Adipocytokine:
Its role in hypertension

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Pathophysiology of Hypertension

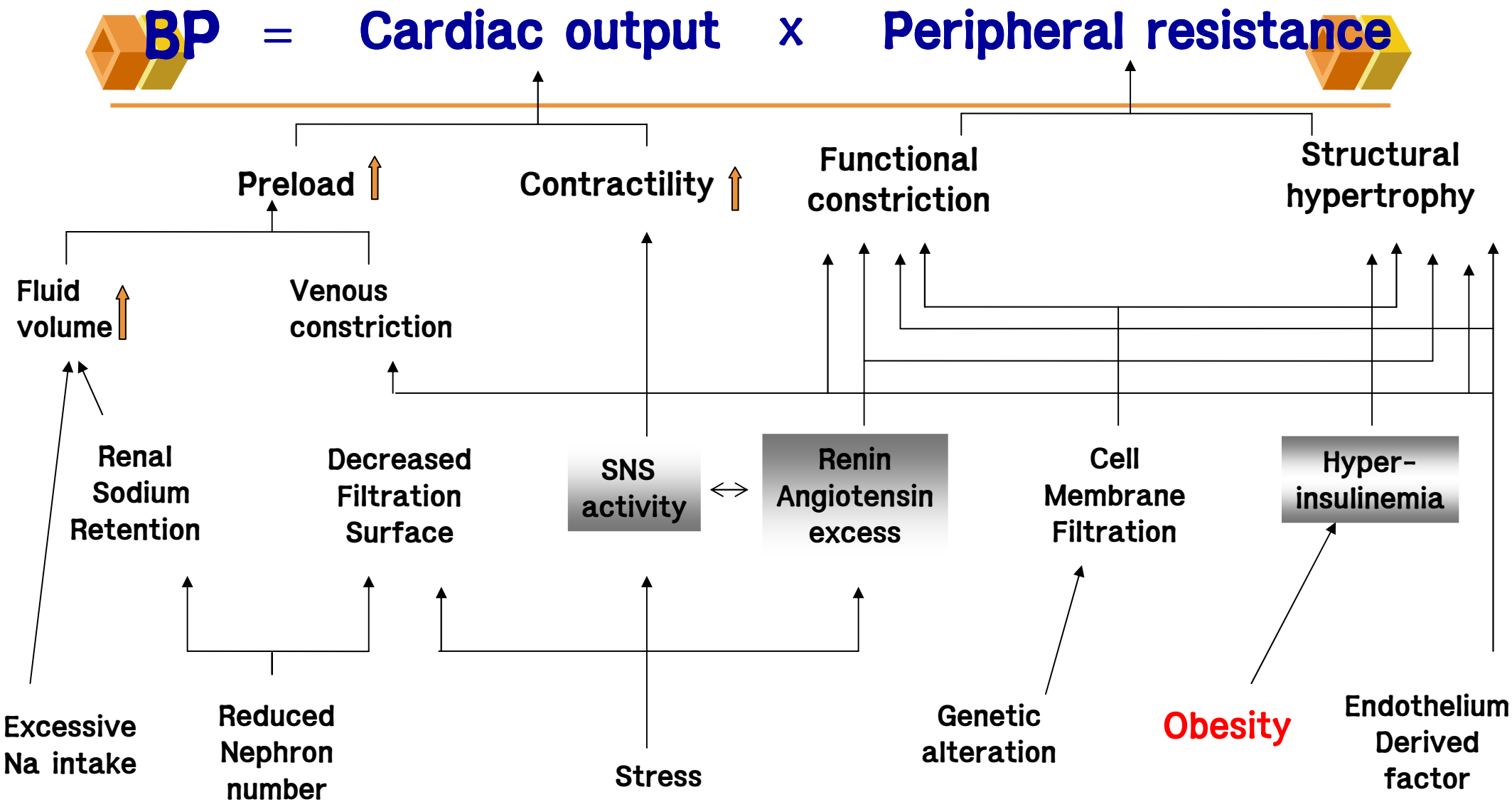
Familial predisposition

Newborn of hypertensive parents higher BP than normotensive parents
ACE gene: DD DI
high risk of HTN
Specific gene +
enviromental factors
– hypertension

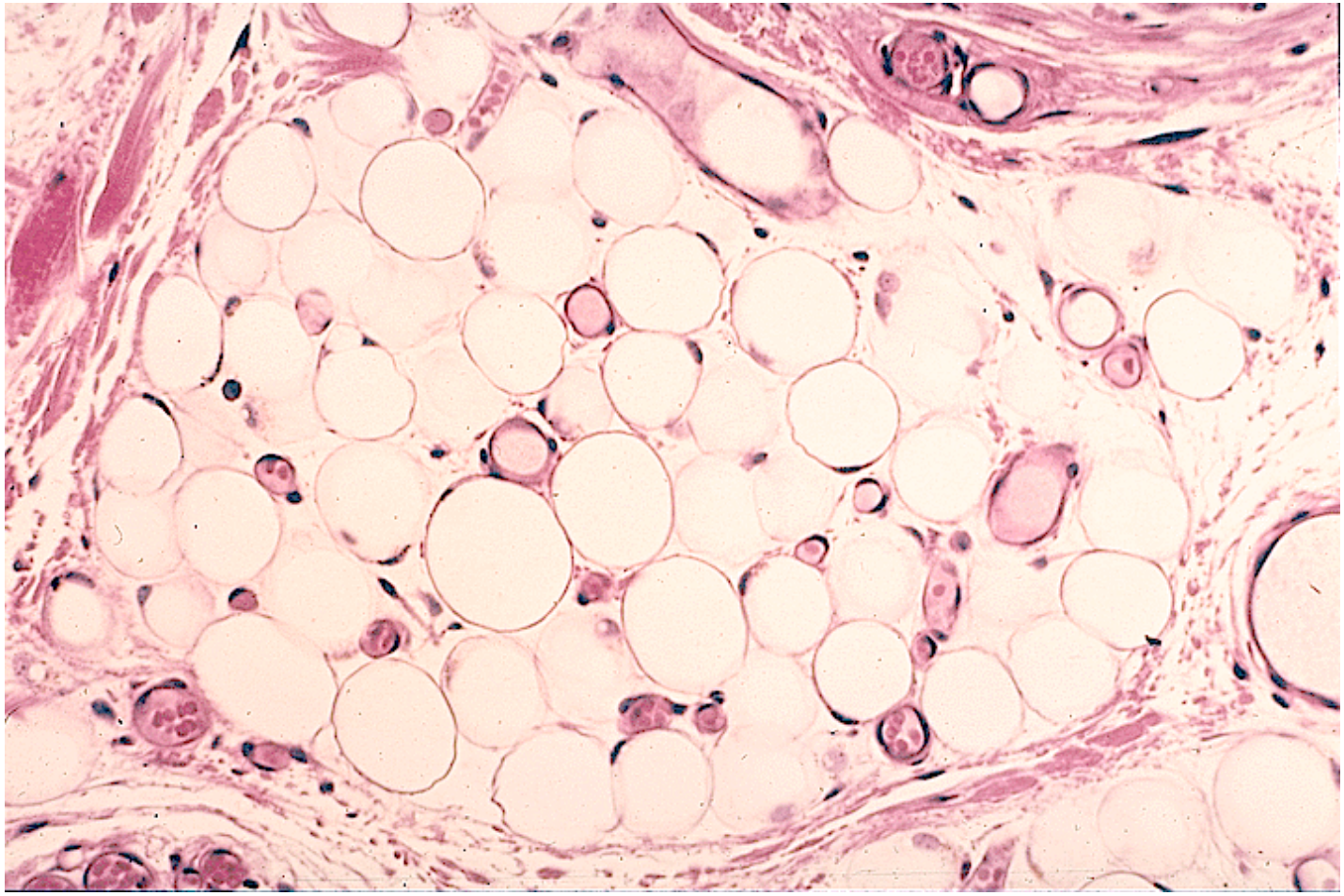
Environmental Influences:

+++ high Na intake:
+ correlation to HTN
+ low K intake
+ low Ca intake
+++ Obesity: central obesity
++ Alcohol: 30g/d
+ psychological stress
+ physical inactivity

Hypertension

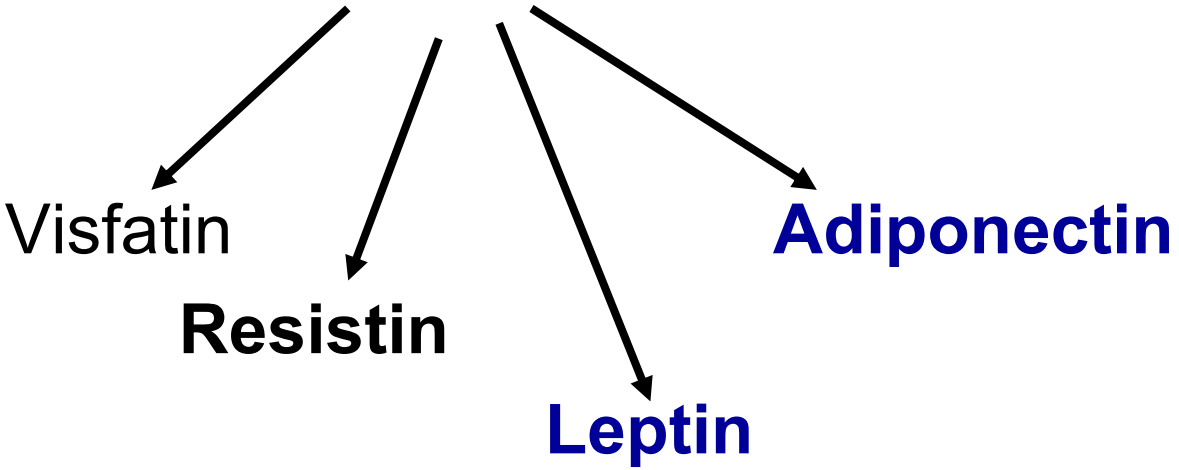

BP = Cardiac output x Peripheral resistance
Preload
Contractility
Functional constriction
Structural hypertrophy
Fluid volume
Venous constriction
Renal Sodium Retention
Decreased Filtration Surface
SNS activity
Renin Angiotensin excess
Cell Membrane Filtration
Hyper-insulinemia
Excessive Na intake
Reduced Nephron number
Stress
Genetic alteration
Obesity
Endothelium Derived factor

Adipose tissue



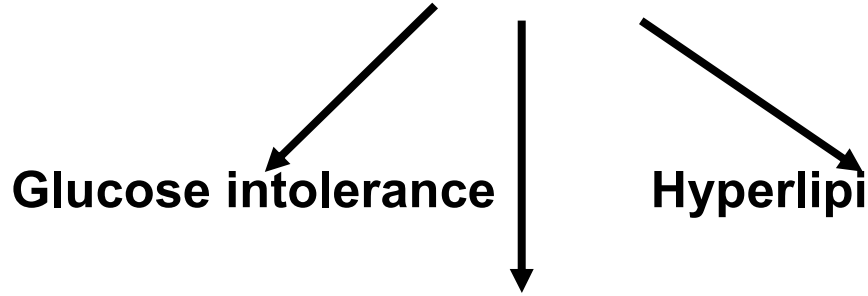
Adipose tissue

- Tradition – “energy storage organ”
- Adipose tissue – endocrine organ
- Secretes adipocytokines



Adipose Tissue Distribution

Visceral fat accumulation (correlates with)

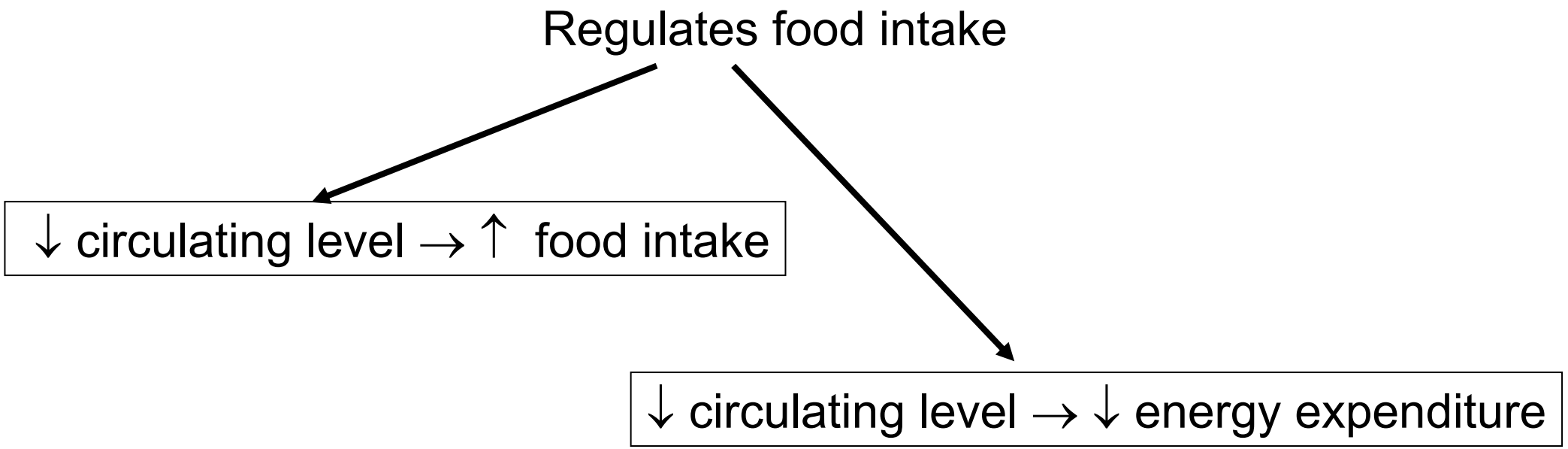


(visceral fat loss, not subcutaneous fat loss: ↓ BP)

Visceral fat accumulation also directly correlates to cardiac dysfunction and sleep apnea

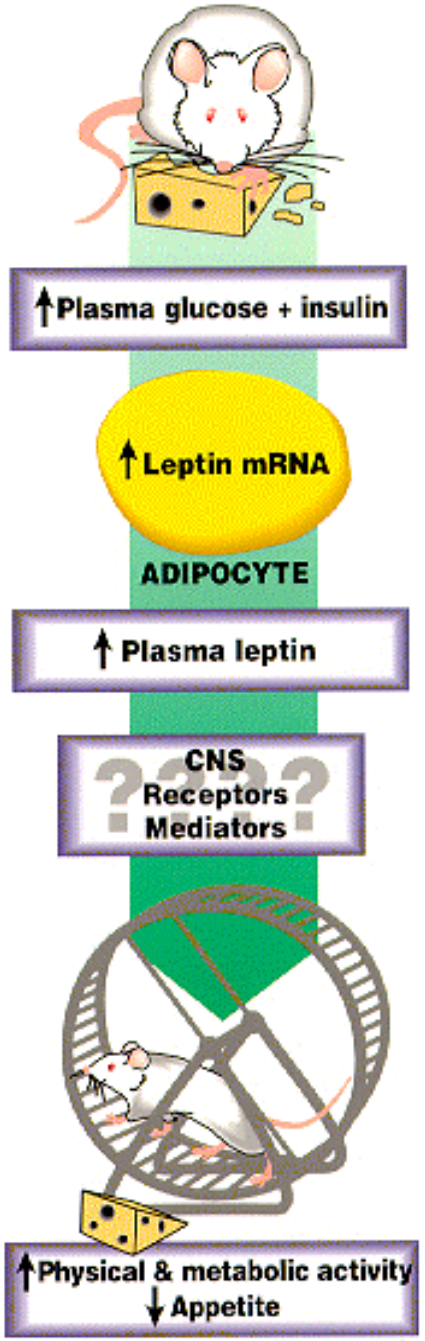
Visceral fat contains far more genes encoding secretory proteins than does subcutaneous fat.

Leptin


Regulates food intake
↓ circulating level → ↑ food intake
↓ circulating level → ↓ energy expenditure

Leptin

- An obesity factor
- Receptors are localized in hypothalamus
- Exogenous leptin reduced fat stores through a combination of increased metabolic activity and decreased food intake
- Induce insulin resistance



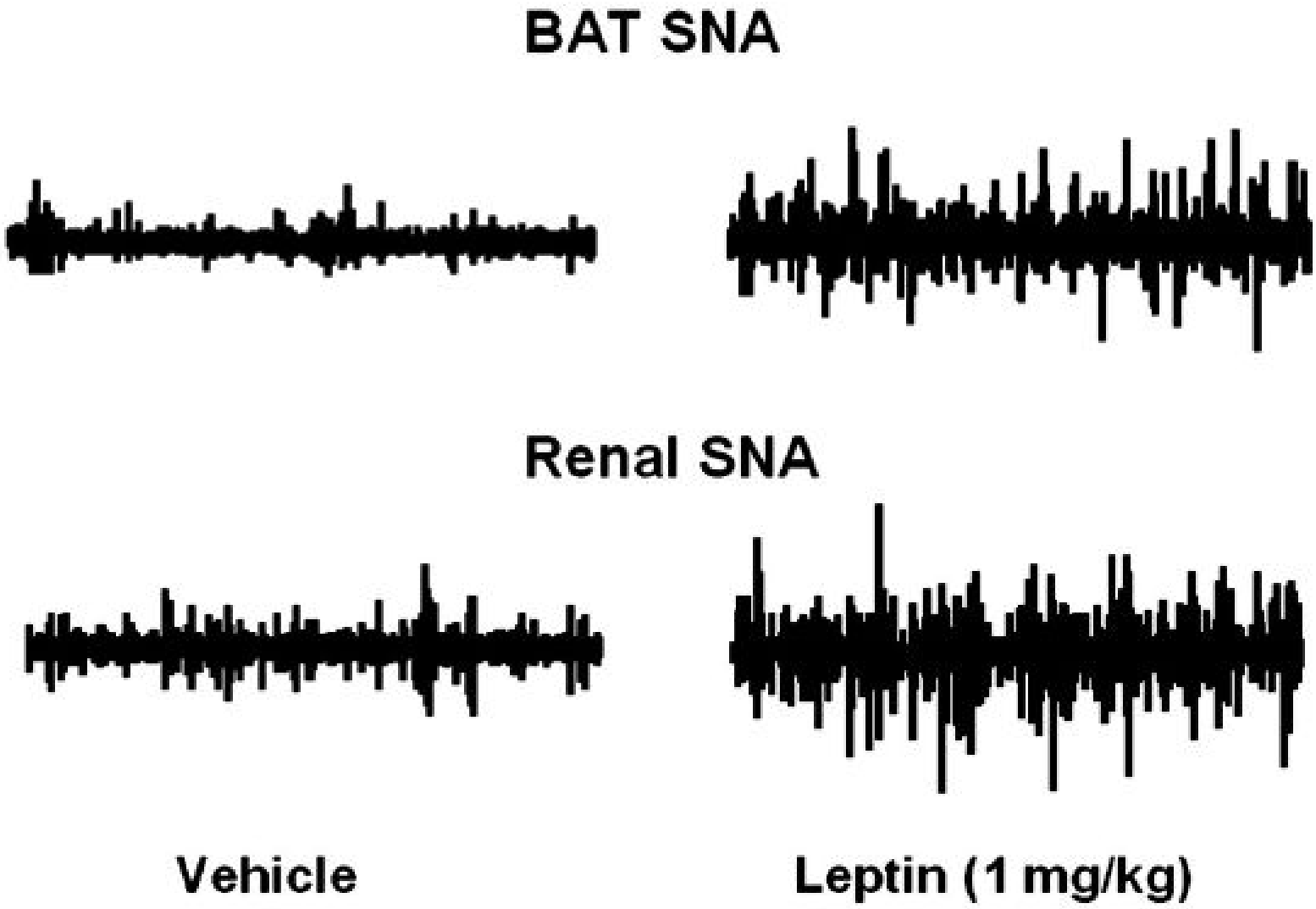
Leptin and blood pressure

- Animal study: clearly indicate an association between leptin and hypertension

- Human studies: less consistent
  - Kokot F et al: no relation with BP and leptin
  - Suter et al: hypertensive women only
  - Kennedy et al: hypertensive men only
  - Makris et al: higher leptin and insulin level in hypertensive offspring

Leptin and Blood pressure

- Pressor effect
  - Activation of SNA
  - Renal SNA activation –vasocnstriction/ renal tubular sodium reabsorption – slow increase mean arterial pressure
  - Shek et al: IV infusion of leptin – increase arterial pressure and heart rate



Effect of IV leptin(1mg/kg), as compared to vehicle, on SNA to brown adipose Tissue(BAT) and kidney in Sprague-Dawley rats. Leptin caused significant increase In both renal and BAT SNA

Leptin; animal experiments

- Intracerebro-ventricular leptin injection: mimic systemic administration(Matsumura et al 2000)
- Blockage of adrenergic system: inhibit pressor effect of leptin (Carlyle et al 2002)
- Transgenic mice overexpression in liver:
  - Leptin level: 10 times
  - Body weight:decrease
  - Urinary secretion of norepinephrine: increase

Leptin deficiency mice(ob/ob)

Zhang et al Nature 1994 372 435

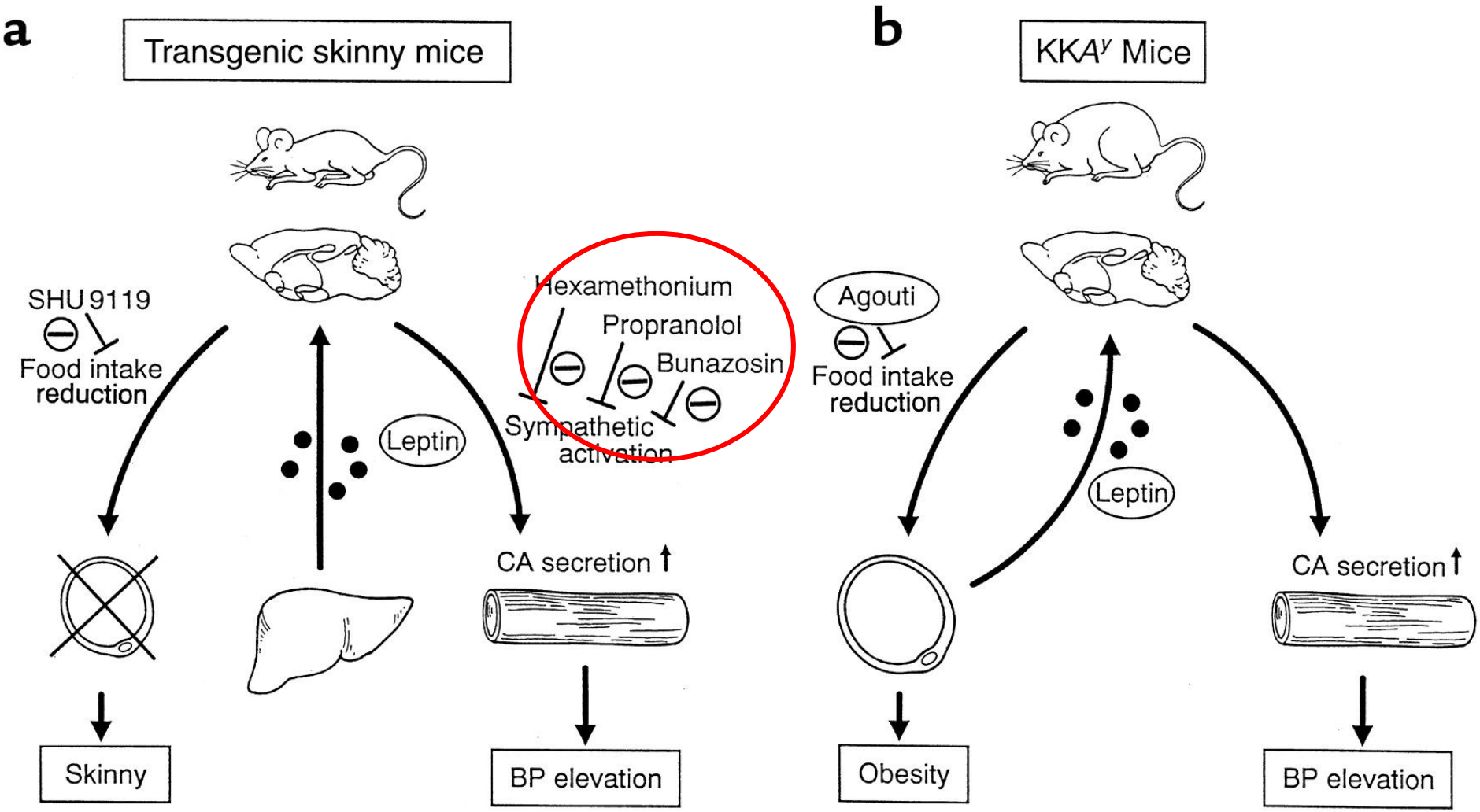
- Leptin deficiency mice(ob/ob)
  - Body weight; increase
  - Lower arterial pressure

  - Administration of leptin
    - Systolic BP: increase
    - Decrease food intake and body weight

Pathophysiological role of leptin in obesity-related hypertension

To explore the pathophysiological role of leptin in obesity-related hypertension, we examined cardiovascular phenotypes of transgenic skinny mice whose elevated plasma leptin concentrations are comparable to those seen in obese subjects. We also studied genetically obese KKA^y mice with hyperleptinemia, in which hypothalamic melanocortin system is antagonized by ectopic expression of the agouti protein. Systolic blood pressure (BP) and urinary catecholamine excretion are elevated in transgenic skinny mice relative to nontransgenic littermates. The BP elevation in transgenic skinny mice is abolished by α_1-adrenergic, β-adrenergic, or ganglionic blockers at doses that do not affect BP in nontransgenic littermates. Central administration of an α-melanocyte–stimulating hormone antagonist causes a marked increase in cumulative food intake but no significant changes in BP. The obese KKA^y mice develop BP elevation with increased urinary catecholamine excretion relative to control KK mice. After a 2-week caloric restriction, BP elevation is reversed in nontransgenic littermates with the A^y allele, in parallel with a reduction in plasma leptin concentrations, but is sustained in transgenic mice overexpressing leptin with the A^y allele, which remain hyperleptinemic. This study demonstrates BP elevation in transgenic skinny mice and obese KKA^y mice that are both hyperleptinemic, thereby suggesting the pathophysiological role of leptin in some forms of obesity-related hypertension.

J. Clin. Invest. **105**:1243–1252 (2000).



Aizawa-Abe, M. et al. J. Clin. Invest. 2000;105:1243-1252

Leptin related with hypertension idependantly body mass index

Table 3. Comparison of age- and BMI-matched overweight participants with different plasma leptin levels

	Low leptin (I tertile)	High leptin (III tertile)	p*
N	25	25	
Age (years)	49.7 ± 5.4	50.0 ± 5.3	NS
BMI (kg/m^2)	27.0 ± 1.6	27.0 ± 1.6	NS
Waist (cm)	93.8 ± 3.7	95.6 ± 4.2	NS
Leptin (ng/mL)	2.01 ± 0.50	5.55 ± 1.02	<0.001
Systolic BP (mm Hg)	123 ± 16	132 ± 16	<0.05
Diastolic BP (mm Hg)	81 ± 8	86 ± 10	<0.05
Heart rate (beats/min)	59.1 ± 9.4	63.7 ± 8.2	NS
Serum insulin (μU/mL)	8.37 ± 3.48	9.21 ± 3.22	NS
HOMA index	2.04 ± 0.94	2.41 ± 1.04	NS
Serum creatinine (μM)	89.0 ± 11.8	92.8 ± 7.2	NS

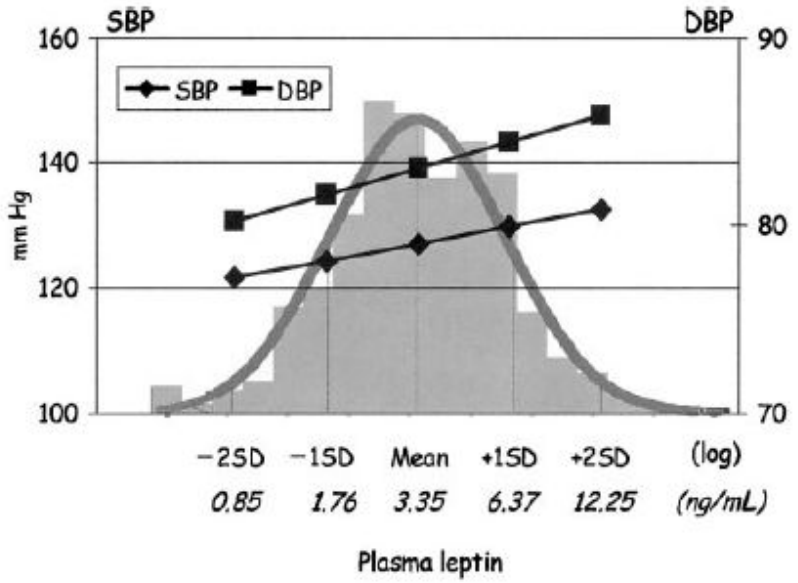
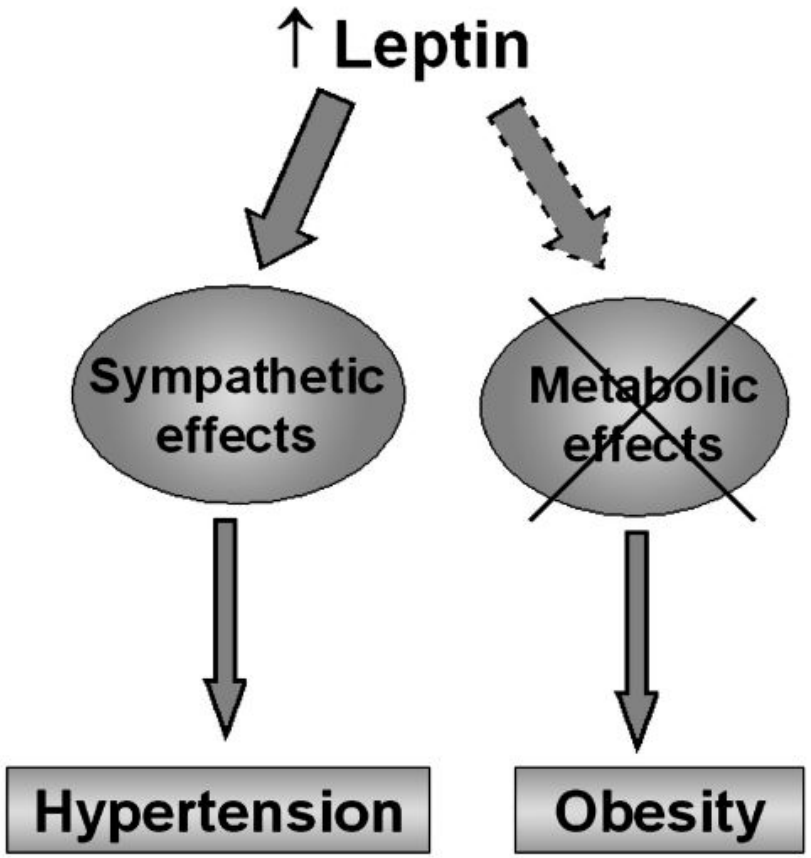


Figure 1: Trends in systolic and diastolic BP according to plasma leptin distribution and levels. Linear regression line of BP on log-leptin after adjustment for age and waist circumference. Each point represents the estimated BP value corresponding to the mean log-leptin concentration for the population and for log-leptin 1 or 2 SDs above or below the median. The corresponding actual plasma leptin levels are also reported.

Obesity reserch 2003, 11;160

Leptin resistance

- High circulating leptin level
- Obesity related hypertension



Other mechanism

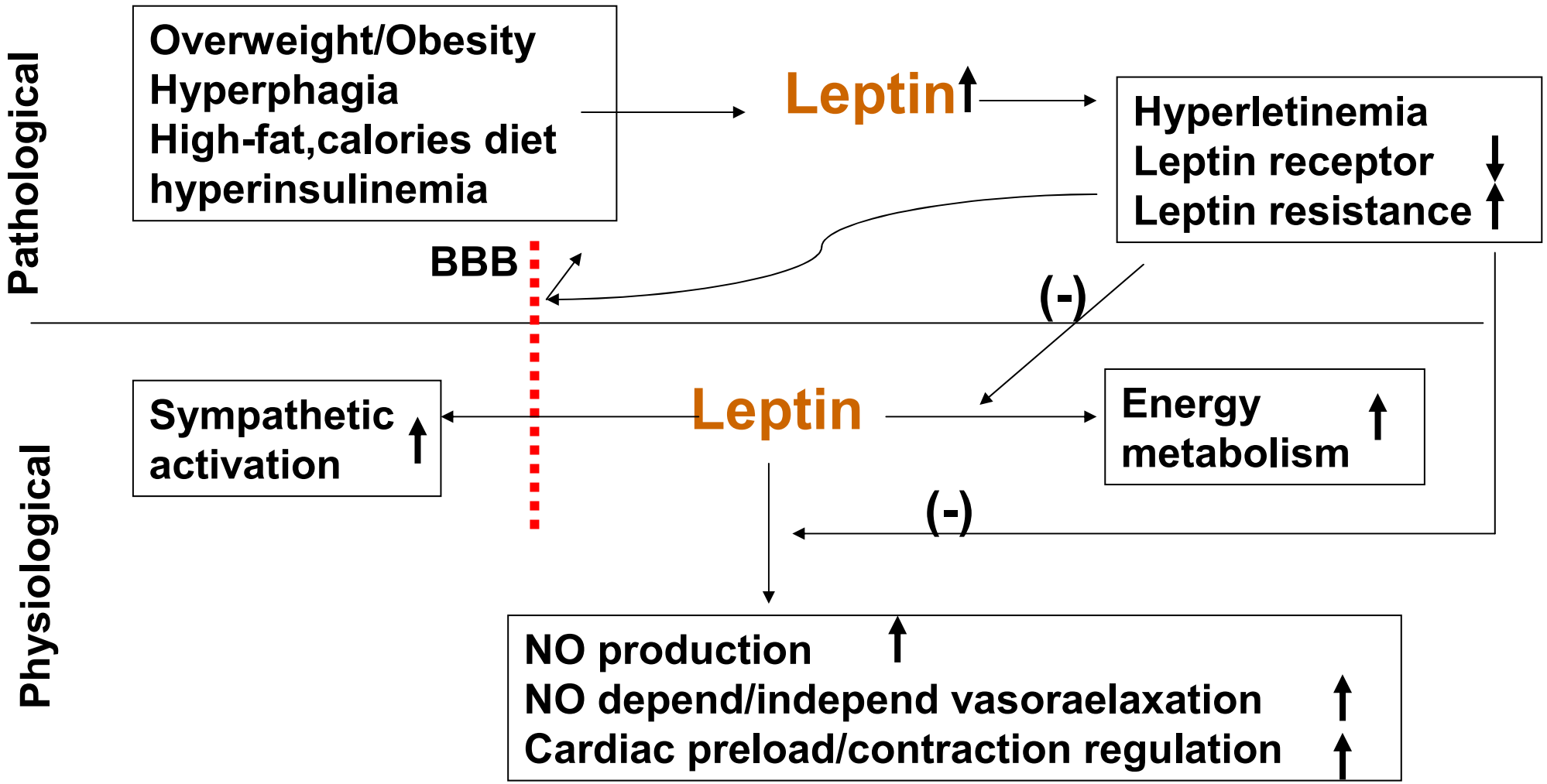
- Generation of ROS – Oxidative stress of endothelium: increase

- Pro-inflammatory cytokines: TNF-alpha, IL-6
  -promote hypertension

Depressor Effect of Leptin

- Leptin receptor of endothelium
  – NO production ↑
- Leptin: dose dependant NO production
  -Blood Pressure ↓
- SNA blocking – leptin administration
  -Blood pressure ↓
- Endothelial dependant vasodilation caused decrease blood pressure

Regulation of the sympathetic, metabolic and cardiovascular function of leptin



ADIPONECTIN

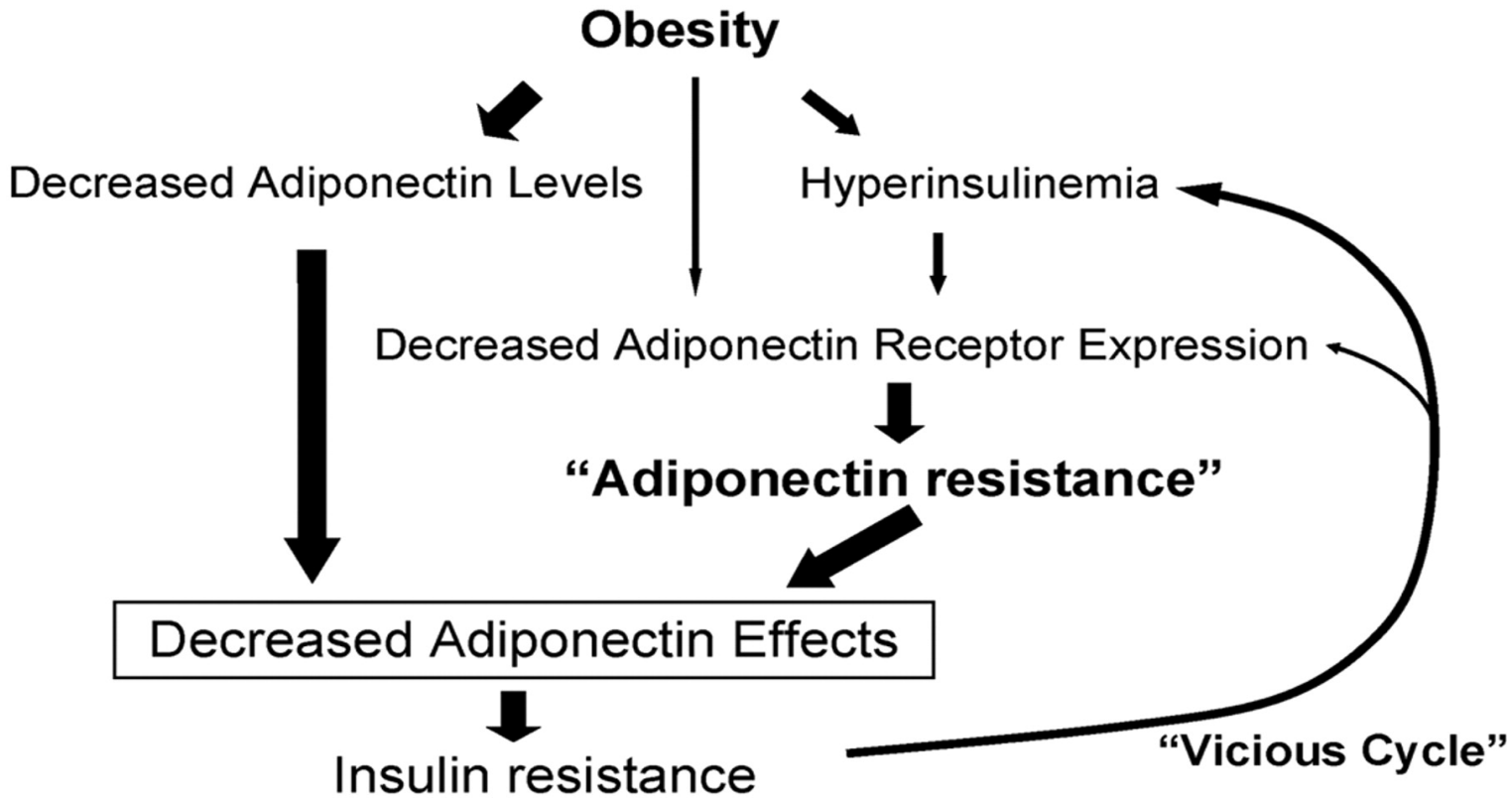
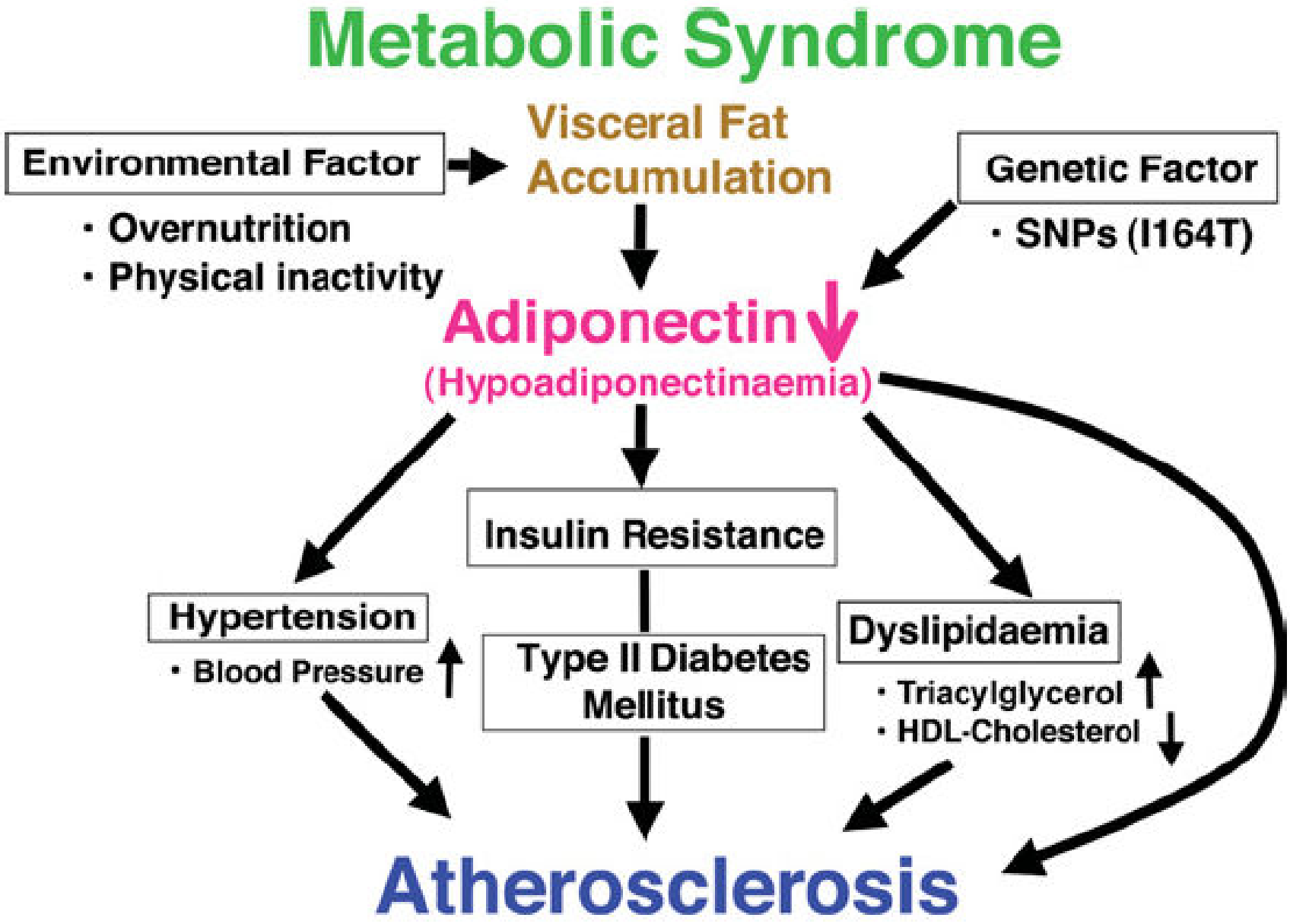


FIG. Obesity, adiponectin resistance, and insulin resistance

Kadowaki, T. et al. Endocr Rev 2005;26:439-451

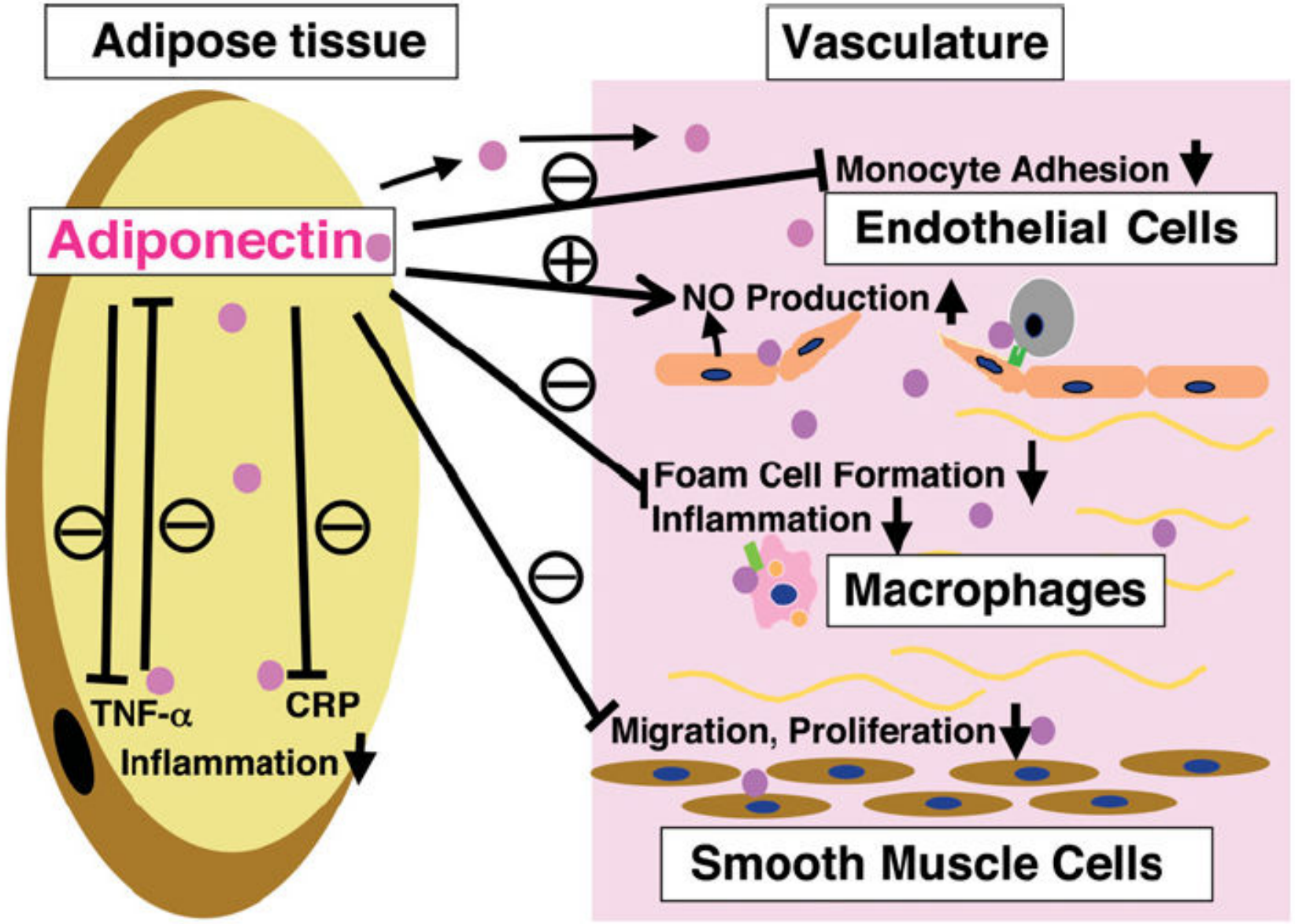

Metabolic Syndrome
Environmental Factor
• Overnutrition
• Physical inactivity
Visceral Fat Accumulation
Genetic Factor
• SNPs (I164T)
Adiponectin
(Hypoadiponectinaemia)
Insulin Resistance
Hypertension
• Blood Pressure
Type II Diabetes Mellitus
Dyslipidaemia
• Triacylglycerol
• HDL-Cholesterol
Atherosclerosis

Adiponectin

- High in plasma in humans (5-10μg/ml) – negatively correlated to BMI
- Negative correlation stronger with visceral fat accumulation than subcutaneous fat accumulation
- Adipocyte hypertrophy (and subsequent insulin resistance) causes ↓ adiponectin secretion

- ↓ adiponectin levels correlate directly with insulin sensitivity
  ↓ adiponectin - ↑ insulin resistance – Metabolic function

- ↓ adiponectin is also associated with hypertension
- endothelium dependent vasoreactivity is ↓ in hypoadiponectinemia – Vascular function



Role of adiponectin

Vascular Effects of Adiponectin

(Matsuzawa et al., 2005)

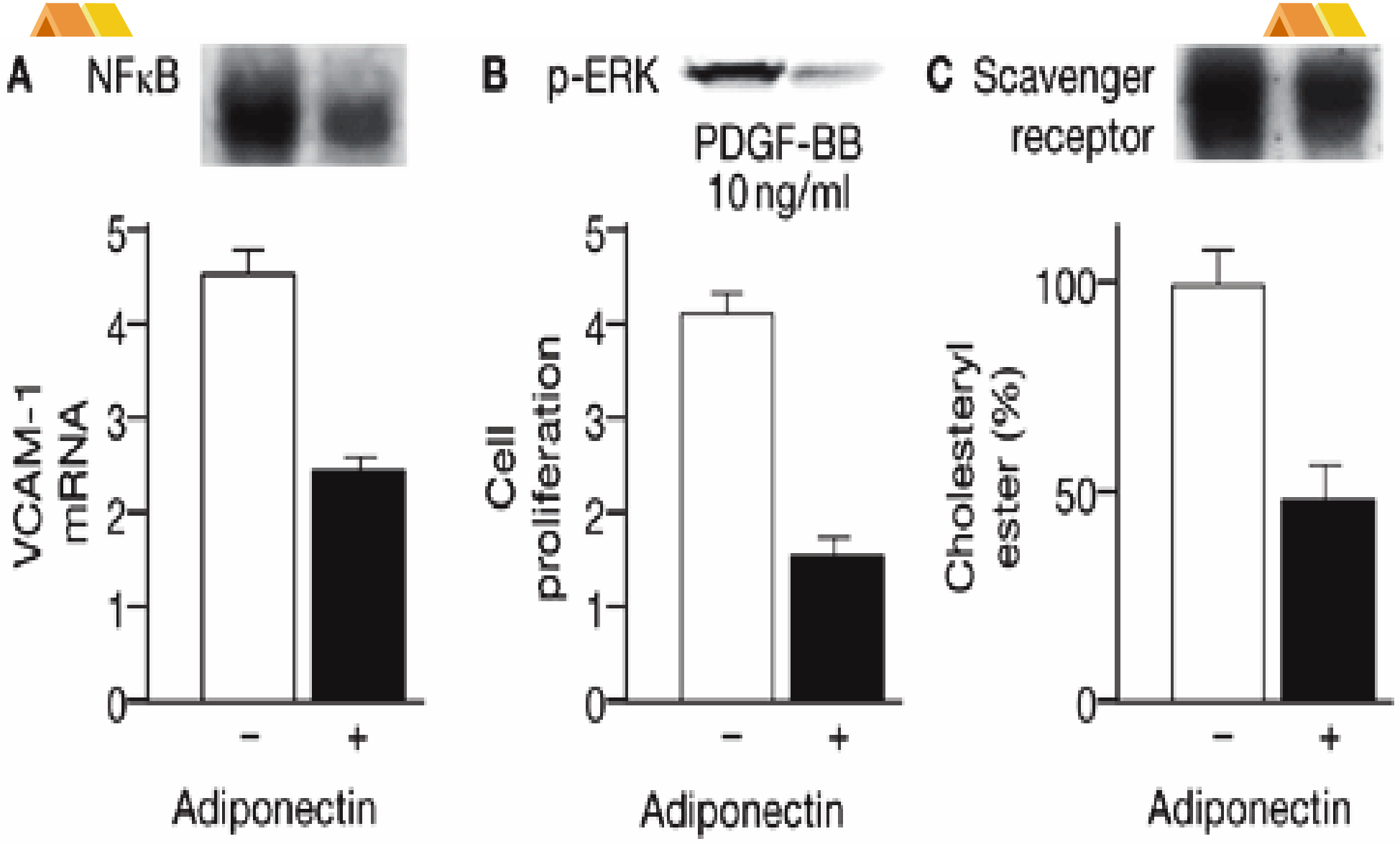
- Adiponectin KO mice develop more severe intimal thickening after endothelial damage
- After balloon induced injury of endothelium , several adiponectin positive cells in vascular wall (immunohistochemistry)

1) Adiponectin binds collagen V, VIII and X.

2) Suppresses monocyte attachment to endothelial cells by inhibiting the expression of adhesion molecules such as VCAM-1 and intracellular-adhesion molecule-1

3) Suppresses growth factor induced proliferation of VSM cells by inhibiting MAP kinases

4) Inhibits foam cell formation (cholesteryl ester accumulation) by inhibiting expression of scavenger receptors on macrophages



Vascular cell adhesion molecule

Adiponectin Replenishment Ameliorates Obesity-Related Hypertension

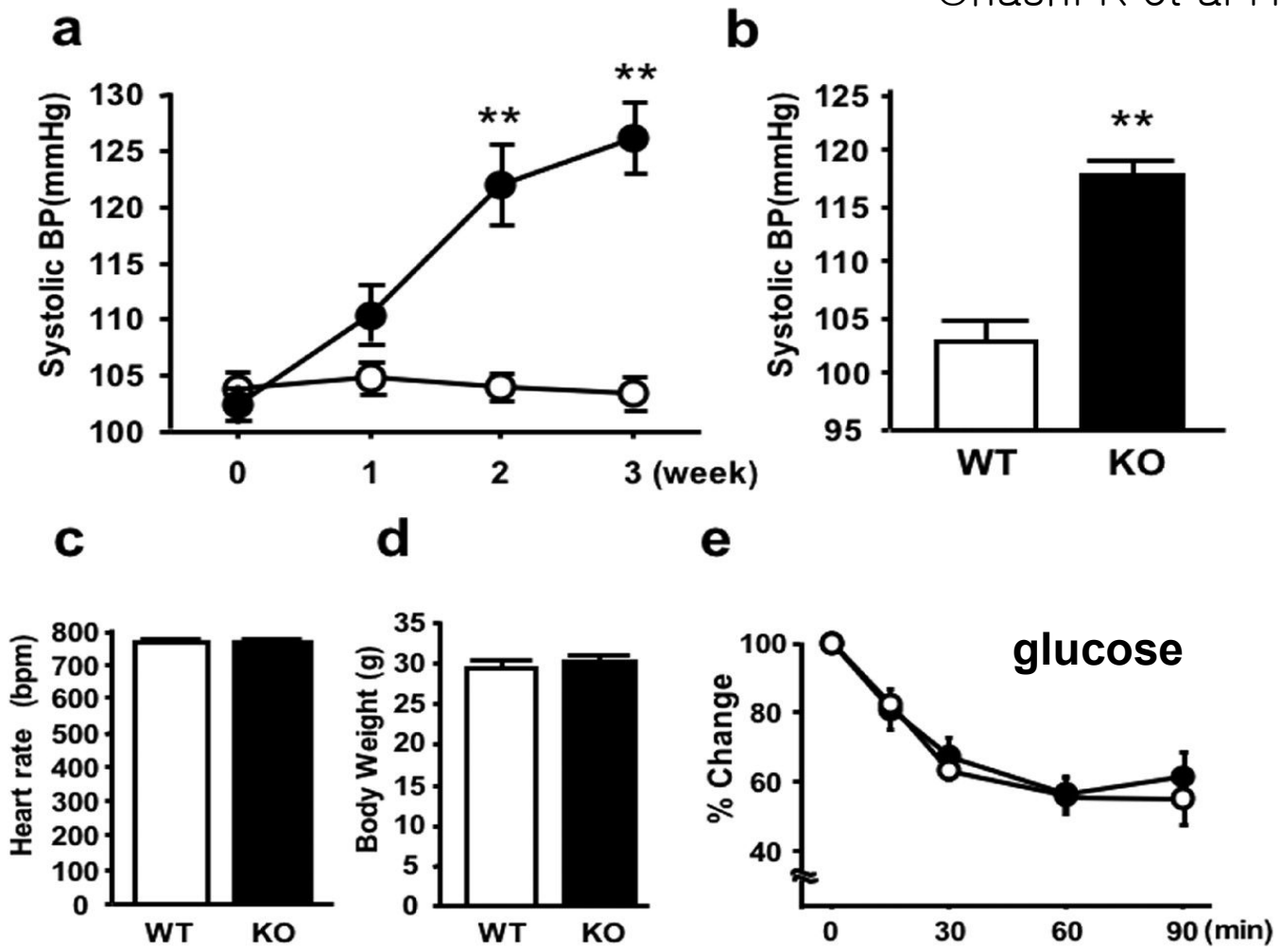
Koji Ohashi, Shinji Kihara, Noriyuki Ouchi, Masahiro Kumada, Koichi Fujita, Aki Hiuge, Toshiyuki Hibuse, Miwa Ryo, Hitoshi Nishizawa, Norikazu Maeda, Kazuhisa Maeda, Rei Shibata, Kenneth Walsh, Tohru Funahashi, Iichiro Shimomura

Abstract—Patients with obesity are susceptible to hypertension. We have reported that the plasma adiponectin levels are decreased in obesity and that adiponectin has many defensive properties against obesity-related diseases, such as type 2 diabetes and coronary artery disease. The aim of this study was to determine the relationship between adiponectin and hypertension in mice. We measured blood pressure and heart rate directly by a catheter in the carotid artery and indirectly by automatic sphygmomanometer at the tail artery. Obese KKAy mice had significantly lower plasma adiponectin levels and higher systolic blood pressure than control C57BL/6J mice at 21 weeks of age. Adenovirus-delivered adiponectin significantly decreased blood pressure in KKAy mice. The direct role of adiponectin on blood pressure regulation under insulin resistance–free state was investigated in adiponectin-knockout (KO) mice. Adiponectin KO mic istance. The hyperter NO synthase (eNOS) rostaglandin I_2 synth: nRNA levels to those of the wild type. Our results suggest that hypoadiponectinemia contributes to the development of obesity-related hypertension, at least in part, directly, in addition to its effect via insulin resistance, and that adiponectin therapy can be potentially useful for hypertension in patients with the metabolic syndrome. (*Hypertension*. 2006;47:1108-1116.)

Adiponectin contribute to the development of obesity related hypertension Adiponectin therapy can be useful for hhypertension in patients with the MS

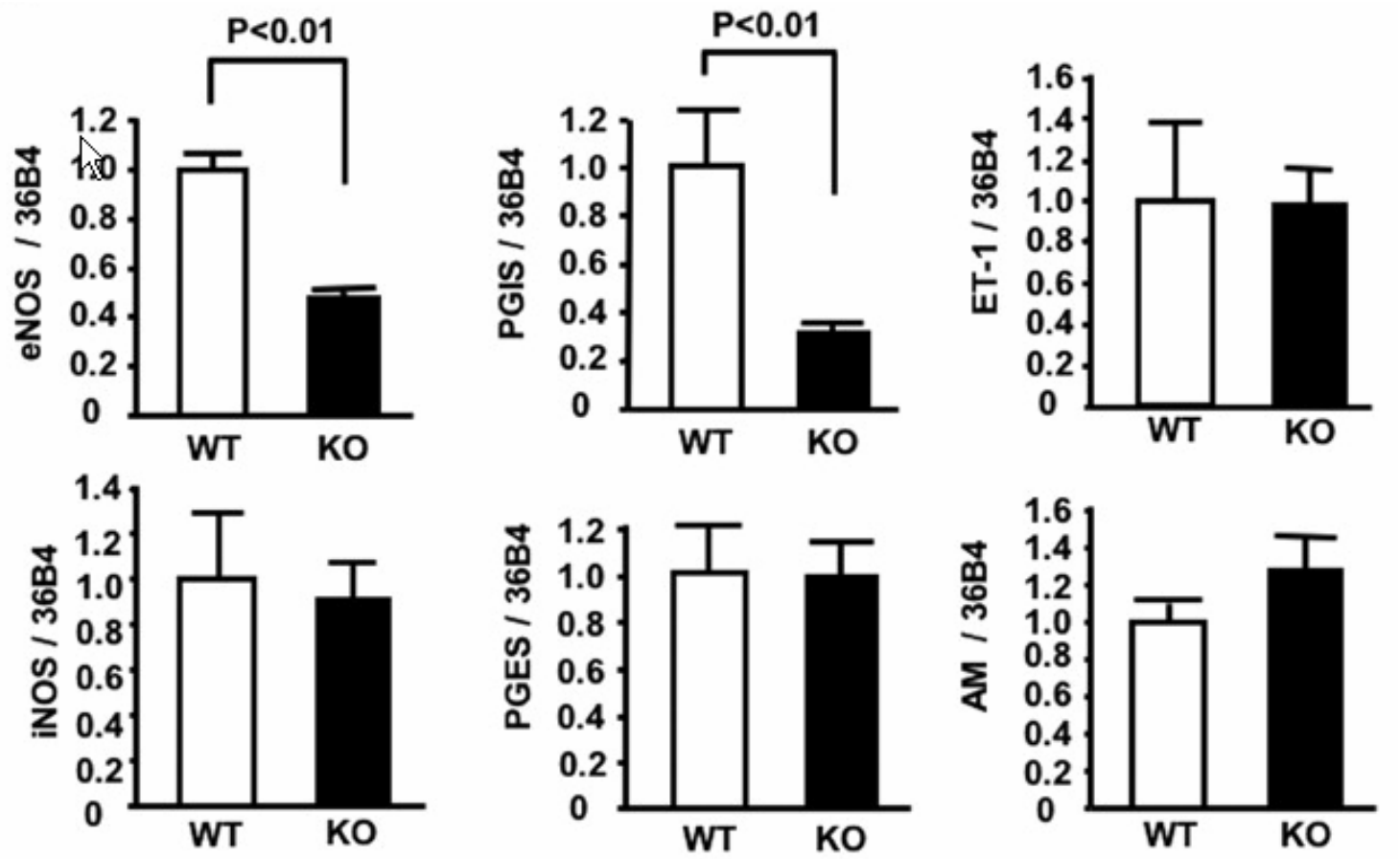
Role of adiponectin on blood pressure in salt induce hypertension

Ohashi K et al Hypertension 2006:47



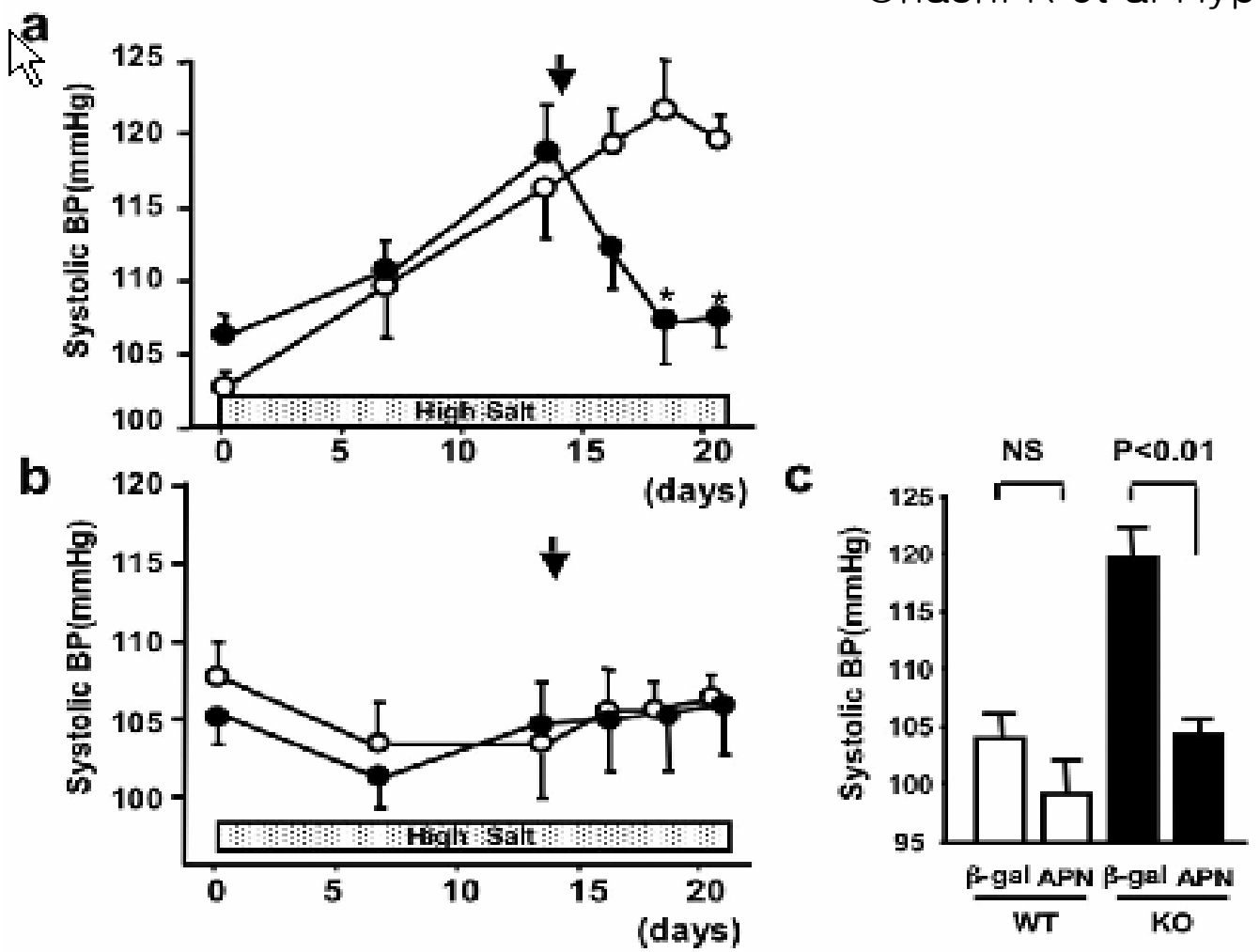
Reduced mRNA levels of eNOS and PGI2 synthase in aorta

Ohashi K et al Hypertension 2006:47



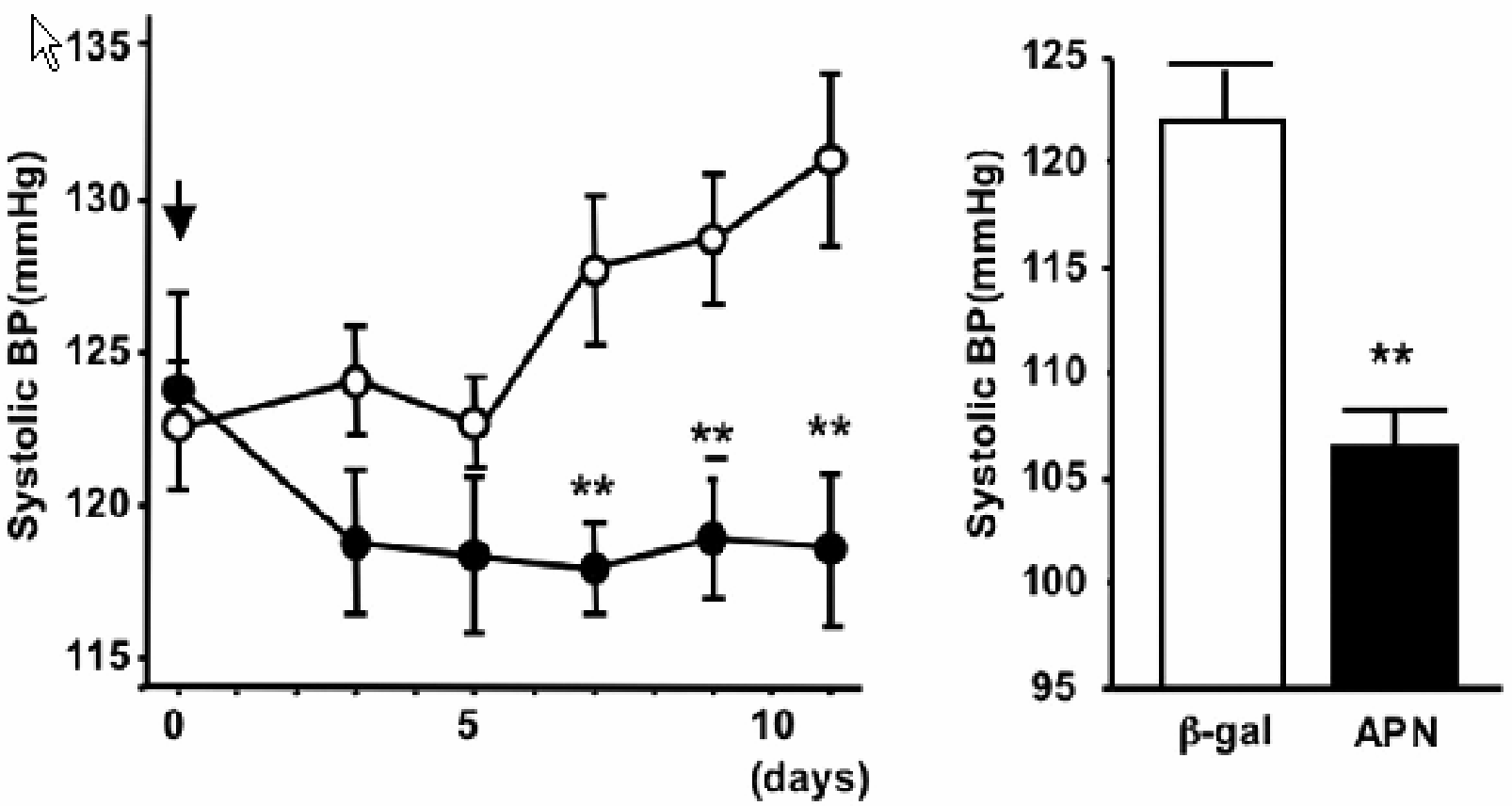
Attenuation of salt induced hypertension in APN-KO mice with Ad-APN supplementation

Ohashi K et al Hypertension 2006:47



Role of adiponectin on blood pressure in obesity related hypertension

Ohashi K et al Hypertension 2006:47

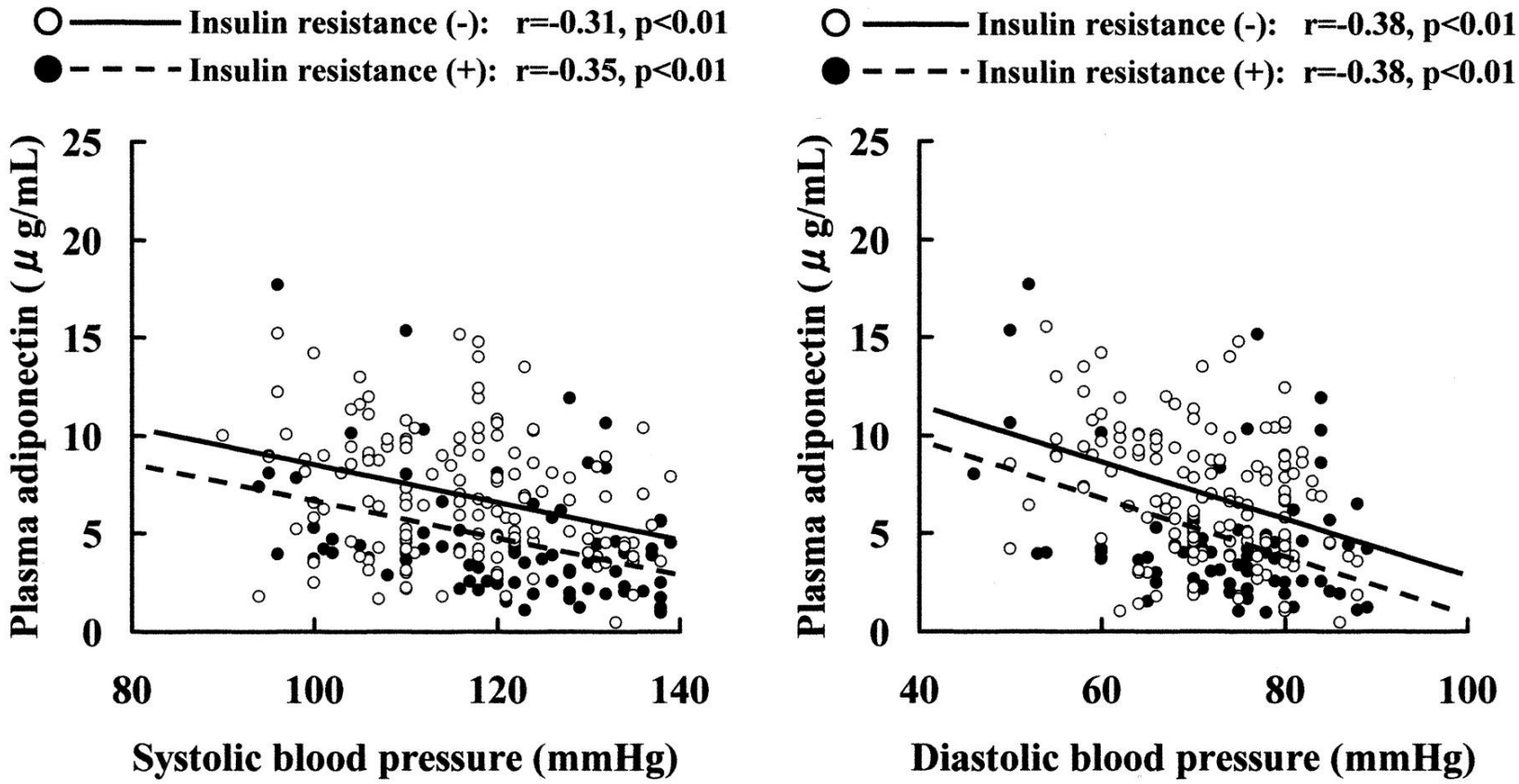


Hypoadiponectinemia Is an Independent Risk Factor for Hypertension

Yoshio Iwashima, Tomohiro Katsuya, Kazuhiko Ishikawa, Noriyuki Ouchi, Mitsuru Ohishi, Ken Sugimoto, Yuxiao Fu, Masaharu Motone, Kouichi Yamamoto, Akiko Matsuo, Koji Ohashi, Shinji Kihara, Tohru Funahashi, Hiromi Rakugi, Yuji Matsuzawa, Toshio Ogihara

Abstract—Adiponectin is one of the key molecules in the metabolic syndrome, and its concentration is decreased in obesity, type-2 diabetes, and coronary artery disease. Genetic investigation has revealed that 2 polymorphisms (I164T and G276T) are related to adiponectin concentration and diabetes. To examine whether adiponectin affects hypertension genetically or biologically, we performed a case-control study. A total of 446 diagnosed cases of hypertension (HT) in men and 312 normotensive (NT) men were enrolled in this study. Plasma adiponectin concentration was measured using an enzyme-linked immunosorbent assay system. Single nucleotide polymorphisms were determined by TaqMan polymerase chain reaction method. After adjustment for confounding factors, adiponectin concentration was significantly lower in HT (HT: 5.2±0.2 μg/mL; NT: 6.1±0.2 μg/mL; $P<0.001$). Furthermore, multiple regression analysis indicated that hypoadiponectinemia was an independent risk factor for hypertension ($P<0.001$). Blood pressure was inversely associated with adiponectin concentration in normotensives regardless of insulin resistance. In subjects carrying the TC genotype of the I164T polymorphism, adiponectin concentration was significantly lower (TC: 2.6±0.9 μg/mL; TT: 5.5±0.1 μg/mL; $P<0.01$), and most of them had hypertension. In contrast, the G276T polymorphism was not associated with adiponectin concentration or hypertension. In conclusion, hypoadiponectinemia is a marker for predisposition to hypertension in men. (***Hypertension*. 2004;43:1318-1323.**)

Correlation between plasma adiponectin concentration and blood pressure in normotensives without diabetes



Adiponectin

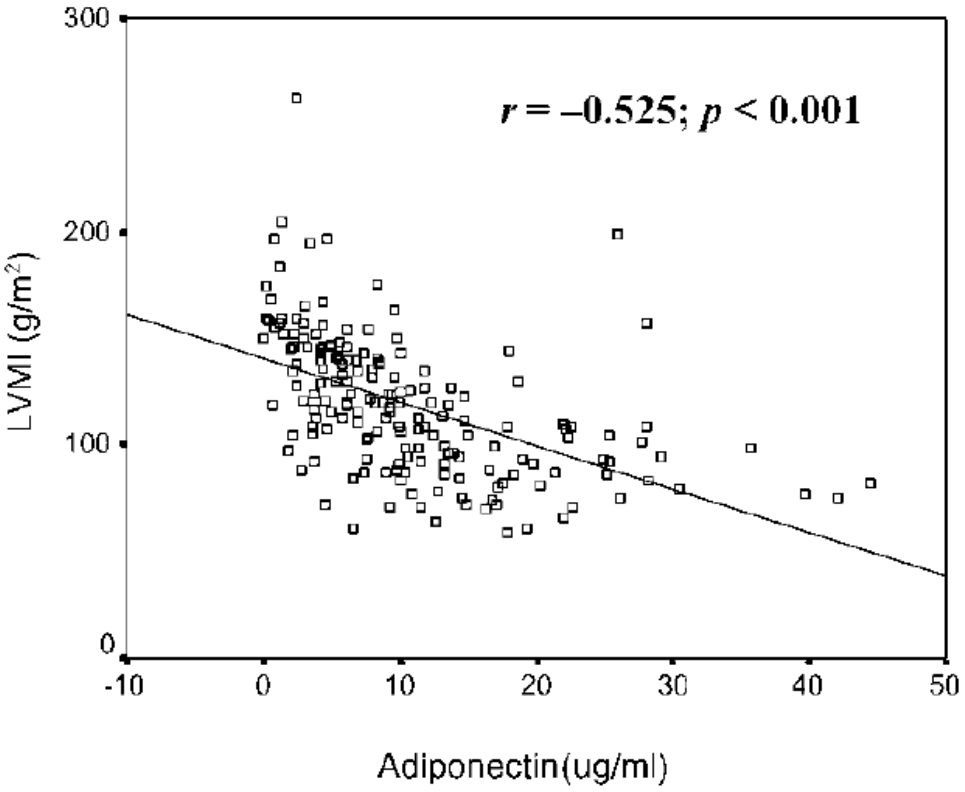


Fig. 3. The correlation between plasma adiponectin and left ventricular mass index (LVMI).

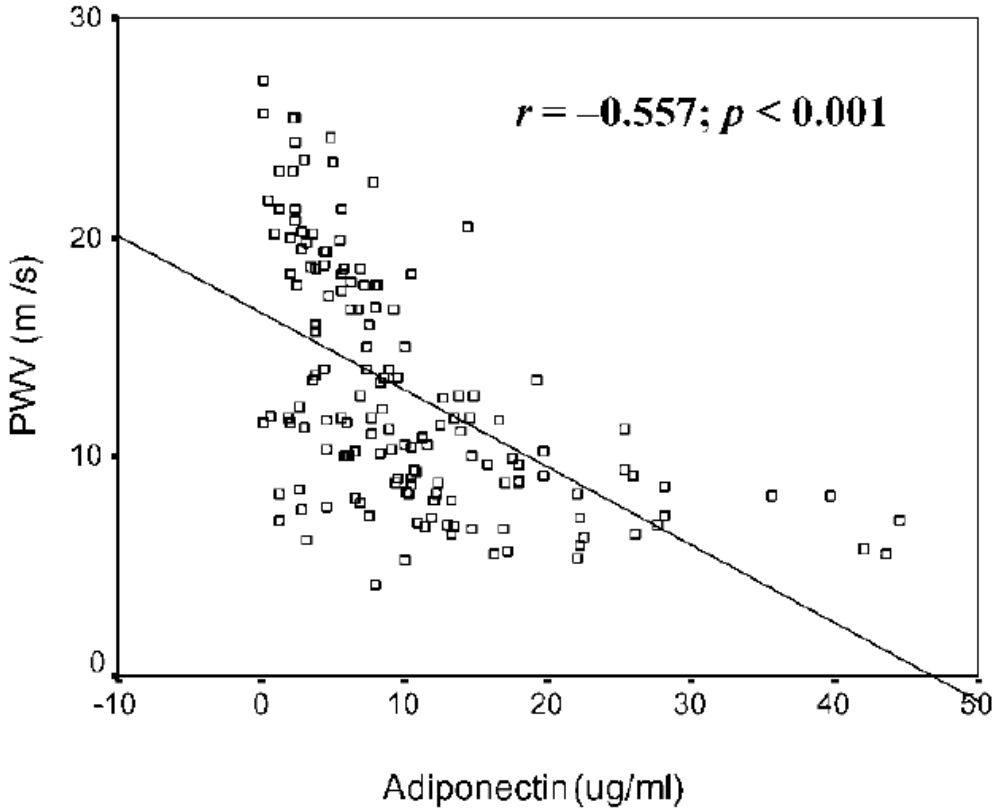


Fig. 4. The correlation between plasma adiponectin and pulse wave velocity (PWV).

Blood pressure 2004 Hong SJ et al

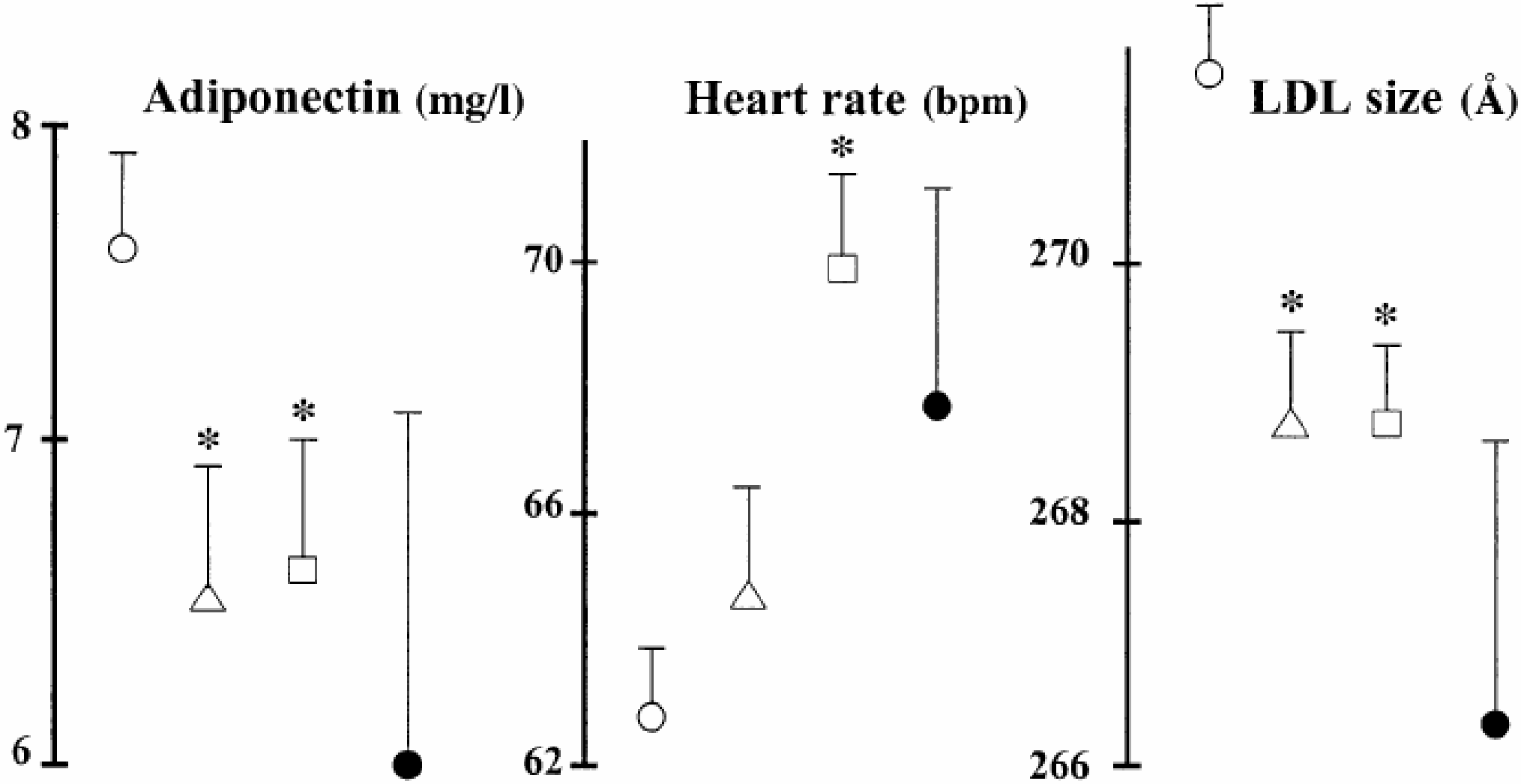


Figure 1—*BMI-adjusted least square means (±SE) of heart rate, serum adiponectin, and LDL size in young men with optimal (○; n = 83–90), normal (△; n = 45–52), high-normal (□; n = 39–46), and high (●, n = 10) BP. *P < 0.05 versus optimal BP analyzed using Tukey-Kramer's multiple comparison procedure.*

Katsumi T et al Diabetic care 2002

Possible mechanisms

- Adiponectin – independant vasodilator response to hyperemia
- Adiponectin gene expression- inhibit SNA
- Hypoadiponectinemia – enhance vascular injury via inflammation of vessel wall
- Activation of renin-angiotenisin system

Intervention to change adiponectin level

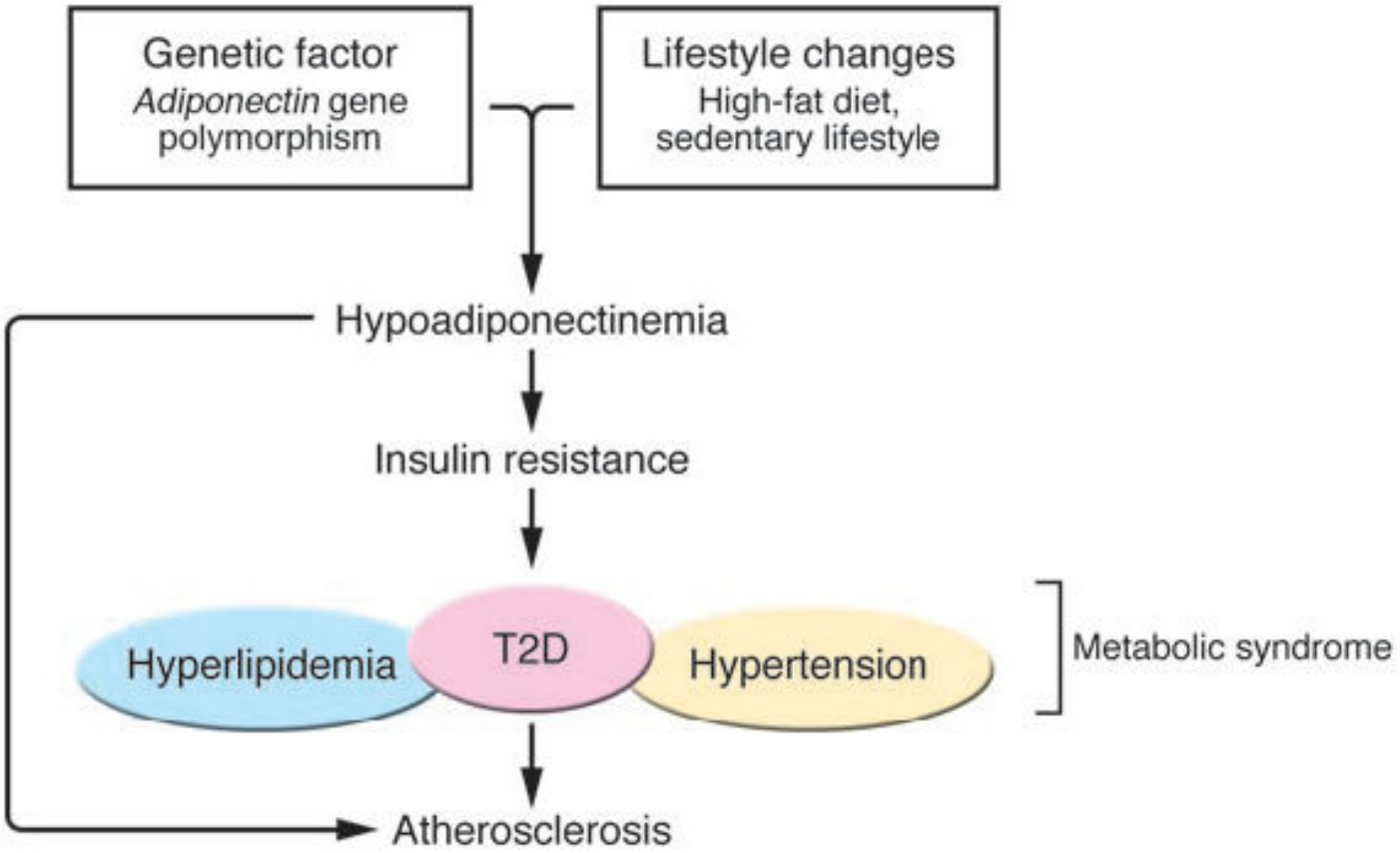


Table 1 Studies investigating the influence of antihypertensive agents on adiponectin levels

Study	*Number (n)*	*Drug(s)*	*Findings*	*Comments*
Furuhashi *et al.*[14]	50 (30 hypertensives, 20 normotensives)	Temocapril/candesartan	Decrease in blood pressure in 16/30 Lower adiponectin levels in insulin-resistant hypertensives than normotensives and non-insulin-resistant hypertensives Increase in adiponectin levels as well as insulin sensitivity with treatment	Hypoadiponectinaemia and insulin resistance are related in essential hypertension RAS blockade increases adiponectin levels with improvement in insulin sensitivity
Tomiyama *et al.*[15]	23 hypertensives	Temocapril–candesartan in a crossover trial	Endothelial function, bradykinin and nitric oxide higher after ACE-I treatment Insulin sensitivity and adiponectin levels similar after both treatments	ACE-I and ARB have similar effects on insulin sensitivity, despite the more pronounced effects of ACE-I on endothelial function Endothelial function, perhaps, is not a major determinant of insulin resistance under physiologic conditions
Nomura *et al.*[16]	53 hypertensives (±diabetes mellitus) vs 20 normotensives	Valsartan	Adiponectin levels significantly low in hypertensives with type II diabetes ($P<0.01$), but increased with valsartan treatment (before vs after: 5.2 ± 2.5 vs 7.6 ± 2.7 Ag/ml, $P<0.001$) Monocyte activation markers, monocyte cheomotactic peptide, monocyte-derived micro particles, endothelial cell activation markers and soluble vascular cell adhesion molecule-1 significantly raised in the above group ($P<0.01$), but found to fall with valsartan treatment	Angiotensin II receptor blockade may be beneficial as an antiatherosclerotic therapy in patients with type II diabetes, in addition to its antihypertensive action
Nowak *et al.*[17]	20 hypertensives	Rilmenidine	Six-month treatment with rilmenidine resulted in a significant decrease in systolic ($P=0.007$), diastolic and mean arterial blood pressure ($P=0.002$) Plasma adiponectin levels increased significantly with treatment (12.5 ± 6.1 to 16.9 ± 11.1; $P=0.0002$)	Rilmenidine therapy correlated with an increase in adiponectin levels without any significant changes of insulin sensitivity and body fat content
Nomura *et al.*[18]	103 (73 hypertensives & 30 normotensives); 40/73 with type 2 diabetes	Nifedipine	Hypertensives with type II diabetes found to have significantly low levels of adiponectin compared to normotensive controls ($P<0.01$) Six-month nifedipine therapy reduced blood pressure, with a significant rise in adiponectin levels in subjects with type II diabetes ($P<0.01$) Significant fall in the baseline high levels of procoagulant markers (platelet- and monocyte-derived microparticles) in hypertensives with diabetes with nifedipine therapy	Nifedipine therapy improved platelet activation markers, micro particles and adiponectin levels in hypertensive patients with type II diabetes Nifedipine has possible beneficial antiatherosclerotic effects in addition to its antihypertensive action

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin–angiotensin system.

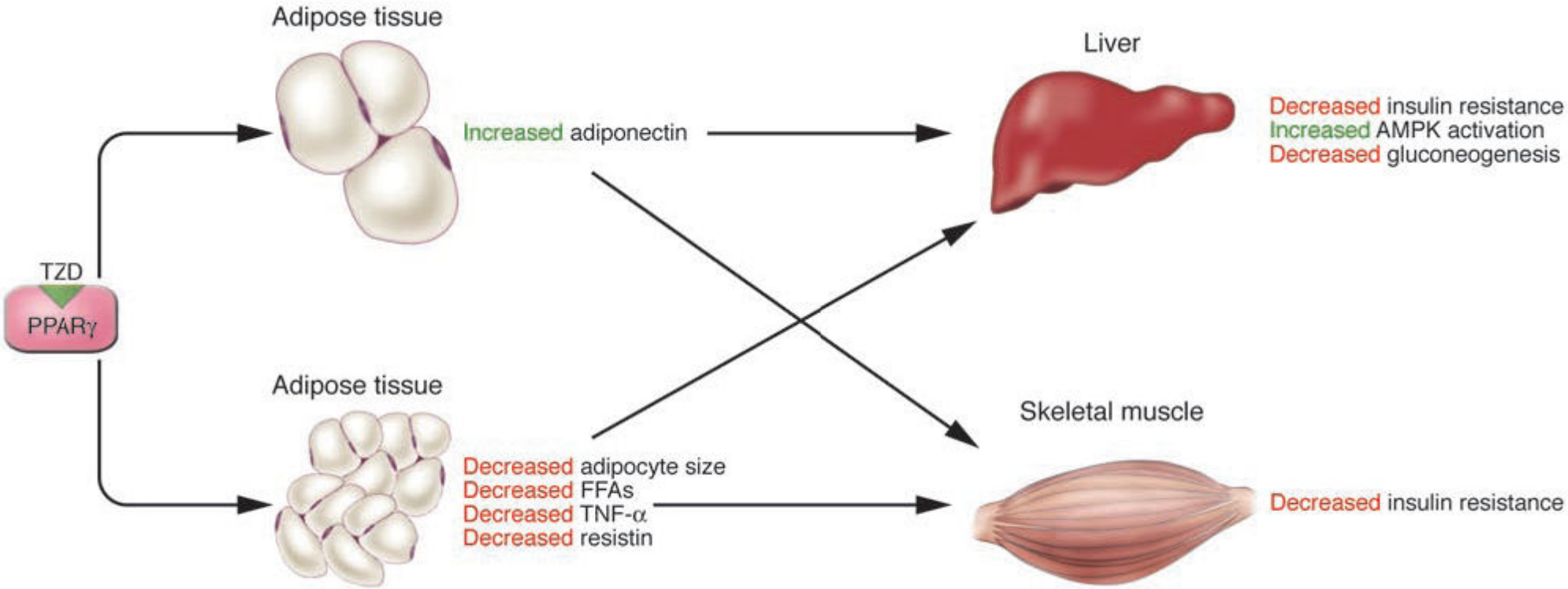
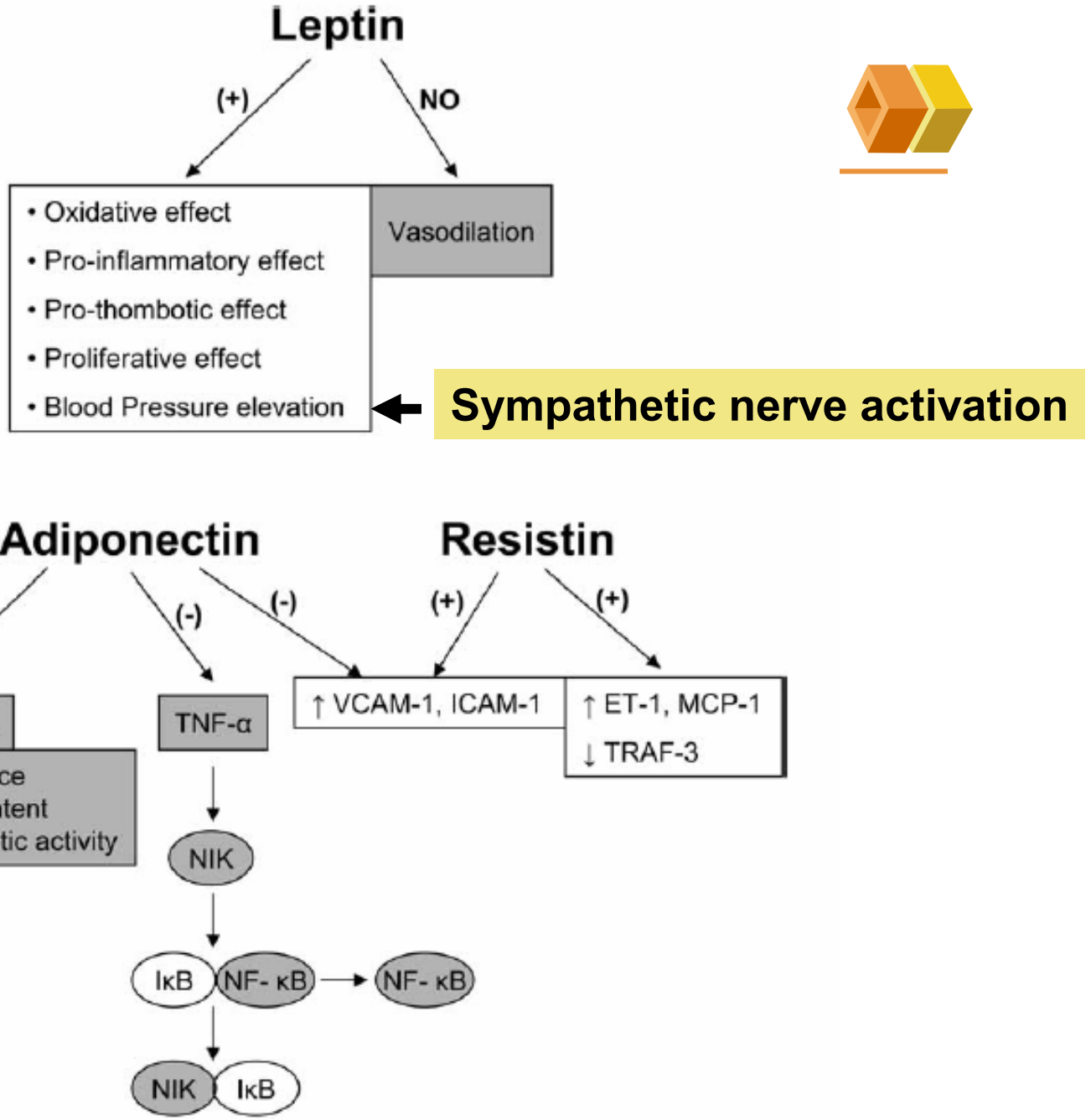


Figure 4

TZDs ameliorate insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. We propose that there are 2 different pathways in the amelioration of insulin resistance induced by the PPARγ agonists TZDs, such as pioglitazone and probably rosiglitazone. One involves an adiponectin-dependent pathway and the other an adiponectin-independent pathway. TZDs increase adiponectin levels, ameliorating insulin resistance, increasing AMPK activation, and decreasing gluconeogenesis in the liver. On the other hand, independently of adiponectin, TZDs decrease adipocyte size, serum FFA levels, and expression of TNF-α and resistin, thus contributing to amelioration of insulin resistance in skeletal muscle.

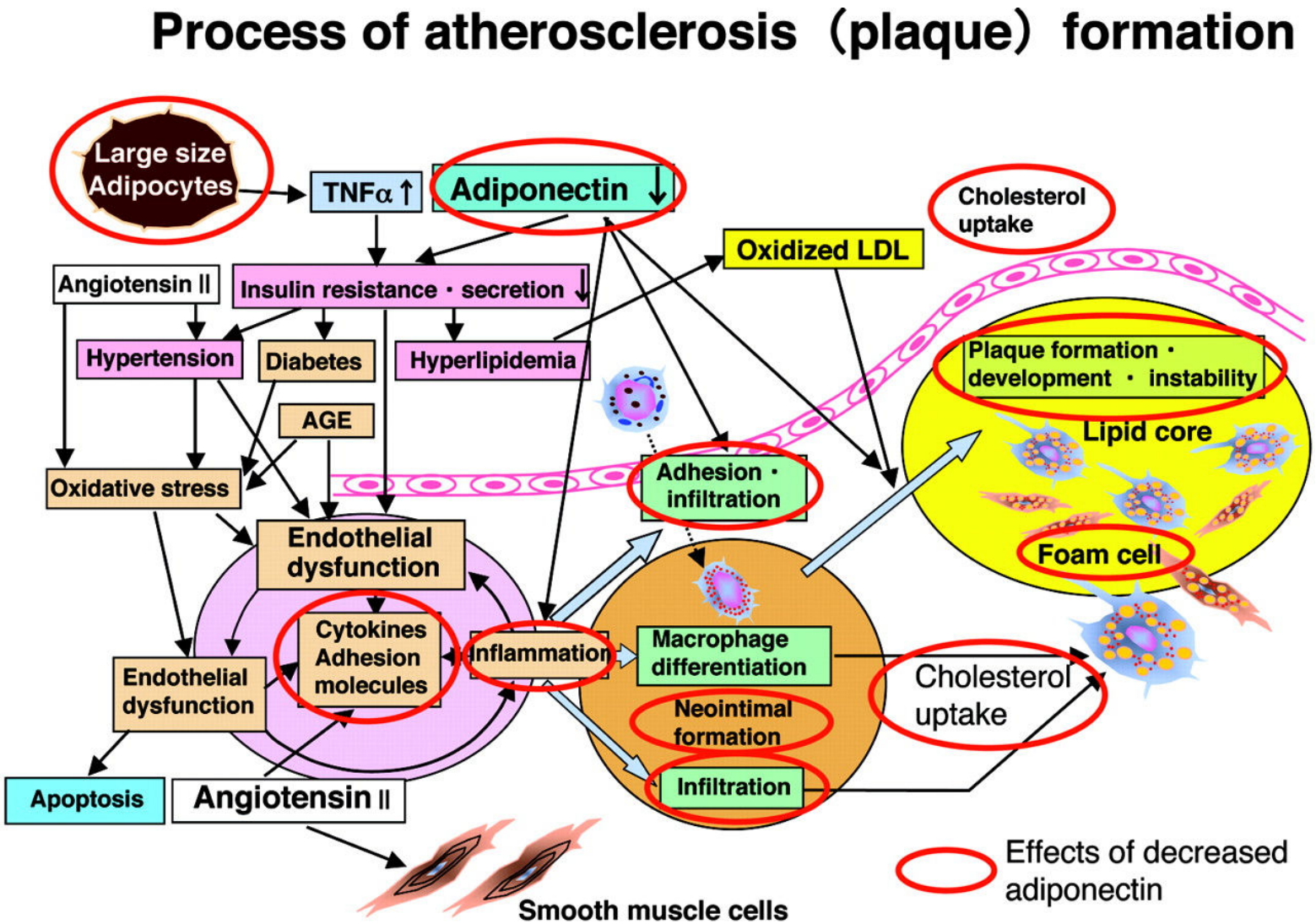
Kadowaki T et al J Clin Invest 116:1784

Summary


Leptin
(+)
NO
• Oxidative effect
• Pro-inflammatory effect
• Pro-thombotic effect
• Proliferative effect
• Blood Pressure elevation
Vasodilation
Sympathetic nerve activation
Endothelial function ↑
SNA activation
RAS activation
Vascular injury ↓
Adiponectin
Resistin
(+)
(-)
(-)
(+)
(+)
Monocytes
•↓ Adherence
•↓ Lipid content
•↓ Phagocytic activity
TNF-α
↑ VCAM-1, ICAM-1
↑ ET-1, MCP-1
↓ TRAF-3
NIK
IκB
NF- κB
NF- κB
NIK
IκB

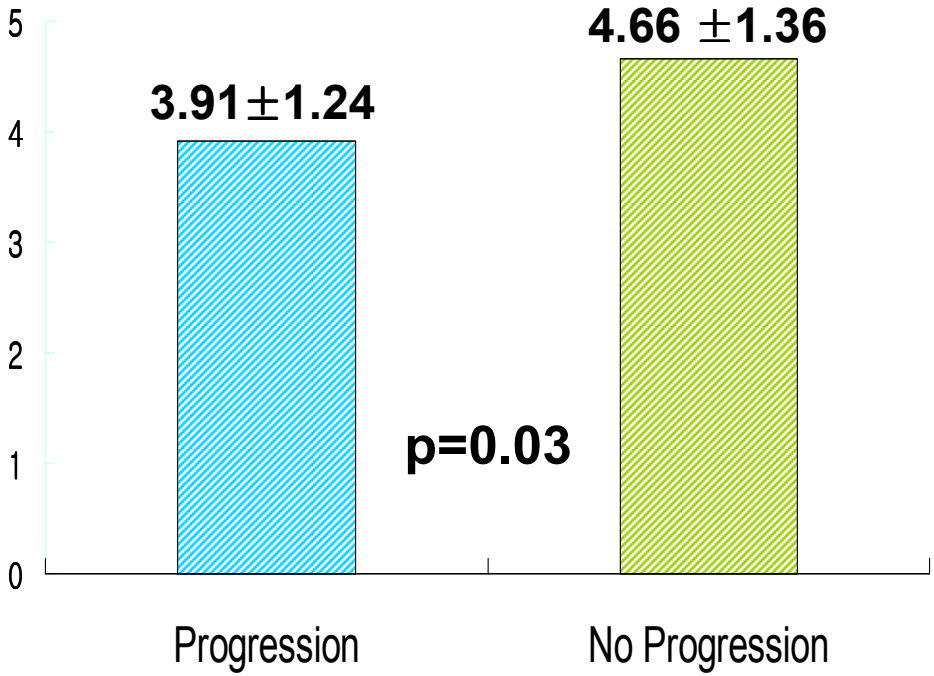

Thank you

Suppression of atherosclerosis by adiponectin

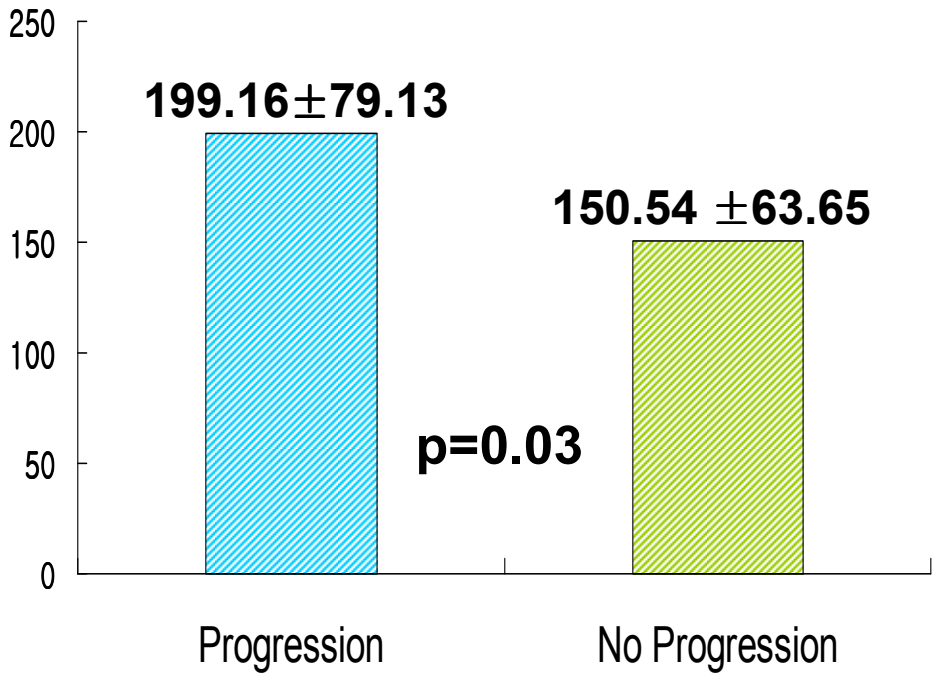


Kadowaki, T. et al. Endocr Rev 2005;26:439-451

Adiponectin(㎍/mL)

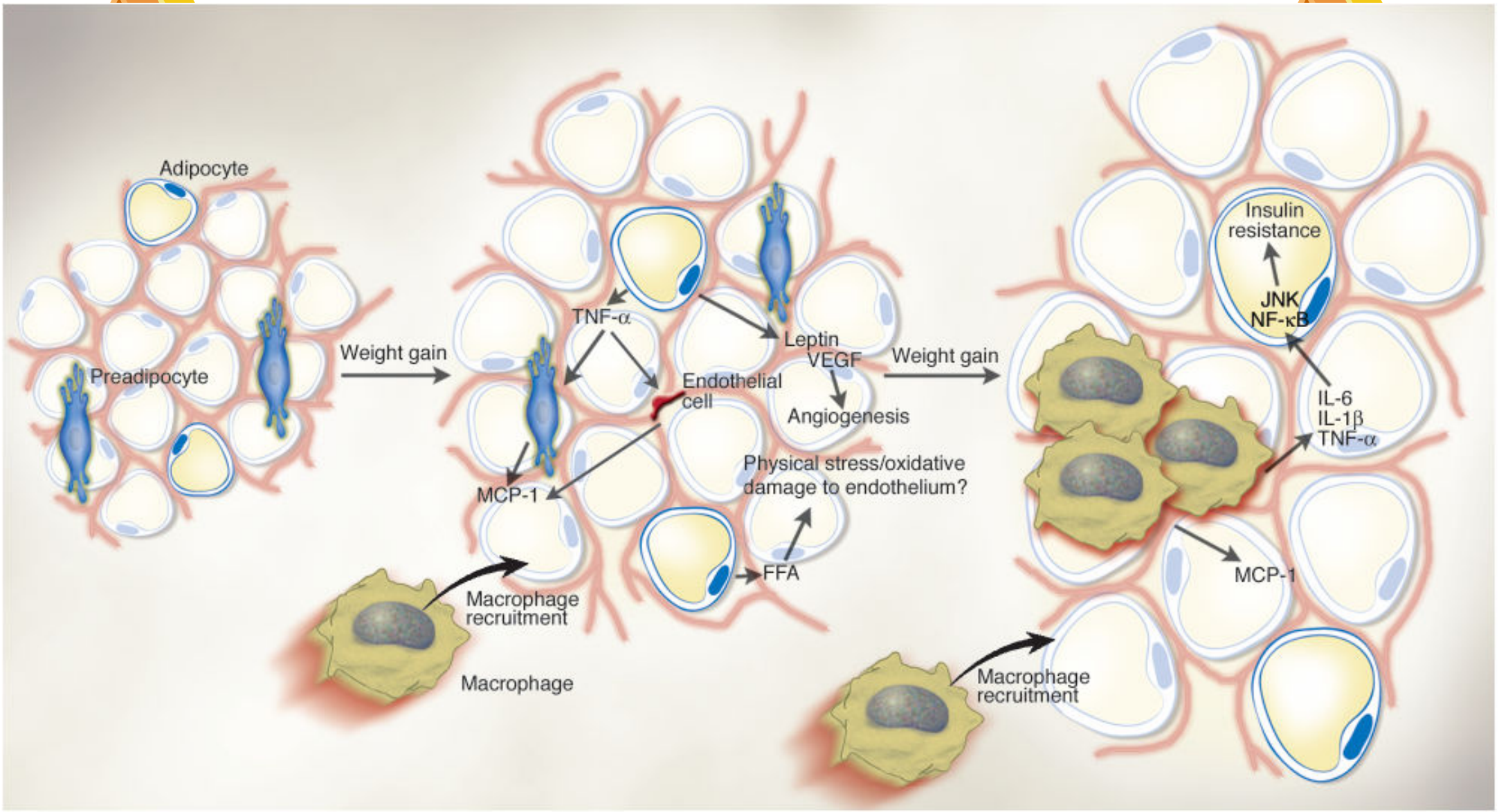


ICAM-1(ng/mL)



Relationship between serum adiponectin, ICAM (intercellular adhesion molecule)-1 level and coronary artery stenosis propression. There was significantly lower serum adiponectin and higher serum ICAM level in progression group.

Kor J of Circulation 2004


Adipocyte
Preadipocyte
Weight gain
TNF-α
Leptin
VEGF
Endothelial cell
Angiogenesis
MCP-1
Physical stress/oxidative damage to endothelium?
FFA
Macrophage recruitment
Macrophage
Weight gain
Insulin resistance
JNK
NF-κB
IL-6
IL-1β
TNF-α
MCP-1
Macrophage recruitment