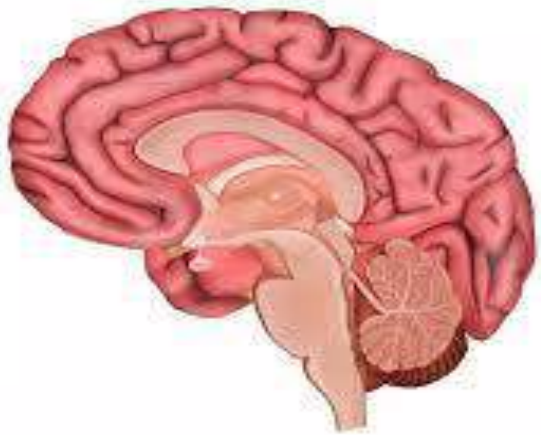
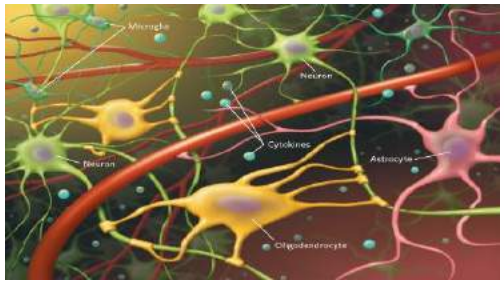
Glukoz Metabolizmasında Santral Sinir Sisteminin Rolü

Prof Dr. Nilgün Güvener Demirağ
Başkent Üniversitesi
Endokrinoloji Bilim Dalı





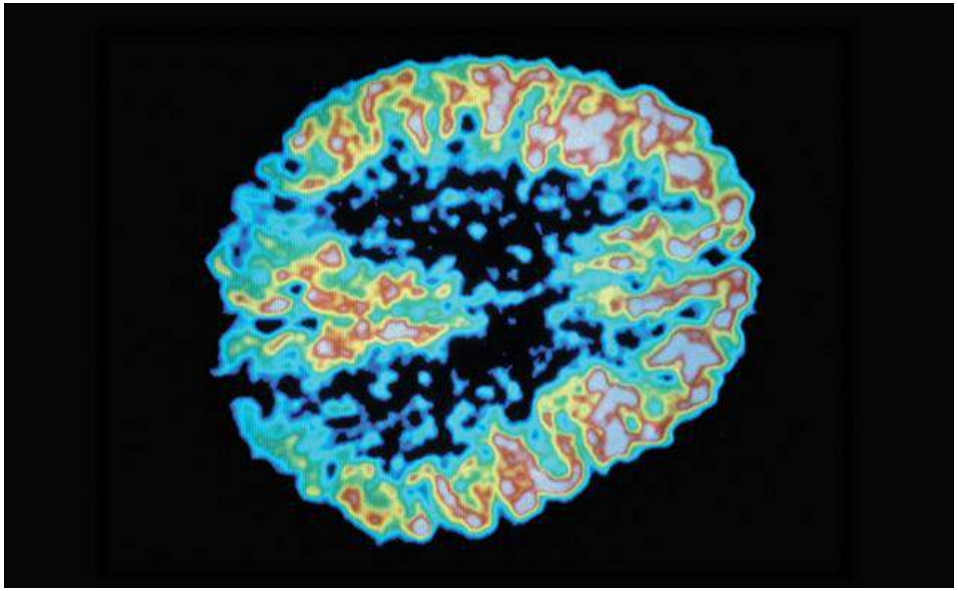
CHAPTER 8

Central Regulation of Insulin Sensitivity

Silvana Obici and Luciano Rossetti*

"...Hence we could say that in a diabetic individual the liver secretes too much. The matter which produces sugar cannot be transformed into a product with a more complex organization. The dis-assimilation has become prevalent. Therefore we can consider diabetes as a disease of the nervous system caused by excessive activation of the disassimilator nerve of the liver, which drives the premature disassimilation of matter that would otherwise be used for nutrition... ...Hence the treatment of diabetes should address the nervous system. Stimulating the sympathetic nerve could be a valuable tool. But, in order to achieve a treatment with a rationale based on physiology, we should answer many questions, which are still awaiting a solution from the science of physiology".

Claude Bernard in *"Leçons sur les phénomènes de la vie"*
Cours de physiologies Generale du Museum d'Histoire Naturelle, 1859



- 1933: Manfred Sakel tarafından Psikoz ve affektif bozukluk tedavisinde **"insulin-shock therapy"** (insulin coma therapy:ICT)
- Yüksek doz insülin ile hipoglisemik koma yaratıp, 1 saat sonra glukoz verilmesi şeklinde haftalarca yada aylarca sürebilen tedavi
- 1940-1950'lerde Amerika ve Avrupa da yaygın kullanım

1970 de terkedildi

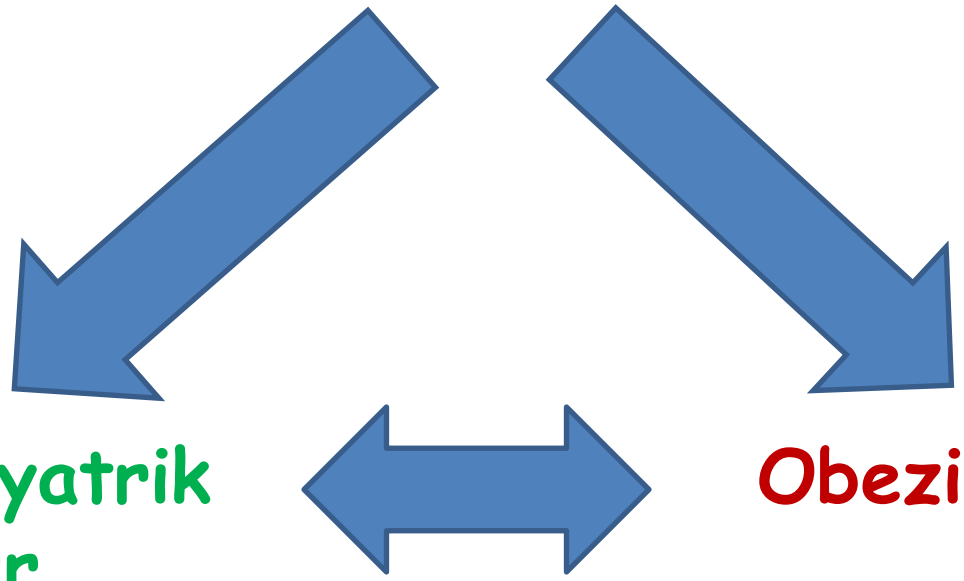
- Bu deneyim beyin ve psikiyatrik bozukluklar ile glukoz metabolizması arasındaki ilişkinin anlaşılmasında katkı sağladı

- ICT kayıtlarında, yüksek doz insulin ile nöropsikiyatrik hastalıkta çarpıcı olumlu etkiler gözlenmiştir.
- Nöropsikyatrik bozukluklar sıklıkla IR, diyabet ve obezite ile ilişkilidir.
- Nörodejeneratif hastalıklarda insülin, patogenezde oldukça önemli (Alzheimer..)
- .

BRAIN DISORDERS ASSOCIATED WITH METABOLIC DISTURBANCES

Psychiatric disorders
Bipolar disorder
Major depressive disorder
Schizophrenia
Neurodegenerative diseases
Alzheimer's disease
Huntington's disease
Parkinson's disease
Vascular dementia
Congenital neurodegenerative disorders
Alstrom syndrome
Ataxia-telangiectasia (Louis-Bar syndrome)
Bardet-Biedl syndrome
Down's syndrome
Niemann-Pick disease
Prader-Willi syndrome
Werner syndrome
Wolfram syndrome
Woodhouse-Sakati syndrome
Other congenital disorders
Familiar hyperinsulinism
Feigenbaum syndrome
Friedreich ataxia
Glut1 deficiency
Kearns-Sayre syndrome
Klinefelter syndrome
MELAS syndrome
Myotonic dystrophy 1
Narcolepsy
Spinocerebellar ataxia 3 (Machado-Joseph disease)
Spinocerebellar ataxia 6
Thiamine-responsive megaloblastic anemia syndrome
Turner syndrome

"Santral insülin etkisi"

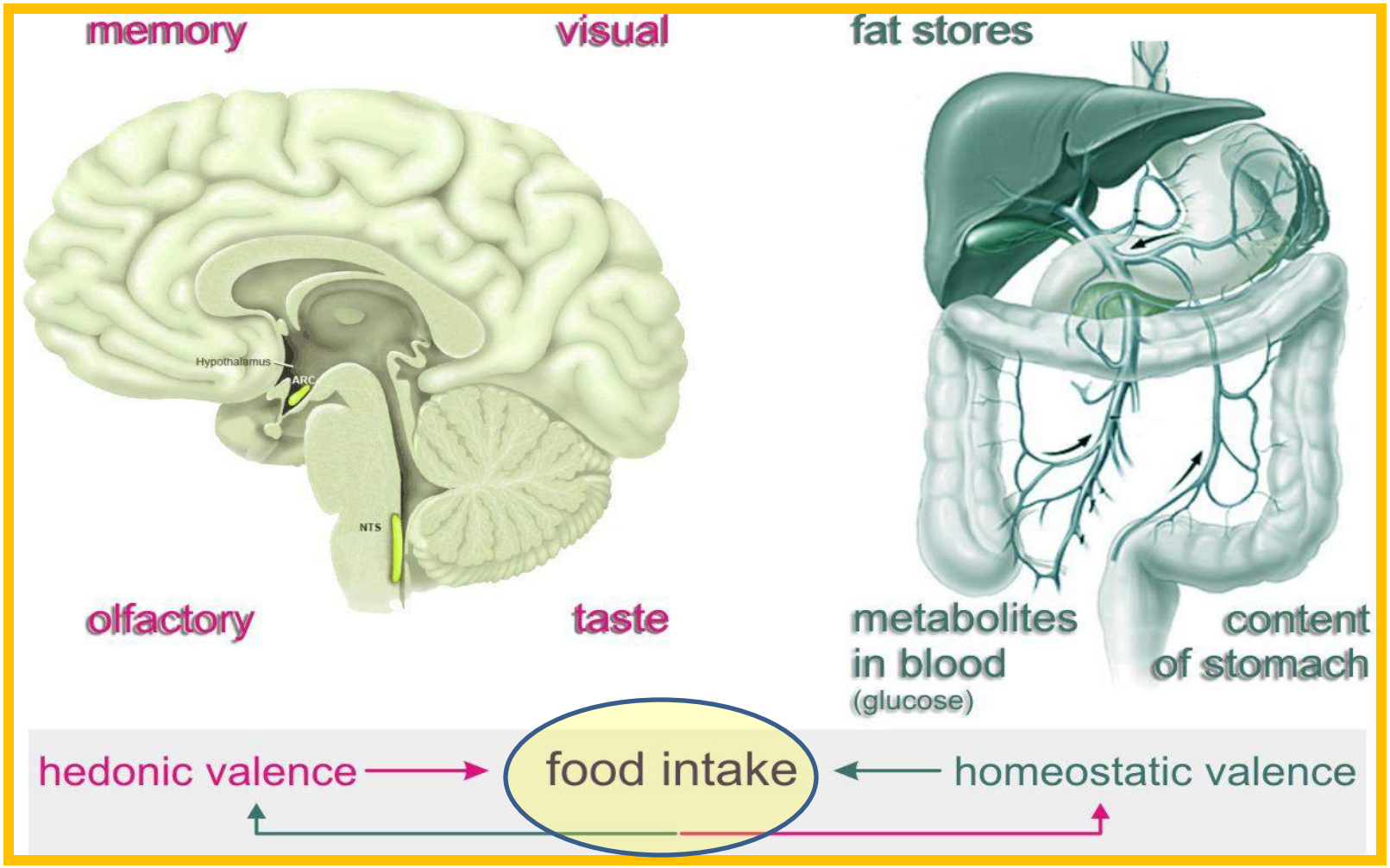


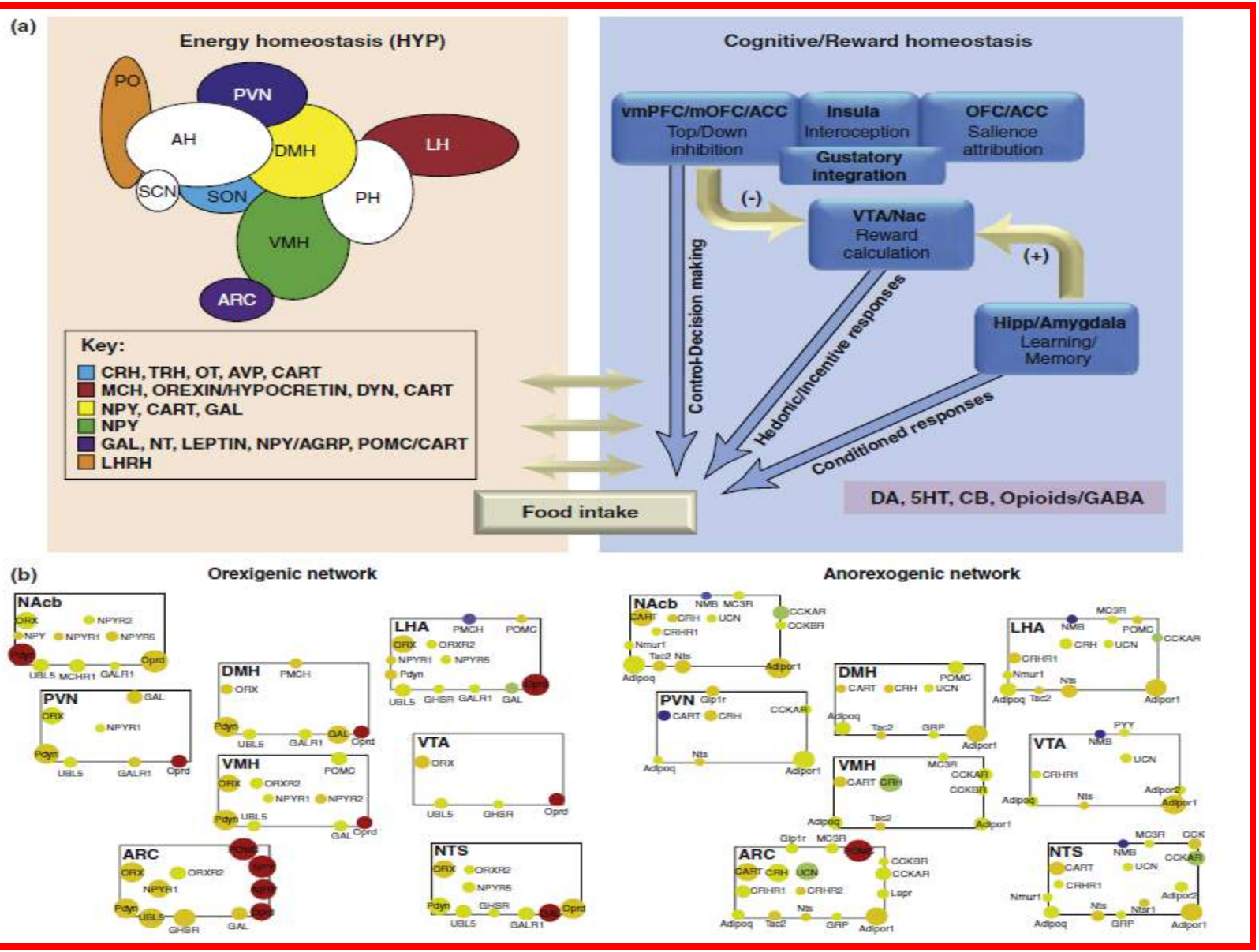
Nöropsikiyatrik hastalıklar

Obezite ve Diyabet

Gıda alımında santral insülin etkisi

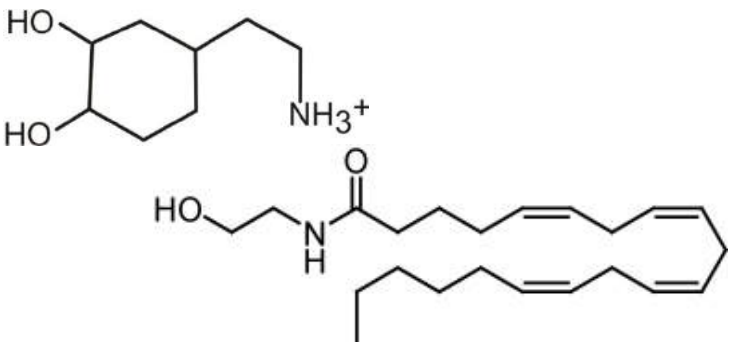
Gıda alımında homeostatik regülasyon (metabolit varlığı) ve hedonik uyarı (ödüllendirme)




(a)
Energy homeostasis (HYP)
PO
PVN
AH
DMH
LH
SCN
SON
PH
VMH
ARC
Key:
CRH, TRH, OT, AVP, CART
MCH, OREXIN/HYPOCRETIN, DYN, CART
NPY, CART, GAL
NPY
GAL, NT, LEPTIN, NPY/AGRP, POMC/CART
LHRH
Cognitive/Reward homeostasis
vmPFC/mOFC/ACC
Top/Down inhibition
Insula
Interoception
OFC/ACC
Salience attribution
Gustatory integration
(-)
VTA/Nac
Reward calculation
(+)
Hipp/Amygdala
Learning/ Memory
Control-Decision making
Hedonic/Incentive responses
Conditioned responses
Food intake
DA, 5HT, CB, Opioids/GABA
(b)
Orexigenic network
Anorexogenic network
NAcb
PVN
DMH
VMH
ARC
LHA
VTA
NTS

Gıda alımının hedonik regülasyonunda rol alan nöro-mediatörler

Dopamine, tyrosine-derived neurotransmitter



endocannabinoids ,

-anandamide , CB1 ve CB2
-2-arachidonoyl glycerol (2-AG)
-2-arachidonoyl glyceryl ethere
-N-arachidonoyl –dopamine (NADA), CB1
-Virodhamine (O-arachidonoyl-ethanolamine, OEA),

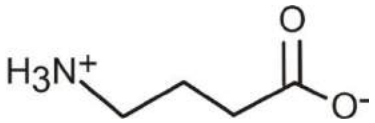
anandamide

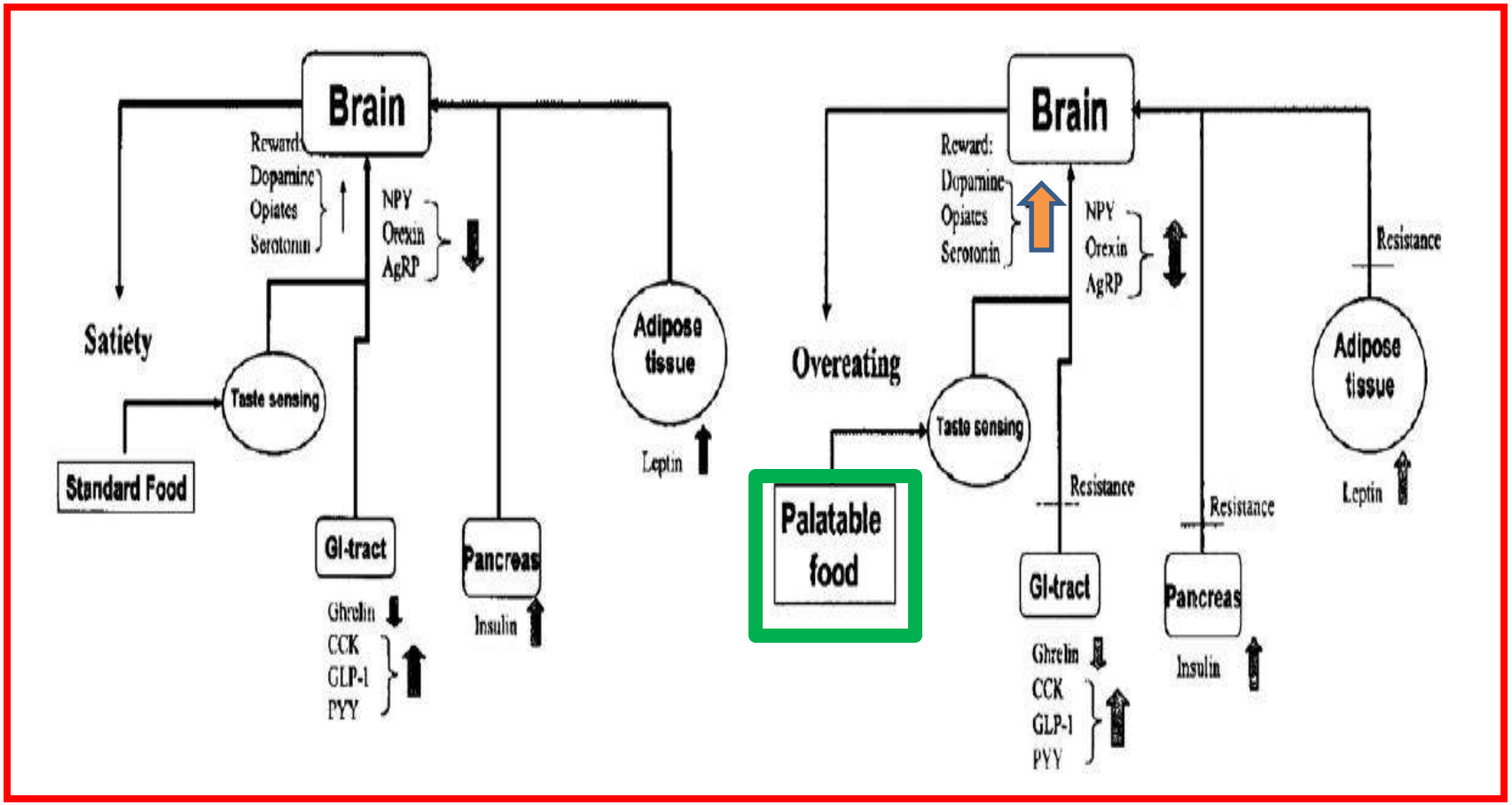
endogenous opioids,

-enkephalin

-endorphin
-dynorphin

GABA, g-aminobutyric acid, amino-acid derived neurotransmitter

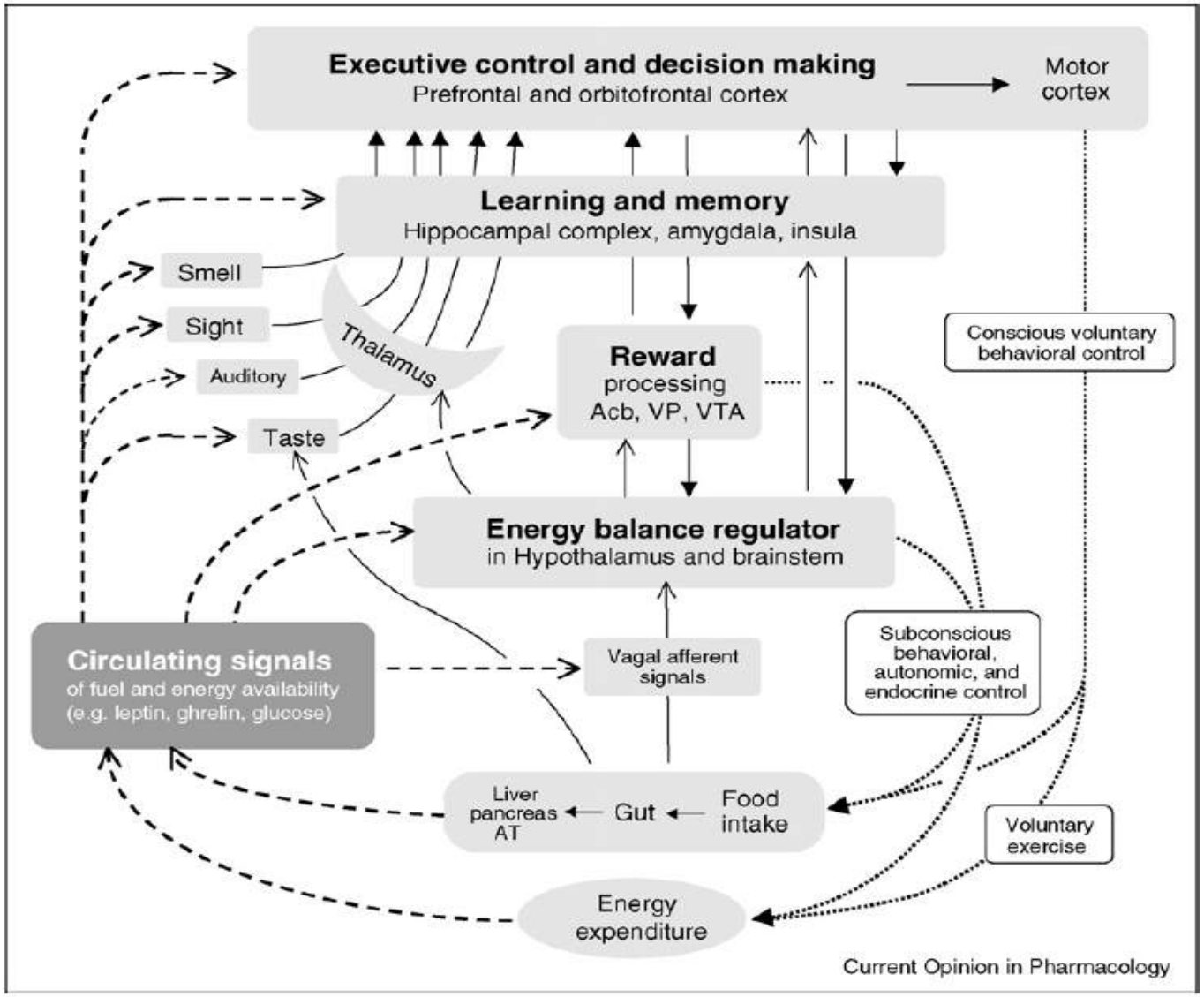


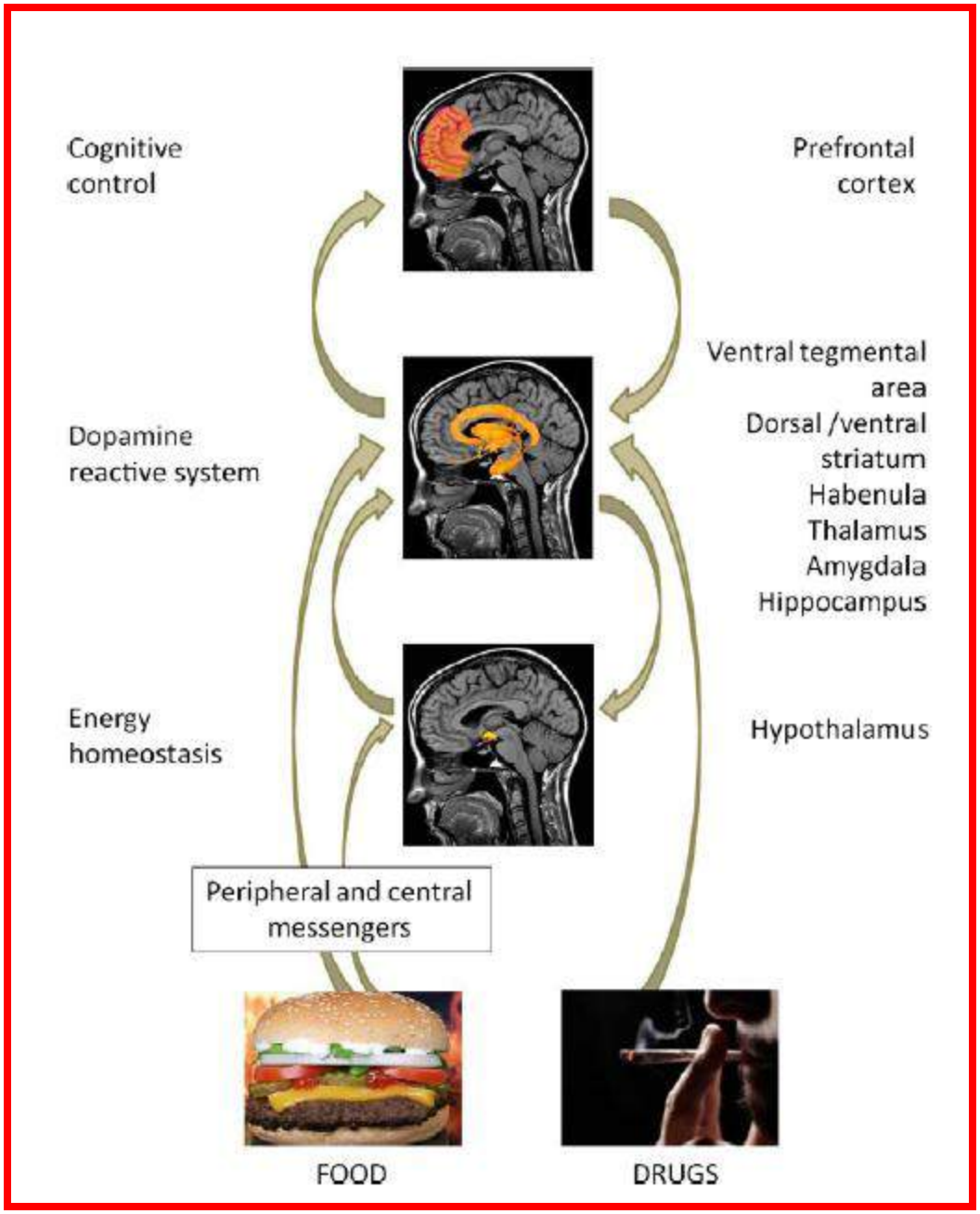


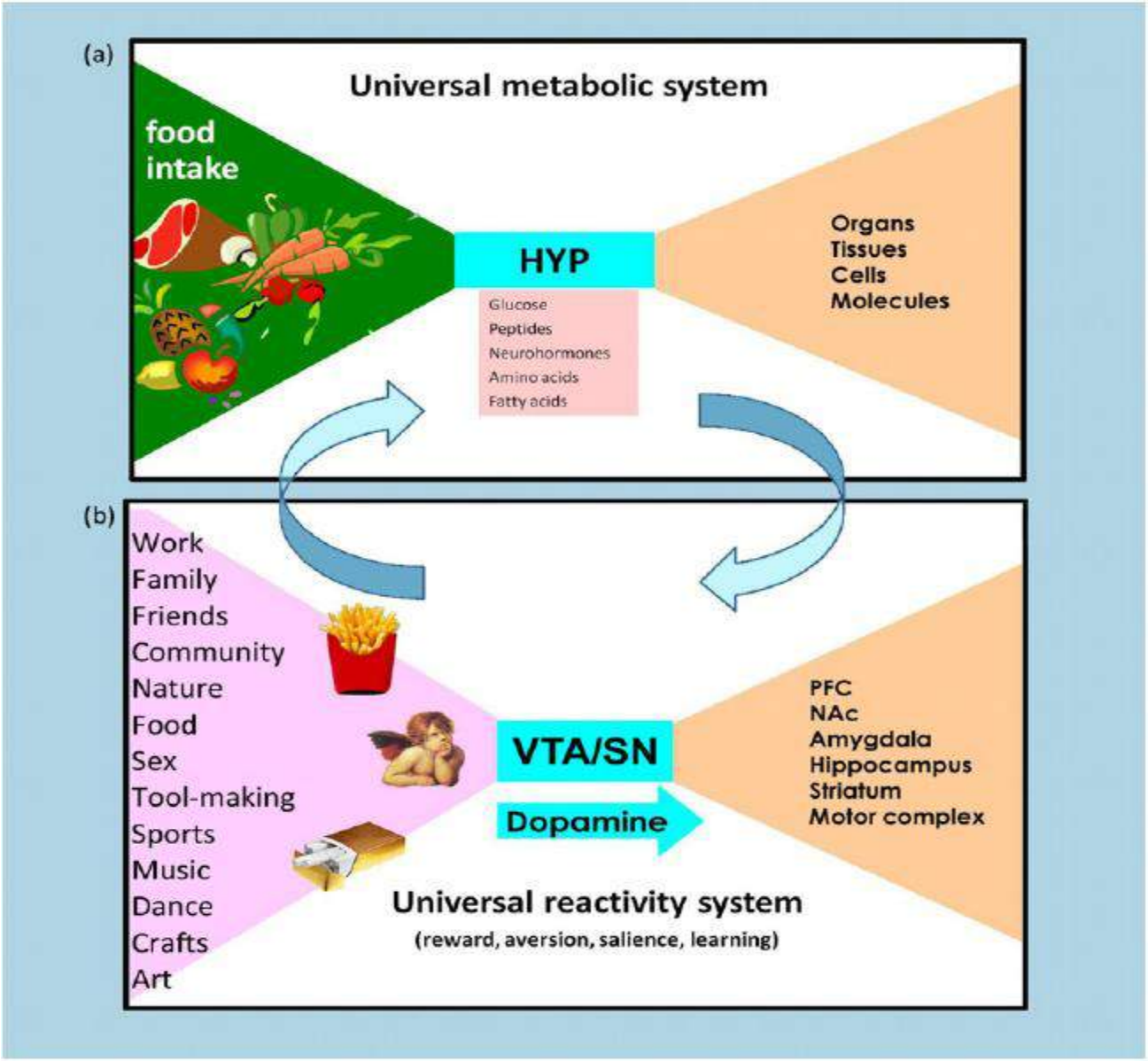
Left. *Hunger and satiety signalling during intake of a standard meal. Hunger signals, such as ghrelin in the stomach and NPY, orexin, AgRP in the hypothalamus, are depressed after intake of standard food, while satiety signals like CCK, GLP-1, PYY, insulin and leptin are raised. Food intake is terminated as a result.*

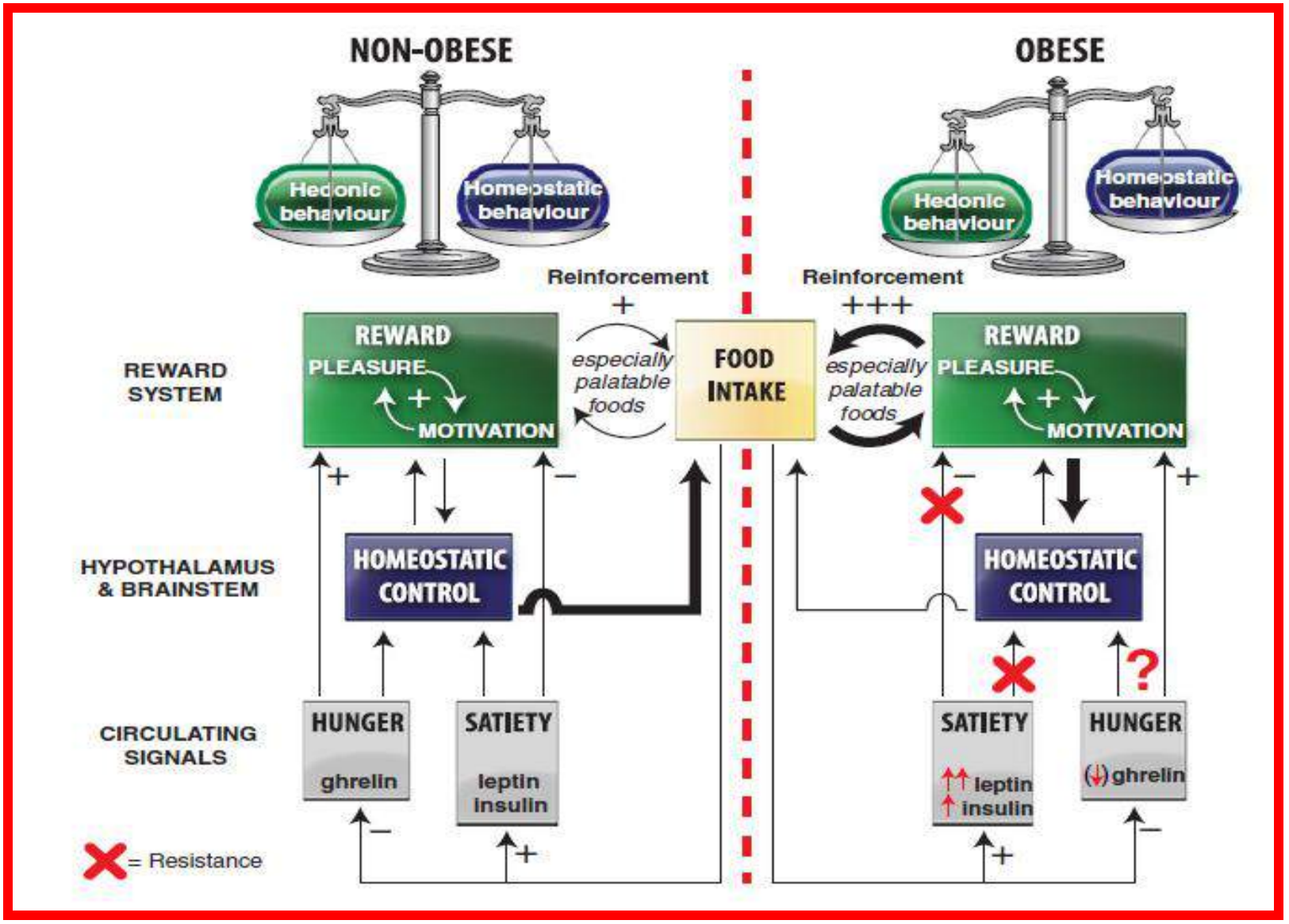
Right. *Hunger and satiety signalling after a period on a diet of palatable food. Hunger signals are either depressed, like ghrelin in the stomach and NPY in the hypothalamus, in response to a meal consisting of palatable food or raised, as for orexin and AgRP in the hypothalamus. Satiety signals like insulin and leptin are increased. Palatable food induces resistance to several satiety signals, documented for CCK, insulin and leptin, resulting in overeating. Food intake is driven by an increased activity in the reward system (dopamine, serotonin and opiates), triggered by the attractiveness of the taste.*

Neuroscience and Biobehavioral Reviews 31 (2007) 987–1002

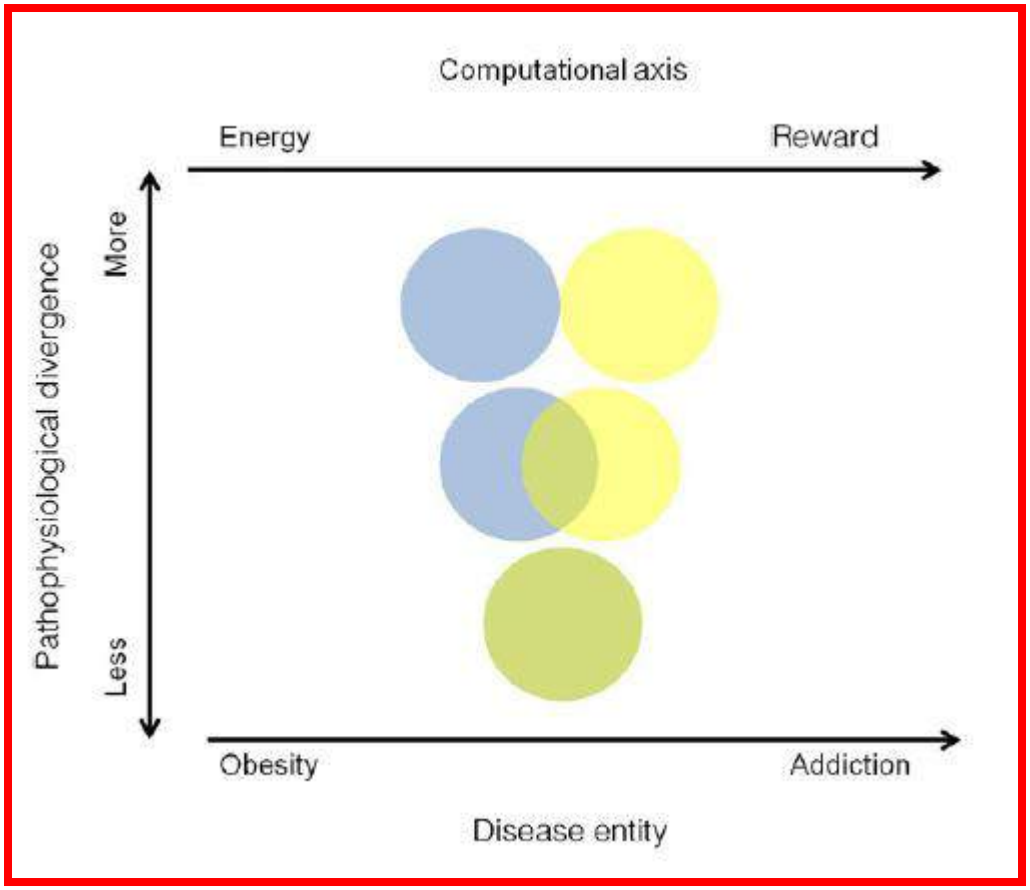

Executive control and decision making
Prefrontal and orbitofrontal cortex
Motor cortex
Learning and memory
Hippocampal complex, amygdala, insula
Smell
Sight
Auditory
Taste
Thalamus
Reward
processing
Acb, VP, VTA
Conscious voluntary behavioral control
Energy balance regulator
in Hypothalamus and brainstem
Circulating signals
of fuel and energy availability
(e.g. leptin, ghrelin, glucose)
Vagal afferent signals
Subconscious behavioral, autonomic, and endocrine control
Liver
pancreas
AT
Gut
Food intake
Voluntary exercise
Energy expenditure
Current Opinion in Pharmacology


Cognitive control
Prefrontal cortex
Ventral tegmental area
Dorsal /ventral striatum
Habenula
Thalamus
Amygdala
Hippocampus
Dopamine reactive system
Energy homeostasis
Hypothalamus
Peripheral and central messengers
FOOD
DRUGS


(a)
Universal metabolic system
food intake
HYP
Glucose
Peptides
Neurohormones
Amino acids
Fatty acids
Organs
Tissues
Cells
Molecules
(b)
Work
Family
Friends
Community
Nature
Food
Sex
Tool-making
Sports
Music
Dance
Crafts
Art
VTA/SN
Dopamine
PFC
NAc
Amygdala
Hippocampus
Striatum
Motor complex
Universal reactivity system
(reward, aversion, salience, learning)



Rev Endocr Metab Disord (2011) 12:141–151



Current Opinion in Pharmacology 2007, 7:607–612

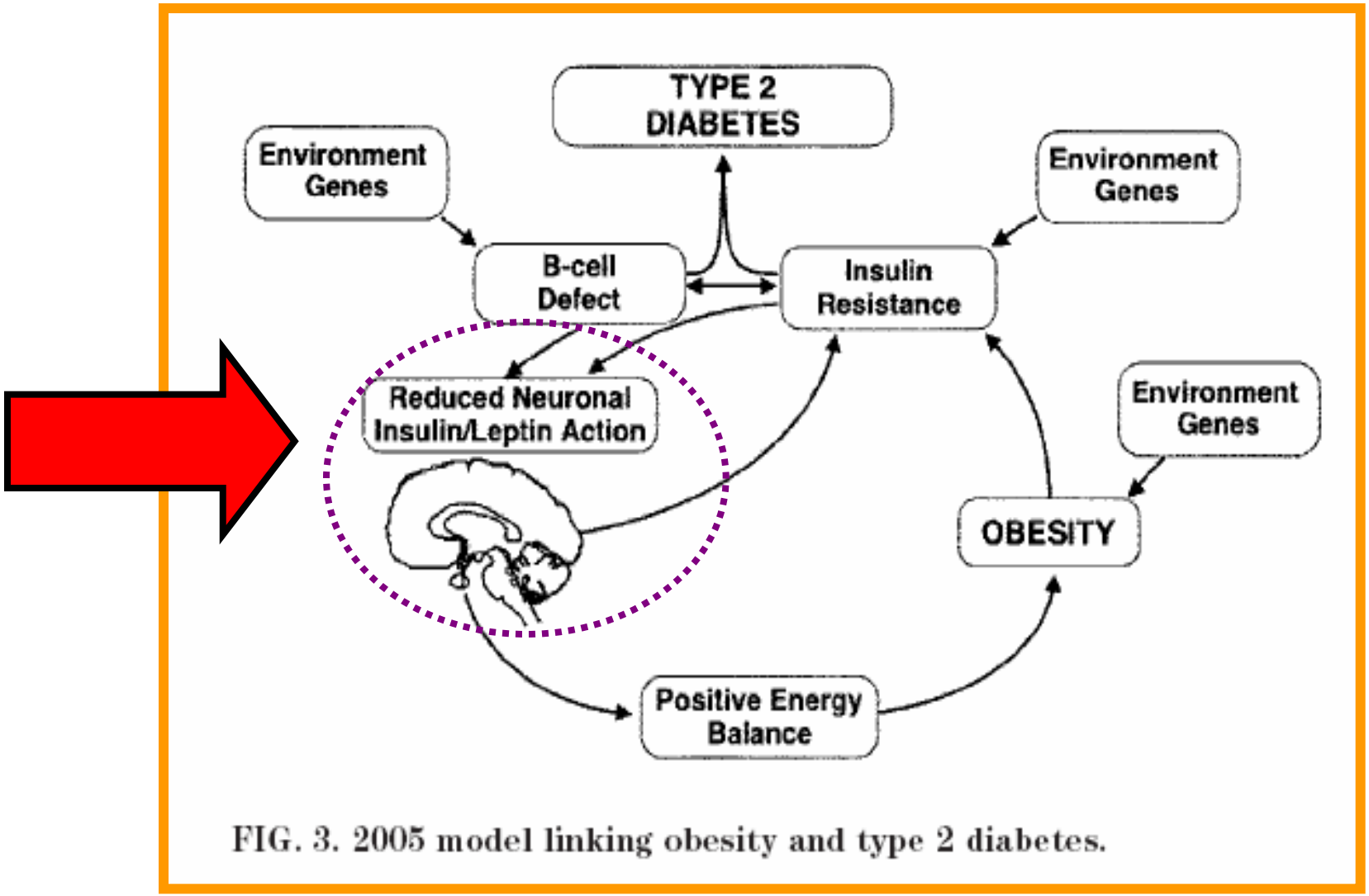
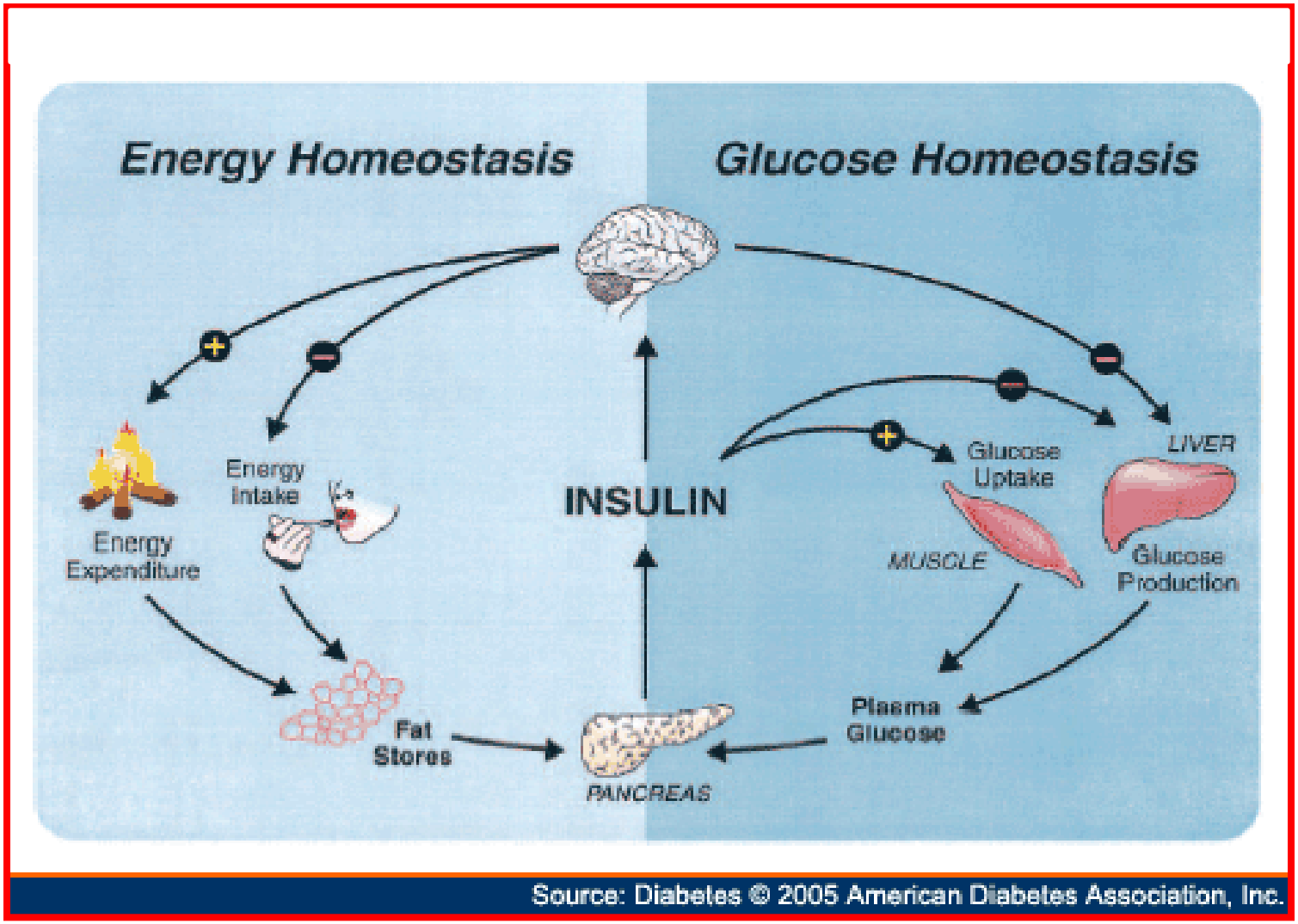
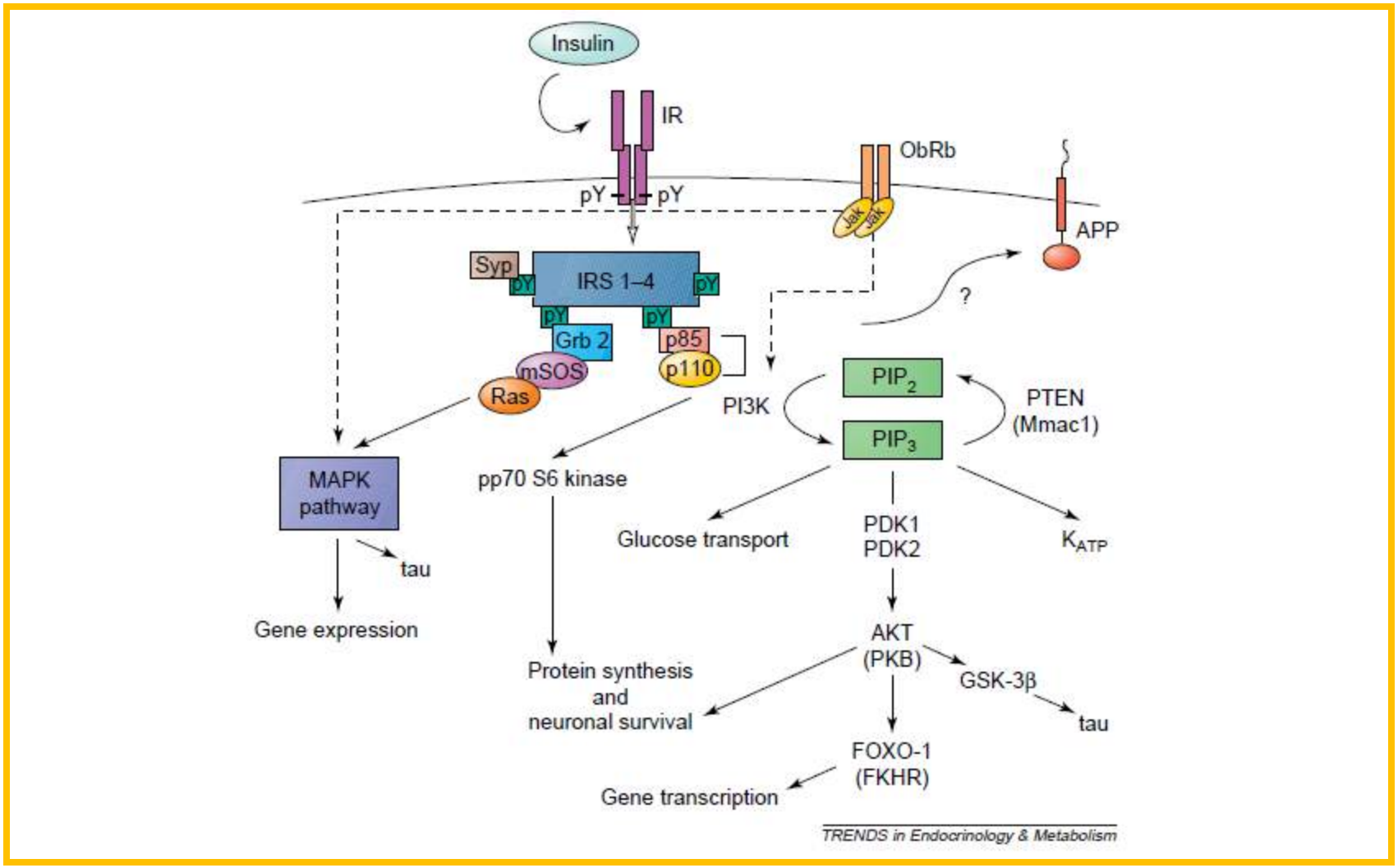
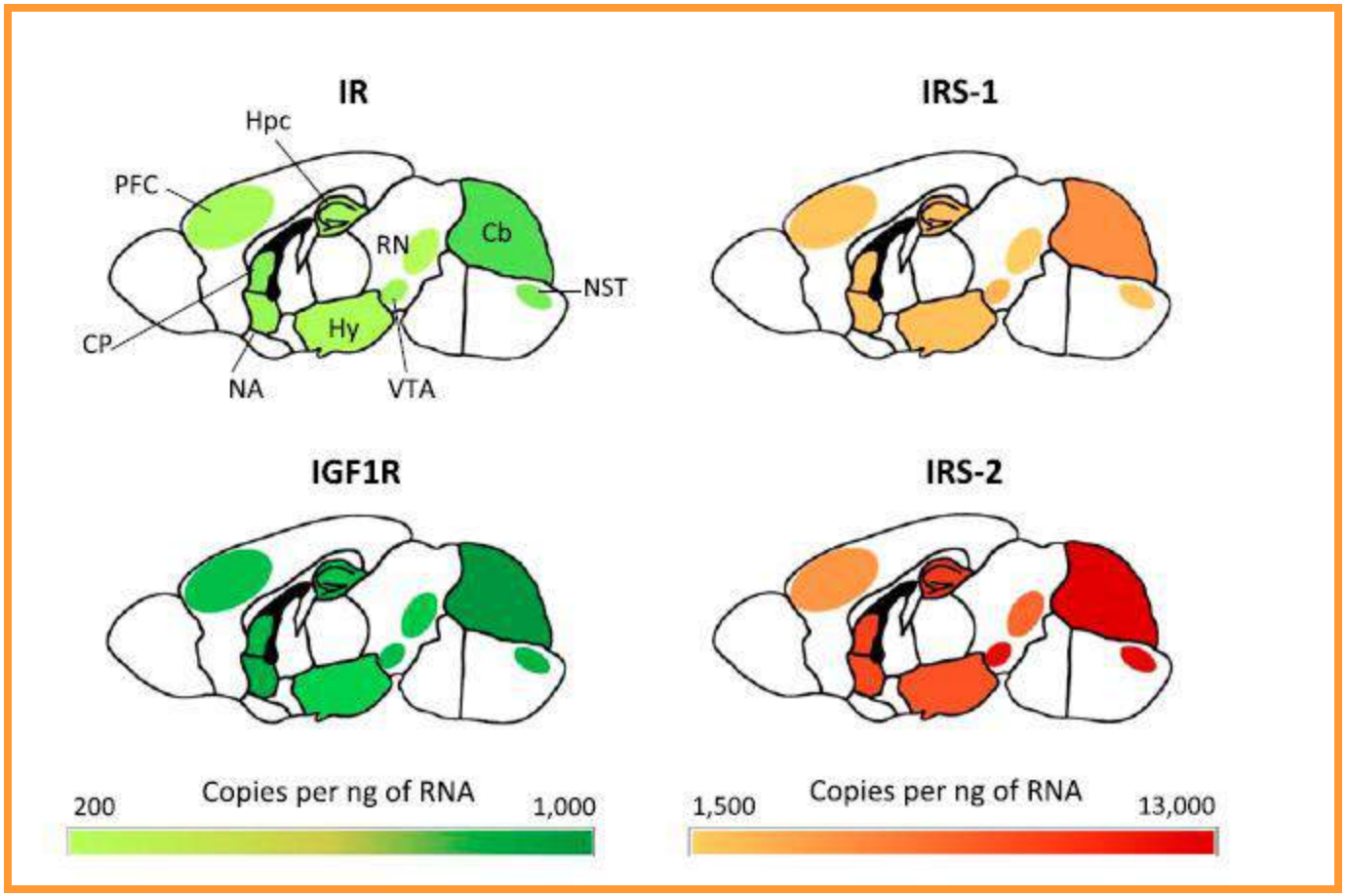


FIG. 3. 2005 model linking obesity and type 2 diabetes.



Source: Diabetes © 2005 American Diabetes Association, Inc.

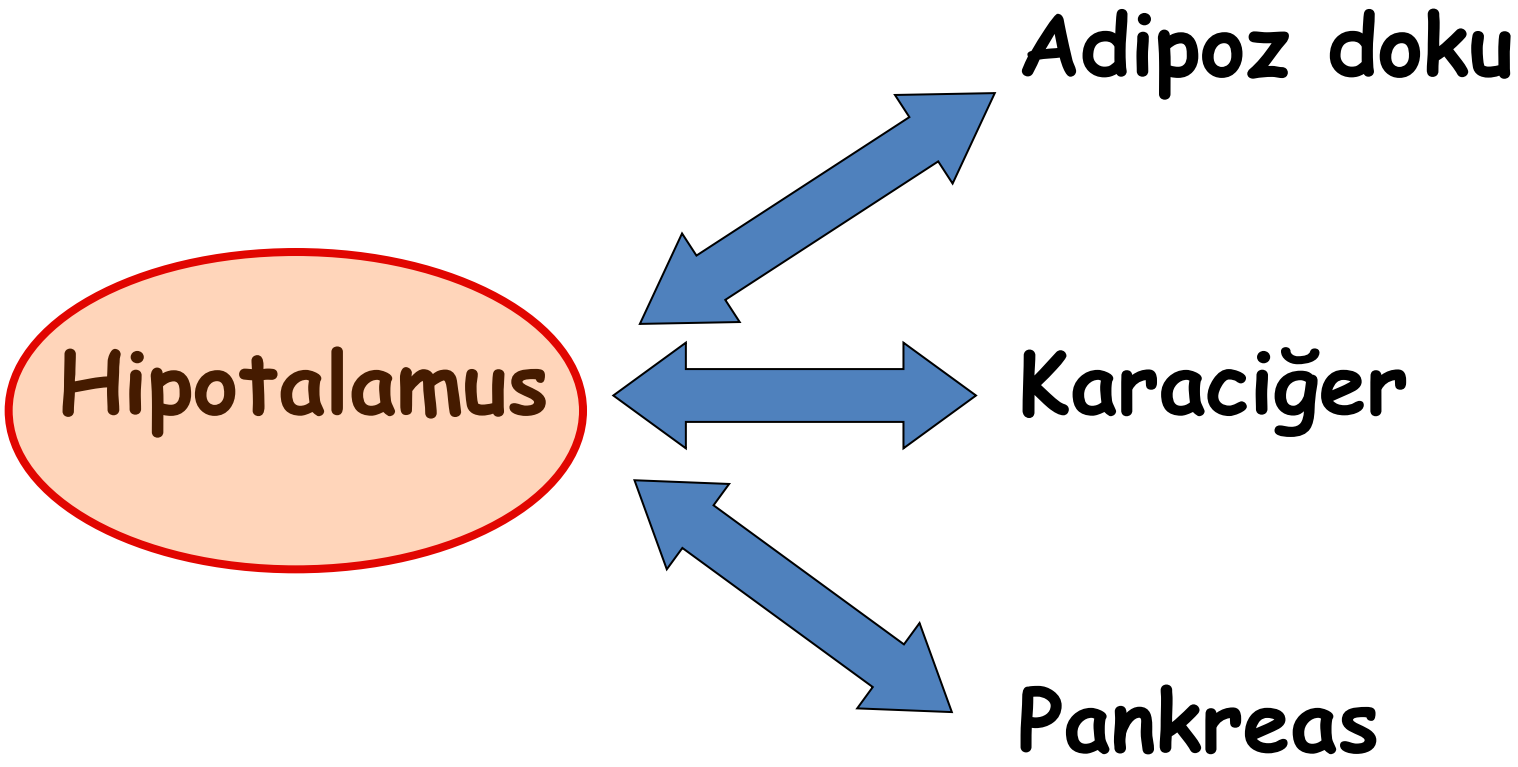

Insulin
IR
ObRb
pY
pY
Jak
Jak
APP
Syp
pY
IRS 1–4
pY
pY
pY
?
Grb 2
p85
mSOS
p110
Ras
PI3K
PIP2
PTEN
(Mmac1)
PIP3
MAPK
pathway
pp70 S6 kinase
Glucose transport
PDK1
PDK2
KATP
tau
Gene expression
AKT
(PKB)
GSK-3β
Protein synthesis
and
neuronal survival
tau
FOXO-1
(FKHR)
Gene transcription
TRENDS in Endocrinology & Metabolism

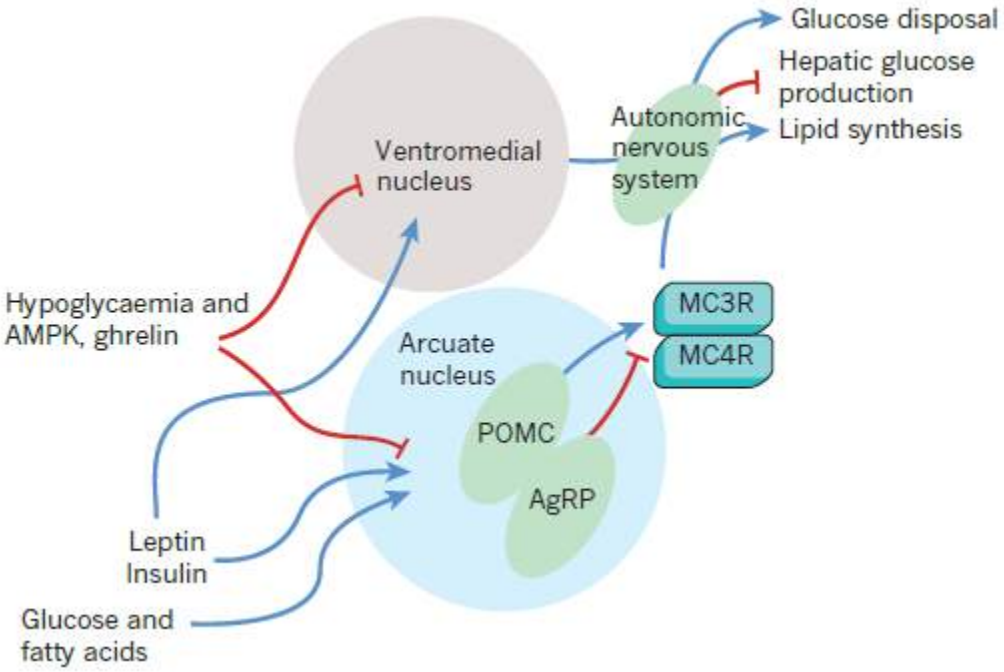

IR
Hpc
PFC
RN
Cb
NST
Hy
CP
NA
VTA
IRS-1
IGF1R
IRS-2
200
Copies per ng of RNA
1,000
1,500
Copies per ng of RNA
13,000

İnsülin reseptörü sinyal yolağının SSS'de fizyolojik fonksiyonları

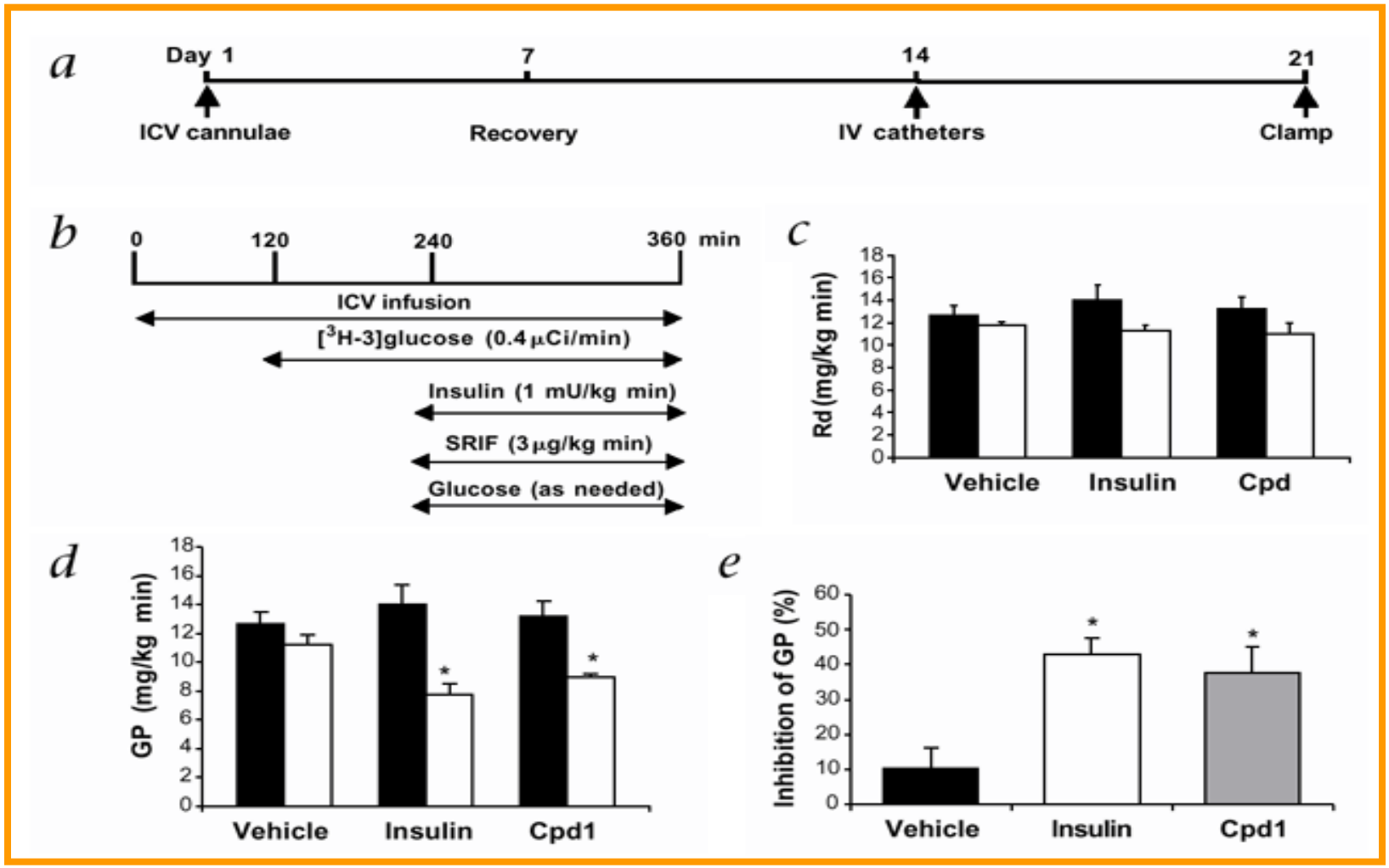
- Gıda alımı kontrolü
- Hepatik glukoneogenez inhibisyonu
- Hipoglisemide kontr-regülatuar cevap
- Reproduksiyon
- Termoregülasyon
- Tau fosforilayonunun modülasyonu
- APP ve beta amyloid klerensi
- Nöronal sağkalım
- Hafıza

-Adipositokinler
-Nöropeptidler
-Otonom sinir sistemi

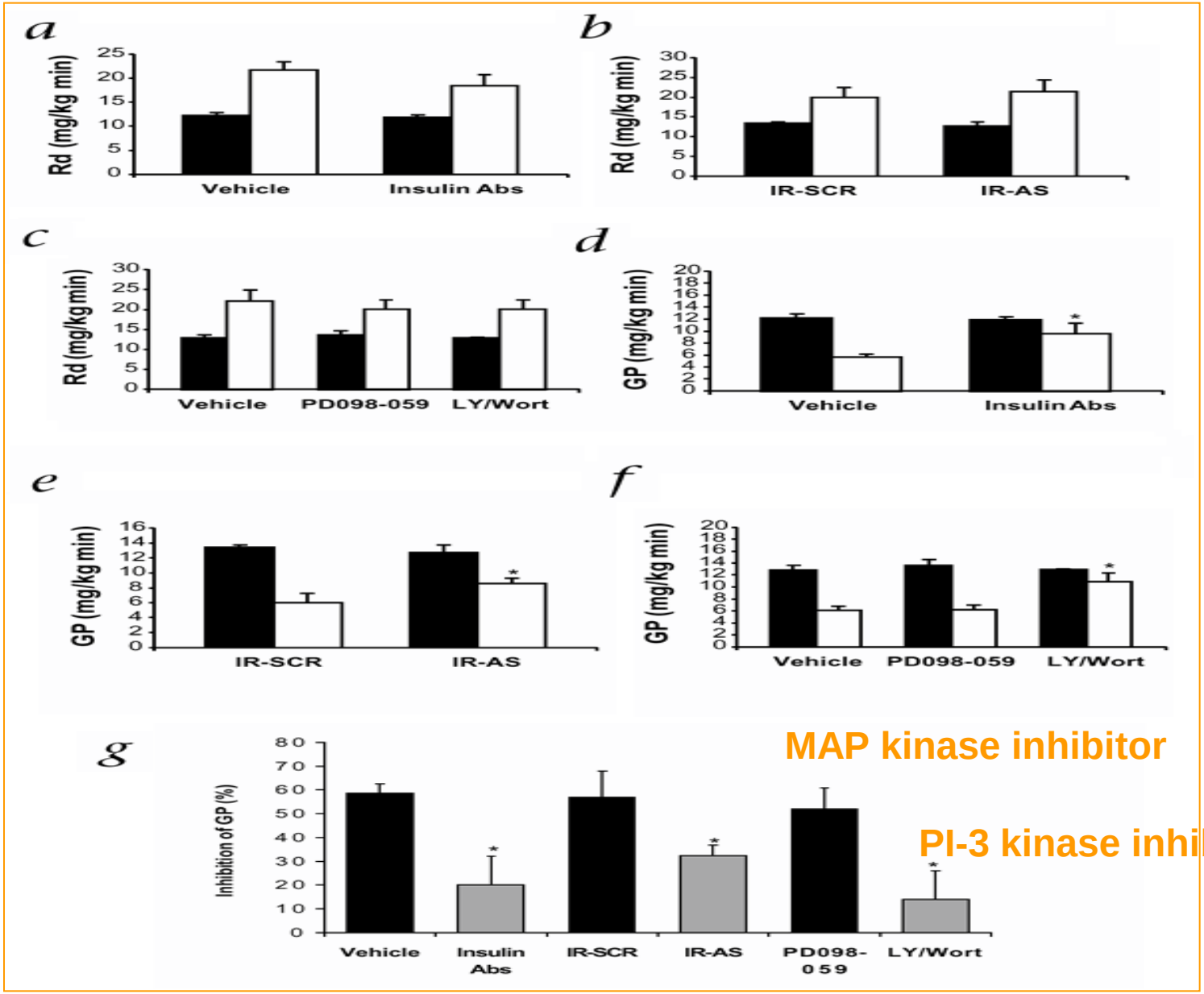



Glucose disposal
Hepatic glucose production
Lipid synthesis
Autonomic nervous system
Ventromedial nucleus
Hypoglycaemia and AMPK, ghrelin
Arcuate nucleus
MC3R
MC4R
POMC
AgRP
Leptin
Insulin
Glucose and fatty acids

"Hypothalamic insulin signaling is required for inhibition of hepatic glucose production"

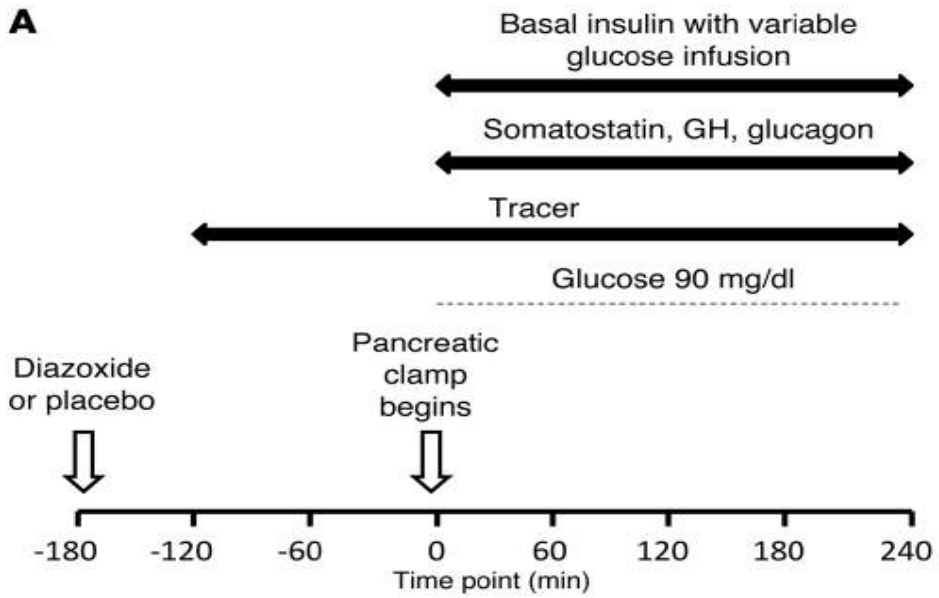


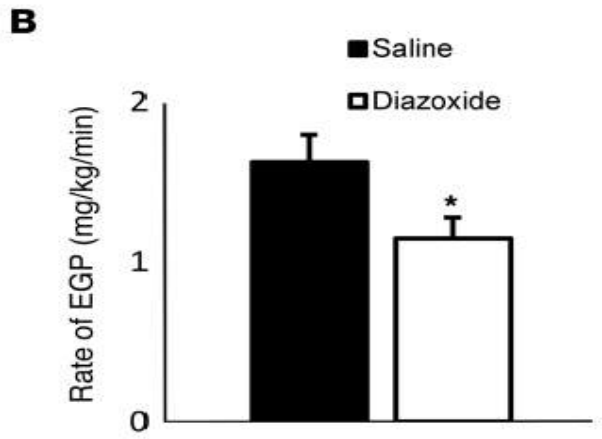
Obici S et al. Nature Medicine **8, 1376 - 1382 (2002)**

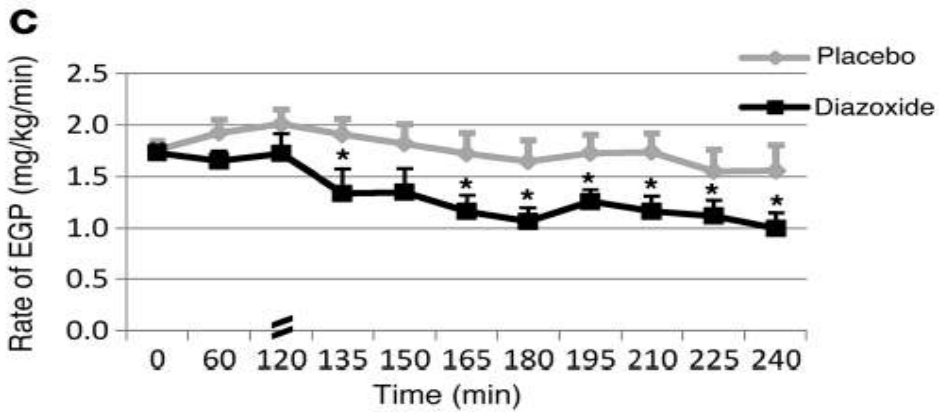


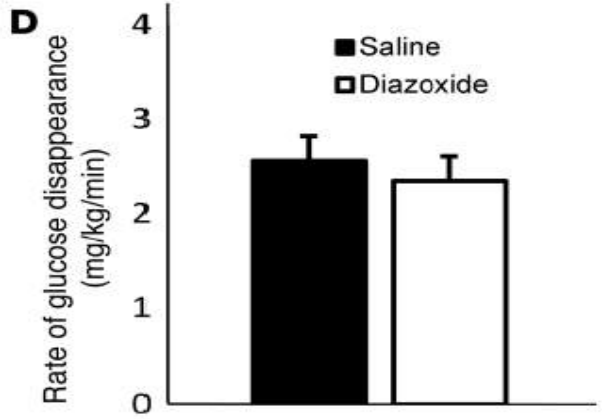
Obici S et al. Nature Medicine **8, 1376 - 1382 (2002)**

Activation of K_{ATP} channels suppresses glucose production in humans

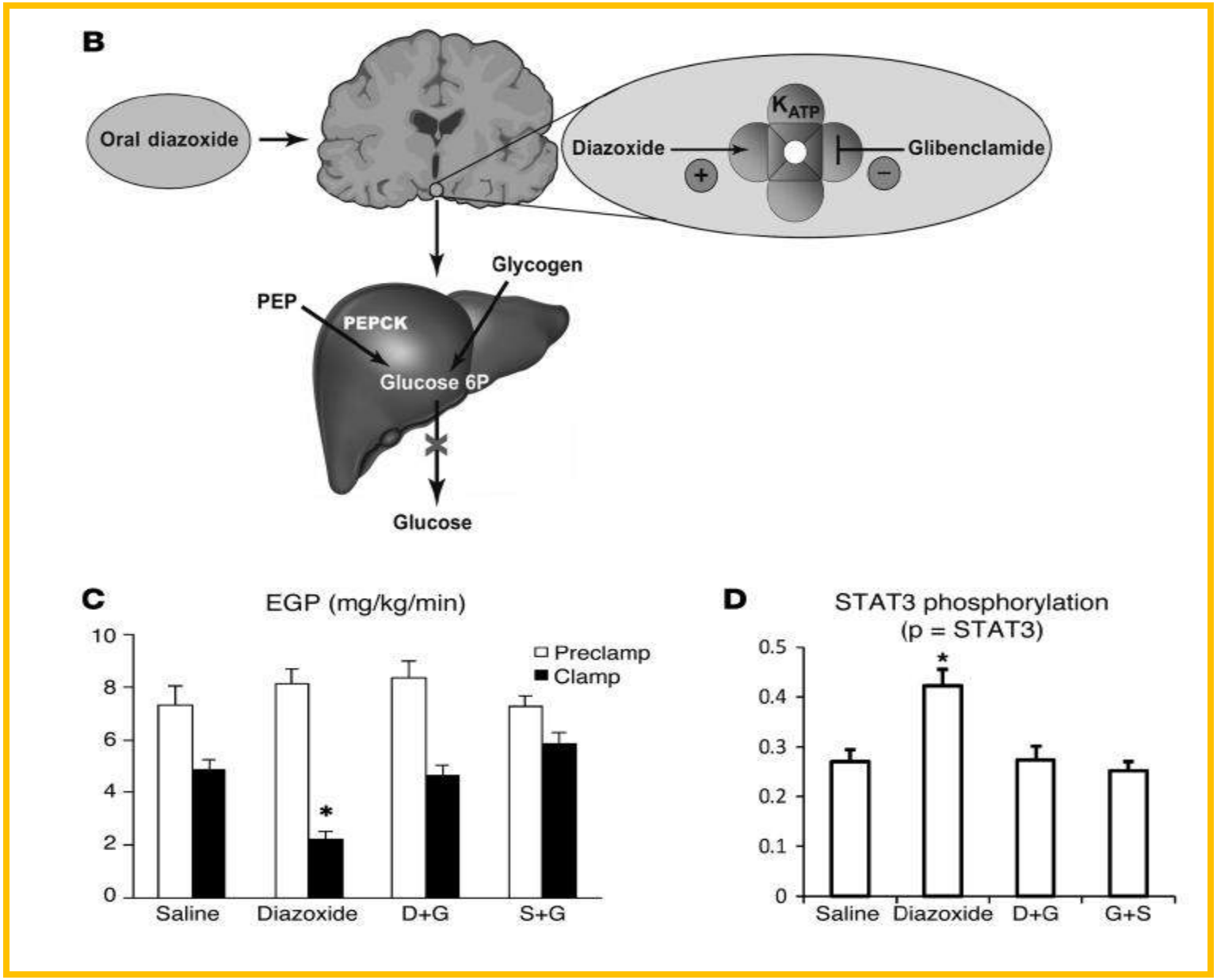






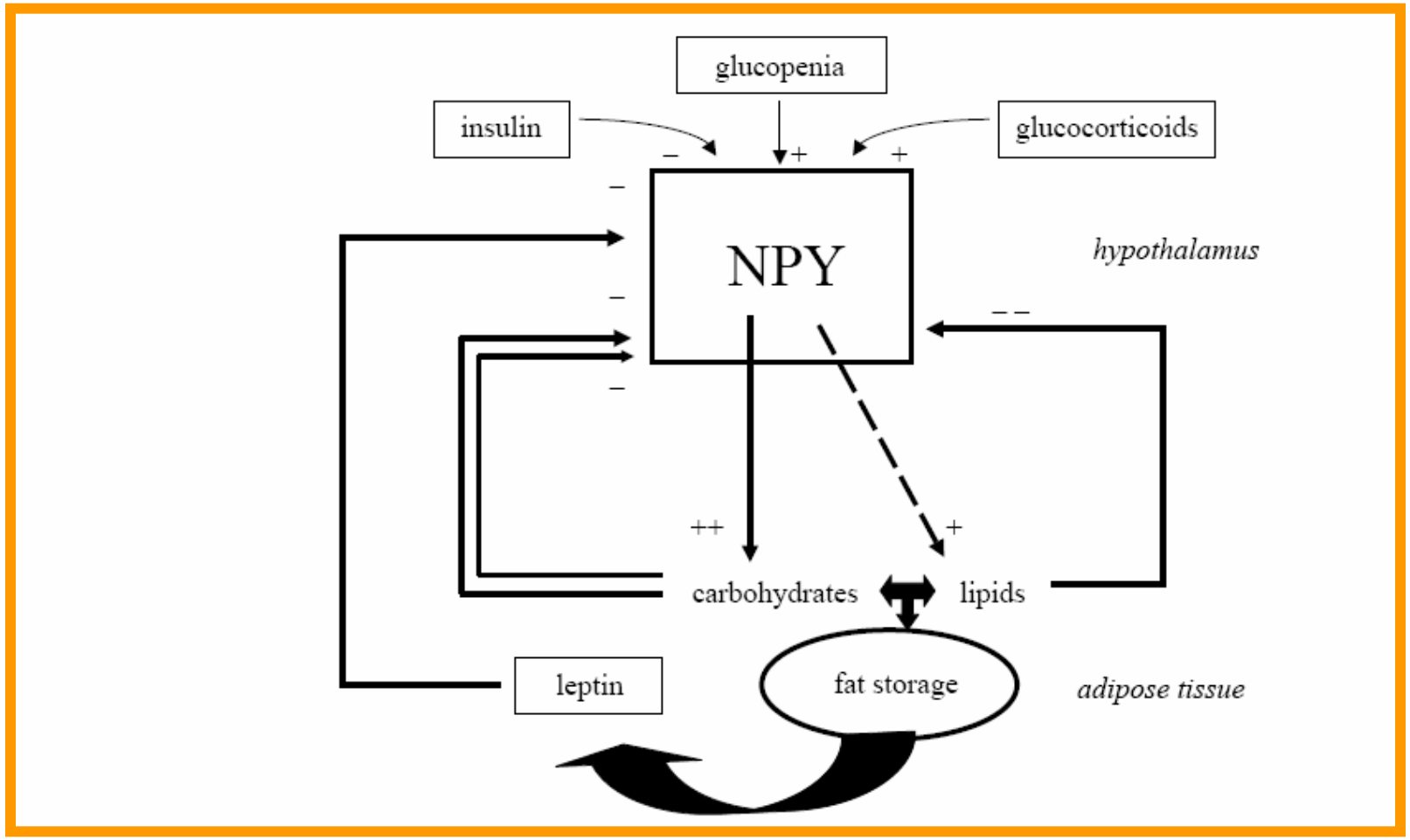


Effects of K_{ATP} channel activation on EGP in humans.

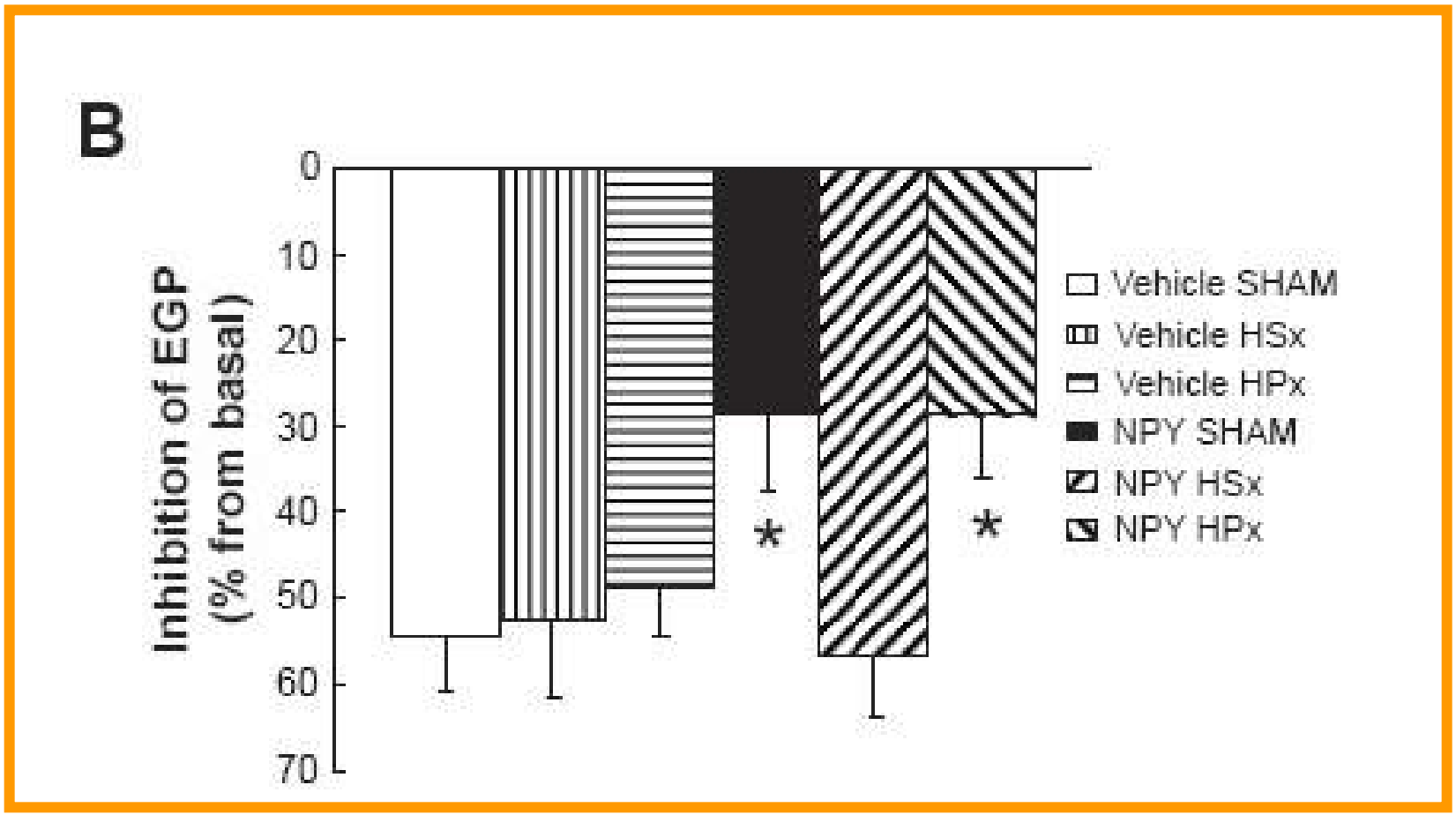

B
Oral diazoxide
K_{ATP}
Diazoxide
Glibenclamide
+
−
Glycogen
PEP
PEPCK
Glucose 6P
Glucose
C
EGP (mg/kg/min)
10
8
6
4
2
0
Preclamp
Clamp
*
Saline
Diazoxide
D+G
S+G
D
STAT3 phosphorylation
(p = STAT3)
0.5
0.4
0.3
0.2
0.1
0
*
Saline
Diazoxide
D+G
G+S

Nöropeptid Y

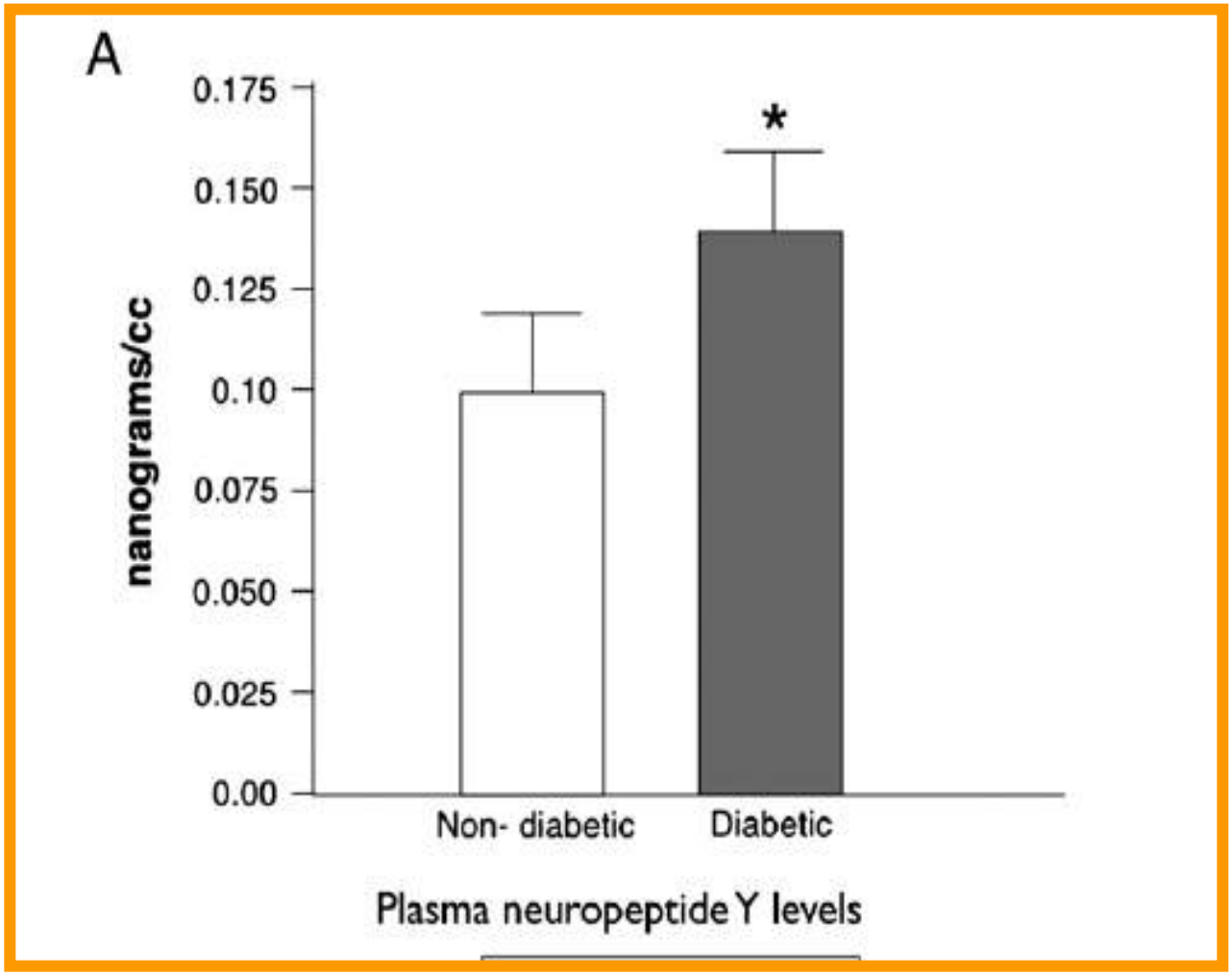
- Distal ince barsaklarda ve santral sistemde yaygın bulunan bir nöropeptiddir.
- Beyindeki en potent oreksijenik peptiddir.


glucopenia
insulin
glucocorticoids
NPY
hypothalamus
carbohydrates
lipids
leptin
fat storage
adipose tissue

Intracerebroventricular Administration of Neuropeptide Y Induces Hepatic Insulin Resistance via Sympathetic Innervation

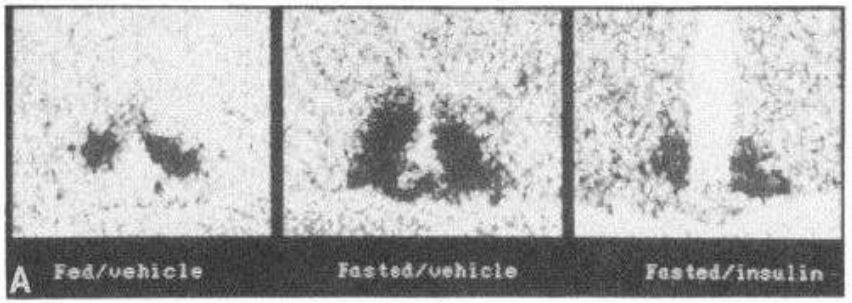


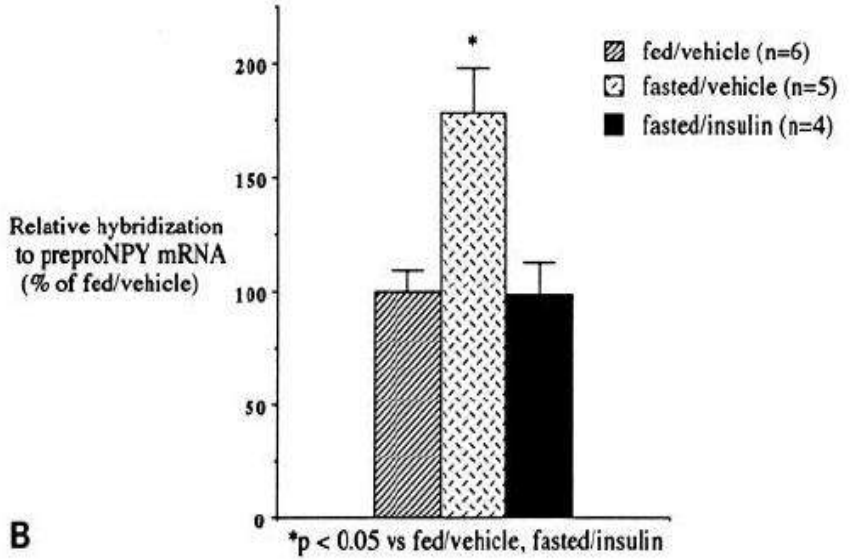
Van den Hock, Diabetes Vol.57, 2008

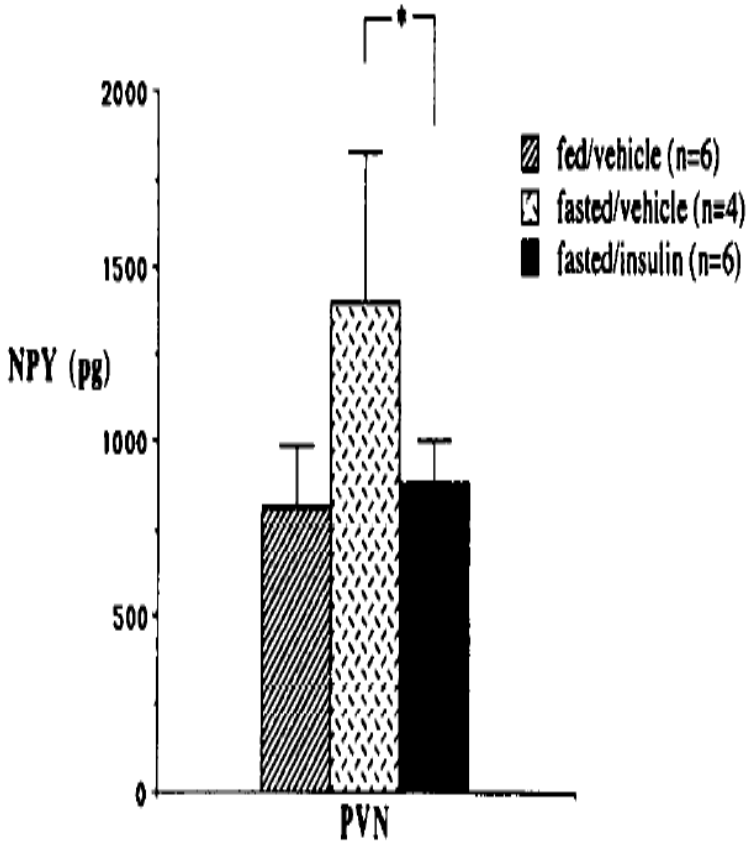


Matyal R , Eur J Pharmacol, 2011

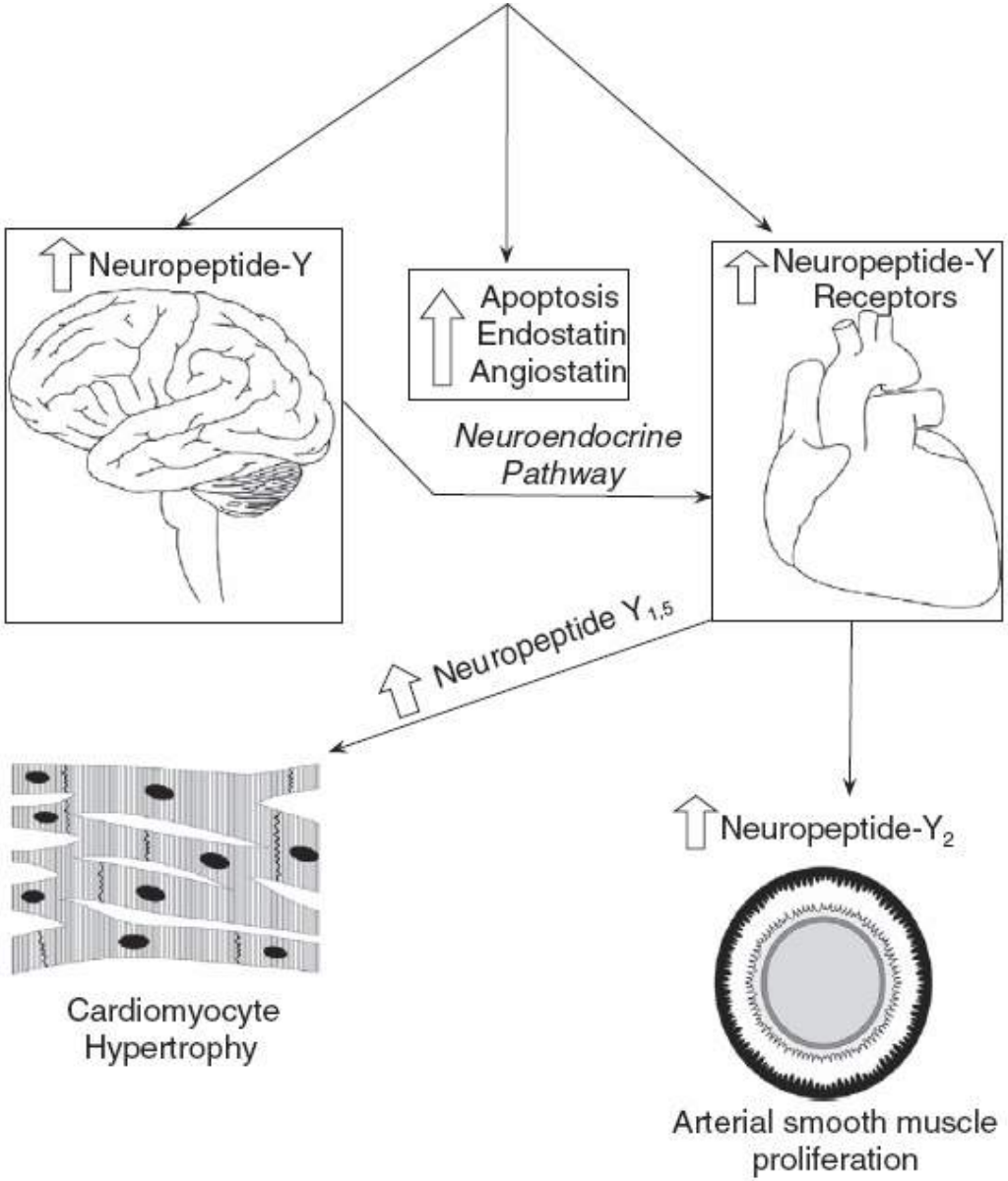
Inhibition of Hypothalamic Neuropeptide Y Gene Expression by Insulin*







Insulin -leptin eksikliği yada rezistansı



Attenuation of Diabetic Hyperphagia in Neuropeptide Y–Deficient Mice

Dana K. Sindelar,[1] Paul Mystkowski,[1] Donald J. Marsh,[2] Richard D. Palmiter,[2] and Michael W. Schwartz[1]

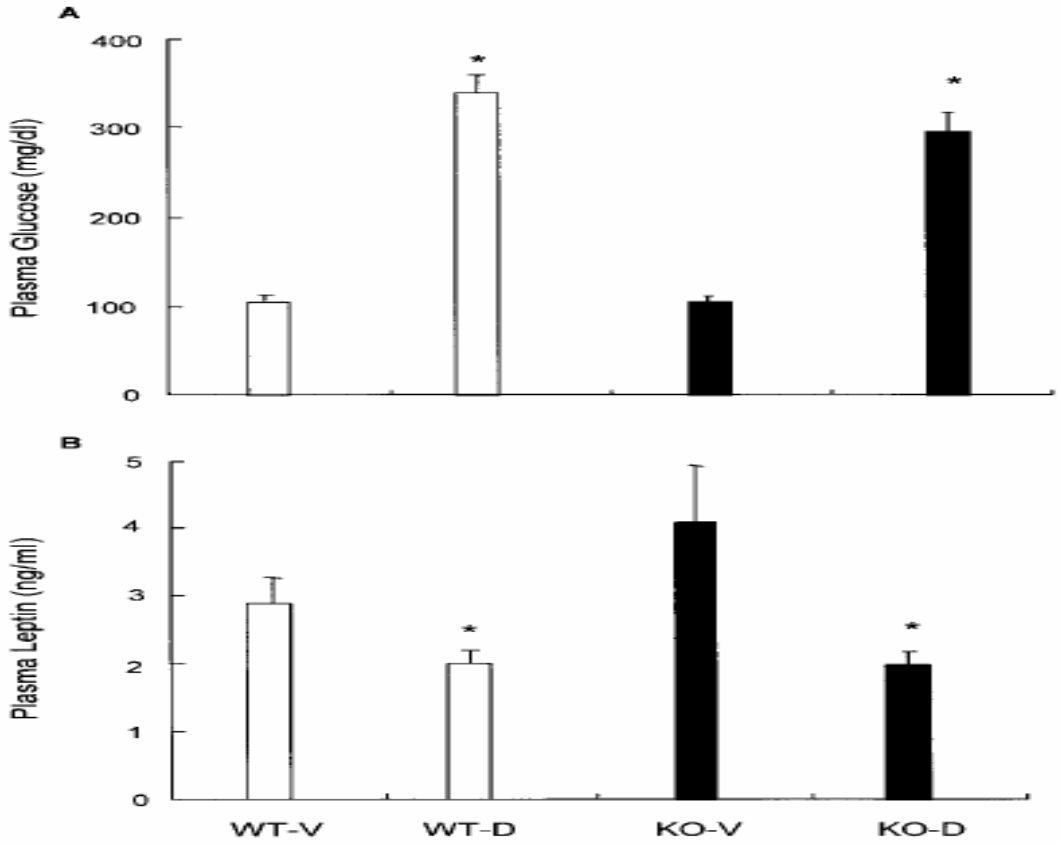
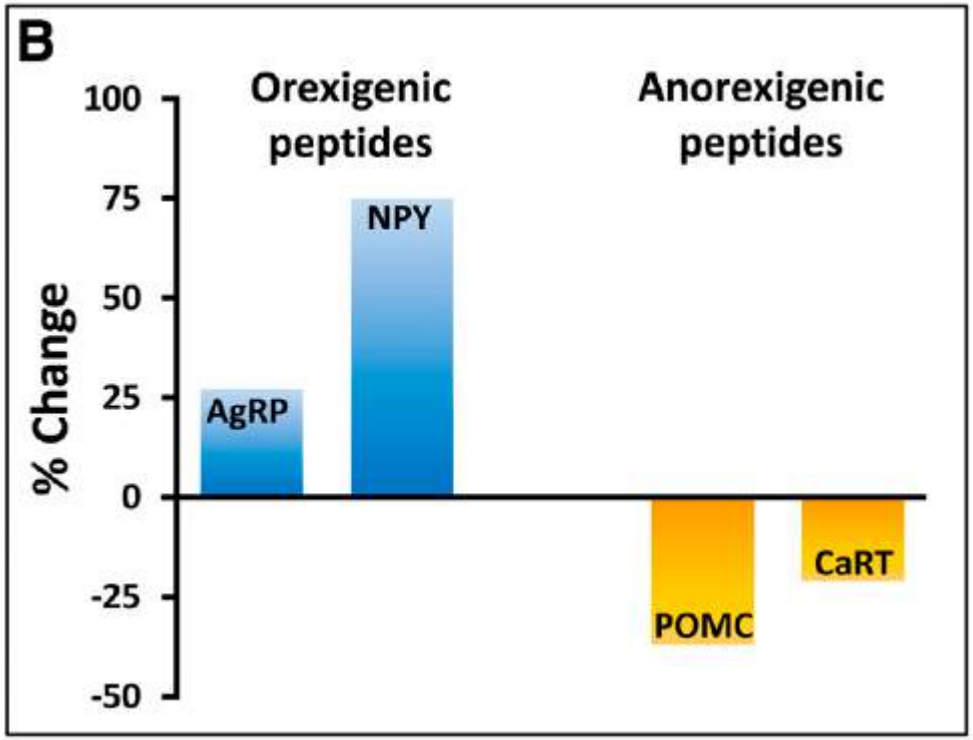
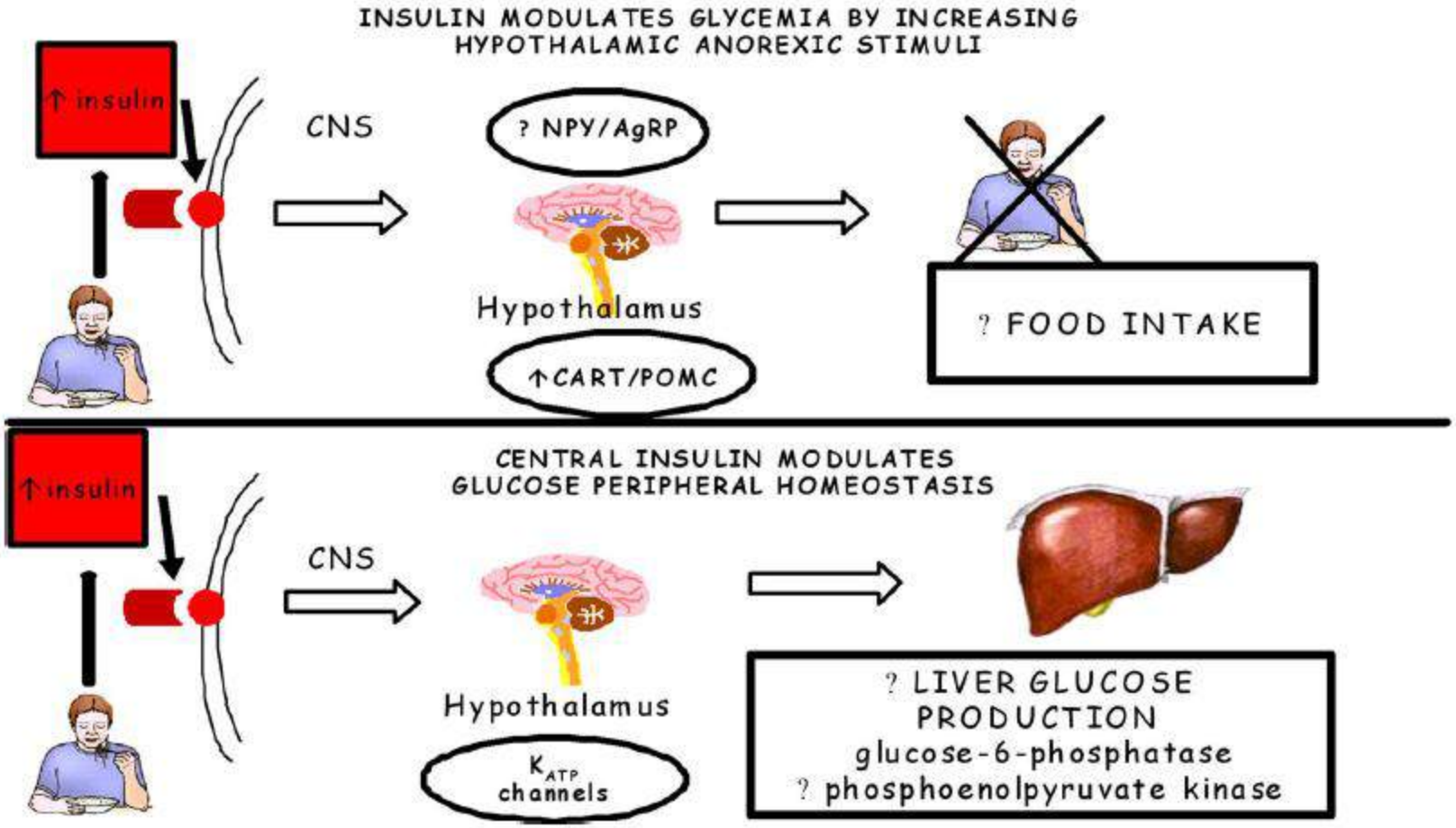


FIG. 1. Plasma glucose and leptin levels in $Npy^{-/-}$ (KO) and $Npy^{+/+}$ (WT) mice. Plasma levels of glucose (*A*) and leptin (*B*) from vehicle-treated (WT-V and KO-V; $n = 7$ per genotype) or STZ-diabetic (WT-D and KO-D; $n = 6$ per genotype) mice obtained on day 18 of experiment 1. $^*P \leq 0.05$ vs. vehicle-treated controls.



Santral insülin eksikliği yada direnci

Diabetes Volume 63, July 2014


INSULIN MODULATES GLYCEMIA BY INCREASING HYPOTHALAMIC ANOREXIC STIMULI
↑ insulin
CNS
? NPY/AgRP
Hypothalamus
↑CART/POMC
? FOOD INTAKE
CENTRAL INSULIN MODULATES GLUCOSE PERIPHERAL HOMEOSTASIS
↑ insulin
CNS
Hypothalamus
K_{ATP} channels
? LIVER GLUCOSE PRODUCTION
glucose-6-phosphatase
? phosphoenolpyruvate kinase

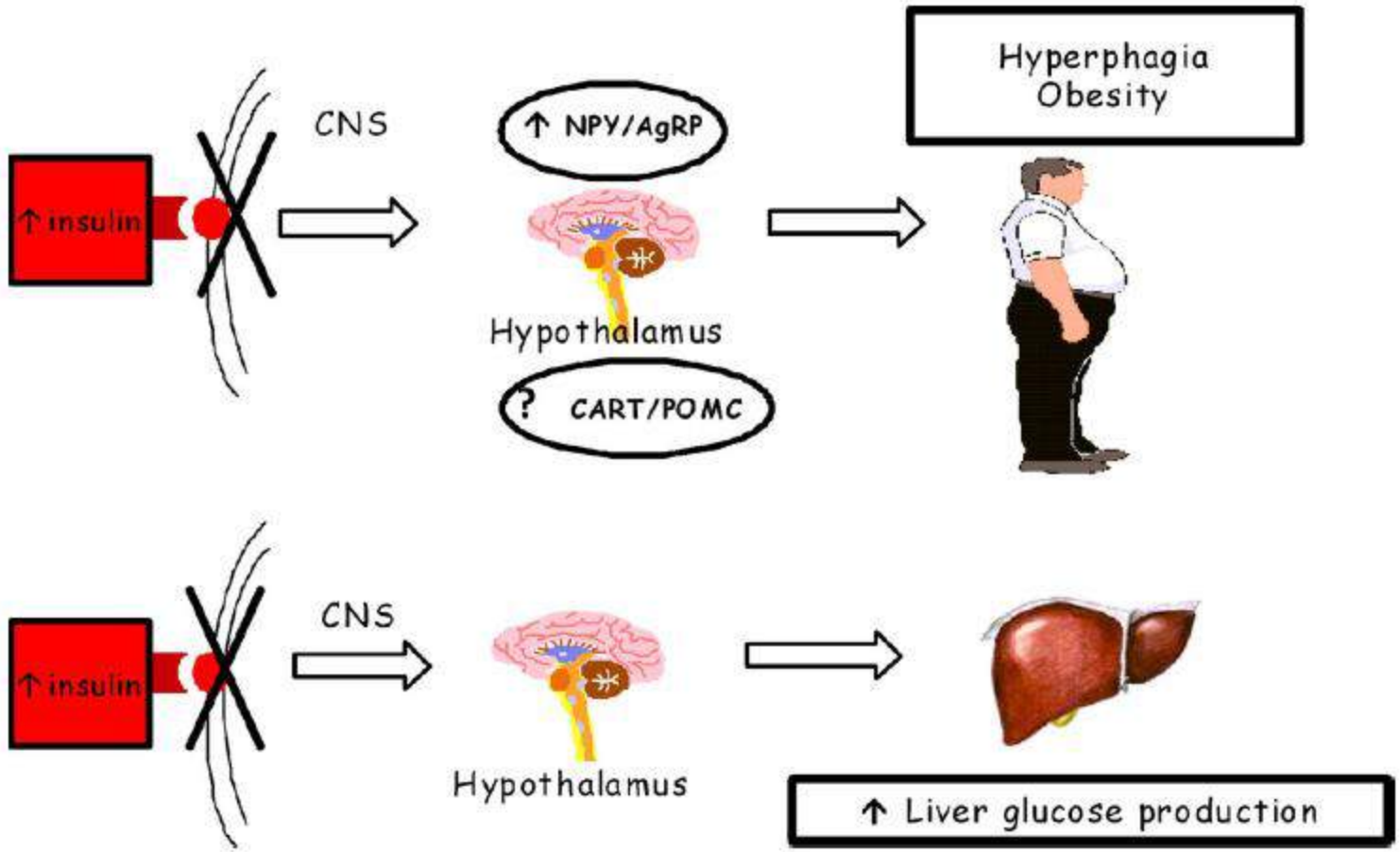


Figure 2—*The consequences of central insulin resistance are depicted. An impairment of insulin signaling in the CNS may lead to hyperphagia, weight gain, and consequently to hyperinsulinemia* (upper part), *but also to a dysregulation of plasma glucose levels for the potentiation of gluconeogenesis.*

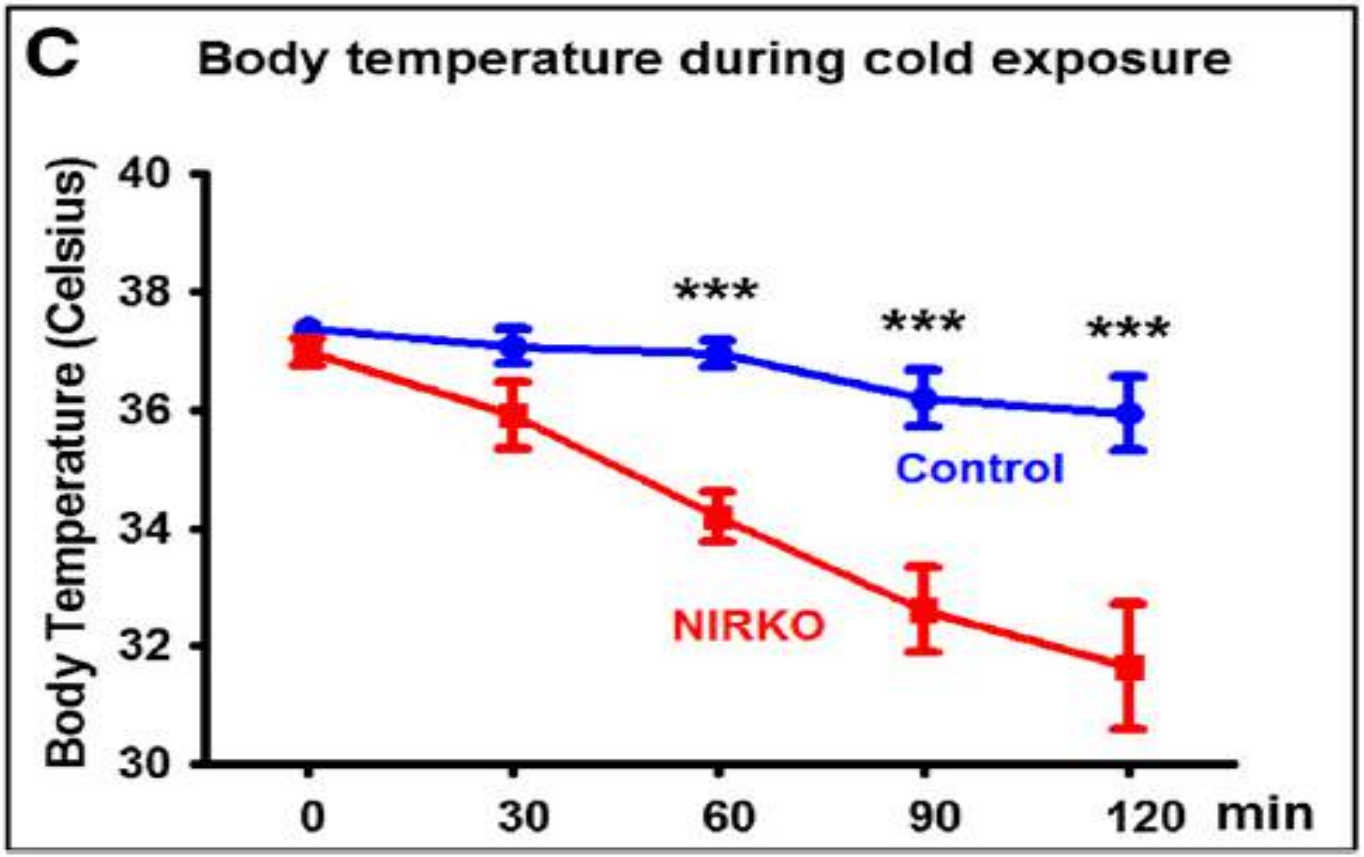
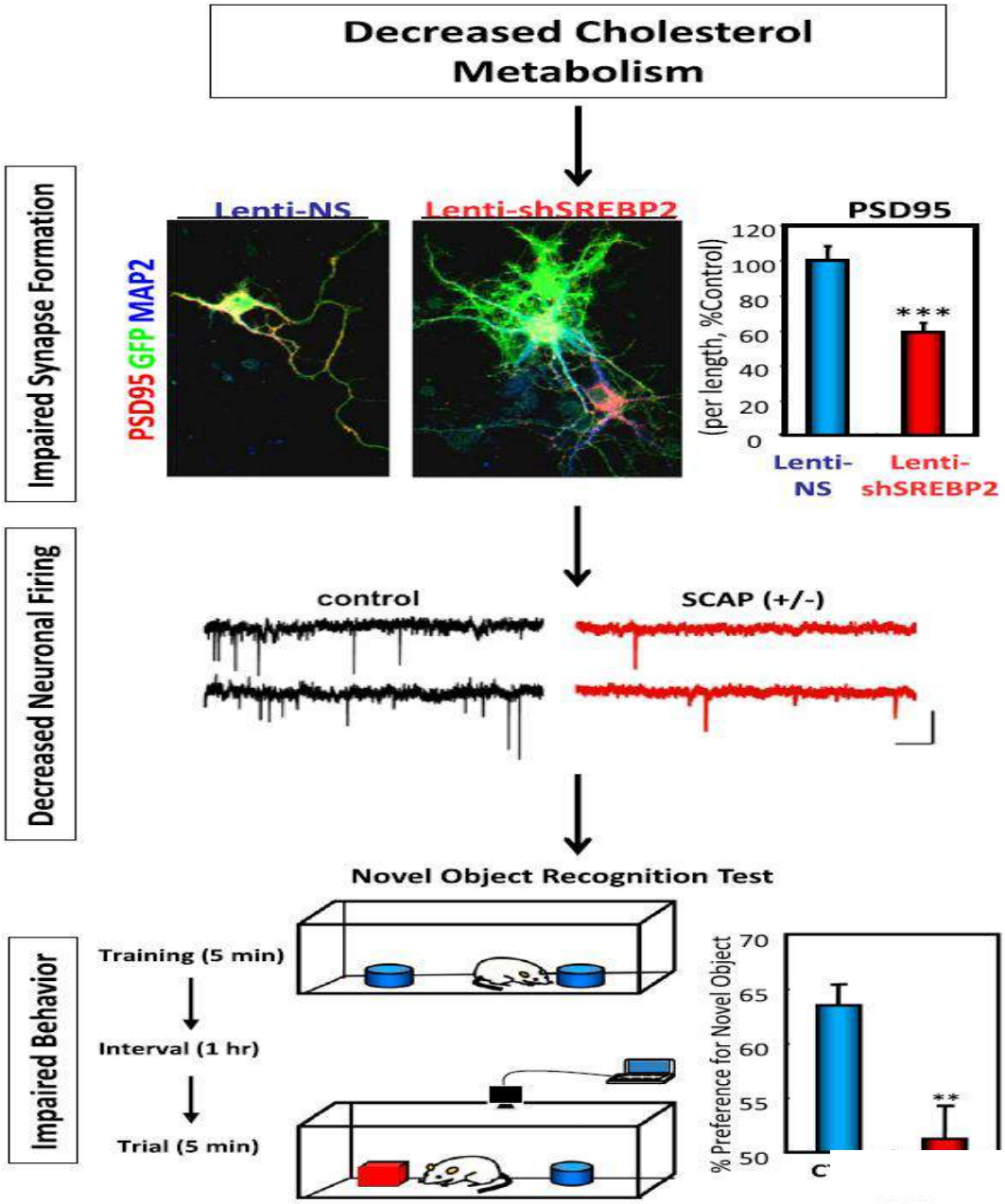
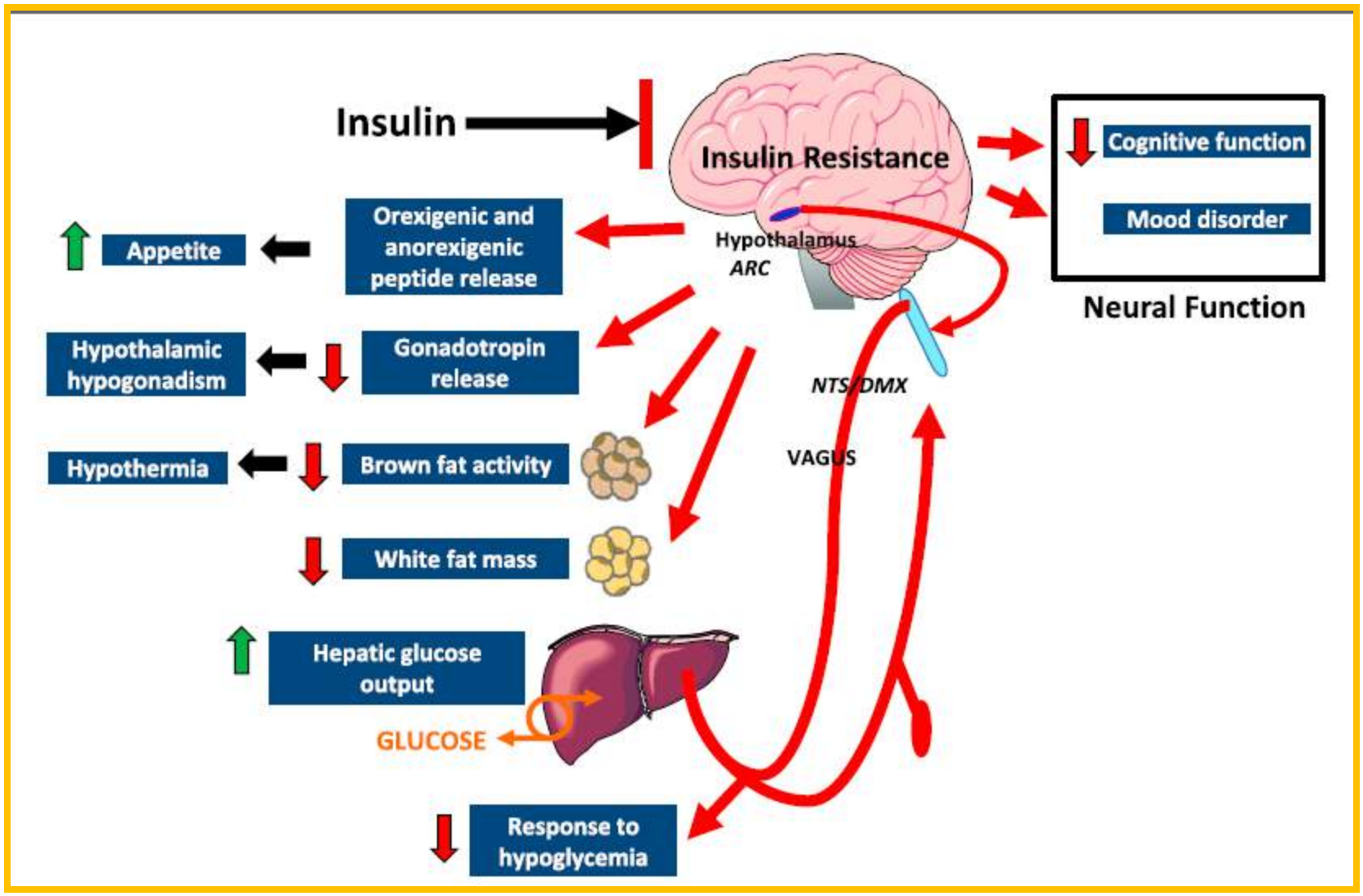


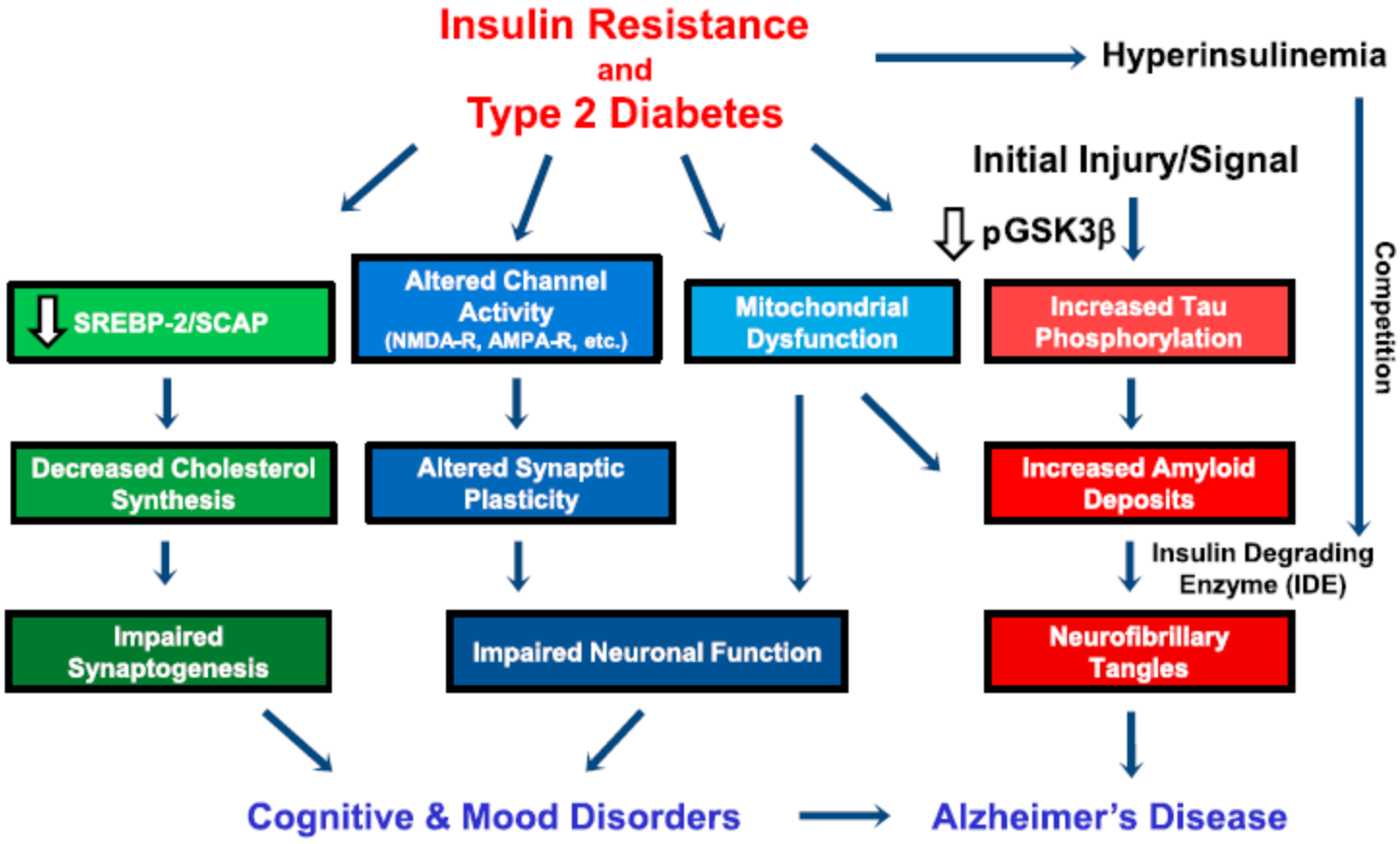
Figure 2—Insulin regulates orexigenic and anorexigenic peptides and body temperature.



Diabetes Volume 63, July 2014



Diabetes Volume 63, July 2014



Diabetes Volume 63, July 2014

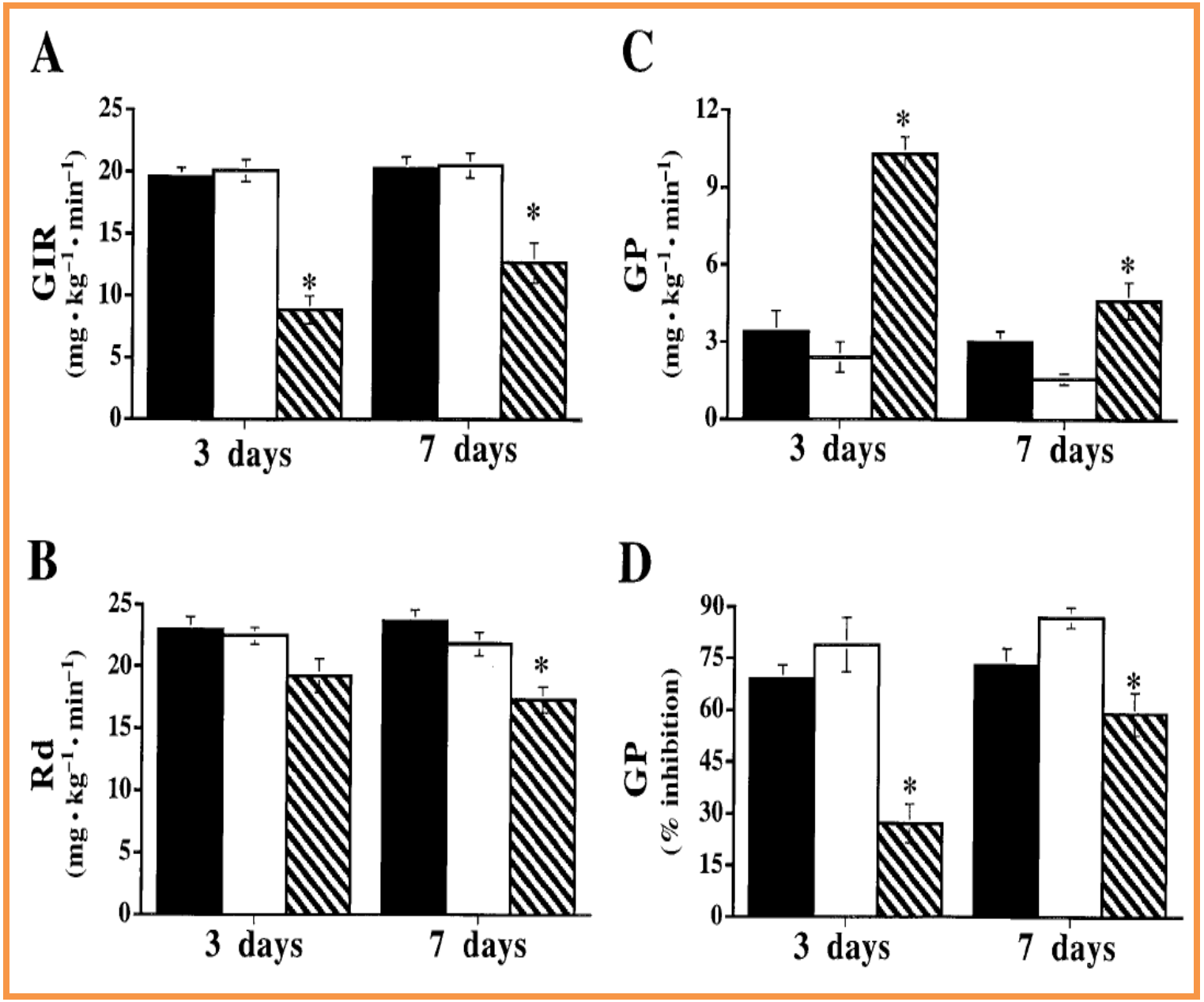
Overfeeding Rapidly Induces Leptin and Insulin Resistance

Effect of overfeeding (ad libitum) on body weight and metabolic parameters

	Control		Pair-fed		Ad libitum	
	3 Days	7 Days	3 Days	7 Days	3 Days	7 Days
n	6	6	8	12	8	10
Body weight (g)	298 ± 8.0	301 ± 7.0	304 ± 6.0	289 ± 6.0	332 ± 14	322 ± 6.0*
Δ Body weight (g)	−6.0 ± 4.0	−8.0 ± 4.0	−13 ± 4.0	−7.0 ± 3.0	25 ± 5.0*	26 ± 4.0*
Calorie intake (kcal/d)	56 ± 4.0	57 ± 5.0	51 ± 2.0	51 ± 2.0	112 ± 8.0*	105 ± 7.0*
Plasma glucose (mmol/l)	6.9 ± 0.2	6.7 ± 0.3	6.8 ± 0.2	6.9 ± 0.1	8.1 ± 0.1*	7.1 ± 0.2
Plasma FFA (mmol/l)	0.9 ± 0.1	0.8 ± 0.2	1.0 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	1.0 ± 0.2
Plasma insulin (ng/ml)	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.3	1.7 ± 0.4*	1.9 ± 0.3*
Plasma leptin (ng/ml)	0.8 ± 0.3	0.7 ± 0.3	1.2 ± 0.2	0.9 ± 0.1	2.8 ± 0.5*	1.8 ± 0.3*
Basal GP ($mg \cdot kg^{-1} \cdot min^{-1}$)	11.1 ± 0.2	10.2 ± 0.3	8.7 ± 0.3	10.0 ± 0.4	14.1 ± 0.4*	12.1 ± 0.7

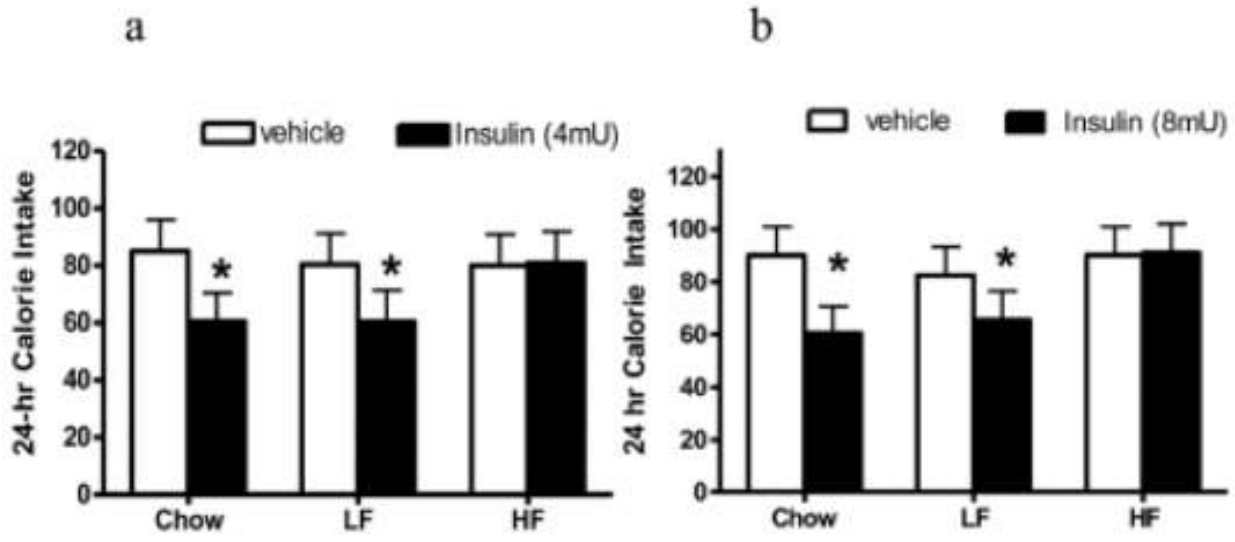
Diabetes 50:2786–2791, 2001

İnsulin action on glucose uptake



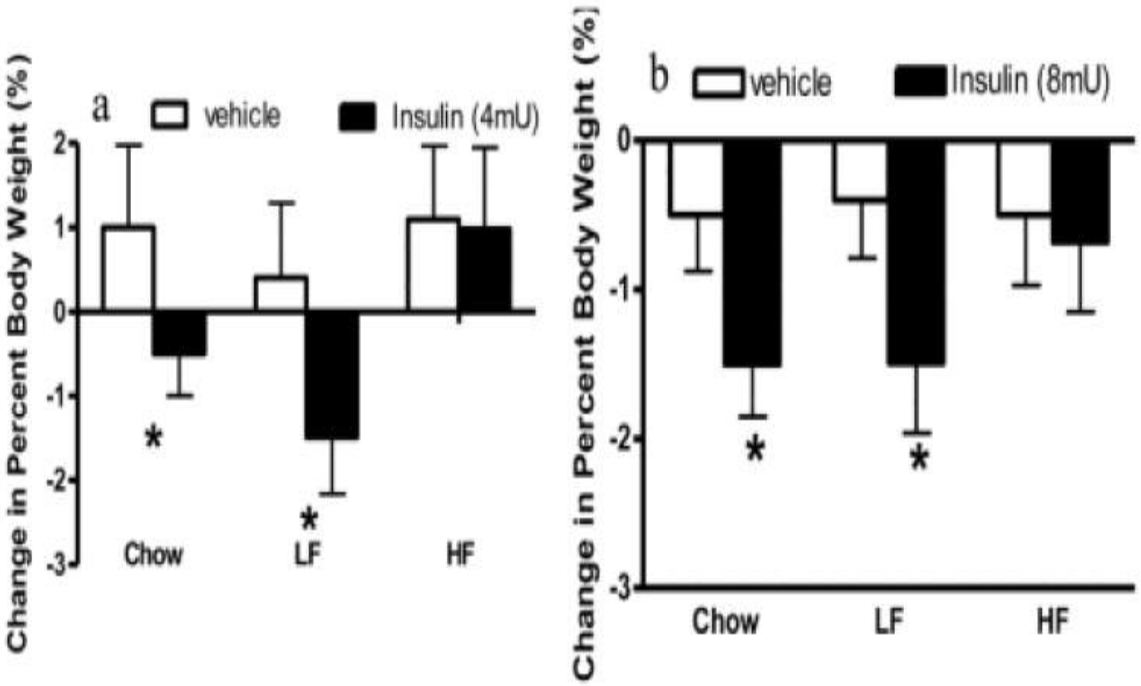
Diabetes 50:2786–2791, 2001

Consumption of a High-Fat Diet Induces Central Insulin Resistance Independent of Adiposity

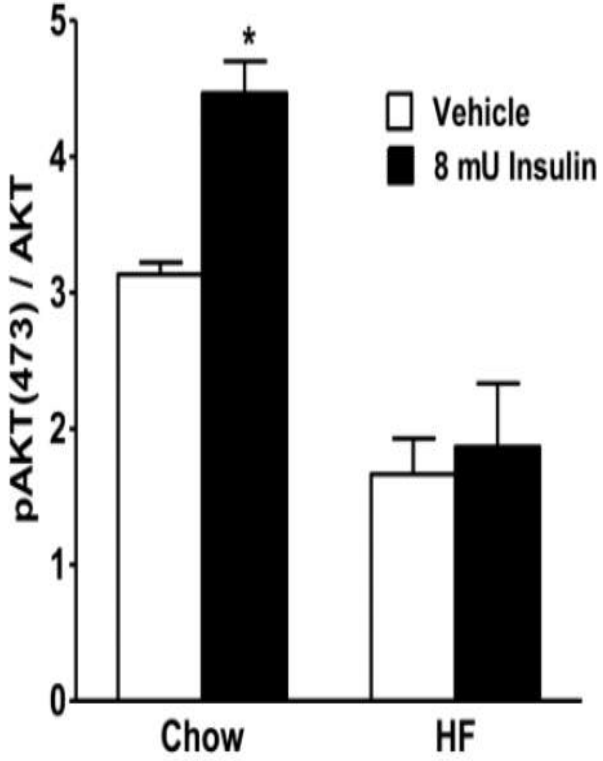


Effect of i3vt saline or insulin [4 mU (a) or 8 mU (b)] on 24-hr caloric intake in rats maintained for 10 weeks on chow, the LF diet, or the HF diet. Values represent mean + SE.
* = $P < 0.05$ compared with saline.

Physiol Behav. 2011 April 18; 103(1): 10–16.



Physiol Behav. 2011 April 18; 103(1): 10–16.



Physiol Behav. 2011 April 18; 103(1): 10–16.

Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity

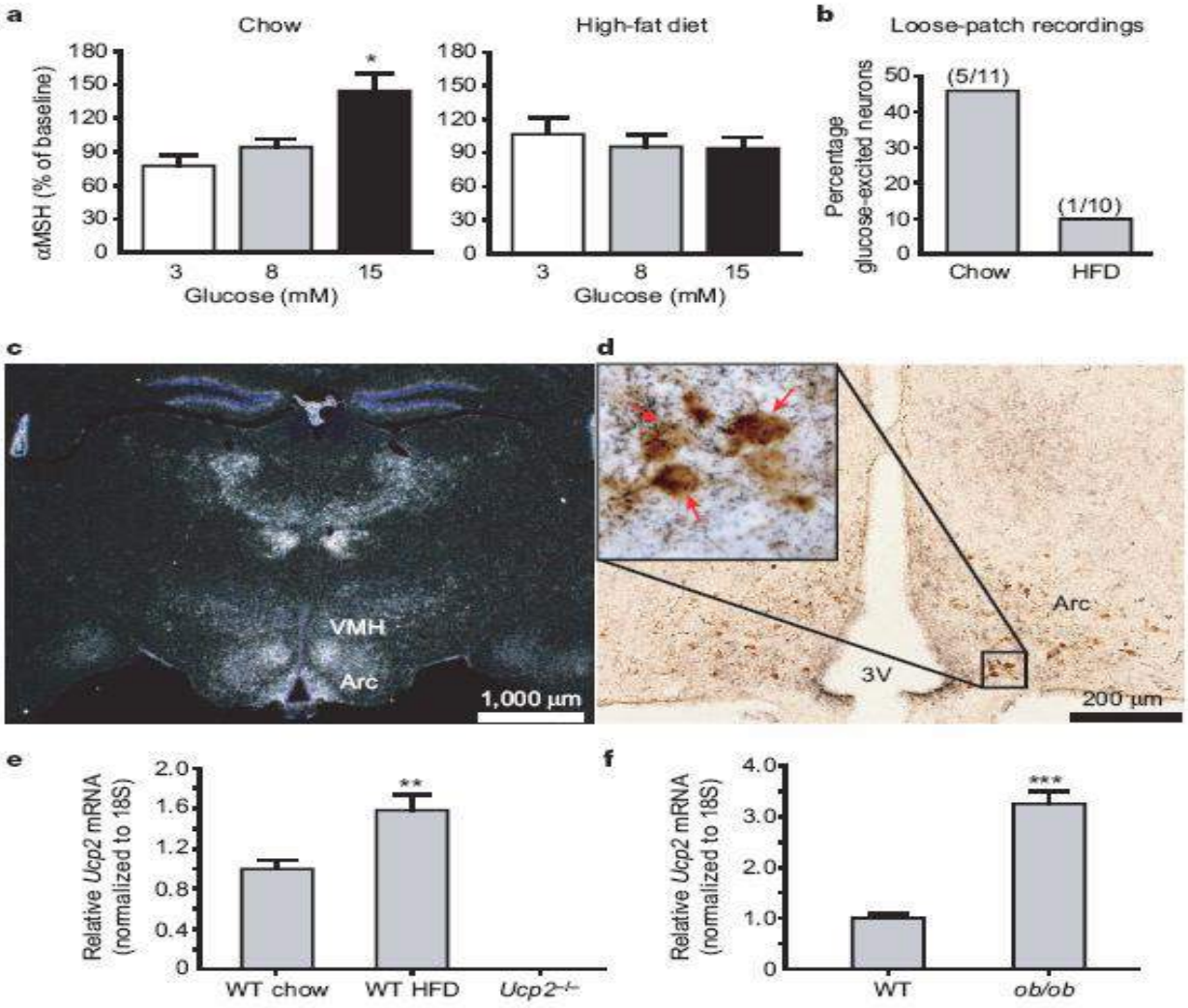
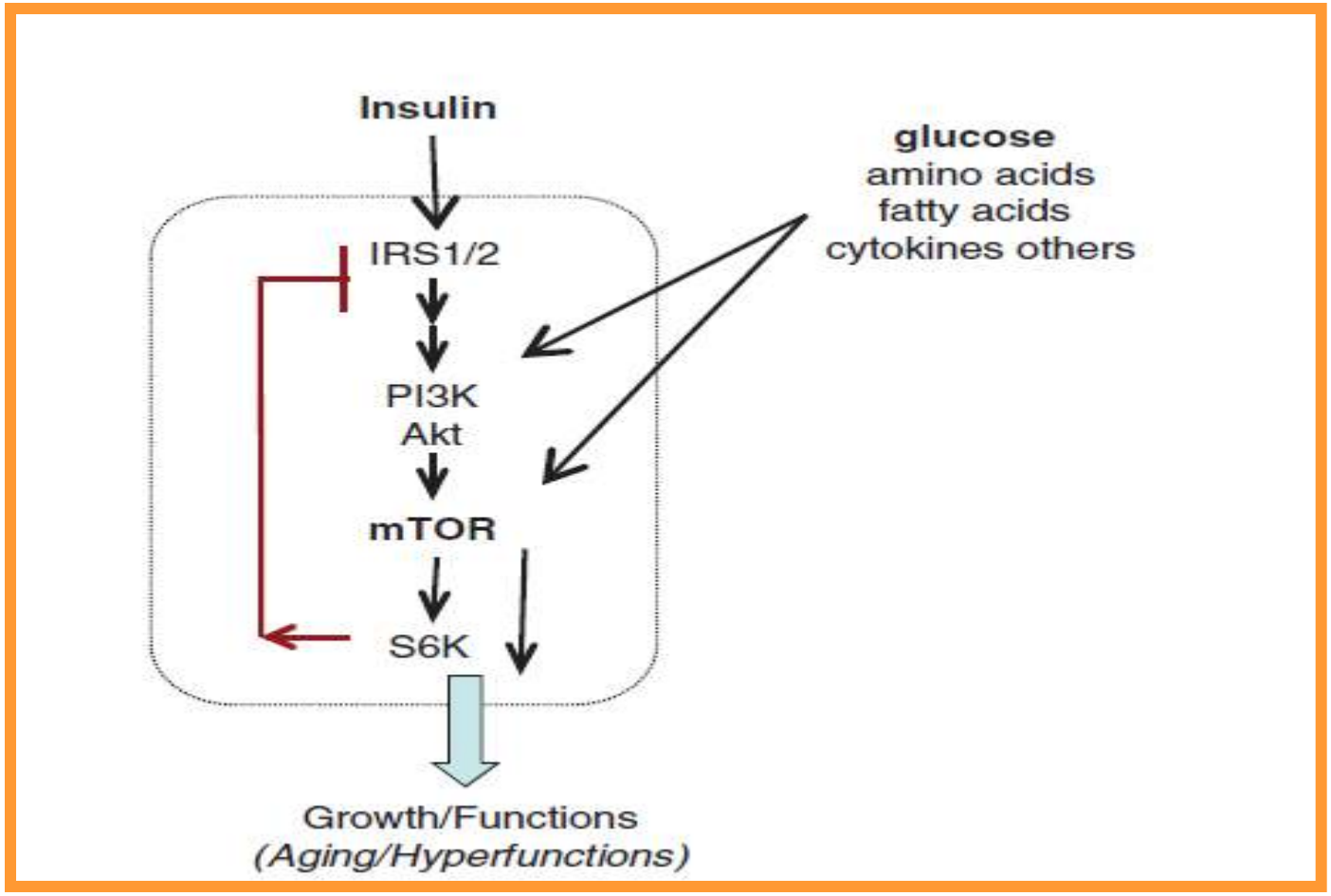
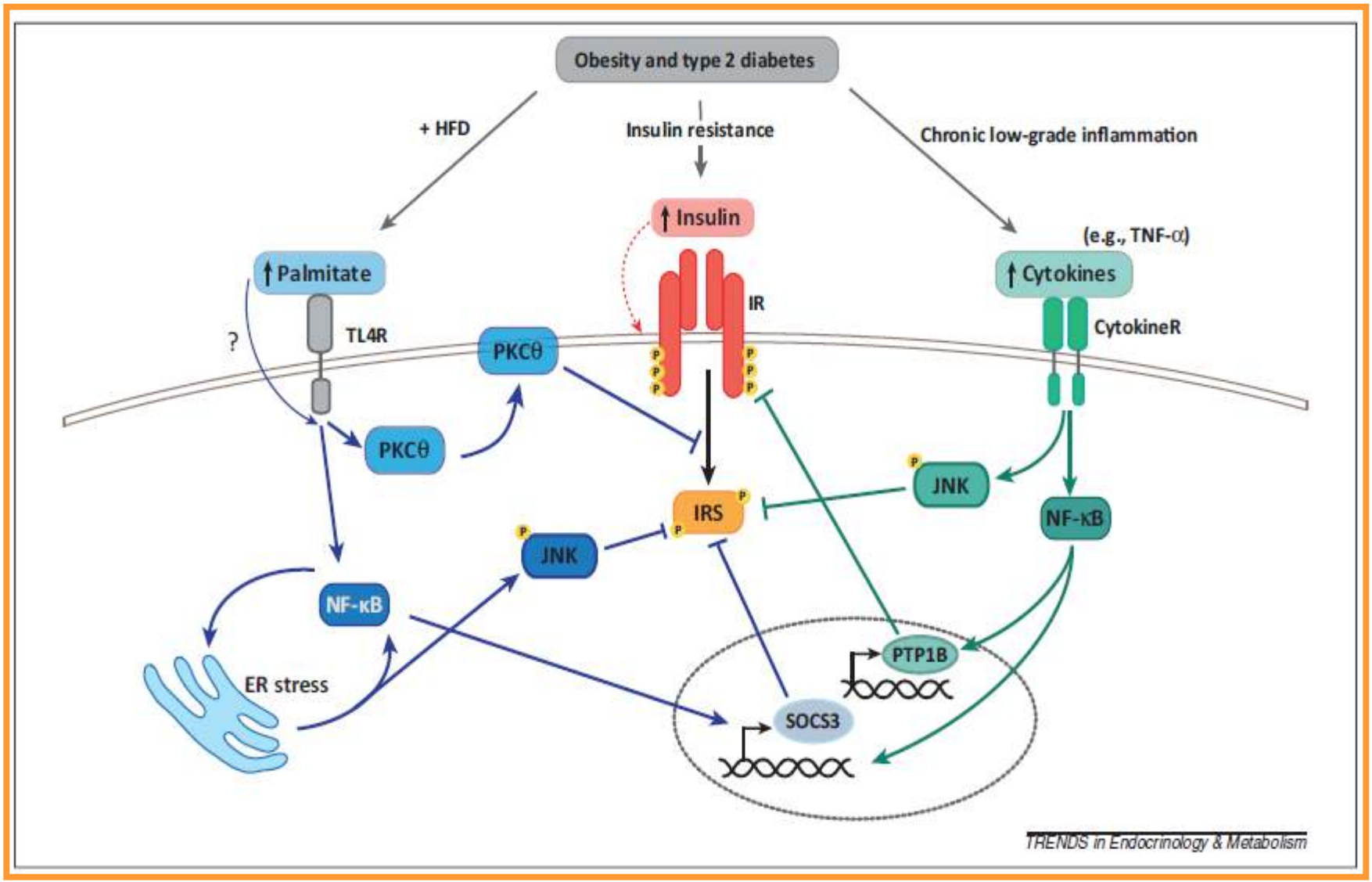


Figure 2 | Glucose-sensing is lost in POMC neurons of mice on a high-fat diet.



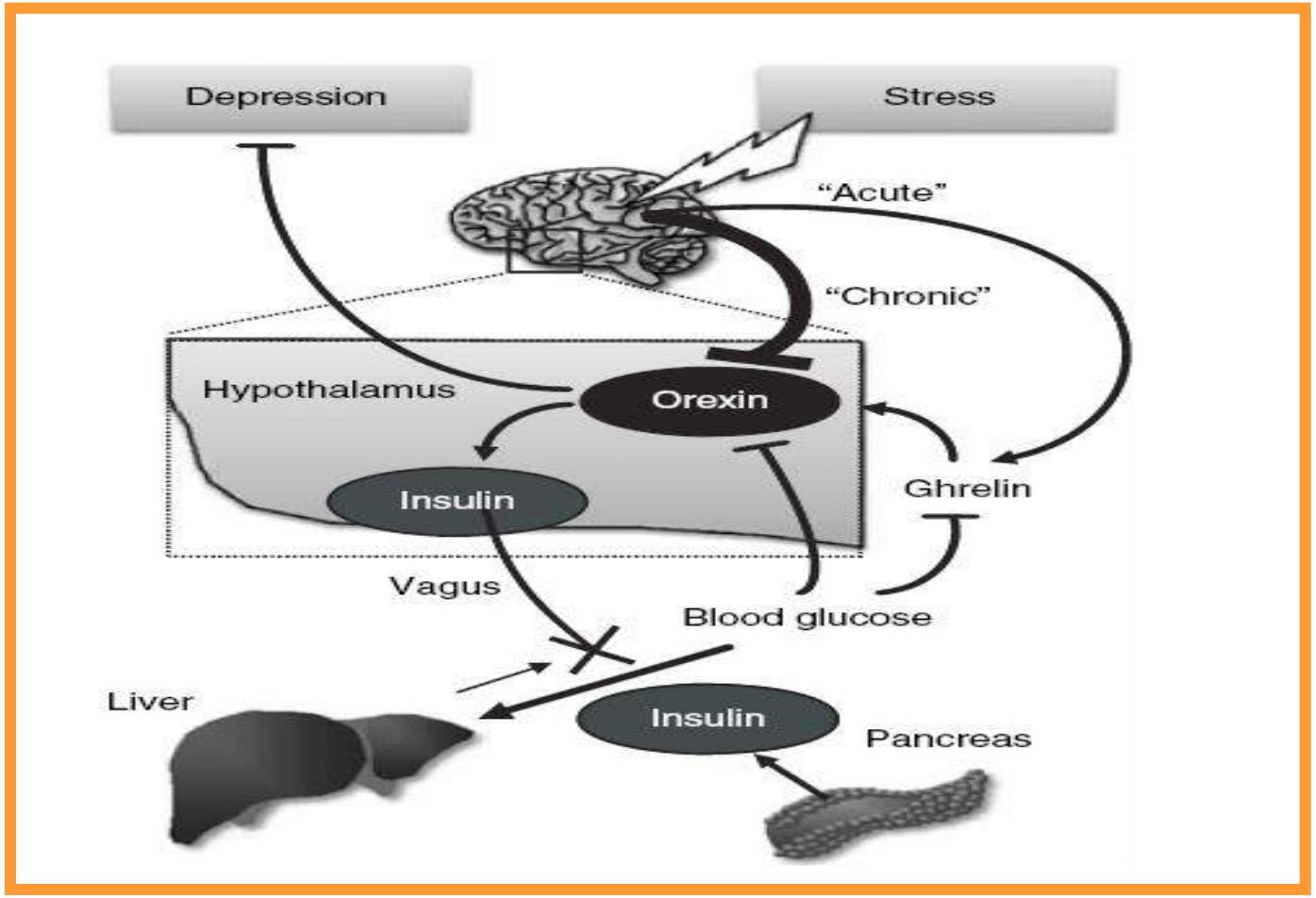
Blagosklonny MV, Cell and death disease, 2013


Obesity and type 2 diabetes
+ HFD
Insulin resistance
Chronic low-grade inflammation
Insulin
(e.g., TNF-α)
Palmitate
Cytokines
IR
?
TL4R
CytokineR
PKCθ
PKCθ
JNK
IRS
NF-κB
JNK
NF-κB
ER stress
PTP1B
SOCS3
TRENDS in Endocrinology & Metabolism

Kronik stres → orexin eksikliği

Hiperglisemik eğilim

Depresyon



Tsuneki H, Acta Physiol, 2010, 198, 335-348

Targeting the CNS to treat type 2 diabetes

Nature Reviews, Vol 8, May 2009

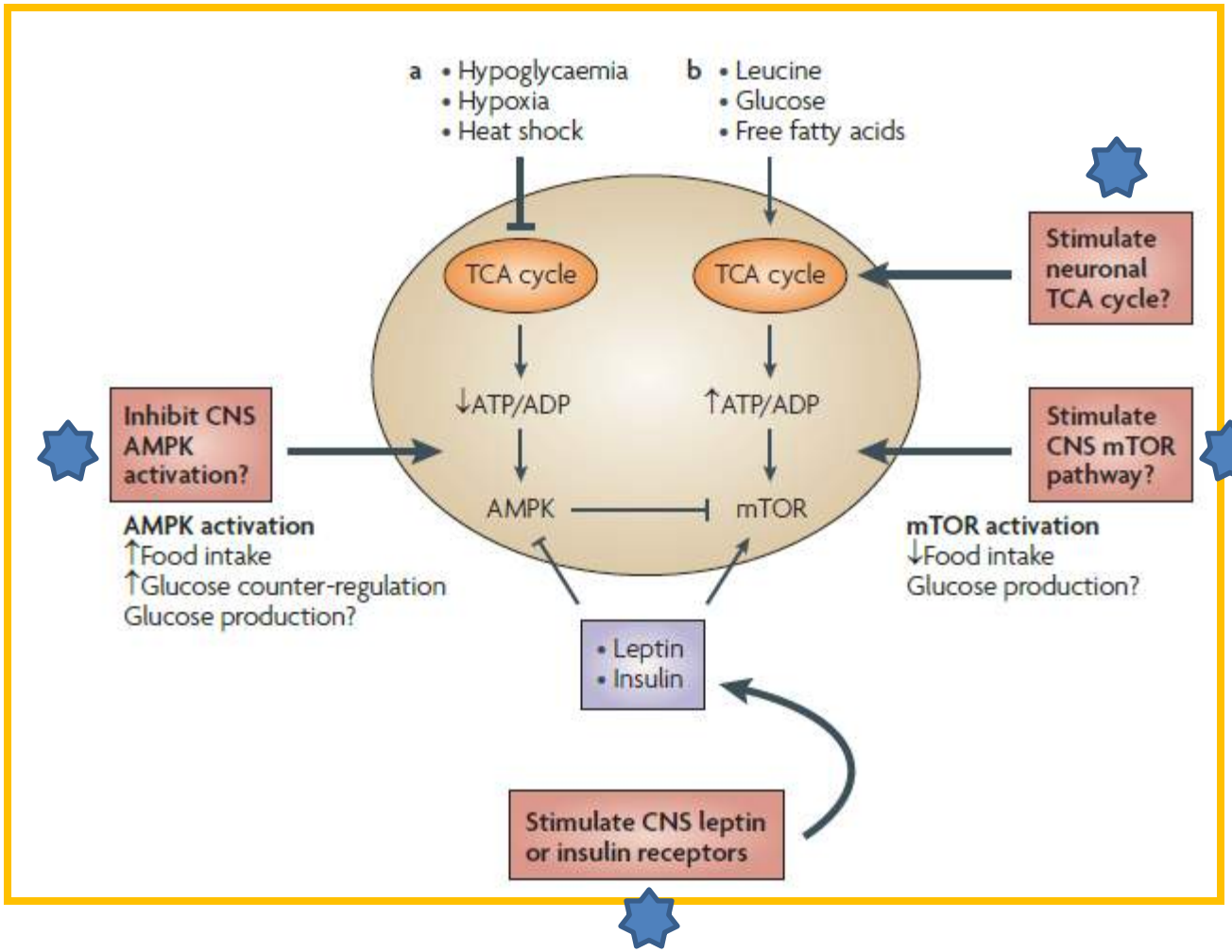


Figure 3 | **Neuronal fuel sensing and regulation of energy and glucose homeostasis.**

Nature Reviews, Vol 8, May 2009

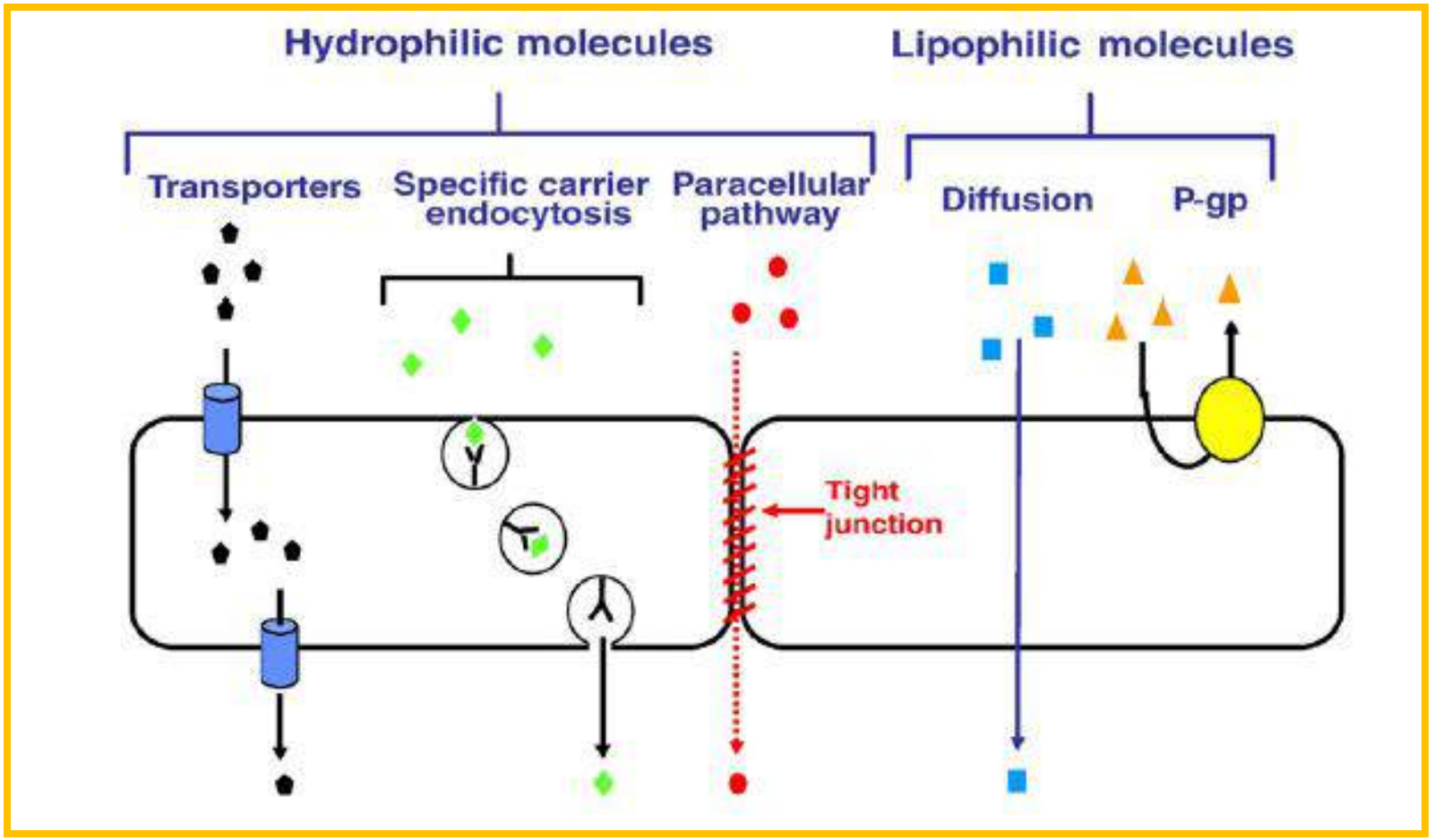
Table 1 | **Potential targets for CNS treatment of type 2 diabetes**

Target peptide	Target signalling pathway	Supporting observations or rationale	Therapeutic strategy	Challenges
CNS insulin	PI3K[49,11]	Potent inhibitor of glucose production[118]	Target CNS-specific receptors; for example, nasal insulin	Opposing peripheral and CNS effects
CNS leptin	PI3K[152,153] and/or possibly STAT3 (REFS 55,56)	Acts indirectly to reduce food intake and body weight, leading to improved glucose homeostasis[40]; acts directly to shift hepatic glucose fluxes towards gluconeogenesis[52,53]	Target CNS-specific receptors	Difficult to specifically target the CNS
CNS GLP1	Possibly PKA	Acts indirectly to reduce food intake and body weight[154]; acts directly to decrease hepatic glucose production[15]	Long-acting GLP1 analogues (exenatide) and DPP4 inhibitors (sitaglipin) are currently available	Difficult to specifically target the CNS
AMPK	Possibly ATP levels	Blocking AMPK may inhibit hepatic glucose production[50,60]	Inhibiting CAMKK2 may specifically inhibit CNS AMPK[135]	Opposing peripheral and CNS effects
mTOR	Possibly ATP levels	Acts indirectly to potentially cause weight loss[155]; direct effect of CNS mTOR on glucose homeostasis unknown	Target enzymes involved in activating mTOR	Opposing peripheral and CNS effects
K_{ATP} channels	K_{ATP} channels	Opening K_{ATP} channels may enhance nutrient- and hormone-induced inhibition of hepatic glucose production[5,8,11,15]	Block sulphonylurea receptor subunit of K_{ATP} channel	Opposing peripheral and CNS effects
Dopamine	Dopamine receptors	Dopamine receptor agonists improve insulin sensitivity[121]	Activate D1 and D2 receptors	Potential CNS side effects
Serotonin	Serotonin receptors	Improves glucose tolerance and insulin resistance in diet-induced obesity[125]	Activate 5HT2C receptors	Potential CNS side effects

Nature Reviews, Vol 8, May 2009

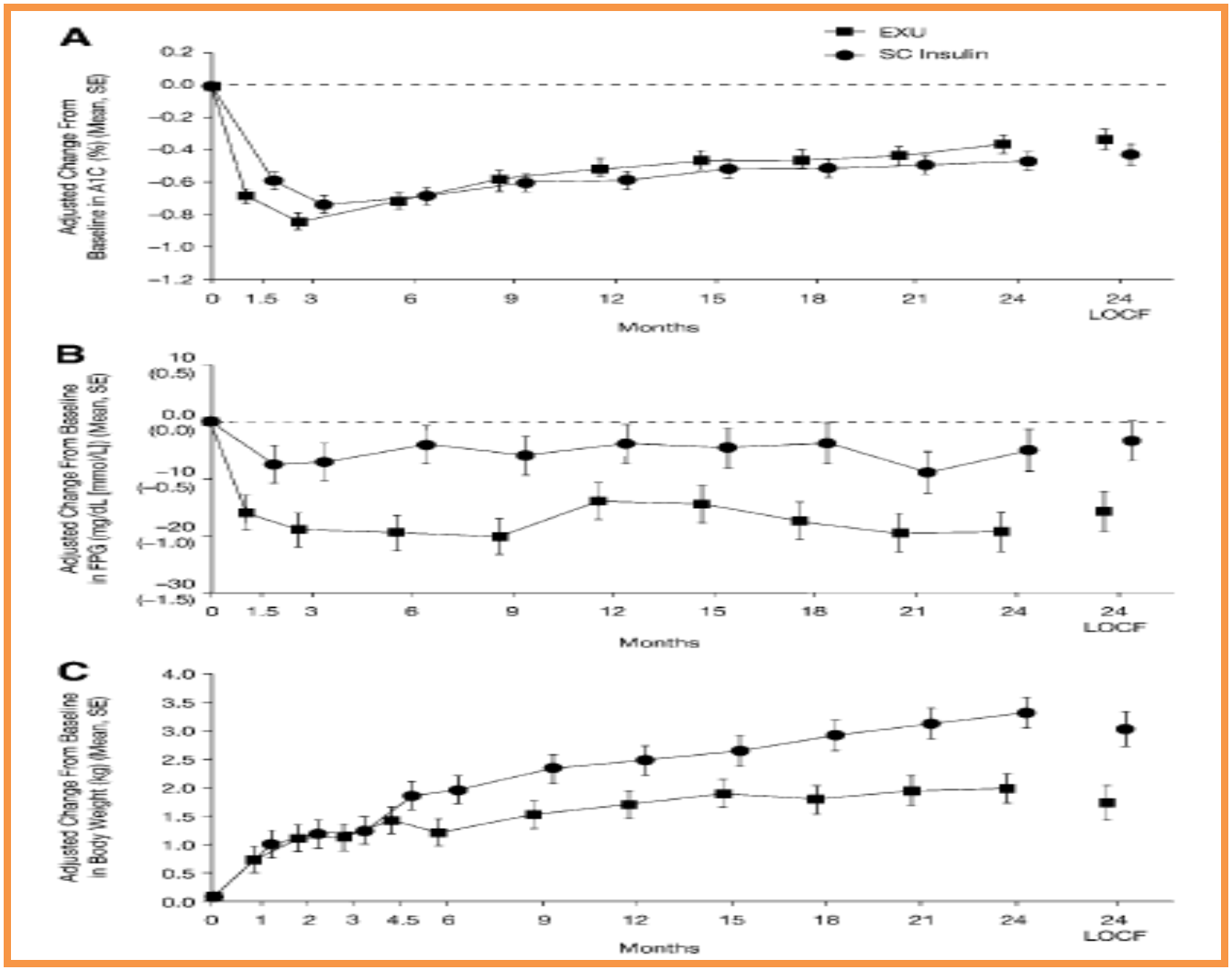
Approaches to transport therapeutic drugs across the blood–brain barrier to treat brain diseases

Reinhard Gabathuler *



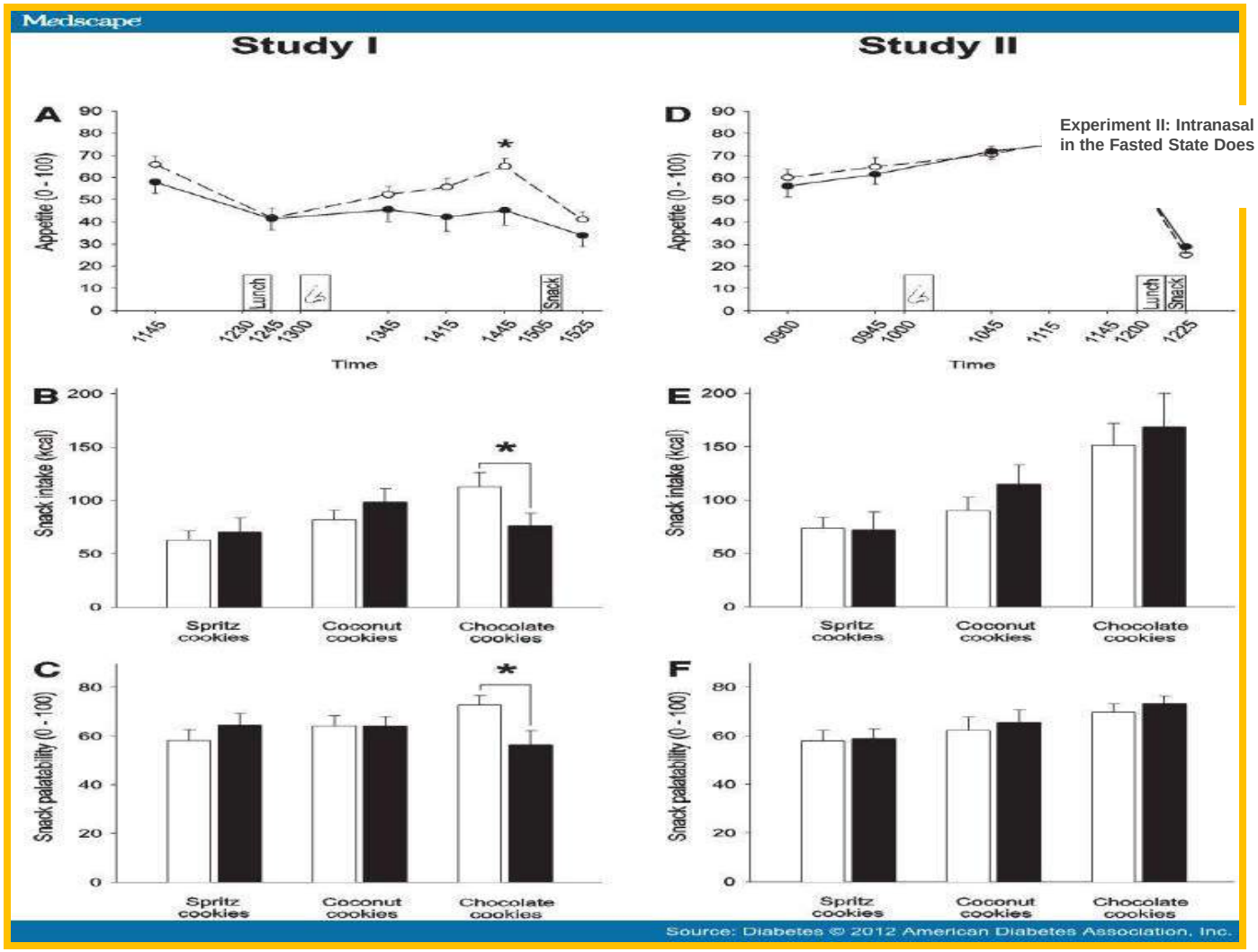
Neurobiology of Disease 37 (2010) 48–57

Two-Year Pulmonary Safety and Efficacy of Inhaled Human Insulin (Exubera) in Adult Patients With Type 2 Diabetes



Rosenstock J, Diab Care,31:1723-1728

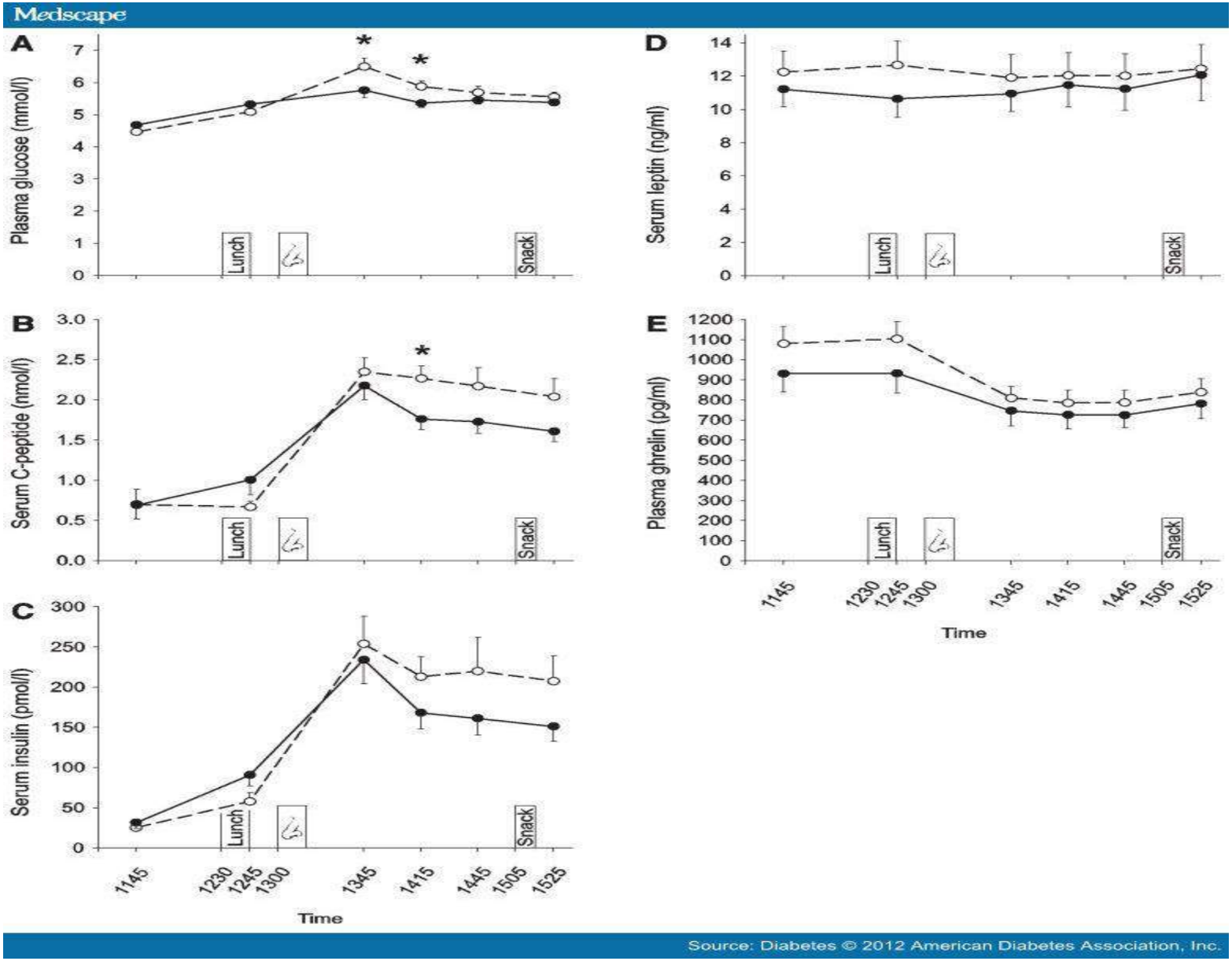
Postprandial Administration of Intranasal Insulin Intensifies Satiety and Reduces Intake of Palatable Snacks in Women



Experiment II: Intranasal Insulin Administration in the Fasted State Does Not Affect Appetite and Snack Intake

postprandial insulin in particular modulates the reward-related, nonhomeostatic control of food intake.

Diabetes. 2012;61(4):782-789.

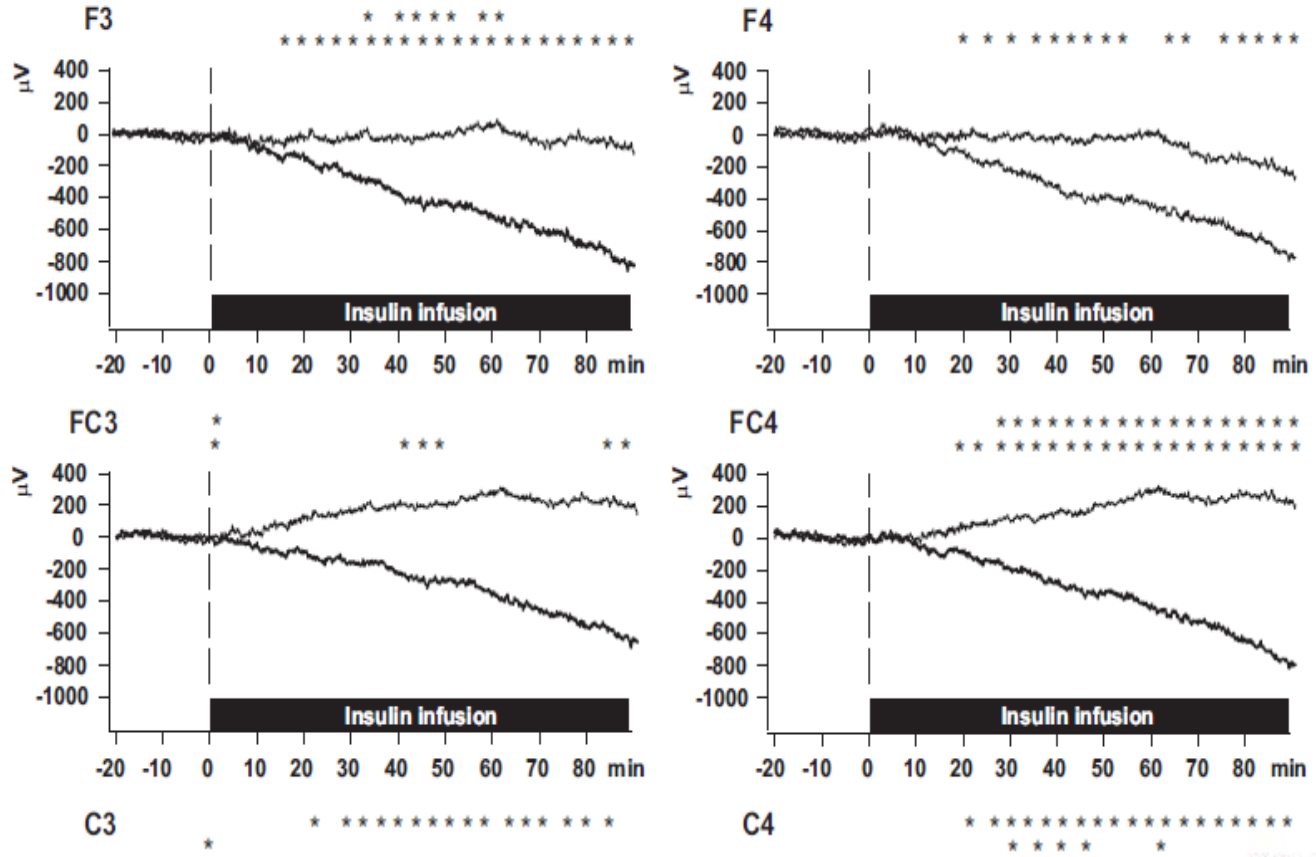


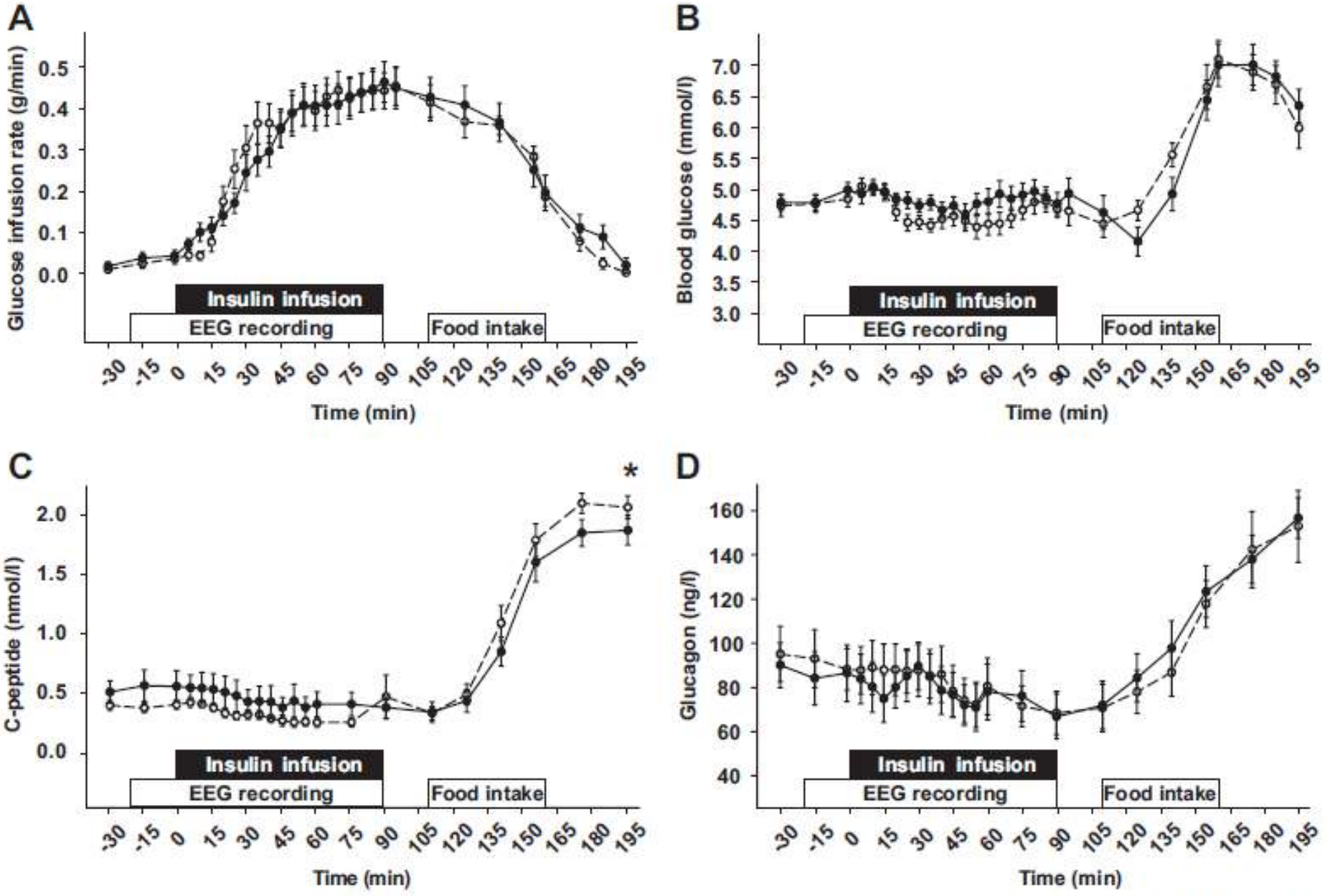
Diabetes. 2012;61(4):782-789.

Euglycemic Infusion of Insulin Detemir Compared With Human Insulin Appears to Increase Direct Current Brain Potential Response and Reduces Food Intake While Inducing Similar Systemic Effects

Manfred Hallschmid,[1] Kamila Jauch-Chara,[2] Oliver Korn,[2] Matthias Mölle,[1] Björn Rasch,[1] Jan Born,[1] Bernd Schultes,[3,4] and Werner Kern[3,5]

REDUCTION OF FOOD INTAKE BY INSULIN DETEMIR



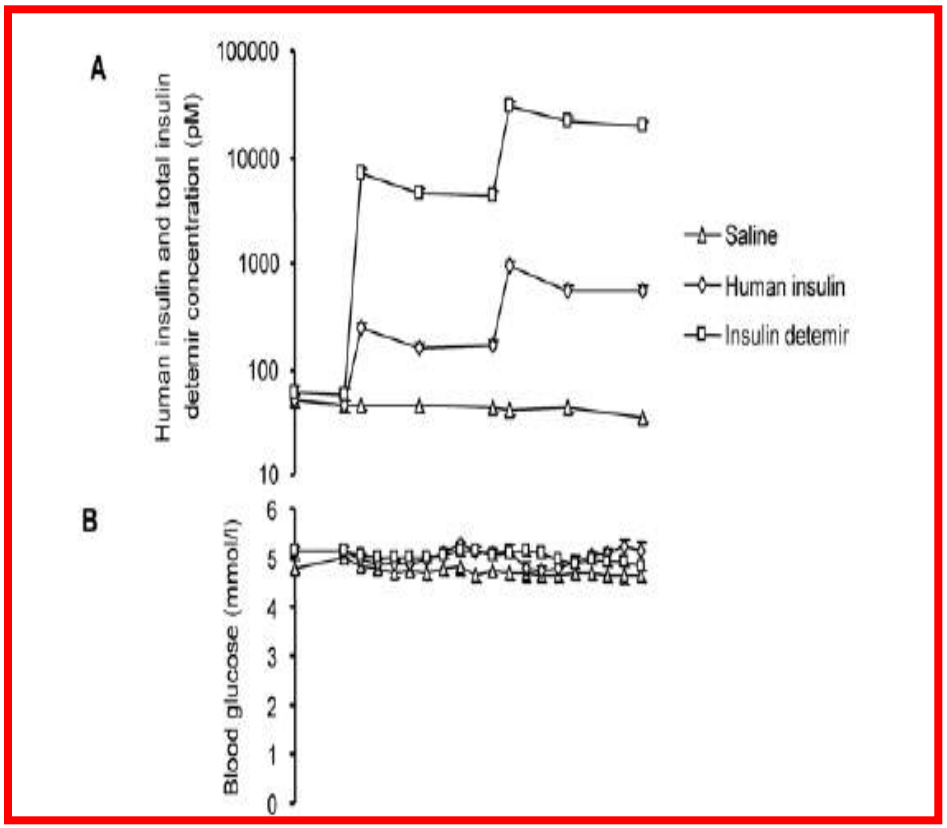

A
Glucose infusion rate (g/min)
0.0
0.1
0.2
0.3
0.4
0.5
Insulin infusion
EEG recording
Food intake
-30 -15 0 15 30 45 60 75 90 105 120 135 150 165 180 195
Time (min)
B
Blood glucose (mmol/l)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
Insulin infusion
EEG recording
Food intake
-30 -15 0 15 30 45 60 75 90 105 120 135 150 165 180 195
Time (min)
C
*
C-peptide (nmol/l)
0.0
0.5
1.0
1.5
2.0
Insulin infusion
EEG recording
Food intake
-30 -15 0 15 30 45 60 75 90 105 120 135 150 165 180 195
Time (min)
D
Glucagon (ng/l)
40
60
80
100
120
140
160
Insulin infusion
EEG recording
Food intake
-30 -15 0 15 30 45 60 75 90 105 120 135 150 165 180 195
Time (min)

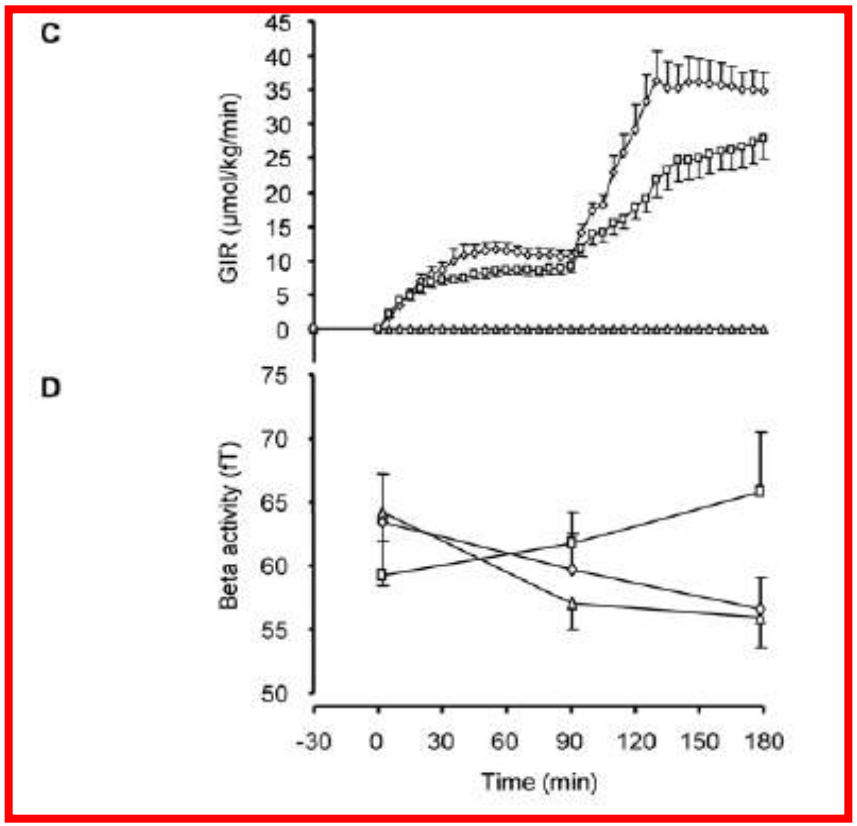
Food intake after euglycemic infusion of human insulin and detemir

	Human insulin (mean ± SE)	Detemir (mean ± SE)	*P* value
Total intake (kcal)	1,559.79 ± 138.72	1,256.78 ± 82.41	0.04
Carbohydrate (kcal)	803.18 ± 50.59	630.14 ± 49.76	0.06
Fat (kcal)	554.53 ± 83.70	472.32 ± 61.31	0.20
Protein (kcal)	202.09 ± 20.40	154.32 ± 13.41	0.004
Carbohydrate (% of total intake)	53.99 ± 3.20	51.39 ± 3.37	0.40
Fat (% of total intake)	33.19 ± 2.91	36.25 ± 3.24	0.32
Protein (% of total intake)	12.82 ± 0.49	12.36 ± 0.70	0.53
Total intake (including glucose infusion; kcal)	1,782.81 ± 133.73	1,475.34 ± 79.49	0.04
Carbohydrate (including glucose infusion; kcal)	1,026.20 ± 54.28	848.69 ± 52.50	0.05

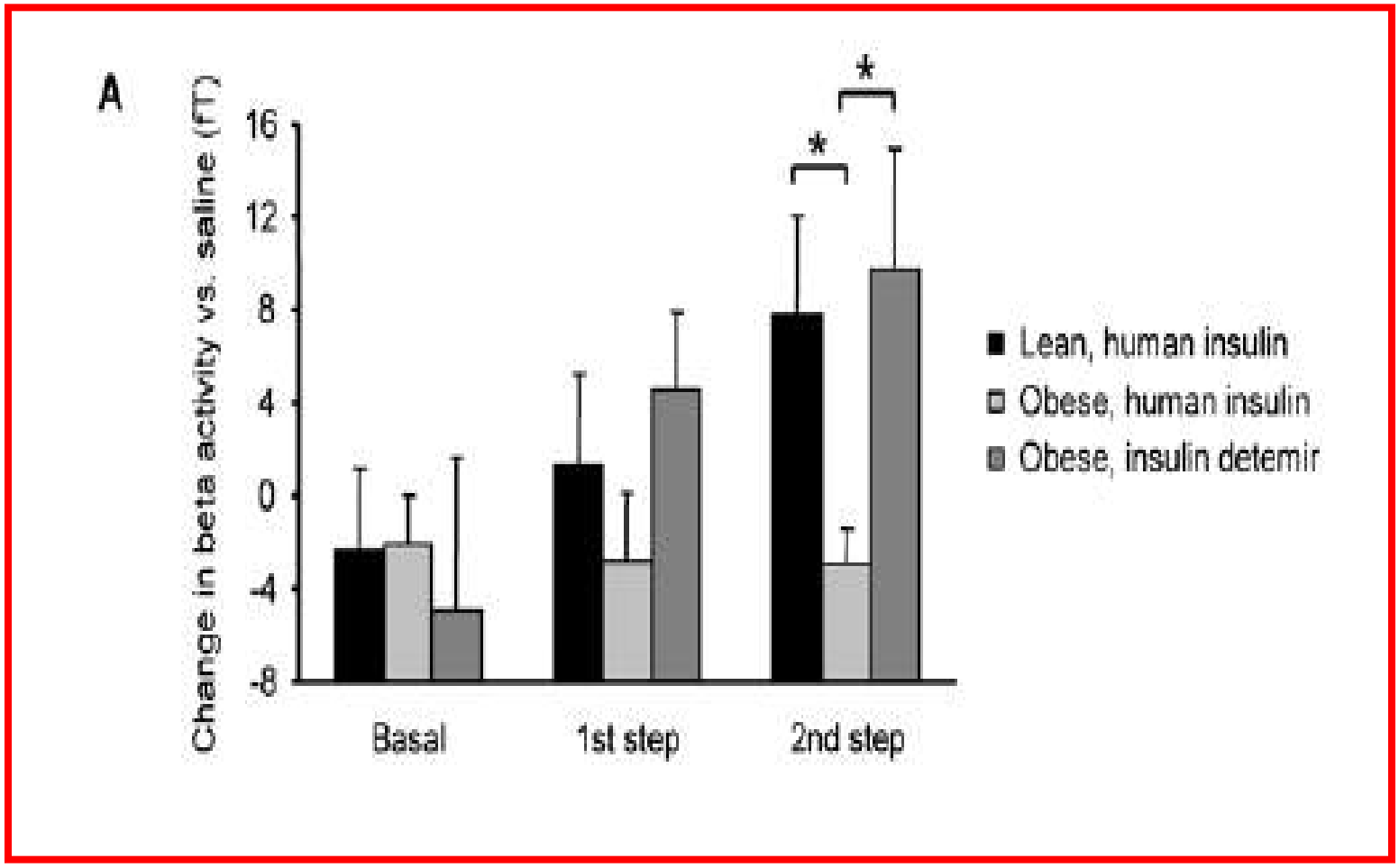
Cerebrocortical Beta Activity in Overweight Humans Responds to Insulin Detemir

Otto Tschritter[1], Anita M. Hennige[1], Hubert Preissl[2,3], Katarina Porubska[2,4], Silke A. Schäfer[1], Werner Lutzenberger[2], Fausto Machicao[1], Niels Birbaumer[2,5], Andreas Fritsche[1], Hans-Ulrich Häring[1]*





: PLoS ONE 2(11): e1196. doi:10.1371/journal.pone.0001196


A
Change in beta activity vs. saline (FT)
16
12
8
4
0
-4
-8
Basal
1st step
2nd step
*
*
Lean, human insulin
Obese, human insulin
Obese, insulin detemir

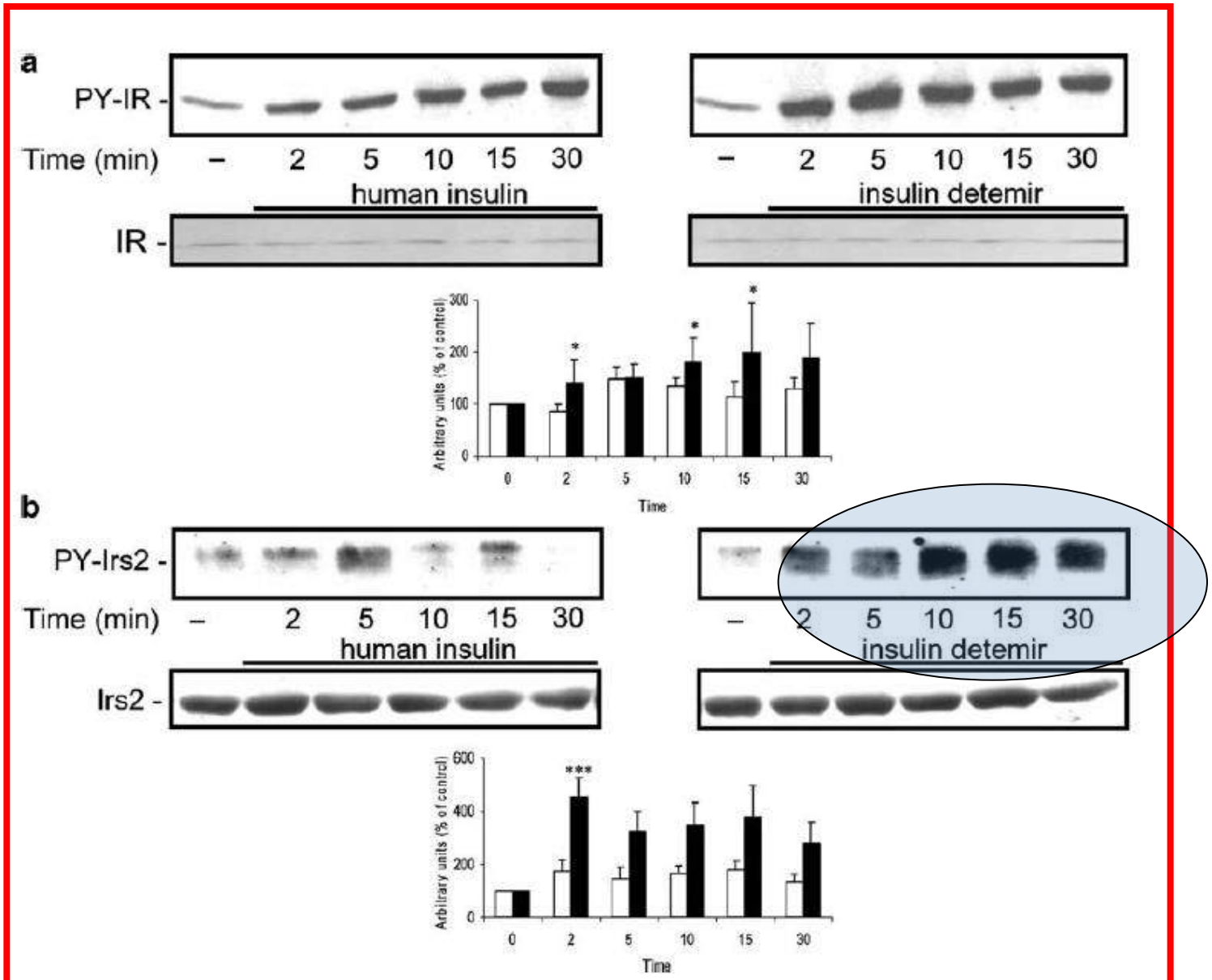
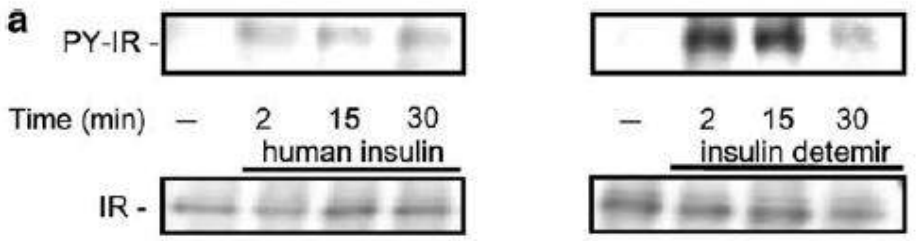
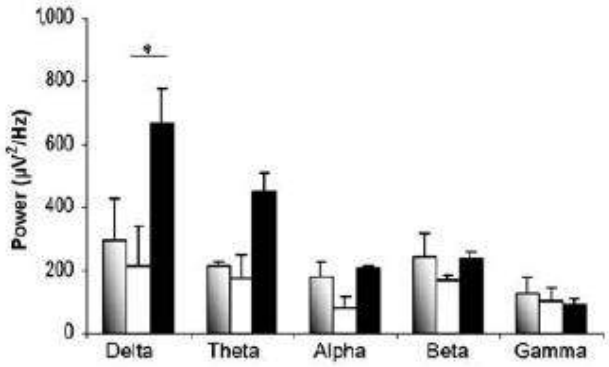


Fig. 5 Phosphorylation kinetics of the IR and Irs2 in hypothalamic tissue. Mice were injected i.v. with either human insulin or insulin detemir. Tissues were harvested at the indicated time points and

Kortikal doku





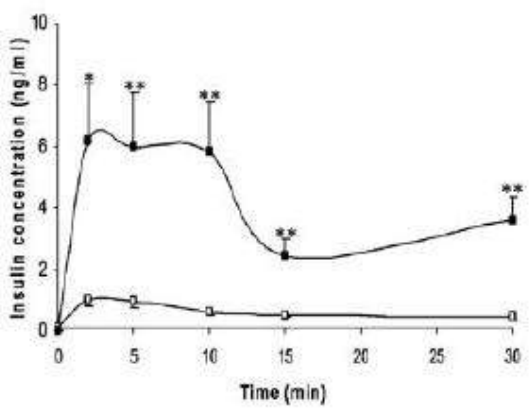
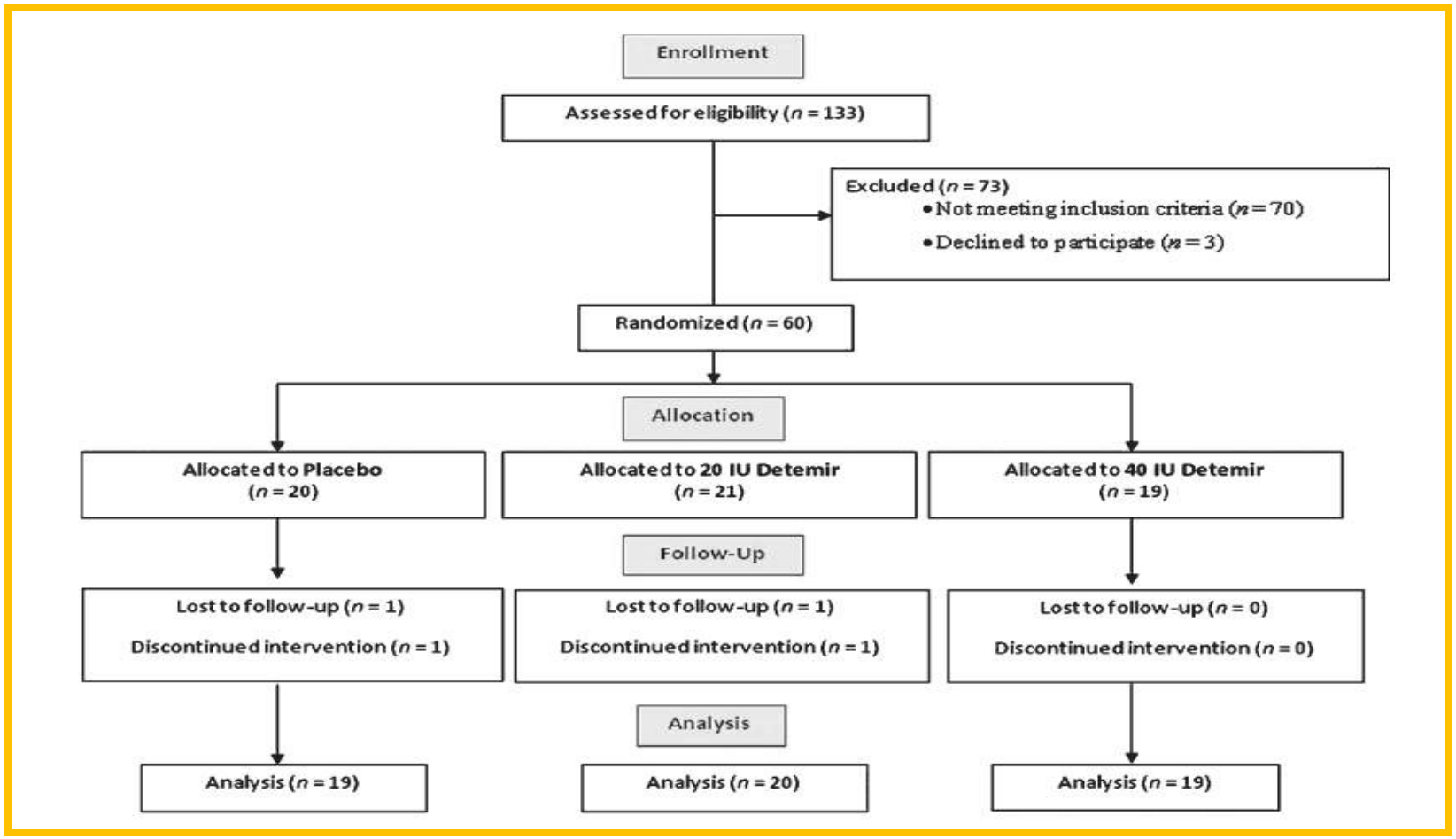


Fig. 6 Phosphorylation kinetics of the IR in cortical tissue and EEG analysis and total brain insulin concentrations following insulin detemir treatment. Mice were injected i.v. with either human insulin

Diabetologia (2006) 49: 1274–1282
DOI 10.1007/s00125-006-0192-9

Long-Acting Intranasal Insulin Detemir Improves Cognition for Adults with Mild Cognitive Impairment or Early-Stage Alzheimer's Disease Dementia



Amy Claxton

Journal of Alzheimer's Disease 44 (2015) 897–906
DOI 10.3233/JAD-141791

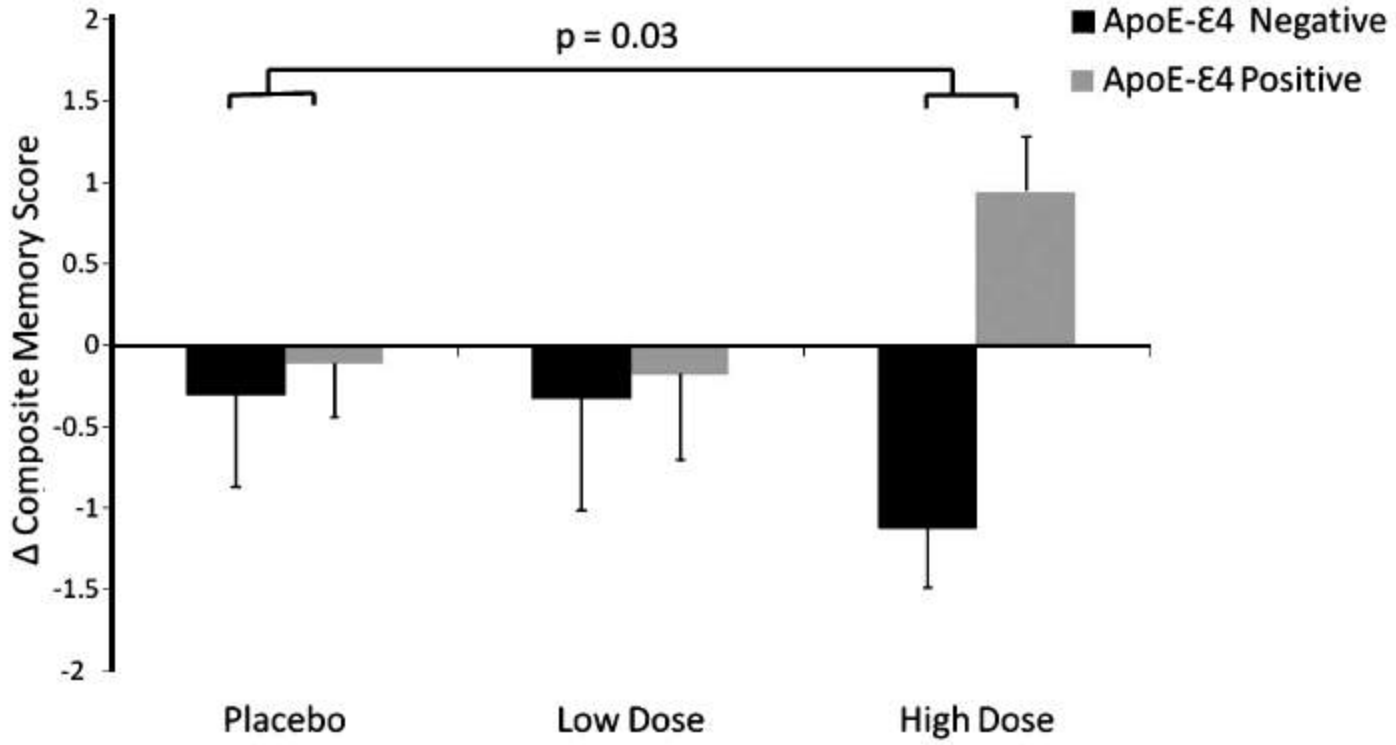


Fig. 2. Change in composite memory score from baseline to day 21, by treatment group and APOE-ε4 carriage.

Journal of Alzheimer's Disease 44 (2015) 897–906
DOI 10.3233/JAD-141791

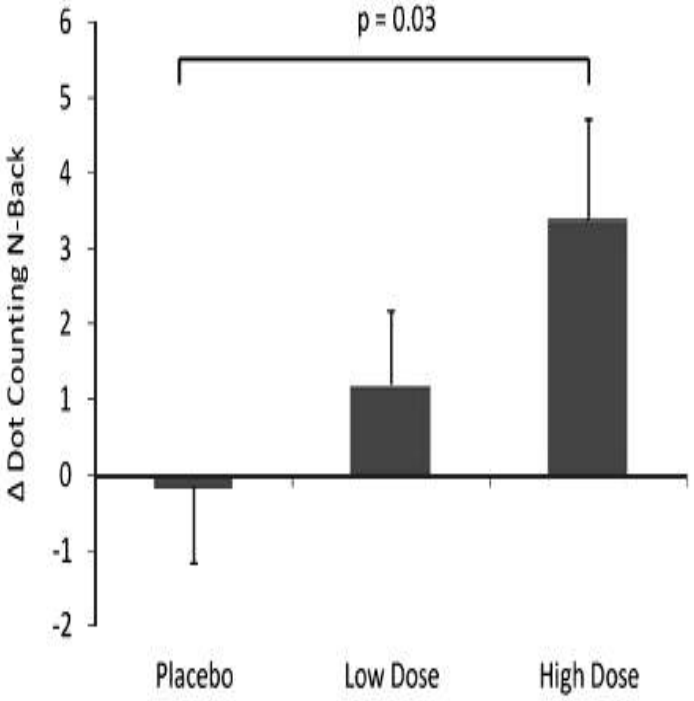


Fig. 3. Change in verbal working memory as measured by the Dot Counting N-Back Task from baseline to day 21, by treatment group.

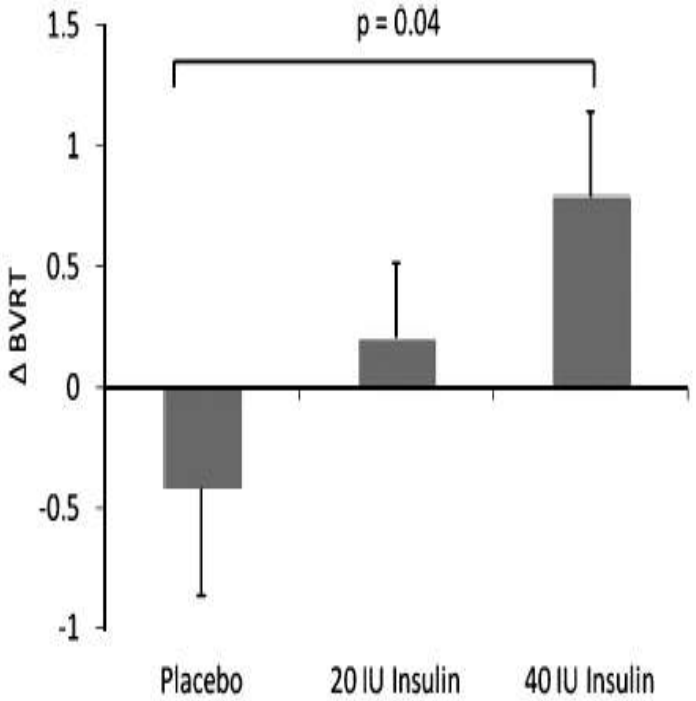


Fig. 4. Change in visuospatial working memory as measured by the BVRT from baseline to day 21, by treatment group.

Journal of Alzheimer's Disease 44 (2015) 897–906
DOI 10.3233/JAD-141791

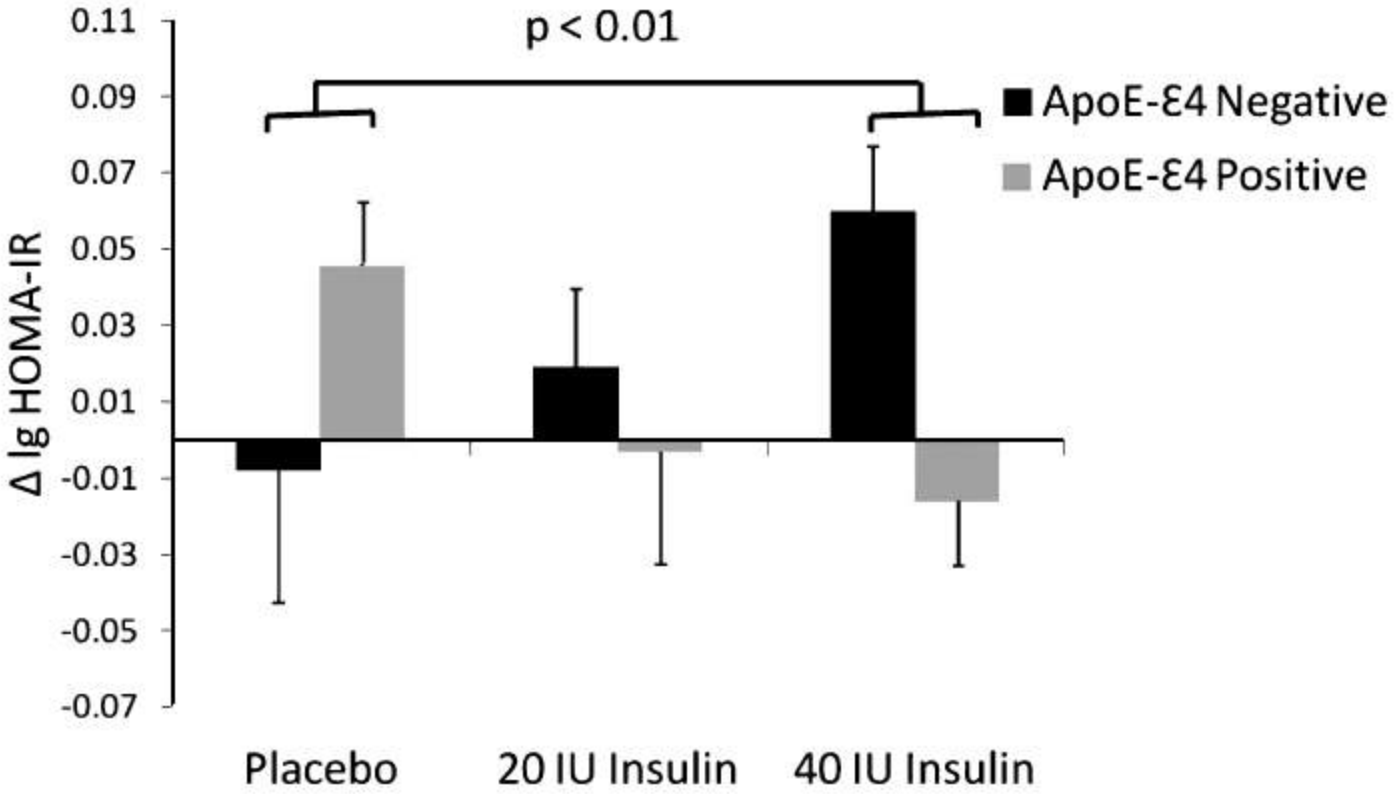


Fig. 5. Change in HOMA-IR from baseline to day 21, by treatment group and APOE-ε4 carriage.

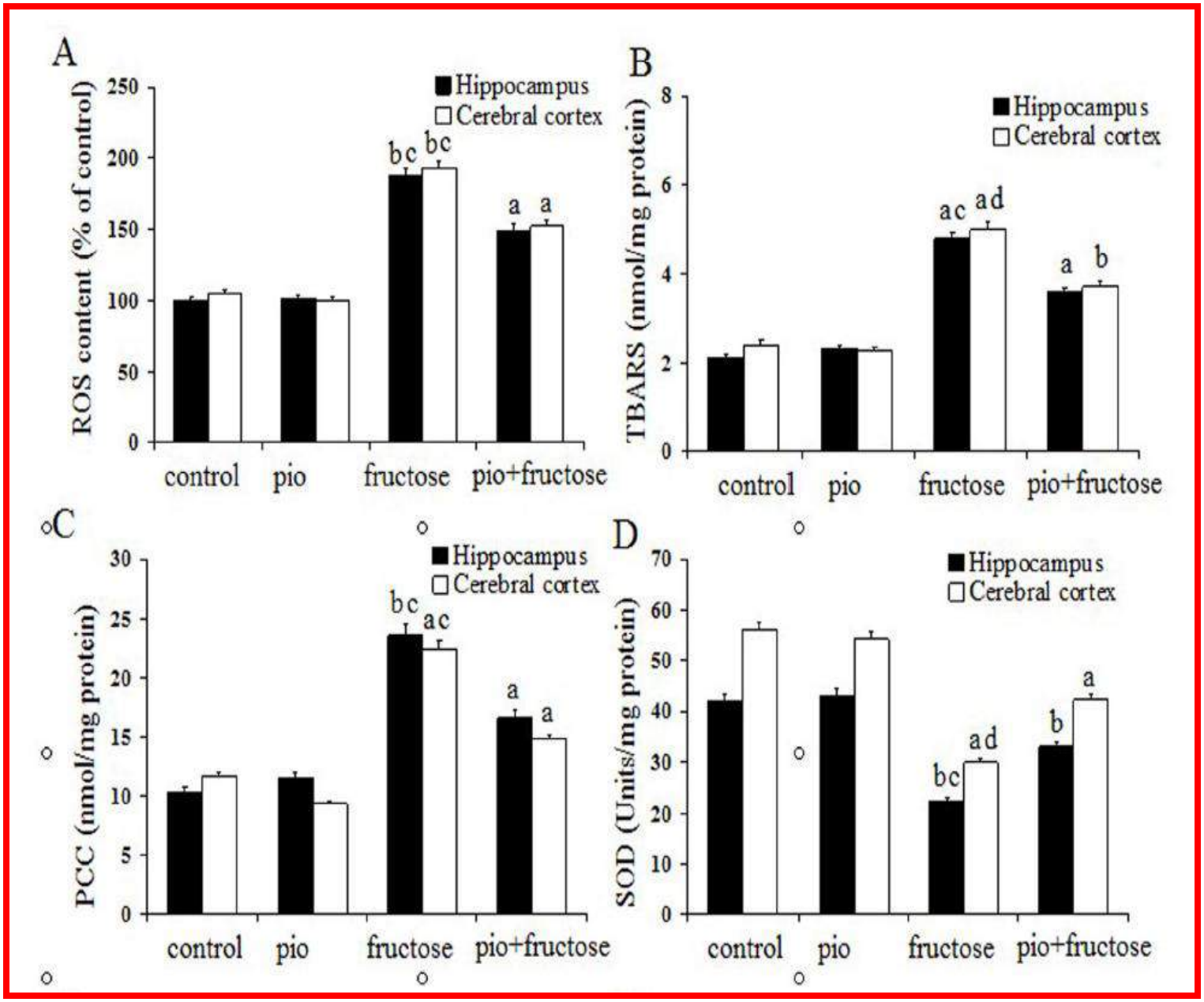
Journal of Alzheimer's Disease 44 (2015) 897–906
DOI 10.3233/JAD-141791

- Daha uzun etkililer
- Hepatik etkinliği yüksek olanlar
- Santral etkinliği yüksek olanlar…

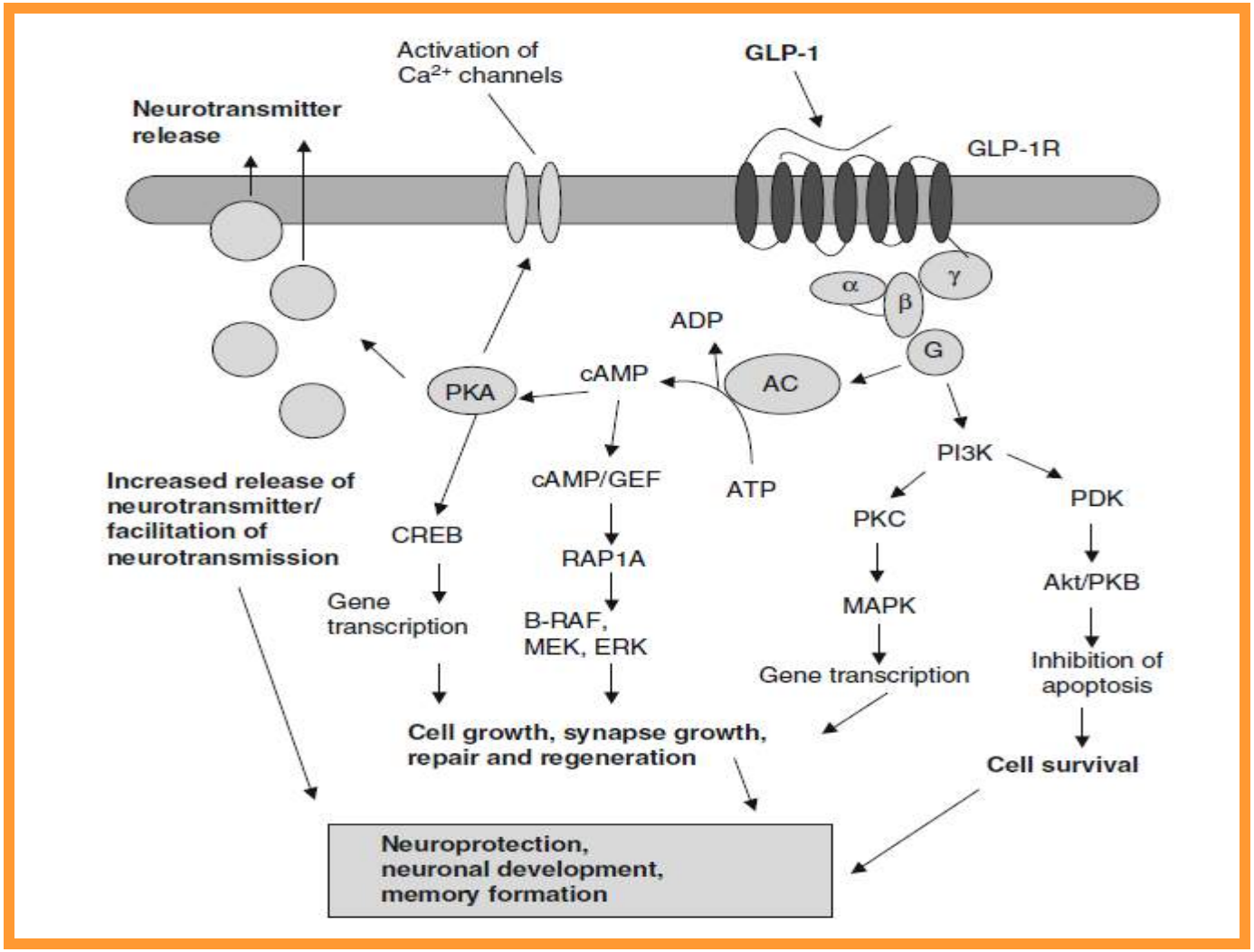
Pioglitazone Improves Cognitive Function via Increasing Insulin Sensitivity and Strengthening Antioxidant Defense System in Fructose-Drinking Insulin Resistance Rats

Table 1. Effects of pioglitazone on plasma glucose and insulin in fructose-drinking insulin resistance rats.

Groups (n)	Body weight (g)	Fasting blood glucose (mmol/L)	Fasting insulin (mU/L)	Insulin resistance index
Control (10)	397.4±19.3	5.12±0.78	14.5±2.9	3.30±0.34
Pioglitazone (9)	401.5±15.9	4.83±0.39	13.9±3.3	2.98±0.28
Fructose (8)	409.3±12.9	5.54±0.58	34.6±4.5[a]	8.52±0.62[a]
Pioglitazone+fructose (8)	412.2±15.9	5.38±0.47	19.4±4.0[bc]	4.64±0.33[a,c]

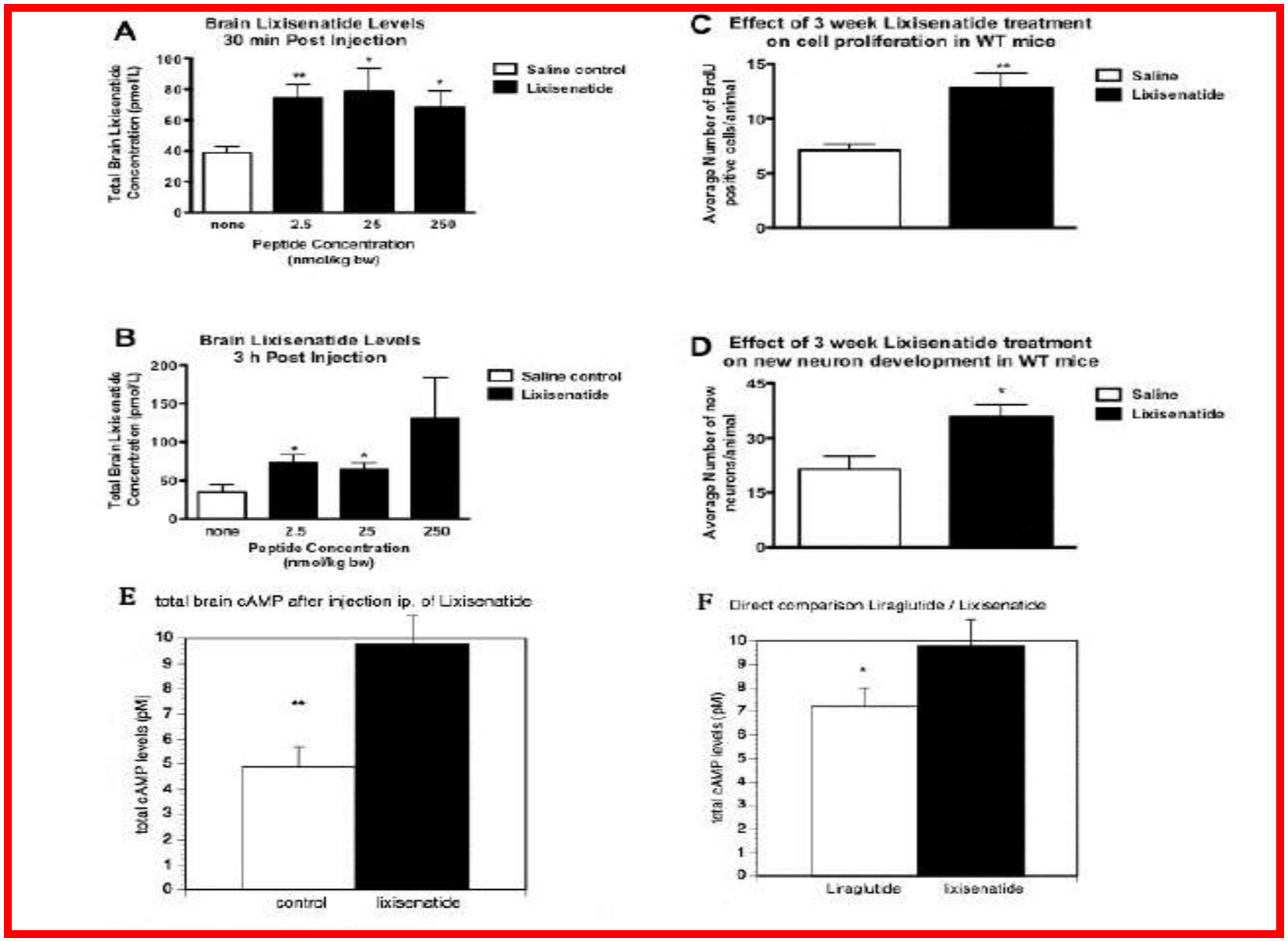

A
ROS content (% of control)
250
200
150
100
50
0
Hippocampus
Cerebral cortex
bc bc
a a
control
pio
fructose
pio+fructose
B
TBARS (nmol/mg protein)
8
6
4
2
0
Hippocampus
Cerebral cortex
ac ad
a b
control
pio
fructose
pio+fructose
C
PCC (nmol/mg protein)
30
25
20
15
10
5
0
Hippocampus
Cerebral cortex
bc ac
a a
control
pio
fructose
pio+fructose
D
SOD (Units/mg protein)
70
60
50
40
30
20
10
0
Hippocampus
Cerebral cortex
bc ad
b a
control
pio
fructose
pio+fructose

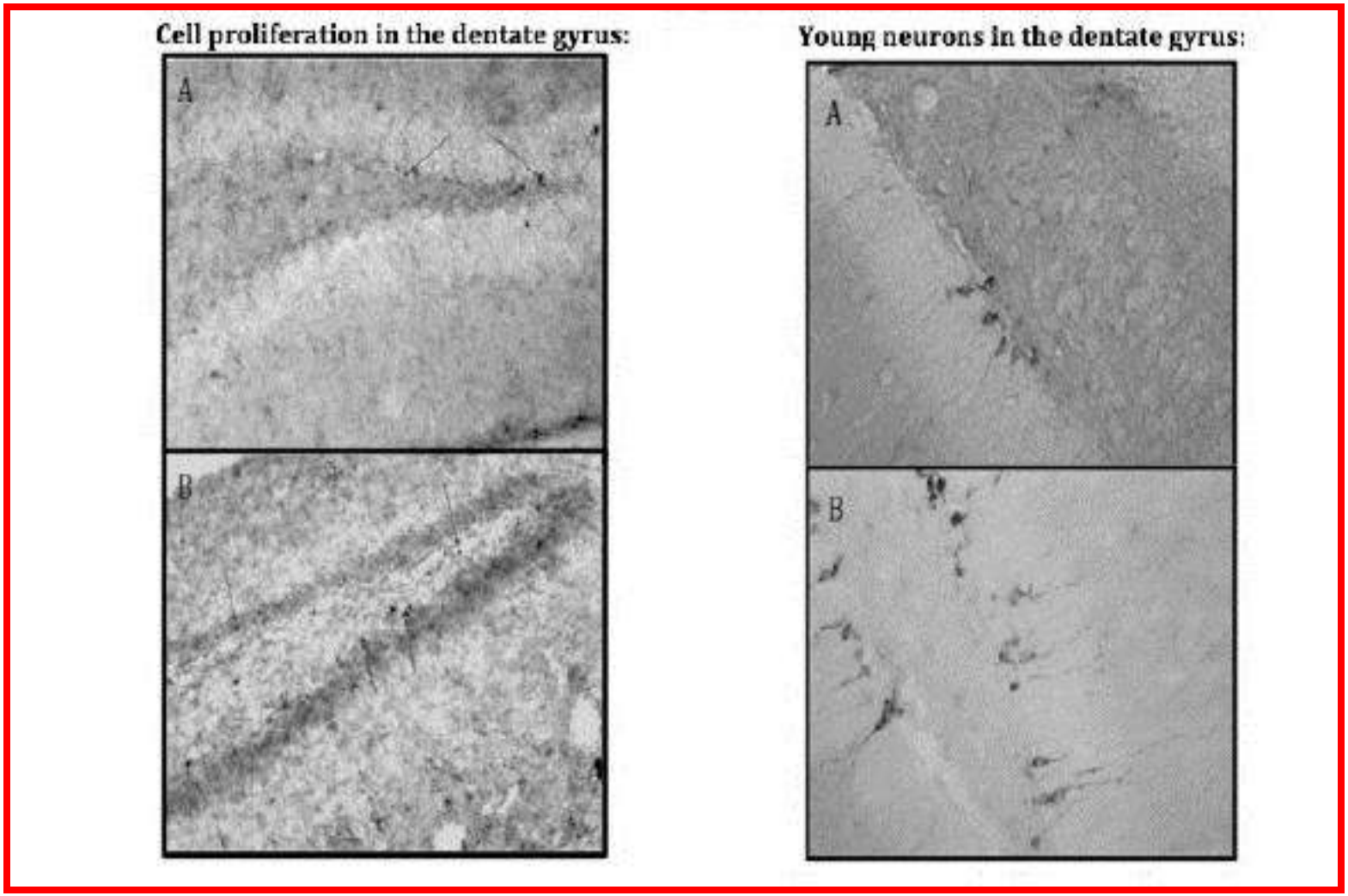
Potential Role of Glucagon-Like Peptide-1 (GLP-1) in Neuroprotection



CNS Drugs 2012; 26 (10)

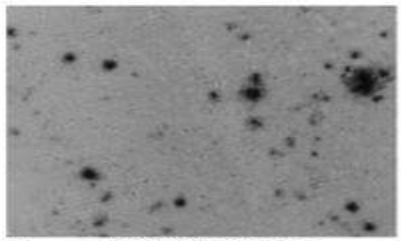
Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis



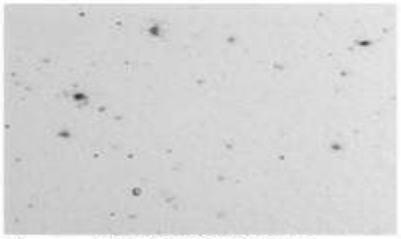


Micrographs: BrdU stain: A Saline control B Lixisenatide treated, 3 weeks once daily i.p. injection.

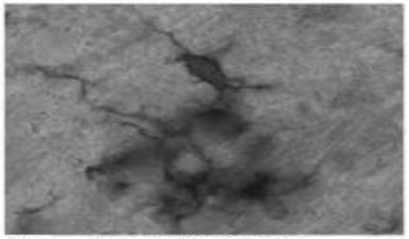
The incretin hormones glucagonlike peptide 1 and glucose-dependent insulinotropic polypeptide are neuroprotective in mouse models of Alzheimer's disease



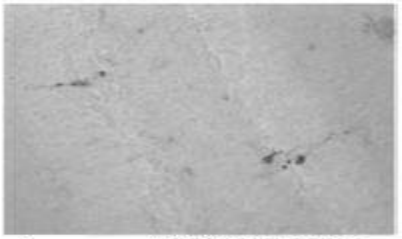
A APP/PS1 Saline



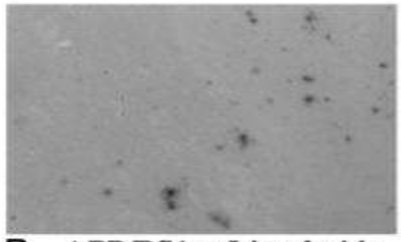
D APP/PS1 Saline



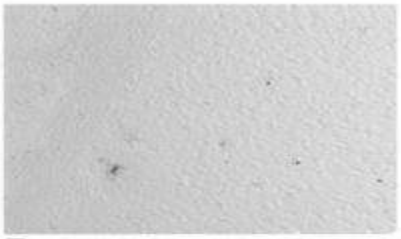
G APP/PS1 Saline



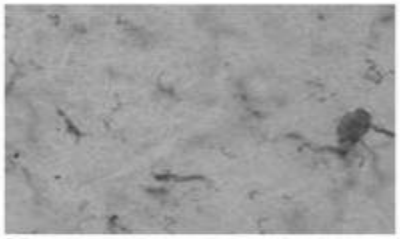
J APP/PS1 Saline



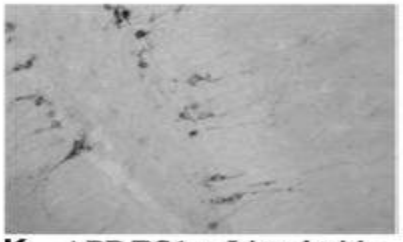
B APP/PS1 + Liraglutide



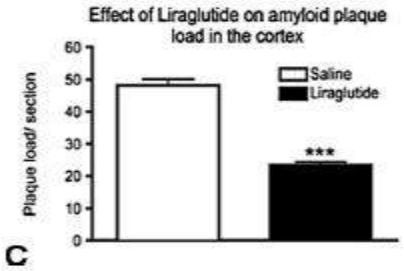
E APP/PS1 + Liraglutide



H APP/PS1 + Liraglutide



K APP/PS1 + Liraglutide



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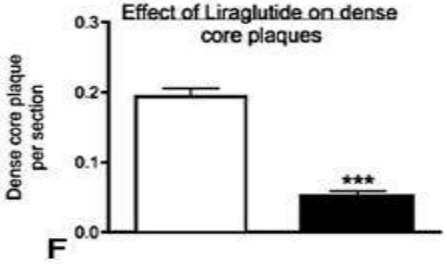

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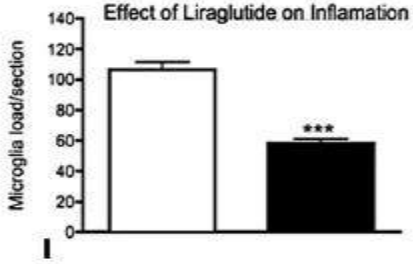

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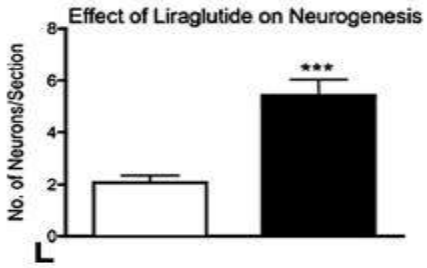

L

Christian Hölscher*

lzheimer's & Dementia 10 (2014) S47–S54

Exenatide as a potential treatment for patients with Parkinson's disease: First steps into the clinic

Table 1
Inclusion and exclusion criteria for completed and planned proof-of-concept exenatide trials

Inclusion criteria	Exclusion criteria
Patient has a diagnosis of idiopathic Parkinson's disease of moderate severity equivalent to Hoehn/Yahr stage 2 to 2.5 (bilateral symptoms but still physically independent). Patient is 45–75 years old. Patient is on L-dopa treatment. Patient demonstrates L-dopa responsiveness. Patient is able to give informed consent Patient is able to comply with trial protocol and willing to attend clinic necessary visits.	Patient has a diagnosis or suspicion of other cause for parkinsonism. Patient has a known abnormality on computed tomographic or magnetic resonance imaging brain images likely to compromise compliance with trial protocol. Patient has concurrent dementia. Patient has concurrent severe depression. Patient has prior intracerebral surgical intervention for Parkinson's disease. Patient is already participating actively in a trial of a device, drug, or surgical treatment for Parkinson's disease. Patient has diabetes mellitus. Patient has end-stage renal disease. Patient has a history of pancreatitis. Patient has severe gastrointestinal disease. Patient is pregnant or breastfeeding.

Alzheimer's & Dementia 10 (2014) S38–S46