Hypothalamic Dysfunction in Obesity

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Global Life Expectancy
-10,000 BCE - 2003

Source: Indur M. Goklany, "The Improving State of our World." Washington, DC: Cato Institute, 2007. 36. Life expectancy is believed to have been 20-30 years prior to 1820. Age 25 is selected as an average.
Causes of Increased Life Expectancy

• Machines – Changes in the agriculture production model
• Industrialized foods – reduced production costs
• Industrialized foods – increased energy density
• Migration from physical to intellectual labor
• Sedentary lifestyle
Global Life Expectancy
-10,000 BCE - 2003

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Life Expectancy at Birth by Region, 1950-2050.

Obesity

- Diabetes
- Hypertension
- Atherosclerosis
- Cancer
- Bone and Joint disease
1950`s
Anatomo-physiological studies


1994
Leptin identification


1996-1998
Leptin resistance

Schwartz Nat Med 2: 589, 1996
Hypothalamic resistance to leptin

- Increased Caloric Intake
- Reduced Energy Expenditure

- Frederich/Flier *Nat Med* 1: 1311, 1995
- Schwartz *Diabetes* 45: 531, 1996
Consumption of a Fat-Rich Diet Activates a Proinflammatory Response and Induces Insulin Resistance in the Hypothalamus

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Fat-rich diet

\[ \text{TNF-}\alpha, \text{IL-1}\beta \]

Hypothalamic resistance to leptin and insulin

NFkB

JNK
Saturated Fatty Acids Produce an Inflammatory Response Predominantly through the Activation of TLR4 Signaling in Hypothalamus: Implications for the Pathogenesis of Obesity

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Hypothalamic resistance to leptin and insulin - Obesity

Palmitate 16:0
Stearate 18:0
Arachidate 20:0

TLR4, Microglia

Citokines
• TNFα
• IL1β
• IL6
Microglia activation under HFD

Saline

LPS (1mg/Kg – 2hr)

Chow

HFD 6w

Coope, Myers Jr., Velloso, Unpublished
High-Fat Diet Induces Apoptosis of Hypothalamic Neurons

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A

B

C

D

E

F

% of control

0
10
20
30
40
50
60
70
80
90
100
110
120

CT

HF

*
Environment + Genetics = Obesity

Palmitic 16:0
Stearic 18:0
Arachidic 20:0

TLR4, microglia

Citokines
• TNFα
• IL1β
• IL6

Resistance
• Leptin
• Insulin

Apoptosis Neurons

De Souza, Endocrinology 2005
Zhang, Cell 2008
Ozcan, Cell Metab 2009
Milanski, J Neurosci 2009
Moraes, PLoS One 2009
Benoit, JCI 2009
Romanatto, JBC 2009
Horvath, PNAS 2010
Arruda, Endocrinology 2011
Thaler, JCI 2012
Li, Nat Cell Biol 2012
Inflammatory

Anti-inflammatory
Neurogenesis
Neurogenesis in the hypothalamus
Partial Reversibility of Hypothalamic Dysfunction and Changes in Brain Activity After Body Mass Reduction in Obese Subjects

Simone van de Sande-Lee, 1 Fabrício R.S. Pereira, 2 Dennys E. Cintra, 1,3 Paula T. Fernandes, 2 Adilson R. Cardoso, 4 Célia R. Garlipp, 5 Eliton A. Chaim, 6 Jose C. Pareja, 6 Bruno Geloneze, 7 Li Min Li, 2 Fernando Cendes, 2 and Licio A. Velloso 1

TCA – Temporal clustering analysis: Analyzes neuronal activity on a given region during a certain time-frame

11 Women; 2 Men

Body mass = 103±11 Kg
BMI = 39 ± 1
Obesity is associated with hypothalamic injury in rodents and humans

Gliosis - sign of inflammation
Conclusions

• Inflammation and dysfunction of the hypothalamus are important features of obesity
• Saturated fats present in the diet have a dramatic damaging effect on neurons of the hypothalamus
• Unsaturated fats reduce inflammation and promote neurogenesis in the hypothalamus
• Neuroimaging methods are non-invasive approaches that may provide advance in the diagnosis and follow-up of patients with obesity related diseases
Thank you!

Collaborations
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