

# Metabolic Syndrome: Good Physiology Gone Bad

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Know Syphilis in all its  
manifestations and reactions,  
and all things clinical will be  
added unto you.

Sir William Osler

*Osler W: Aequanimitas. New York, McGraw-Hill, 1906, p  
134*

# Features of Metabolic Syndrome

- Obesity (Abdominal Obesity)
- Insulin Resistance/ Type 2 Diabetes
- Elevated Insulin Levels
- Elevated Fasting Glucose
- Vascular Endothelial Dysfunction (Stroke, MI, PVD)
- Hyperlipidemia
- Hypertension

# Features (cont.)

- Obstructive Sleep Apnea
- Low Grade Inflammatory State (Elevated CRP and Acute Phase Markers)

All of these lead to a significant  
Increased CV Risk

# Diabetes in America

- Over 24,000,000 Americans have either Type 1 or Type 2 Diabetes
- 25% of Patients over 60 have Diabetes
- 7th leading cause of Death in the U.S.
- Most Common Cause of End Stage Renal Disease
- Most Common Cause of Blindness
- One of the Most Significant Risk Factor for Stroke or M.I.

Center For Disease Control and Prevention, Diabetes Fact Sheet 2007

# Type 2 Diabetes in Adolescents

- Directly related to obesity
- In 1999, depending on location, the number of new Type 2 Diabetic cases was between 8-45%.
- Females were 1.7 times more likely to develop Diabetes compared to boys.
- Polycystic Ovary Syndrome and Insulin resistance were commonly seen in females
- Impaired Glucose Tolerance was seen in 25% of Obese Children 4-10 years old and 21% of Obese Adolescents 11-18 years

Kaufman, Endocrinol Metab Clin N Am. 2005;34:659-676

# Ethnic Distribution of Type 2 Diabetes

- Native Americans 16.5%
- African-Americans 11.8
- Hispanic 10.4%
- Asian 7.5%
- Caucasian 6.6%

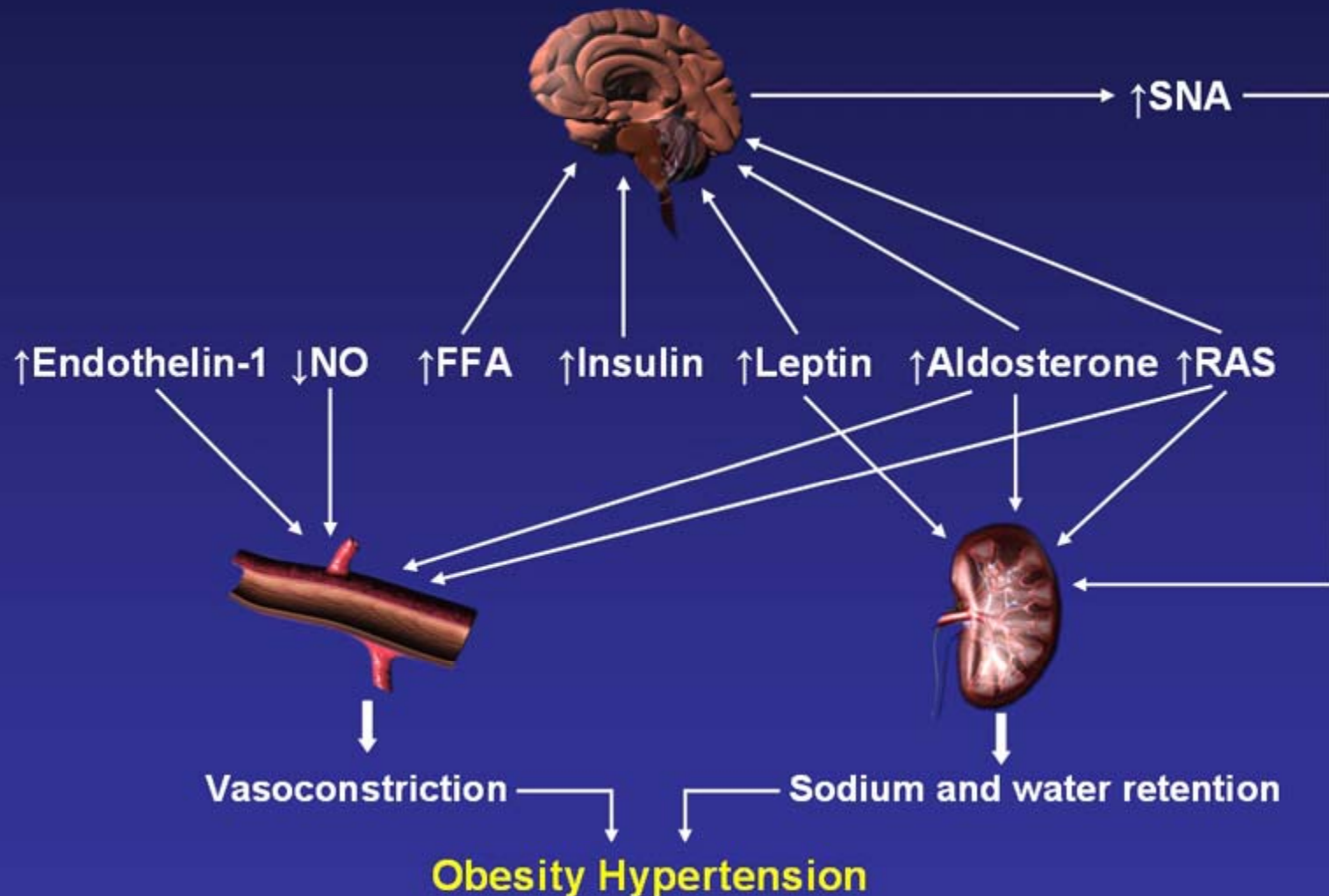
Center For Disease Control and Prevention, Diabetes Fact Sheet 2007

# Pathophysiology of Metabolic Syndrome An Alteration of Multiple Neuroendocrine Systems

*A Perfect Storm of Genetics and Environment*

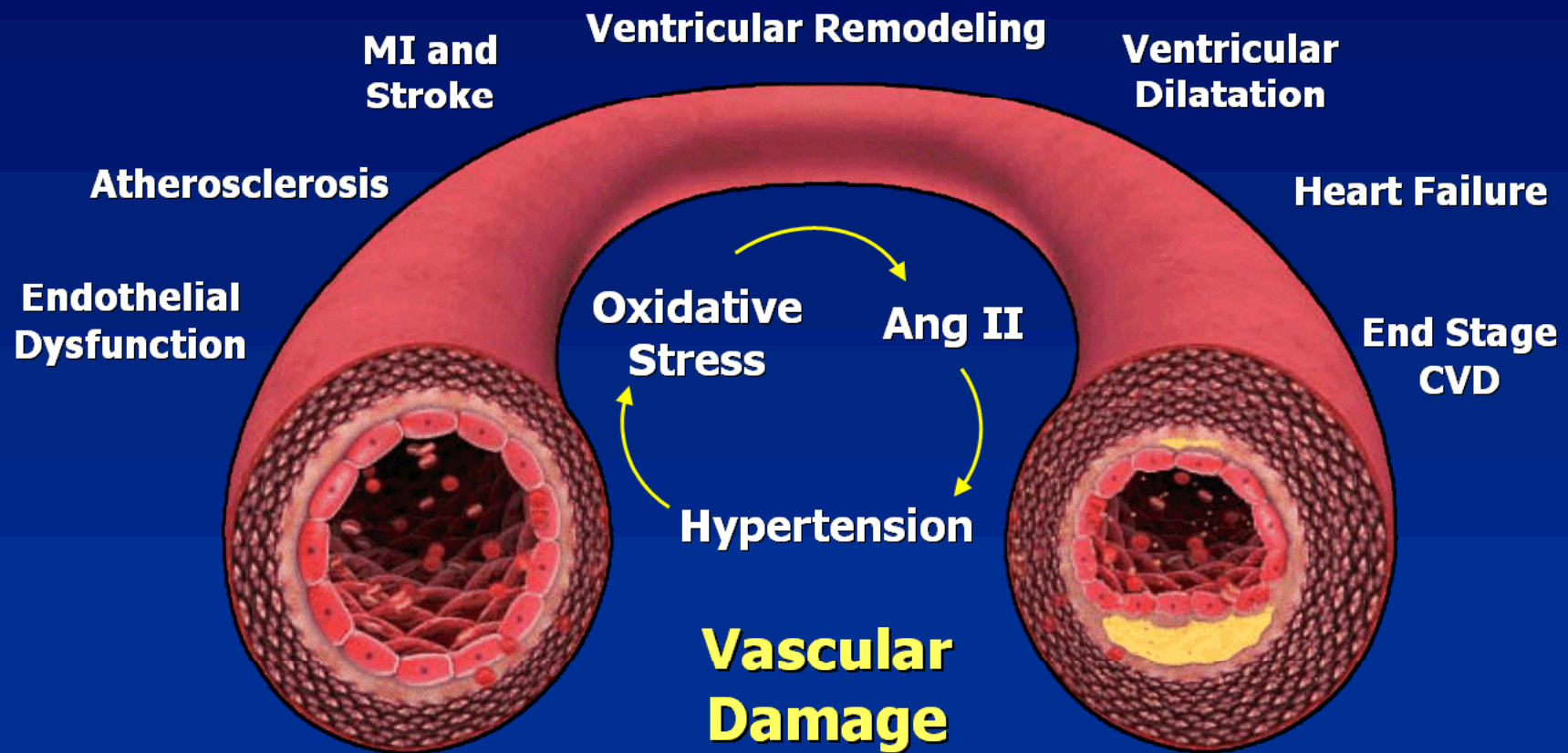
- Renin-Angiotensin-Aldosterone
- Insulin-Glucose-Glucagon-Glucocorticoids
- Catecholamines
- Endocannabinoids
- Adipokines

# Mechanisms and Hormonal Systems Involved in Obesity-Associated Hypertension



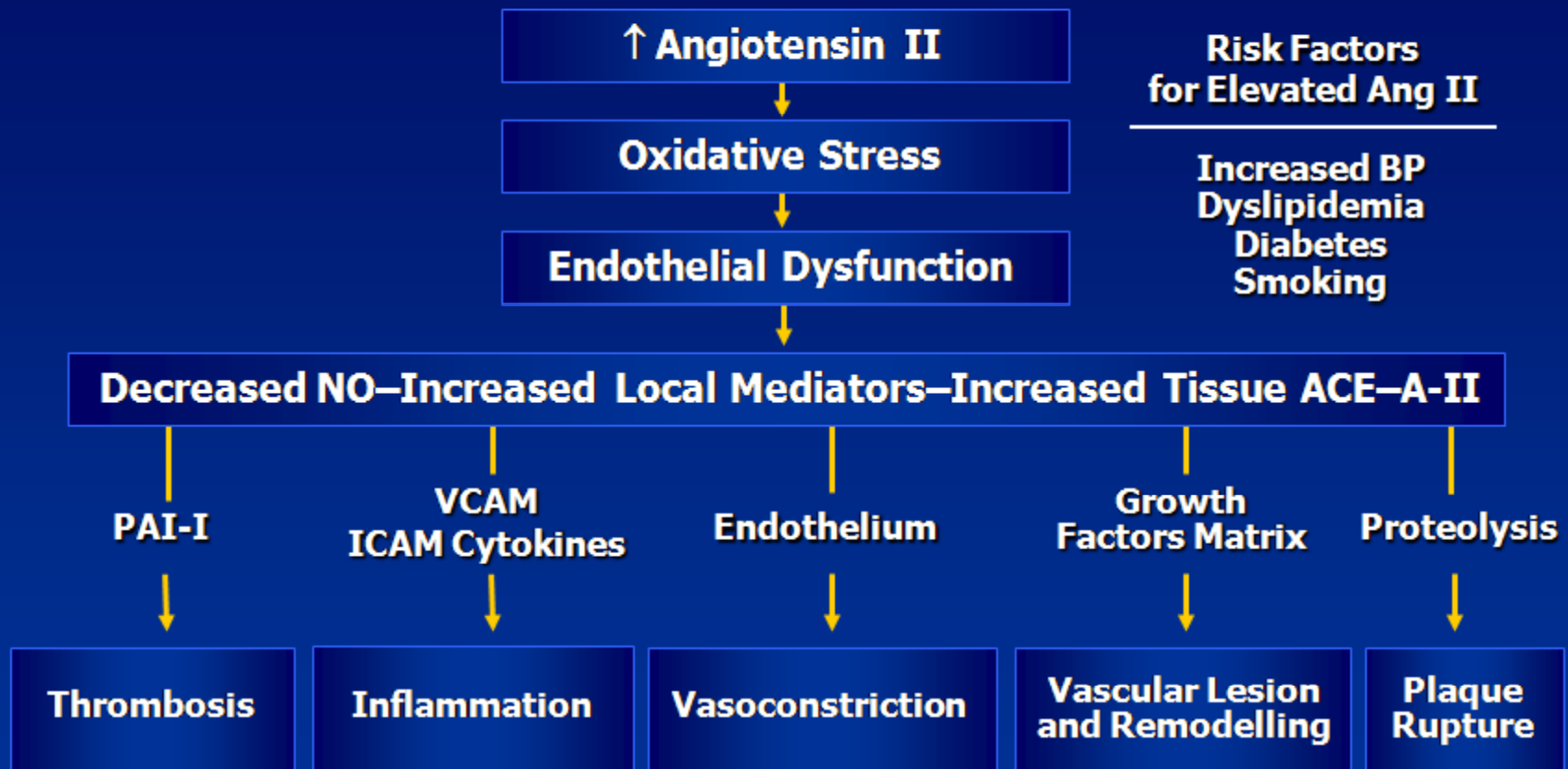
NO= nitric oxide; FFA= free fatty acids; RAS= renin-angiotensin system; SNA= sympathetic nerve activity.  
Rahmouni K et al. *Hypertension*. 2005;45:9–14.

# Ang II and Cardiovascular Risk



Adapted from Dzau V. *J Hypertens Suppl.* 2005;23:S9-S17.

# Effect of Tissue-Specific Angiotensin II Upregulation



## Autocrine or paracrine production of Ang II is not ACE-dependent

Ang II=angiotensin II; NO=nitric oxide; PAI-1=plasminogen activator type 1; VCAM=vascular cell adhesion molecule.

Adapted from Weir MR et al. *Am J Hypertens.* 1999;12:205S–213S.

# Enhanced R-A-A Activity

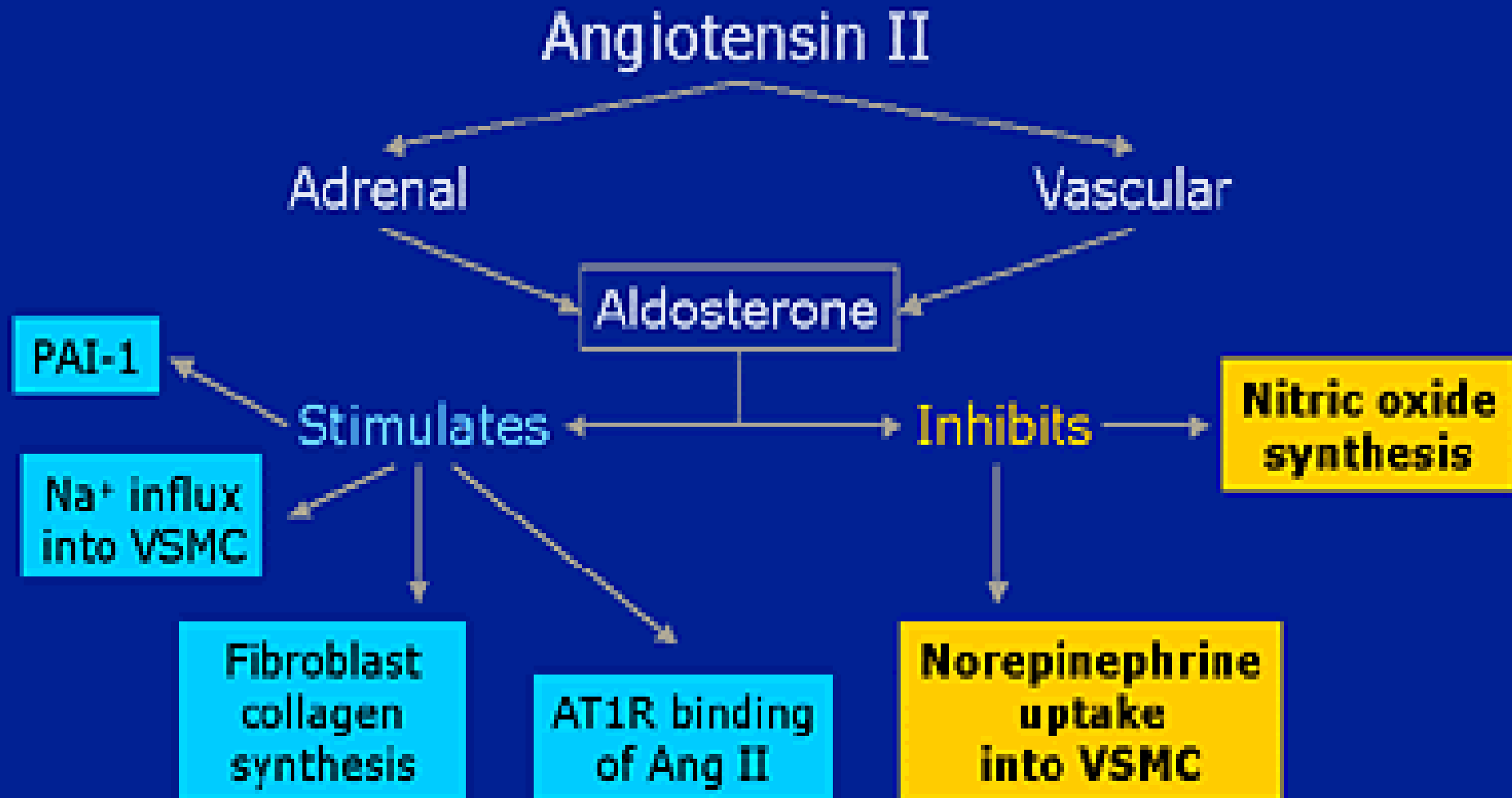
- Elevated Pro-Renin levels are a predictor for future for Diabetic Renal Disease in **Type 1 Diabetics** Wilson N Engl J Med 1990 Oct 18;323(16):1101-6. Deneman et al Kidney Int 1994 Oct;46(4):1154-9
- Patient with Primary Hyperaldosteronism have a higher incidence of CV events, Insulin Resistance, and, Impaired Glucose **Tolerance** Stas et al j Clin HTN 2008 Feb;10(2) 94-96.

# RAAS Modulation

- In a Meta-analysis of 13 studies involving 125,356 patients of whom 90,474 did not have Diabetes and were in a study using an ACE-I or an ARB, new onset Diabetes was prevented in:
  - 24% of patients for ACE-I
  - 23% of patients on an ARB

O'Keefe, J.H. et al J Am Coll Cardiol 2005;45:10A Abstract

# Aldosterone Promotes Renal Fibrosis by Multiple Mechanisms



# Hyperinsulinism

- Elevated Insulin Levels or Normal Levels with Elevated Glucose
- Acanthosis nigricans/ skin tags/ alopecia
- Hyperandrogenism/ Polycystic Ovary Syndrome
- Hirsutism
- Virilization
- Infertility

# Acanthosis nigricans

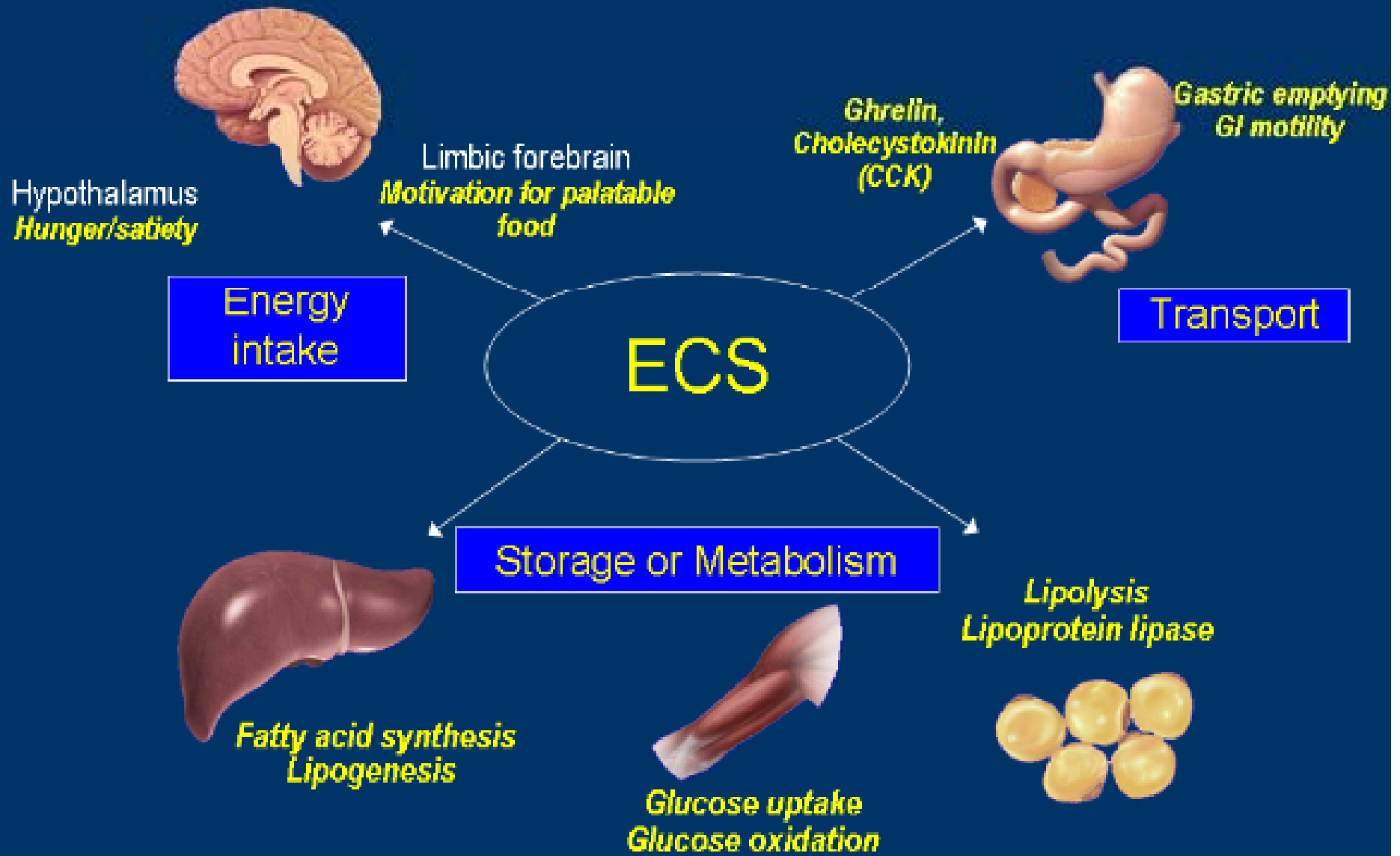


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# Endocannabinoids

- Central (Brain) and Systemic Effects/  
Actions
- Multiple Actions of Glucose and Lipid  
Metabolism
- Inflammatory Markers

# Sites of Action for CB<sub>1</sub> Receptor Modulation of Nutrient Intake, Transport, Storage and Metabolism



Fatty diet (unbalanced  $\omega 3/\omega 6$  PUFAs, leptin/Insulin resistance, genetic factors, etc)

## Overactivity of the EC system

**Brain**  
Increased  
need to consume

**Visceral  
Adipocytes**  
Increased  
lipogenesis

**Liver**  
Increased  
lipogenesis

**Endocrine  
Pancreas**

**Skeletal  
Muscle**

Increased  
food intake

Abdominal  
obesity – low  
adiponectin

Steatosis  
High FFA







Dysregulated  
insulin/  
glucagon  
release

Reduced  
glucose  
uptake-  
energy  
expenditure

### CV risk factors

- Insulin resistance
- Glucose intolerance
- Low HDL/High TG

# Summary: Potential Sites and Effects of CB<sub>1</sub> Receptor Blockade

	Site of Action	Mechanism(s)	Clinical Implications
	Hypothalamus/ nucleus accumbens	↓ Food intake	↓ Body weight
	Adipose tissue	↑ Adiponectin ↑ Lipolysis	↓ Waist circumference ↓ Dyslipidemia
	Muscle	↑ Insulin-stimulated glucose uptake	↓ Insulin resistance
	Liver	↓ Regulatory enzymes involved in fatty acid synthesis	↓ Insulin resistance ↓ Dyslipidemia
	GI tract	↑ Satiety signals Altered motility, gastric emptying	↓ Fatty liver ↓ Body weight
	Pancreas	Effect on insulin secretion?	↓ Energy intake Glucose/insulin metabolism

Ravinet Trillou C et al. *Am J Physiol Regul Integr Comp Physiol*. 2003;284:R345-R353.

Cota D et al. *Int J Obes Relat Metab Disord*. 2003;27:289-301.

Liu YL et al. *Int J Obes Relat Metab Disord*. 2005;29:183-187.

Osei-Hyiaman D et al. *J Clin Invest*. 2005;115:1298-1305.

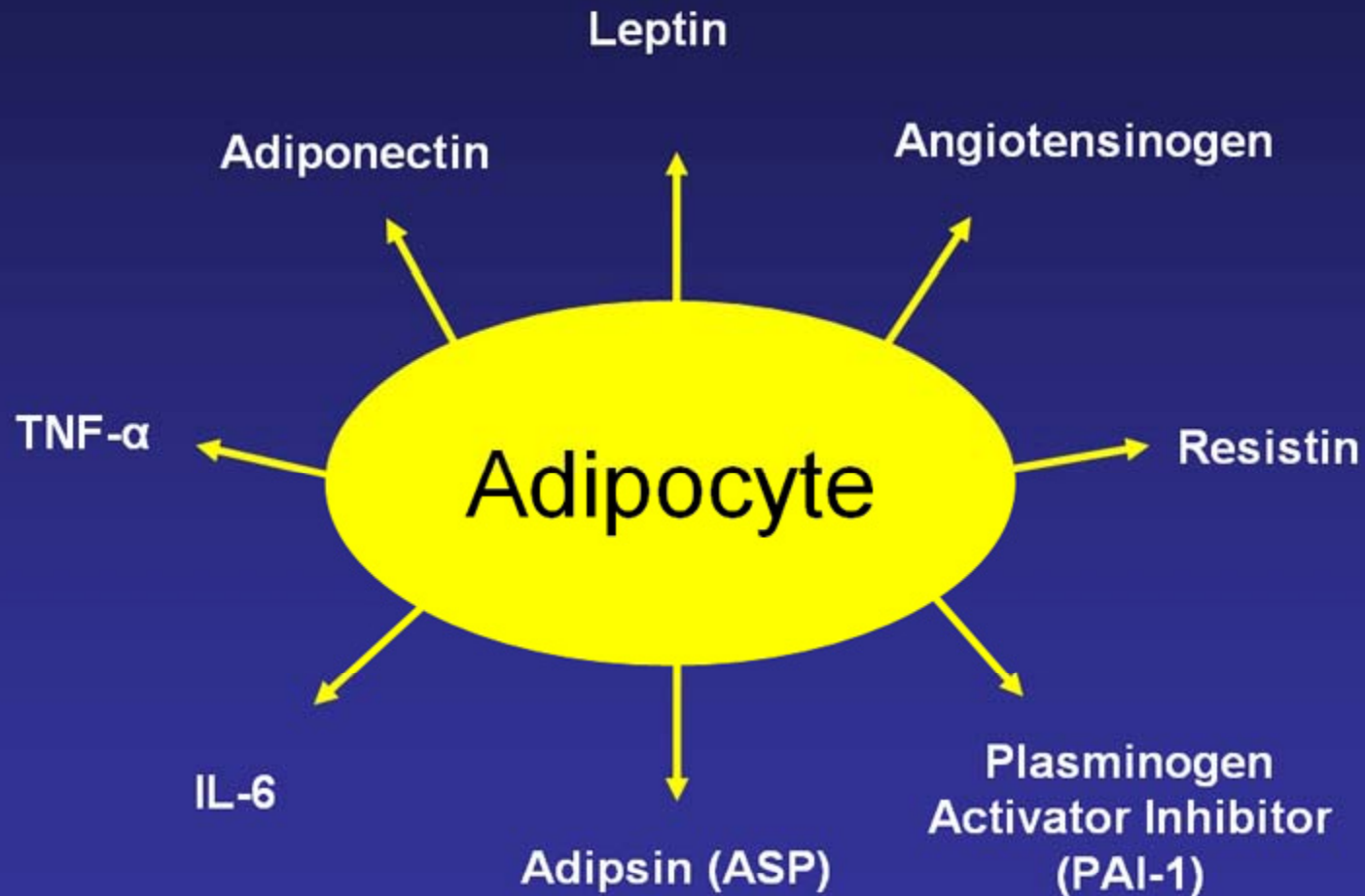
Liu B et al. *Presented at the 41st EASD Annual Meeting; Athens, Greece, 10-15 September, 2005.*

# White Adipose Tissue As an Endocrine Organ

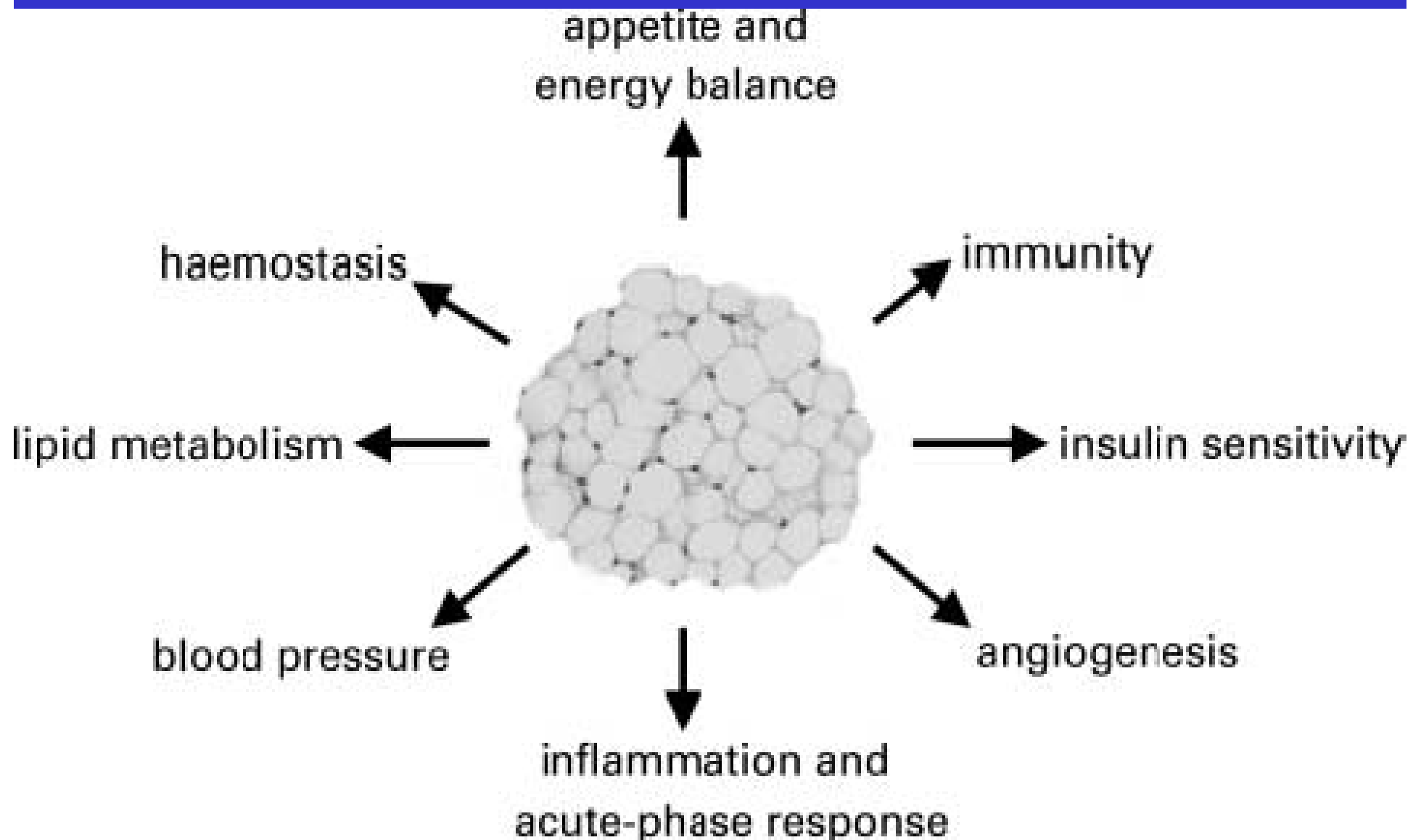
- Adipose Tissue is a source of Inflammatory Mediators leading to Insulin Resistance and other feature of Metabolic Syndrome
- Increased Adipose Tissue outstrips vasculature leading to local tissue hypoxia with subsequent Inflammation and Angiogenesis
- The Net Effect is **ACCELERATED** Artherosclerosis and Increased CV Risk

British J Nutrition 2004;92:347

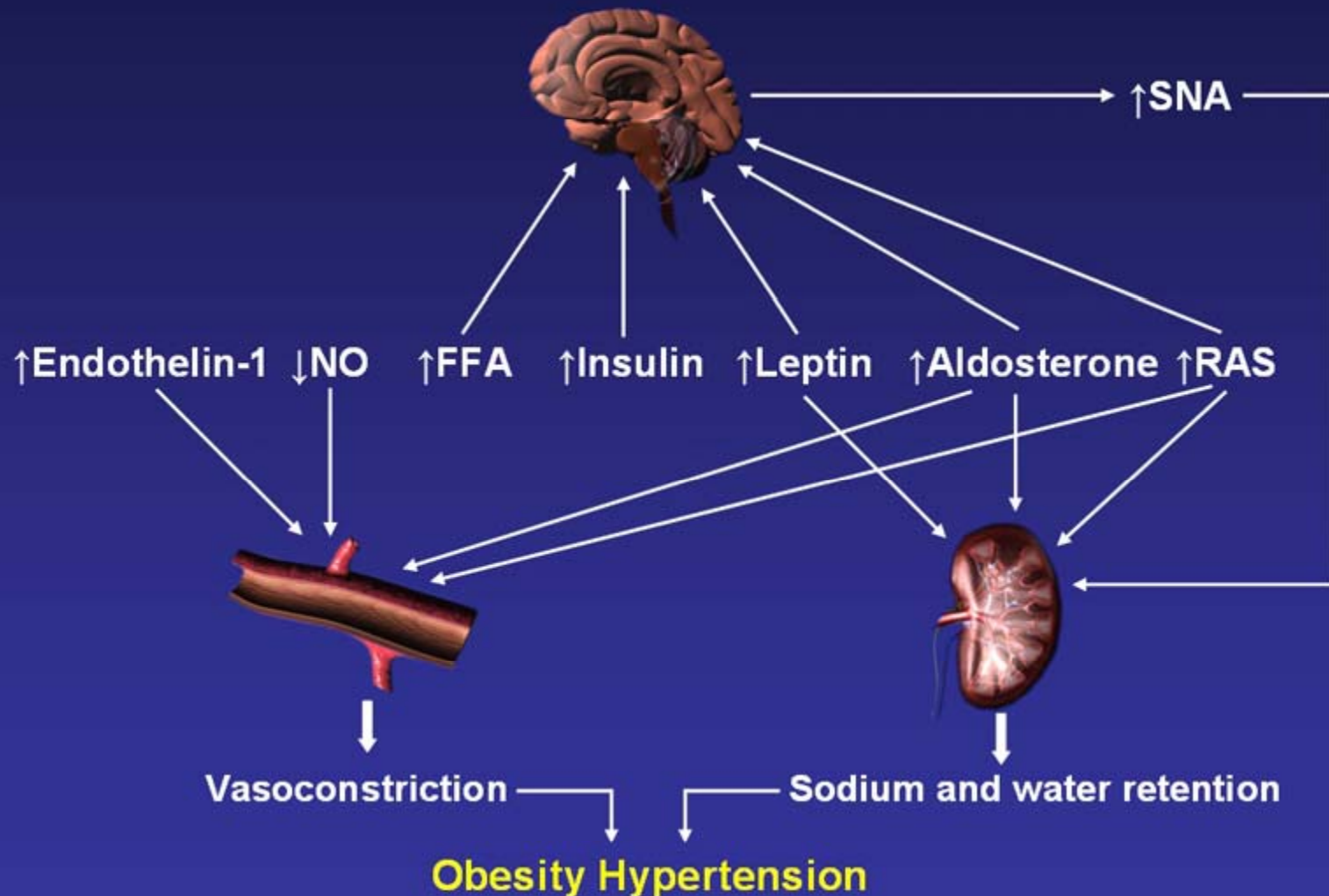
# The Adipocyte and Associated Adipokines



# Adipokines Actions



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# Management of High Risk Patients

- All Patients should have a spot urine for Microalbumin yearly, whether Diabetic or not
- Strict BP control
- Lipid screening
- Waist Circumference
- Strict Glycemic control
- Early Cardiac referral-The Most Common Cause of Death in Diabetics is Cardiac Disease

# Treatment Goals

- Treatment of Underlying Causes (weight loss, cessation of smoking, exercise)
- Treatment of CV Risk Factors