Metabolic Integration and Organ Specialization

张梦杰

98061@tongji.edu.cn

65986853

- 办公室：医学楼辅楼405

Outline

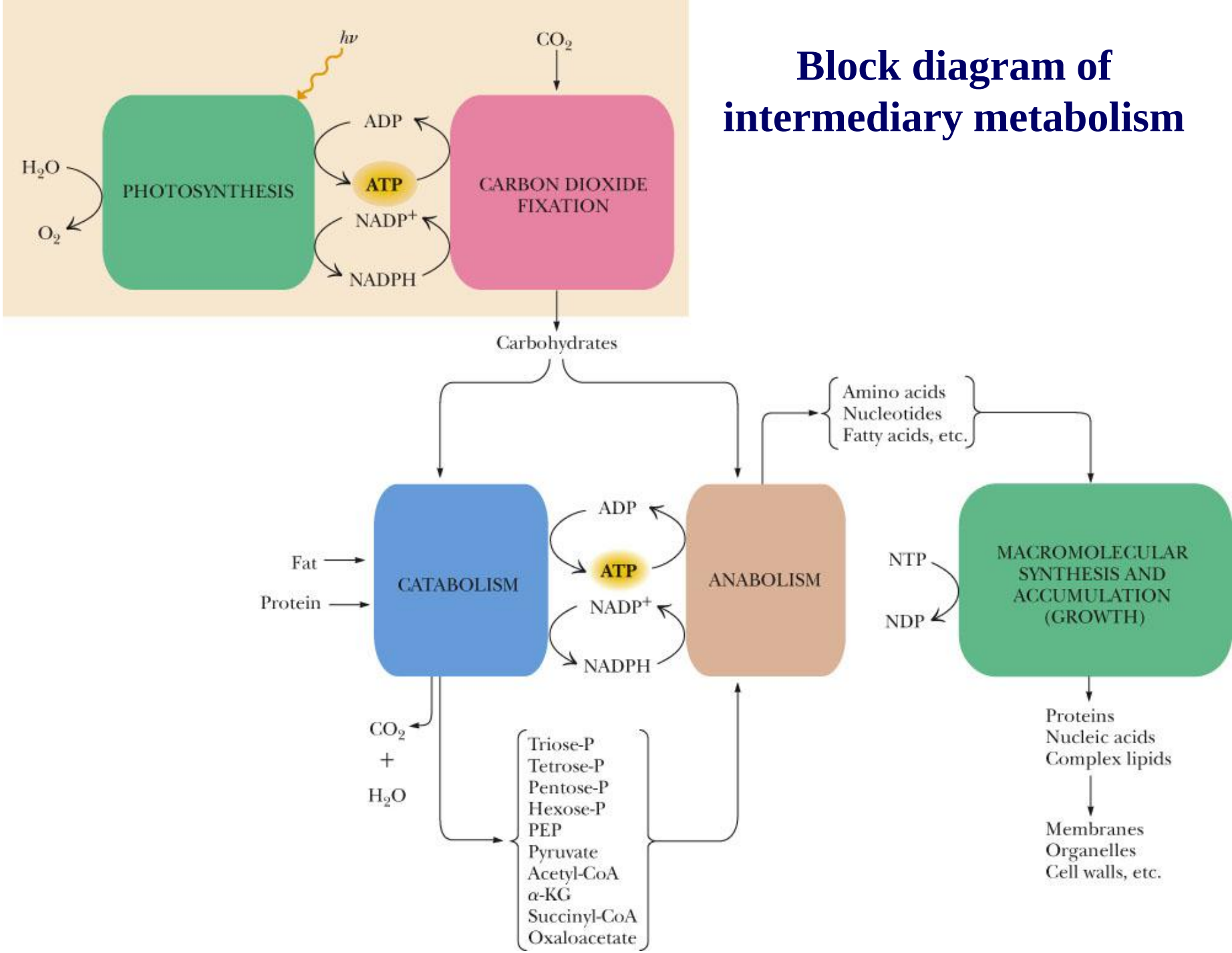
1. introduction
2. What underlying principle relates ATP coupling to the thermodynamics of metabolism?
3. Is there a good index of cellular energy status?
4. How is overall energy balance regulated in cells?
5. How is metabolism integrated in a multicellular organism?
6. What regulates our eating behavior?
7. Can you really live longer by eating less?

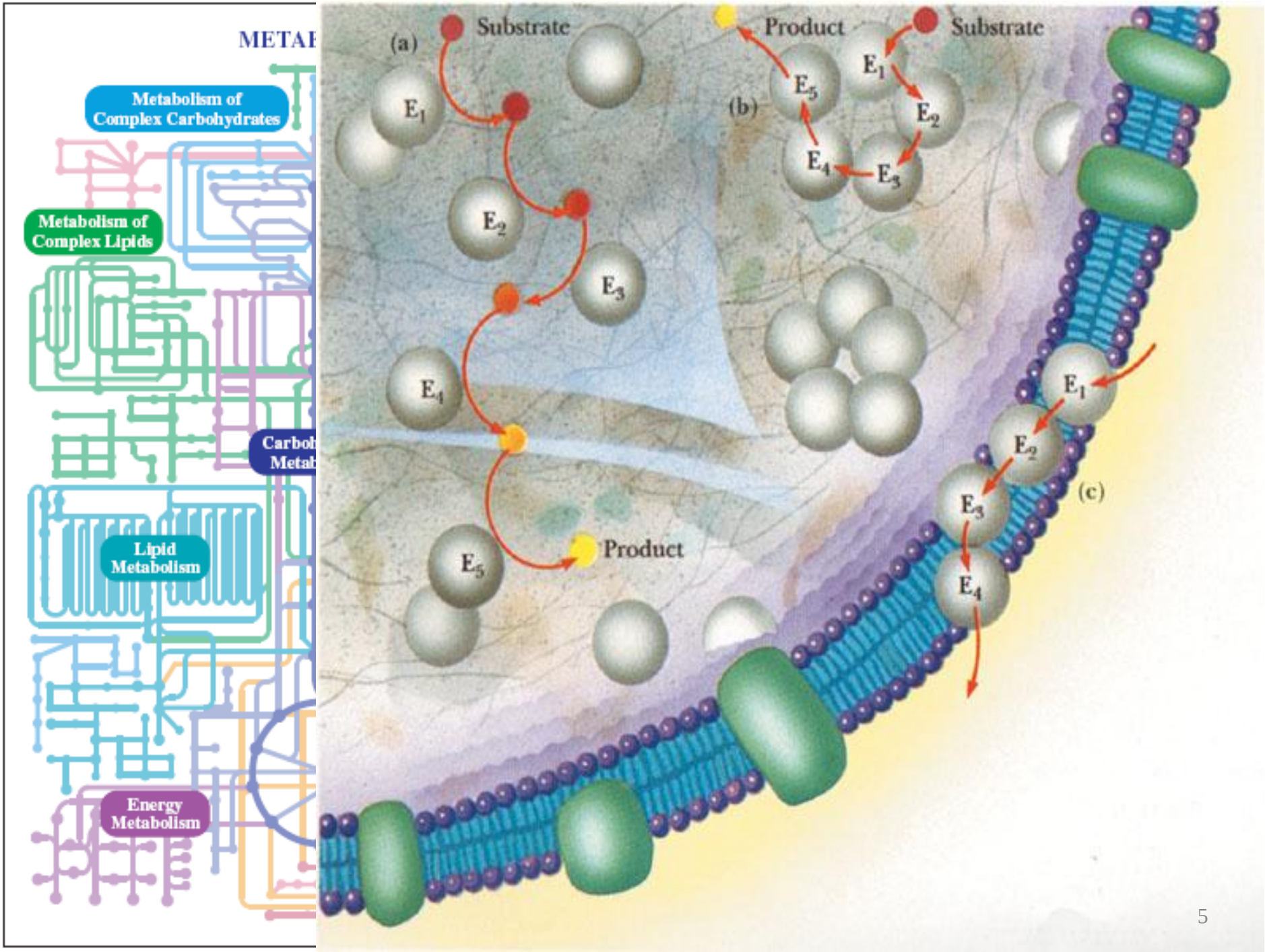
1. Introduction

- Metabolism consists **three** interconnected **functional block**:
  - **Catabolism**
  - **Anabolism**

macromolecular synthesis and growth

Block diagram of intermediary metabolism




METAB
Metabolism of Complex Carbohydrates
Metabolism of Complex Lipids
Carbol Metab
Lipid Metabolism
Energy Metabolism
(a)
Substrate
E1
E2
E3
E4
E5
Product
(b)
Product
Substrate
E1
E2
E3
E4
E5
(c)
E1
E2
E3
E4

2.What Underlying Principle Relates ATP Coupling to the Thermodynamics of Metabolism?

① **Reaction stoichiometry** - the number of each kind of **atom** in a reaction

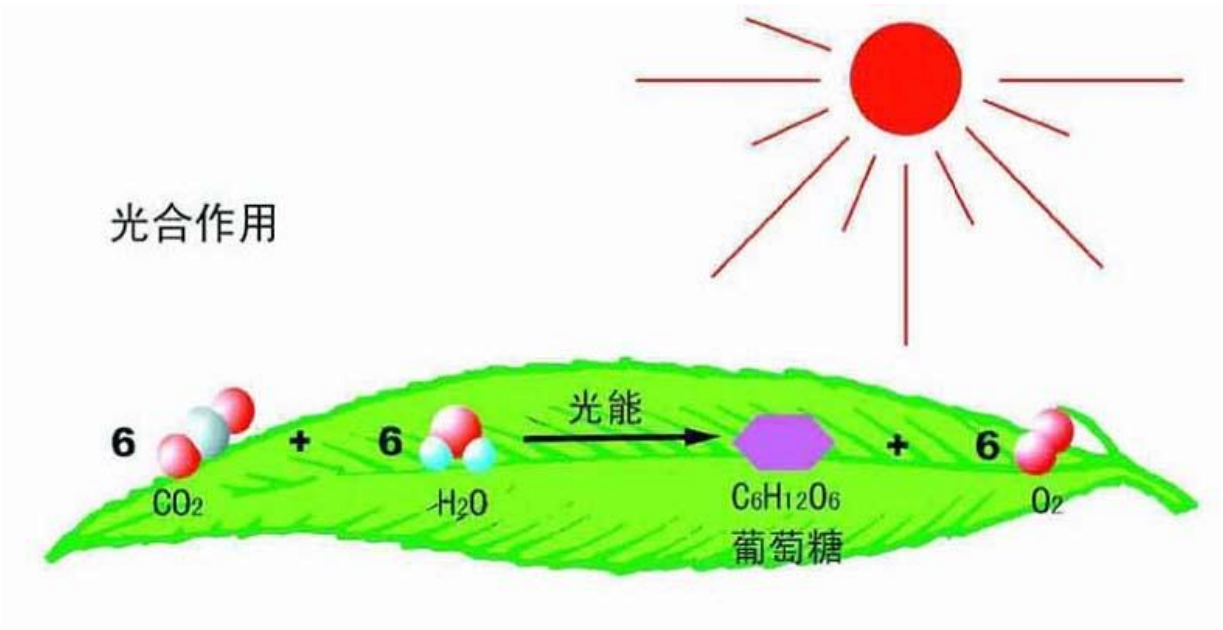
② **Obligate coupling stoichiometry** - the required coupling of **electron carriers，reduction of NAD^+ and FAD**

③ **Evolved coupling stoichiometry** - the number of **ATP** that pathways have evolved to consume or produce

① Reaction stoichiometry

The number of atom remains the **same** on both sides of the equation

$$6\ CO_2 + 6\ H_2O \rightarrow C_6H_{12}O_6 + 6\ O_2$$



② Obligate coupling stoichiometry

- **Cellular respiration** is an oxidation-reduction process, and the **oxidation of glucose** is coupled to the **reduction of NAD^+ and FAD**

- (a) $C_6H_{12}O_6 + 10\ NAD^+ + 2\ FAD + 6\ H_2O \rightarrow 6\ CO_2 + 10\ NADH + 10\ H^+ + 2\ FADH_2$

(b) $10\ NADH + 10\ H^+ + 2\ FADH_2 + 6\ O_2 \rightarrow 12\ H_2O + 10\ NAD^+ + 2\ FAD$

Total： $C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$

③ Evolved coupling stoichiometry

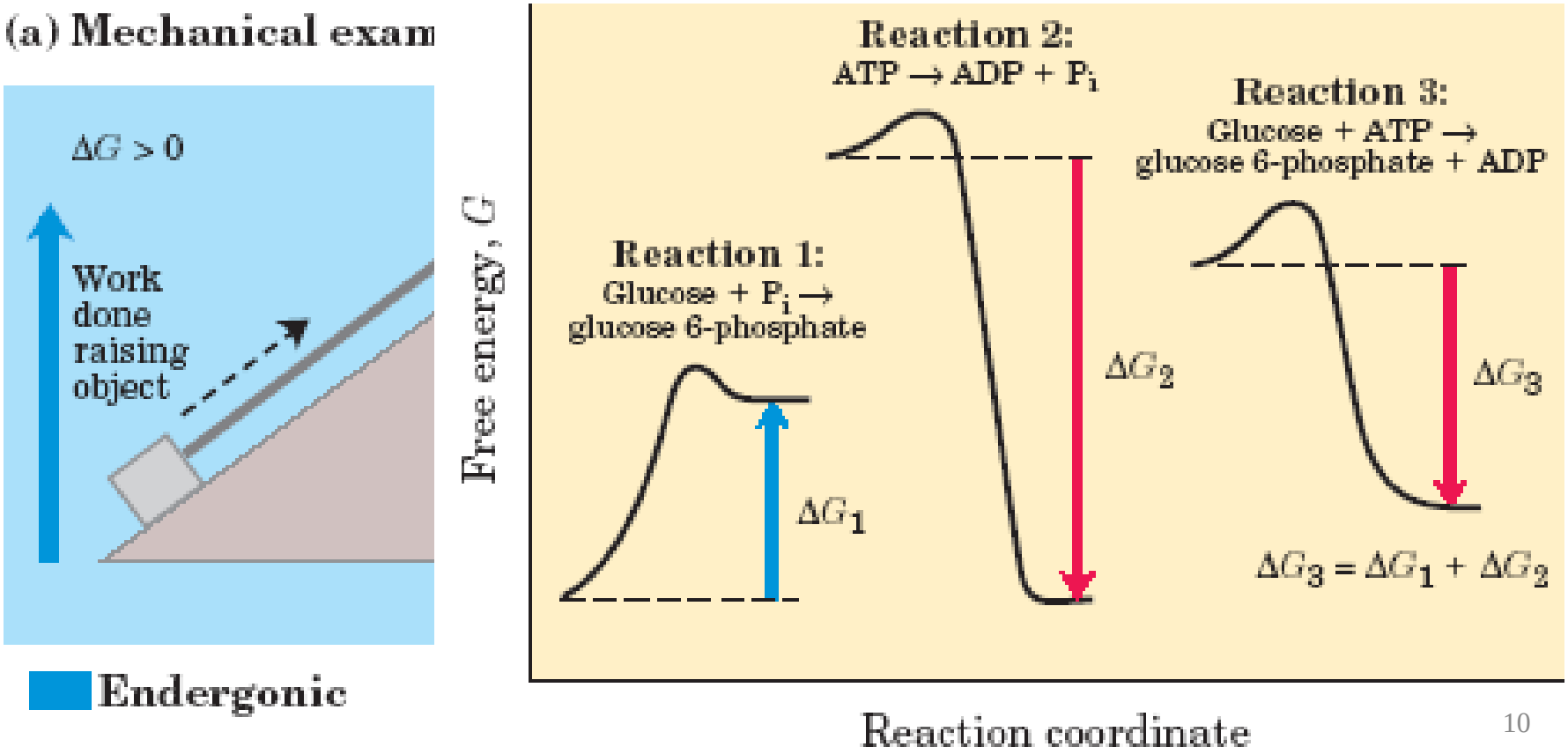
- The coupled formation of **ATP** by oxidative phosphorylation

$$C_6H_{12}O_6 + 6\,O_2 + 30\,ADP + 30\,Pi \rightarrow 6\,CO_2 + 30\,ATP + 6\,H_2O$$

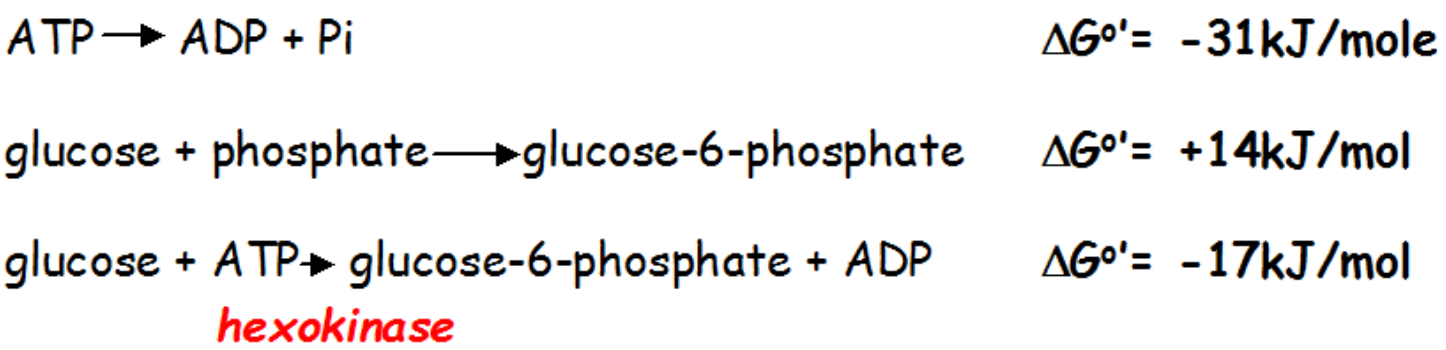
- Eukaryotes: 32 or 30 ATP

ATP coupling stoichiometry determines the K_{eq} for metabolic

- The energy release （ATP hydrolysis）→ ΔG>0 reaction → the overall free energy for the coupled process is negative (ΔG<0)



- **The cell maintains a high [ATP]/([ADP][Pi]) ratio**
  - ATP serves as the **driving force** for biochemical events



  - Living cells break down energy-yielding molecules to **generate ATP**

3. Is there a good index of cellular energy status?

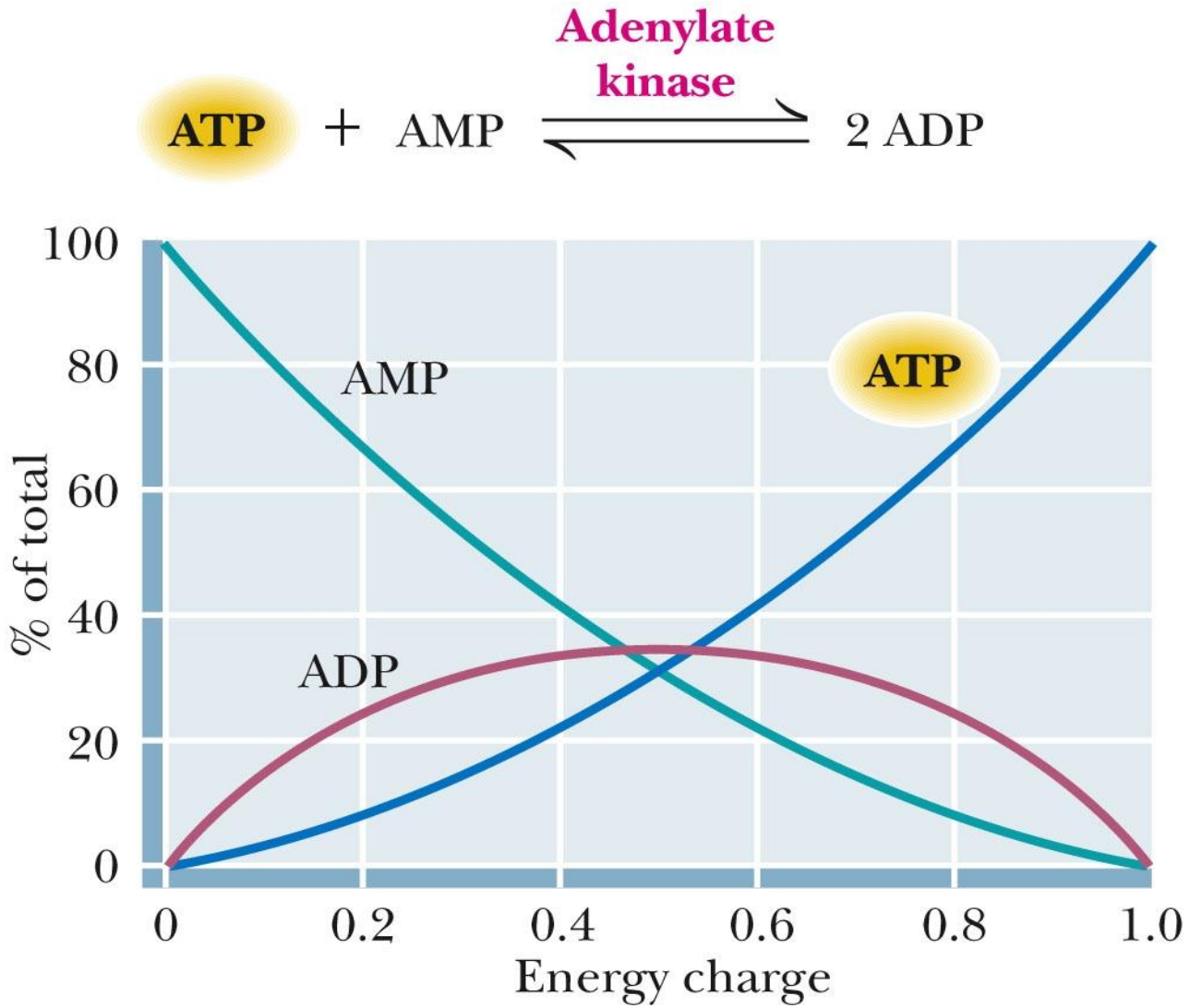
◆ Energy transduction and storage in the adenylate system （**Adenylate pool**）– ATP, ADP, AMP

$$ATP + AMP \xleftrightarrow{\text{Adenylate kinase}} 2\,ADP$$

◆ **Energy charge *relates the ATP levels to the total adenine nucleotide pool***

$$\textbf{Energy charge} = \frac{[ATP] + \frac{1}{2}[ADP]}{[ATP] + [ADP] + [AMP]}$$

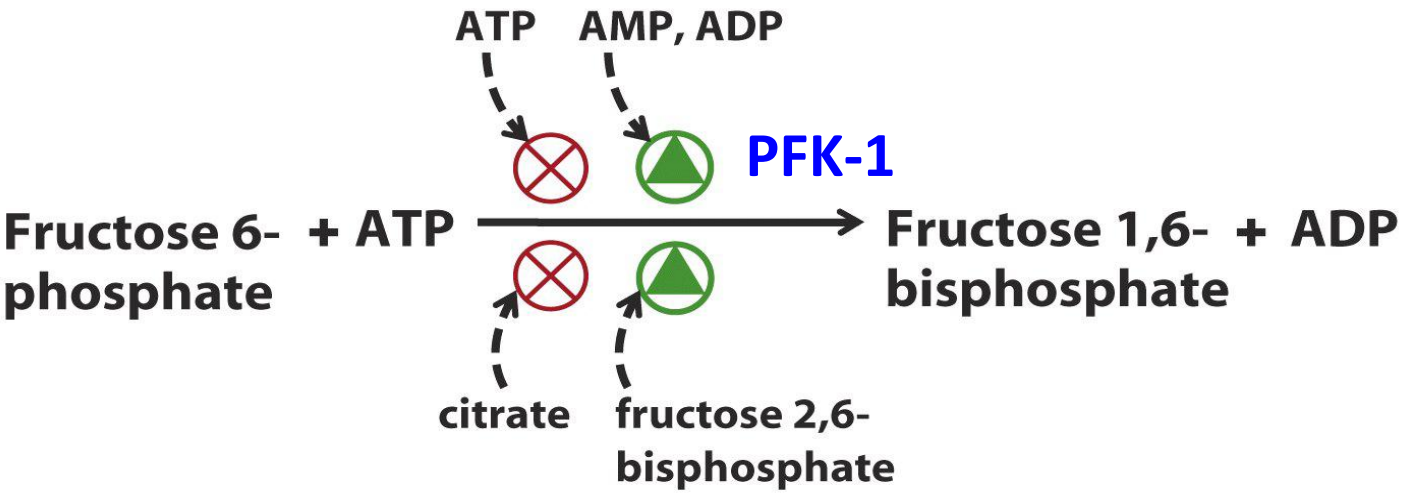
- In living cell , E.C.→ 0.80-0.95



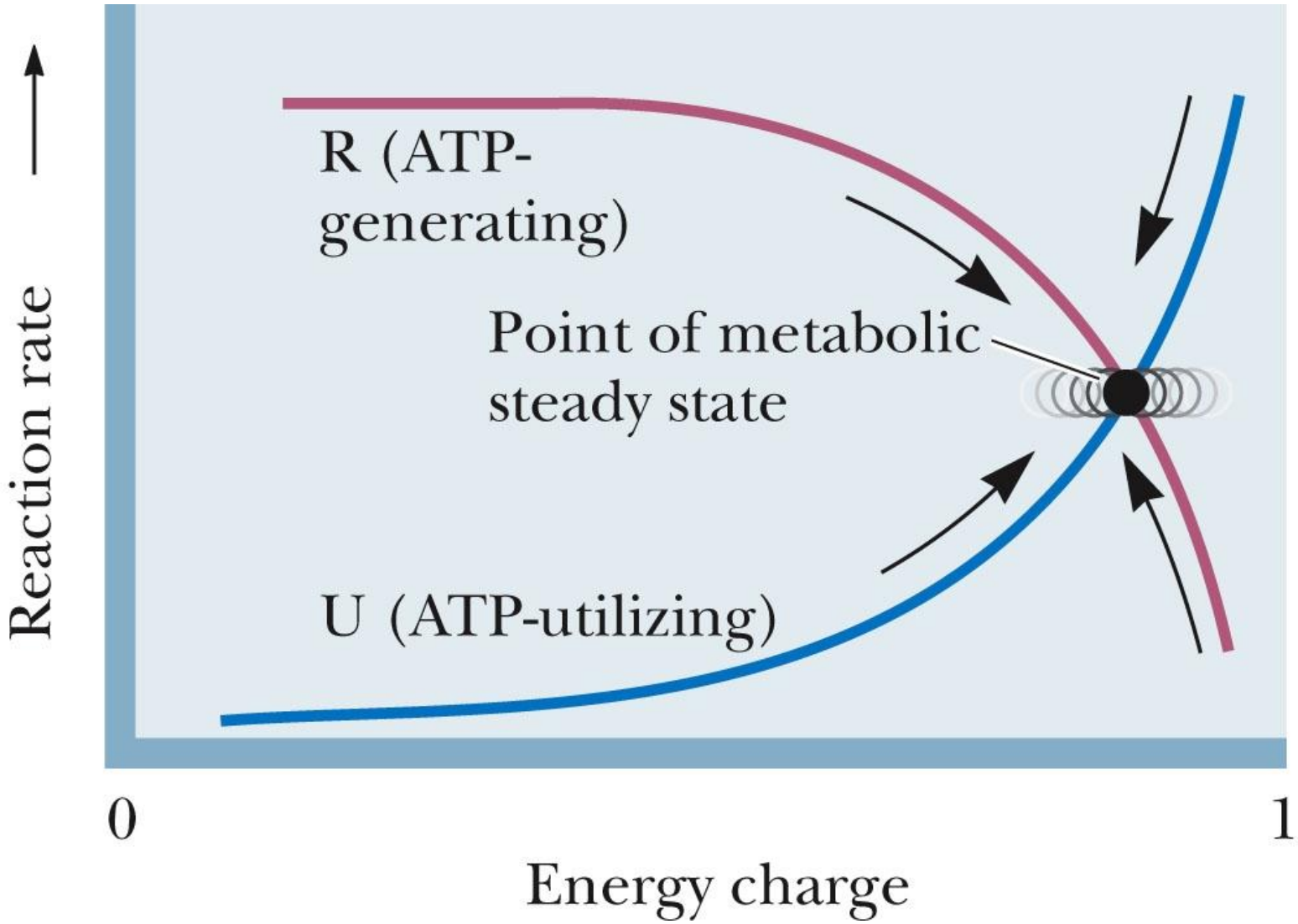
In living cell , E.C.→0.80-0.95

Key enzymes are regulated by Energy charge

- **Regulatory enzymes** respond in reciprocal fashion to adenine nucleotides
  - **PFK-1** stimulated by **AMP** and inhibited by **ATP**

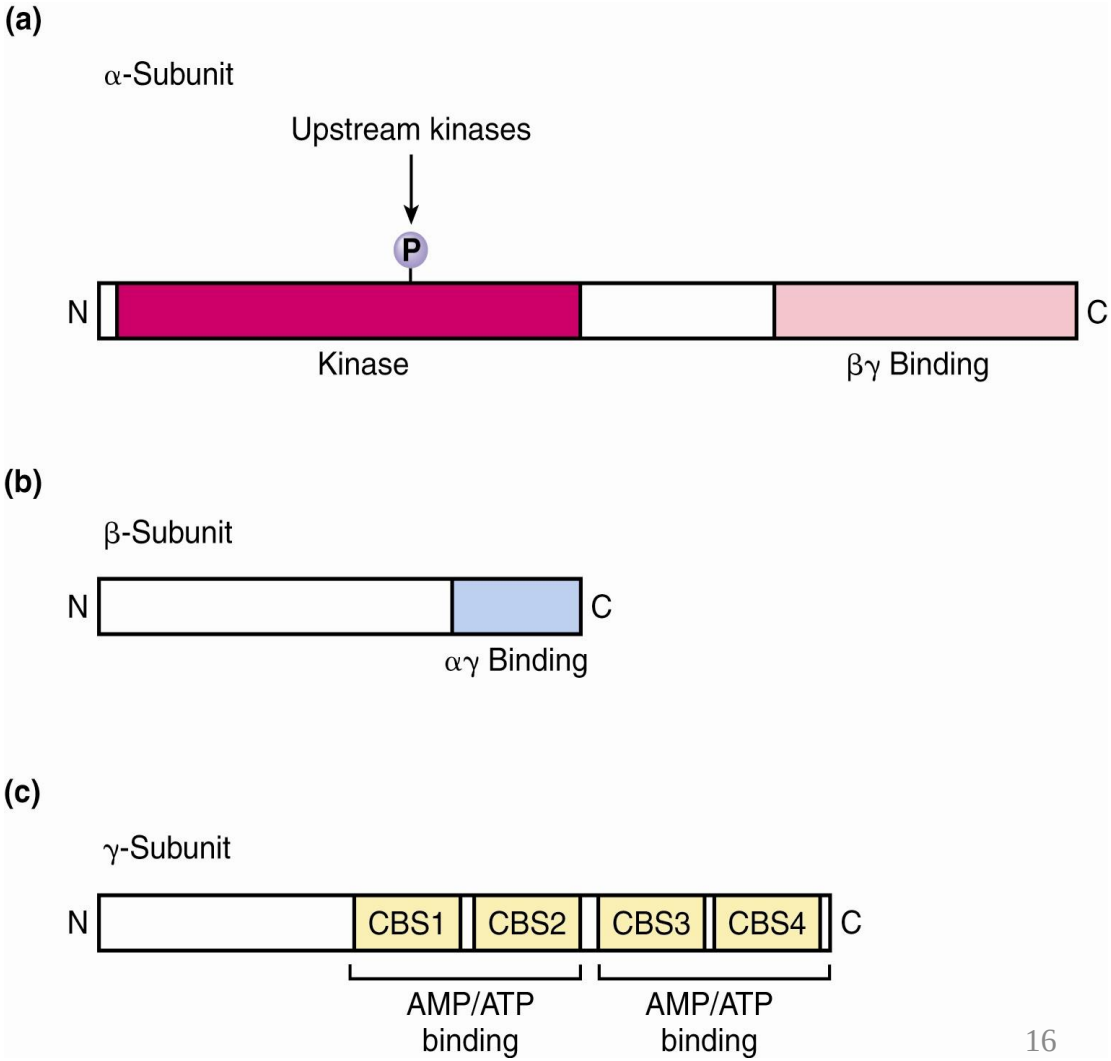


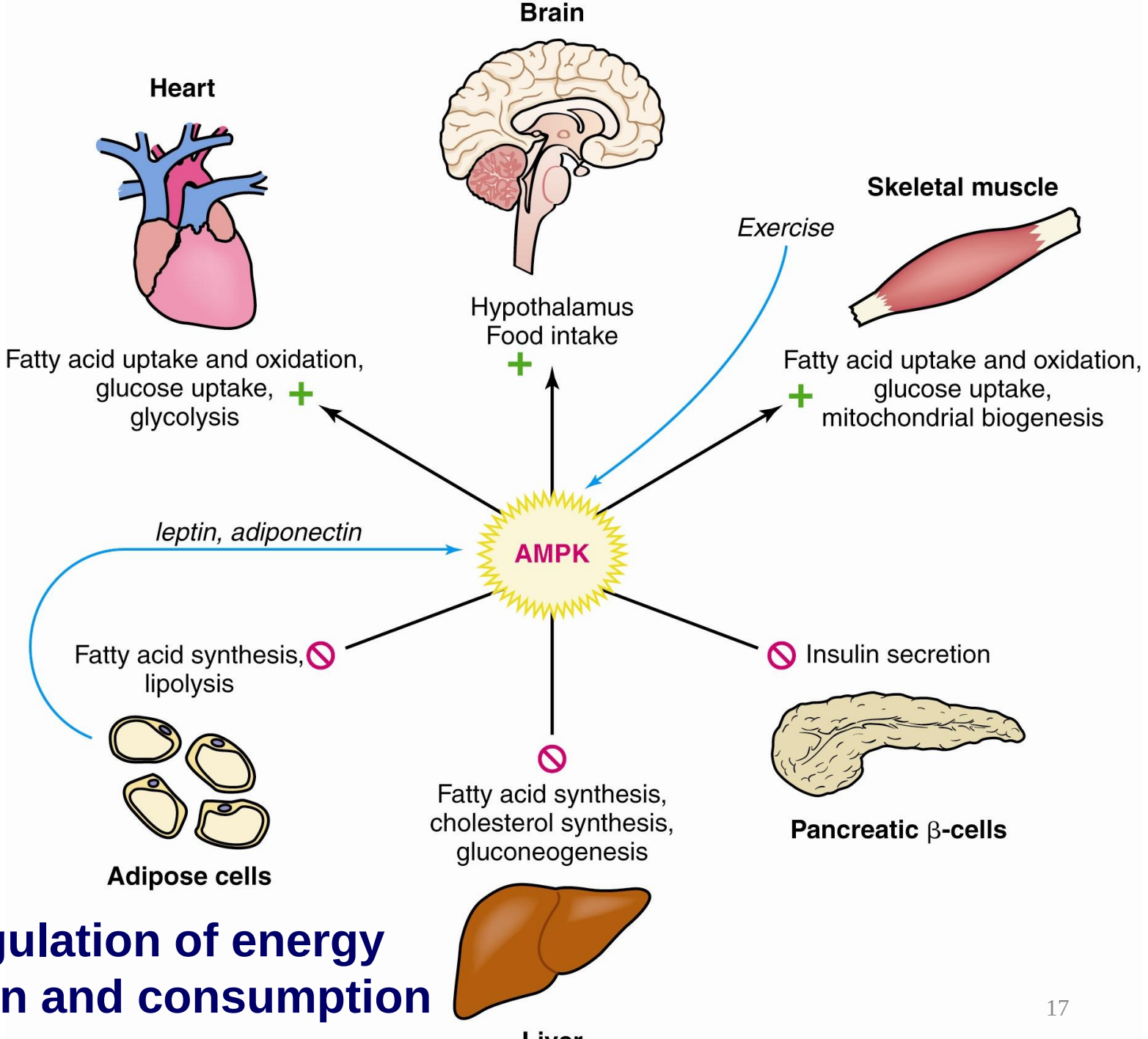
Responses of regulatory enzymes to variation in energy charge



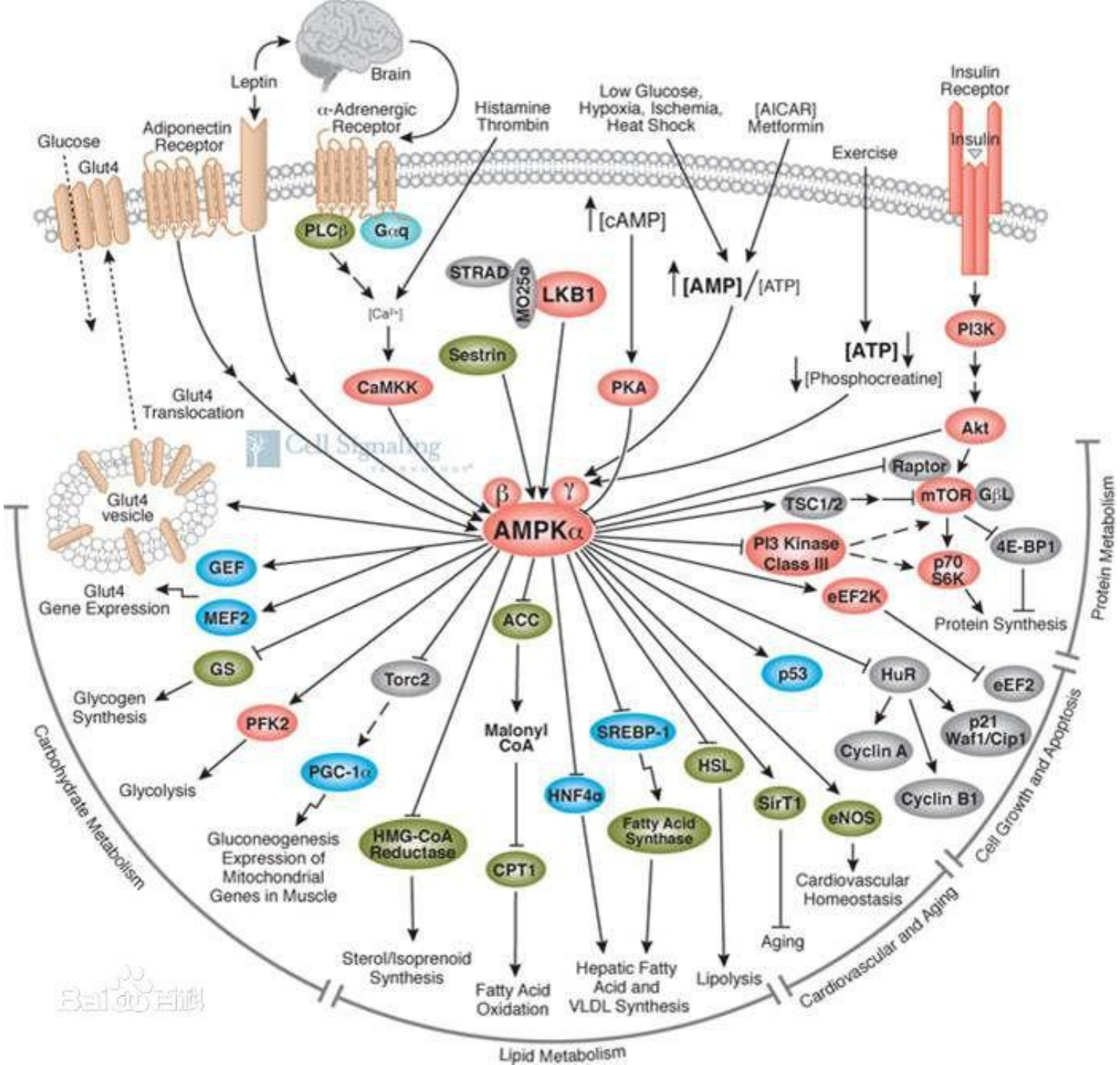
4. How is Overall Energy Balance Regulated in Cells?

- AMP-activated protein kinase (AMPK) is the cellular energy sensor
- ATP inhibits AMPK
- AMP actives AMPK

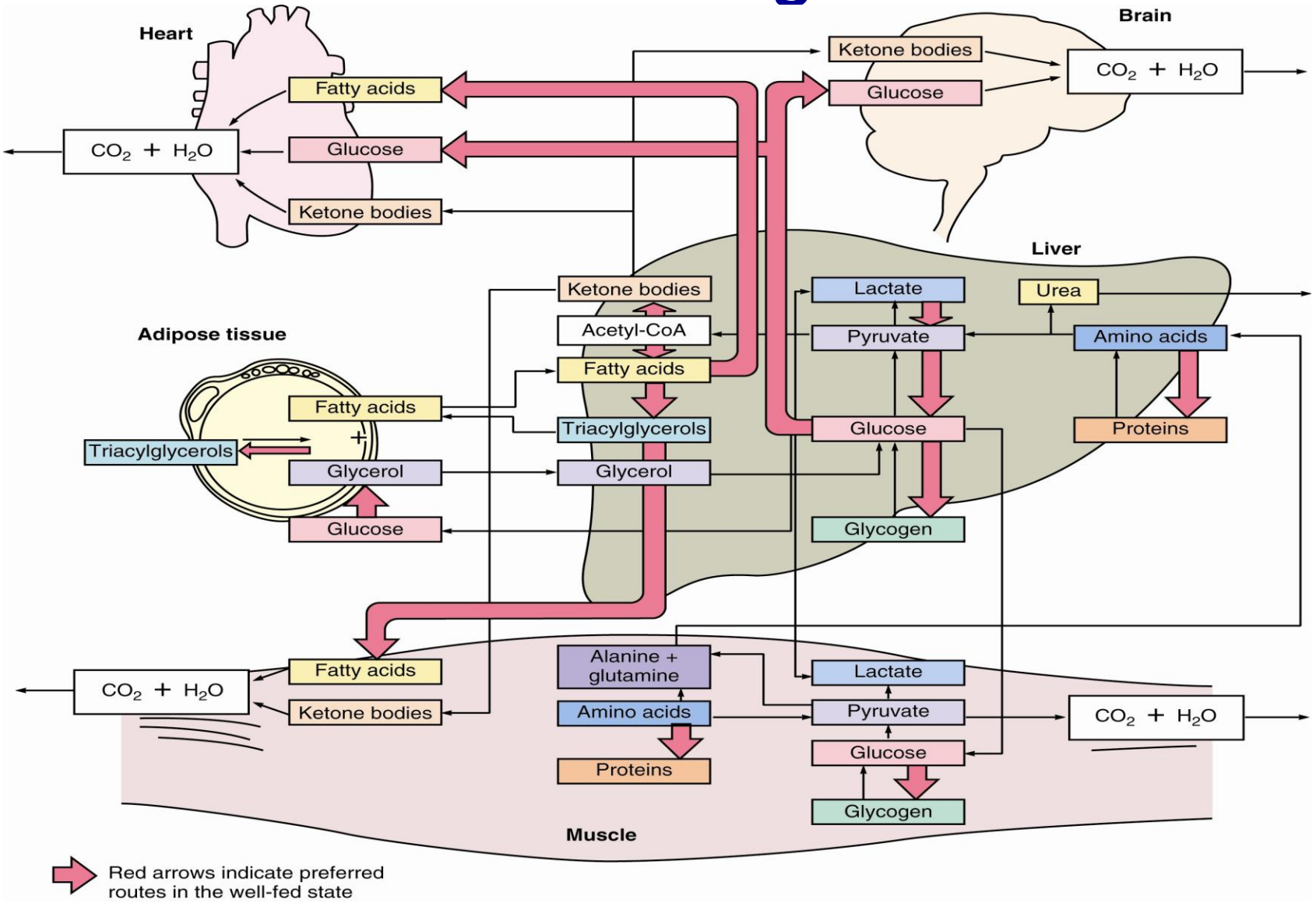




AMPK regulation of energy production and consumption

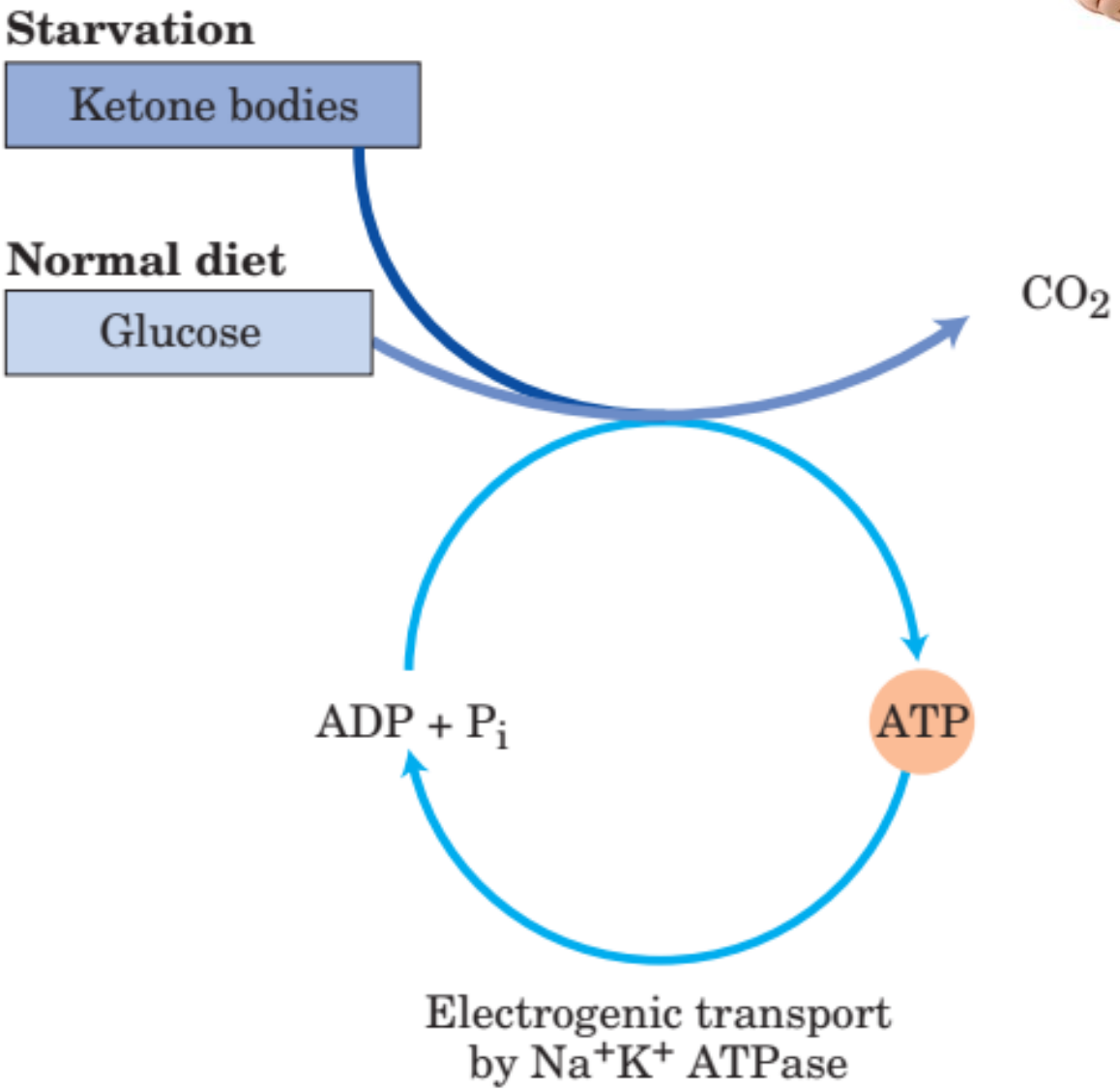

Leptin
Brain
α-Adrenergic Receptor
Histamine Thrombin
Low Glucose, Hypoxia, Ischemia, Heat Shock
[AICAR] Metformin
Insulin Receptor
Insulin
Glucose
Glut4
Adiponectin Receptor
Exercise
PLCβ
Gαq
[cAMP]
STRAD
MO25α
LKB1
[AMP]/[ATP]
[Ca2+]
PI3K
Sestrin
[ATP]
[Phosphocreatine]
CaMKK
PKA
Glut4 Translocation
Akt
Raptor
Glut4 vesicle
β
γ
AMPKα
TSC1/2
mTOR
GβL
PI3 Kinase Class III
4E-BP1
p70 S6K
GEF
eEF2K
Glut4 Gene Expression
MEF2
Protein Synthesis
ACC
p53
HuR
eEF2
GS
Torc2
Glycogen Synthesis
PFK2
Malonyl CoA
SREBP-1
p21 Waf1/Cip1
Cyclin A
HSL
PGC-1α
Glycolysis
HNF4α
SirT1
Cyclin B1
eNOS
Gluconeogenesis Expression of Mitochondrial Genes in Muscle
HMG-CoA Reductase
Fatty Acid Synthase
CPT1
Cardiovascular Homeostasis
Aging
Sterol/Isoprenoid Synthesis
Fatty Acid Oxidation
Hepatic Fatty Acid and VLDL Synthesis
Lipolysis
Protein Metabolism
Carbohydrate Metabolism
Cell Growth and Apoptosis
Cardiovascular and Aging
Lipid Metabolism

5. How Is Metabolism Integrated in a Multicellular Organism?



- **The major fuel depots in animals:**
  - **Glycogen** in live and muscle
  - **TGs** in adipose tissue
  - **Protein**, mostly in skeletal muscle
- **The usual order of preference for use:**
  - **glycogen > triacylglycerol > protein**
- **The tissues of the body work together to maintain energy homeostasis**

Brain


Starvation
Ketone bodies
Normal diet
Glucose
CO_2
ADP + P_i
ATP
Electrogenic transport
by Na^+K^+ ATPase

Brain

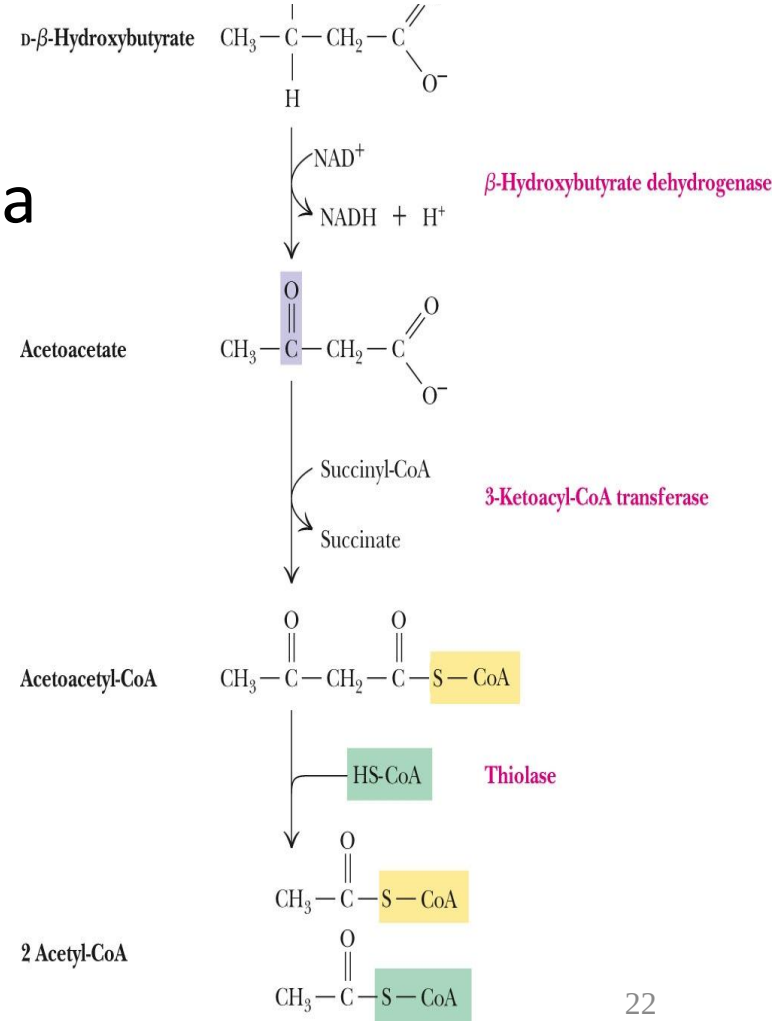
- **Brain has two metabolic features**

1. high respiratory metabolism- **20 % of oxygen** consumed
2. no fuel reserves-Uses glucose as a fuel (120g per day)

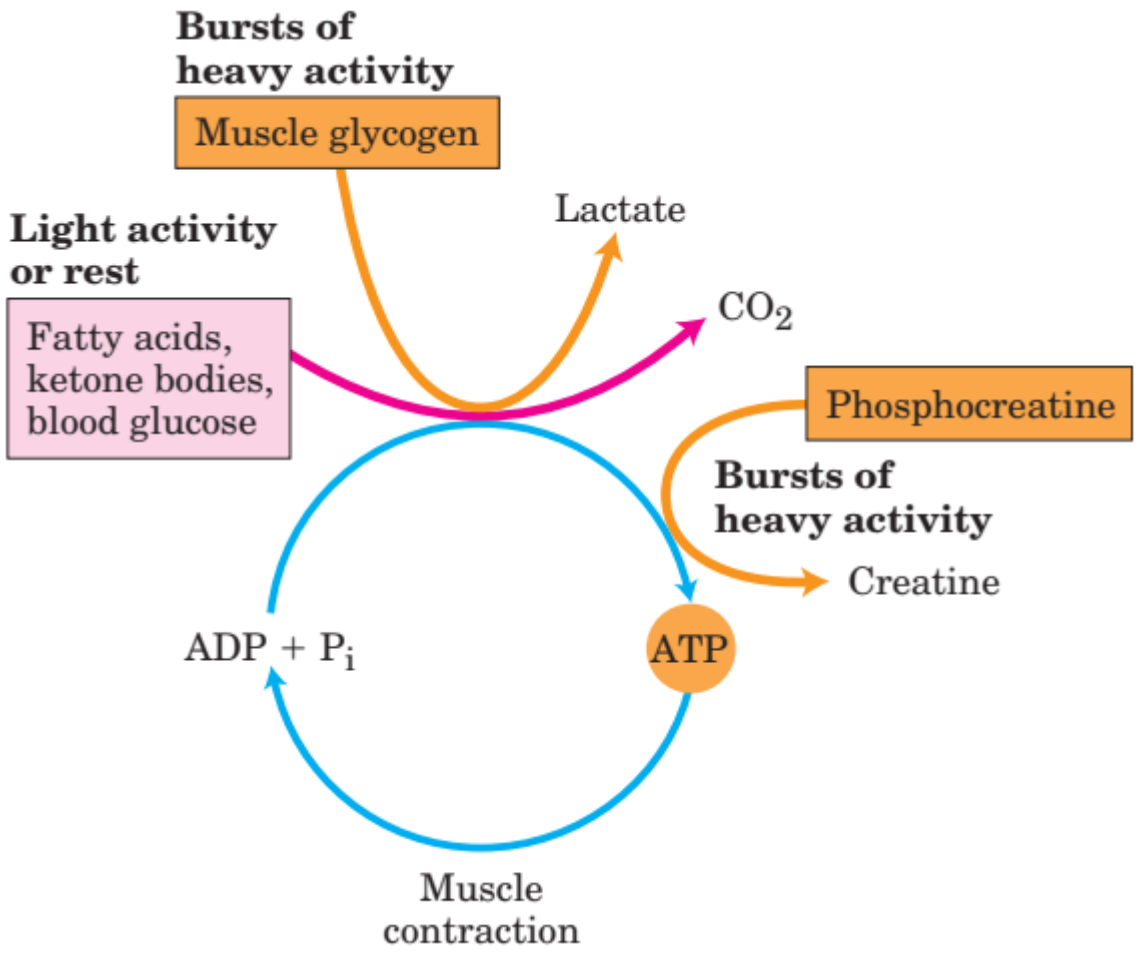
- **In fasting conditions**

  - use **β-hydroxybutyrate**, converting it to acetyl-CoA

- **Generate ATP** to maintain the **membrane potentials** essential for transmission of nerve impulses

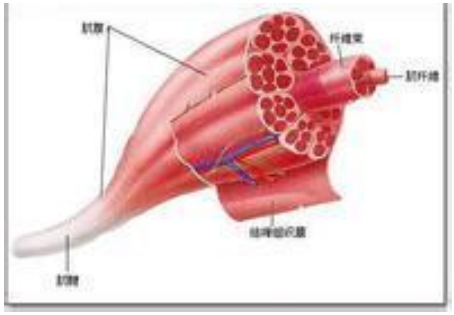


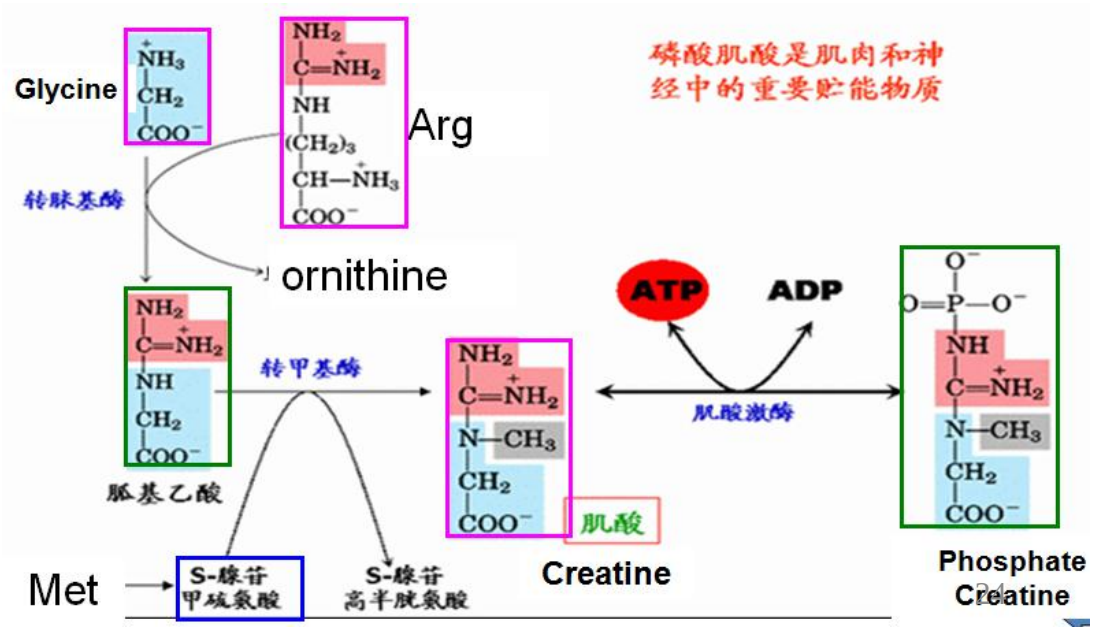
Muscle


Bursts of heavy activity
Muscle glycogen
Lactate
Light activity or rest
Fatty acids, ketone bodies, blood glucose
CO_2
Phosphocreatine
Bursts of heavy activity
Creatine
ADP + P_i
ATP
Muscle contraction

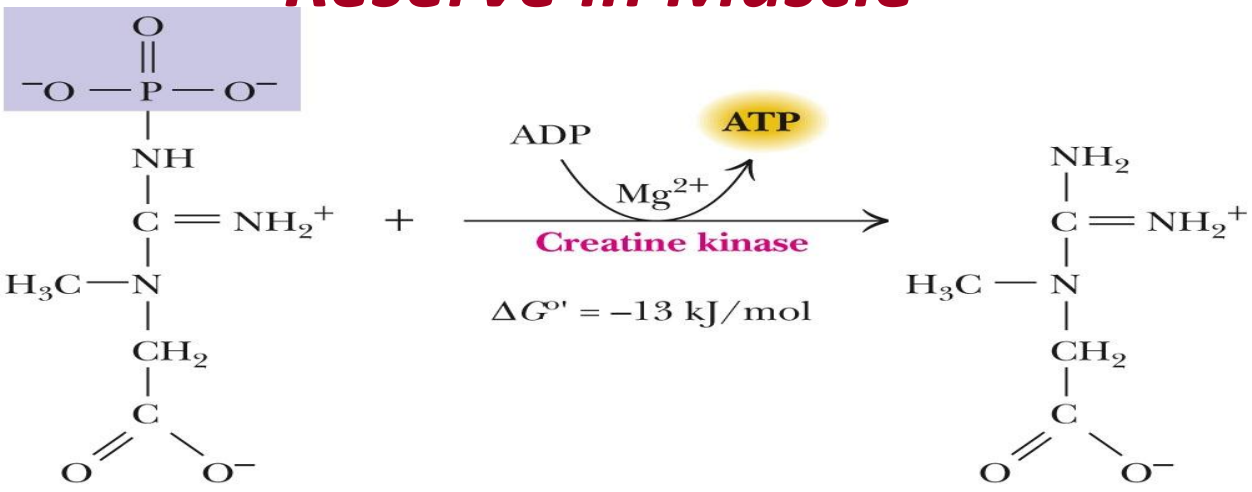
Muscle

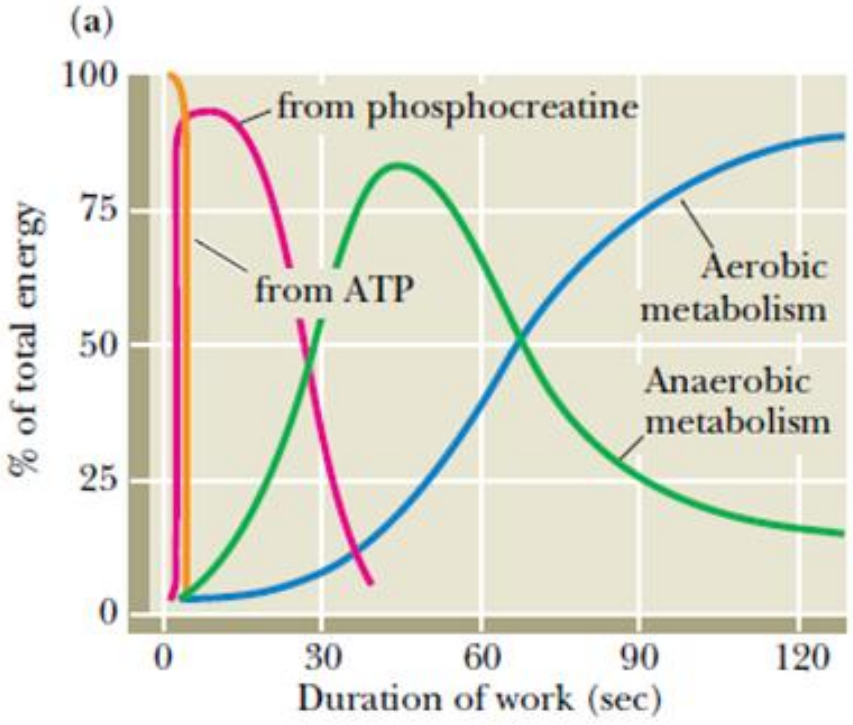
- Skeletal muscles -- 30% of O_2 consumption at rest
- **Muscle contraction** occurs when a motor nerve impulse causes Ca^{2+} release
- Muscle fuels – glucose, fatty acids, and ketone bodies
- **Rest muscle** contains **2% glycogen** and **0.08% phoshpocreatine**

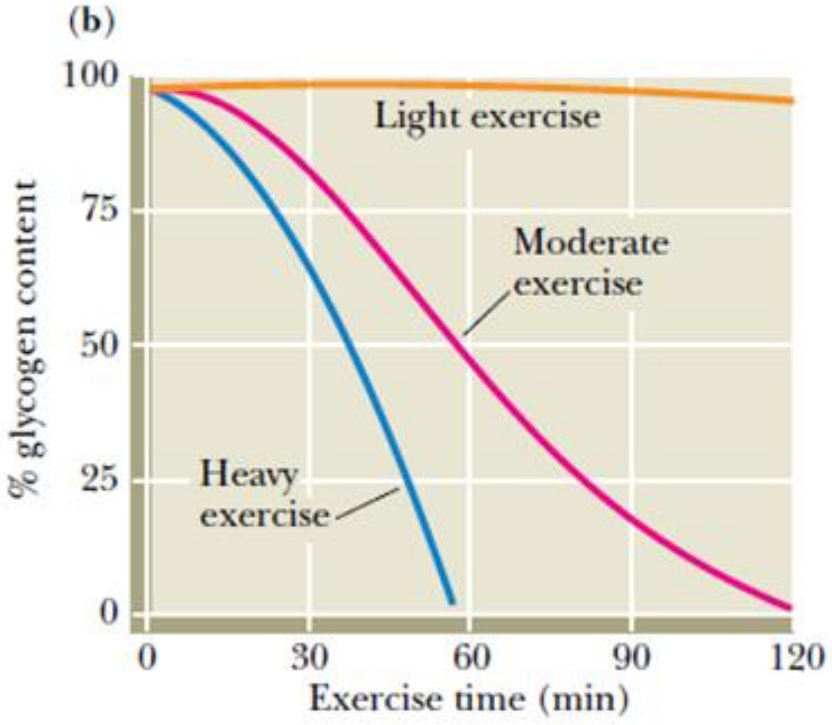




Phosphocreatine Provide an Energy Reserve in Muscle

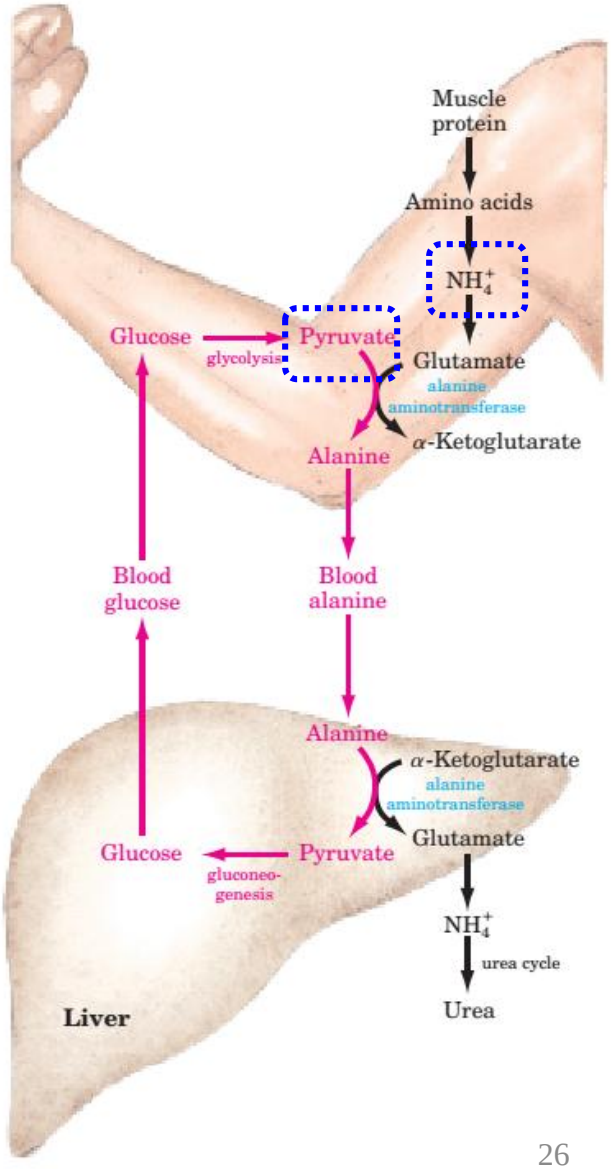






Muscle Protein Degradation

- During fasting or excessive activity, aa are degraded to **pyruvate**, → **Ala**
- Ala → liver →pyruvate
- This is a fuel of last resort for the fasting or exhausted organism

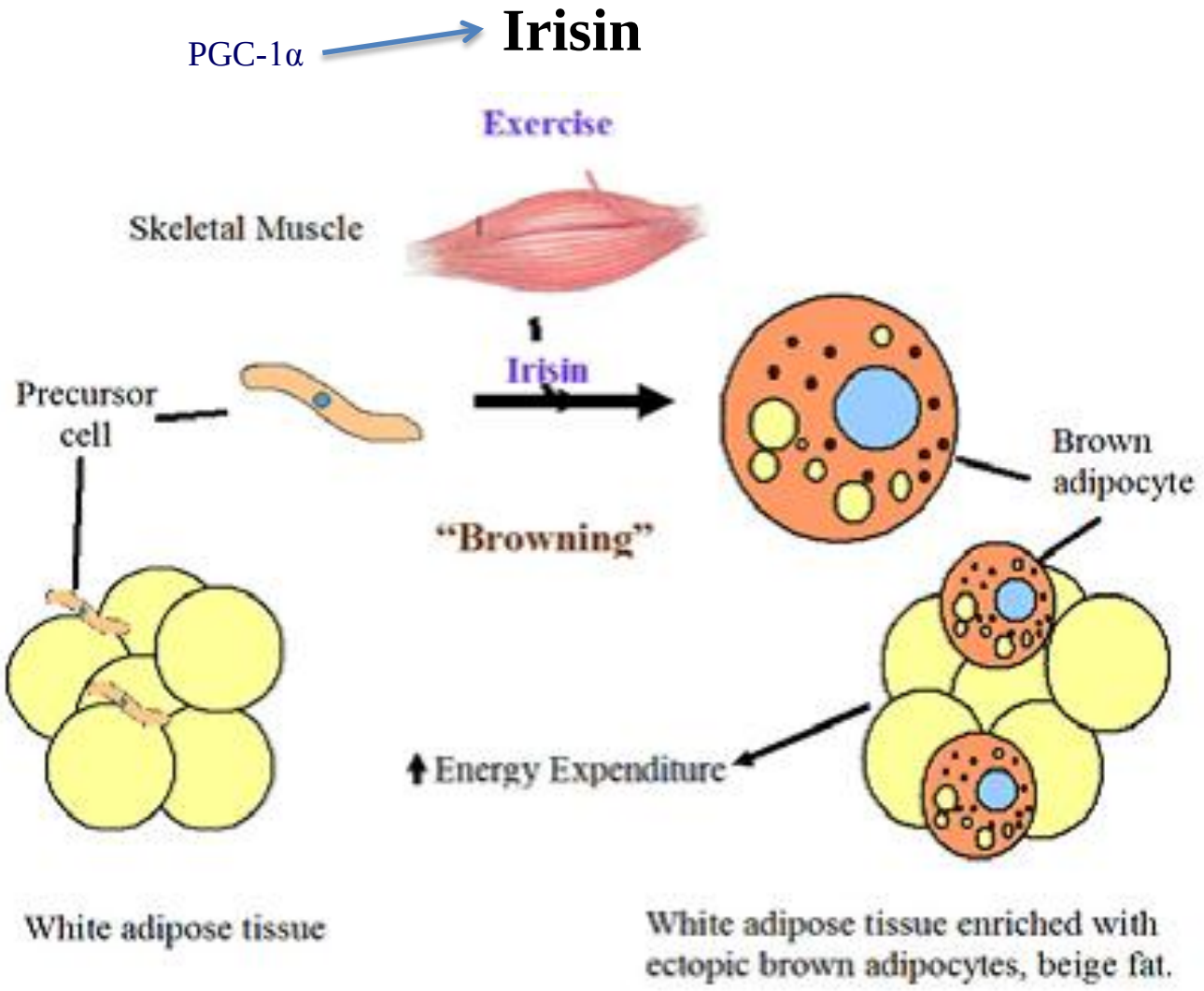


Heart

- The activity of heart muscle - constant & rhythmic
- A completely aerobic organ & rich in mitochondria
- Prefers **fatty acid** as fuel
- Continually nourished with oxygen and free fatty acid, glucose, or ketone bodies as fuel

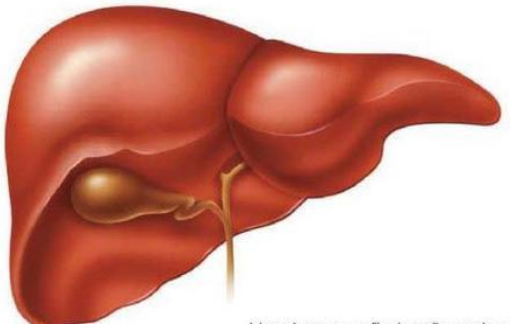
Adipose tissue

- Amorphous tissue widely distributed
- Consist of adipocytes
- ~65% of the weight of adipose tissue is triacylglycerol
- Breakdown controlled *via* **hormone-sensitive lipase**
- Lack **glycerol kinase**; cannot recycle the glycerol of TGs



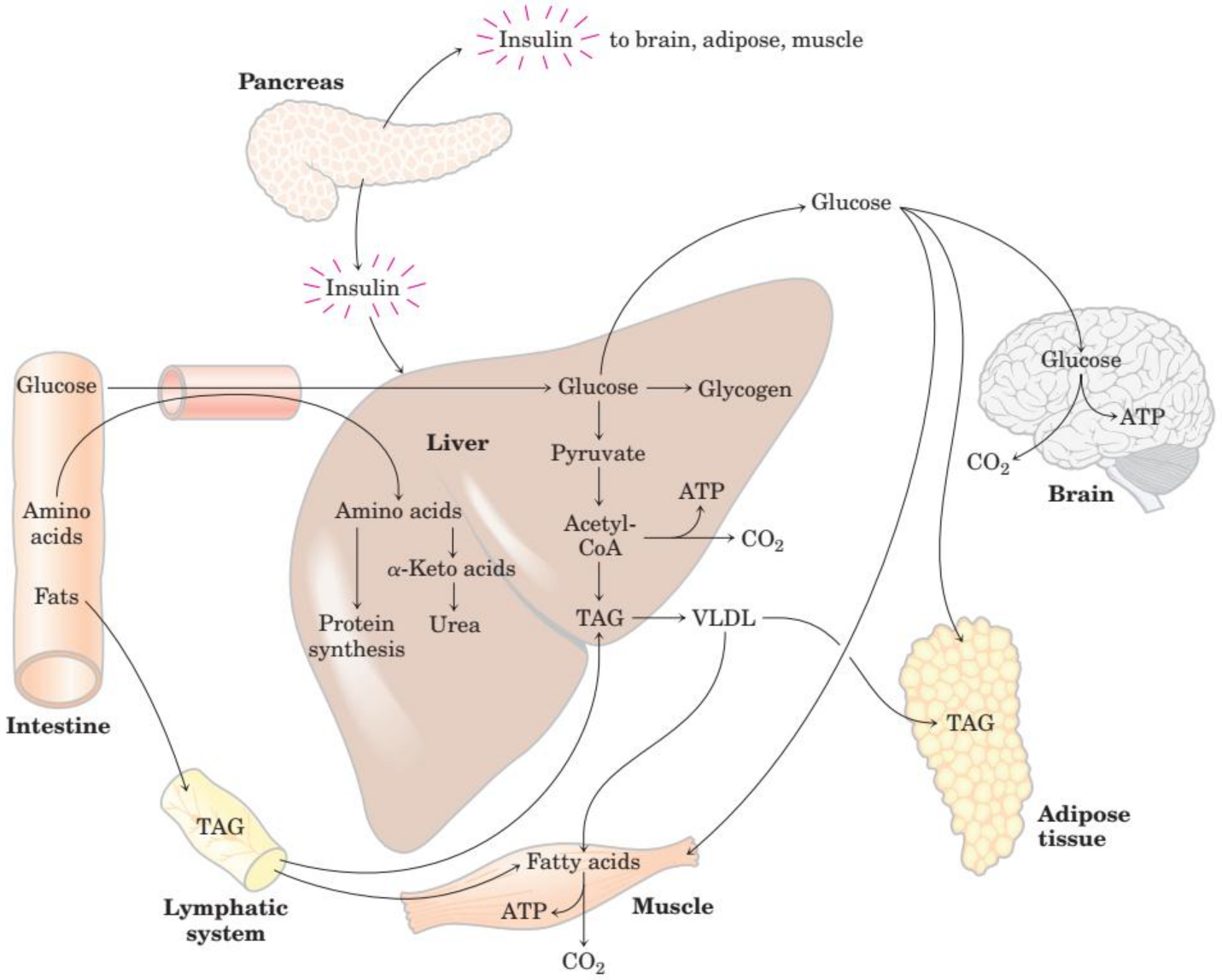
Pontus et al. A PGC1-a-dependent myokine that drives **brown-fat-like** development of white fat and thermogenesis. Nature (2012)

Liver



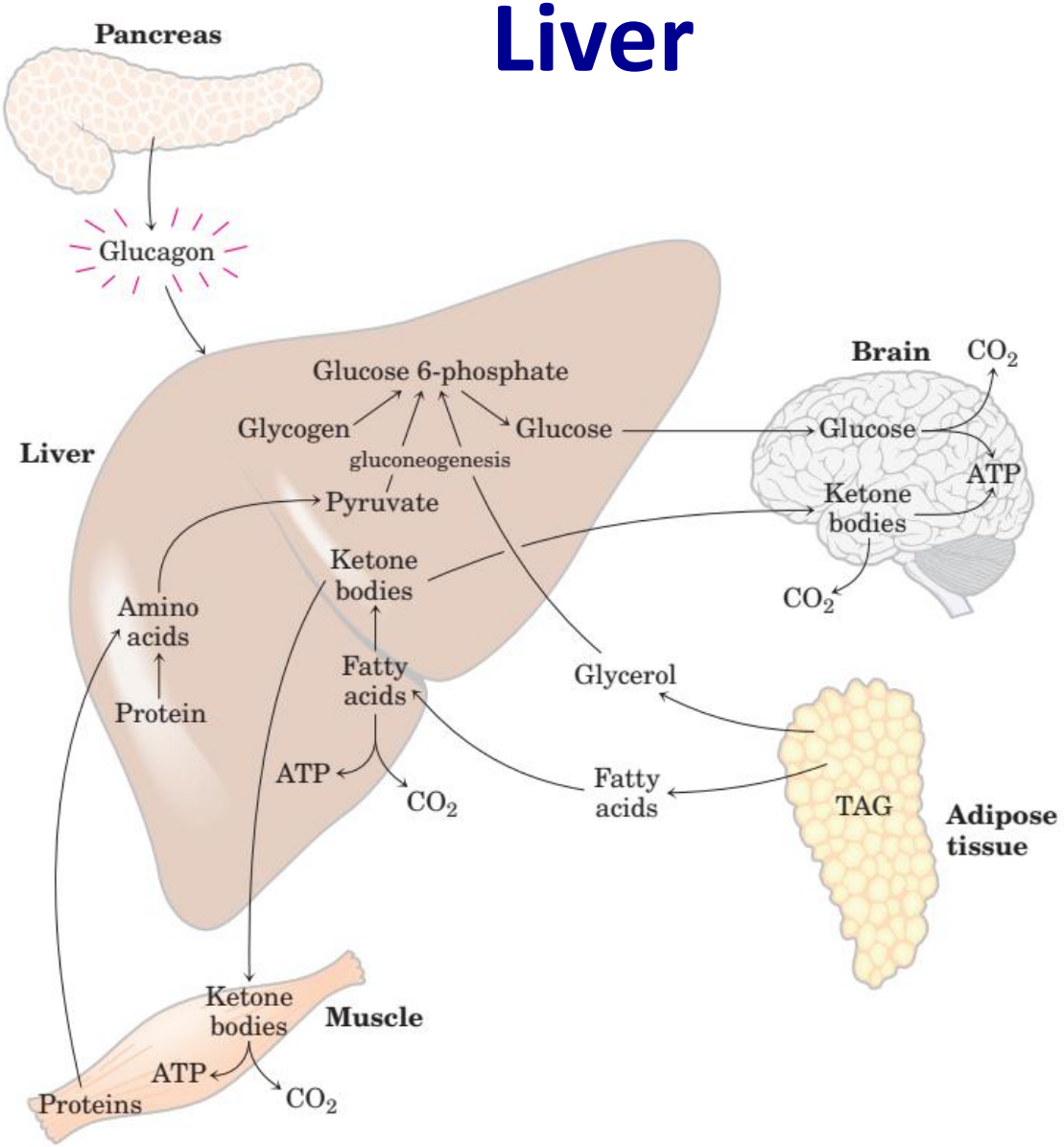
- Metabolic center
- The nutrients → intestines → *via* the portal vein → liver
- Liver activity centers around **glucose-6-phosphate**
- Fatty acid turnover
- Cholesterol synthesis
- Detoxification organ

Liver



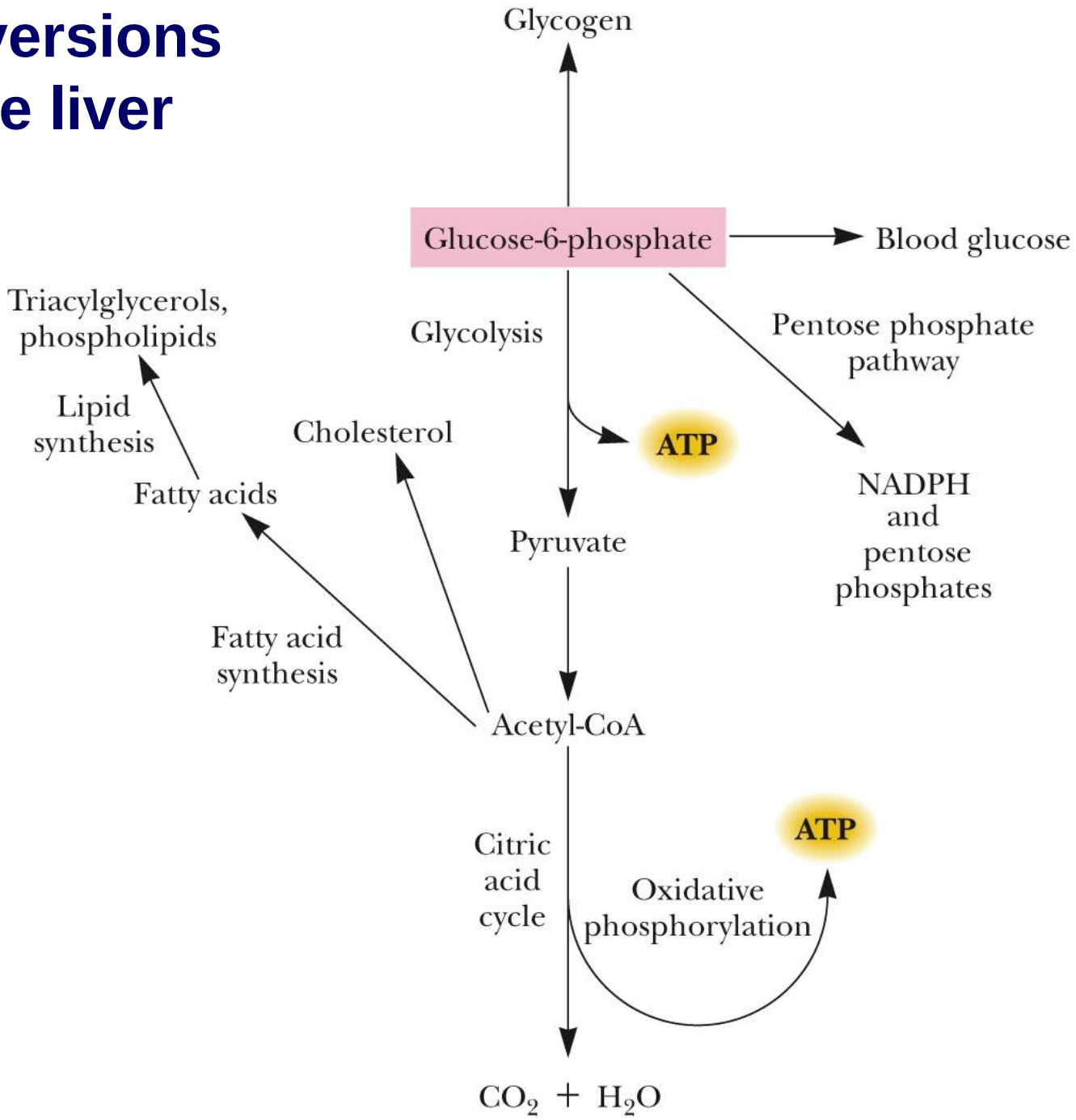
The well-fed state: the lipogenic liver

Liver



The fasting state: the glucogenic liver

Metabolic conversions of G-6-P in the liver



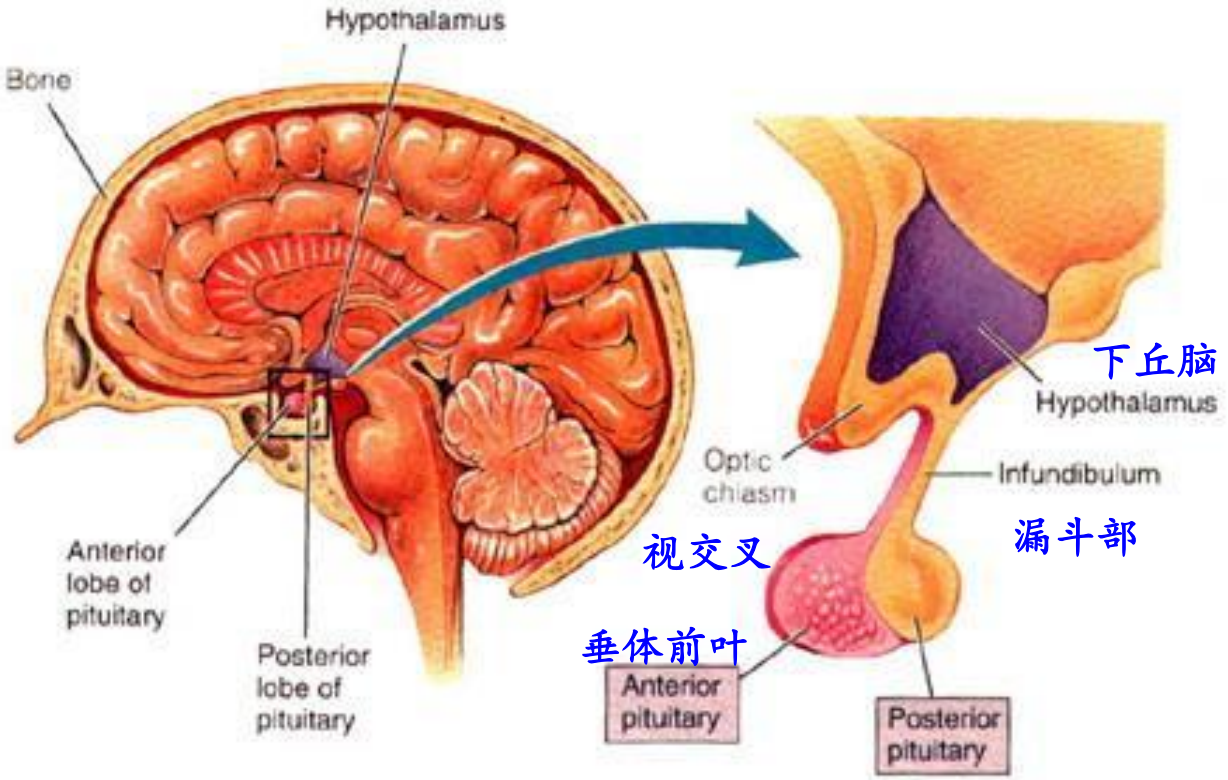
6. What Regulates Our Eating Behavior?

Are you hungry?

- The hormones control eating behavior
  - **Ghrelin**, produced in the stomach, liver
  - Move to brain and act on neurons within the arcuate nucleus region of the hypothalamus

弓形核

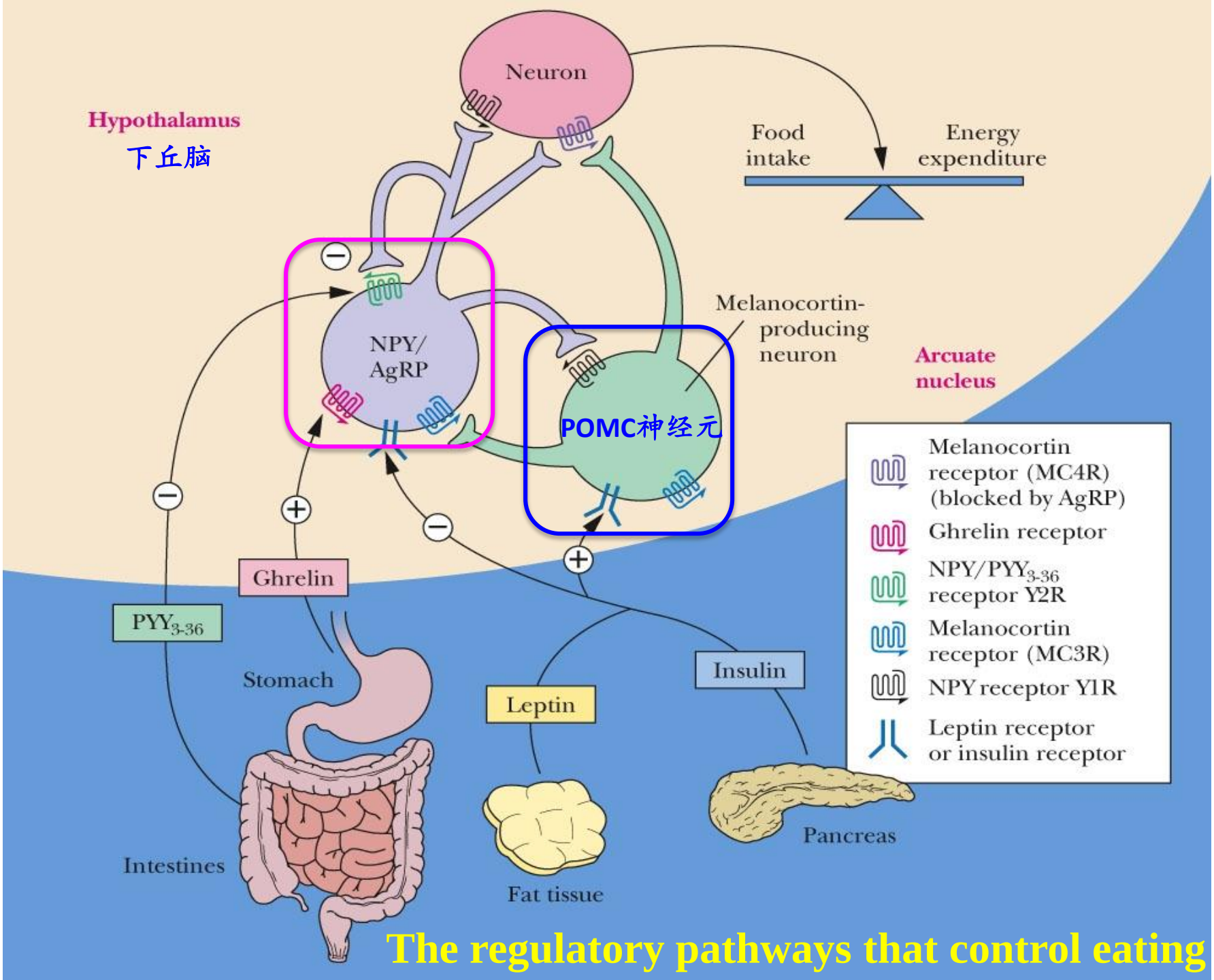
下丘脑



Two subset neurons in hypothalamus（下丘脑）

1. NPY(neuropeptide Y)/ AgRP(Agouti-related peptide) producing neurons -- **stimulating**
2. Melanocortin producing neurons（POMC） -- **inhibiting**

黑皮质素



The regulatory pathways that control eating

- **The hormones are divided：**
  - **Short-term regulator**: determine individual meal
  - **Ghrelin** and **cholecystokinin (CCK)** are short-term regulators of eating behavior
    胆囊收缩素
  - **Ghrelin** -- appetite-stimulating hormone produced in the stomach
  - **CCK** -- appetite-suppressing signal-小肠粘膜细胞分泌–刺激下丘脑产生饱腹感

➢ **Long-term regulator: stablize** body fat deposit

- **AgRP (agouti-related peptide)**

– Block the activity of melanocortin-producing neurons

- **NPY**

– an appetite-stimulating hormone, increases food intake

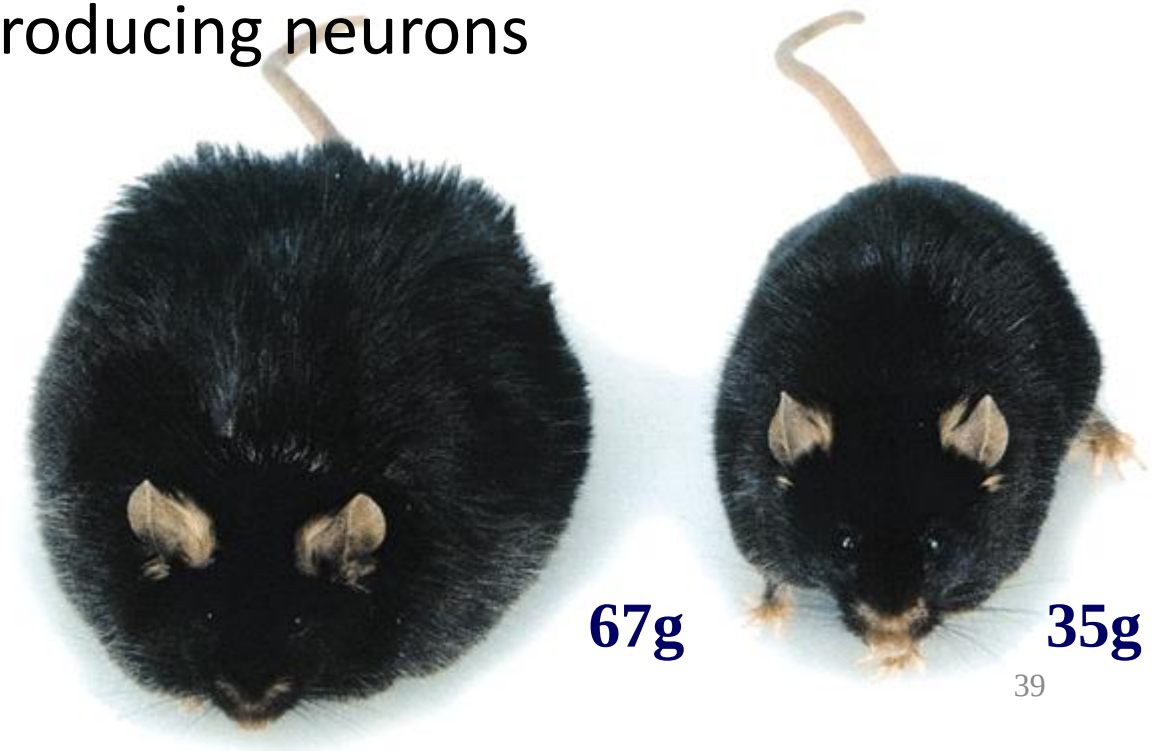
- **Melanocortin** 黑皮质素

– Inhibit the neurons initiating eating behavior

– Including α- and β-**MSH** (melanocyte-stimulating hormone)

- **Insulin** and **leptin** are **long-term** regulators of eating behavior
  - **Insulin** stimulates **fat cells** to make **leptin**
    - Leptin （1994, 167aa）- appetite suppressing
  - **Gut hormone PYY_{3-36}** inhibits eating by acting on the NPY/AgRP-producing neurons

Lack Leptin to cause obesity



- hypothalamic AMPK respond to hormones
  下丘脑

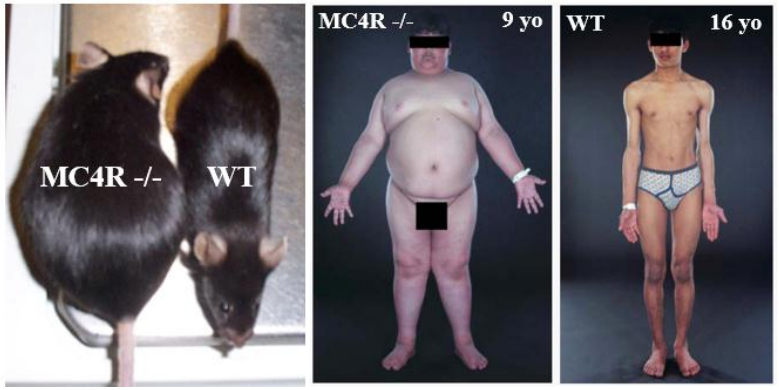
  - **Leptin inhibits** AMPK-- appetite-suppressing
  - **Gherlin** and **NPY** activate hypothalamic AMPK
    - AMPK phosphorylates (inhibits) acetyl-CoA carboxylase
    - malonyl-CoA levels decreased
    - Low [malonyl-CoA] is associated with increased food intake

Eating Disorders: Obesity

Leptin KO

POMC(α-MSH) KO---Color Change

MC4R（α-MSH receptor，KO---Height Boost



Excess MC4R

ARE YOU FAT OR LEAN?

BMI:
(**B**ody **M**ass **I**ndex)

$$\mathrm{BMI} = \frac{\mathrm{mass\ (kg)}}{(\mathrm{height(m)})^2}$$

People with BMI above ? are obese?

A： 25 **B: 30 √** **C: 35**

	WHO标准	亚洲标准	中国标准	肥胖相关疾病发病危险性
偏瘦	<18.5			低（但其它疾病危险性增加）
正常	18.5-24.9	18.5-22.9	18.5-23.9	平均水平
超重	≥25.0	≥23.0	≥24.0	略微增加
偏胖	25.0～29.9	23.0～24.9	24.0～27.9	增加
肥胖	30.0～34.9	25.0～29.9	≥28.0	中度增加
重度肥胖	35.0～39.9	≥30.0	≥32.0	严重增加
极重度肥胖	≥40.0			极度增加

Guinness World Records of BMI

Lowest BMI

俄裔摩纳哥人**瓦莱丽娅 莱维汀**，1.73m，27kg，BMI：

9

Highest BMI

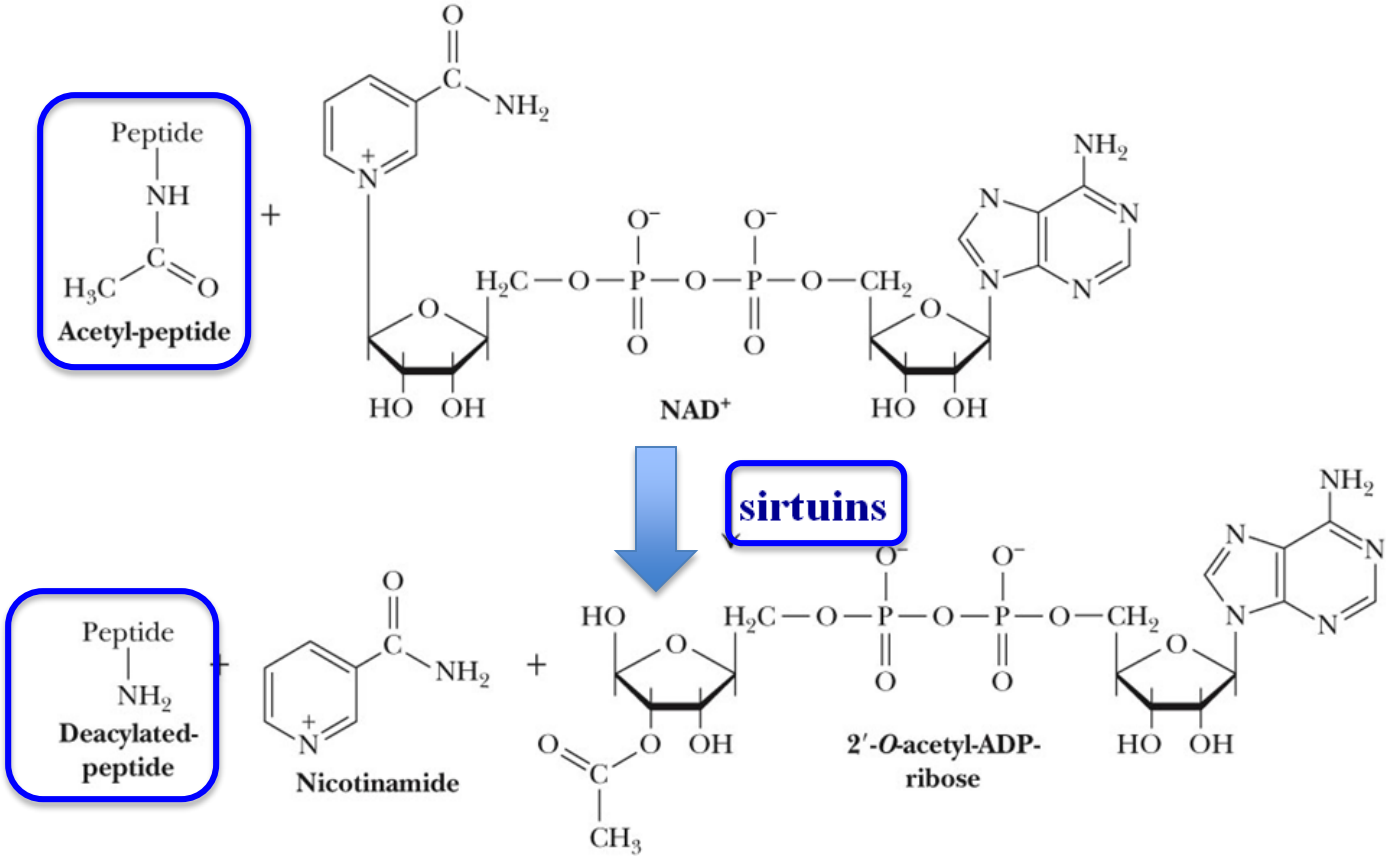
美国华盛顿州的焦 米诺克，1.85m，635kg，BMI:

185.5

7. Can You Really Live Longer by Eating Less?

- **Caloric restriction leads to longevity**
- **Mutations in the *SIR2* Decrease Life Span**
  - Deletion of *SIR2* (silent information regulator 2) abolishes the ability of caloric restriction to lifespan in yeast and roundworms
    - *SIR2* gene in longevity
  - The human analogous to *SIR2* is *SIRT1*

- **Sirtuins -- NAD$^+$-dependent protein deacetylases**
  去乙酰化酶
  - The NAD$^+$/NADH controls sirtuin deacetylase activity
  - Nicotinamide（烟酰胺） & NADH inhibit sirtuin activity
  - NAD$^+$ ↑, sirtuin activity ↑



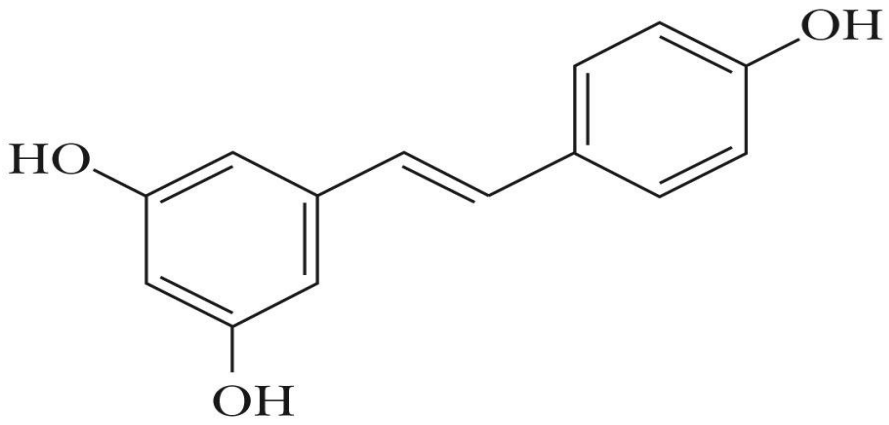
SIRT1 is a Key Regulator in Caloric Restriction

- **SIRT1** participates in the transcriptional regulation of adipogenesis through interaction with PPARg (peroxisome proliferator-activator receptor- g)
- **PPARg** activates adipogenesis genes
- SIRT1 binding to PPARg **represses adipogenesis** genes, leading to loss of fat stores

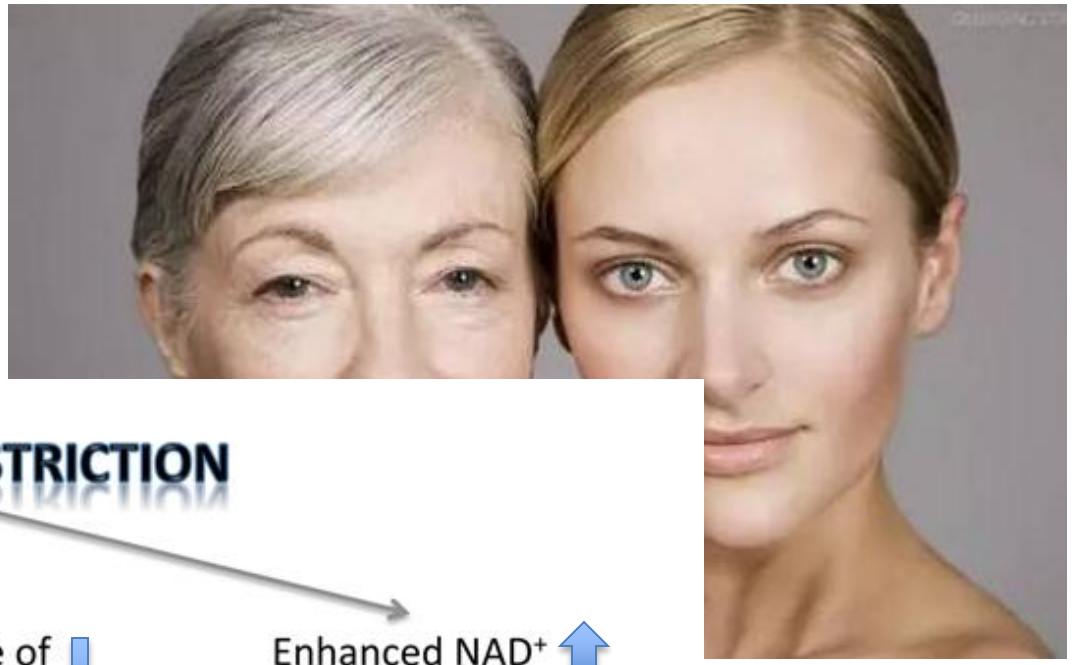
Resveratrol (白藜芦醇) in Red Wine is a Potent Activator of Sirtuin Activity

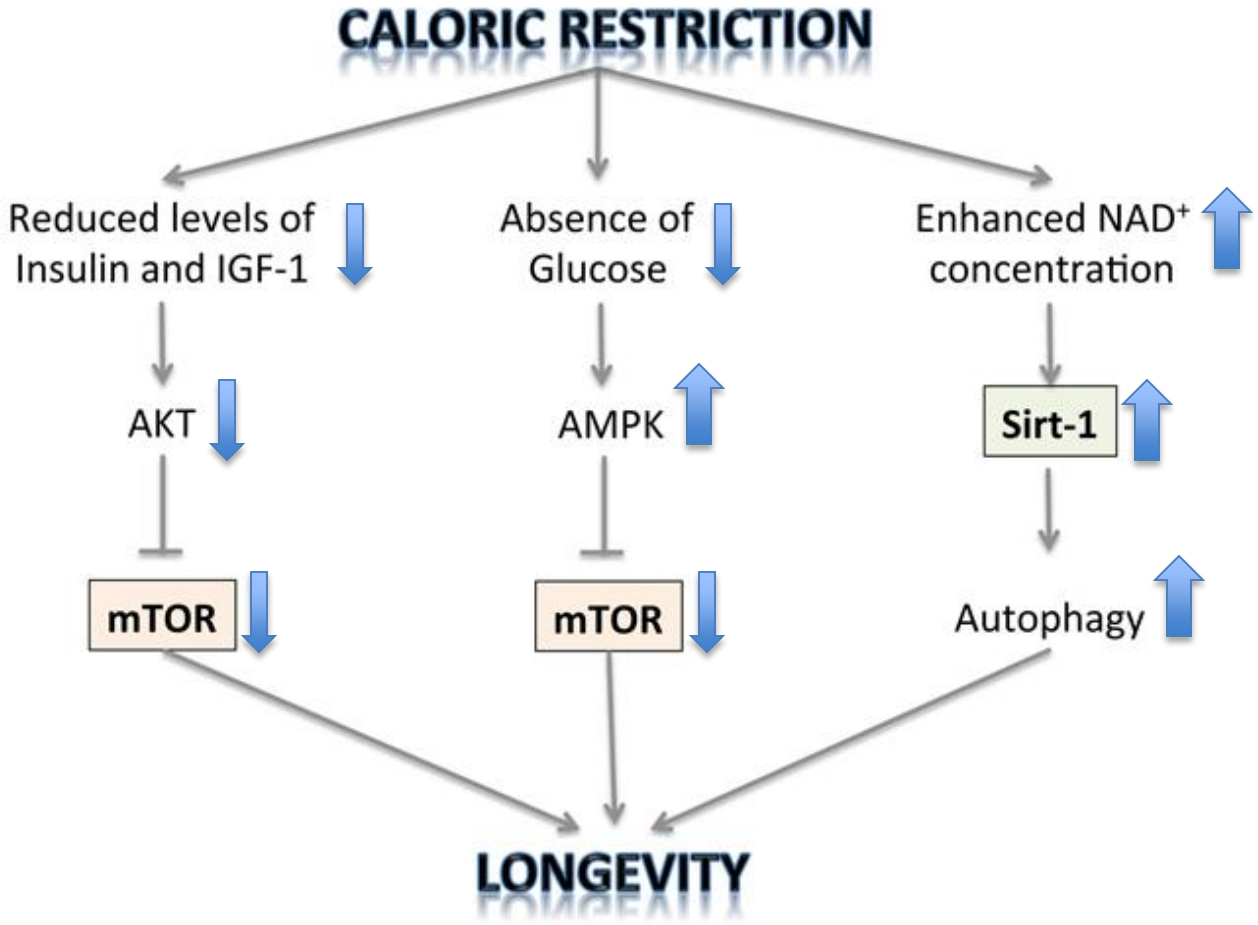
French people enjoy longevity despite a high-fat diet.

Resveratrol may be the basis of this “French paradox”.

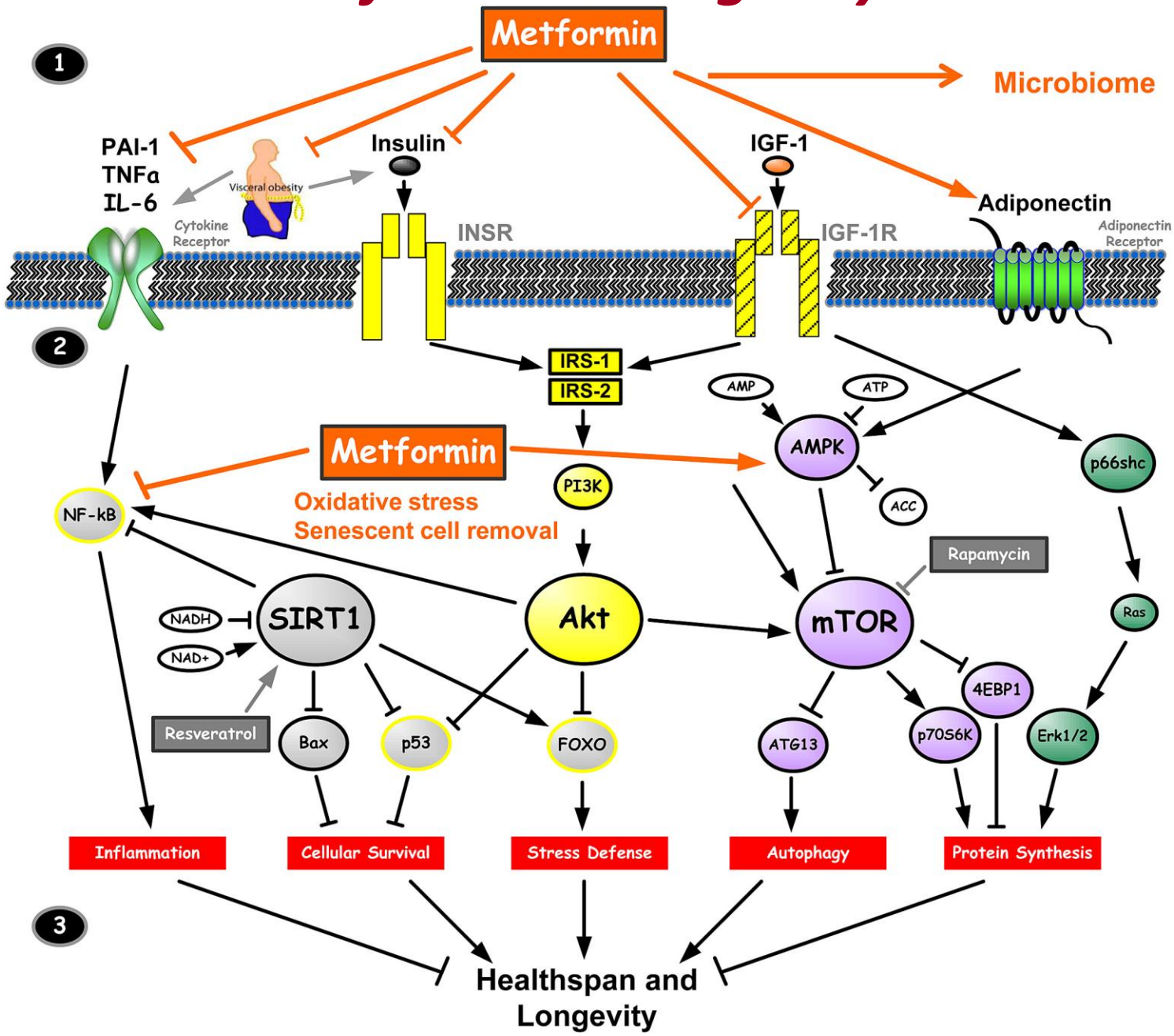


Resveratrol (*trans*-3,4′,5-trihydroxystilbene)




CALORIC RESTRICTION
Reduced levels of Insulin and IGF-1
Absence of Glucose
Enhanced NAD+ concentration
AKT
AMPK
Sirt-1
mTOR
mTOR
Autophagy
LONGEVITY

Metformin & longevity



- 什么是能荷？为何说ATP处于能量代谢的中心？
- AMPK如何调控机体能量代谢？
- 大脑、肌肉、心脏、脂肪组织和肝脏中代谢特点是什么？
- 饮食行为如何被调控的？
- 为何限制饮食可以长寿？