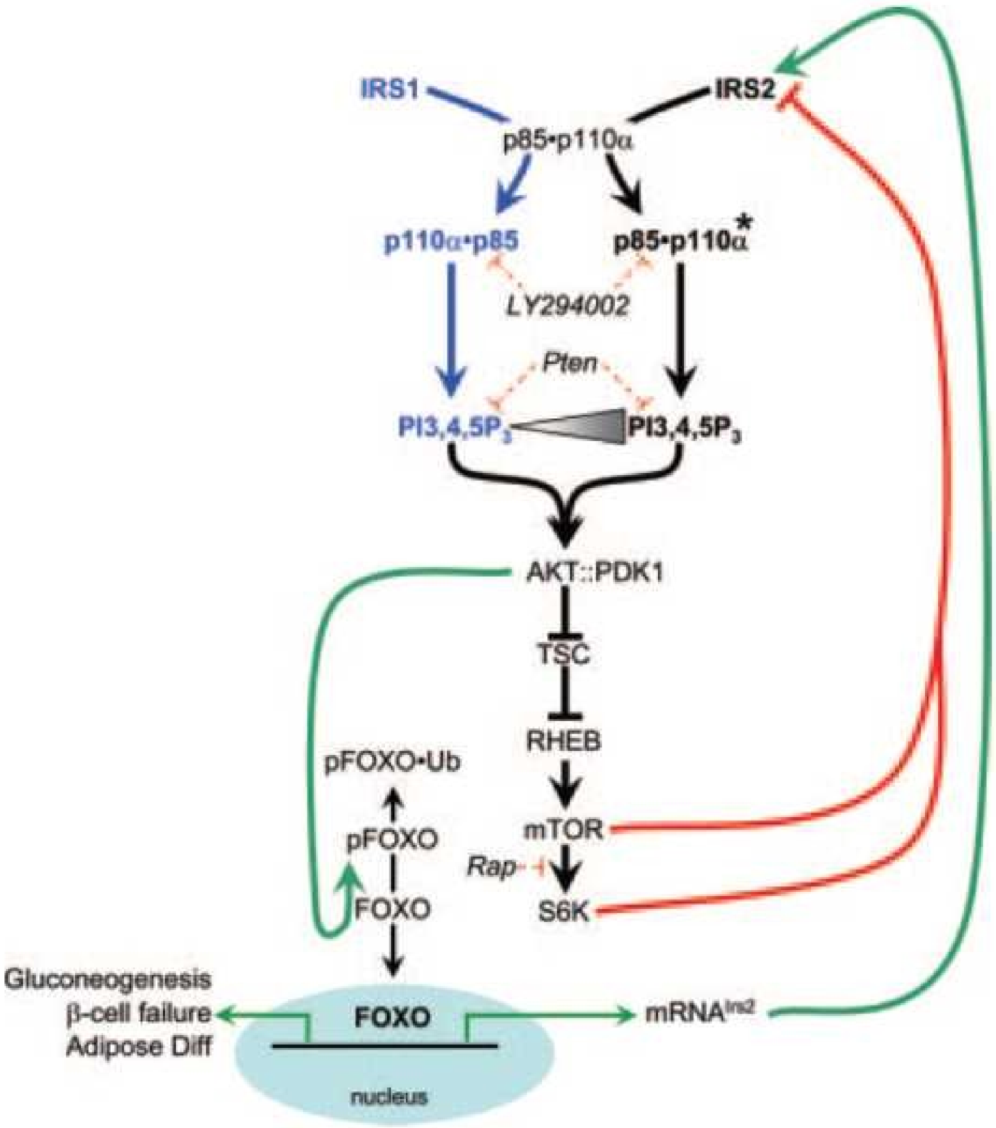
Insulin- FoxO interplay: Foxo1 signaling increases insulin sensitivity and prepares for nutrient intake in drosophila

Puig & Tijan 2005; Genes Development 19: 2435



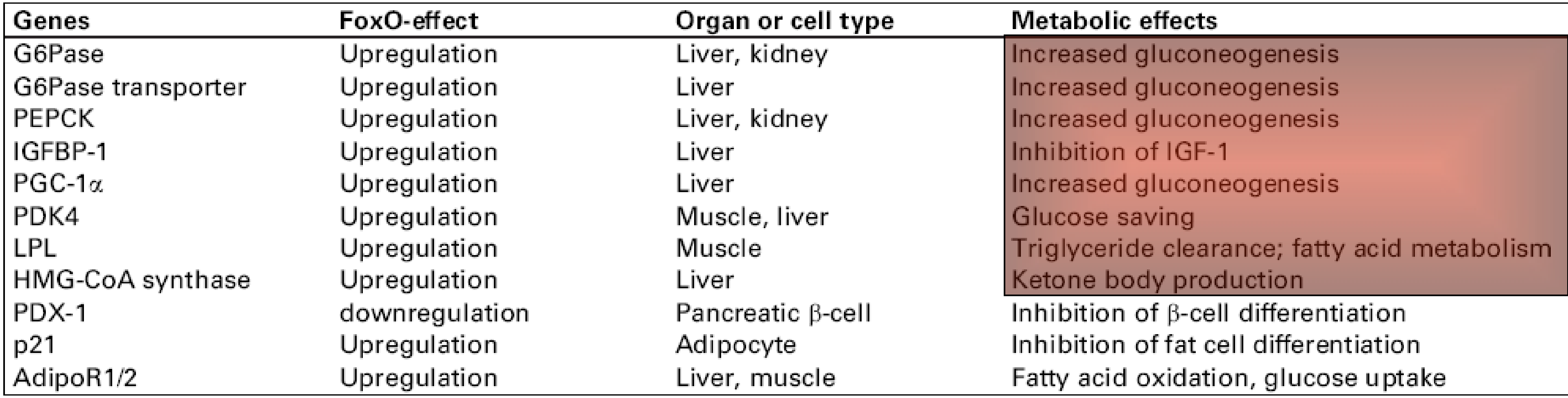
The Reciprocal Stability of FOXO1 and IRS2 Creates a Regulatory Circuit that Controls Insulin Signaling

Guo et al., Mol Endocrinol 2006

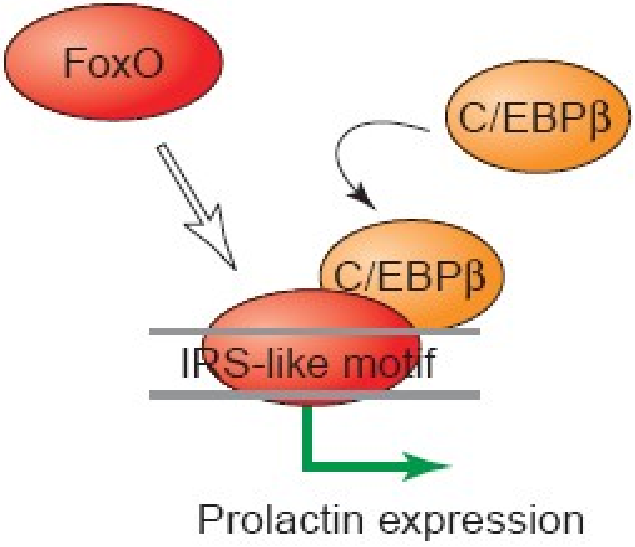


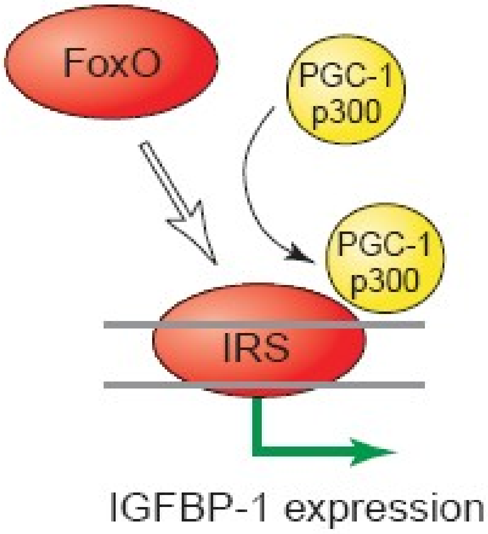
FoxO1 regulated genes – tuning for famine

Barthel et al., TEM 2005



Genes	FoxO-effect	Organ or cell type	Metabolic effects
G6Pase	Upregulation	Liver, kidney	Increased gluconeogenesis
G6Pase transporter	Upregulation	Liver	Increased gluconeogenesis
PEPCK	Upregulation	Liver, kidney	Increased gluconeogenesis
IGFBP-1	Upregulation	Liver	Inhibition of IGF-1
PGC-1α	Upregulation	Liver	Increased gluconeogenesis
PDK4	Upregulation	Muscle, liver	Glucose saving
LPL	Upregulation	Muscle	Triglyceride clearance; fatty acid metabolism
HMG-CoA synthase	Upregulation	Liver	Ketone body production
PDX-1	downregulation	Pancreatic β-cell	Inhibition of β-cell differentiation
p21	Upregulation	Adipocyte	Inhibition of fat cell differentiation
AdipoR1/2	Upregulation	Liver, muscle	Fatty acid oxidation, glucose uptake





FoxO1 activation in mice causes insulin resistance

Zhang et al., JBC 2006

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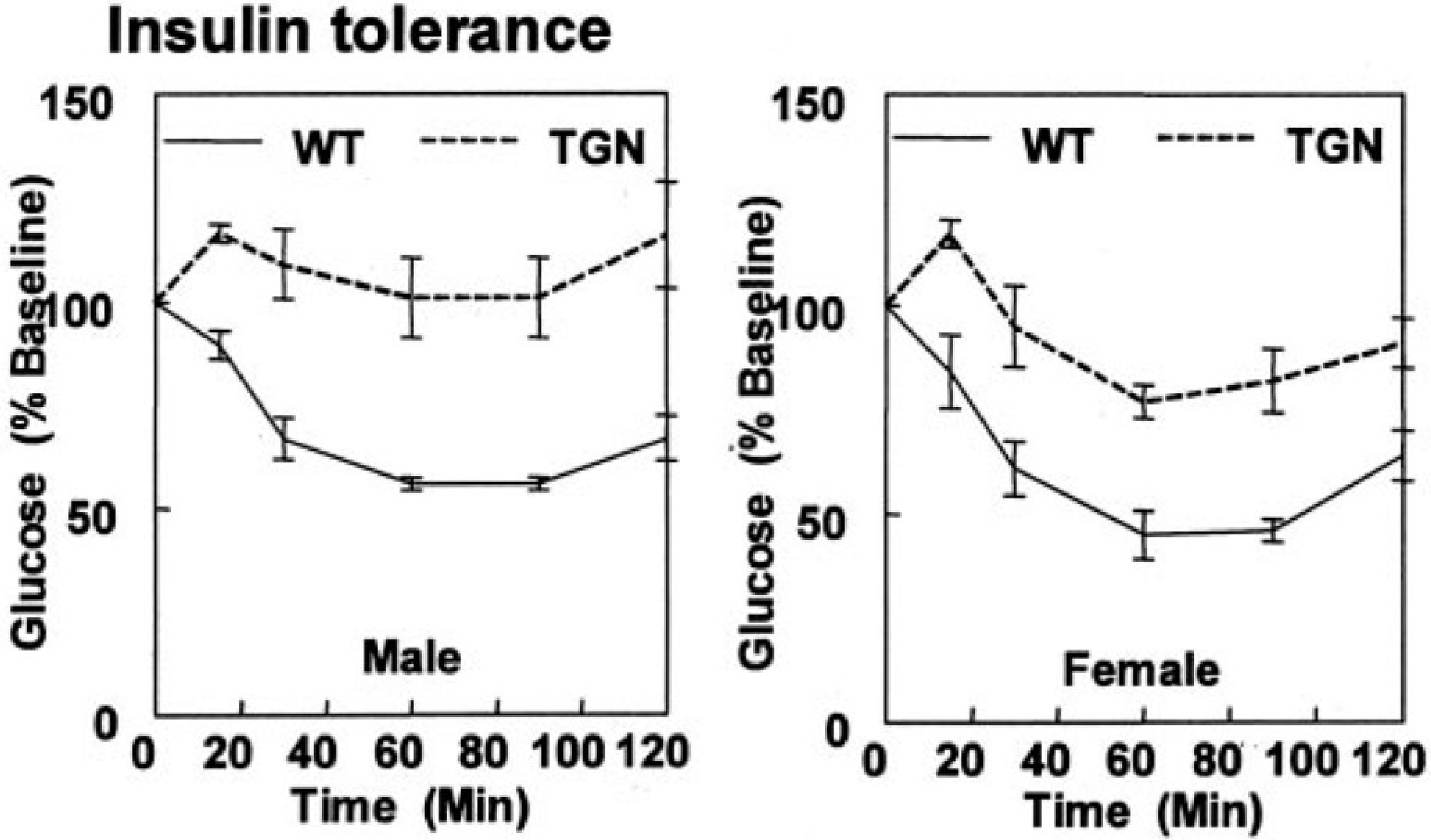
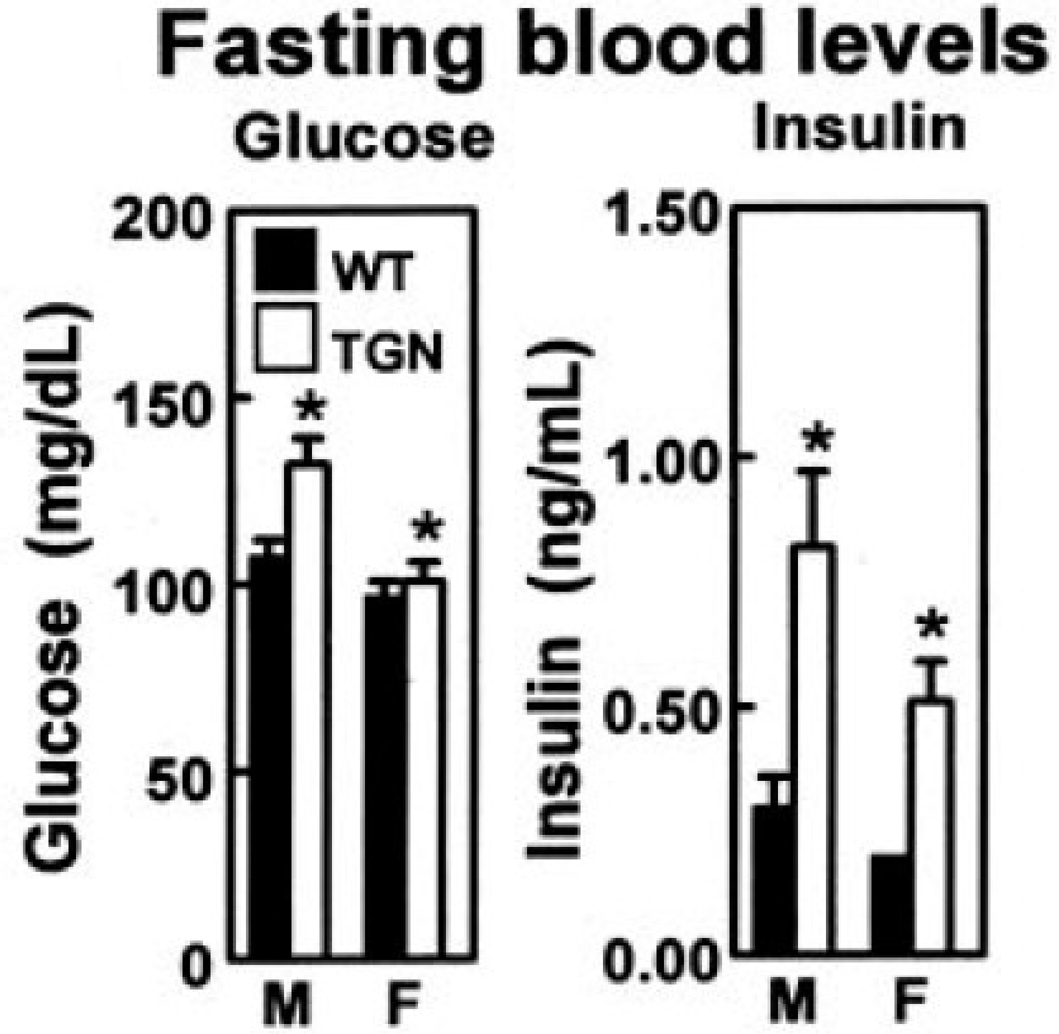


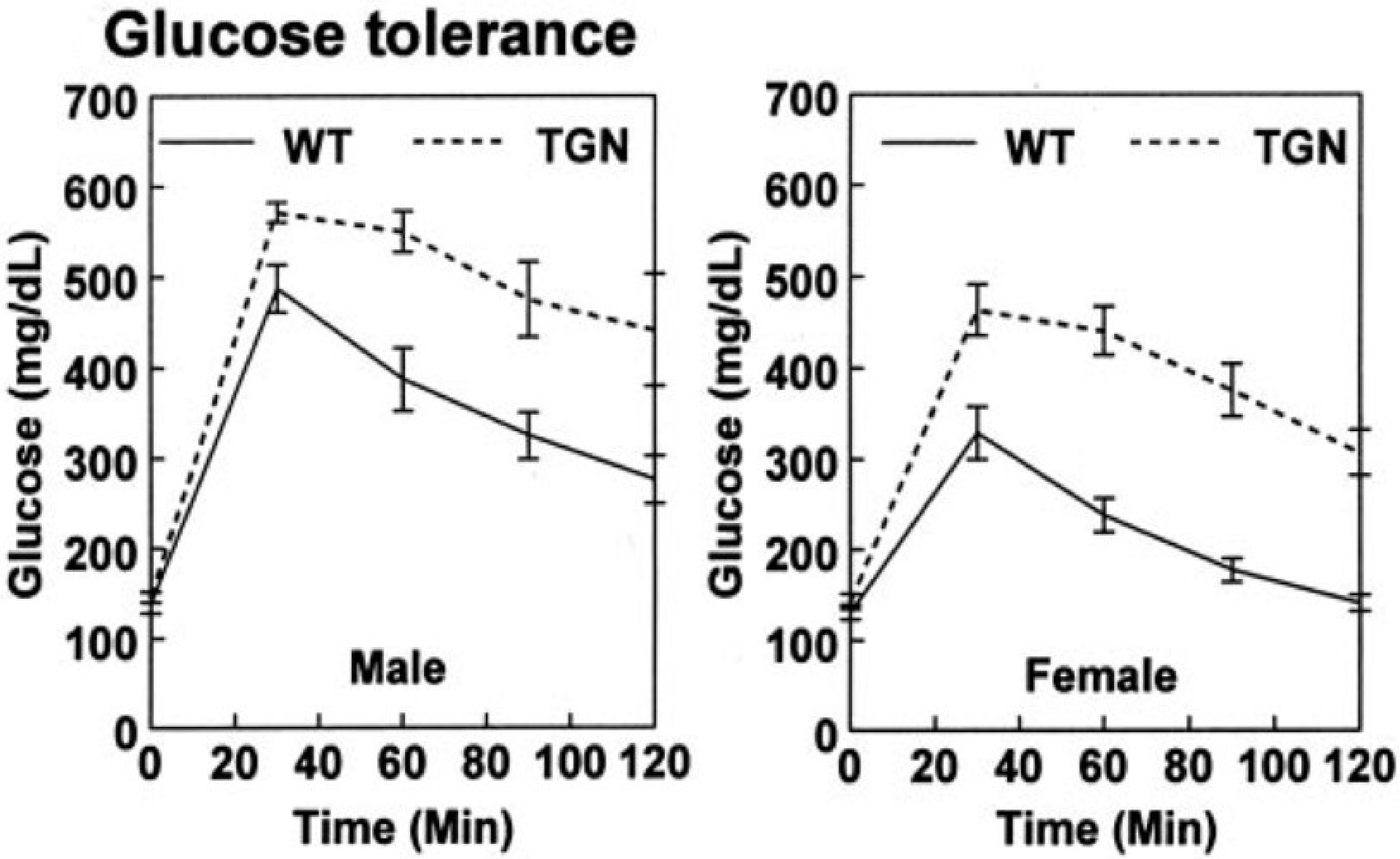
FoxO1 activation in mice: insulin resistance

Zhang et al., JBC 2006



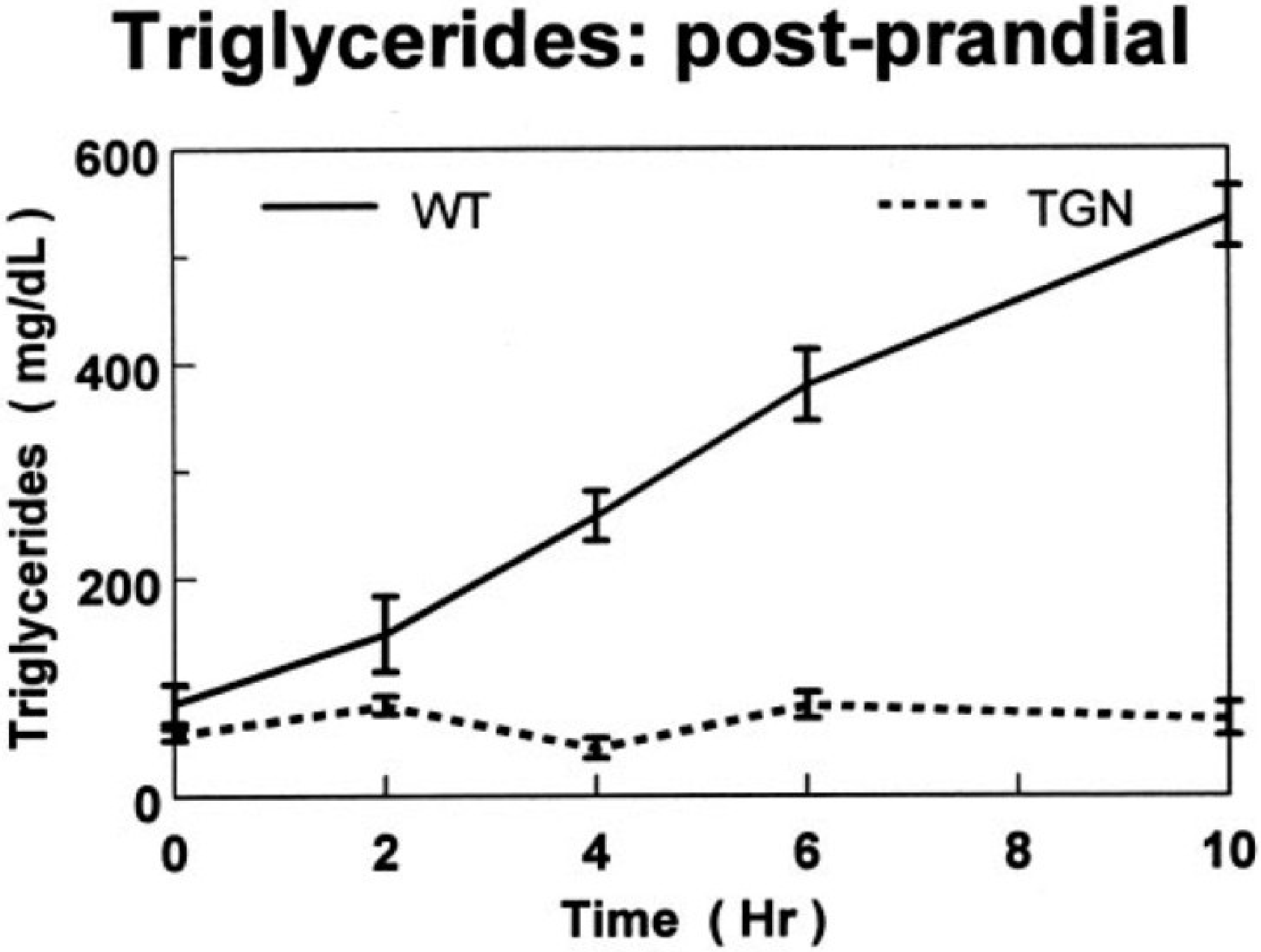
FoxO1 activation in mice: impaired glucose tolerance

Zhang et al., JBC 2006



FoxO1 activation in mice: improved fat metabolism

Zhang et al., JBC 2006



Mice after 4 days 65% sucrose diet and a high carbohydrate meal

FoxO1 translocates to the nucleus upon oxidative stress and colocalizes with Sirt1 in hepatoma cells

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Frescas et al., JBC 2005

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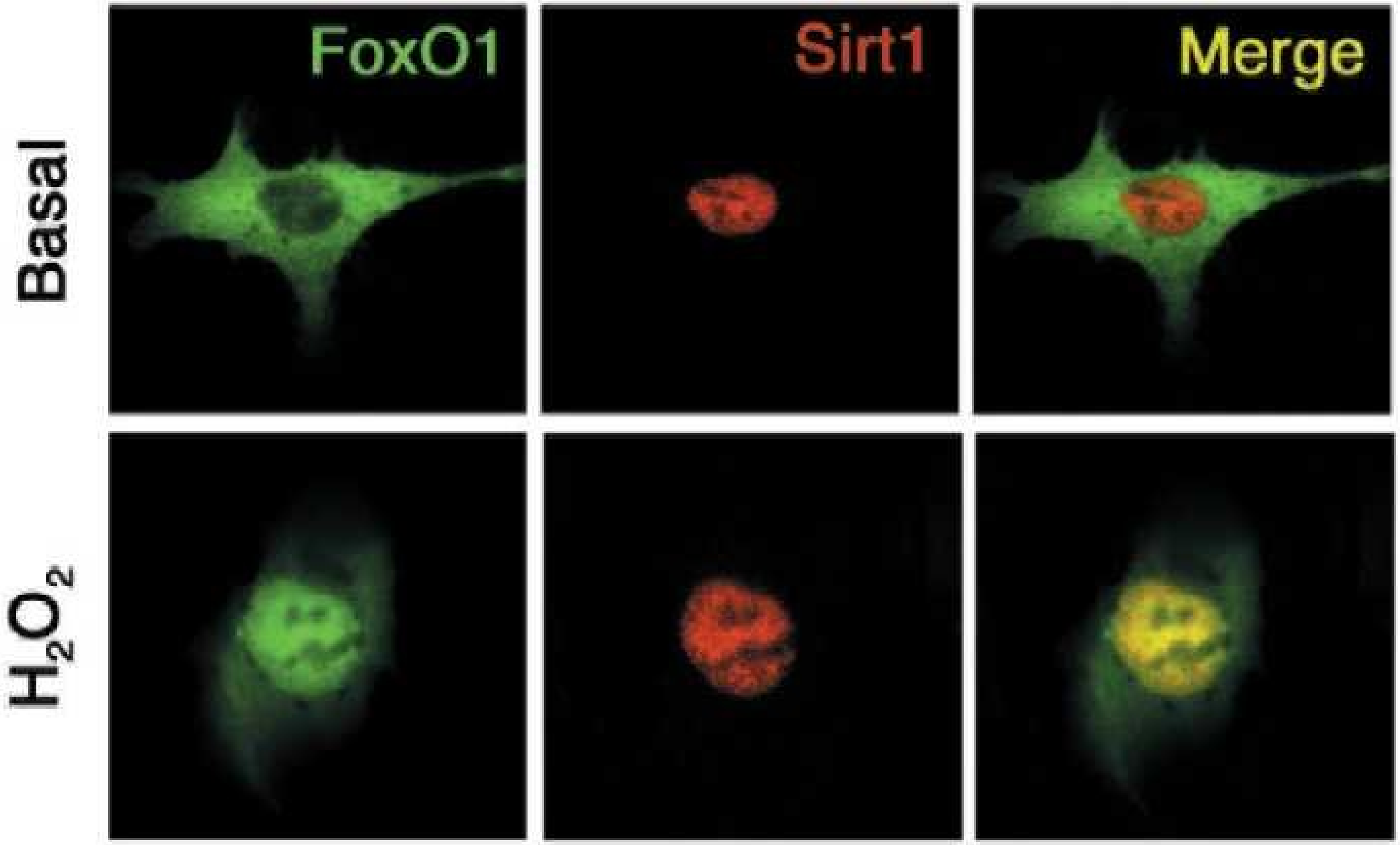
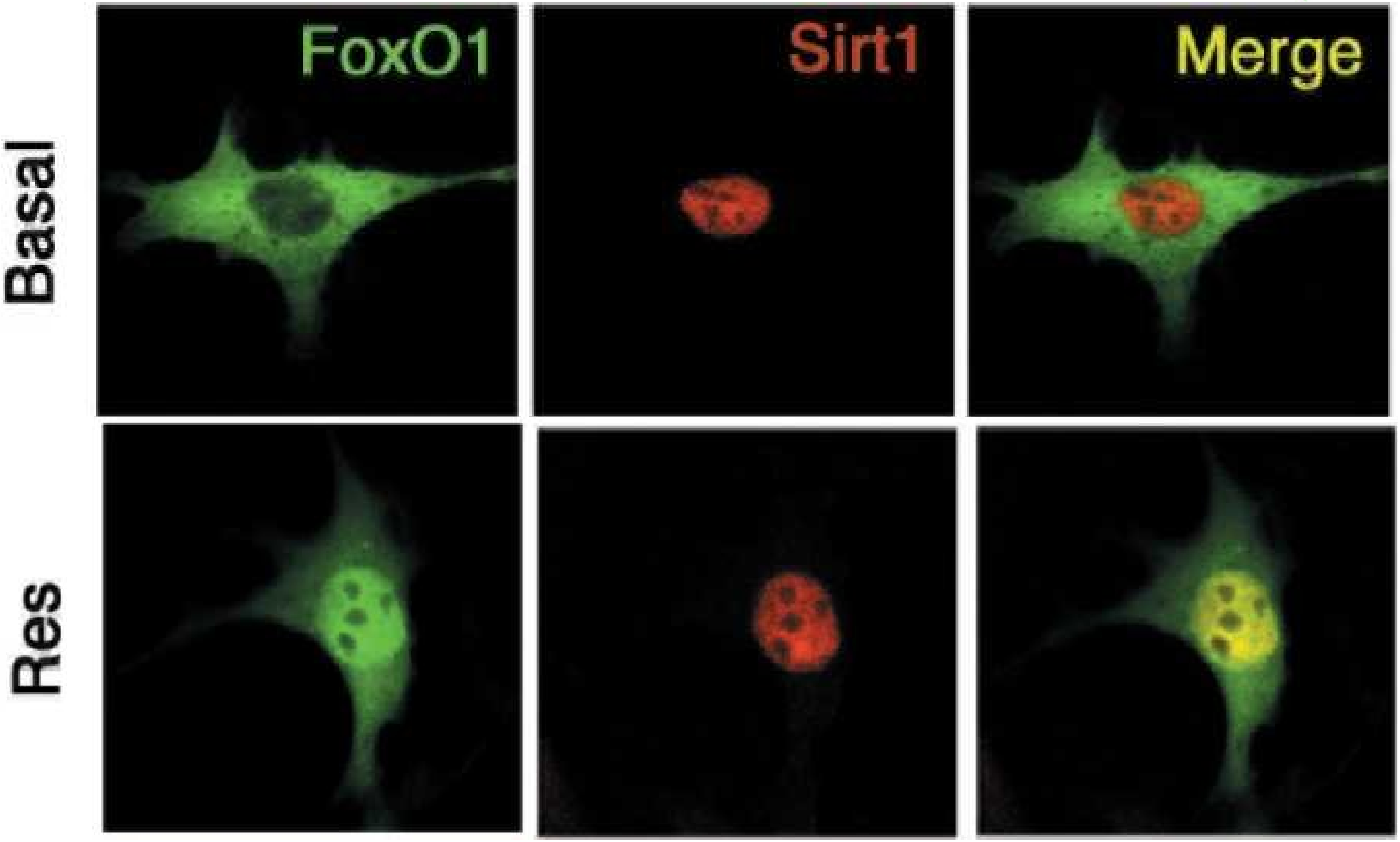


FoxO1 translocates to the nucleus upon ***resveratrol*** treatment and colocalizes with Sirt1 in hepatoma cells

Frescas et al., JBC 2005

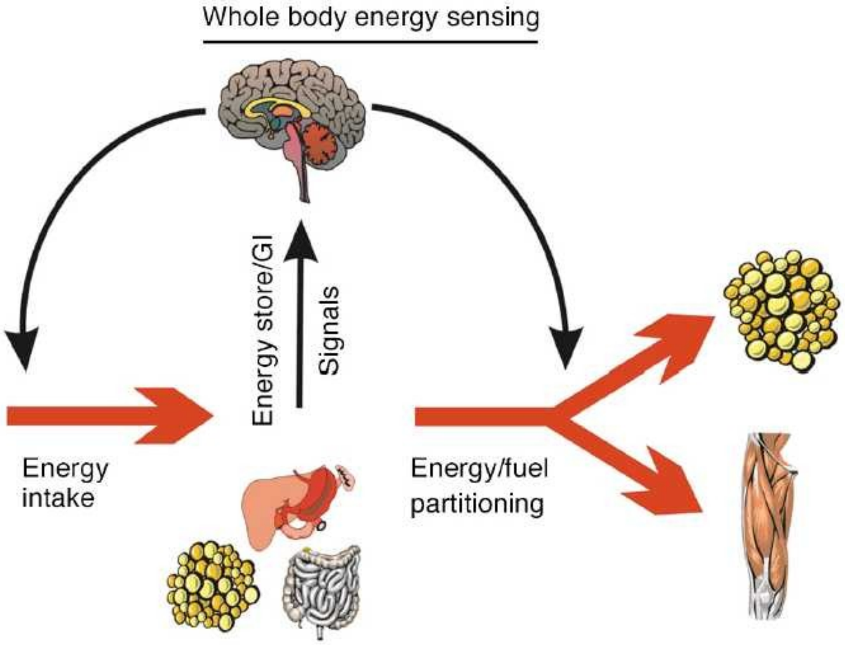


Kalorienrestriktion = weniger Essen
ohne Nährstoffmangel - Beste Ernährung für gesunde Energiebilanz, Zellpflege, Anti-aging, Anti-diseasing…..

Funktioniert das auch durch Sirtuine bei Adipösen?
Sirtuine aktivieren den FOXO1 Signalweg – Insulinresistenz?

Was können wir daraus übernehmen für „intelligente Ernährung“

Welche Ernährung ist am besten?

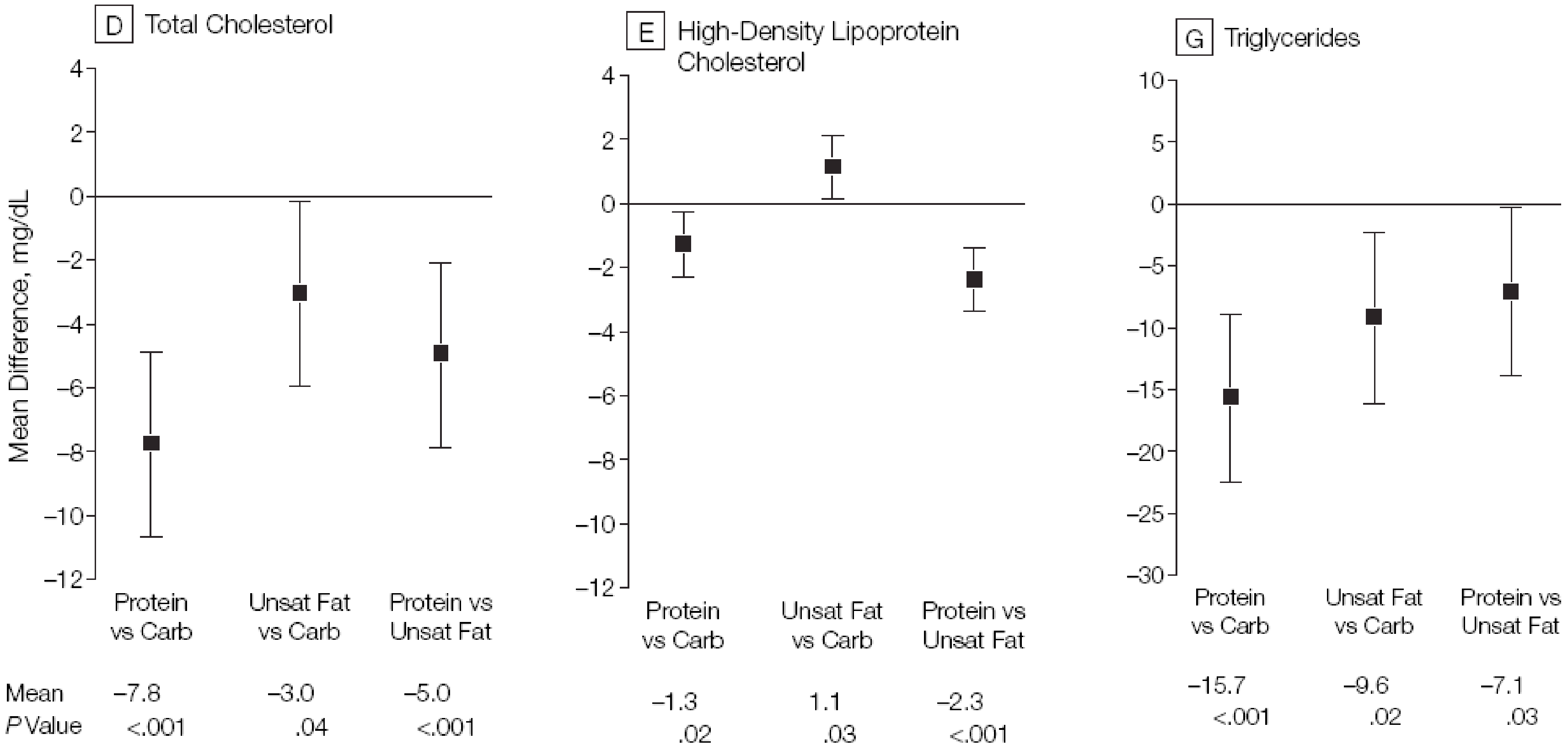


- **Viel Protein ?**
- **Viele Kohlenhydrate ?**
- **Viel pflanzliche Fette (MUFA) ?**

OmniHeart Study

Vergleich von Hoch-Protein, Hoch-Kohlenhydrat und Hoch Olivenöl (MUFA) in 6 Wochen Cross-Over Studie an 164 freiwilligen Teilnehmern

Appel et al., 2005; JAMA 294: 2455



Prot= 25% prot/27% fat/48%carb; Unsat Fat=37%fat/15%prot/48%carb; Carb: 58%carb/15%prot/27%fat

Vergleich von Hoch-Protein, Hoch-Kohlenhydrat und Hoch Olivenöl (MUFA) BLUTDRUCK und BLUTFETTE

CHARITÉ CAMPUS BENJAMIN FRANKLIN

Appel et al., 2005; JAMA 294: 2455

DIfE

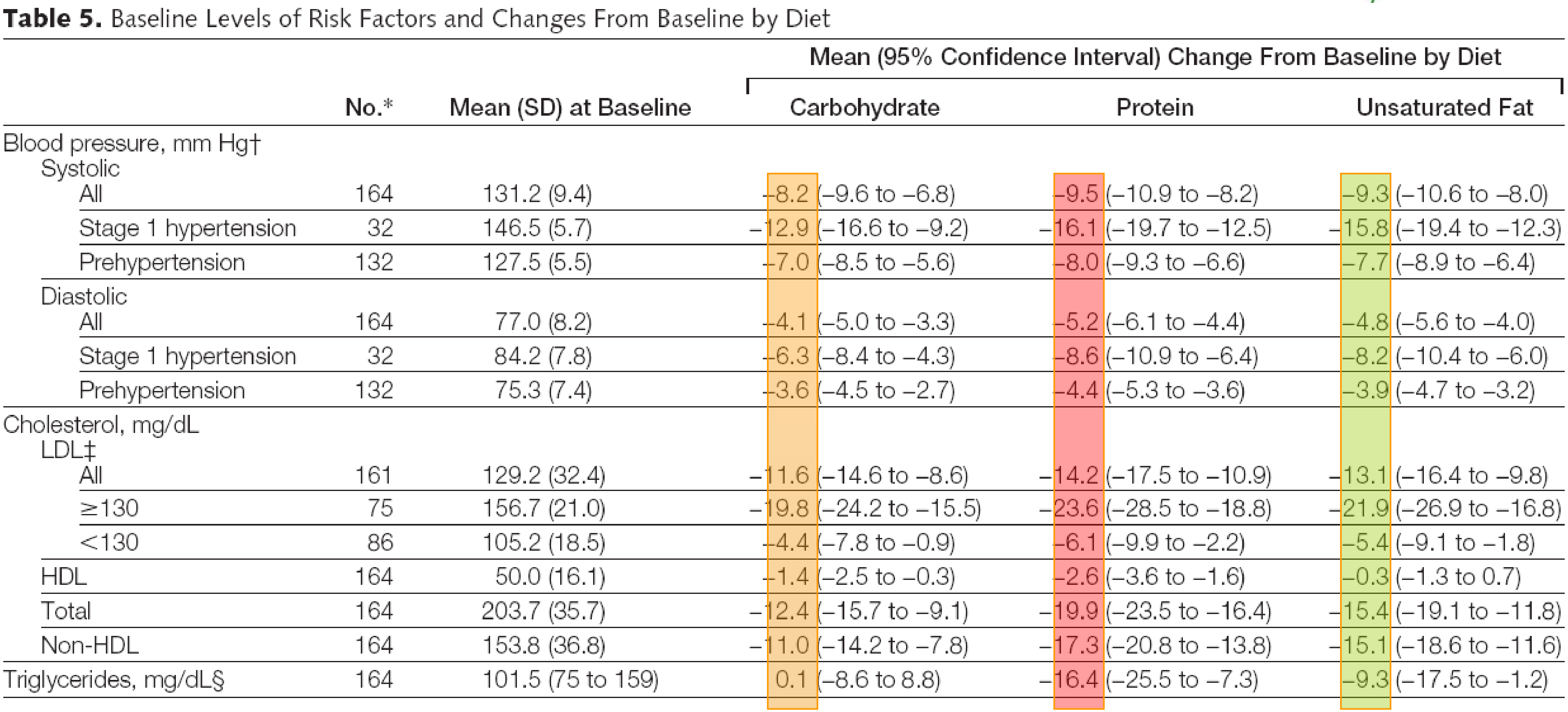


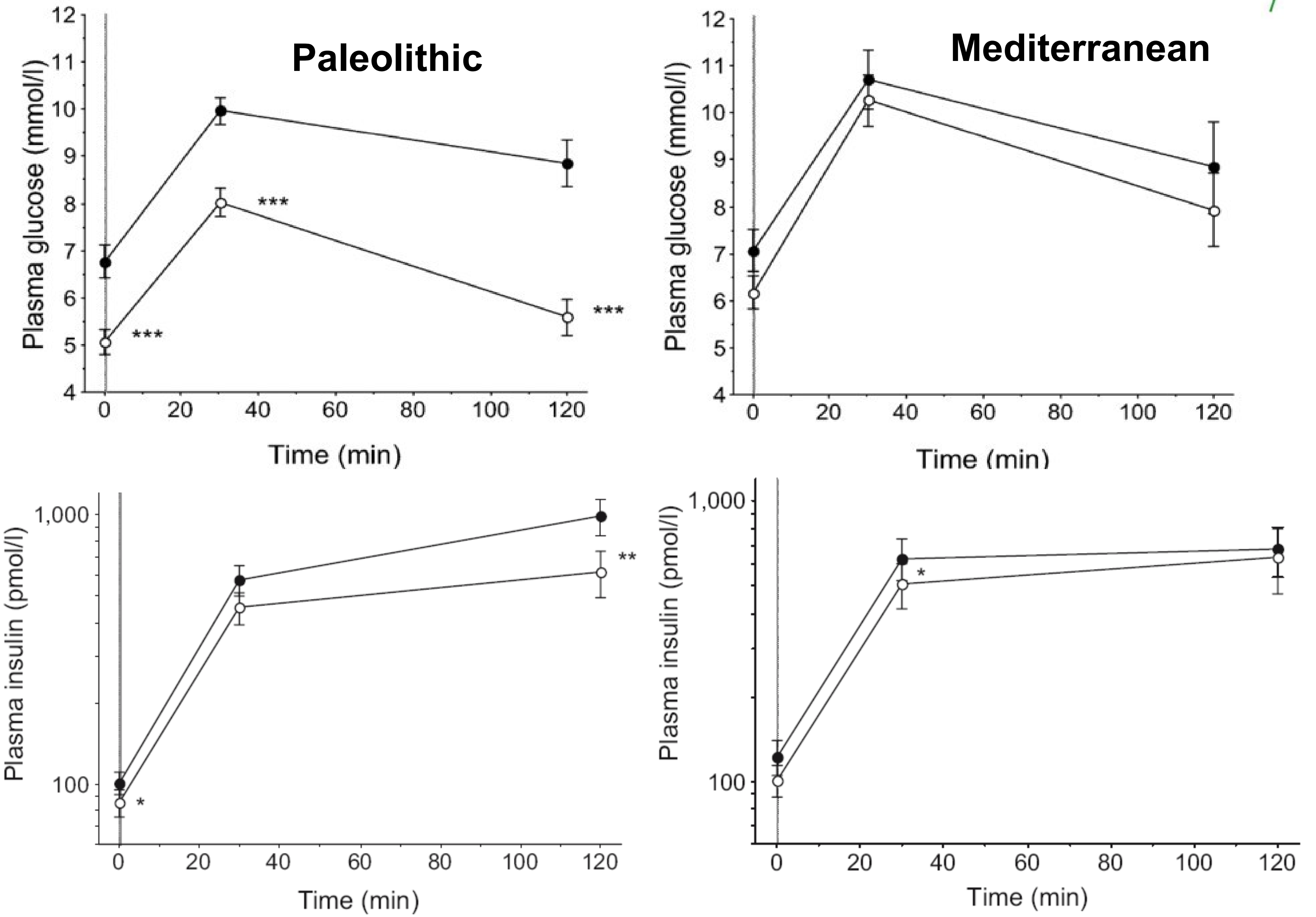
Table 5. Baseline Levels of Risk Factors and Changes From Baseline by Diet

			Mean (95% Confidence Interval) Change From Baseline by Diet		
	No.*	Mean (SD) at Baseline	Carbohydrate	Protein	Unsaturated Fat
Blood pressure, mm Hg†					
Systolic					
All	164	131.2 (9.4)	−8.2 (−9.6 to −6.8)	−9.5 (−10.9 to −8.2)	−9.3 (−10.6 to −8.0)
Stage 1 hypertension	32	146.5 (5.7)	−12.9 (−16.6 to −9.2)	−16.1 (−19.7 to −12.5)	−15.8 (−19.4 to −12.3)
Prehypertension	132	127.5 (5.5)	−7.0 (−8.5 to −5.6)	−8.0 (−9.3 to −6.6)	−7.7 (−8.9 to −6.4)
Diastolic					
All	164	77.0 (8.2)	−4.1 (−5.0 to −3.3)	−5.2 (−6.1 to −4.4)	−4.8 (−5.6 to −4.0)
Stage 1 hypertension	32	84.2 (7.8)	−6.3 (−8.4 to −4.3)	−8.6 (−10.9 to −6.4)	−8.2 (−10.4 to −6.0)
Prehypertension	132	75.3 (7.4)	−3.6 (−4.5 to −2.7)	−4.4 (−5.3 to −3.6)	−3.9 (−4.7 to −3.2)
Cholesterol, mg/dL					
LDL‡					
All	161	129.2 (32.4)	−11.6 (−14.6 to −8.6)	−14.2 (−17.5 to −10.9)	−13.1 (−16.4 to −9.8)
≥130	75	156.7 (21.0)	−19.8 (−24.2 to −15.5)	−23.6 (−28.5 to −18.8)	−21.9 (−26.9 to −16.8)
<130	86	105.2 (18.5)	−4.4 (−7.8 to −0.9)	−6.1 (−9.9 to −2.2)	−5.4 (−9.1 to −1.8)
HDL	164	50.0 (16.1)	−1.4 (−2.5 to −0.3)	−2.6 (−3.6 to −1.6)	−0.3 (−1.3 to 0.7)
Total	164	203.7 (35.7)	−12.4 (−15.7 to −9.1)	−19.9 (−23.5 to −16.4)	−15.4 (−19.1 to −11.8)
Non-HDL	164	153.8 (36.8)	−11.0 (−14.2 to −7.8)	−17.3 (−20.8 to −13.8)	−15.1 (−18.6 to −11.6)
Triglycerides, mg/dL§	164	101.5 (75 to 159)	0.1 (−8.6 to 8.8)	−16.4 (−25.5 to −7.3)	−9.3 (−17.5 to −1.2)

<u>Prot</u>= 25% prot/27% fat/48%carb; <u>Unsat Fat</u>=37%fat/15%prot/48%carb; <u>Carb</u>: 58%carb/15%prot/27%fat

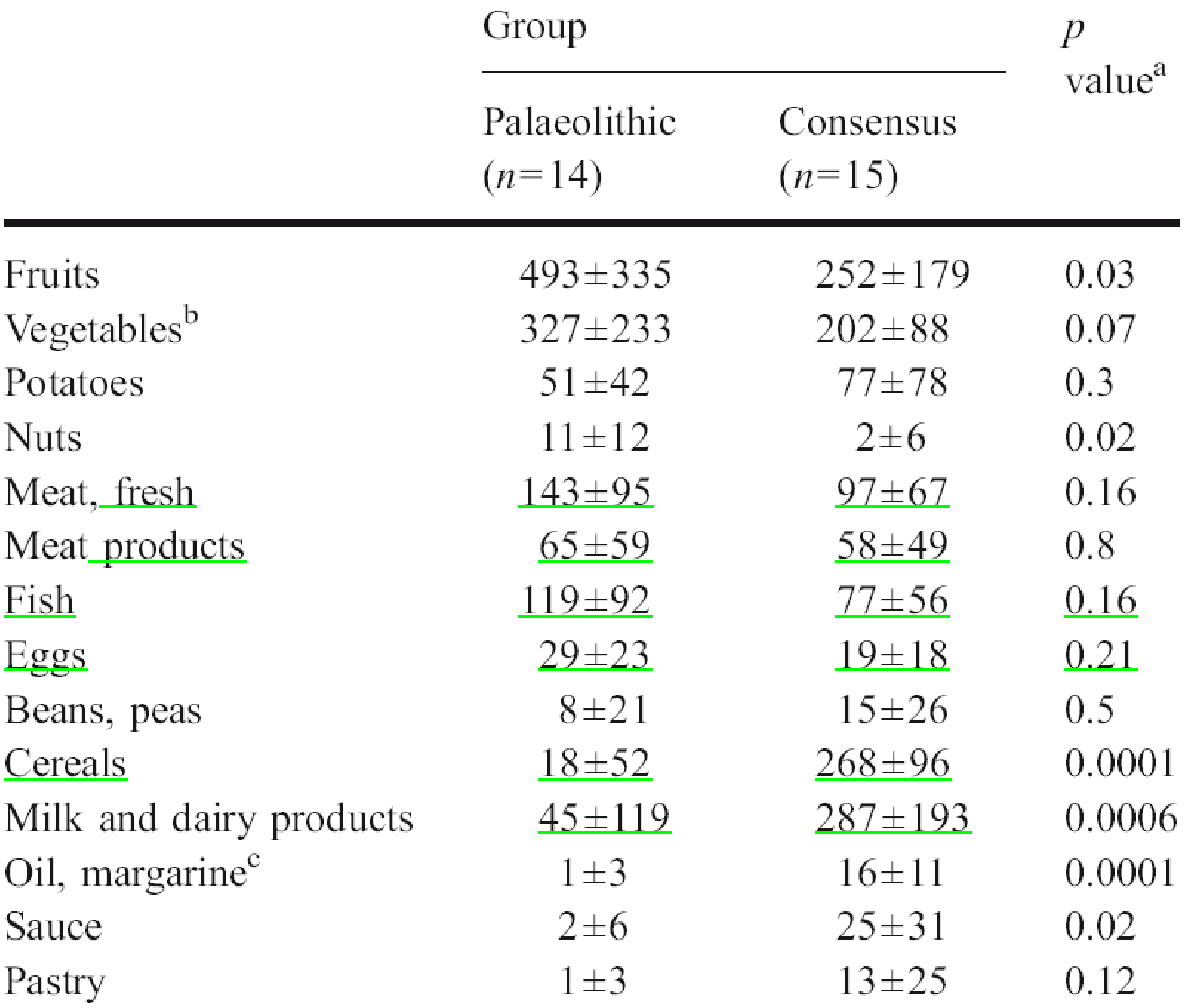
Steinzeit gegen mediterrane Diät bei Menschen mit Herzerkrankung: Zucker und Insulinprofil vor und nach 8 Wochen Diät im Zuckertest

Lindeberg et al., Diabetologia 2007



Paleolithische vs mediterrane Diät: Komposition

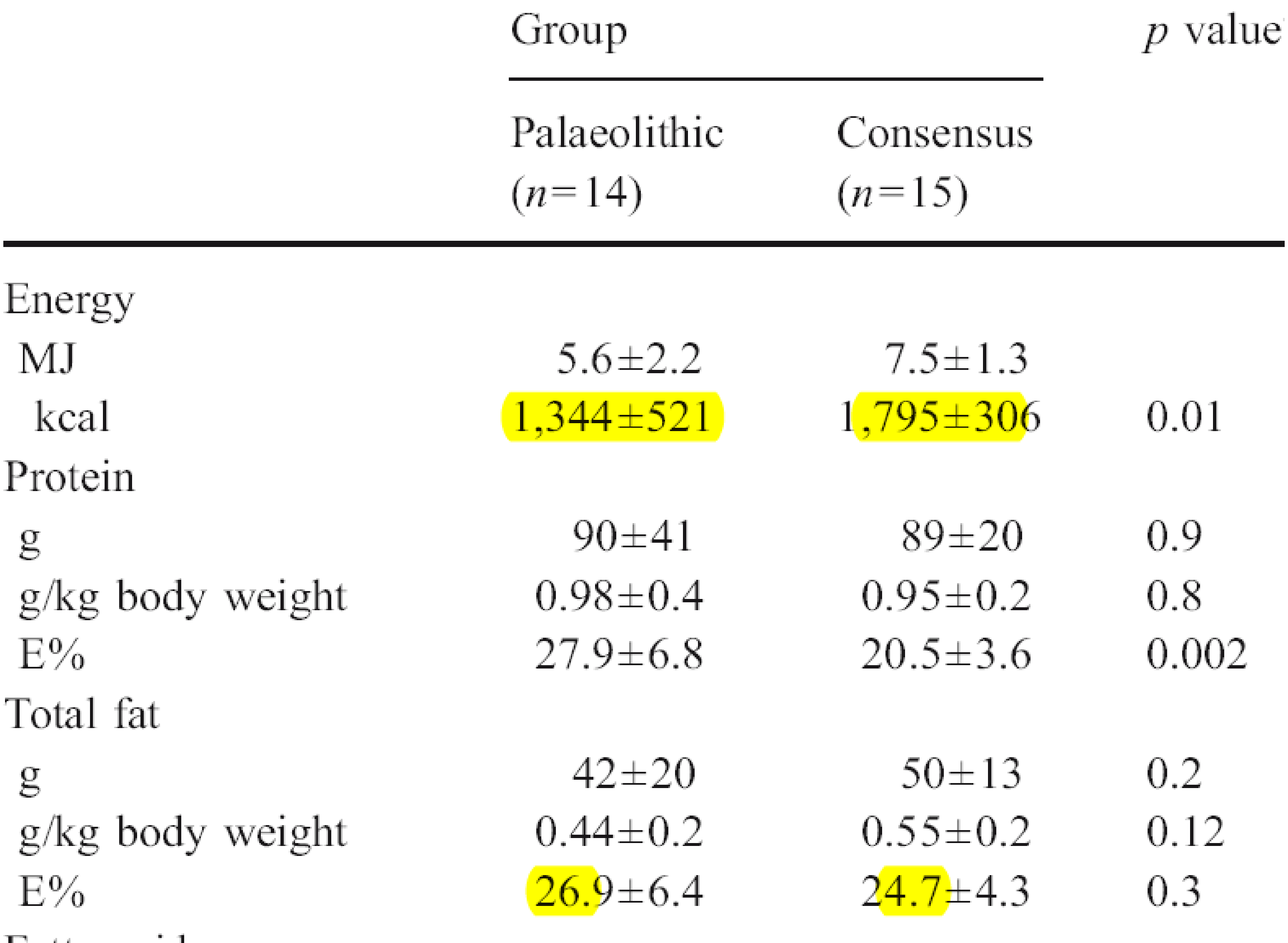
Lindeberg et al., Diabetologia 2007



	Group		*p* value[a]
	Palaeolithic (*n*=14)	Consensus (*n*=15)	
Fruits	493±335	252±179	0.03
Vegetables[b]	327±233	202±88	0.07
Potatoes	51±42	77±78	0.3
Nuts	11±12	2±6	0.02
Meat, fresh	143±95	97±67	0.16
Meat products	65±59	58±49	0.8
Fish	119±92	77±56	0.16
Eggs	29±23	19±18	0.21
Beans, peas	8±21	15±26	0.5
Cereals	18±52	268±96	0.0001
Milk and dairy products	45±119	287±193	0.0006
Oil, margarine[c]	1±3	16±11	0.0001
Sauce	2±6	25±31	0.02
Pastry	1±3	13±25	0.12

Paleolithic vs Mediterranean diet in subjects with CVD

Lindeberg et al., Diabetologia 2007

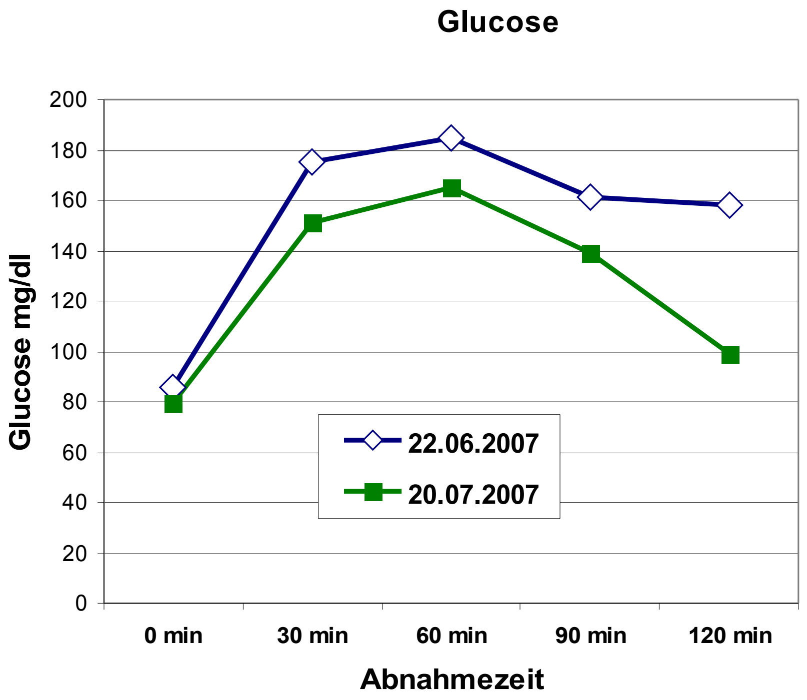


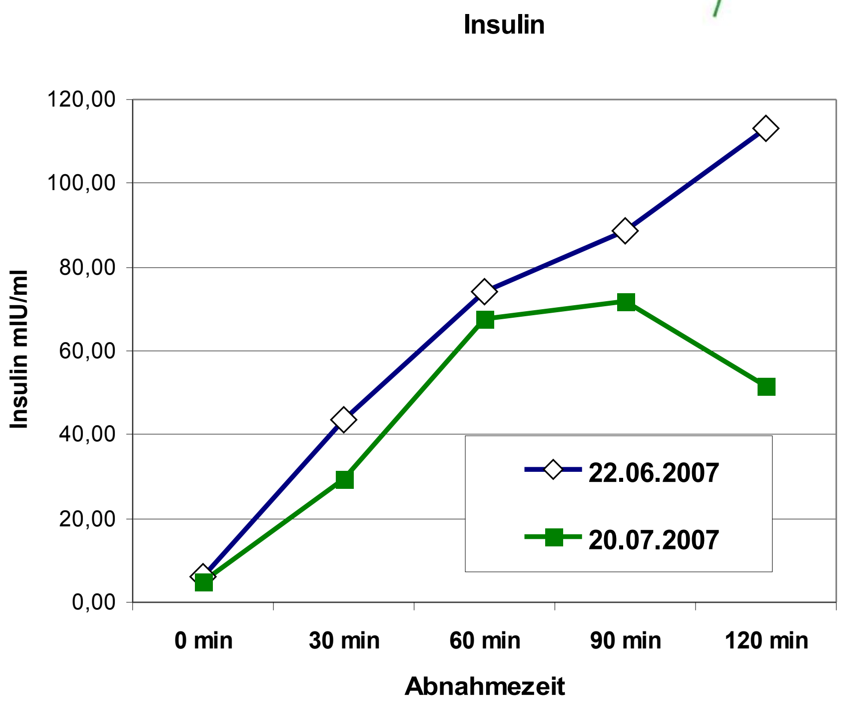
	Group		*p* value
	Palaeolithic ($n=14$)	Consensus ($n=15$)	
Energy			
MJ	5.6±2.2	7.5±1.3	
kcal	1,344±521	1,795±306	0.01
Protein			
g	90±41	89±20	0.9
g/kg body weight	0.98±0.4	0.95±0.2	0.8
E%	27.9±6.8	20.5±3.6	0.002
Total fat			
g	42±20	50±13	0.2
g/kg body weight	0.44±0.2	0.55±0.2	0.12
E%	26.9±6.4	24.7±4.3	0.3

Einfluss der Ernährung: kleine Studie mit 2 Zwillingspaaren

- Kann Ernährung den Stoffwechsel beeinflussen?
- Hat Nahrung nur bei Übergewicht und Adipositas einen Einfluss oder auch bei gesunden normalgewichtigen Menschen?
- Wie schnell wirkt Nahrung?

Nahrungseinflüsse auf das Risiko metabolischer Erkrankungen durch hormonelle Regulation:
4 Wochen gesunde Ernährung nach DGE


Glucose

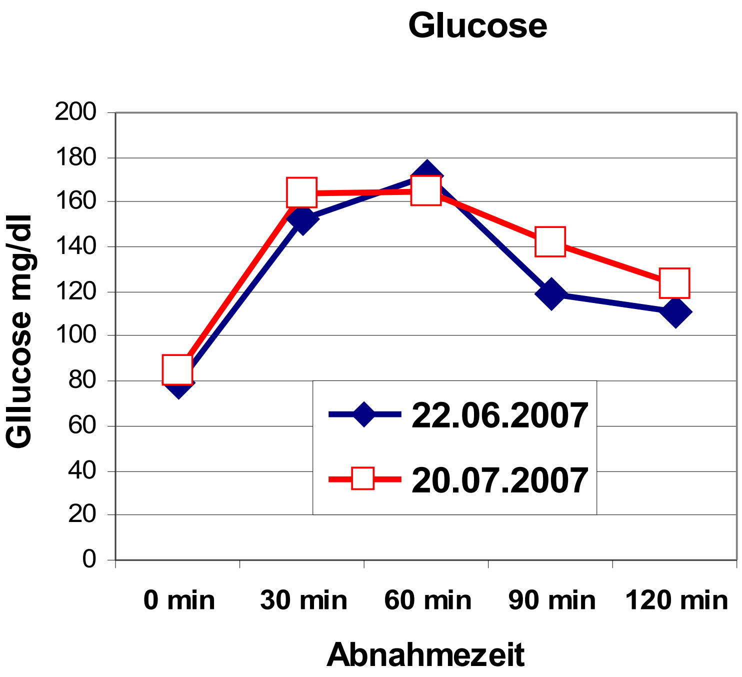

Insulin

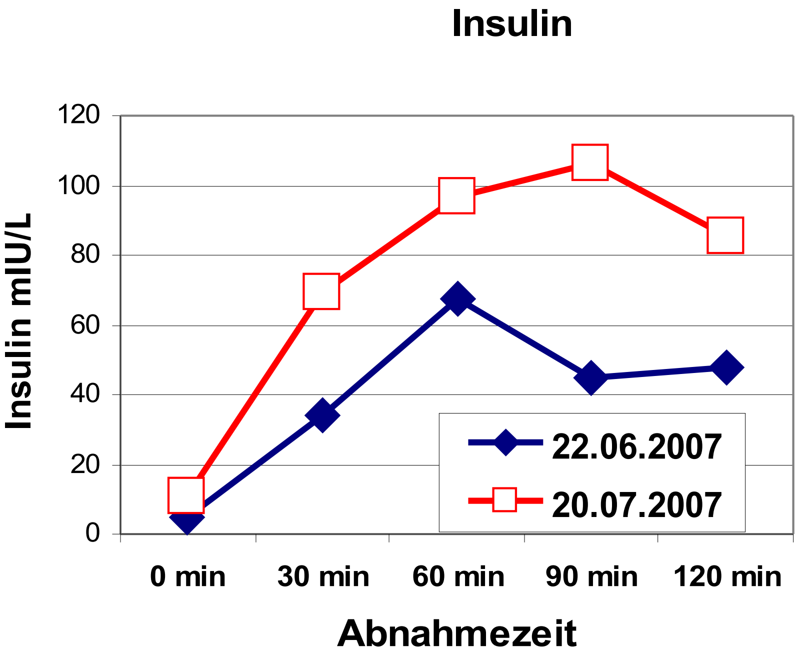
21 jährige Frau, 162 cm, 64,5 kg (BMI 24,6 kg/m²) => 63,7 kg (BMI 24,3 kg/m²)
Taille: 76,5 => 74,9 cm. Hüfte: 98,5 => 96,5 (WHR: 0,777 => 0,776)
24,3 kg (37,7%) Fettanteil => 24,1 kg (37,7%)
40,1 kg (62,3%) fettfreie Masse => 39,7 kg (62,3%)

Ernährungsmuster steuern die Insulinempfindlichkeit: 4 Wochen ungesunde Ernährung verschlechtert die Insulinsensitivität bei gesunden normalgewichtigen Menschen

CHARITÉ CAMPUS BENJAMIN FRANKLIN

DIfE



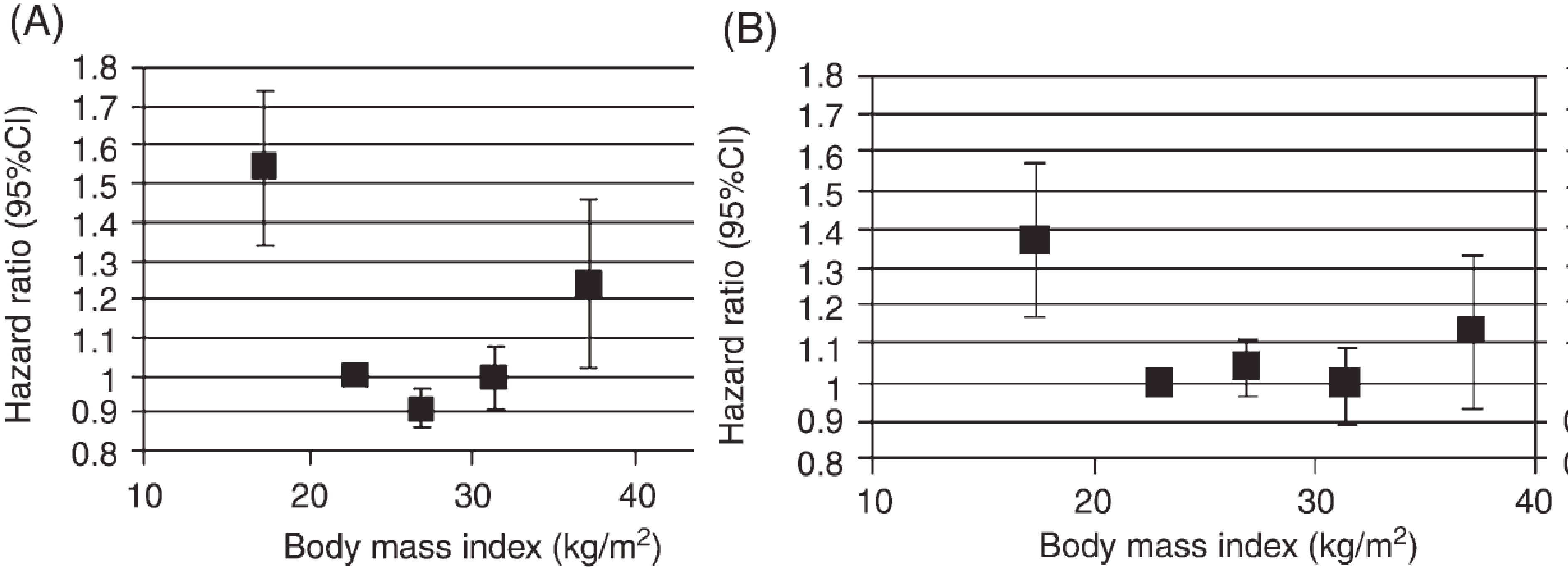


21 jährige Frau, 163,6 cm, **61,1 kg** (BMI 22,7 kg/m²) => **64 kg** (BMI 23,7 kg/m²)
Taille: 72,5 => 73,3 cm. Hüfte: 93,6 => 94,4 (WHR: 0,774 => 0,776)
21,7 kg (35,6%) Fettanteil => 24,6 kg (38,2%)
39,4 kg (64,4%) fettfreie Masse => 39,7 kg (61,8%)

Nicht jeder sollte Abnehmen !

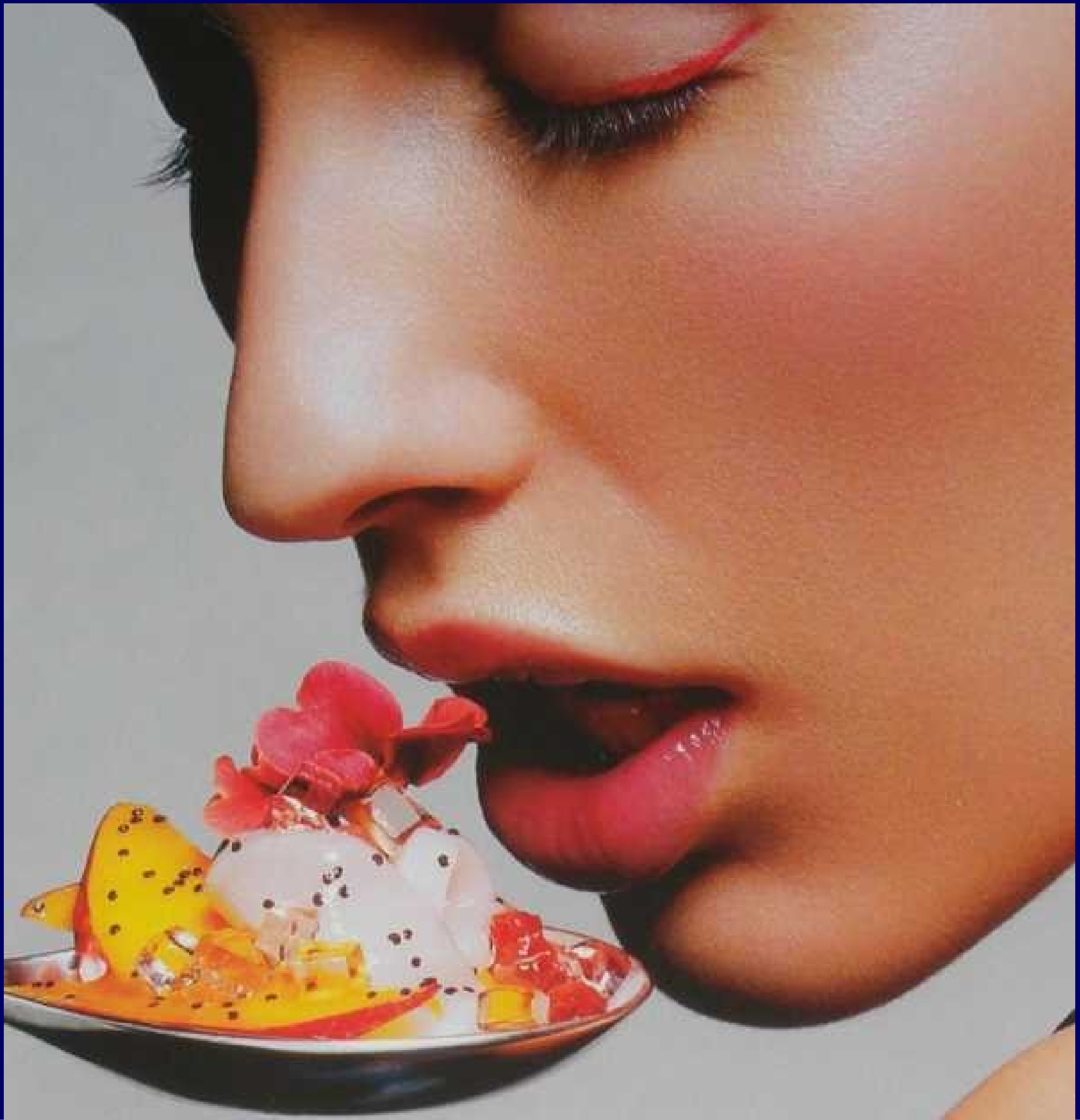
Unterschiedlicher Einfluss der Adipositas auf die Sterblichkeit nach (A) Herzinfarkt und (B) Herzinsuffizienz

Abdullah et al., Eur Heart J. 2008



21.570 Patienten aus 5 Dänischen Registern mit 10,4 Jahren follow up

Food for the future ?



Caloric restriction – adaptation to lack of energy

- Increased insulin sensitivity
- Reduced body temperature
- Reduced stores of glycogen and fat
- No reduction of BMR when corrected for body weight
- Resistance against heat and oxidative stress
- Reduced inflammation
- Increased life span