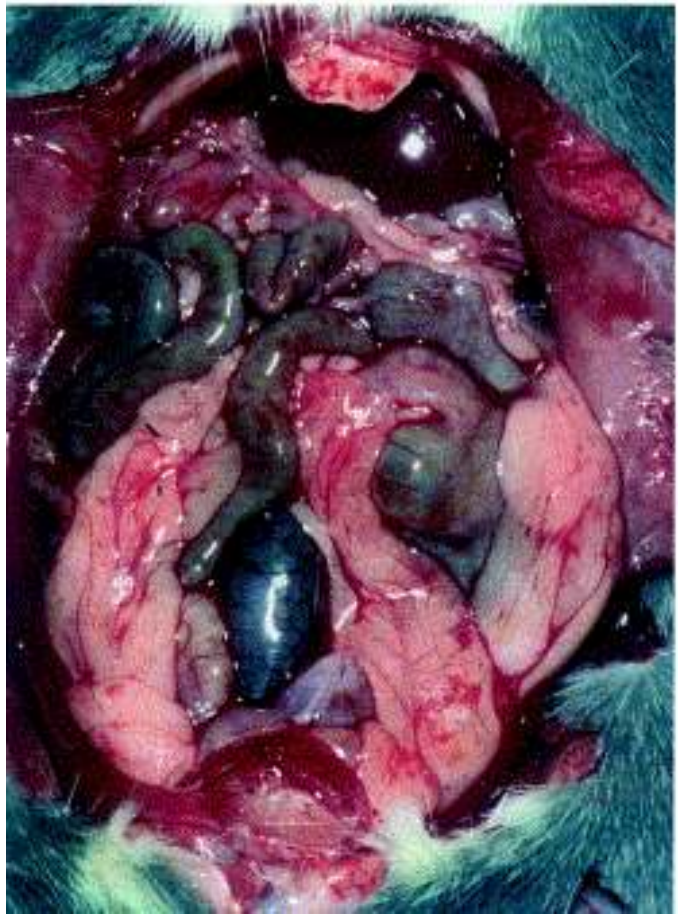
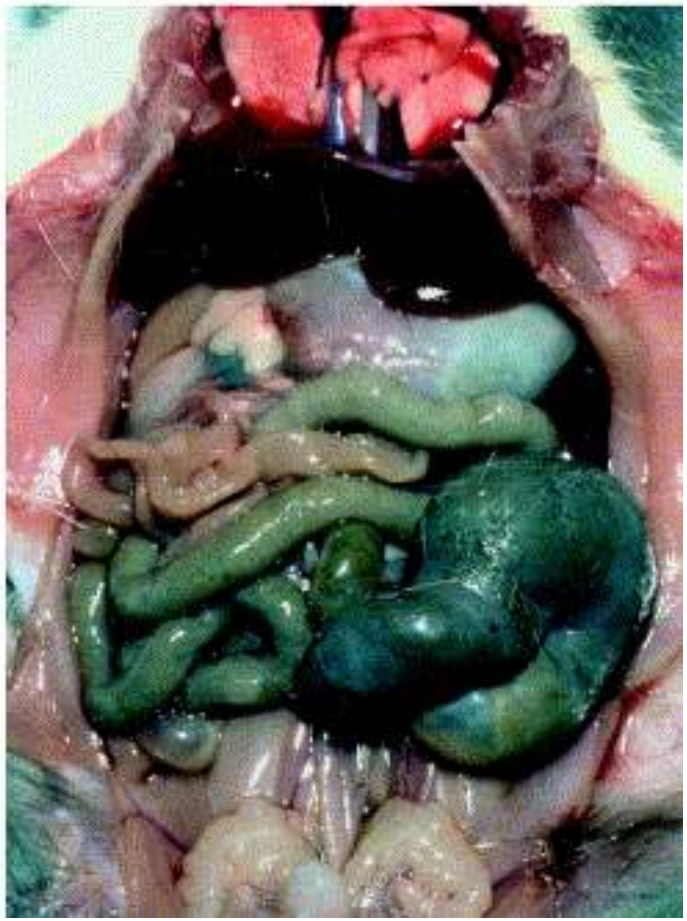
Improvement of Leptin Resistance

김 용 운
영남의대 생리학교실

Effect of leptin gene transfection into the hypothalamus in lean rats





7 days

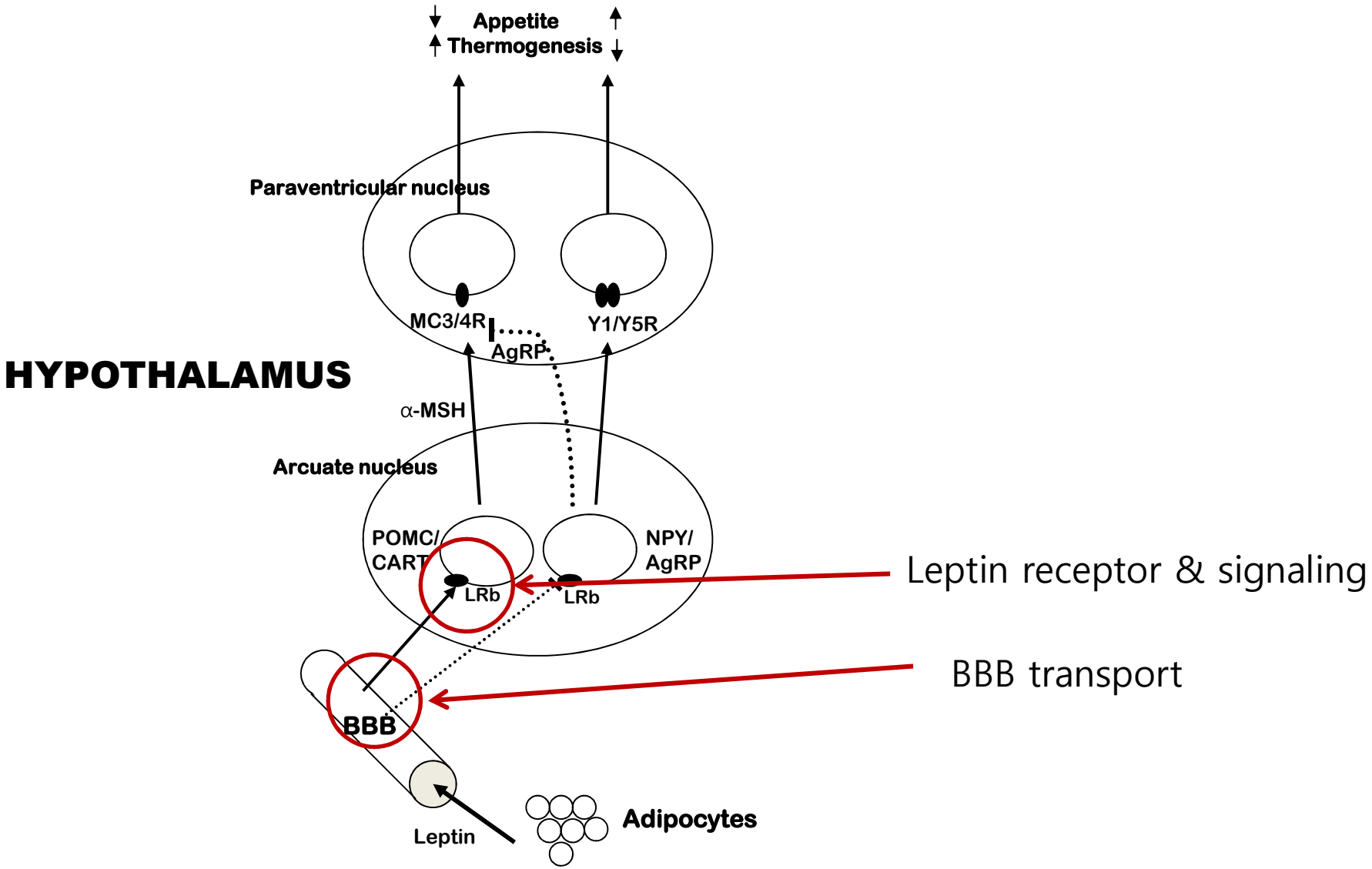
Leptin Resistance

- Decreased leptin's physiological effect
- Accompany with obesity
- Characterized by hyperleptinemia

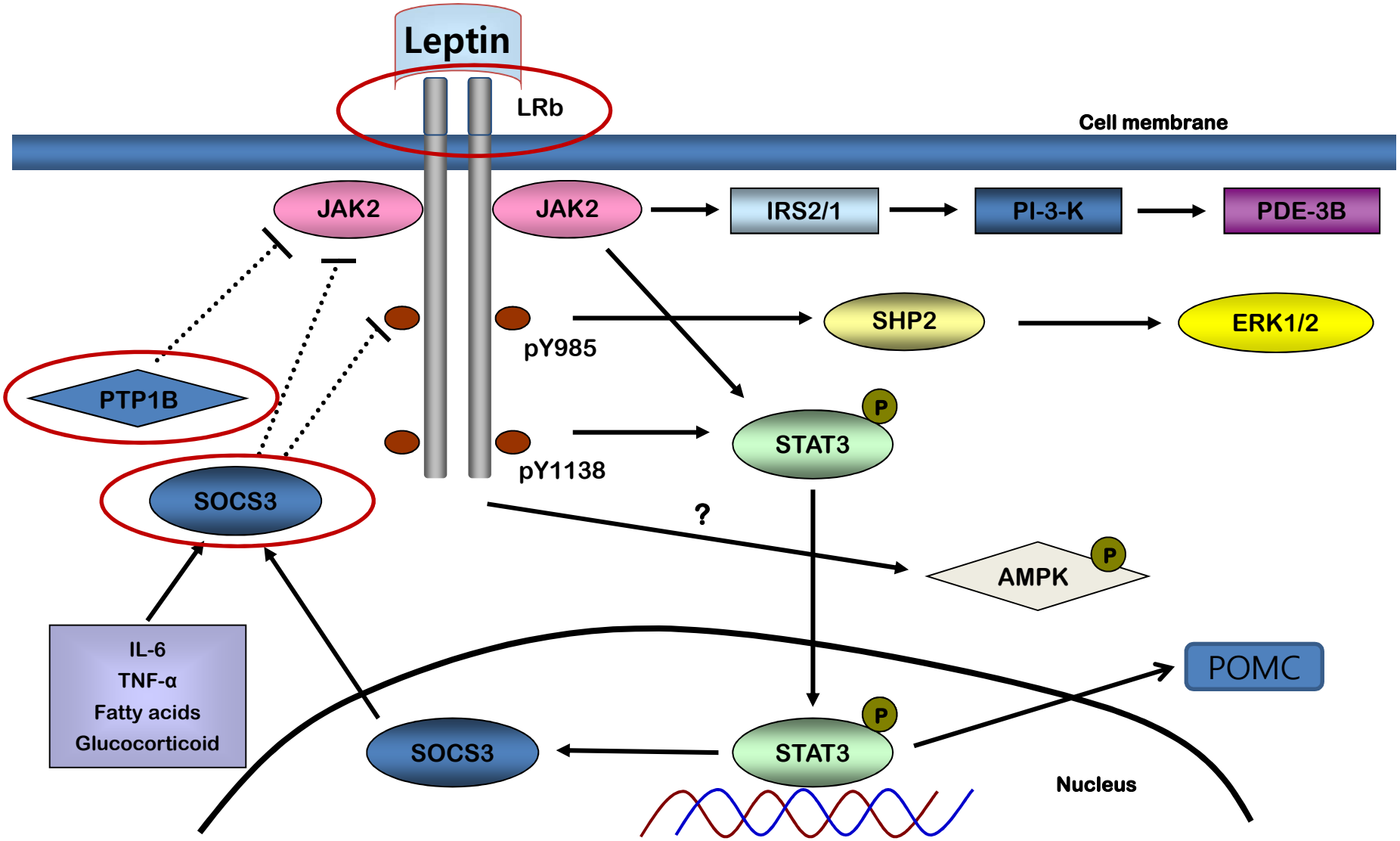
순서

- 렙틴의 작용기전
- 위치별 저항성 발생 과정과 개선노력
- 원인별
  - -유전적
  - -후천적
    - 지속적인 고렙틴증
    - 고중성지방증
    - 염증
    - ER stress…
- 기타

Leptin action mechanism in the hypothalamus



Leptin signaling



BBB transport

Partial saturation and regional variation in the blood-to-brain transport of leptin in normal weight mice

William A. Banks, Cecilia M. Clever and Catherine L. Farrell

Am J Physiol Endocrinol Metab 278:E1158-E1165, 2000.

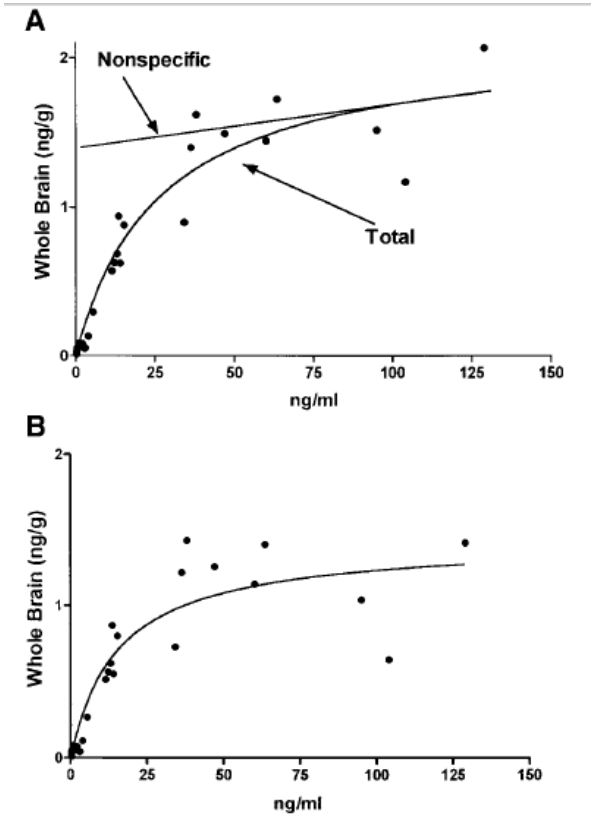


Fig. 4. Measurement of total and nonspecific transport (*A*) and specific transport (*B*) into whole brain. Whole brain had a maximum velocity (V_{max}) of 1.42 ± 0.15 ng/g and a Michaelis-Menten constant value (K_m) of 15.6 ± 5.2 ng/ml.

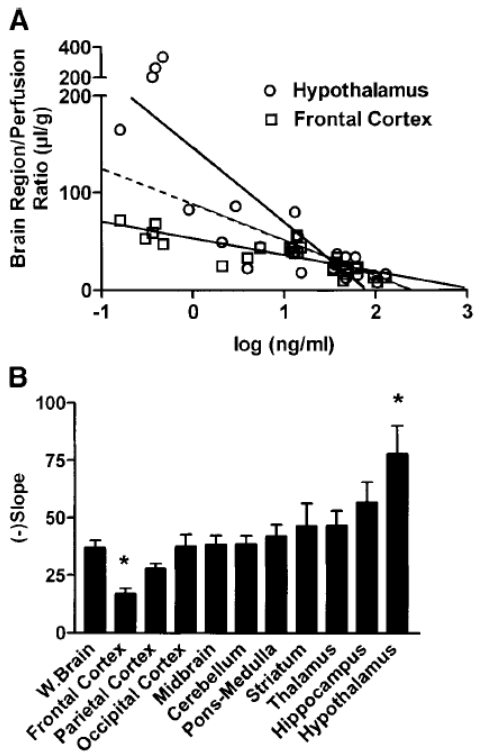


Fig. 2. *A*: brain region/perfusion ratios vs. log(perfusion concentration) for hypothalamus and frontal cortex. Slope for whole brain is indicated by dashed line. Hypothalamus had the highest brain/perfusion ratios and the steepest saturation slope, whole brain the lowest. B: slopes for all brain regions. W. Brain, whole brain. The greater the slope the more readily the regional leptin transporter was saturated. *Values statistically different ($P < 0.05$) from whole brain; other statistical differences are shown in Table 1.

Diabetes. 2000 Jul;49(7):1219-23.

Obesity is associated with a decreased leptin transport across the blood-brain barrier in rats.

Burguera B, Couce ME, Curran GL, Jensen MD, Lloyd RV, Cleary MP, Poduslo JF.
Endocrine Research Unit, University of Minnesota, Austin, USA. barto.burguera@bmc.org

TABLE 3
Body weight and serum and CSF leptin levels in lean *FA/FA*, HFD obese, and *fa/fa* rats

	Lean *FA/FA*	Obese HFD	*fa/fa*
Body weight (g)	440.0 ± 53.2	547.0 ± 34.9*	686.6 ± 42.6*
Serum leptin levels (ng/ml)	8.8 ± 9.6	14.3 ± 7.1*	45.4 ± 16.3*
CSF leptin levels (ng/ml)	0.19 ± 0.03	0.21 ± 0.08	0.24 ± 0.06

Data are means ± SE. To obtain sufficient CSF for leptin assay, equal volumes of 4 or 5 CSF samples from rats of the same group were pooled and run in duplicate. *$P < 0.001$ vs. lean *FA/FA* rats.

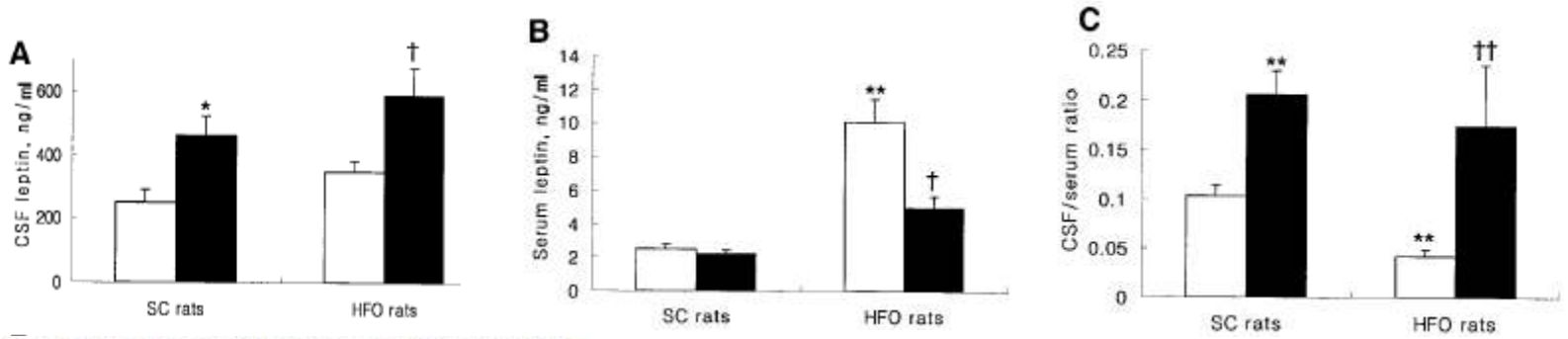


FIG. 4. Concentrations of leptin in CSF (*A*), serum (*B*), and their ratios (*C*) in standard chow (SC) and high-fat–fed obese (HFO) rats. Data are the means ± SE of eight rats per group. *$P < 0.05$ and **$P < 0.01$ vs. untreated standard chow rats; †$P < 0.05$ and ††$P < 0.01$ vs. untreated high-fat–fed obese rats. □, untreated; ■, treated.

Kim et al, 2006, Diabetes

Diabetes. 2004 May;53(5):1253-60.

Triglycerides induce leptin resistance at the blood-brain barrier.

Banks WA, Coon AB, Robinson SM, Moinuddin A, Shultz JM, Nakaoke R, Morley JE.

Department of Internal Medicine, Division of Geriatrics, Geriatric Research, Education, and Clinical Center, Veterans Affairs Medical Center, St. Louis University School of Medicine, 915 N. Grand Boulevard, St. Louis, MO 631056, USA. bankswa@slu.edu

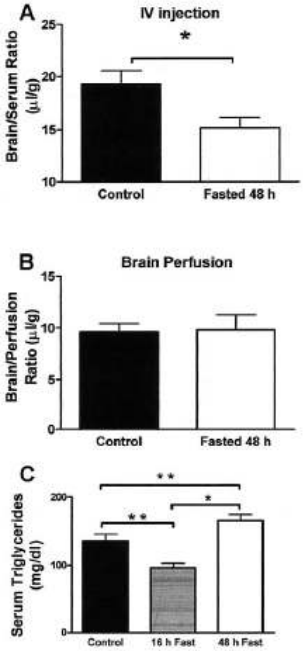


FIG. 1. Starvation-induced inhibition of leptin transport across the BBB is caused by a circulating factor. *A*: Replication of classic work (20) showing that the leptin transporter is inhibited with starvation. *B*: With brain perfusion, a method that negates the effect of circulating substances, the transporter returns to normal. *C*: Triglyceride levels in serum in control mice, mice fasted for 16 h, and mice fasted for 48 h. IV, intravenous. $^{*}P < 0.05$; $^{**}P < 0.01$.

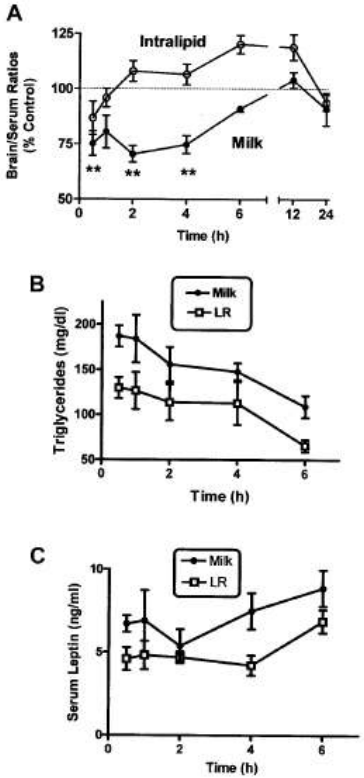


FIG. 2. Leptin resistance to BBB transport is induced by milk fats. *A*: Intraperitoneal injection of whole milk, but not intralipid, induced an impairment in leptin transport across the BBB. Intraperitoneal injection of milk increased serum triglycerides (*B*) and serum leptin levels (*C*) by ~40%. $^{**}P < 0.01$.

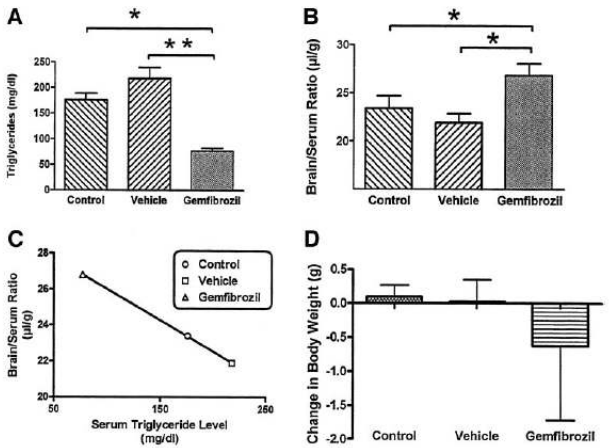


FIG. 8. Effect of gemfibrozil on serum triglyceride levels and leptin transport. I-Lep was injected intravenously, brain and blood samples were collected 10 min later, and triglyceride levels were measured in serum. *A*: In comparison to mice that received the vegetable oil vehicle only, gemfibrozil responders (four of six treated mice) had lower triglyceride levels ($^{**}P < 0.01$). *B*: Gemfibrozil responders had higher leptin transport rates than vehicle ($^{*}P < 0.05$) or control ($^{*}P < 0.05$) mice. *C*: A significant correlation ($P < 0.01$) existed between brain/serum ratios for leptin and serum triglyceride levels for the three groups. *D*: The weight loss for the gemfibrozil group was not statistically significant.

Physiology & Behavior 105 (2011) 145–149

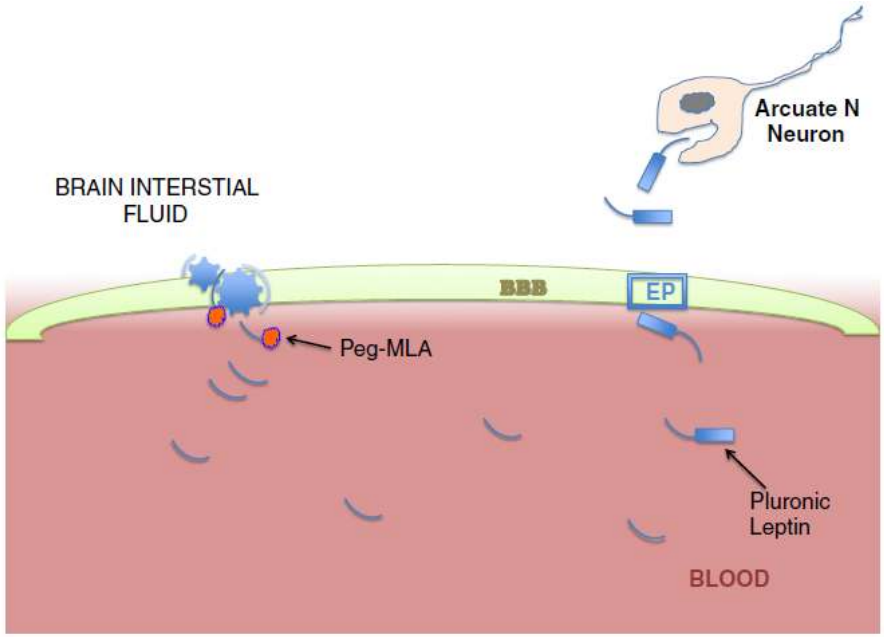
Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Principles of strategic drug delivery to the brain (SDDB): Development of anorectic and orexigenic analogs of leptin

W.A. Banks [a,*], A. Gertler [b], G. Solomon [b], L. Niv-Spector [b], M. Shpilman [b], X. Yi [c], E. Batrakova [c], S. Vinogradov [c], A.V. Kabanov [c,d]



Pluronic leptin: a leptin agonist modified by the addition of pluronic block copolymers

Peg-MLA: a leptin antagonist modified by pegylation

Fig. 2. Drug development strategies: the leptin antagonist PEG-MLA binds to the leptin transporter at the blood–brain barrier but is not transported across by it. This binding blocks the ability of endogenous leptin in the blood from being transported into brain. Pluronic leptin crosses the BBB by way of an endocytic pathway (EP) to reach CNS receptors.

Circumvent BBB

Intranasal Leptin Reduces Appetite and Induces Weight Loss in Rats with Diet-Induced Obesity (DIO)

Carla Schulz,* Kerstin Paulus,* Olaf Jöhren, and Hendrik Lehnert

Endocrinology, January 2012, 153(1):143–153 endo.endojournals.org 143

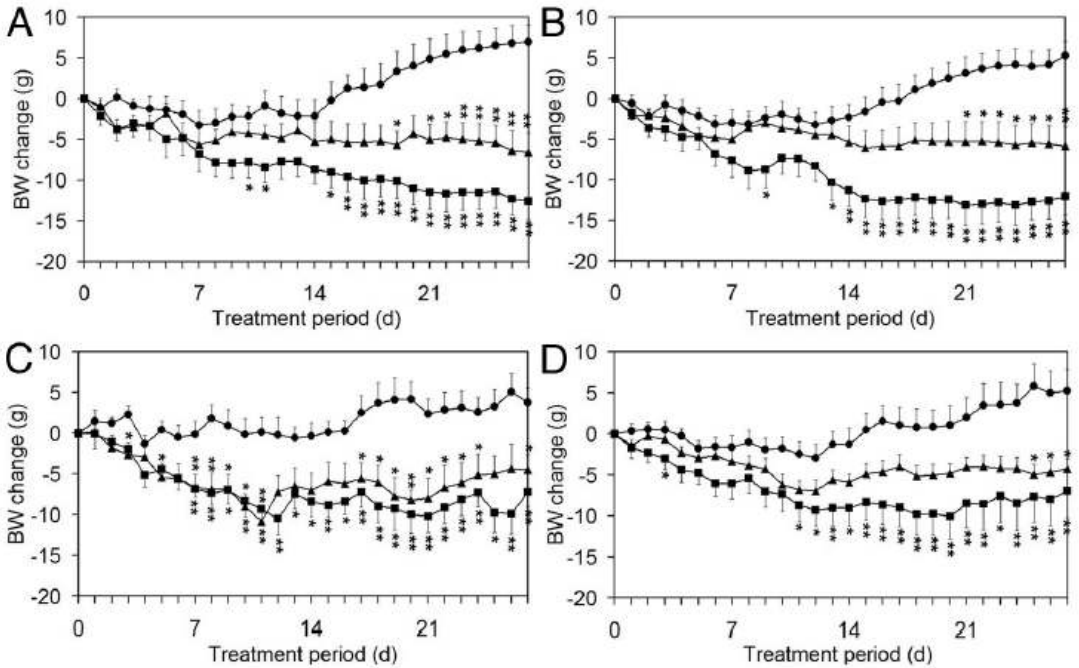
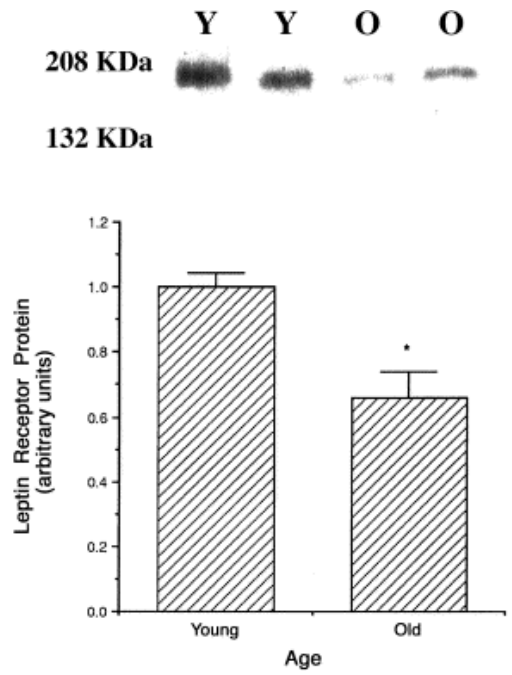
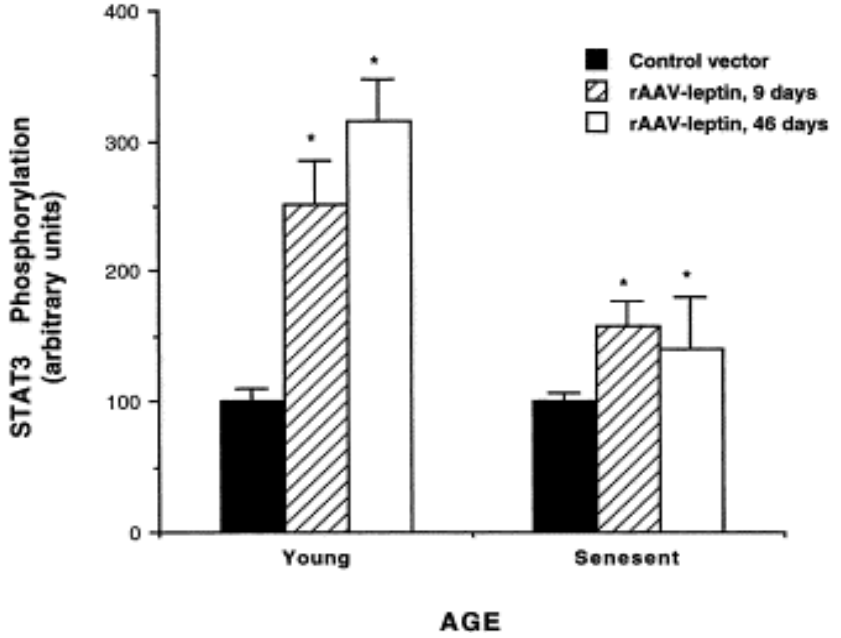


FIG. 1. BW development in male Wistar rats during the 28-d treatment period (initial BW of animals are given in Table 1). A, Lean animals, after 25-wk diet period. B, DIO, after 25-wk diet period. C, Lean animals, after 32-wk diet period. D, DIO, after 32-wk diet period. *Solid circles*, control solution; *solid triangles*, 0.1 mg/kg leptin; *solid squares*, 0.2 mg/kg leptin. */**, Significant/highly significant differences from control group in ANOVA with repeated measures with Bonferroni's *t* test (*post hoc*).

Leptin recepter binding & signaling





Scarpace et al, Neuropharmacology, 2002

OPEN ACCESS Freely available online

PLoS one

Over-Expression of Leptin Receptors in Hypothalamic POMC Neurons Increases Susceptibility to Diet-Induced Obesity

Kevin M. Gamber, Lihong Huo, Sangdeuk Ha, Joyce E. Hairston, Sarah Greeley, Christian Bjørbæk*

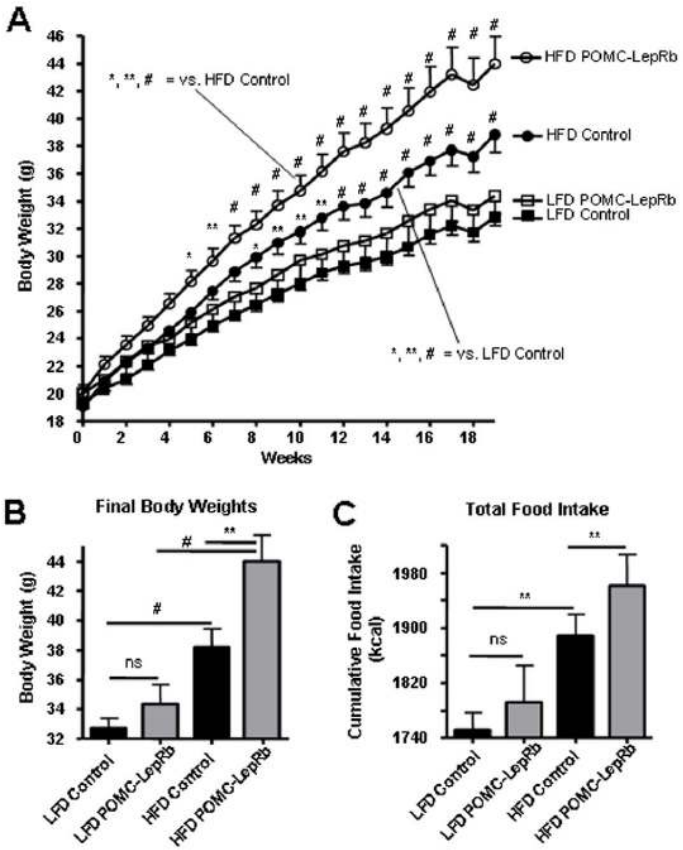


Figure 6. Body weight and caloric intake of POMC-LepRb mice on HFD and LFD. A. Body-weight curves of C57Bl/6J control mice and POMC-LepRb (C57Bl/6J) mice given HFD or LFD diets. B. Final average body weights after 19 weeks on diets. C. Cumulative food intake during the 19 weeks on diets. *=p<0.05; **=p<0.01; #=p<0.001; ns=Not significant. All mice are littermates. N=8–9 POMC-LepRb and N=20–21 control animals per group. Data are means +/− SEM.
doi:10.1371/journal.pone.0030485.g006

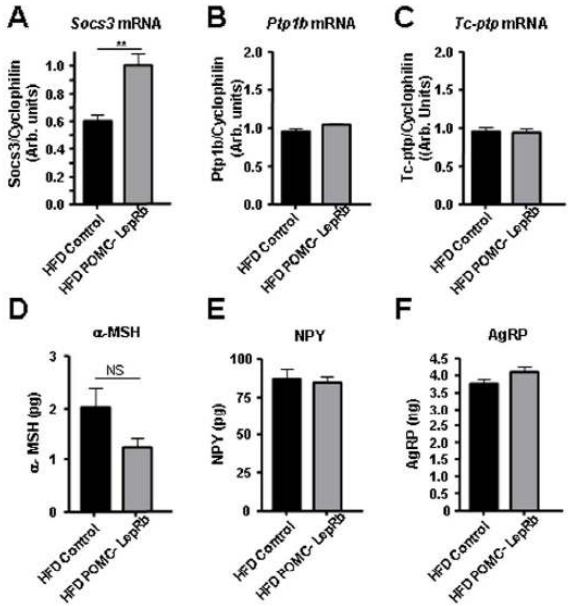


Figure 9. Arcuate mRNA and hypothalamic neuropeptide levels in HFD POMC-LepRb mice. A–C. Arcuate SOCS3 mRNA, PTP1B mRNA and TC-PTP mRNA in POMC-LepRb and control mice after 19 weeks of HFD. Each mRNA was normalized to cyclophilin mRNA in the same samples. N=6 POMC-LepRb and N=11 control mice. D-F. Whole hypothalamic α-MSH, NPY and AgRP neuropeptide levels in POMC-LepRb and control mice after 19 weeks of HF diet. α-MSH: N=6 POMC-LepRb and N=13 control mice. NPY and AgRP: N=3 POMC-LepRb and N=10 control mice. **=p<0.01. Data are means +/− SEM.
doi:10.1371/journal.pone.0030485.g009

PTP1B (protein tyrosine phosphatase)

- A negative regulator of insulin and leptin signaling
- Inhibits leptin receptor/JAK2 signaling
- Elevated in high fat obese and aged rodents

MOLECULAR AND CELLULAR BIOLOGY, Aug. 2009, p. 4563–4573 Vol. 29, No. 16
0270-7306/09/$08.00+0 doi:10.1128/MCB.01914-08

Neuronal Protein Tyrosine Phosphatase 1B Deficiency Results in Inhibition of Hypothalamic AMPK and Isoform-Specific Activation of AMPK in Peripheral Tissues▽†

Bingzhong Xue,[1]‡§ Thomas Pulinilkunnil,[1]‡¶ Incoronata Murano,[2] Kendra K. Bence,[3]‖ Huamei He,[4]#
Yasuhiko Minokoshi,[1]†† Kenji Asakura,[1] Anna Lee,[1] Fawaz Haj,[3]‡‡ Noboru Furukawa,[1]
Karyn J. Catalano,[1] Mirela Delibegovic,[3]§§ James A. Balschi,[4] Saverio Cinti,[2]
Benjamin G. Neel,[3]* and Barbara B. Kahn[1]*

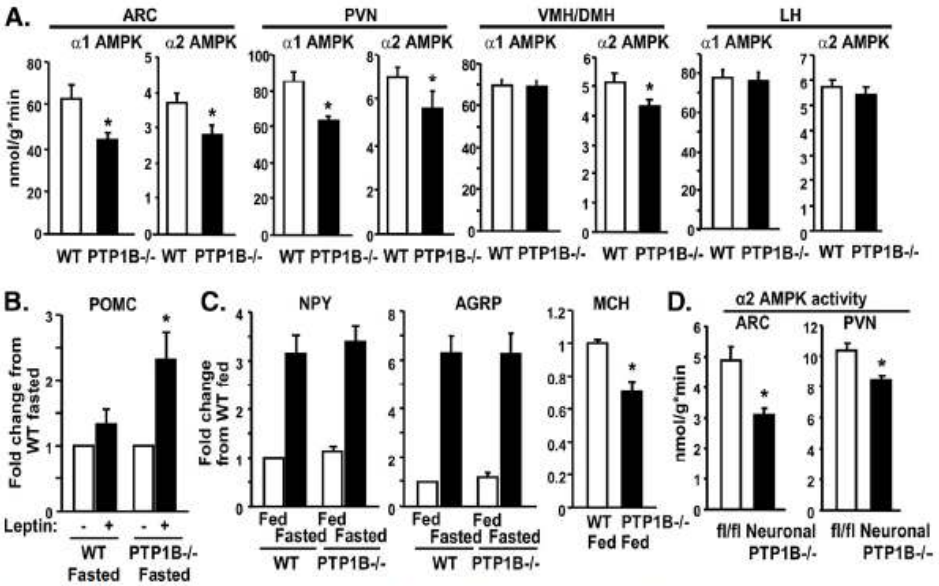


FIG. 7. Effect of PTP1B deficiency on hypothalamic AMPK activity and neuropeptide expression. Panels A to C show data from whole-body PTP1B$^{-/-}$ mice, and panel D shows data from neuronal PTP1B$^{-/-}$ mice. (A) α1 and α2 AMPK activities in ARC, PVN, VMH/DMH, and LH of whole-body PTP1B$^{-/-}$ mice in the fed state. (B) POMC expression in hypothalamus of fasted mice injected with saline or leptin (intraperitoneally). (C) NPY and AgRP mRNA expression in hypothalamus of fasted and fed mice and MCH mRNA expression in hypothalamus of fed mice. (D) α2 AMPK activity in ARC and PVN hypothalamus of neuronal PTP1B$^{-/-}$ mice in the fed state. All experiments were carried out using 12-week-old (A) or 8- to 10-week-old (B to D) male WT and whole-body (A to C) or neuronal (D) PTP1B$^{-/-}$ mice on a chow diet. For panel A, $n = 6$ to 8 for each genotype; panels B and C, $n = 12$ per genotype; and panel D, $n = 11$ to 12 per genotype. Data are expressed as means ± SEM. *, $P < 0.05$ compared to results for WT mice.

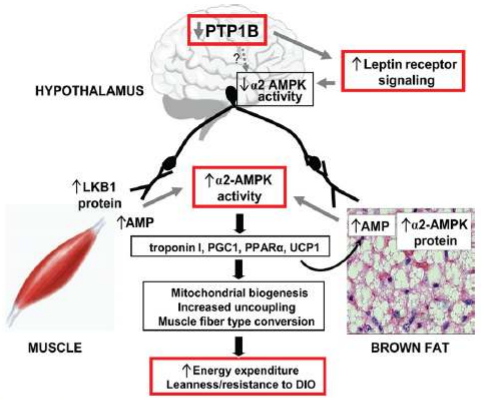


FIG. 8. Proposed model for leanness and resistance to diet-induced obesity following PTP1B inhibition. The reduction of PTP1B in neurons leads to suppression of hypothalamic α2 AMPK activity and activation of α2 AMPK in muscle and BAT. Multiple mechanisms are involved, including increased AMP levels and increased LKB1 and AMPK α2 subunit protein expression in peripheral tissues. These alterations in AMPK activity are accompanied by the induction of genes that regulate muscle fiber type, mitochondrial biogenesis, the uncoupling of oxidative phosphorylation, and fatty acid oxidation, with resultant biologic changes that contribute to increased energy expenditure, leanness, and resistance to diet-induced obesity (DIO).

ARTICLES
INTEGRATIVE PHYSIOLOGY

nature publishing group

Obesity (2010) **18,** 1516–1523. doi:10.1038/oby.2009.444

Inhibition of PTP1B by Trodusquemine (MSI-1436) Causes Fat-specific Weight Loss in Diet-induced Obese Mice

Kristen A. Lantz[1], Susan G. Emeigh Hart[1], Sonia L. Planey[1], Mitchell F. Roitman[2], Inez A. Ruiz-White[1], Henry R. Wolfe[1] and Michael P. McLane[1]

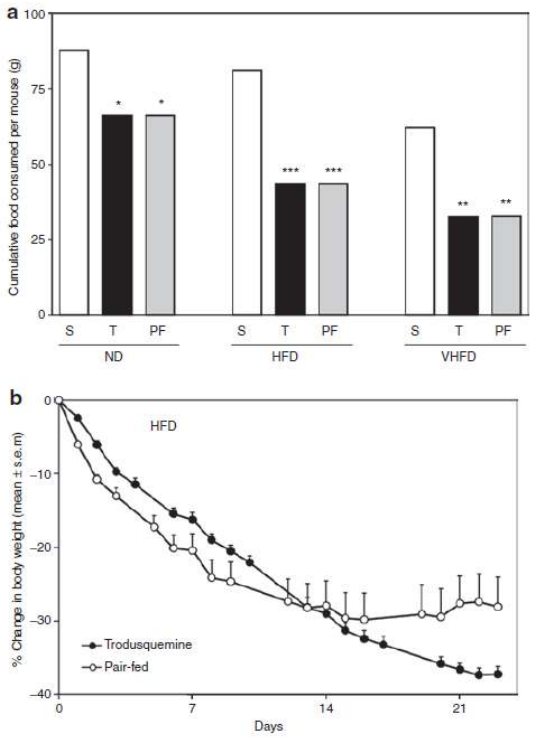
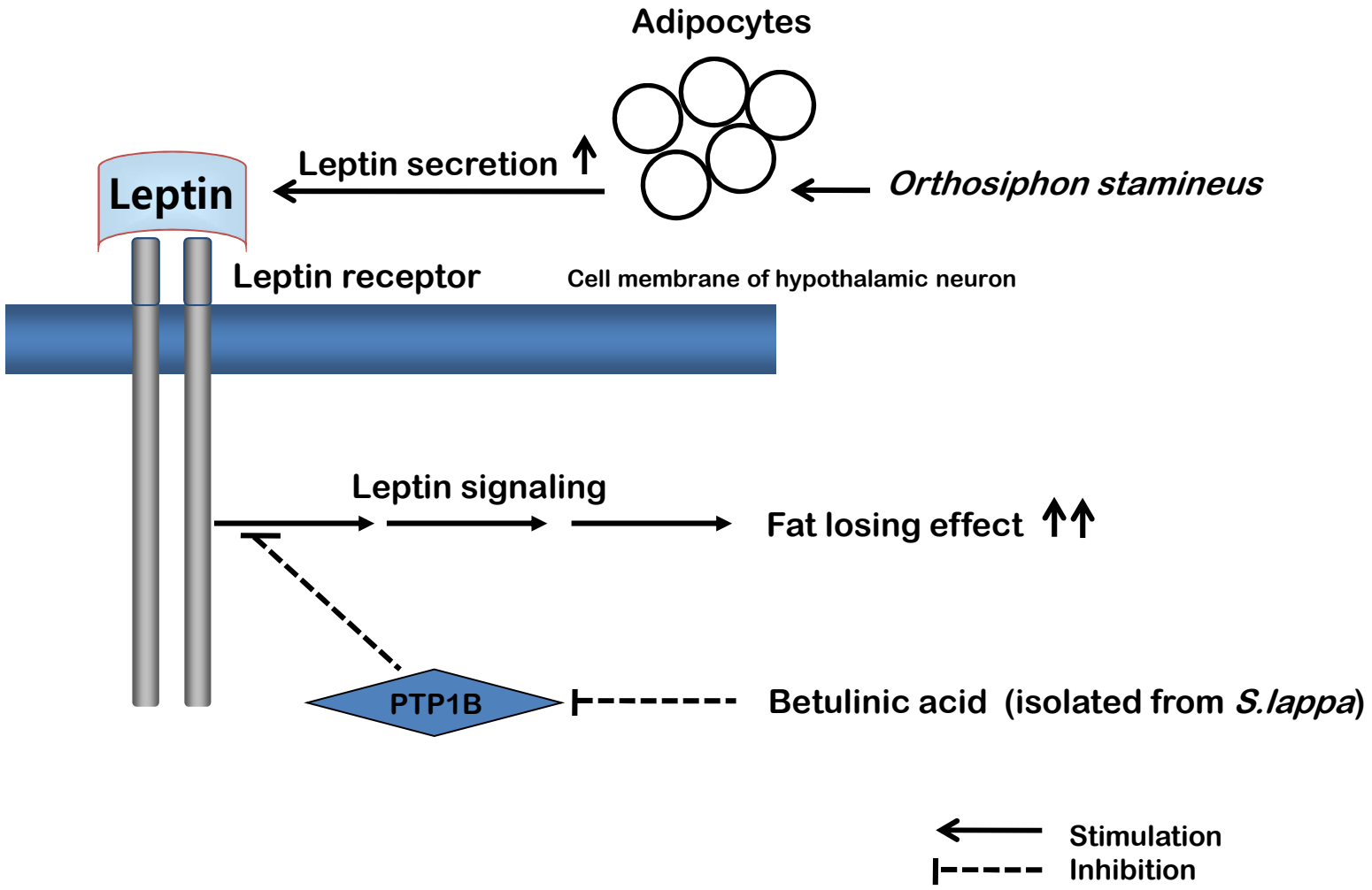


Figure 2 Trodusquemine reduces food intake to produce sustained weight loss. (**a**) Trodusquemine-treated mice consume less food over the course of the study as compared to saline-treated controls. (**b**) Although HFD pair-fed mice consumed the same amount of food as trodusquemine-treated mice, pair-fed mice begin to plateau and regain body weight on day 13, whereas trodusquemine-treated mice continue to lose weight. S, saline-treated; T, trodusquemine-treated; PF, pair-fed; ND, normal diet (10%); HFD, high-fat diet (45%); VHFD, very high-fat diet (60%). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ vs. saline controls within the same diet.

Table 1 Effect of trodusquemine on plasma hormones

Hormone	Diet	Vehicle	Trodusquemine	Pair-fed
Insulin	10% Fat	1.6 ± 0.3	1.6 ± 0.7	0.6 ± 0.4[a]
	45% Fat	33.4 ± 12.9	0.9 ± 0.2[c]	1.3 ± 0.8[c]
	60% Fat	15.2 ± 5.3	1.1 ± 0.2[c]	3.0 ± 1.4[b]
Leptin	10% Fat	14.3 ± 2.7	2.2 ± 0.6[c]	2.4 ± 0.6[c]
	45% Fat	47.0 ± 5.9	1.4 ± 0.4[c,e]	7.7 ± 3.5[c]
	60% Fat	51.9 ± 3.9	1.7 ± 0.3[c,d]	4.7 ± 1.3[c]
Corticosterone	10% Fat	58.6 ± 14.3	130.2 ± 23.7[d]	238.9 ± 44.9[b]
	45% Fat	94.7 ± 41.7	126.5 ± 44.8[e]	317.2 ± 53.5[c]
	60% Fat	59.9 ± 14.6	120.9 ± 28.5	201.3 ± 43.3[a]

[a]$P \le 0.01$, [b]$P \le 0.001$, [c]$P \le 0.0001$ vs. vehicle within the same diet; [d]$P \le 0.05$, [e]$P \le 0.01$ vs. pair-fed groups.


Adipocytes
Leptin secretion
Leptin
Orthosiphon stamineus
Leptin receptor
Cell membrane of hypothalamic neuron
Leptin signaling
Fat losing effect
PTP1B
Betulinic acid (isolated from S.lappa)
Stimulation
Inhibition

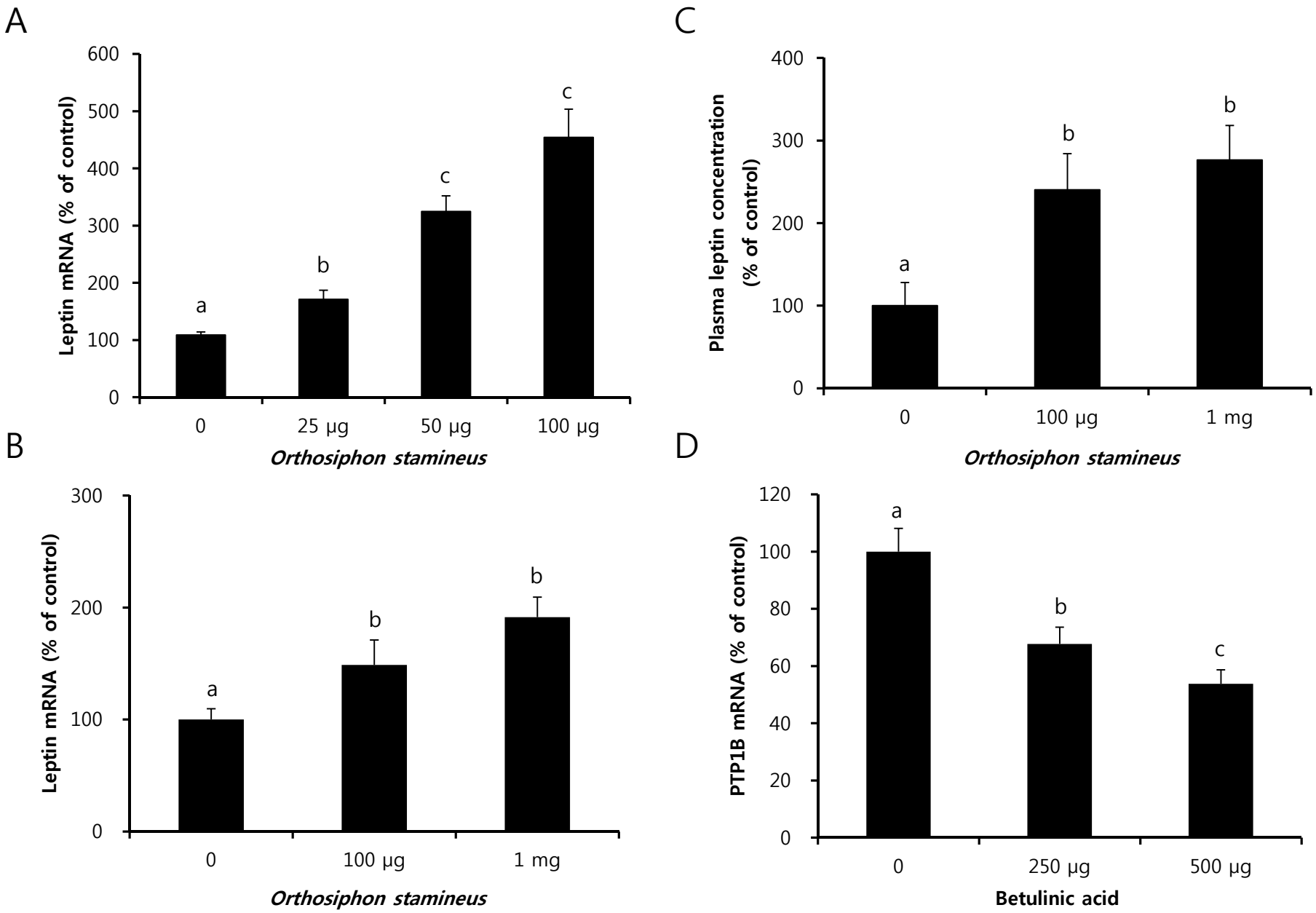


Fig.1

Unpublished data

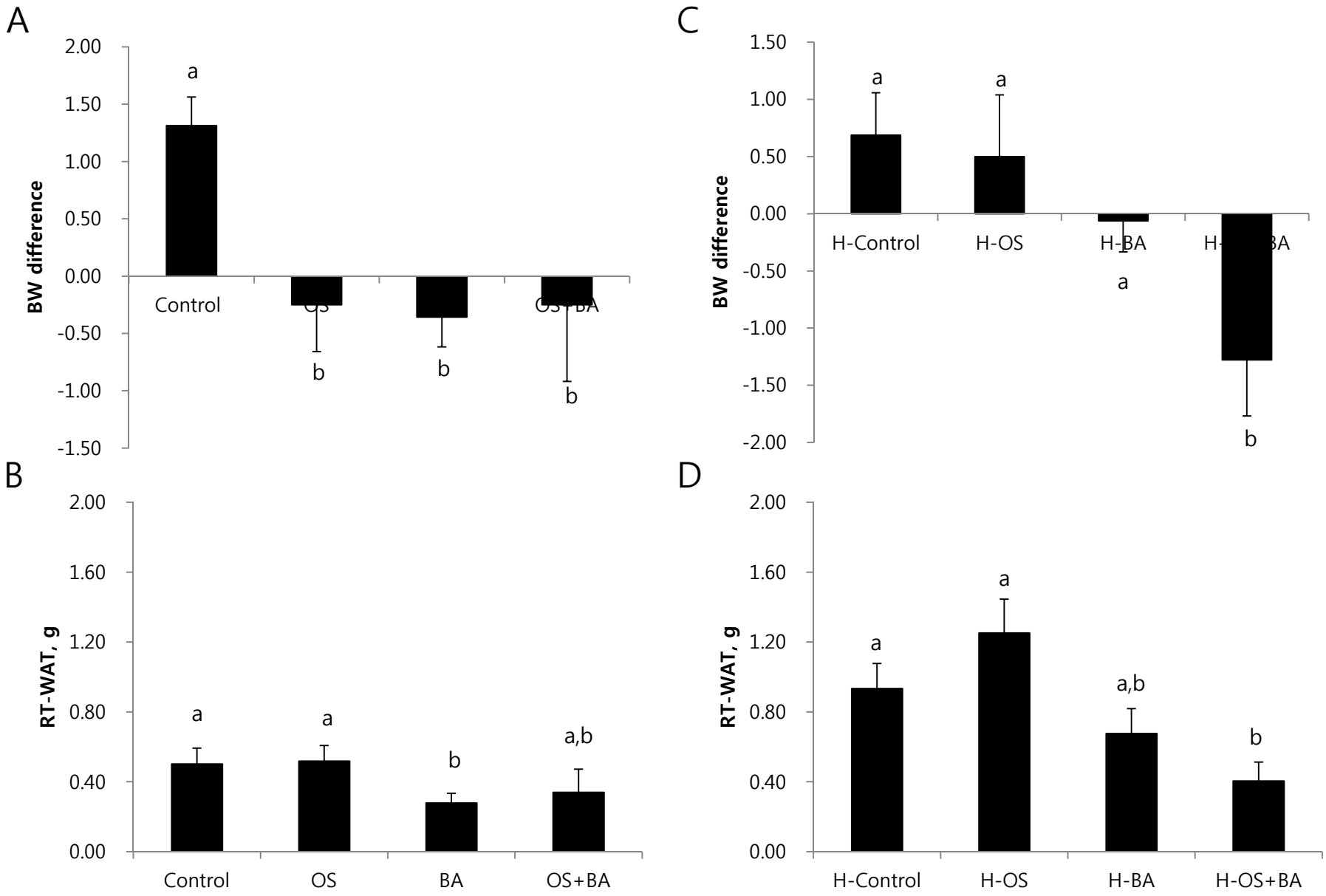


Fig.

Unpublished data

SOCS3

- cytosolic suppressors of cytokine signalling
- feedback inhibition of leptin receptor signaling
- increased in hyperleptinemic state

Enhanced leptin sensitivity and improved glucose homeostasis in mice lacking suppressor of cytokine signaling-3 in POMC-expressing cells

Cell Metabolism, 2006

Paul Kievit,[1] Jane K. Howard,[1] Michael K. Badman,[1] Nina Balthasar,[1] Roberto Coppari,[1] Hiroyuki Mori,[2] Charlotte E. Lee,[1] Joel K. Elmquist,[1] Akihiko Yoshimura,[2] and Jeffrey S. Flier[1,*]

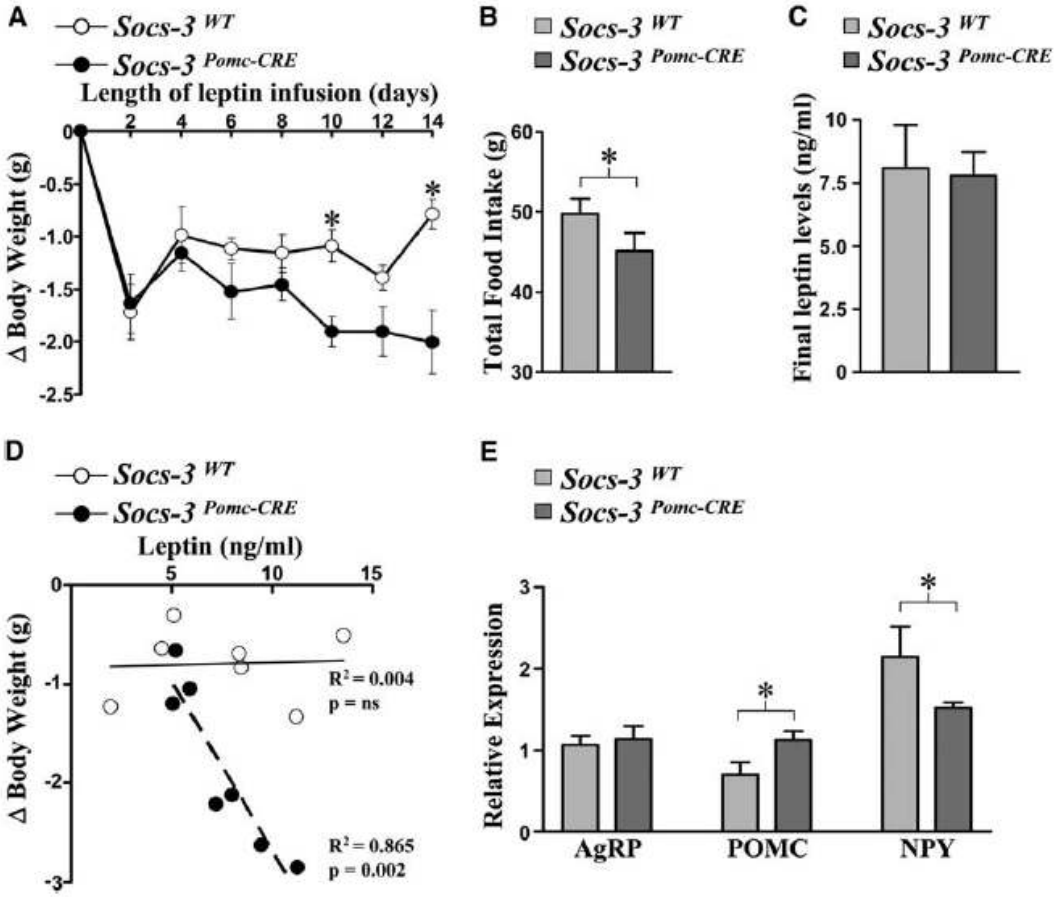


Figure 2. Socs-3$^{lox/lox}$; POMC-Cre mice are more sensitive to exogenous leptin

A) The change in body weight over 14 days in response to implantation of a osmotic minipump delivering 0.3 μg leptin per hour in Socs-3$^{lox/lox}$ (*Socs-3* ^{WT}) (n = 7) and Socs-3$^{lox/lox}$; POMC-Cre mice (*Socs-3* $^{POMC\text{-}Cre}$) (n = 6).

B) Total food intake (g) over 14 days.

C) Final leptin levels (ng/ml).

D) Linear regression of the body weight loss correlated to terminal leptin levels.

E) Hypothalamic expression of POMC, NPY, and AgRP, relative to total 18S RNA content.

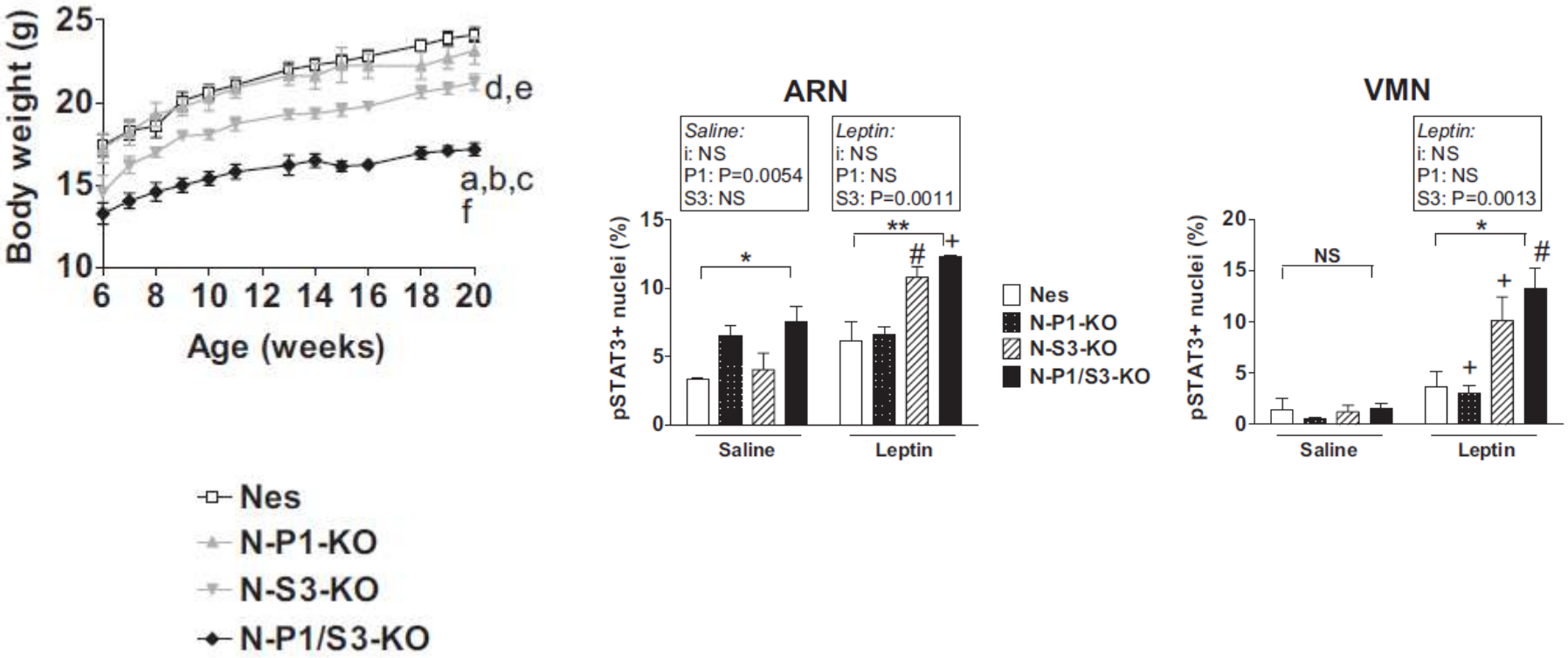
*p < 0.05 by Student's t test.

ORIGINAL ARTICLE

Combined Neural Inactivation of Suppressor of Cytokine Signaling-3 and Protein-Tyrosine Phosphatase-1B Reveals Additive, Synergistic, and Factor-Specific Roles in the Regulation of Body Energy Balance

Nadege Briancon,[1] David E. McNay,[1] Eleftheria Maratos-Flier,[1] and Jeffrey S. Flier[1,2]

Diabetes, 2010

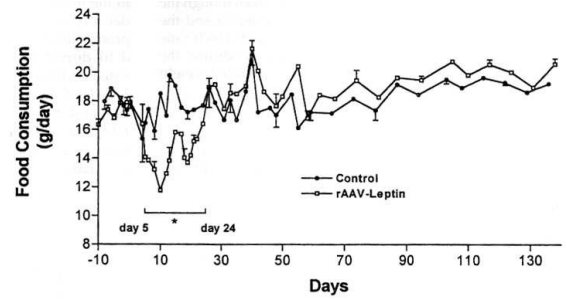


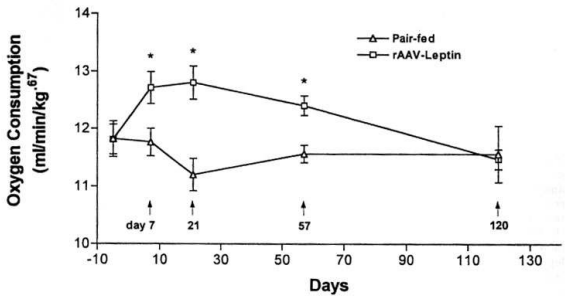
Causative factors for leptin resistance

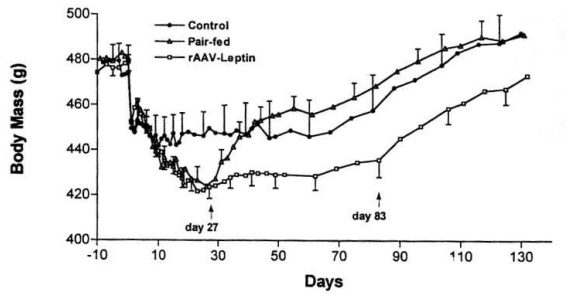
- Hyperleptinemia
- Inflammation
- ER stress
- FFA (saturated)

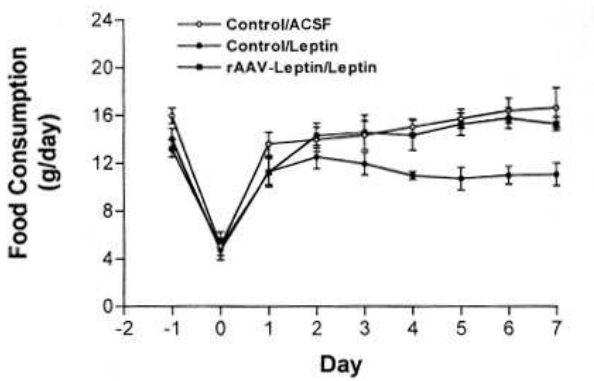
Leptin induced leptin resistance

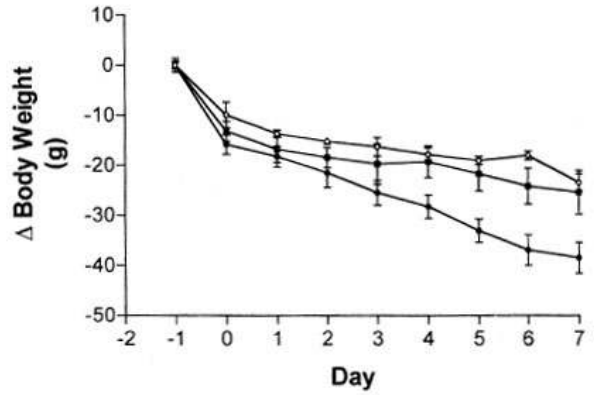
Leptin Gene Transfer (rAAV-leptin) (i.c.v.) (long term, 130 days)











Scarpace et al, Endocrinology, 2002

Metabolic inflexibility

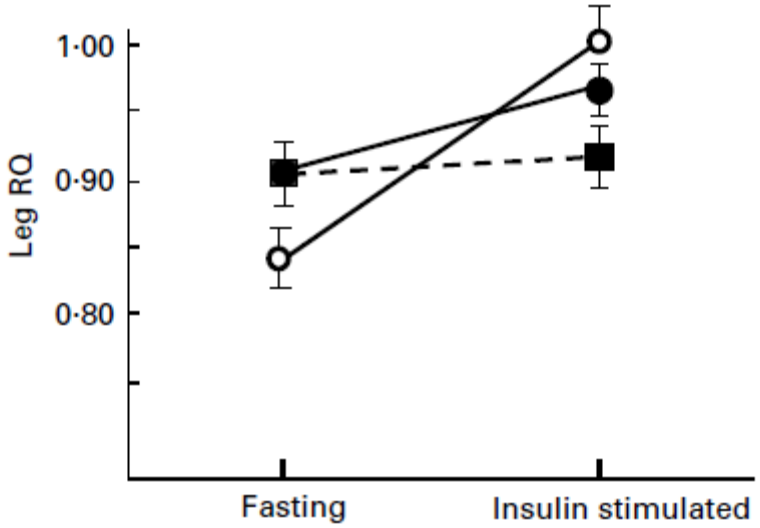


Fig. 3. Illustration of the metabolic response in the leg (largely indicative of skeletal muscle response) to elevation of insulin levels at euglycaemia in lean (○), obese (■) and obese maintained at plateau after substantial (approximately 15 kg) weight loss (●). Values are means with their standard errors represented by vertical bars. The results show the complete metabolic inflexibility of the obese individual compared with lean healthy individuals, which is only very partially restored by weight loss. (Redrawn, with permission from the American Physiological Society, from Kelley *et al.* 1999.)

Kelley, 2000, Diabetes

반복적인 금식으로 인한 렙틴 농도 변동이 렙틴 감수성에 미치는 영향

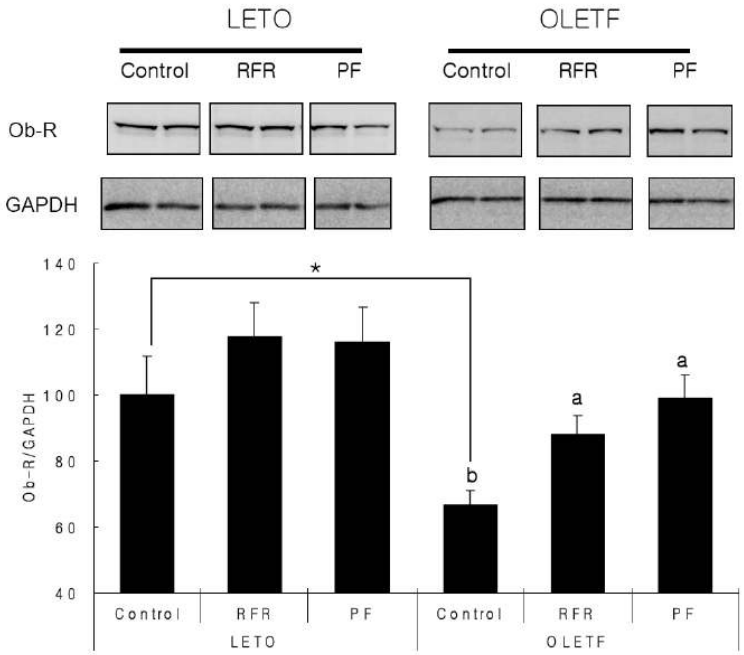


Fig. 3. Leptin receptor (Ob-R) level in the hypothalamus of the experimental groups. Protein level was determined by Western blot. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control. Values are the means ± SE for groups of 5 or 6 rats. * $P < 0.05$. The Ob-R levels were elevated by RFR and PF compared to Control in OLETF rats ($P = 0.004$), however, there was no significant difference in LETO rats. Values that do not share a common superscript are significantly different at $P < 0.05$. RFR, repeated fasting and refeeding; PF, pair fed.

대한내분비학회지: 제 23권 제 5 호 2008

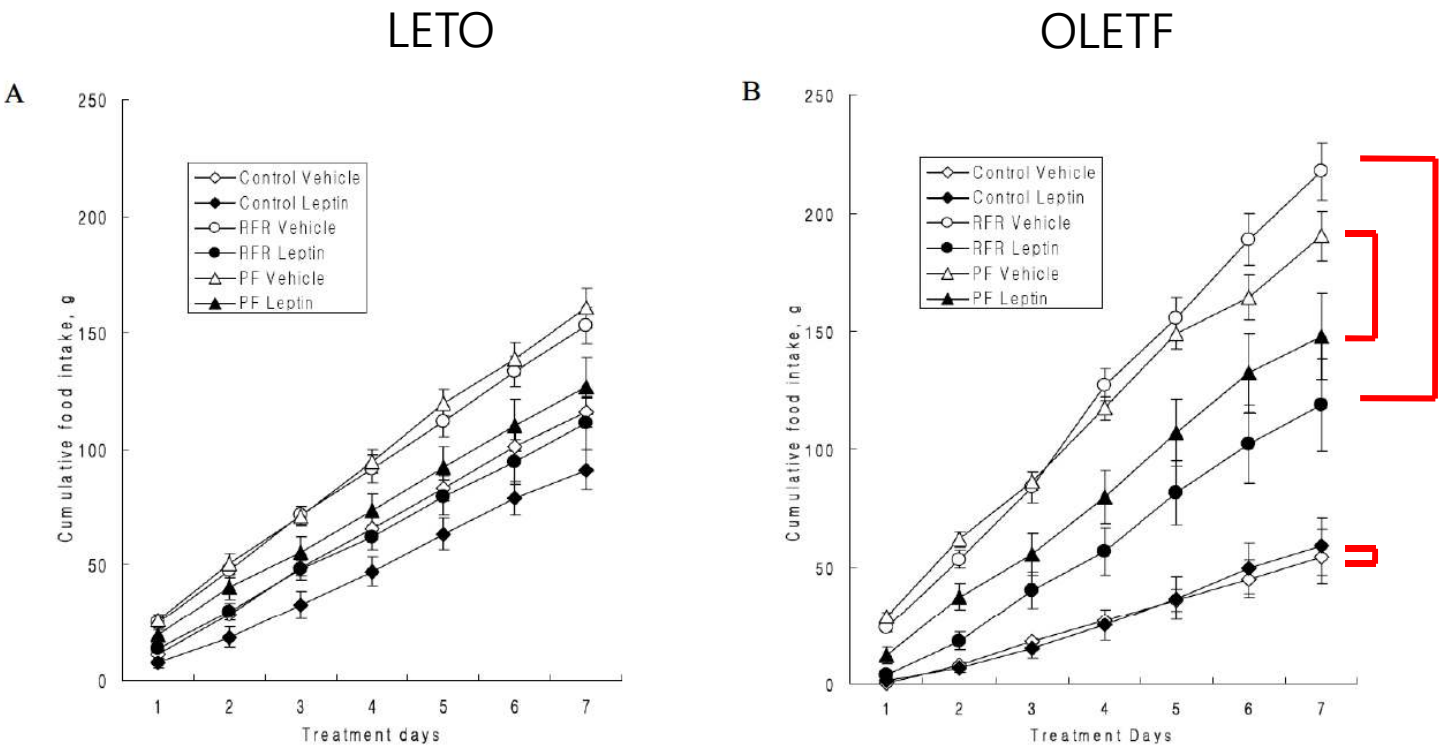


Fig. 1. Effects of intracerebroventricular (i.c.v.) leptin infusion on cumulative food intake in the LETO (A) and OLETF (B) rats. Leptin (15 μg/day) or vehicle (artificial cerebrospinal fluid) was infused for 7 days. Food intake was measured everyday. Values are means ± SE of 5-6 rats per group. $P < 0.01$ for difference between Vehicle and Leptin by ANOVA with repeated measures in the LETO-Control, -RFR, and -PF rats and OLETF-RFR and -PF rats. The difference between Vehicle and Leptin in each group at the seventh day represented the anorexic effect of i.c.v. infused leptin. RFR, repeated fasting and refeeding; PF, pair fed.

Inflammation

1. IKKβ (inhibitor of κB kinase)
2. SOCS3 (suppressor of cytokine signaling)
3. PTP1B
4. UPR (unfolded protein response)
5. ER stress

Curr Opin Lipidol. 2009 October ; 20(5): 379–385. doi:10.1097/MOL.0b013e32832fa5c4.

Toll-like receptor signaling links dietary fatty acids to the metabolic syndrome

Michael B. Fessler[b], **Lawrence L. Rudel**[a], and **Mark Brown**[a]

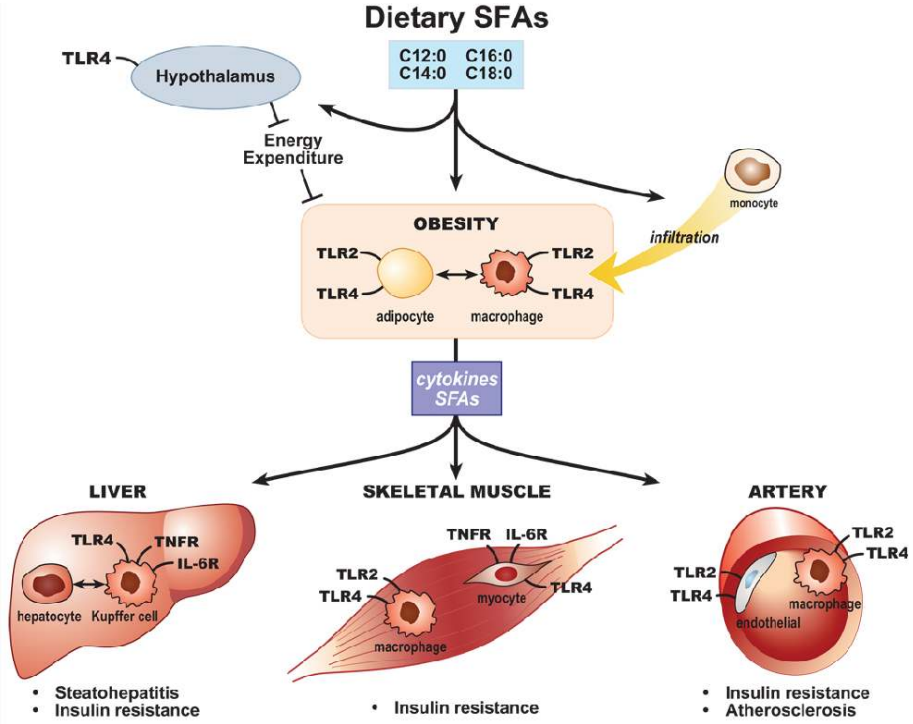


Figure 1. Scheme of saturated fatty acid activity upon Toll-like receptor 2 and Toll-like receptor 4 as a crossroads for metabolic diseases and inflammation

Saturated fatty acids (SFAs) derived from the diet and/or adipose tissue lipolysis enter the circulation and influence several tissues through activity upon resident cells expressing TLR 2 and TLR4. TLR pathway activation via TNFR induces proinflammatory cytokines [e.g., tumor necrosis factor (TNF), and IL-6, chemokines, and adhesion molecules, which may promote inappropriate macrophage recruitment to tissues, including the arterial subintima and adipose tissue. Intercellular communications also modify the obesity phenotype itself in part through activity upon the hypothalamus and lead to steatohepatitis, atherosclerosis, and insulin resistance.

Cell Metabolism
Article

MyD88 Signaling in the CNS Is Required for Development of Fatty Acid-Induced Leptin Resistance and Diet-Induced Obesity

MyD88:TLR adaptor molecule

André Kleinridders,[1,2,3,5] Dominik Schenten,[4,5] A. Christine Könner,[1,2,3,5] Bengt F. Belgardt,[1,2,3,5] Jan Mauer,[1,2,3] Tomoo Okamura,[1,2,3] F. Thomas Wunderlich,[1,2,3] Ruslan Medzhitov,[4] and Jens C. Brüning[1,2,3,*]

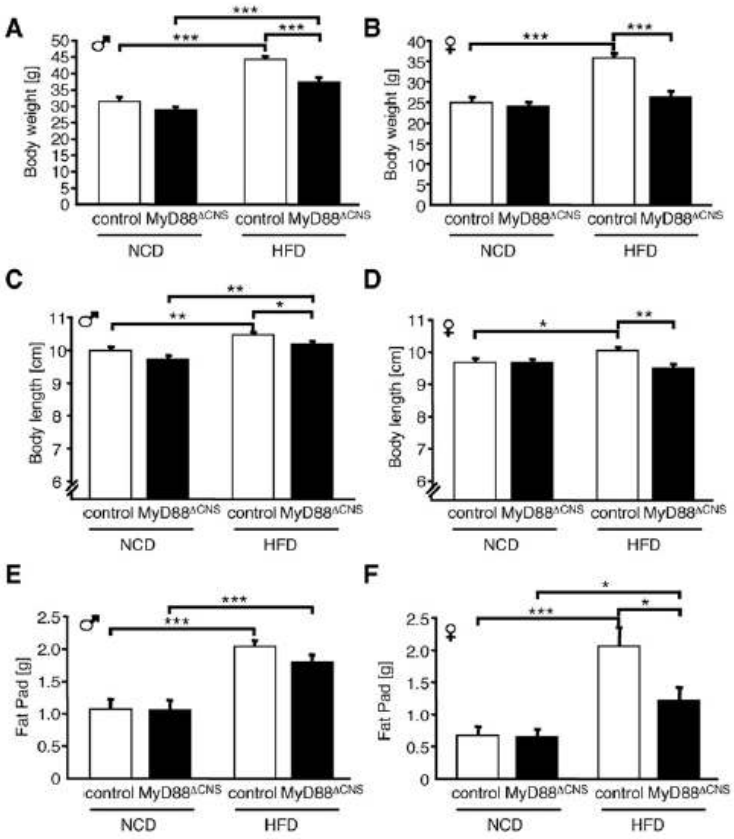


Figure 2. MyD88$^{\Delta CNS}$ Mice Are Protected from Diet-Induced Obesity

(A) Average body weight of male control and MyD88$^{\Delta CNS}$ mice on normal chow diet (NCD) (n = 12–15) and high-fat diet (HFD) (n = 11–13) at the age of 16 weeks.

(B) Average body weight of female control and MyD88$^{\Delta CNS}$ mice on NCD (n = 12–14) and HFD (n = 7–12) at the age of 16 weeks.

(C) Naso-anal body length of male control and MyD88$^{\Delta CNS}$ mice on NCD (n = 15) and HFD (n = 19–21) at the age of 16 weeks.

(D) Naso-anal body length of female control and MyD88$^{\Delta CNS}$ mice on NCD (n = 12–14) and HFD (n = 12–18) at the age of 16 weeks.

(E) Epididymal fat pad weights of male control and MyD88$^{\Delta CNS}$ mice on NCD (n = 15) and HFD (n = 19–21) at the age of 16 weeks.

(F) Parametrial fat pad weights of female control and MyD88$^{\Delta CNS}$ mice on NCD (n = 12–14) and HFD (n = 12–18) at the age of 16 weeks.

(G) H&E stain of epididymal/parametrial adipose tissue of male and female control and MyD88$^{\Delta CNS}$ mice on NCD and HFD at the age of 16 weeks. Scale bar, 100 μm.

(H) Quantification of mean adipocyte surface in epididymal/parametrial adipose tissue of male (n = 3–5) and female (n = 3–5) control and MyD88$^{\Delta CNS}$ mice on NCD and HFD at the age of 16 weeks.

Displayed values are means ± SEM. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

OPEN ACCESS Freely available online

PLoS one

Unsaturated Fatty Acids Revert Diet-Induced Hypothalamic Inflammation in Obesity

Dennys E. Cintra[1,3], Eduardo R. Ropelle[2], Juliana C. Moraes[1], José R. Pauli[2], Joseane Morari[1], Claudio T. de Souza[1], Renato Grimaldi[4], Marcela Stahl[4], José B. Carvalheira[2], Mario J. Saad[2], Licio A. Velloso[1,2]*

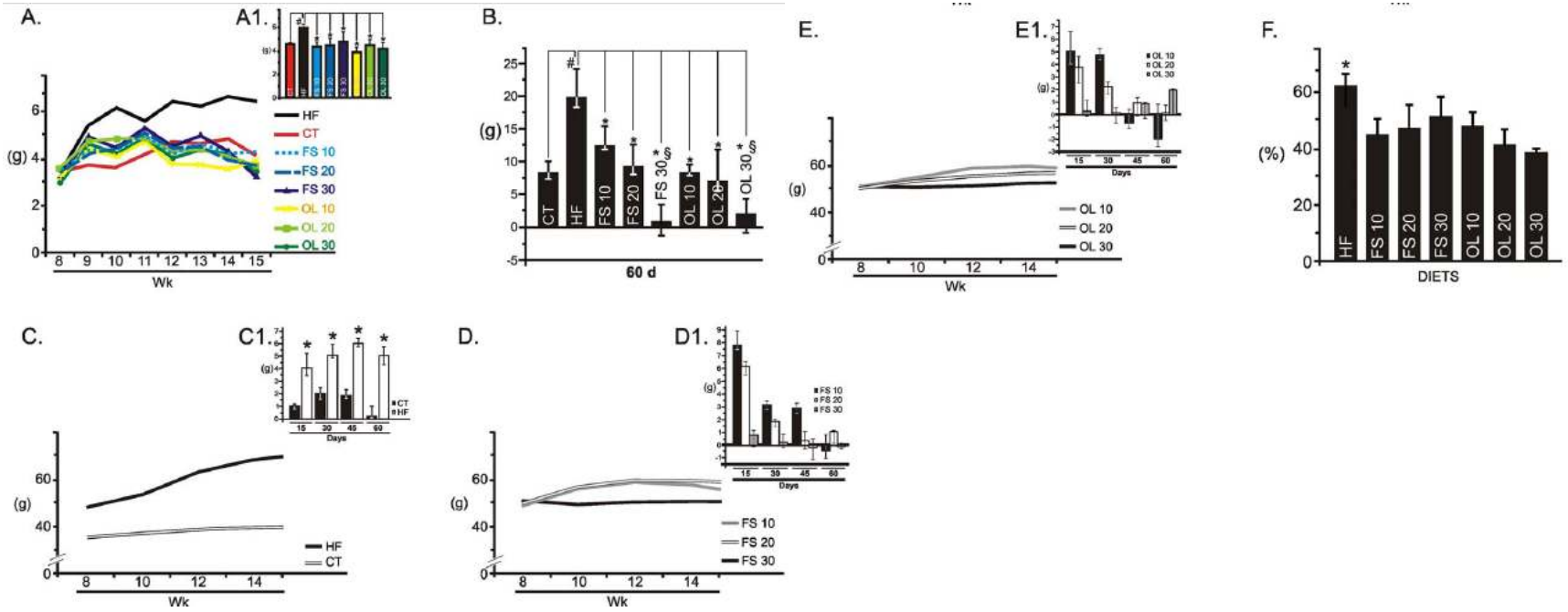


Figure 2. Food intake and body mass variation. A, Mean daily spontaneous food intake (g) of Swiss mice fed on regular chow (CT), high-fat diet (HF), flax seed- (FS) or olive oil- (OL) substituted (10, 20 or 30%) diets for eight weeks; results are depicted as daily food intake along the time (A), and as the means obtained during the whole period (A1). B, Body mass variation for each group during the whole experimental period. C-E, Body mass variation (g) during the 60-day experimental period (C-E) or during each of the four 15-day experimental periods (C1-E1) for CT and HF groups (C, C1); for the FS substituted groups (D, D1); and for the OL substituted groups (E, E1). F, Diet preference assay, lean Swiss mice were fasted for 10 h and then similar amounts of CT or HF (HF) diets were offered; the same approach was used to compare the preference for each of the FS or OL substituted diets against HF; results are presented as the relative caloric consumption of the tested diet during 12h. In all experiments, n = 5; in A and B, #$p<0.05$ *vs.* CT and *$p<0.05$ *vs.* HF; in C and F *$p<0.05$ *vs.* CT; in B, §$p<0.05$ *vs.* FS10 or OL10.

doi:10.1371/journal.pone.0030571.g002

Cell

Hypothalamic IKKβ/NF-κB and ER Stress Link Overnutrition to Energy Imbalance and Obesity

Xiaoqing Zhang,[1,4] Guo Zhang,[1,4] Hai Zhang,[1,2,4] Michael Karin,[3] Hua Bai,[1] and Dongsheng Cai[1,*]

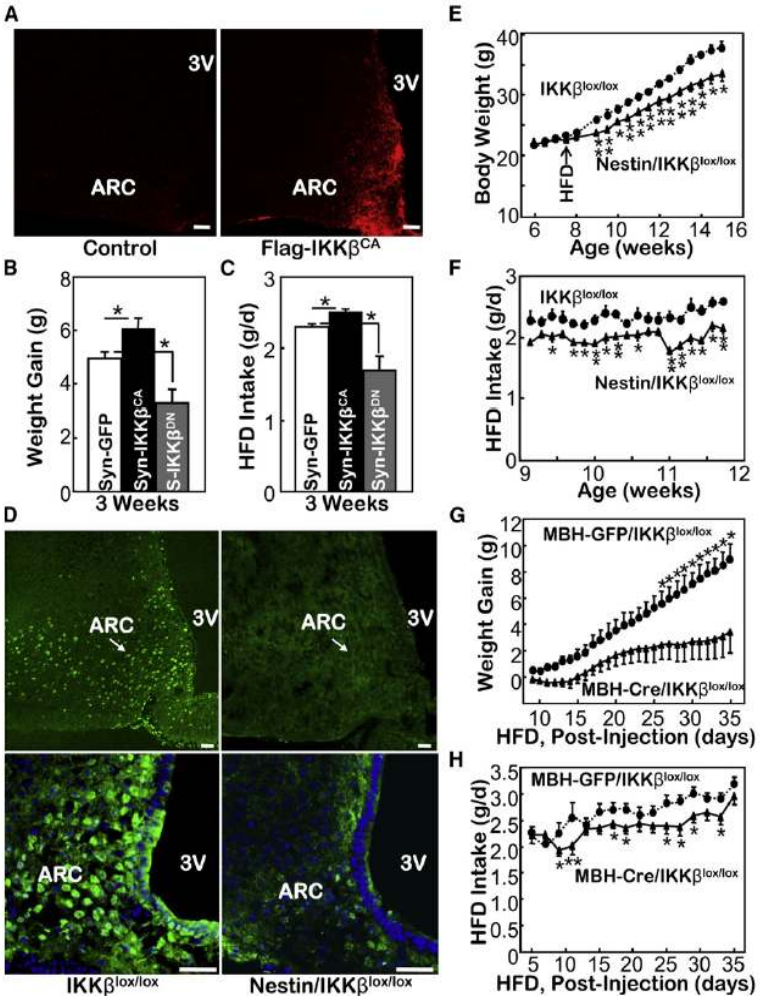


Figure 2. Mouse Phenotypes with Brain or Hypothalamic IKKβ Manipulations

(A) Immunostaining using anti-Flag antibody for the hypothalamic sections from mice that received intra-MBH injections of Flag-IKKβ^{CA} lentivirus and the control lentivirus. Bar = 50 μm.

(B and C) HFD-fed C57BL/6 mice received intra-MBH injections of a lentivirus in which the synapsin (Syn, S) promoter was employed to direct the neuronal expression of IKKβ^{CA}, IKKβ^{DN}, and control GFP. Weight gain (B) and food intake (C) were followed after the mice recovered from injections and surgeries (n = 4–6 per group, *p < 0.05).

(D) Immunostaining of IKKβ in the hypothalamus of Nestin/IKKβ$^{lox/lox}$ mice versus the control IKKβ$^{lox/lox}$ mice. Lower panels: the IKKβ staining (green) was merged with the nuclear staining of the MBH cells (blue) by DAPI. Bar = 50 μm.

(E and F) Body weight (E) and daily food intake (F) were measured for HFD-fed Nestin-IKKβ$^{lox/lox}$ mice versus littermate IKKβ$^{lox/lox}$ mice (n = 5–6 per group, *p < 0.05, **p < 0.01).

(G and H) Body weight gain (G) and HFD intake (H) were measured in IKKβ$^{lox/lox}$ mice that received MBH injections of Cre- or GFP-adenovirus (n = 11–13 per group, *p < 0.05, **p < 0.01). Error bars reflect mean ± SEM (B, C, and E–H).

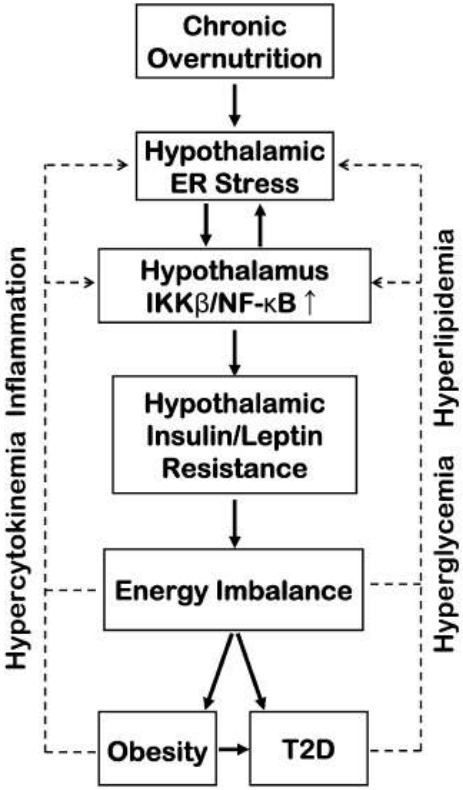


Figure 7. Schematic of the Proposed Role of Hypothalamic IKKβ/NF-κB and ER Stress in Obesity-Related Disease Pathways

We propose that IKKβ/NF-κB connects with ER stress in the hypothalamus and translates overnutrition into central insulin and leptin resistance, leading to the development of obesity and T2D (solid arrows). We also further postulate that, as obesity and T2D progress, IKKβ/NF-κB participates in cumulative feedback loops (broken arrows).

DIABETICMedicine

DOI: 10.1111/j.1464-5491.2009.02747.x

Original Article: Treatment

The effect of anti-inflammatory (aspirin and/or statin) therapy on body weight in Type 2 diabetic individuals: EAT, a retrospective study

M. Boaz, L. Lisy*, G. Zandman-Goddard* and J. Wainstein†

Epidemiology and Research Unit, *Internal Medicine Department C and †Diabetes Unit, E. Wolfson Medical Center, Holon, Israel

Accepted 24 April 2009

Table 3 Follow-up weight and BMI by weight status anti-inflammatory therapy exposure

	Weight stable or weight gain (n = 102)	Weight loss (n = 100)	P-value	Anti-inflammatory Unexposed (n = 44)	Anti-inflammatory Exposed (n = 158)	P-value
Weight (kg)	82.7 ± 14.3	77.7 ± 14.6	0.015	79.6 ± 12.7	80.3 ± 15.2	0.8
Change from baseline weight (kg)	3.1 ± 3.1	−3.3 ± 3.2	< 0.0001	1.0 ± 4.1	−0.37 ± 4.6	0.6
BMI (kg/m^2)	30.4 ± 4.8	29.3 ± 4.6	0.1	29.1 ± 4.7	29.9 ± 4.8	0.5
Change from baseline BMI (kg/m^2)	1.1 ± 1.1	−1.3 ± 1.2	< 0.0001	0.4 ± 1.5	−0.18 ± 1.7	0.04
HbA_{1c} (%)	7.9 ± 1.4	7.9 ± 1.7	0.9	7.5 ± 1.5	7.9 ± 1.5	0.09
Change from baseline HbA_{1c} (%)	−0.37 ± 1.4	−0.52 ± 1.6	0.24	−0.8 ± 1.1	−0.30 ± 1.5	0.07
Fasting blood glucose (mmol/l)	7.6 ± 3.14	7.6 ± 3.16	0.9	7.7 ± 2.22	7.6 ± 3.60	0.9
Change from baseline fasting blood glucose (mmol/l)	−2.4 ± 2.7	−1.3 ± 2.7	0.5	−2.4 ± 2.5	−1.3 ± 2.8	0.2
Received nutrition counselling (%)	75.2	75.5	0.9	73.8	76.1	0.9

BMI, body mass index; HbA_{1c}, glycated haemoglobin.

Table 2 Baseline characteristics of the study population by anti-inflammatory therapy exposure

	Unexposed (n = 44)	Exposed (n = 158)	P-value
Age (years)	60.6 ± 11.2	64.2 ± 9.4	0.04
Years since DM diagnosis	9.0 ± 9.4	14.5 ± 9.5	0.001
Sex (% females)	45.2	54.4	0.3
Lost weight during follow-up (%)	33.3	53.8	0.02
Weight (kg)	78.5 ± 12.7	80.6 ± 15.3	0.4
BMI (kg/m^2)	28.9 ± 4.7	30.1 ± 4.9	0.2
HbA_{1c} (%)	8.4 ± 1.5	8.3 ± 1.7	0.9
Fasting blood glucose (mmol/l)	10.1 ± 3.5	8.7 ± 3.8	0.2
Present smoker (%)	14.3	13.3	0.9
Co-morbid conditions			
Dyslipidaemia (%)	19.0	72.0	< 0.0001
Hypertension (%)	38.1	57.3	0.03
Cardiovascular disease (%)	9.5	37.7	< 0.0001
Oral glucose-lowering agents			
Metformin (%)	54.8	65.2	0.7
Sulphonylurea (%)	52.4.2	32.3	0.02
Acarbose (%)	7.1	13.3	0.4
Rosiglitazone (%)	7.1	13.9	0.3
Repaglinide (%)	0	8.2	0.07
Pioglitazone (%)	16.7	1.9	< 0.0001

Mean ± SD or %.
BMI, body mass index; DM, diabetes mellitus; HbA_{1c}, glycated haemoglobin; SD, standard deviation.

Endoplasmic Reticulum Stress Plays a Central Role in Development of Leptin Resistance

Lale Ozcan,[1,4] Ayse Seda Ergin,[1,4] Allen Lu,[1] Jason Chung,[1] Sumit Sarkar,[1] Duyu Nie,[2] Martin G. Myers, Jr.,[3] and Umut Ozcan[1,*]

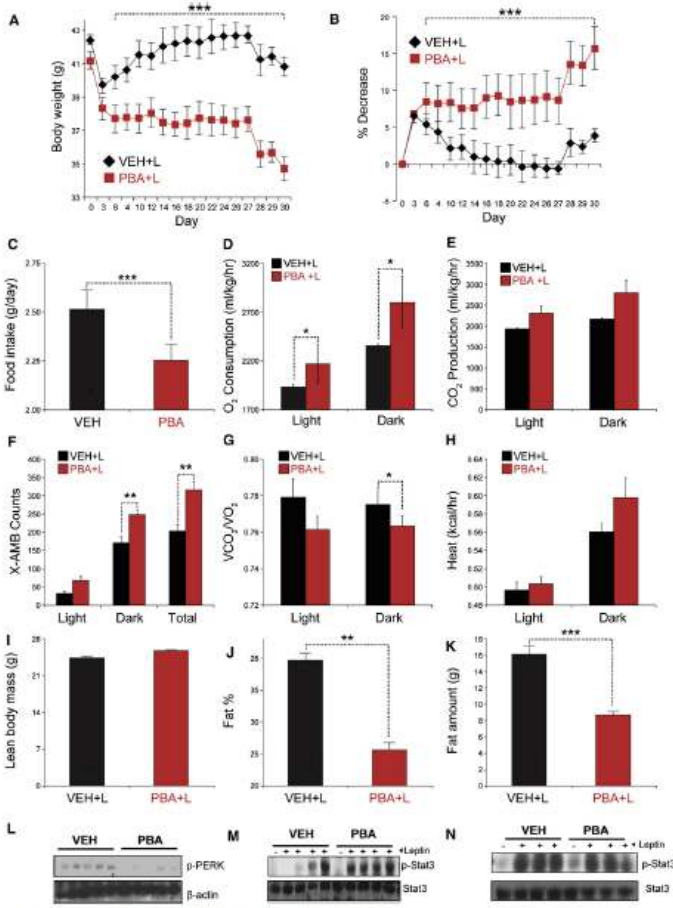


Figure 6. Effect of PBA on the Leptin Sensitivity of Diet-Induced Obese Mice

...6 mice that were kept on high-fat diet feeding for 25 weeks were either treated with vehicle or PBA (1 g/kg/day) for 10 days. Following the pretre..., mice were given daily leptin (5 mg/kg/day, IP) treatment.

(A) Body weight (g), (B) percent of decrease in the body weight, and (C) 24 hr food intake (g) during the 30 days of leptin administration. Metaboli... was performed after 25 days of treatment. (D) O_2 consumption (ml/kg/hr), (E) CO_2 production (ml/kg/hr), (F) x axis ambulatory activity, (G) resp... ratio (VCO_2/VO_2), (H) heat generation (kcal/hr).

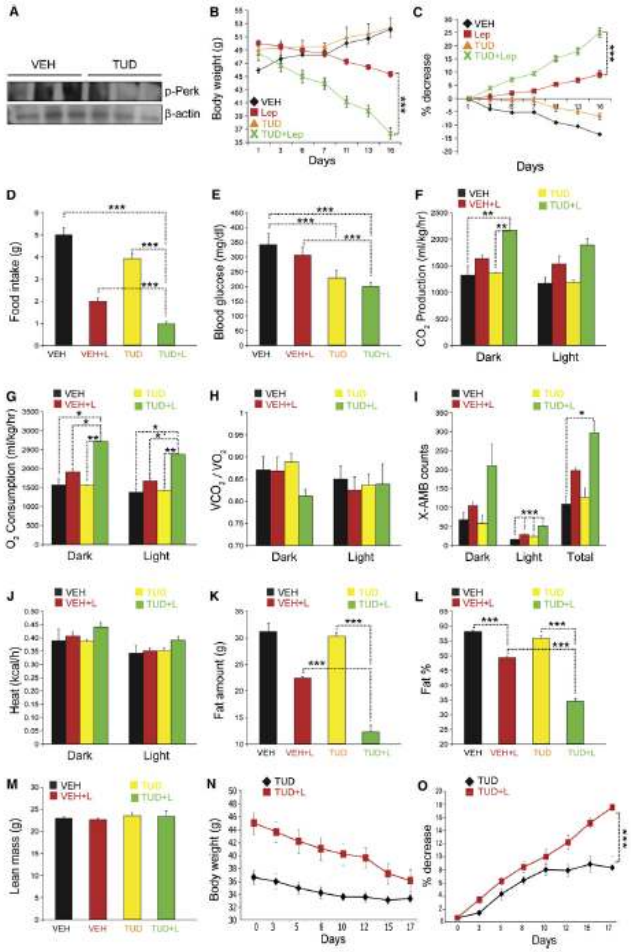


Figure 7. Chemical Chaperone TUDCA Also Acts as a Leptin Sensitizer

(A) Hypothalamic PERK phosphorylation (Thr980) after 21 days of vehicle or TUDCA (150 mg/kg/day) treatment. Following a 5 day pretreatment with TUDCA (150 mg/kg/day) or vehicle, 9- to 10-week old *ob/ob* mice were treated either with leptin (1 mg/kg/day) or vehicle.

(B–D) (B) Body weight (g), (C) percent of decrease in body weight, and (D) daily food intake of the *ob/ob* mice during 18 days of treatment period with the indicated regimens.

(E) Blood glucose (mg/dl) levels at the eighteenth day of treatment. Metabolic cage studies were performed.

(F) CO_2 production (ml/kg/hr).

(G) O_2 consumption (ml/kg/hr).

(H) Respiratory exchange ratio (VCO_2/VO_2).

(I) X axis ambulatory activity.

(J) Heat generation (kcal/hr).

(K–M) Dexa scan analysis of (K) total fat amount (g), (L) fat percentage, and (M) lean body mass (g).

(N) C57BL/6 male WT mice were kept on HFD feeding for 32 weeks and, following a 5 day acclimation period, were pretreated with TUDCA (150 mg/kg/day) for 5 days. At the end of the pretreatment period, intraperitoneal vehicle and leptin (1 mg/kg/day) treatments were started. (N) Body weight (g) and (O) percent of decrease in body weight of the HFD-fed mice during the 16 day treatment (n = 6 for VEH, n = 7 for Lep, n = 7 for TUD, and n = 8 for TUD + Lep group).

Error bars, ± SEM. p values are determined by Student's t test. *p < 0.05, **p < 0.01, ***p < 0.001.

Other trials

- Metformin
- Vanadate
- Sugar restriction
- Exercise
- Caloric restriction
- Cytokines (IL-6, TNF-α)
- Target brain stem nuclei (NST, VTA)

Original Article

Metformin Restores Leptin Sensitivity in High-Fat–Fed Obese Rats With Leptin Resistance

Yong-Woon Kim,[1] Jong-Yeon Kim,[1] Yong-Hoon Park,[2] So-Young Park,[1,3] Kyu-Chang Won,[4] Kwang-Hae Choi,[2] Jung-Yoon Huh,[1] and Ki-Hak Moon[5]

DIABETES, VOL. 55, MARCH 2006

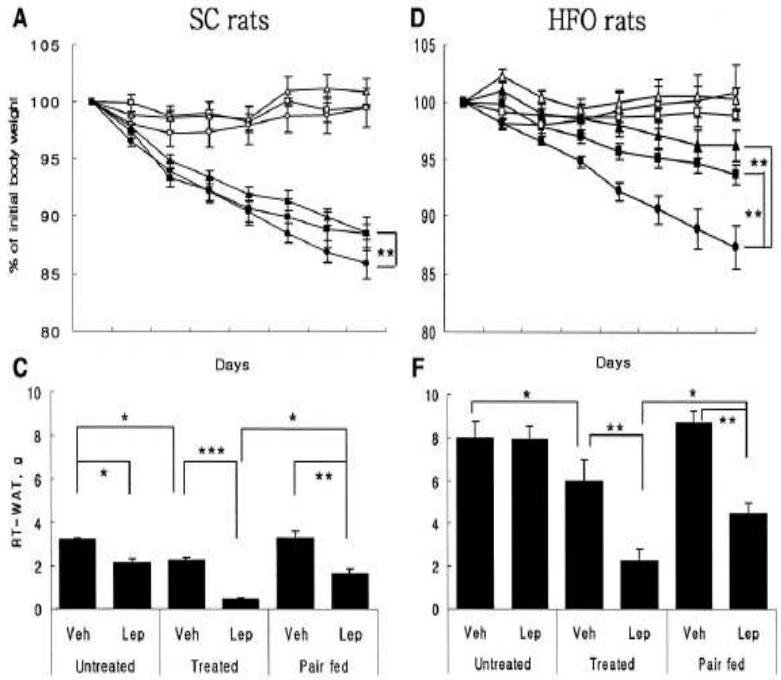


FIG. 3. Comparisons of the effects of metformin (followed by intracerebroventricular leptin infusion) in standard chow (SC) and high-fat–fed obese (HFO) rats on body weight (*A* and *D*), cumulative caloric intake (*B* and *E*), and retroperitoneal white adipose tissue (RT-WAT) weights (*C* and *F*). Leptin (15 μg daily) or vehicle (artificial CSF) was infused for 7 days. Data are the means ± SE of eight rats per group. □, untreated vehicle; ■, untreated leptin; ○, treated vehicle; ●, treated leptin; △, pair-fed vehicle; ▲, pair-fed leptin. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Lep, leptin; Veh, vehicle.

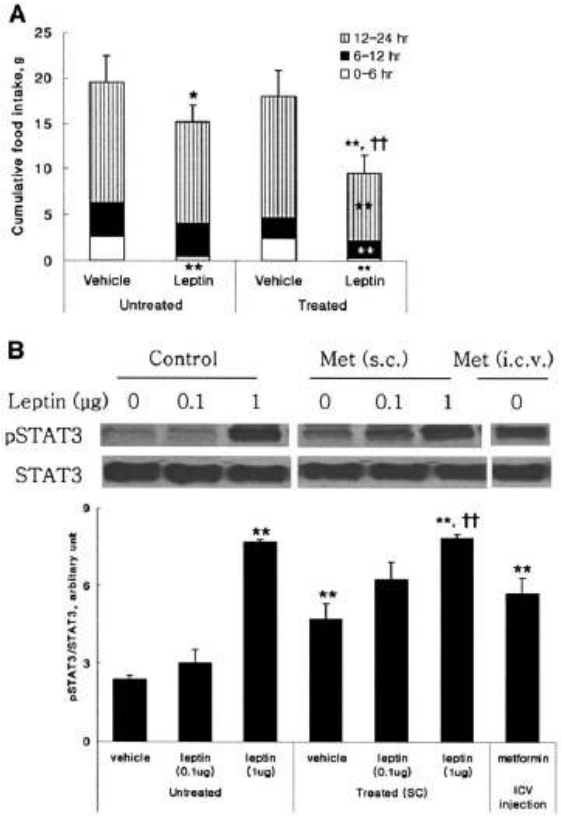


FIG. 6. Cumulative food intake during 24 h after intracerebroventricular (i.c.v) injection of leptin (5 μg) in unrestrained rats (*A*) and pSTAT3 level in the hypothalamus 1 h after leptin injection (*B*). Data are the means ± SE of five rats per group. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. their untreated vehicle; $^{\dagger\dagger}P < 0.01$ vs. treated vehicle. Met, metformin; SC and s.c., subcutaneous.

0013-7227/06/$15.00/0
Printed in U.S.A.

Endocrinology 147(1):493–501

doi: 10.1210/en.2004-1358

Oral Vanadium Enhances the Catabolic Effects of Central Leptin in Young Adult Rats

Jared Wilsey, Michael K. Matheny, and Philip J. Scarpace

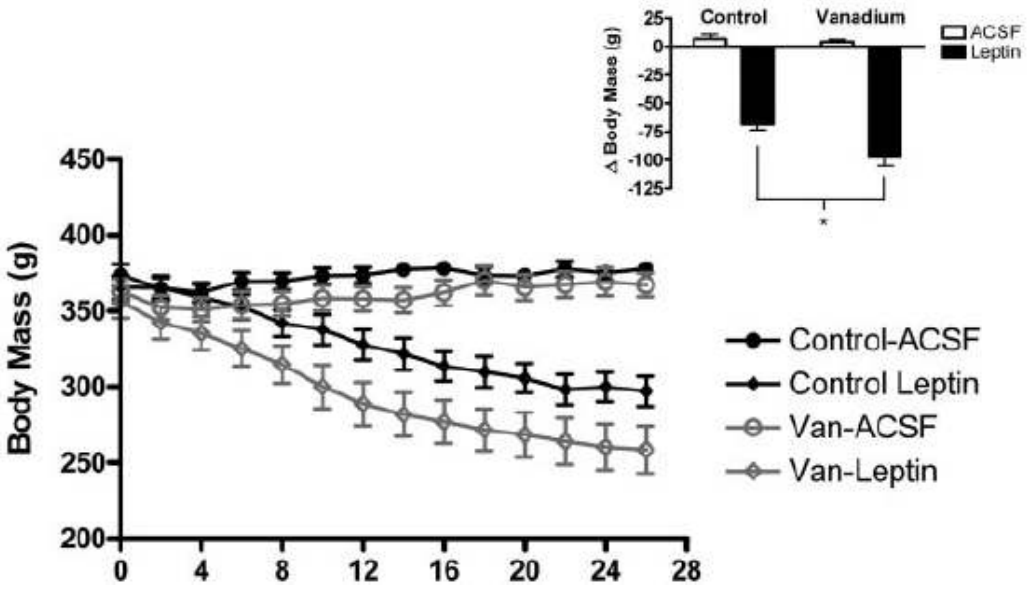


FIG. 3. Body weight after implantation of minipump providing intracranial leptin (5 μg/d) or ACSF vehicle. Day 0 represents the day of pump implantation. Data were analyzed by three-way ANOVA, with time, leptin, and vanadium as factors. Significance was found for all three main effects: time ($F = 17.61$; $P < 0.001$), leptin ($F = 55.51$; $P < 0.0001$), and vanadium ($F = 6.64$; $P < 0.05$). The interaction between time and leptin was significant ($F = 46.67$; $P < 0.0001$), and the interaction between leptin and vanadium was significant ($F = 5.17$; $P < 0.05$). No other interactions were significant. *Inset*, Net change in body mass 26 d after minipump implantation. By two-way ANOVA, significance was found for both the vanadium ($F = 10.93$; $P < 0.01$) and leptin ($F = 338.41$; $P < 0.0001$) main effects. The interaction between main effects was also significant ($F = 7.92$; $P < 0.05$). By *post hoc* analysis, V-leptin lost significantly more weight than C-leptin animals ($P < 0.01$).

British Journal of Nutrition (2011), **106**, 390–397
doi:10.1017/S000711451100033X

Prevention and reversal of diet-induced leptin resistance with a sugar-free diet despite high fat content

Alexandra Shapiro[1]*, Nihal Tümer[1,2], Yongxin Gao[1], Kit-Yan Cheng[1] and Philip J. Scarpace[1,3]

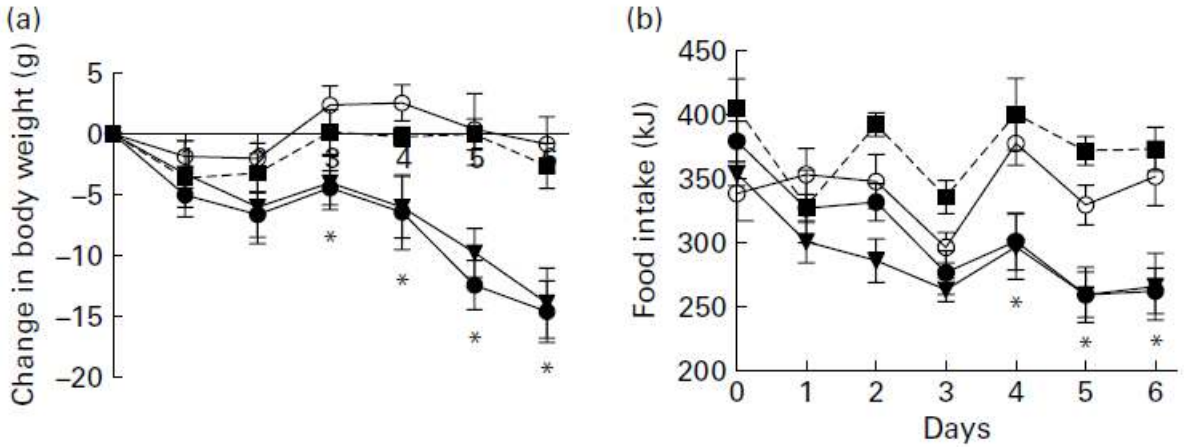


Fig. 5. (a) Body-weight change and (b) daily food intake from day 1 to day 6 during the central infusion of artificial cerebrospinal fluid (ACSF) in rats fed the sugar-free (SF)/high-fat (HF) diet (○, *n* 5) or leptin (1·5 μg/d) in rats fed the SF/HF diet (●, *n* 5), high-fructose (HFr)/HF diet (■, *n* 6) and in rats switched from the HFr/HF to the SF/HF diets (switched, ▼, *n* 8). Body-weight change in the SF/HF-fed rats is significantly different between the vehicle (ACSF) and leptin-treated rats beginning at day 3 (*$P<0{\cdot}01$ by *t* test), and food intake is significantly different starting on day 4 (*$P<0{\cdot}01$ by *t* test). Values are means, with standard errors represented by vertical bars.

Gerontology

Experimental Section / Original Paper

Gerontology 2011;57:335–342
DOI: 10.1159/000321343

Received: December 10, 2009
Accepted: June 23, 2010
Published online: September 24, 2010

The Act of Voluntary Wheel Running Reverses Dietary Hyperphagia and Increases Leptin Signaling in Ventral Tegmental Area of Aged Obese Rats

Alexandra Shapiro[a] Kit-Yan Cheng[a] Yongxin Gao[a] Dong-oh Seo[b]
Steve Anton[b, c] Christy S. Carter[b] Yi Zhang[a, d] Nihal Tumer[a, d]
Philip J. Scarpace[a, b]

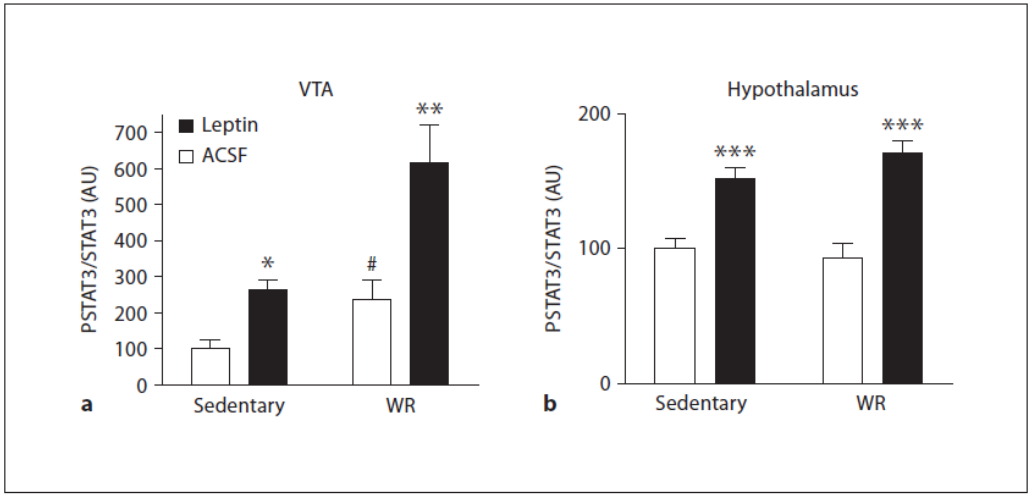


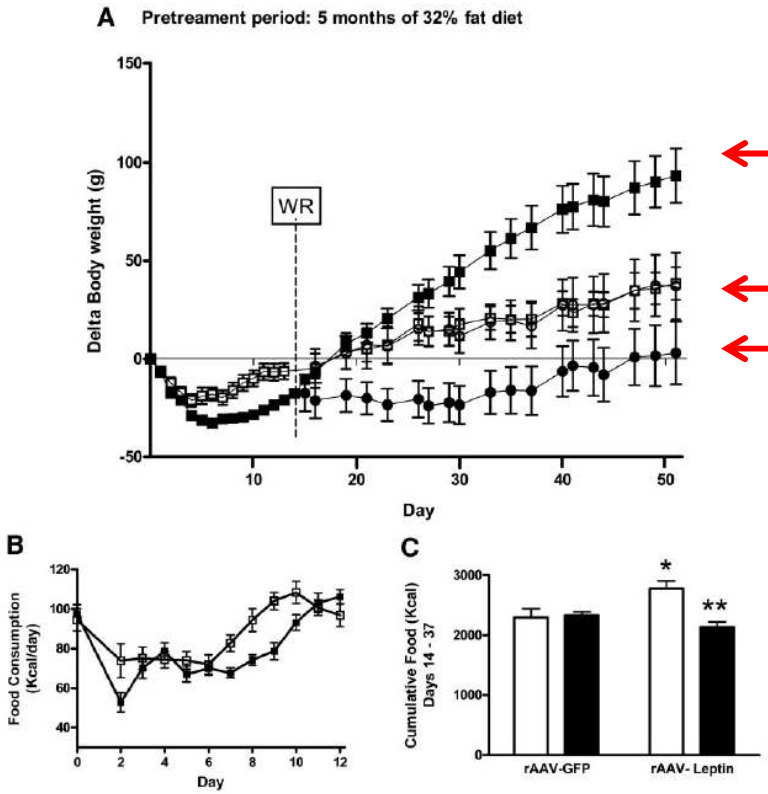
Fig. 4. Basal and leptin-stimulated protein levels of phosphorylated STAT3 in VTA (**a**) and hypothalamus (**b**) in sedentary rats and rats that were exposed overnight (18 h) to running wheels. Values represent the mean ± SE (n = 6). **a** $p = 0.0004$ for leptin stimulated compared to vehicle (ACSF) by two-way ANOVA. $p = 0.001$ for WR compared to sedentary by two-way ANOVA. * $p < 0.05$ for leptin stimulated compared to vehicle in sedentary rats by post-hoc analysis. ** $p < 0.05$ for leptin stimulated compared to vehicle in WR rats by post-hoc analysis. # $p < 0.05$ for WR compared to sedentary rats among ACSF treated rats by post-hoc analysis. **b** $p < 0.0001$ for difference with leptin by two-way ANOVA, *** $p < 0.001$ for leptin stimulated compared to vehicle by post-hoc analysis.

ORIGINAL ARTICLE

Synergy Between Leptin Therapy and a Seemingly Negligible Amount of Voluntary Wheel Running Prevents Progression of Dietary Obesity in Leptin-Resistant Rats

Alexandra Shapiro,[1] Michael Matheny,[1] Yi Zhang,[1,2] Nihal Tümer,[1,2,3] Kit-Yan Cheng,[1] Enda Rogrigues,[1] Sergei Zolotukhin,[4] and Philip J. Scarpace[1,3]

Diabetes, 2008



Sedentary/rAAV-leptin

Sedentary/rAAV-control

Wheel running/rAAV-leptin

FIG. 2. *A*: Body mass changes in high-fat–raised rats following administration of control vector (open symbols) or rAAV-leptin (closed symbols) in sedentary rats (squares) or rats provided access to running wheels (circles) beginning at day 14. The rAAV-leptin or control vectors were administered at day 0 in rats raised on a high-fat diet for 5 months and continued on the high-fat diet throughout the experiment. Values represent the mean ± SE of six sedentary and eight wheel-running rats per group. $P < 0.05$ (control versus corresponding AAV-leptin; sedentary/AAV-leptin vs. wheel running/AAV-leptin) for difference in slops following division of groups into sedentary and wheel running. □, sedentary/control vector; ■, sedentary/AAV-leptin; ○, wheel running/control vector; ●, wheel running/AAV-leptin. *B*: Daily food consumption following control vector (□) or rAAV-leptin (■) before division into sedentary or wheel-running groups. Food consumption is significantly less ($P < 0.05$) between days 7 and 10, but cumulative food consumption during entire period is not significantly different. *C*: Cumulative food consumption between days 14 and 37 during the first part of the sedentary (○) and wheel-running (●) period. $P = 0.015$ (wheel running) and $P = 0.008$ (interaction) by two-way ANOVA; $^{*}P < 0.001$ for difference with wheel running among rAAV-leptin groups by post hoc analysis; $^{**}P < 0.05$ for difference between sedentary rAAV-leptin and sedentary rAAV-GFP. After day 37, food consumption was not different among groups.

Diabetologia (2002) 45:997–1003
DOI 10.1007/s00125-002-0851-4

Diabetologia

Long-term food restriction prevents ageing-associated central leptin resistance in wistar rats

C. Fernández-Galaz[1], T. Fernández-Agulló[1], C. Pérez[2], S. Peralta[3], C. Arribas[3], A. Andrés[4], J. M. Carrascosa[2], M. Ros[1]

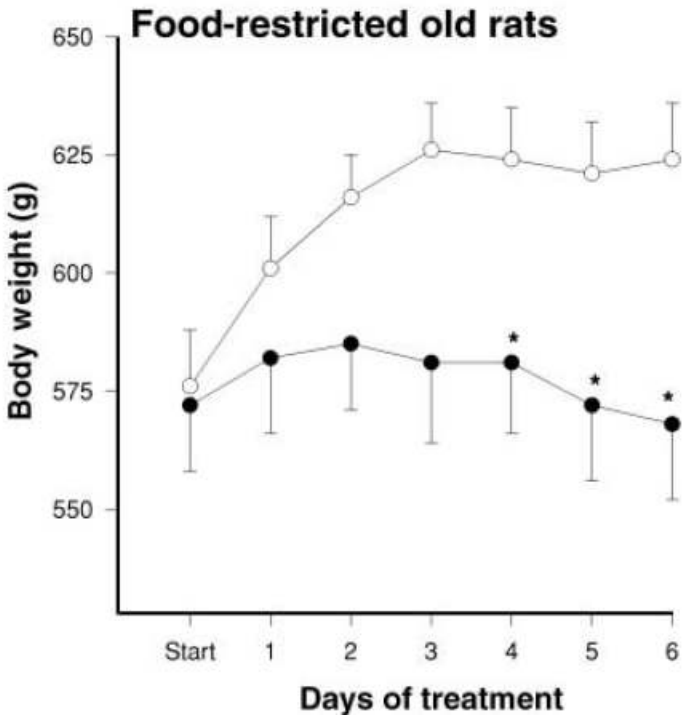


Fig. 4. Evolution of body weight of food-restricted old rats during treatment with either saline or 0.2 μg/day of leptin. Osmotic minipumps containing saline (○) or leptin (●) were implanted in food-restricted old rats, and the rats were fed during 6 days. Figure shows the evolution of body weight throughout the treatment. Data are means ± SEM of five animals per group. Two-way ANOVA shows an effect of leptin treatment ($p<0.0001$) on body weight. One-way ANOVA shows an increase in body weight during the treatment for vehicle-treated animals ($p=0.048$). *$p<0.05$ compared with vehicle-treated rats

POMC overexpression in the ventral tegmental area ameliorates dietary obesity

Lourdes M Andino[1], Daniel J Ryder[1], Alexandra Shapiro[1], Michael K Matheny[1], Yi Zhang[1,3], Melanie K Judge[1], K Y Cheng[1], Nihal Tümer[1,3] and Philip J Scarpace[1,2]

Journal of Endocrinology (2011) 210, 199–207

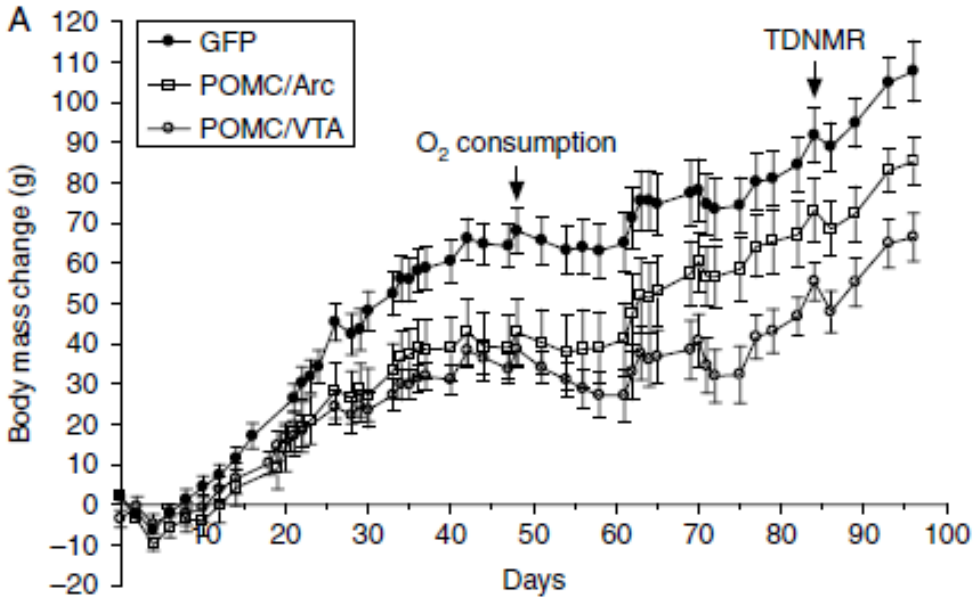


Figure 1 Body weight and caloric intake. Body weight change (A) in 4-month-old 344×BN rats that were injected into either the VTA (open circles) or the ARC (squares) with rAAV-POMC or rAAV-GFP (closed circles), the control group. Beginning on day 26 post gene delivery, significantly smaller increases in body weight gain were observed in VTA-treated animals compared with controls ($P<0{\cdot}01$). As compared with controls, significantly smaller increases in body weight gain were observed in ARC-treated animals beginning on day 30 ($P<0{\cdot}05$). The differences in weight gain amongst the ARC and VTA treated groups began to significantly diverge ($P<0{\cdot}05$) on day 86 throughout the duration of the experiment. Assessments including oxygen consumption and TD-NMR were measured on days 48 and 85 respectively. Average caloric intake (B) did not differ amongst any of the three groups. Values represent the mean±S.E.M. of seven rats per group.

Neuroscience 169 (2010) 1662–1671

PRO-OPIOMELANOCORTIN GENE TRANSFER TO THE NUCLEUS OF THE SOLITARY TRACK BUT NOT ARCUATE NUCLEUS AMELIORATES CHRONIC DIET-INDUCED OBESITY

Y. ZHANG,[a,b*] E. RODRIGUES,[a,b] Y. X. GAO,[a,b]
M. KING,[a,b] K. Y. CHENG,[a,b] B. ERDÖS,[a,b] N. TÜMER,[b,c,d]
C. CARTER[c] AND P. J. SCARPACE[b,c]

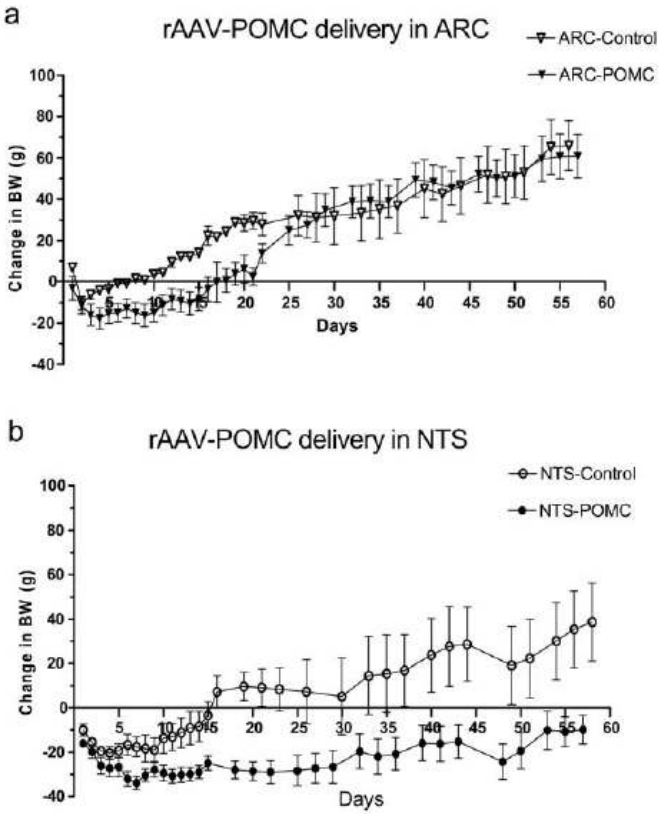


Fig. 3. Change in body weight (BW) following rAAV-POMC gene transfer in the ARC (a) or NTS (b). Data are means±SE of 5–6 rats per group. According to ANOVA followed by post-hoc analysis at the individual time point, the ARC-POMC rats had significantly lower body weight than that of ARC-Control rats only from days 4 through 22 (a), whereas the NTS-POMC rats displayed significantly reduced change in body weight relative to the NTS-Control rats from day 6 until termination (b).

Summary

- Multifactorial causes
- Convergence
- Cause-specific approach
- Combinational treatment of leptin sensitizer and leptin supplementation

감사합니다.