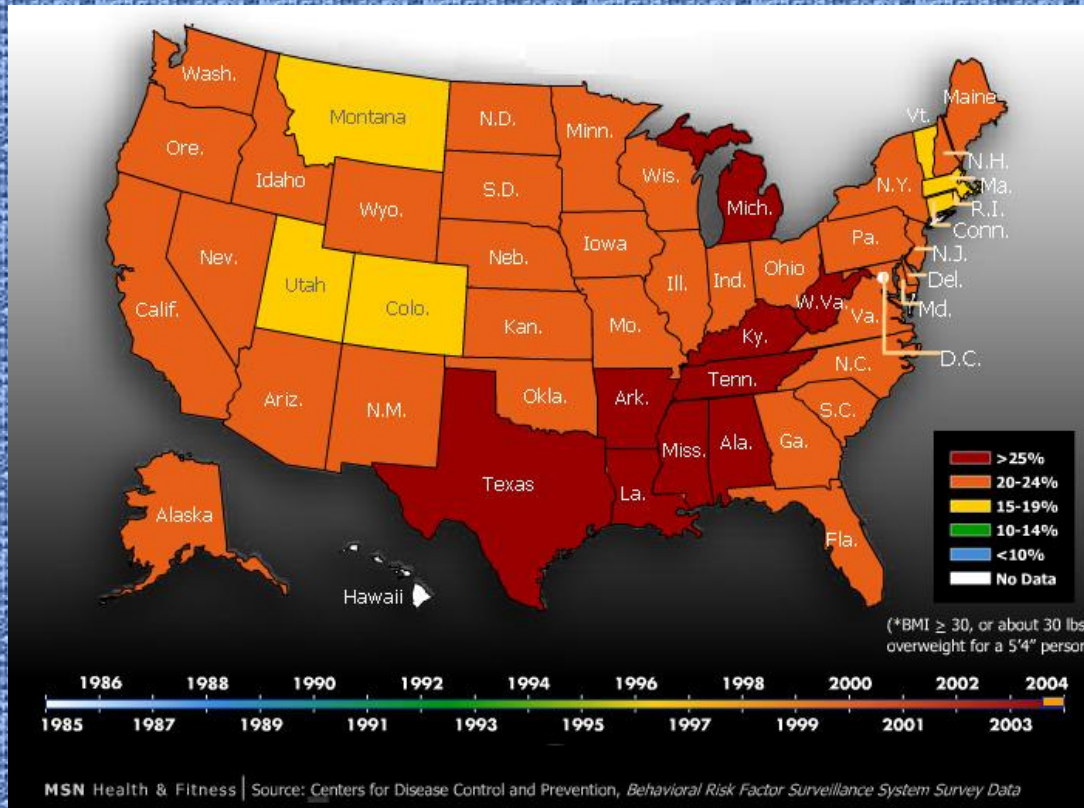
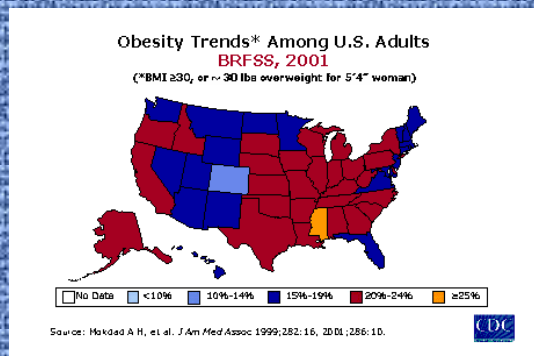
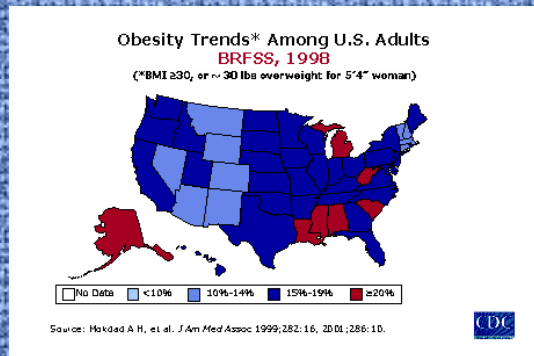
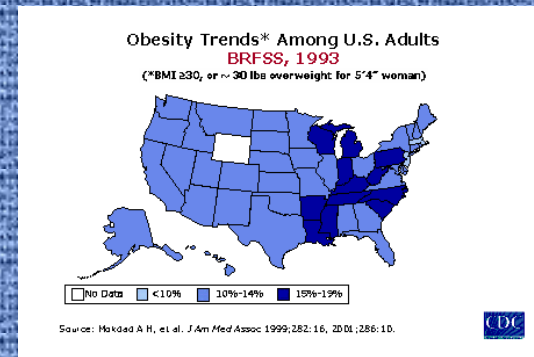
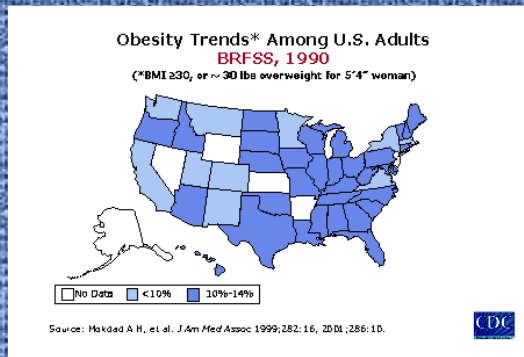
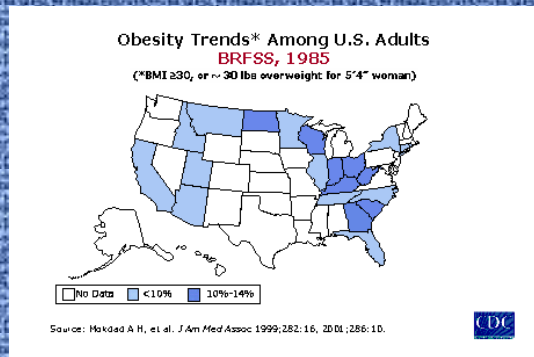


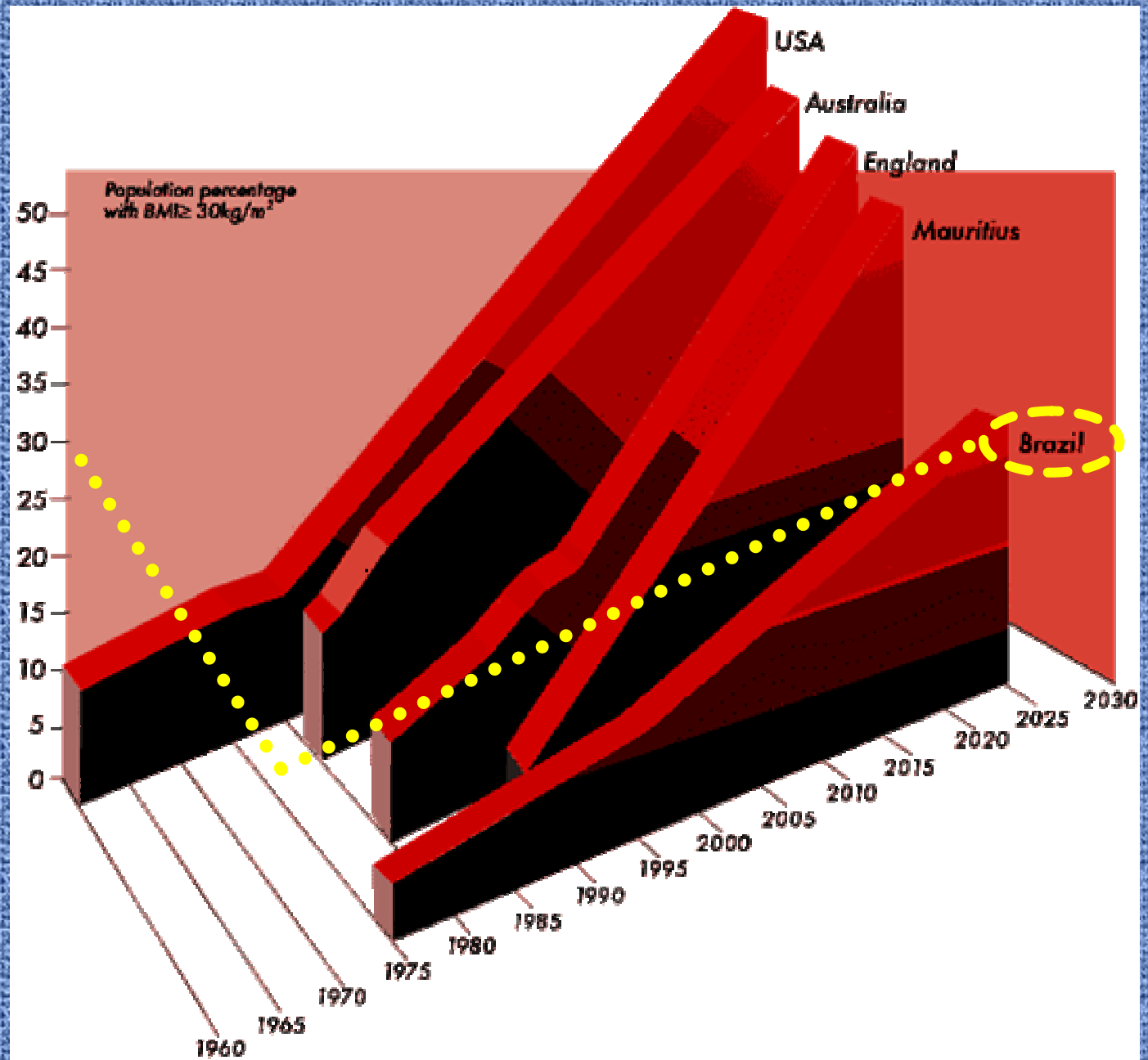
"Os órgãos adiposos e suas versatilidades"

Fábio Bessa Lima
ICB-USP

A EPIDEMIA DE OBESIDADE: O dilema dos E.U.A



A epidemia mundial de obesidade:



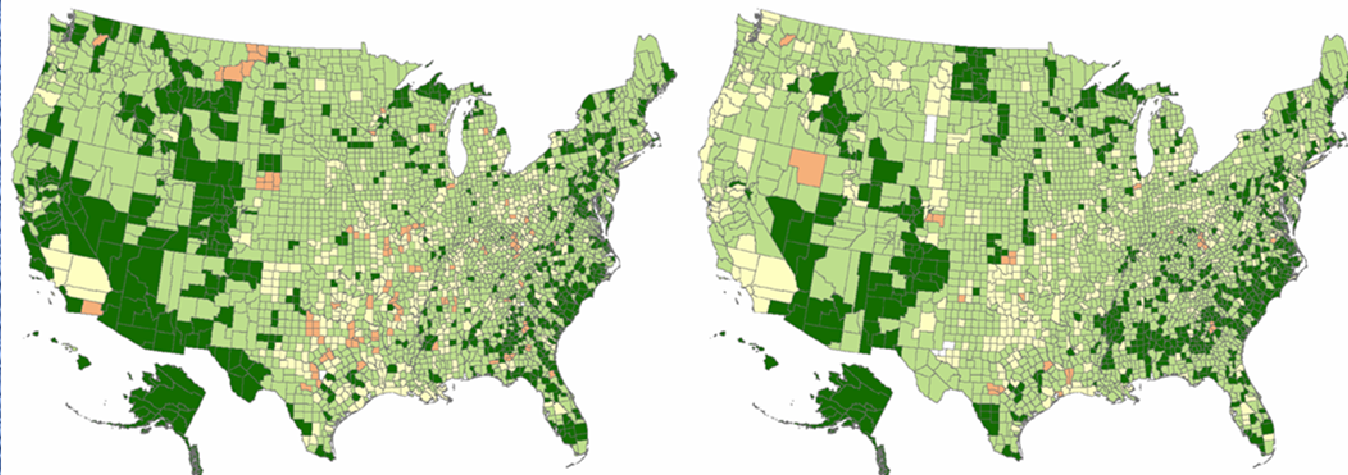
Kopelman, Nature, 2000

A OBESIDADE E A EXPECTATIVA DE VIDA NOS USA

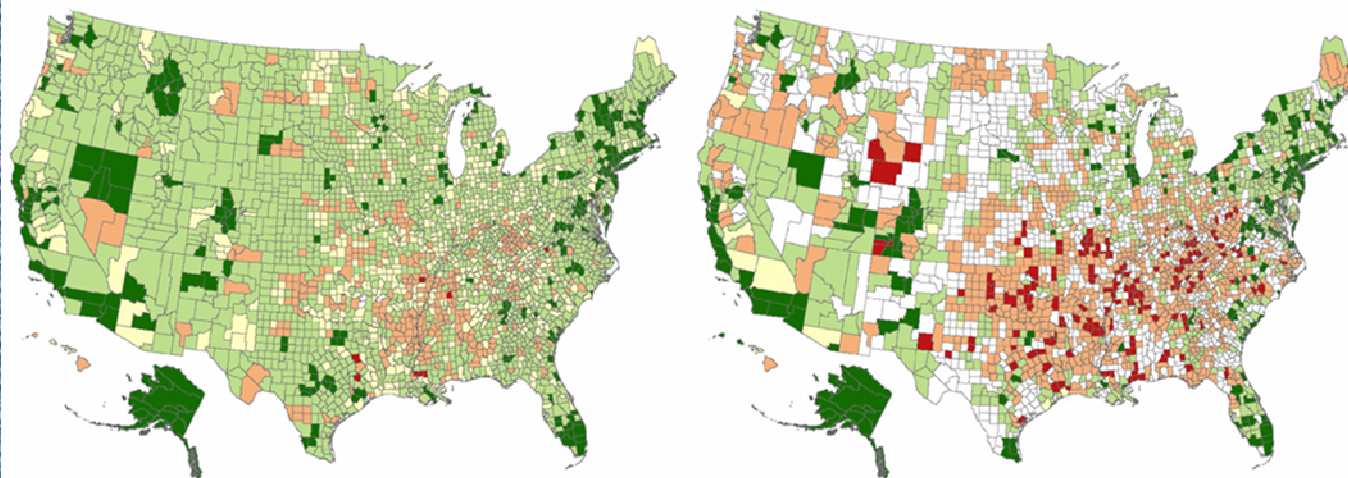
Male

Female

1961-1983



1983-1999



As facetas perversas do T.A.

Obesidades



Lipodistrofias



LIPODISTROFIA

OBESIDADE

Lipotoxicidade

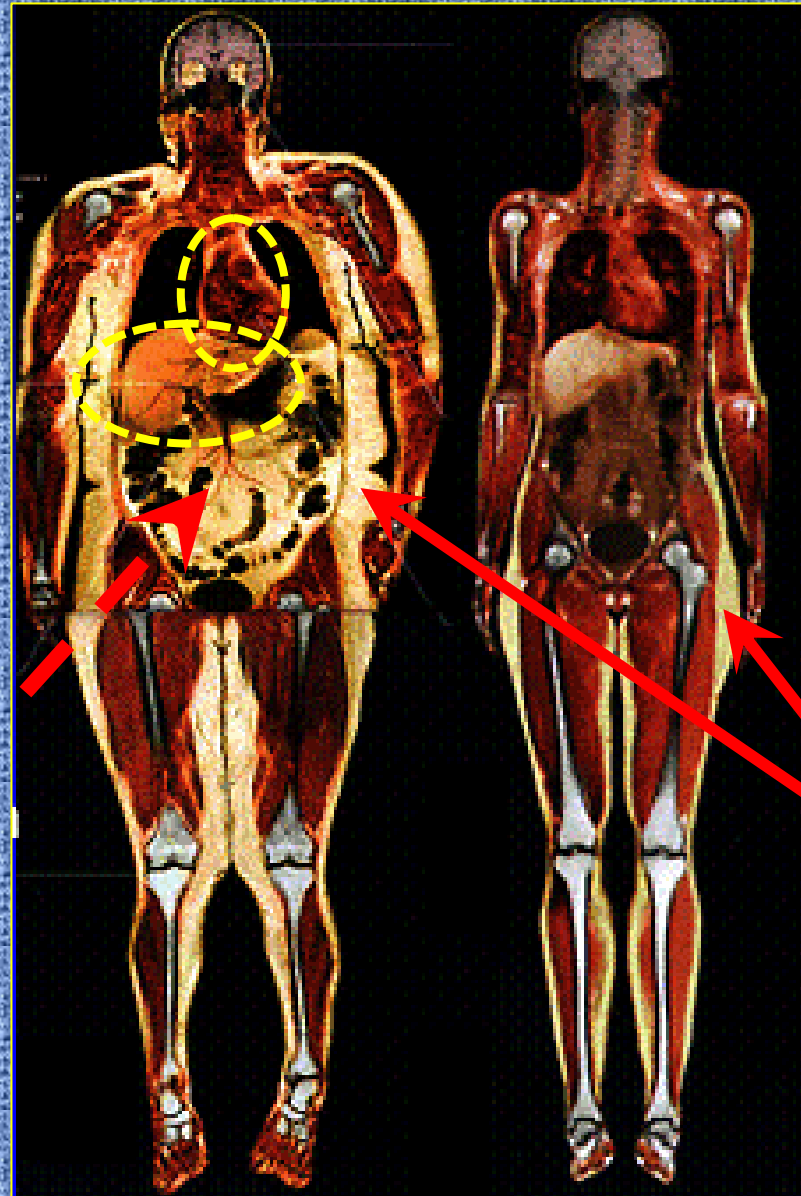
***Resistência
à Insulina***

- **T2DM**
- **Síndrome Metabólica**
 - **Hipertensão**
 - **Aterosclerose**
- **Doenças Respiratórias**
- **Doenças Vasculares**
 - **Câncer**
- **Esteato-hepatite**

Distribuição da gordura corporal

Idade: 40 a
Alt.: 1.65 m
Peso: 114 kg
IMC: 42 kg/m²

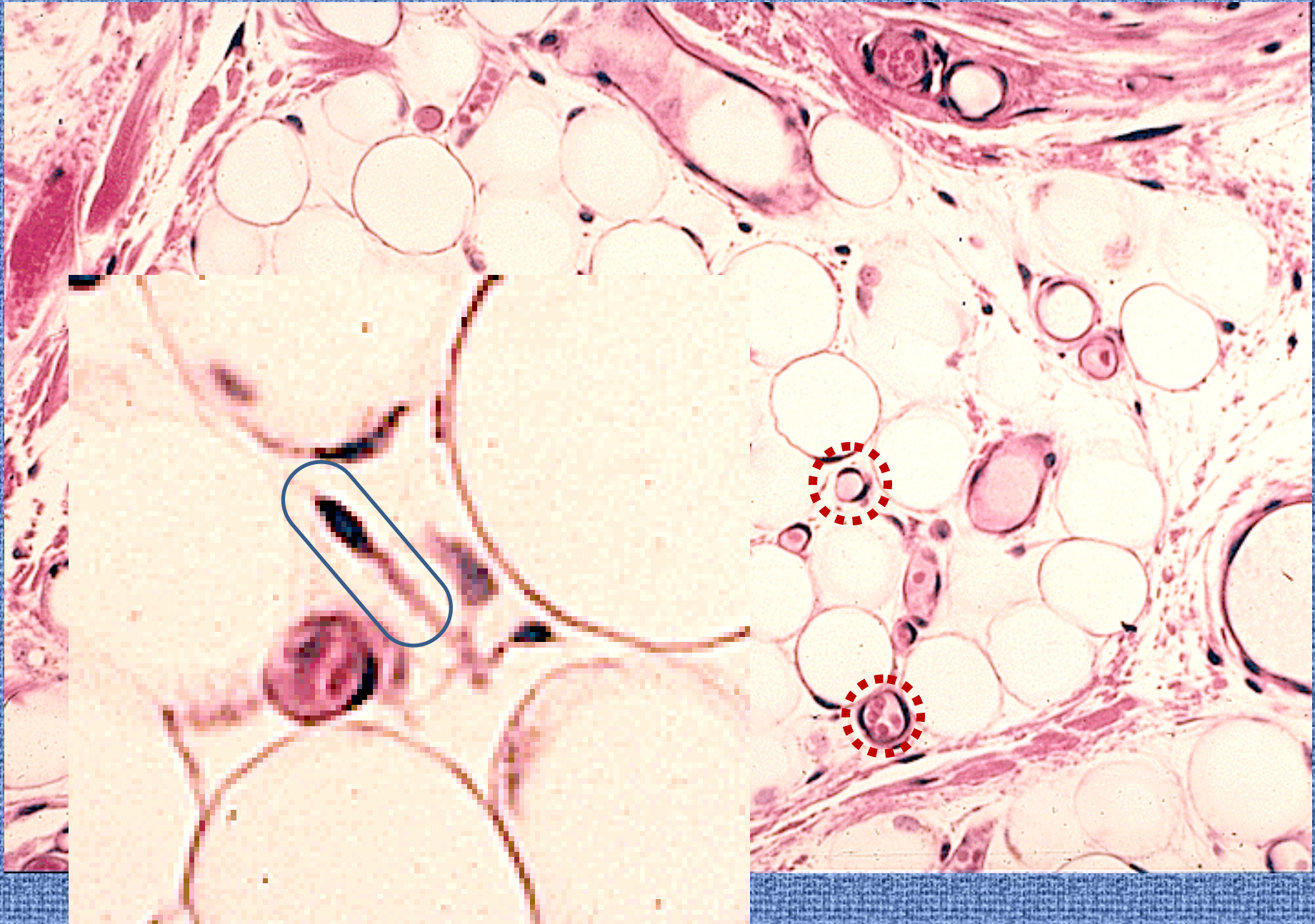
Visceral



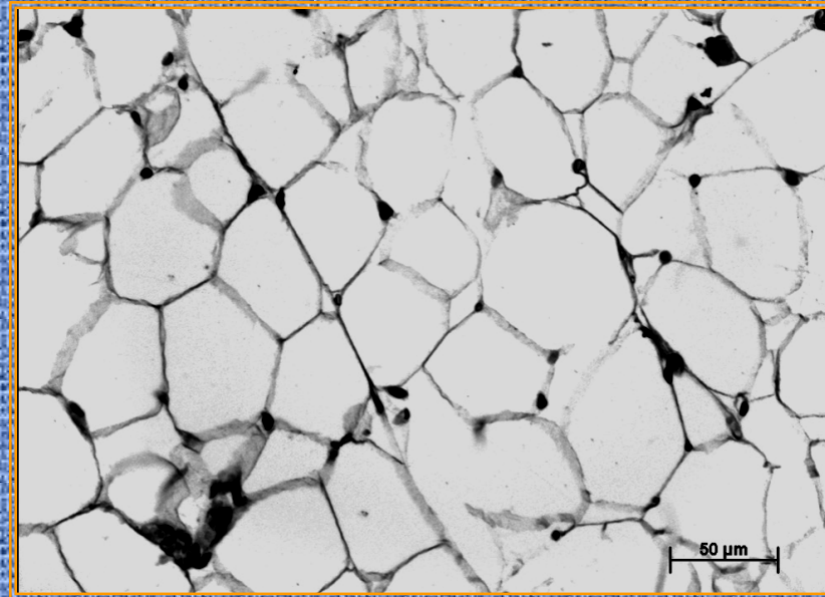
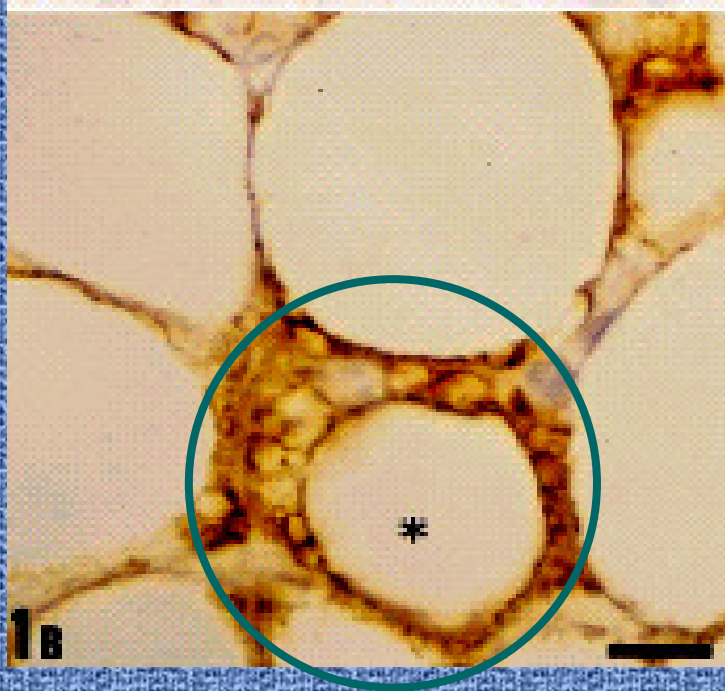
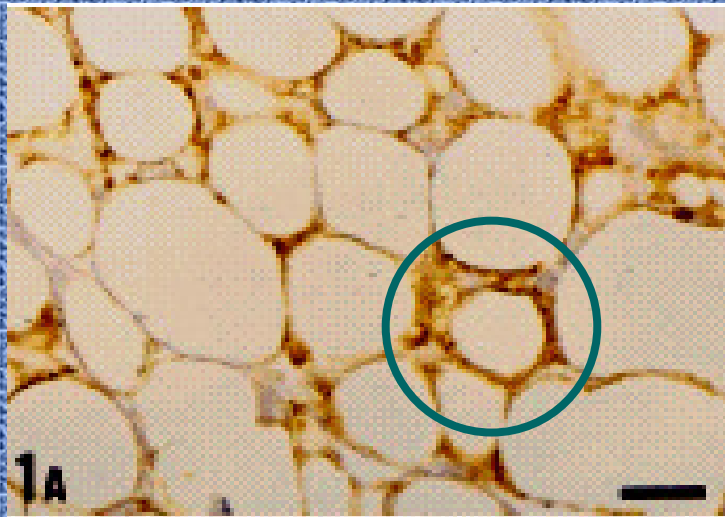
Idade: 36 a
Alt.: 1.65 m
Peso: 65 kg
IMC: 24 kg/m²

Subcutânea

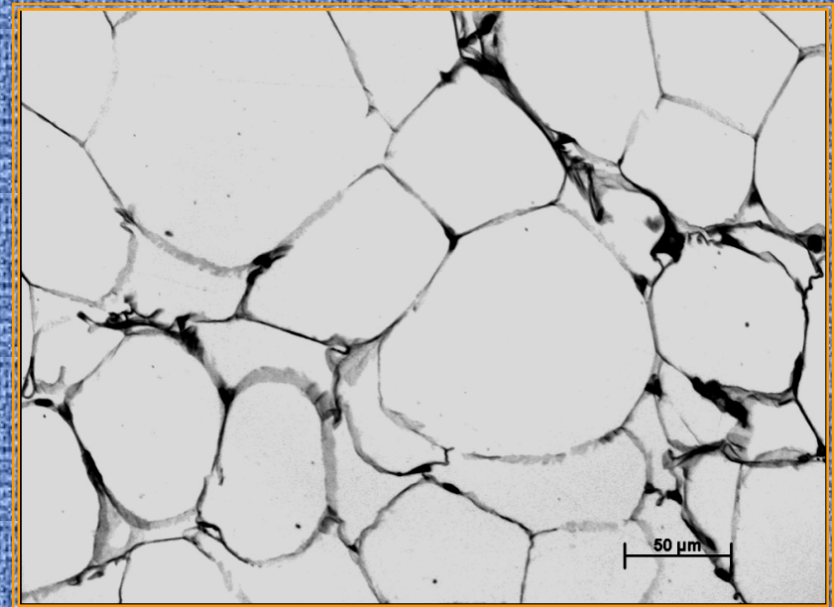
MORFOLOGIA DO TAB



TECIDO ADIPOSO BRANCO



**M
a
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**O
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o**

FUNÇÕES DO TEC. ADIPOSO

METABÓLICAS

- ⇒ Armazenamento de energia (TAG)
- ⇒ Suprimento em períodos de carência ou aumento de demanda
- ⇒ Tamponamento metabólico

FÍSICAS

- ⇒ Proteção contra choques mecânicos
- ⇒ Deslizamento de músculos e vísceras
- ⇒ Isolamento térmico

ENDÓCRINA

- ⇒ Leptina
- ⇒ Adiponectina
- ⇒ Resistina
- ⇒ TNF α
- ⇒ IL6
- Etc.



COMUNICAÇÃO INTERCELULAR EM ORGANISMOS PLURICELULARES

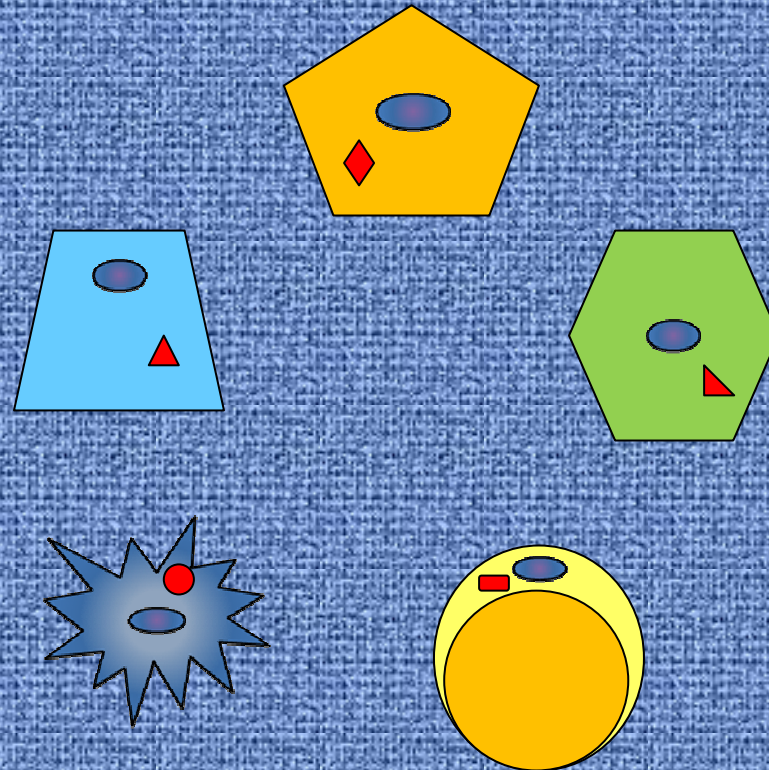
➤ *Em um organismo pluricelular as células se comunicam intensamente entre si.*

➤ *A linguagem desta comunicação é química.*

➤ *As palavras dessa comunicação são moléculas.*

➤ *Essas moléculas conduzem mensagens aos seus destinos (alvos). Os alvos têm que ser capazes de reconhecer a mensagem (receptores) e de decodificá-la (sinalização)*

➤ *Tanto o significado das mensagens como as suas particularidades, em muitos casos, ainda não se encontram completamente elucidados.*



O TAB é alvo de grande número de hormônios
O adipócito "entende" inúmeras mensagens

RECEPTORES DE MEMBRANA

Leptina (OB-R)
Insulina (IR)
Glucagon
IGF I e II
GH
TSH
TNF α
IL6
Gastrina/CCK-B
GIP
GLP1
NPY-Y1
Angiotensina II
ANP
EGF
TGF β
PDGF
FGF
Adenosina
Prostaglandina (PGE2;PGF2 α ; PGI2)
Toll-like (TLR4)
Melatonina

RECEPTORES ADRENÉRGICOS E COLINÉRGICOS

Epi e NE ($\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$)
Nicotínico E Muscarínico

RECEPTORES NUCLEARES

GR - GLICOCORTICÓIDES
AR - ANDROGÊNICOS
ER - ESTROGÊNICOS
PR - PROGESTAGÊNICOS
TR - TIREOIDIANOS
PPAR
RAR/RXR

RECEPTORES DE LIPOPROTEÍNAS

QM; VLDL
LDL
HDL

O ÓRGÃO ADIPOSEO ENDÓCRINO

O adipócito "envia" inúmeras mensagens para vários alvos
ADIPOCINAS

Comunicação Parácrina

IGF 1
Hepatocyte GF
TGF β
Angiotensinogênio
MCP 1
Fatores Angiogênicos
Bradicinina
Monobutirina
PG

Comunicação Endócrina

Leptina
Adiponectina
TNF α
IL-6
IL-8
Resistina
PAI-1
Adipsina
ASP
VEGF
Visfatina

Outras Mensagens

CETP
LLP
Apo E
Retinol BP
CRP
Haptoglobina
SAA

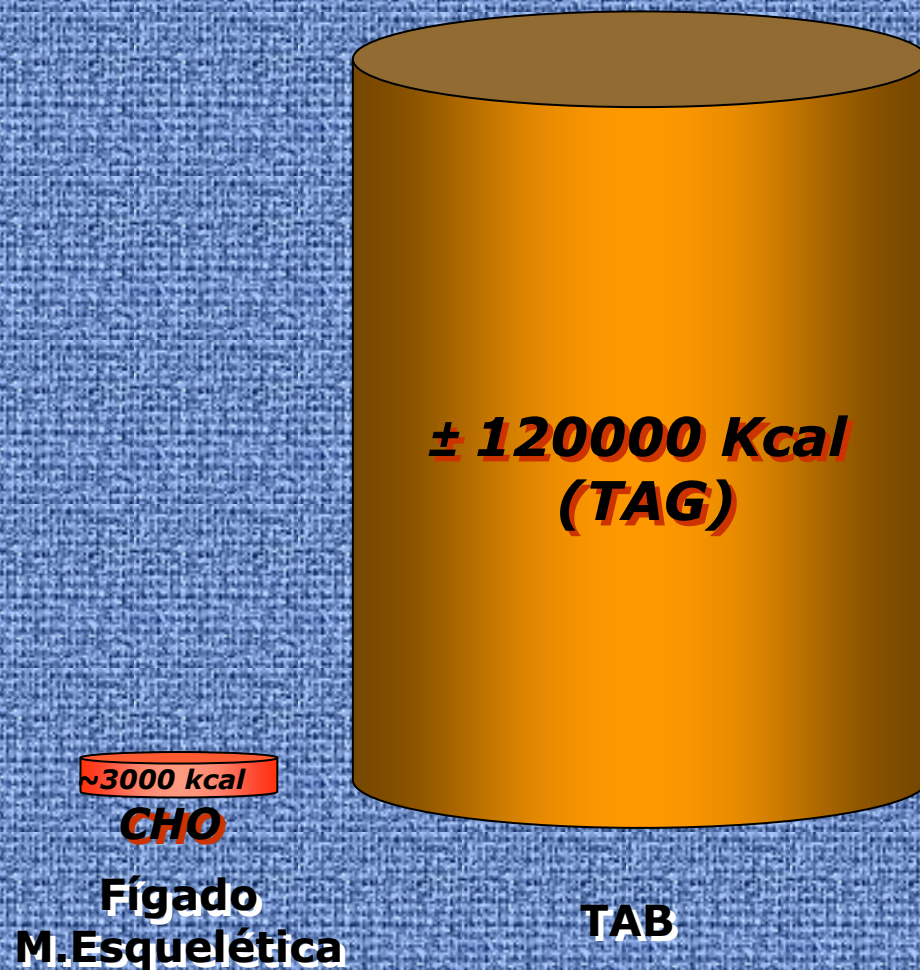
Modificação de mensagens

Cortisona → Cortisol
Andrógenos → Estrógenos

O TAG é o grande reservatório energético do organismo

O Tecido Adiposo é capaz de armazenar grande quantidade de energia na forma de TAG.

Este tipo de depósito, por ser hidrofóbico, não ocupa água que fica disponível para processos metabólicos intracelulares.



***SOBRE AS RELAÇÕES
ENTRE TAB E SNC***

O TAB e o controle do peso e do comportamento alimentar

(1940's)

- Hetherington e Ranson
- Brobeck et al.

(1950's)

Keneddy – Teoria lipostática:

Fatores liberados pelo TAB (?FFA) e **insulina** atuam sobre o hipotálamo (?VMH) controlando o grau de ingestão alimentar

KENNEDY GC AND MITRA J (1963). Hypothalamic control of energy balance and the reproductive cycle in the rat. *J. Physiol.* **166**: 395-407.

KENNEDY GC (1955). The central nervous control of food intake. *Adv. Sci. (Lond.)* 123-126.

KENNEDY GC (1957). The development with age of hypothalamic restraint upon the appetite of the rat. *J. Endocrin.* **16**: 9-17.

HALES CN & KENNEDY GC (1964). Plasma Glucose, Non-Esterified Fatty Acid and Insulin Concentrations in Hypothalamic-Hyperphagic Rats. *Biochem. J.* **90**: 620-624.

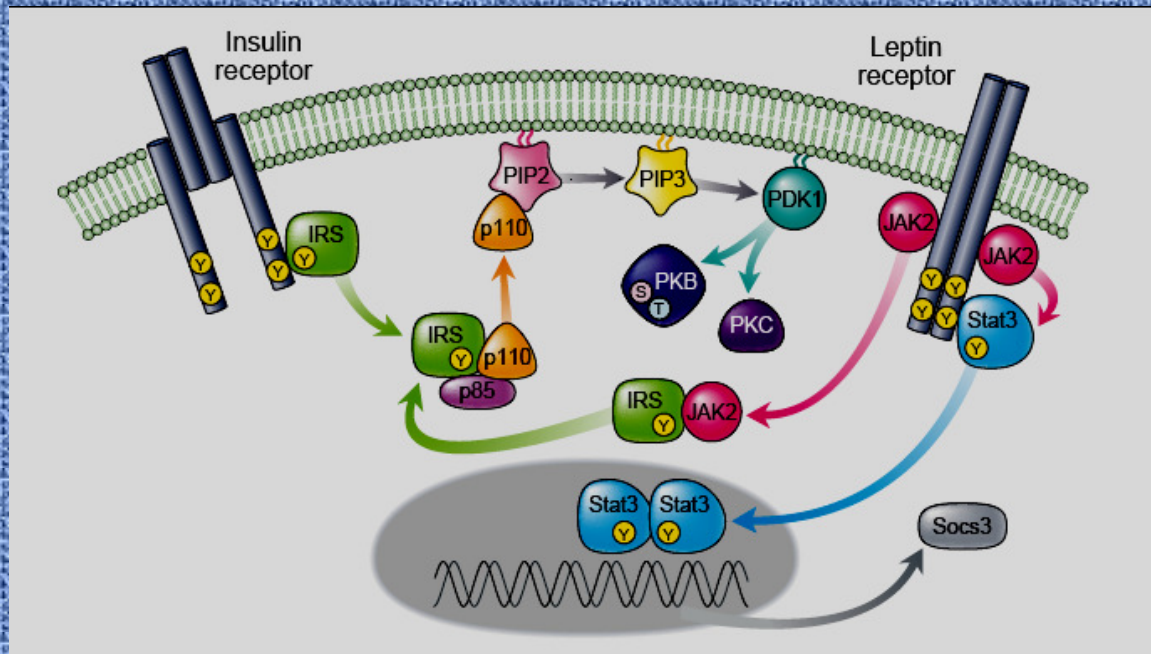
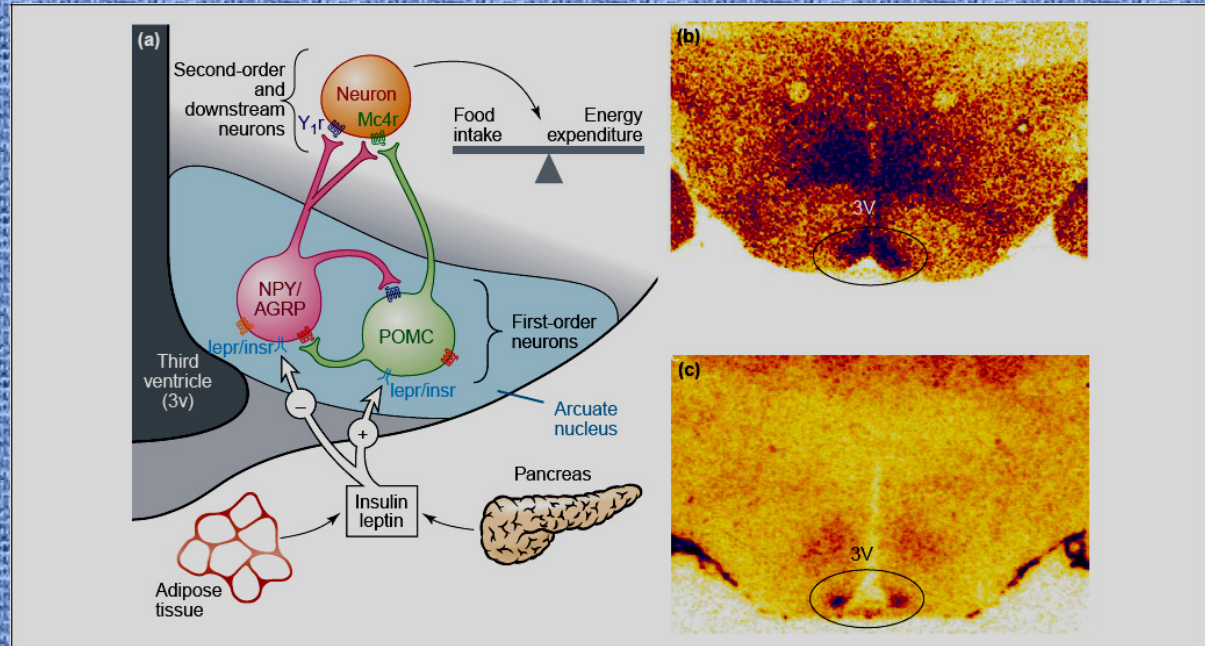
KENNEDY GC (1966). Hypothalamic obesity. *Proc. Royal Soc. Med.*, **153**: 1276-7.

Zhang et al., 1994 – LEPTINA

Positional cloning of the mouse **obese gene** and its human homologue.
Nature

A releitura atual da teoria lipostática

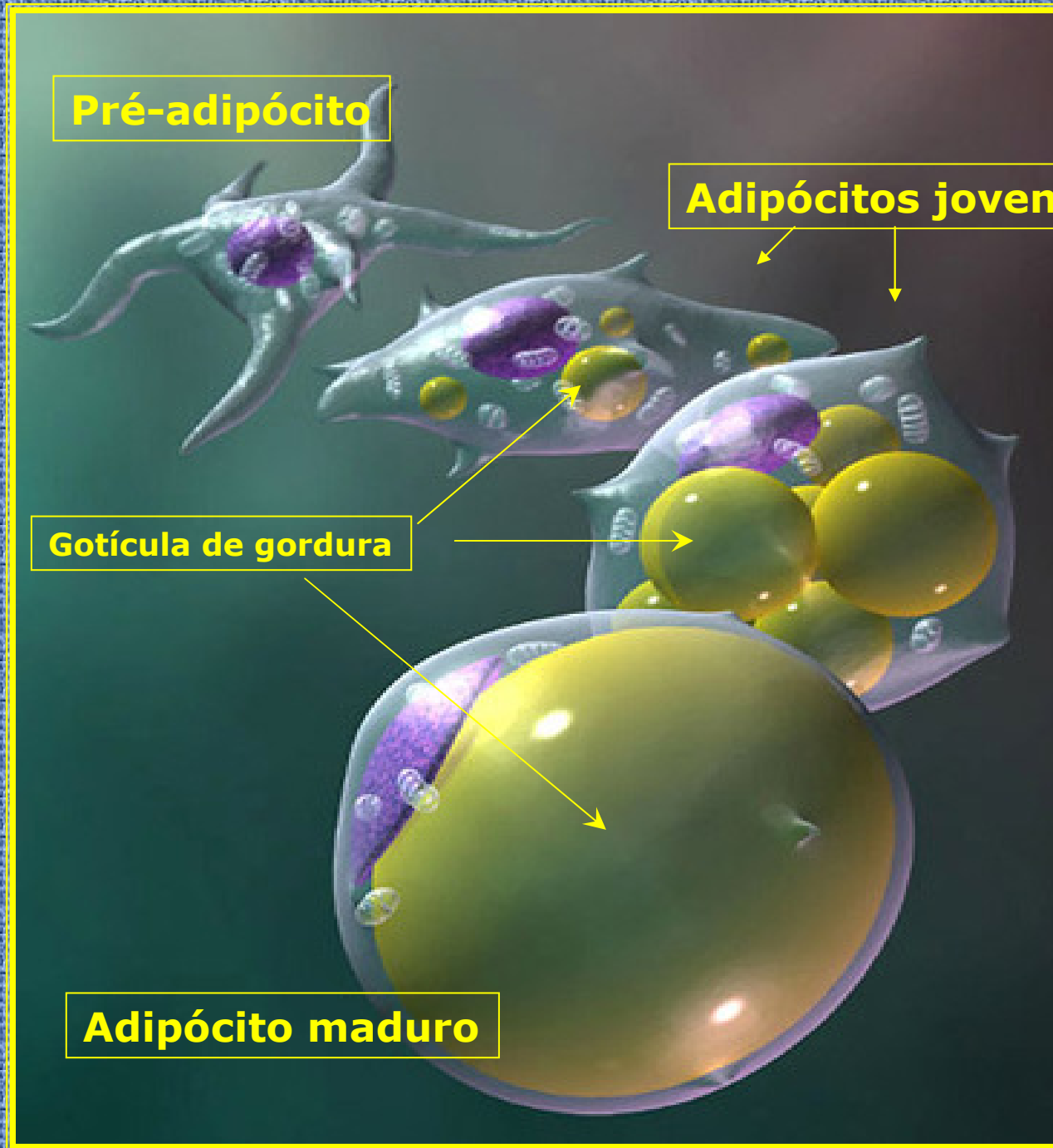
INS e LEP no controle hipotalâmico do comportamento alimentar



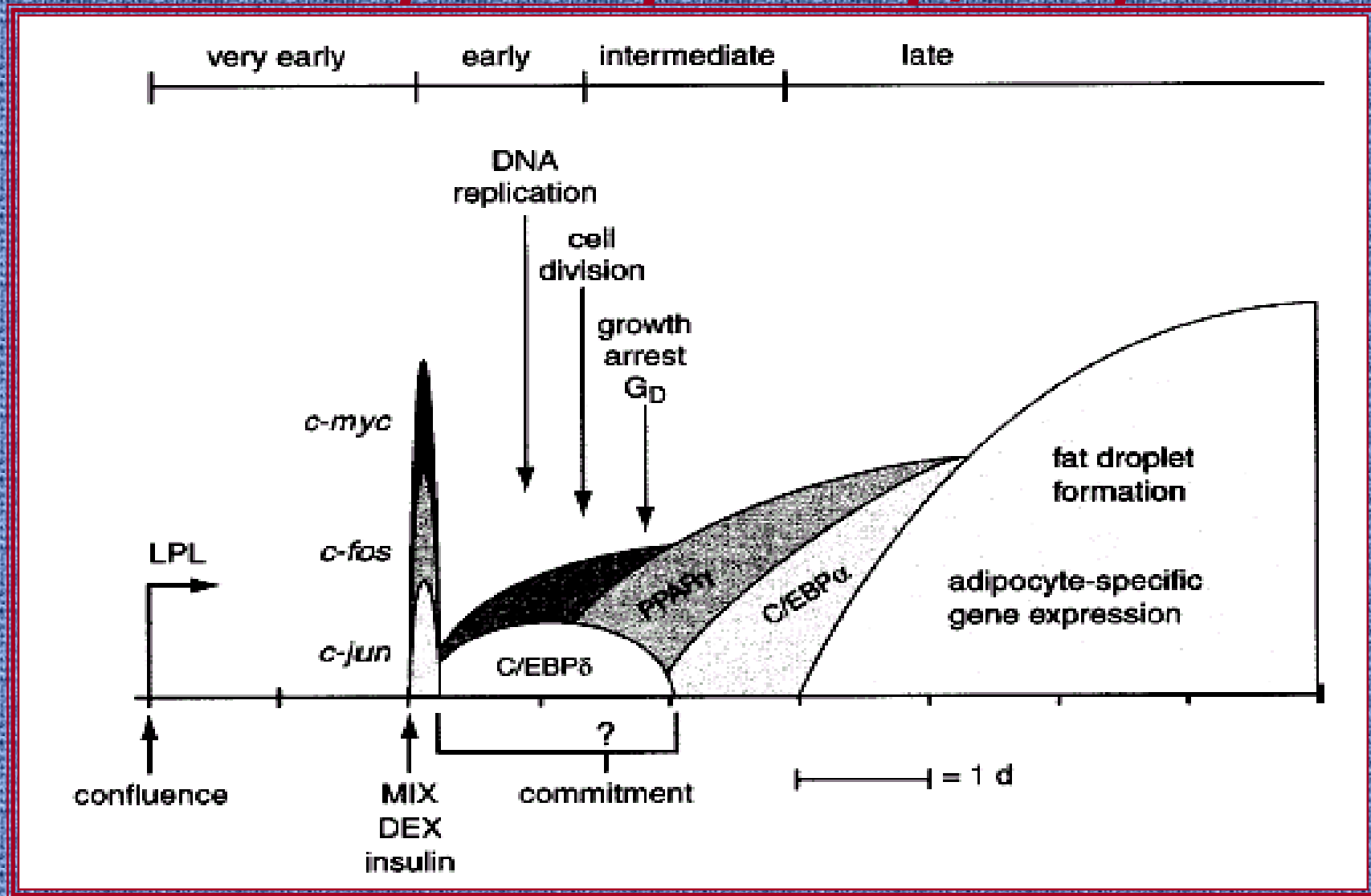
Ahima
Flyer
Elias

Carvalho
Velloso
Saad

A D I P O G É N E S E



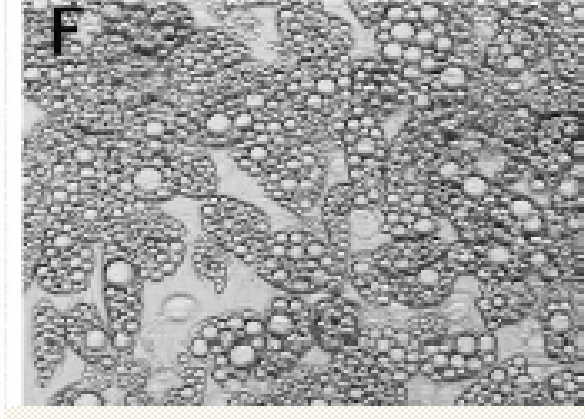
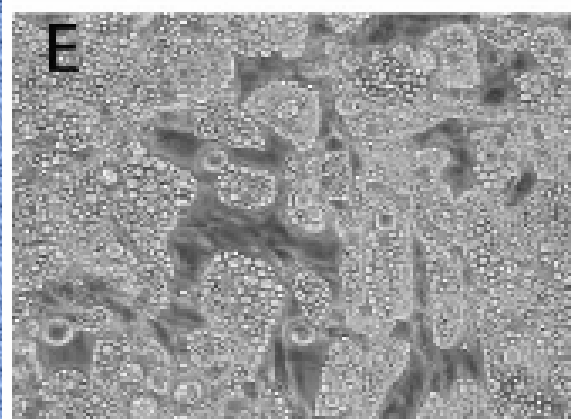
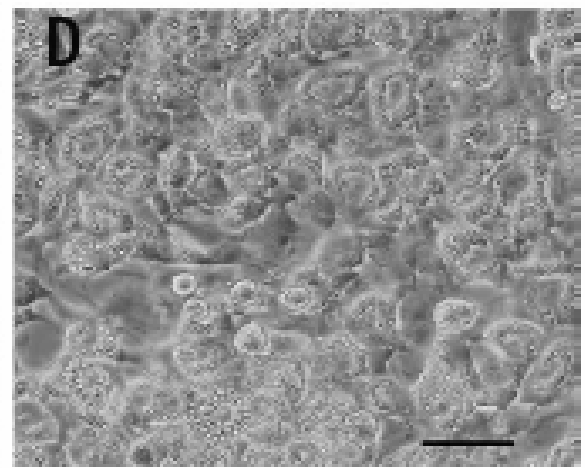
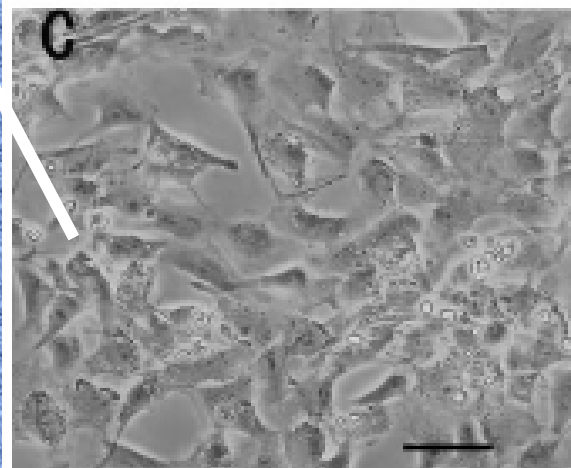
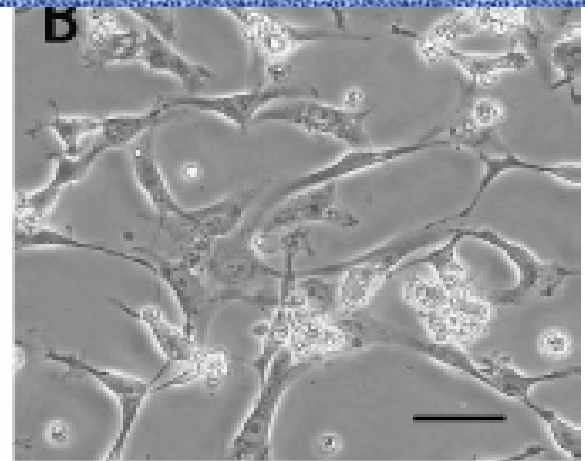
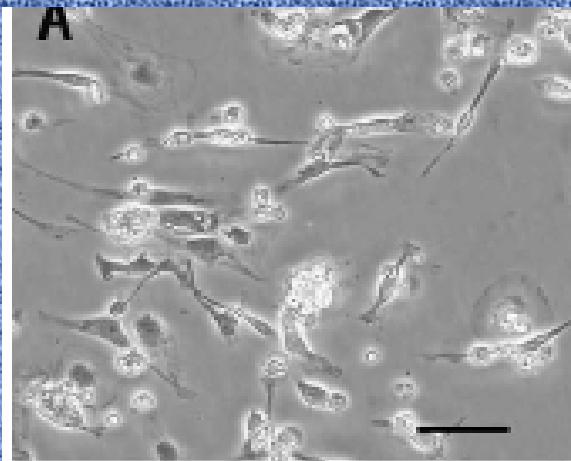
Evolução temporal da diferenciação celular de pré-adipócitos p/ adipócitos



Ntambi et al, J Nutr, 2000

DIFERENCIAÇÃO DE ADIPÓCITOS

MIX
DEX
INS



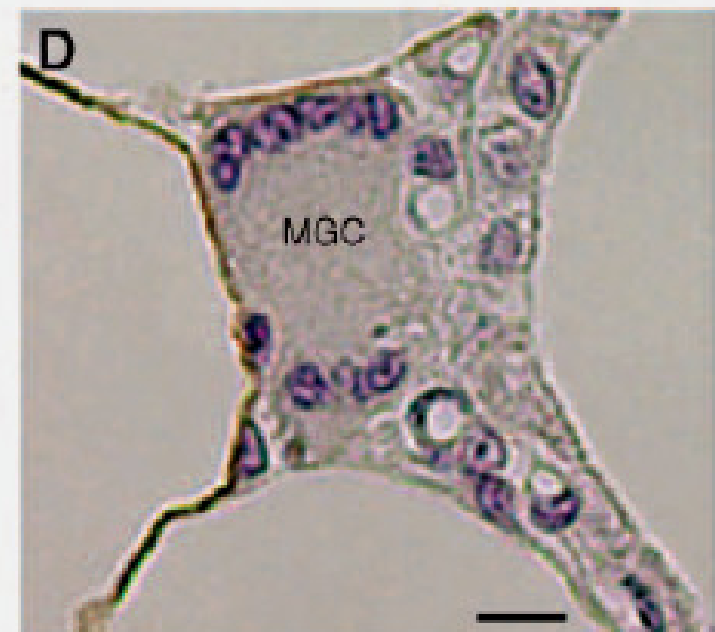
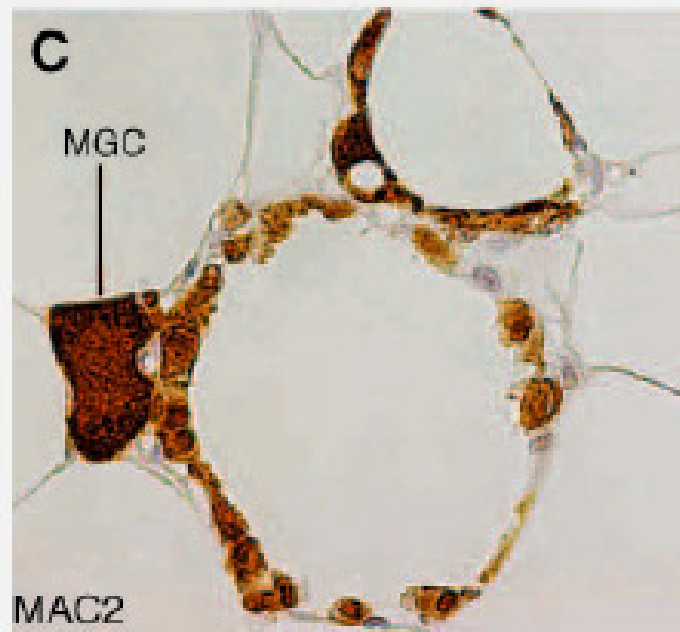
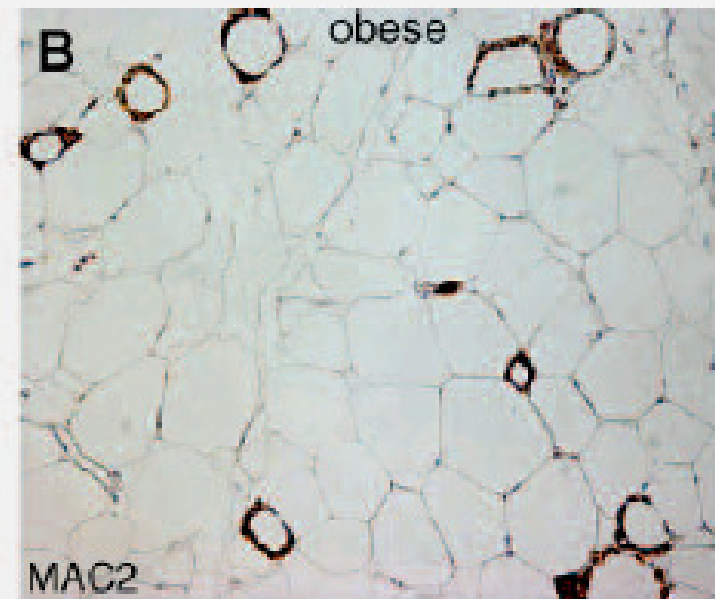
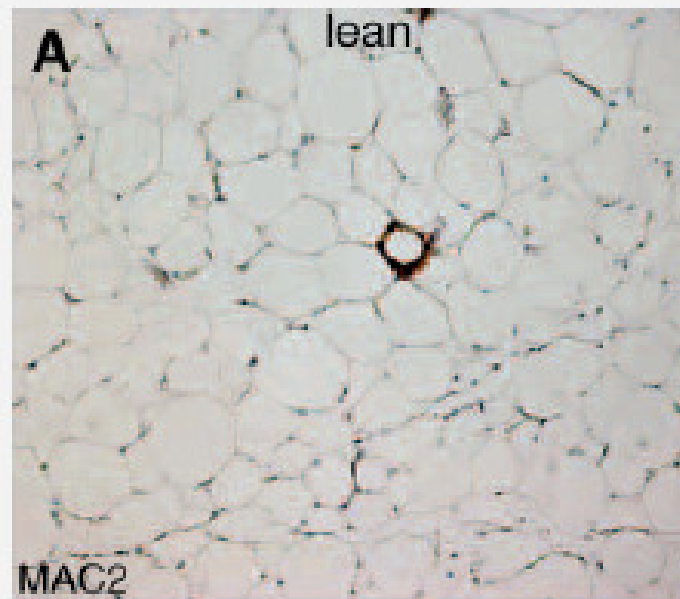
TURNOVER CELULAR DO TECIDO ADIPOSEO

APOPTOSE

PROCESSO INFLAMATÓRIO

NECROSE

**MACRÓFAGOS
NO TAB**



Dynamics of fat cell turnover in humans.

Spalding KL et al. *Nature*, 2008.

Obesity is increasing in an epidemic manner in most countries and constitutes a public health problem by enhancing the risk for cardiovascular disease and metabolic disorders such as type 2 diabetes^{1,2}. Owing to the increase in obesity, life expectancy may start to decrease in developed countries for the first time in recent history³. The factors determining fat mass in adult humans are not fully understood, but increased lipid storage in already developed fat cells (adipocytes) is thought to be most important^{4,5}. Here we show that adipocyte number is a major determinant for

Here we show that adipocyte number is a major determinant for the fat mass in adults. However, the number of fat cells stays constant in adulthood in lean and obese individuals, even after marked weight loss, indicating that the number of adipocytes is set during childhood and adolescence. To establish the dynamics

generation rate is altered in early onset obesity, suggesting a tight regulation of fat cell number in this condition during adulthood. The high turnover of adipocytes establishes a new therapeutic target for pharmacological intervention in obesity.

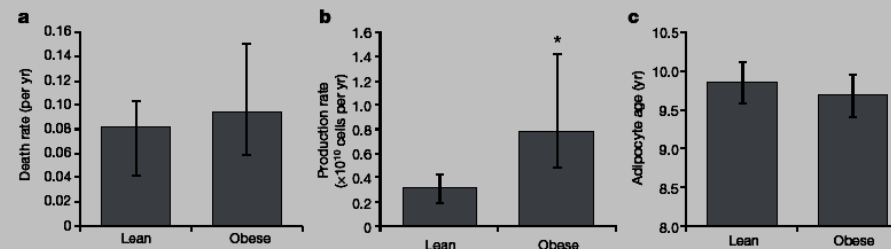
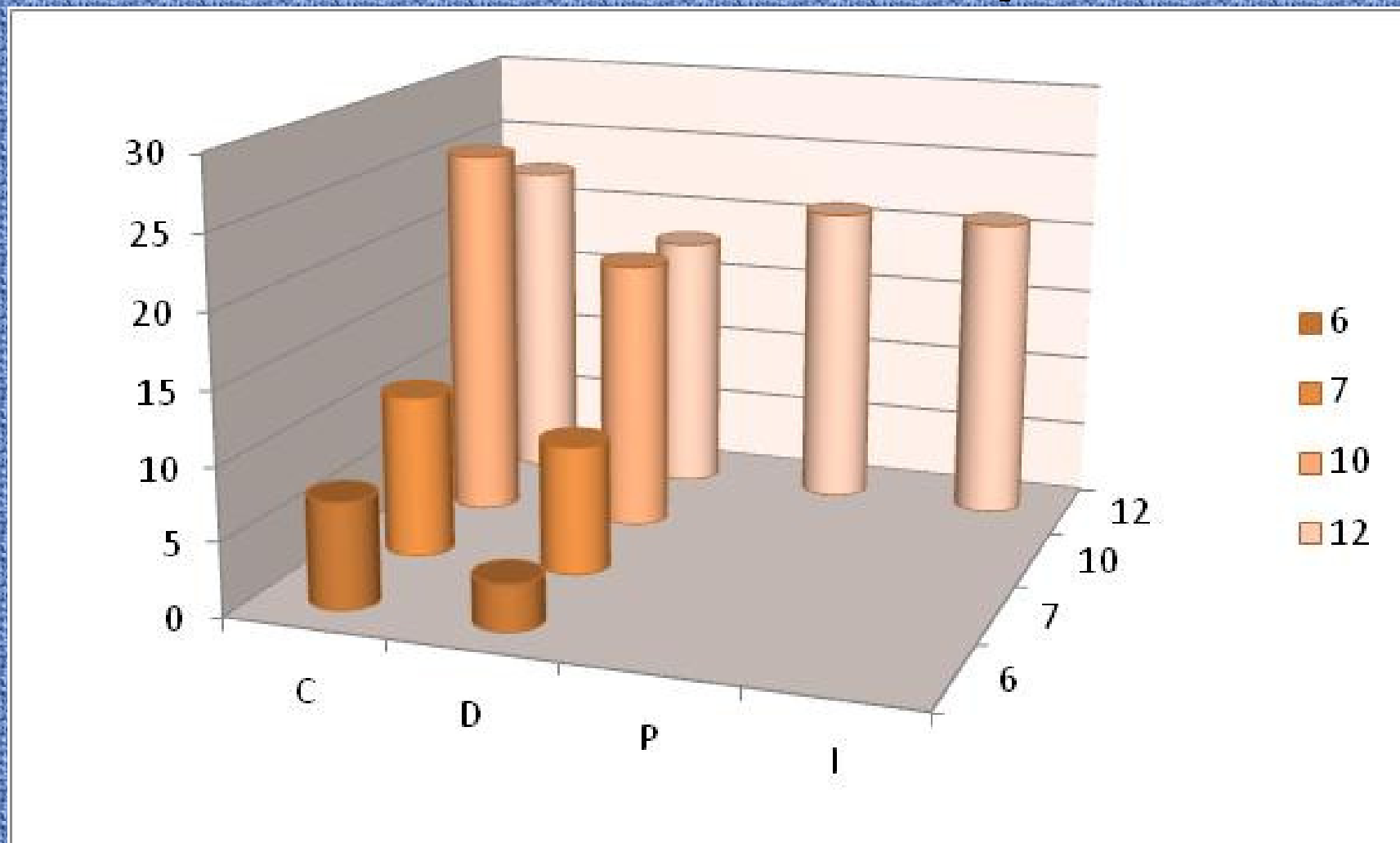


Figure 4 | Effect of obesity on adipocyte generation and death. a, No significant difference in adipocyte death rate per year was seen across the different BMIs. b, Obese individuals had a significantly greater number of adipocytes added per year than lean individuals. c, No significant difference in

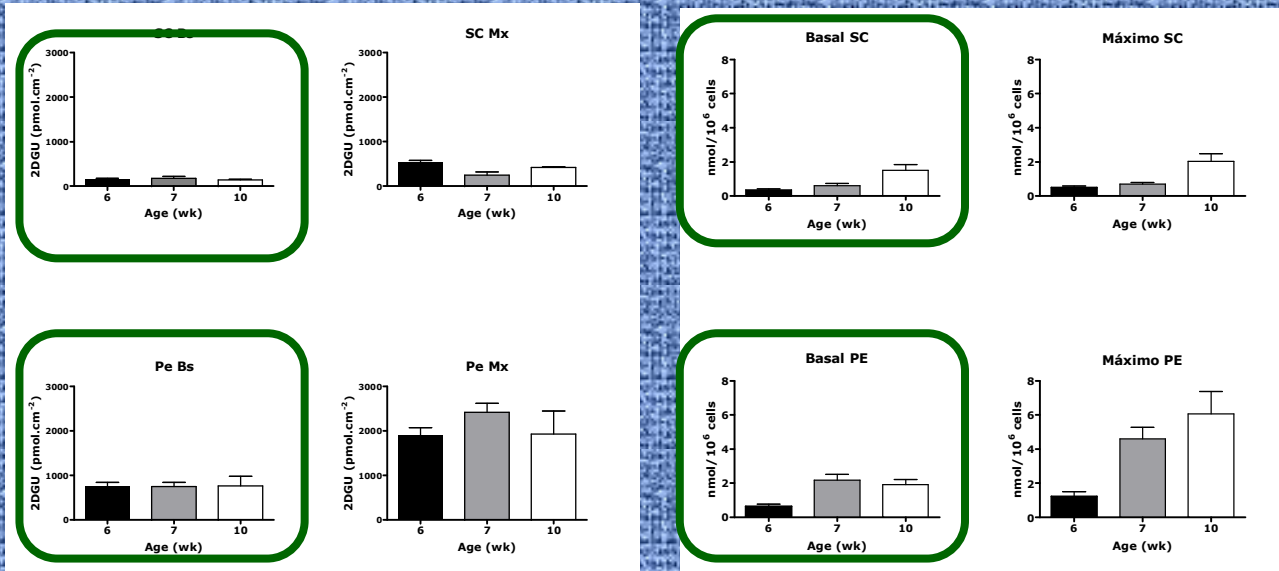
the average age of adipocytes in lean versus obese individuals was found. In a and b, values are the medians and error bars indicate the location of the first and third quartiles; in c, data are shown as mean \pm s.e.m. Asterisk, $P < 0.01$ for lean ($n = 13$) versus obese ($n = 14$) individuals, Kruskal–Wallis test.

Efeito da puberdade e do tratamento de ratos diabéticos sobre a celularidade do tecido adiposo PE



CAMPANA AB; TAKADA J; LIMA FB. 2008 (em preparação)

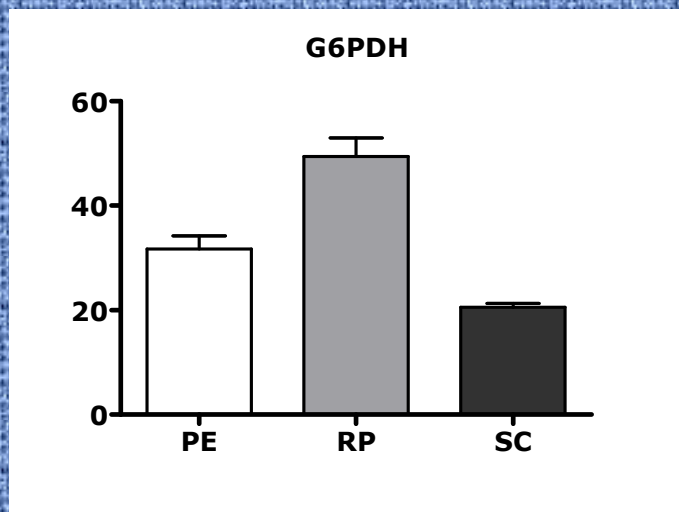
Heterogeneidade da resposta celular em função do território adiposo



Campana AB...Lima FB.
2008. Em preparação

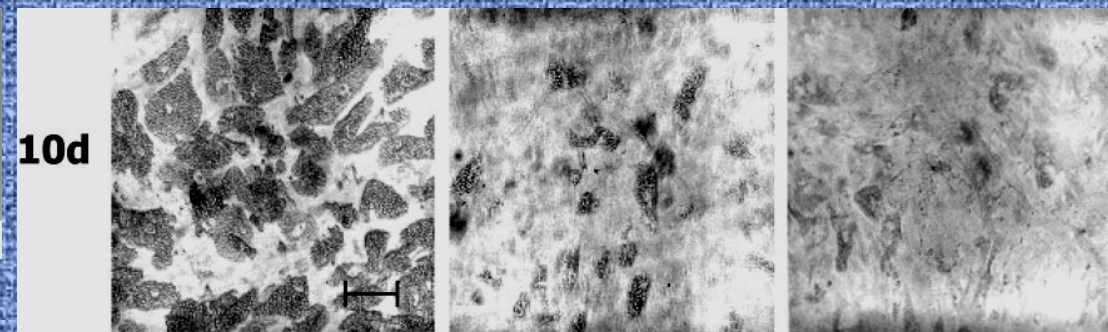
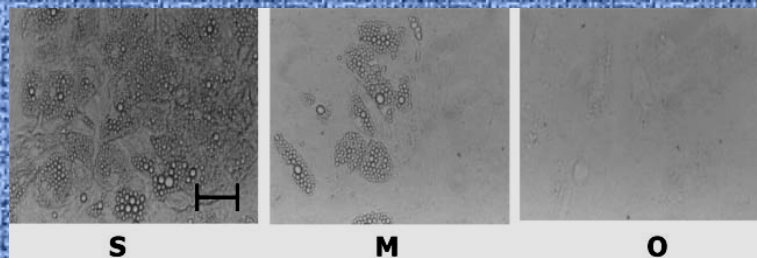
Captação
de glicose

Lipogênese

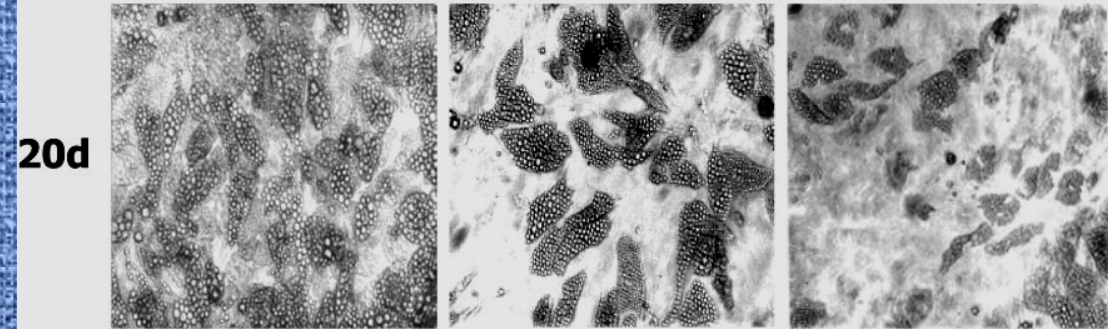
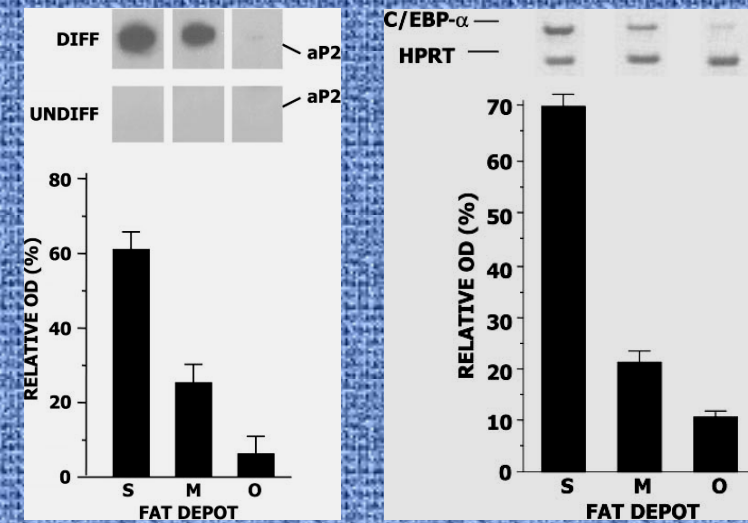


Machado MA ... Lima FB.
2008. Em preparação

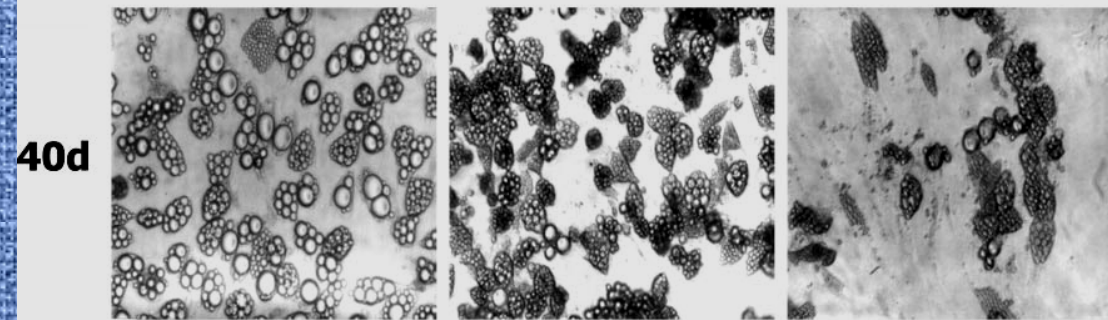
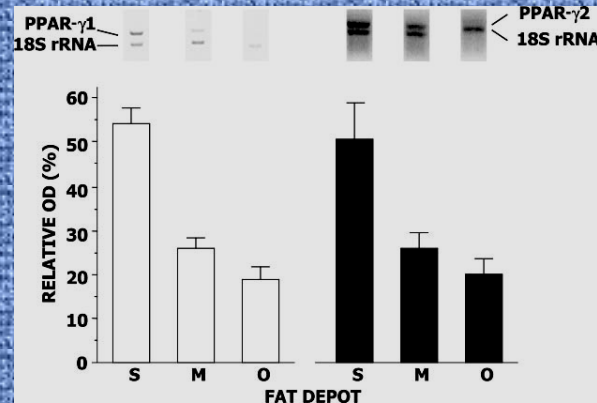
Heterogeneidade na diferenciação



10d



20d

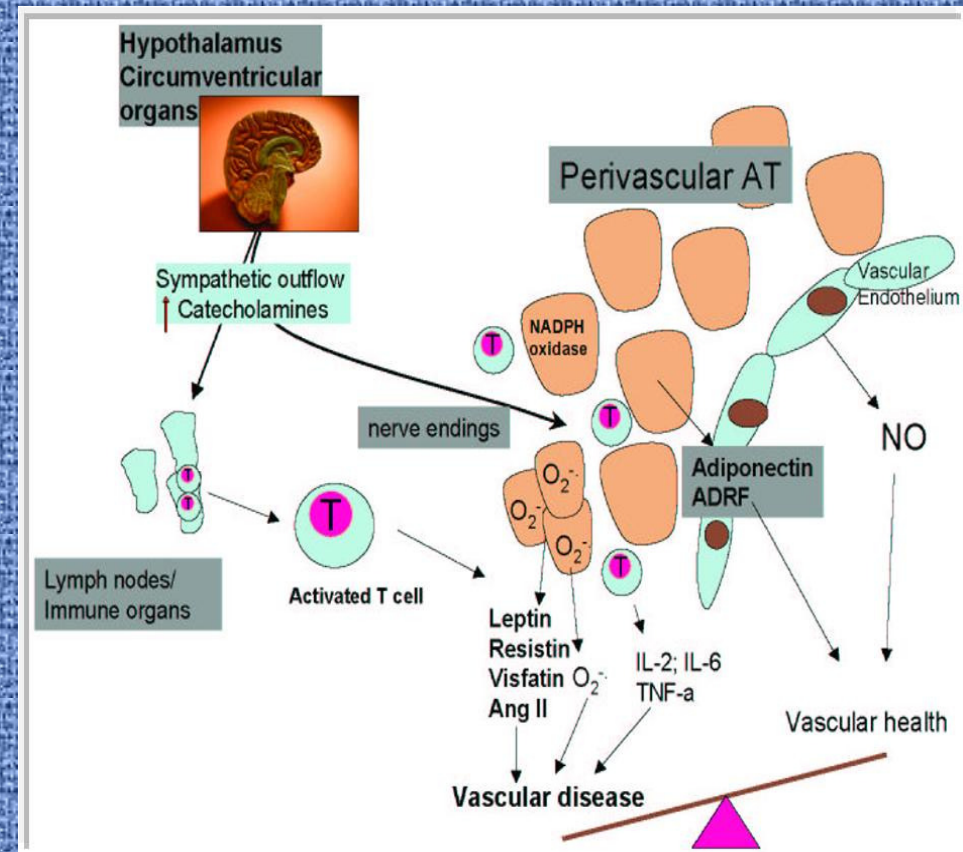
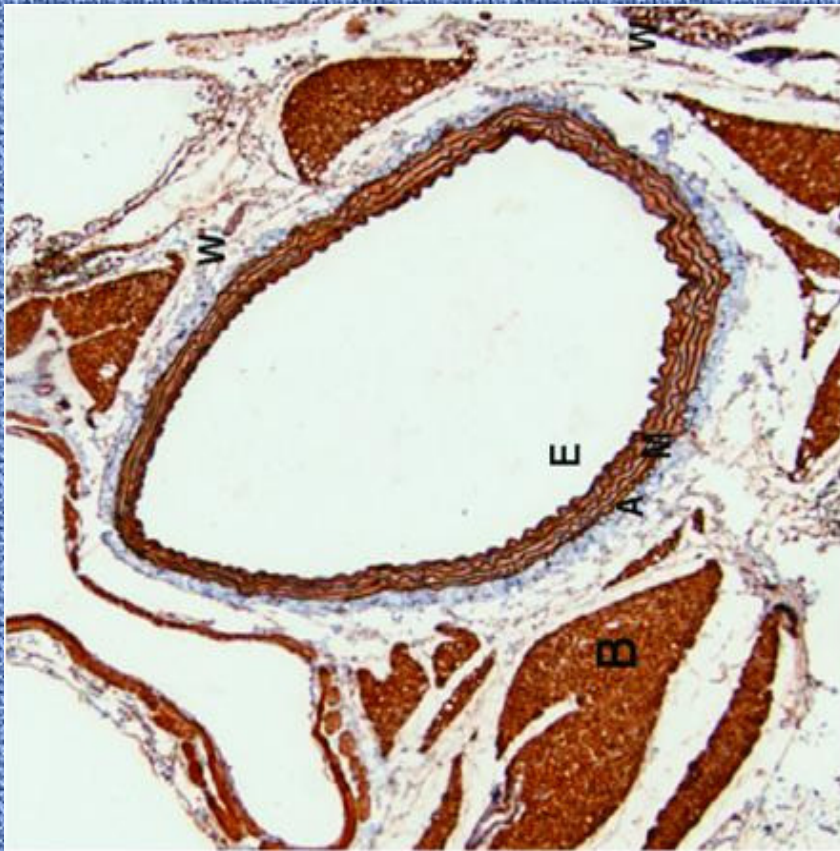


40d

Tchkonia et al., *Am J Physiol RICP*, 2002

A Gordura Perivascular como um sistema de comunicação intercelular especial. A importância do efeito parácrino

GUSIK et al. J.Physiol.Pharmacol. 58, 2007



Reflexões finais

1. Haveria um sistema de regulação da adiposidade?

2. Em vista da disparidade do fenômeno ser tecido específica, como seria a regulação regional?

3. Quais as conexões deste processo com a regulação do peso e da ingestão?