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GENE-ENVIRONMENT INTERACTIONS CONTROLLING ENERGY AND GLUCOSE HOMEOSTASIS AND THE DEVELOPMENTAL ORIGINS OF OBESITY

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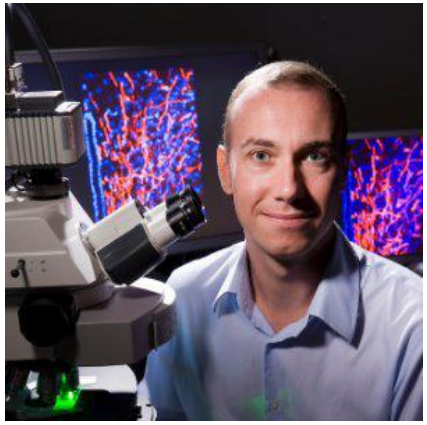
Physiological Reviews

近四年影响因子	2014年度	2013年度	2012年度	2011年度
	27.324	29.041	30.174	26.866
非自引影响因子	需要登录可见		5年影响因子	需要登录可见
中国人发表文章比例	需要登录可见			
JCR杂志分区	生理学分类下的1 区期刊			

作者信息



- **Sebastien Bouret**
- Associate Professor of Pediatrics at University of Southern California & Inserm
- Society for Pediatric Research (SPR), 2011-present
- Invited speaker, Kavli Japanese-American Frontiers of Science Symposium, 2010
- Invited speaker, Japanese-French Frontiers of Science Symposium, 2009

1. The Problem: Obesity, Diabetes, and Their Interactions

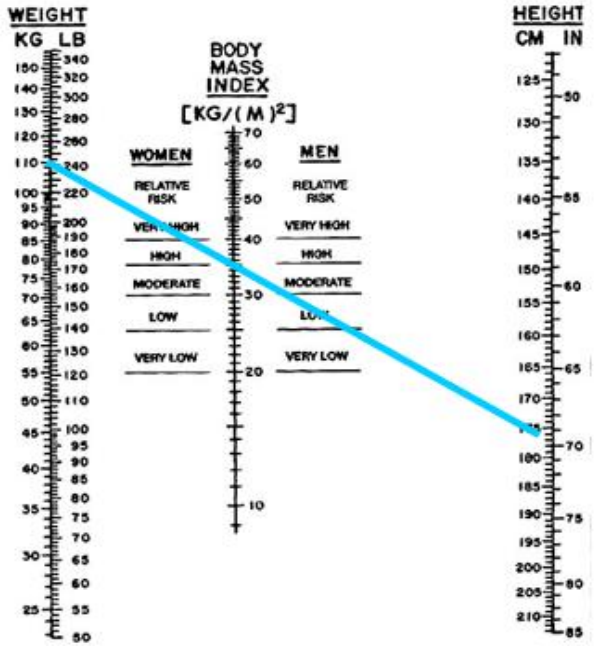
?

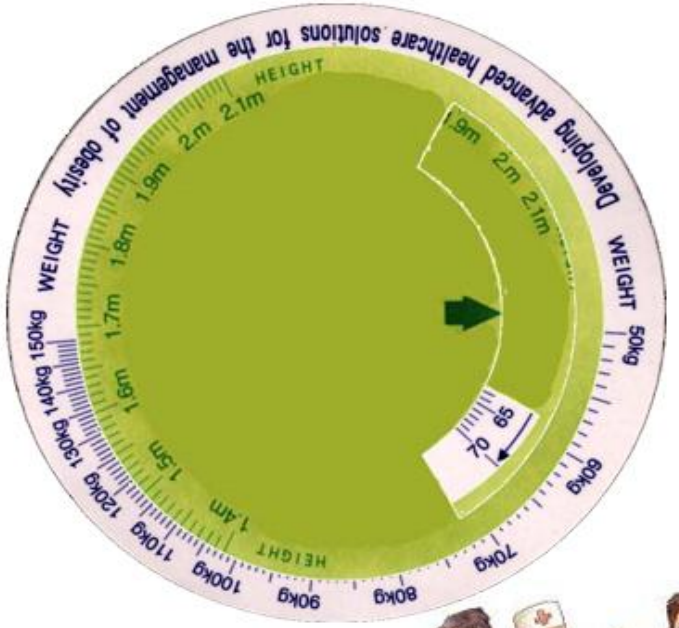
1.1 Obesity

- Overweight is defined as a BMI of 25–29.9 kg/m^2
- Obesity as a BMI of >30 kg/m^2.
- The category of obesity is further divided into subcategories of class I (BMI 30.0–34.9 kg/m^2), class II (BMI 35.0–39.9 kg/m^2), and class III (BMI >40 kg/m^2) .
- Other: waist circumference, waist-hip ratio, as well as percent body fat using DEXA, CT, and MRI.

身高和体重

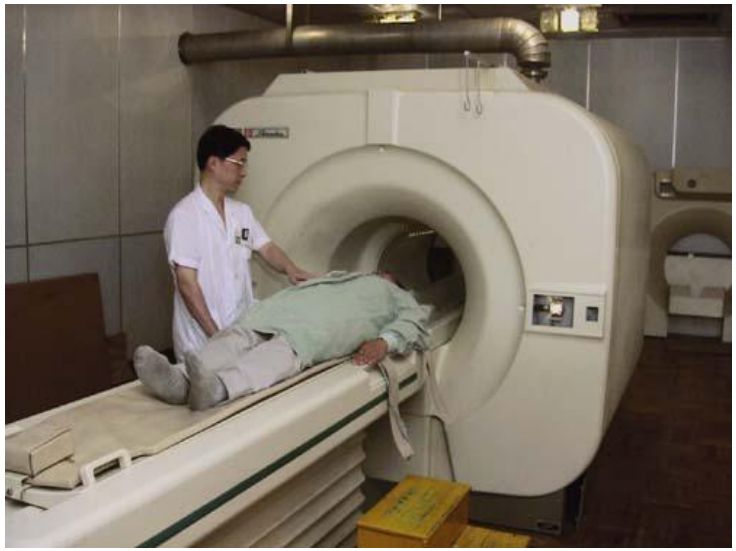
- 查表法

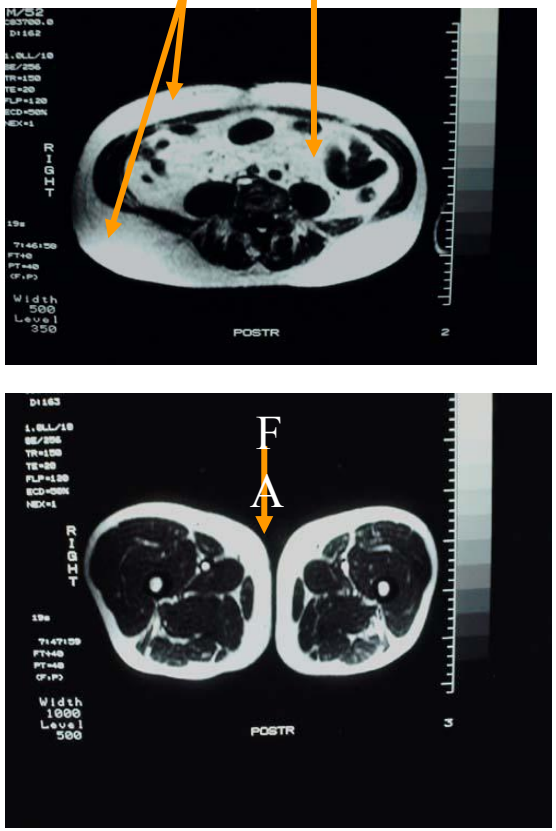




changing diabetes
让我们一起改变糖尿病

MRI-脂肪测定





计算截面的脂肪面积

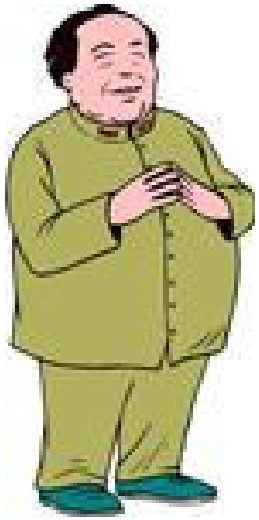
生物电阻抗法（BIA）

- 原理：脂肪组织导电量不如含电解质的组织，可通过身体导电性或电阻程度计算人体脂肪含量%；
- 低廉、快速简便，重复性好，适用流行病学调查。

1.2 Diabetes-1 and -2

- ✓ **Hemoglobin A1C of >6.5%, fasting plasma glucose of 126 mg/dl**
- ✓ **2h after a 75 g oral glucose tolerance test or a random plasma glucose measurement 200 mg/dl**

1型糖尿病
T1DM



2型糖尿病
T2DM

1.2 Diabetes-1 and -2

- ✓ 遗传易感性
- ✓ 免疫功能紊乱：针对胰岛β细胞抗原的自身免疫
- ✓ 病毒感染
- ✓ 牛乳喂养
- ✓ 药物及化学物

1型糖尿病
T1DM

Diabetes-1 and 2

- 体力活动减少及/或能量摄入增多
- 肥胖病（总体脂增多或腹内体脂相对或者绝对增多）
- 低体重出生儿
- 中老年
- 吸烟、药物及应激（可能）

2型糖尿病
T2DM

2. Prevalence and Associated Morbidity and Mortality of Obesity

- ✓ **The prevalence of obesity and overweight in the United States is high.**
- ✓ **In 2007–2008, 32% of US men and 36% of US women were obese, and an additional 40% of men and 28% of women were overweight.**
- ✓ **Cardiovascular disease, T2DM, cancer, and respiratory diseases.**
- ✓ **Obesity reduces life expectancy by 6–20 yr depending on age and race.**

3. Genes ×Environment Interactions: Imprinting (Epigenetics) as a Concept

- ✓**Although a number of common genetic susceptibility loci for obesity and T2DM have been identified over the last decade, the rapid rise in prevalence of these conditions in the last two decades, a time frame which is not compatible with a change in our genetic make-up, suggests that the environment in which we live is an important determinant of obesity risk.**
- ✓**Highly processed foods that are high in saturated fat and refined carbohydrates as well as reduced physical activity.**
- ✓**?**

4. Historical Background

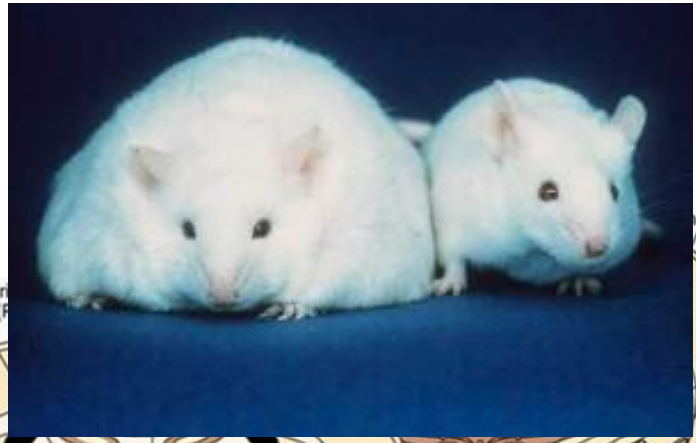
✓**4.1 Early concepts of energy homeostasis regulation**

✓**4.2 The discovery of leptin and how it changed things**

✓**4.3 Early studies implicating the perinatal environment in the pathogenesis of obesity and diabetes**

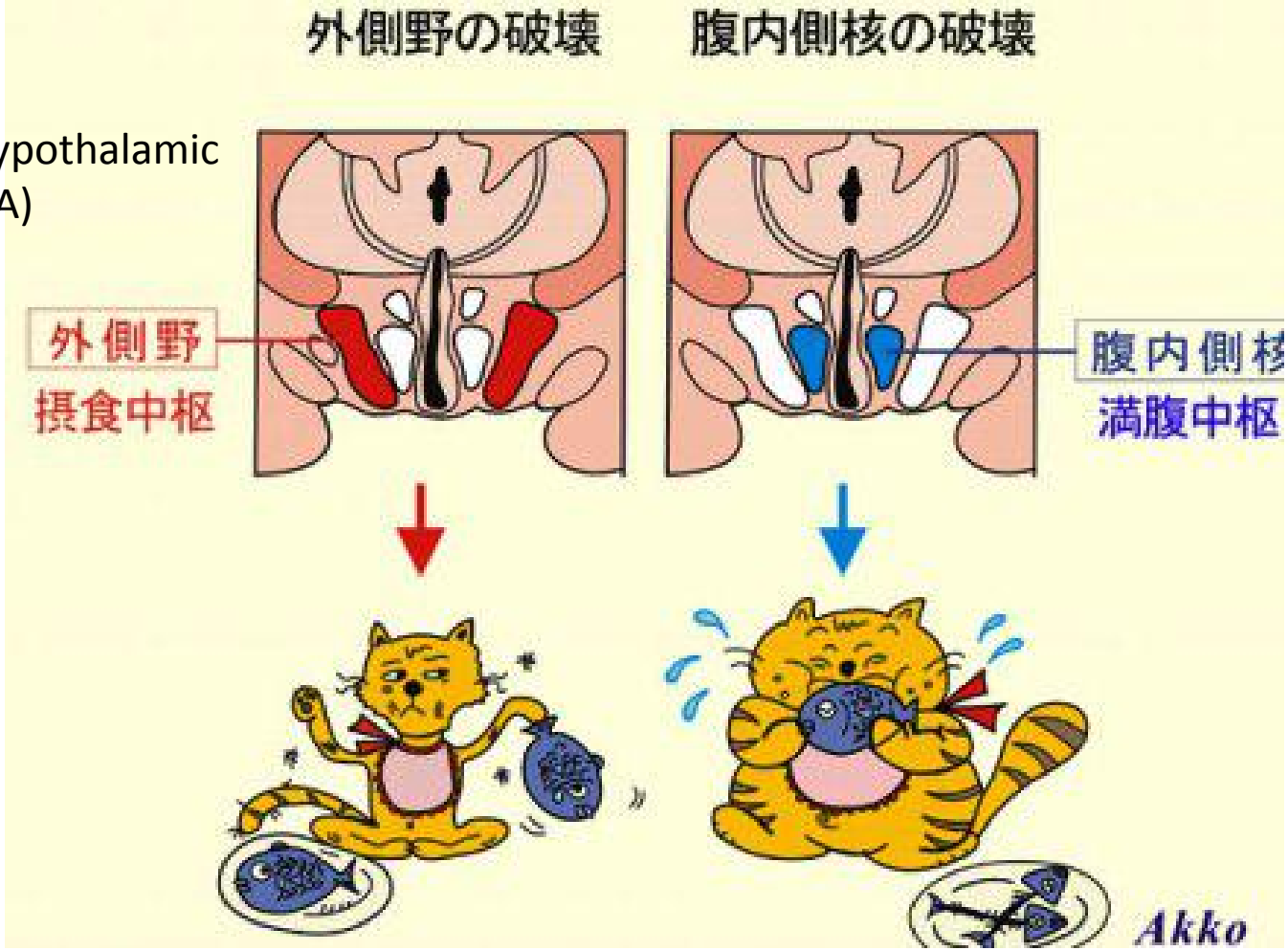
4.1 Early concepts of energy homeostasis regulation

- ✓In 1940, Hetherington and Ranson， VMH lesion
- ✓VMN and ARC
- ✓POMC, NPY, AgRP in the regulation of energy and glucose homeostasis were recognized .



VMH was the “satiety center” and LHA was the “feeding center.”

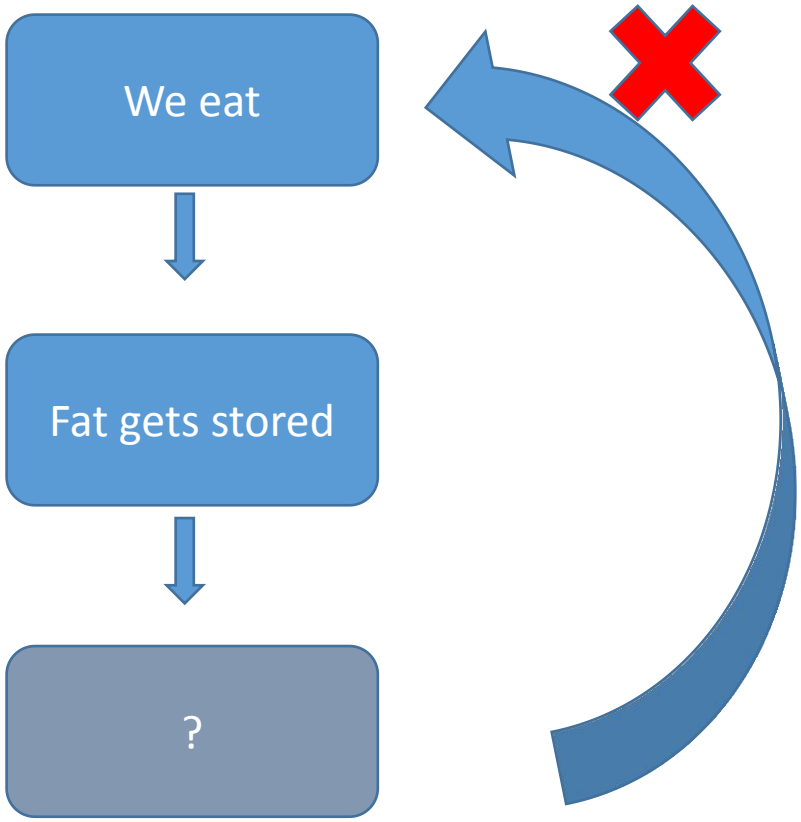
lateral hypothalamic area (LHA)



下丘脑腹内侧核(VMH)

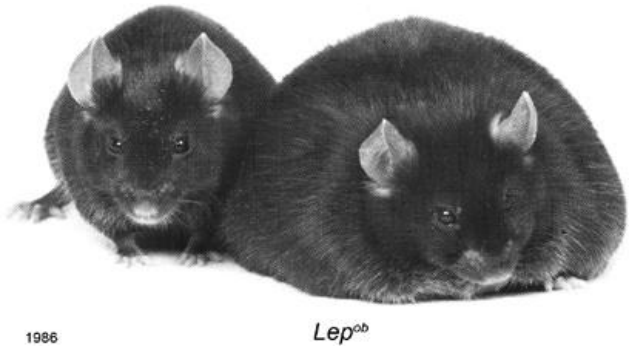
VMH

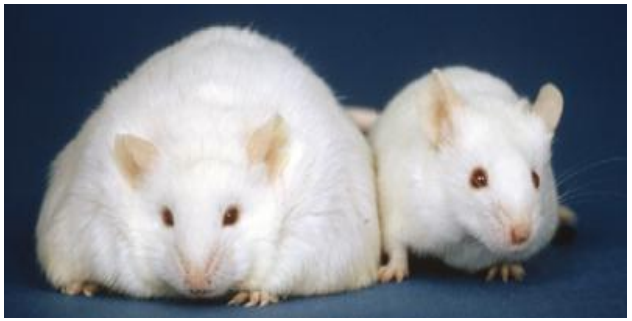
4.1 Early concepts of energy homeostasis regulation



Kennedy, 1953

4.2 The discovery of leptin and how it changed things



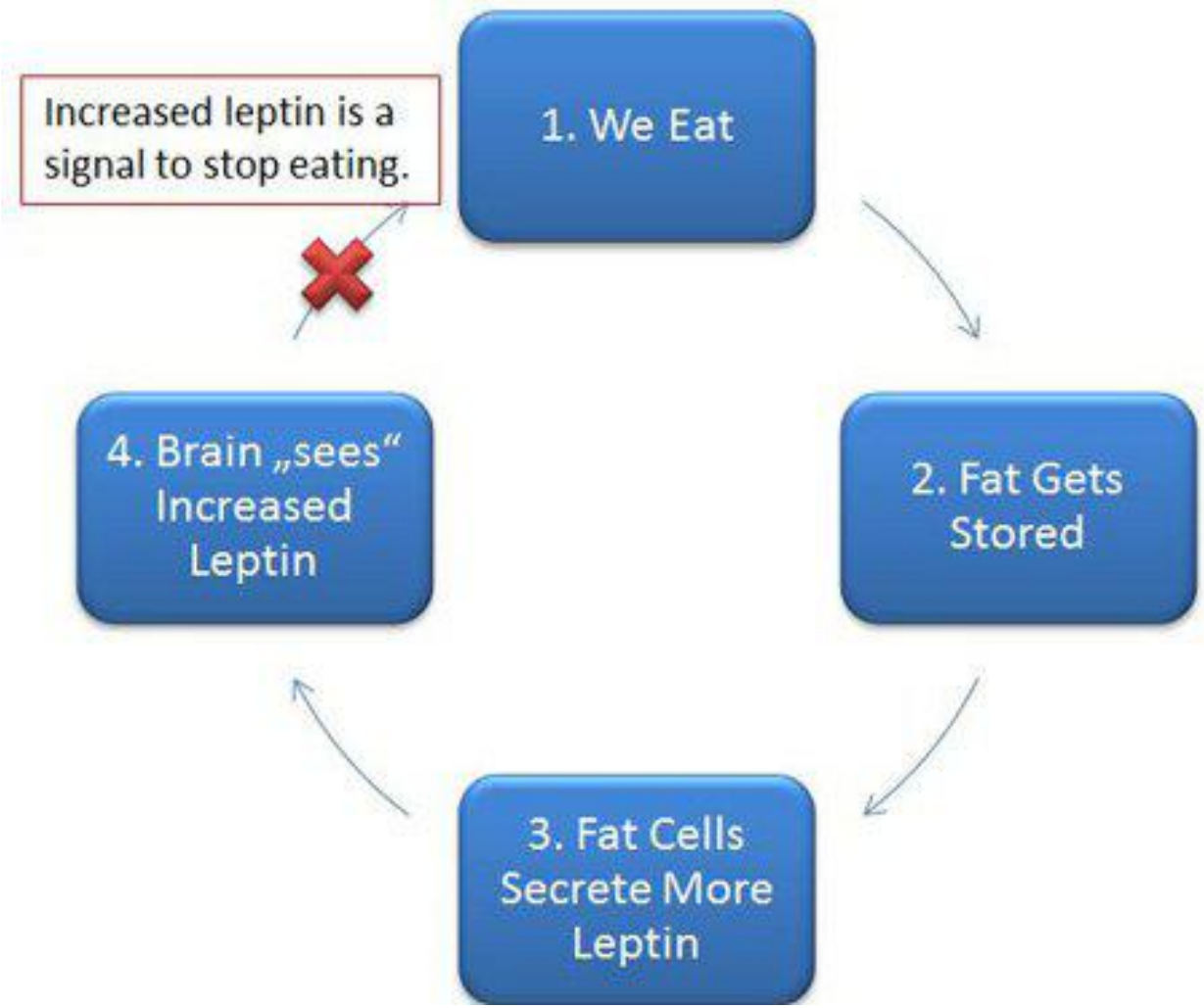


In 1949, investigators at the Jackson Ob (now lep)

1966, Coleman and colleagues
Db mouse （糖尿病）

Ob mice lacked a circulating satiety factor and that db mice overproduced that circulating factor but could not respond to it.
Positional cloning，4.5 kb RNA
Friedman named the peptide “leptin”.

4.2 The discovery of leptin and how it changed things



4.3 Early studies implicating the perinatal environment in the pathogenesis of obesity and diabetes

- ✓Early life environment in determining long-term health.
- ✓Death rates were most affected by the date of birth and not the year of death.
- ✓Forsdahl demonstrating that geographical variations in atherosclerotic disease were not associated with current mortality rates but correlated strongly with past infant mortality rates.

4.3 Early studies implicating the perinatal environment in the pathogenesis of obesity and diabetes

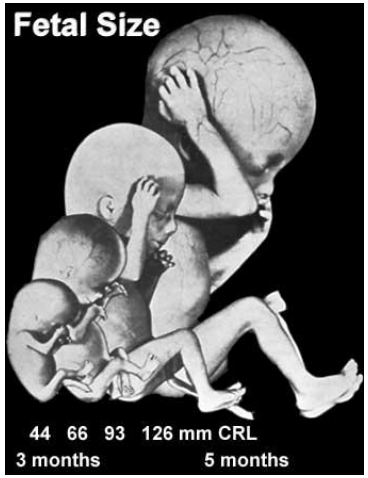
- ✓**Dutch Hunger Winter**
- ✓**Low nutrient intake during early postnatal life actually reduced the risk of obesity at age 19**

Manipulation of litter size.

Appetite determined during the suckling period

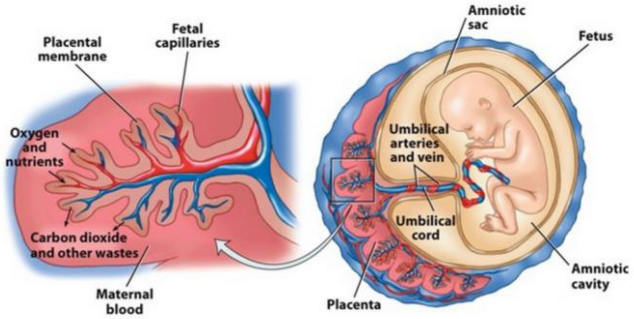
4.3 Early studies implicating the perinatal environment in the pathogenesis of obesity and diabetes

- ✓Barker and colleagues： a strong association between birth weight and subsequent risk of development of T2DM and other features of the metabolic syndrome.



- ✓Lowest birth weight were around six times more likely to have T2DM or impaired glucose tolerance at age 64 compared with those individuals with the highest birth weight.

Dutch hunger winter



- **Maternal nutrition**
- **Long-term risk of T2DM**
- **Before and after Dutch hunger winter: well-nourished population**
- **Dutch hunger winter: onset of the famine and its short duration (5 mo) (1944-1945年荷兰西部)**
- **At age 50， Worse glucose tolerance**

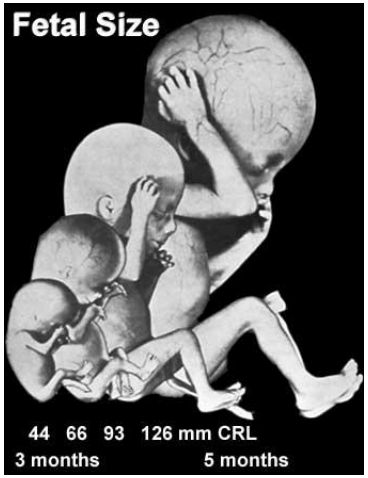
Nature Communications

Dutch hungry winter

- **Leiden大学、哈佛大学和哥伦比亚大学的研究团队对这段时间内孕育的人进行了研究，并将结果发表在近期的Nature Communications杂志上。**

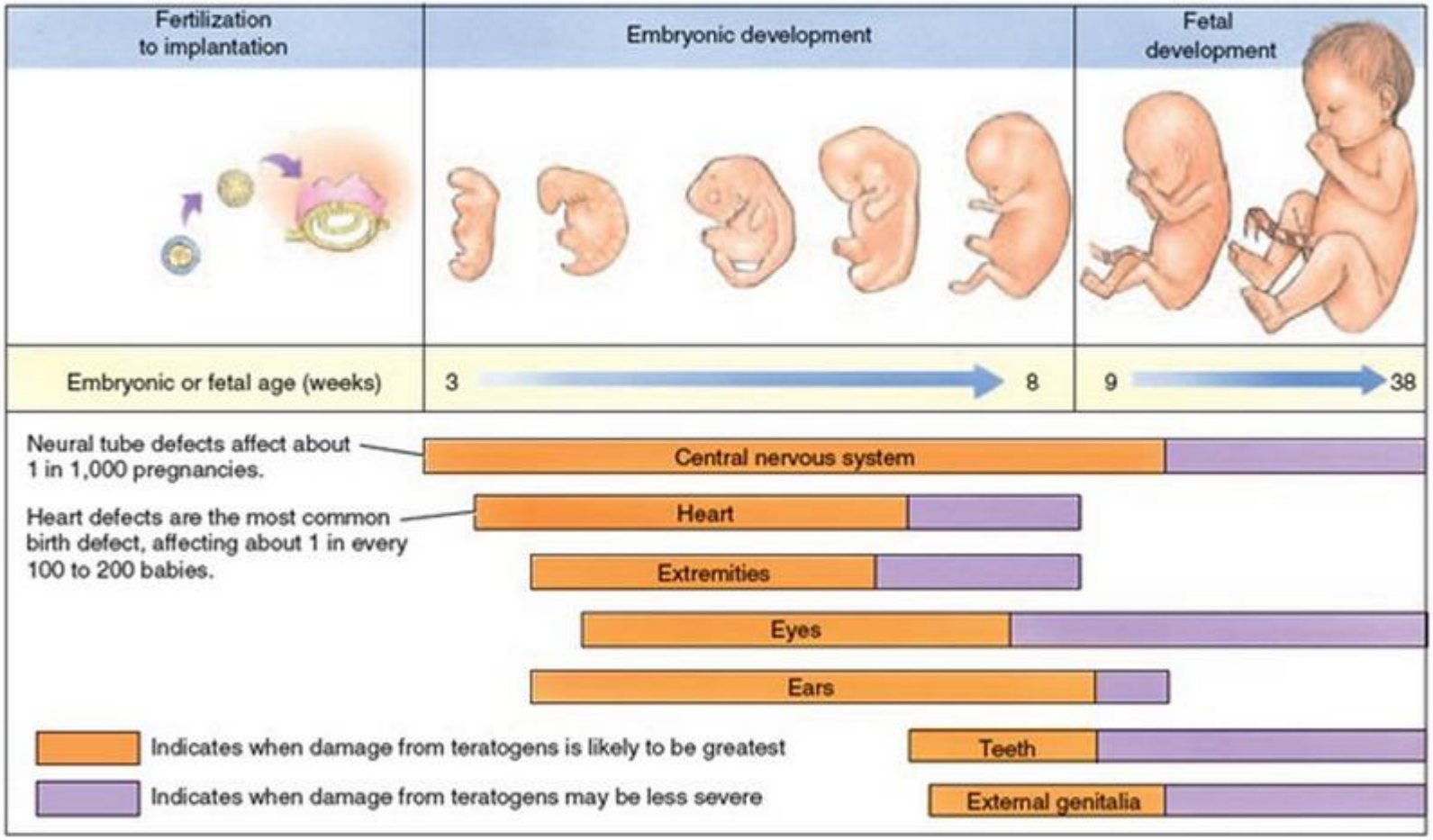
- **比较了Hunger Winter儿童与其兄弟姐妹的DNA，尤其是一百二十万CpG甲基化位点。**

- **环境印迹。**



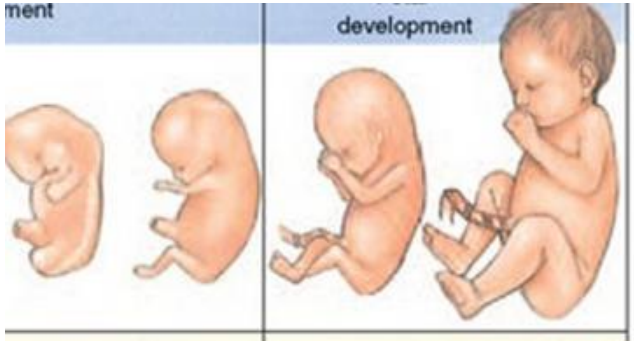
Nature Communications，2014

Critical periods of development

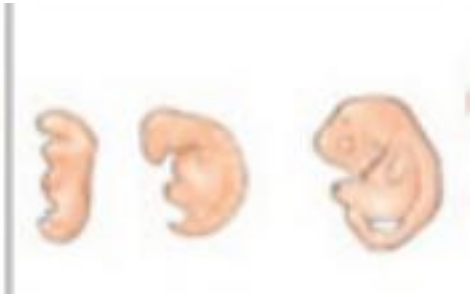


Dutch hungry winter

- **Vulnerable developmental period in terms of long-term regulation of glucose homeostasis.-late gestation**



- **Risk of cardiovascular disease and obesity ---early gestation**



Nature Communications

Great Chinese Famine(1959–1961)

ORIGINAL ARTICLE

Exposure to the Chinese Famine in Early Life and the Risk of Hyperglycemia and Type 2 Diabetes in Adulthood

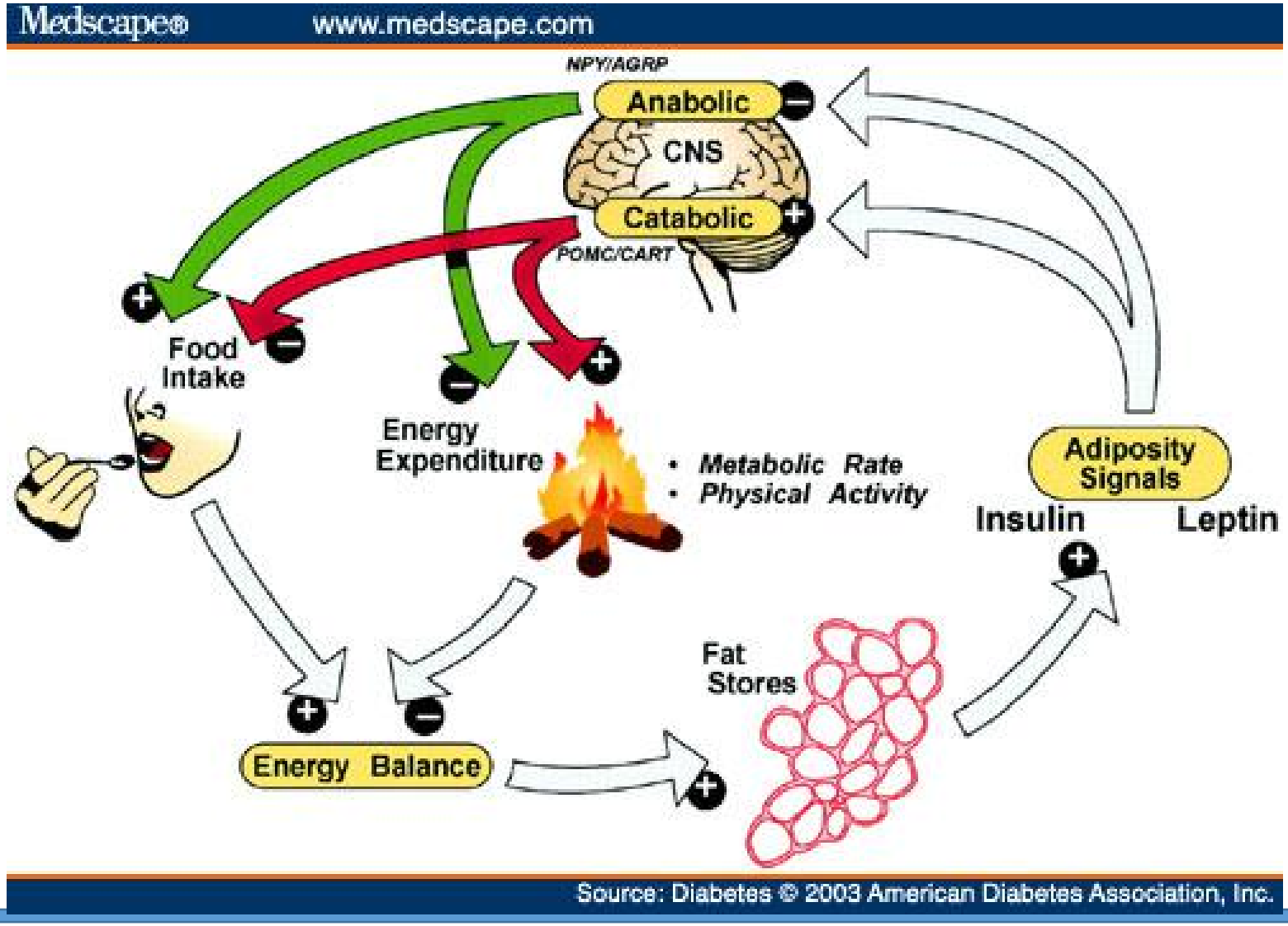
Yanping Li,[1,2] Yuna He,[1,3] Lu Qi,[2,4] Vincent W. Jaddoe,[2,5] Edith J.M. Feskens,[3] Xiaoguang Yang,[1] Guansheng Ma,[1] and Frank B. Hu[2,4]

5. Central regulation of energy and glucose homeostasis

- 5.1 The Central-Peripheral Conversation in the Control of Energy and Glucose Homeostasis
- 5.2 Metabolic Sensing Neurons: the Basic Integrators and Regulators of Glucose and Energy Homeostasis
- 5.3 Homeostatic and Reward-Based Systems

Schwartz et al., 2003

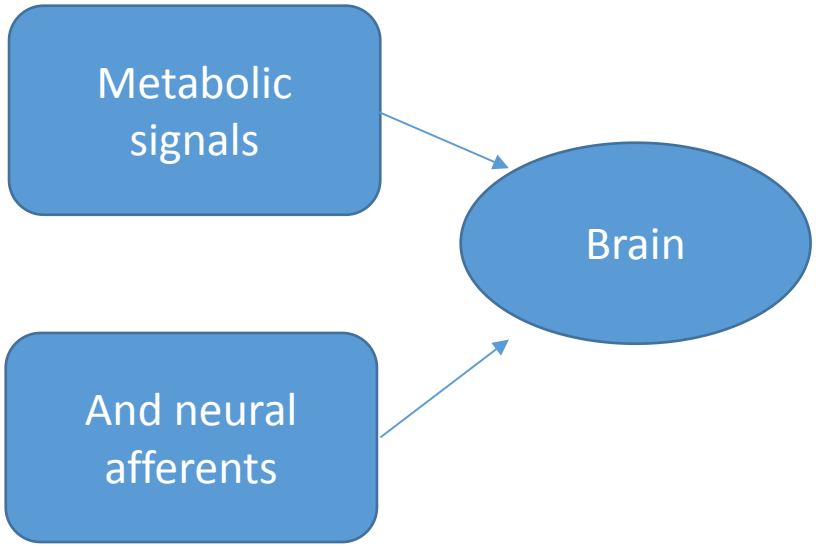
5.1 The Central-Peripheral Conversation in the Control of Energy and Glucose Homeostasis



Schwartz et al., 2003

5.1 The Central-Peripheral Conversation in the Control of Energy and Glucose Homeostasis

The brain is the controller of energy and glucose homeostasis.



Schwartz et al., 2003

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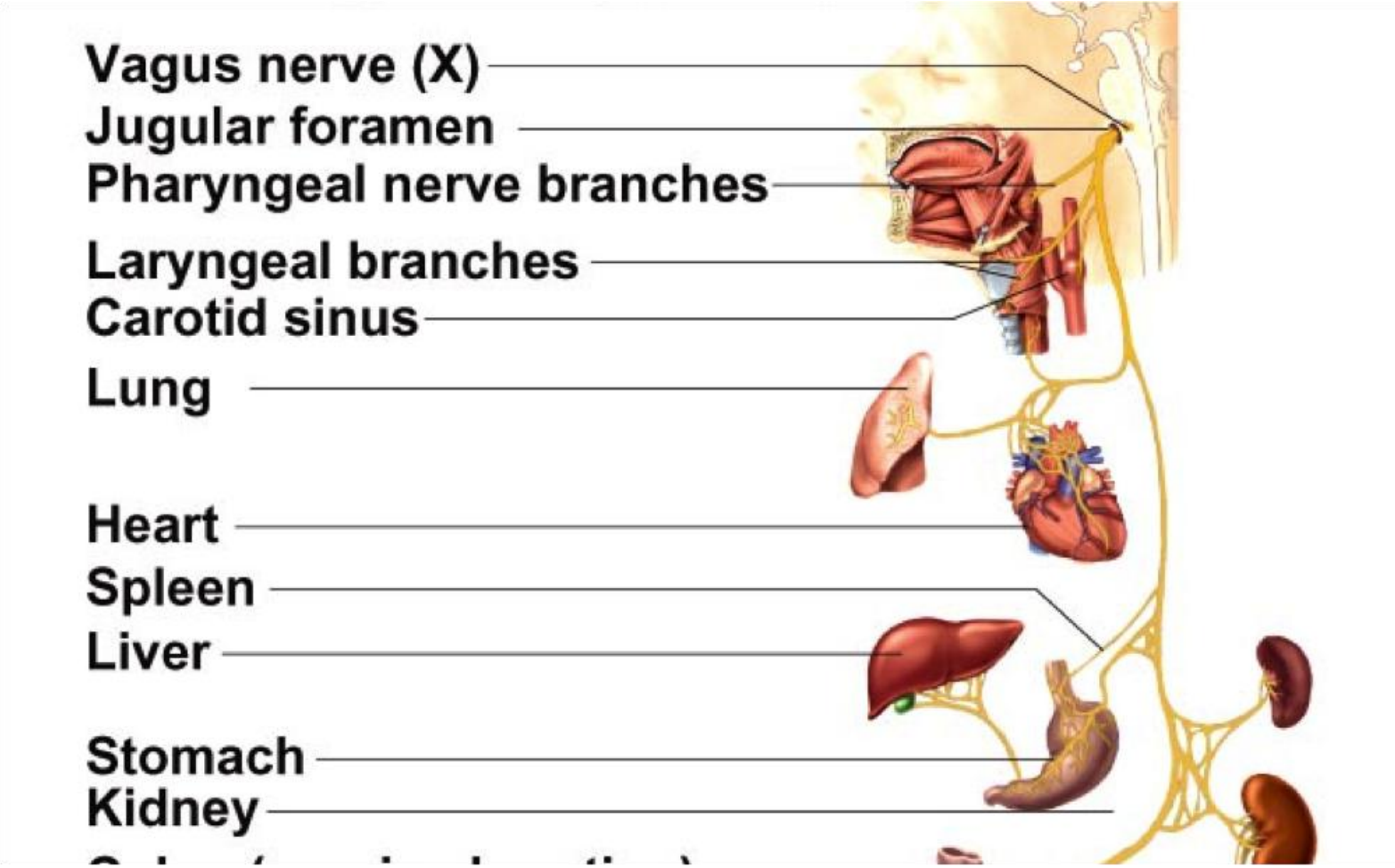

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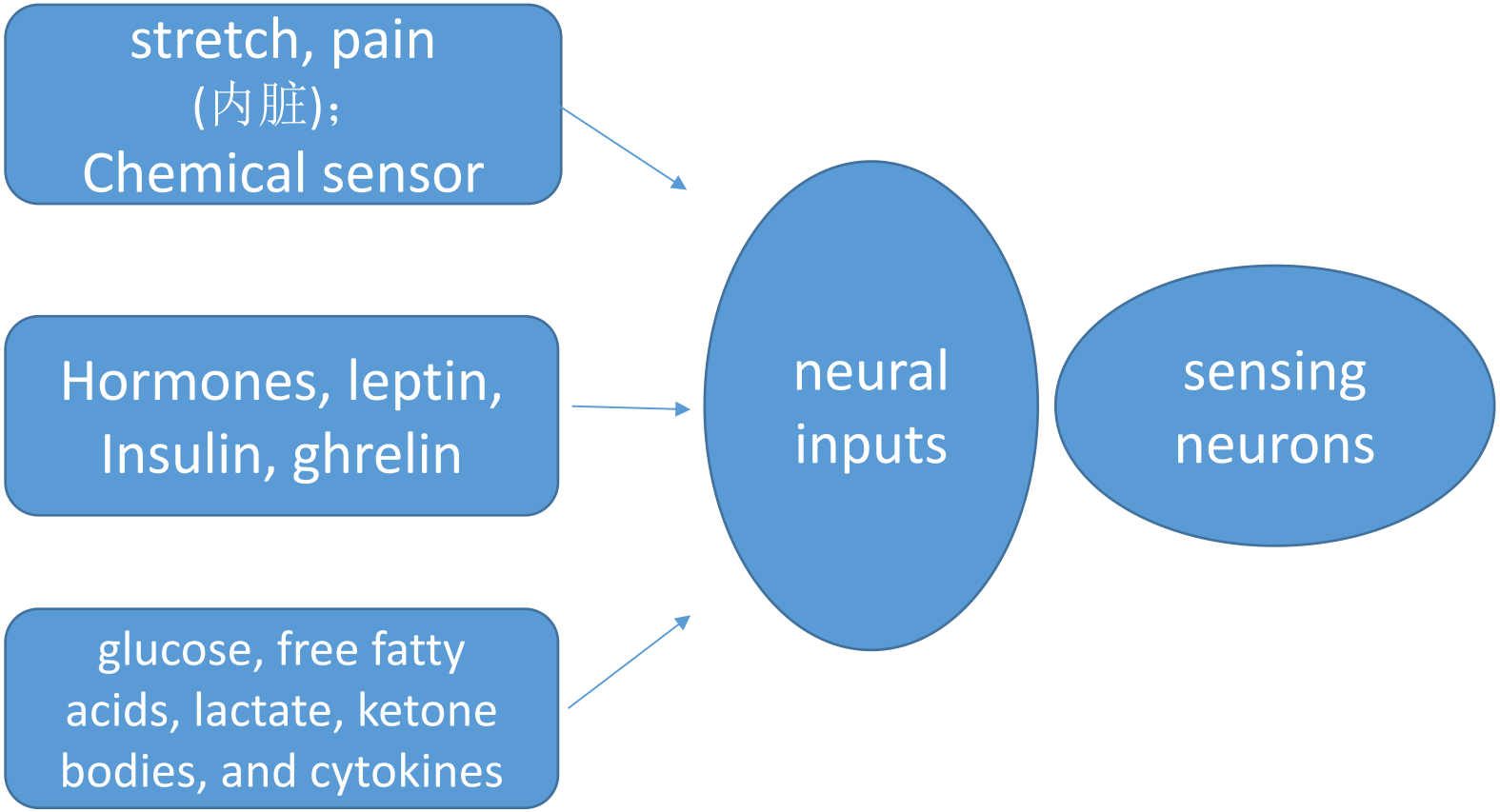

5.2 Metabolic Sensing Neurons: the Basic Integrators and Regulators of Glucose and Energy Homeostasis

- **In the 1950s Jean Mayer** neurons in the hypothalamus that sensed changes in glucose oxidation as a means of regulating feeding.
- Until 1964 that Oomura identified such glucosensing neurons.
- **Glucose**
- lactate, long-chain fatty acids, and ketone bodies as alternate fuels in some instances
- **sensing neurons：** ambient extracellular levels of glucose and other metabolic substrates are “sensed”

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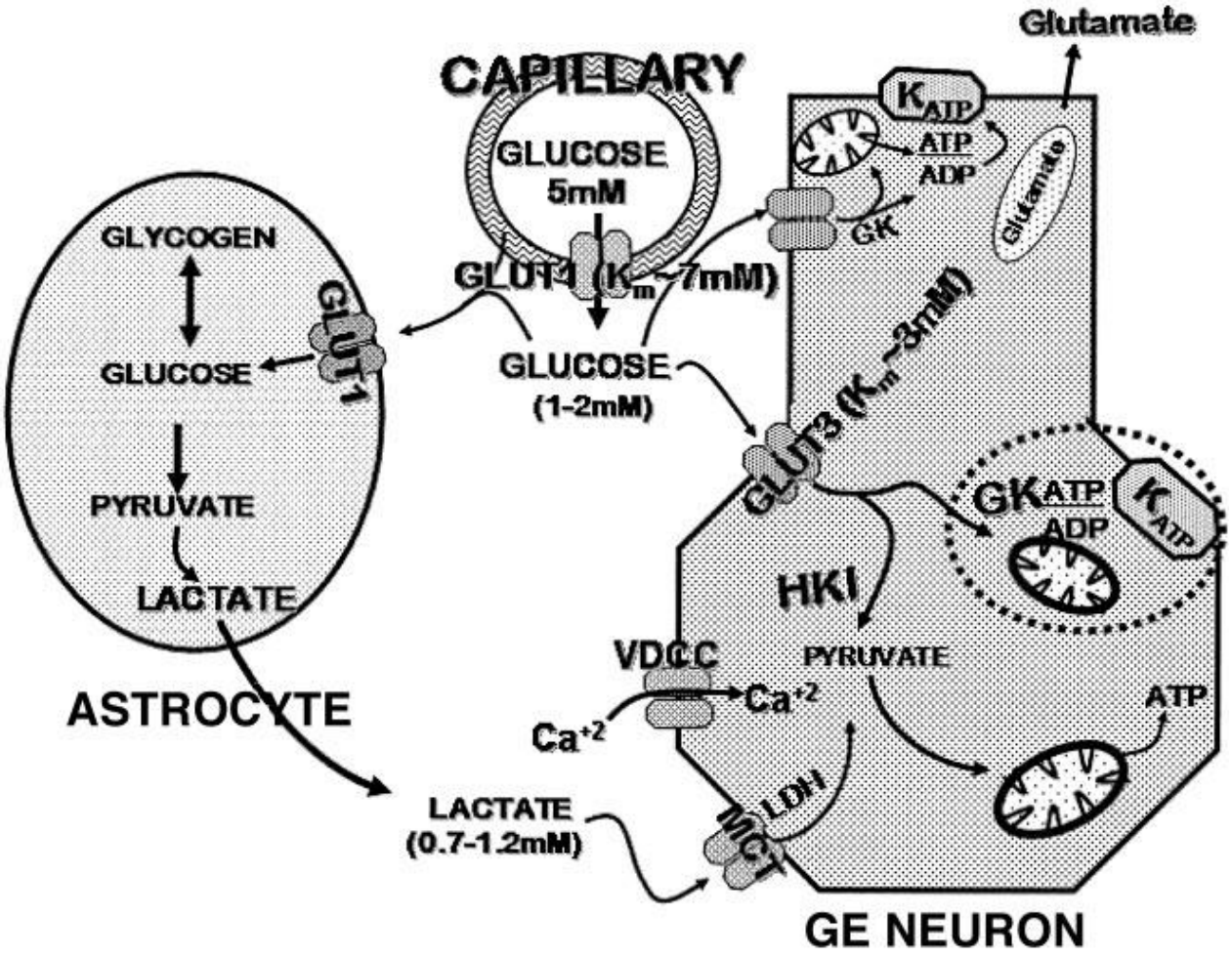

Levin et al., 2004

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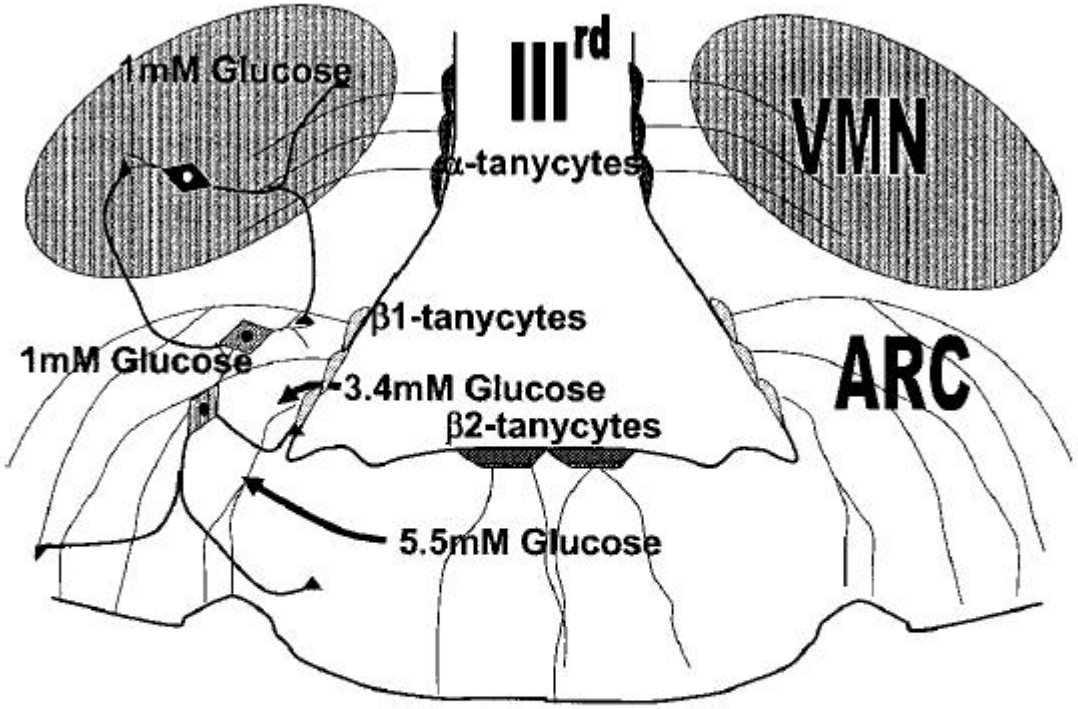

FIG. 1. Location of ARC and VMN neurons relative to blood, CSF, and brain glucose levels. ARC neurons are potentially exposed to glucose from the CSF, which diffuses across the β1-tanycytes lining the IIIrd cerebral ventricle; blood glucose, which diffuses across the fenestrated capillaries in the median eminence; and glucose, which is transported across the blood-brain barrier. Some of these neurons synapse with VMN neurons, which are exposed primarily to glucose transported from blood and diffusing from CSF.

Levin et al., 2004

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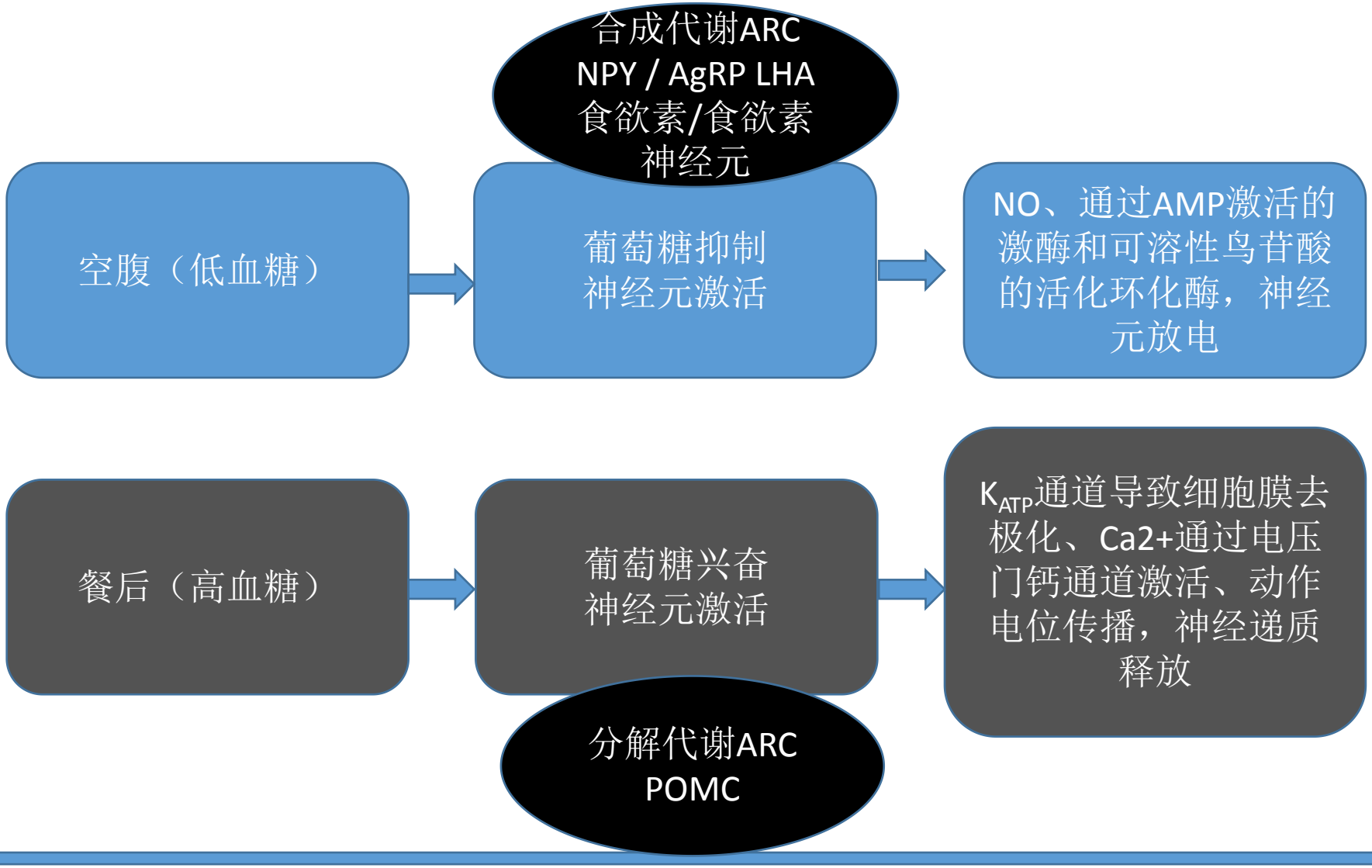

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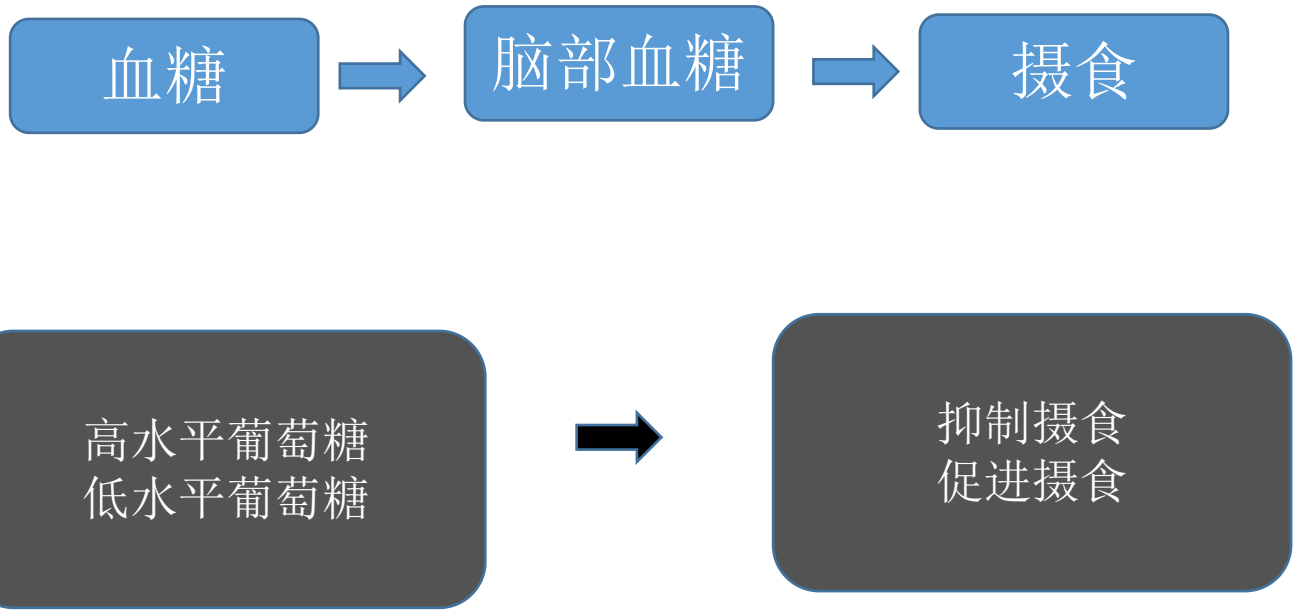

Especially in the brain

5.2 Metabolic Sensing Neurons: the Basic Integrators and Regulators of Glucose and Energy Homeostasis

- Many of these same VMH glucosensing neurons are also fatty acid sensors.
- Fatty acid translocator/CD36 (which appears to act as a receptor and may also be a transporter of fatty acids) in many VMH neurons.
- Impairment of VMH , has no effect on energy homeostasis.
- Depletion of VMH neuronal CD36 inhibits linear growth as well as causes redistribution of fat stores from visceral to subcutaneous adipose depots and marked insulin resistance .

5.2 Metabolic Sensing Neurons: the Basic Integrators and Regulators of Glucose and Energy Homeostasis

- Many of these same VMH glucosensing neurons are also lactate, ketone bodies sensors.
- Lactate ketone bodies are produced by astrocytes.
- They are also respond to leptin, insulin and ghrelin.
- The network of brain areas containing these metabolic sensors forms a distributed network that functions as an integrated system.

5.3 Homeostatic and Reward-Based Systems

neural circuits

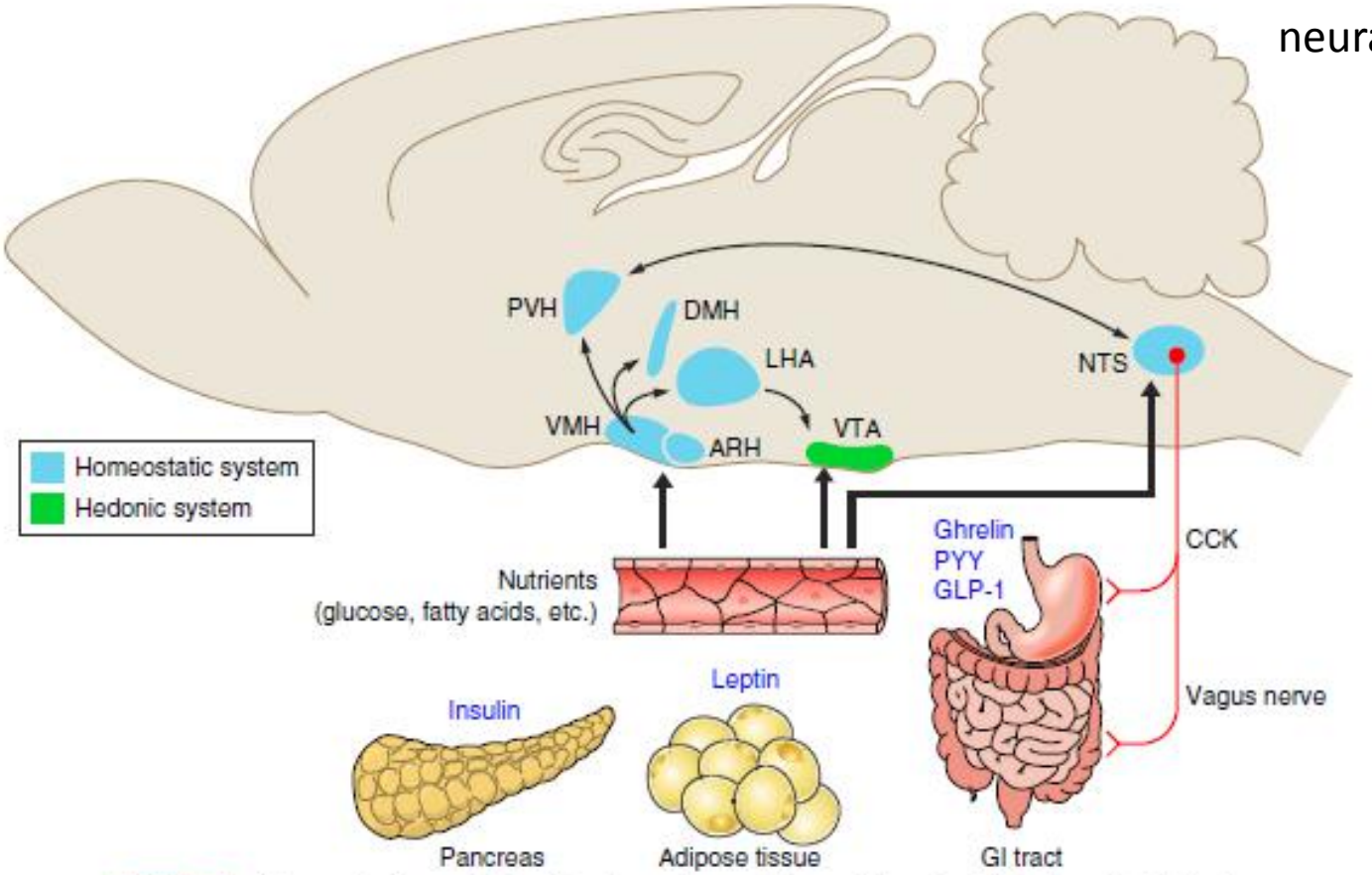

FIGURE 1. Major routes for regulation of feeding and energy balance. These simplified schematics illustrate the possible neural networks relaying metabolic signals from the periphery to the brain. The regulatory effects

- GENETIC BASIS OF OBESITY
- PERINATAL ENVIRONMENT AND THE DEVELOPMENT OF OBESITY AND T2DM
- GENE-ENVIRONMENT INTERACTIONS
- HOW CAN WE USE THIS INFORMATION TO PREVENT AND TREAT OBESITY AND DIABETES?

THANKS!