Brain Energy Metabolism I

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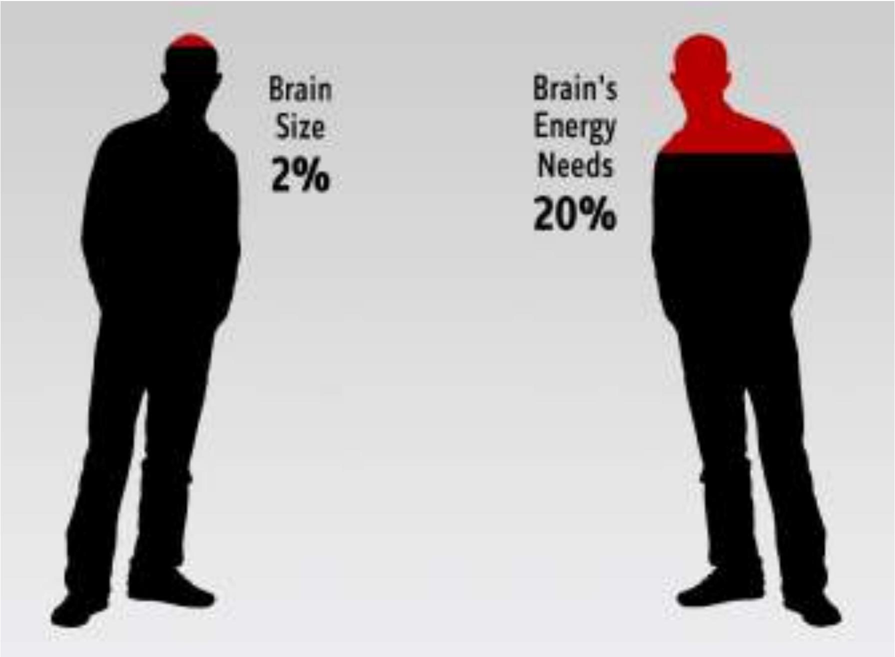
Central Nervous System

- Nervous system is that part of our body which coordinates all voluntary and involuntary missions and transmits signals to and from various parts of the body
- Nervous system is divided into two main parts: central nervous system (CNS) and peripheral nervous system (PNS)
- The **CNS** consists of *Brain* and *Spinal cord* whereas **PNS** is composed mainly of *Nerves* that connect the CNS to every other part of the body
- The *brain* is an information processing center like computer. To function properly, cerebral tissue requires constant supply of energy

Brain Energy Needs

- Although the human brain constitutes only **2 %** of the total body weight, its metabolic demands are extremely high
- The brain receives **15%** of the cardiac output, **20%** of total body oxygen consumption and **25%** of total body glucose utilization



- The brain needs a constant supply of oxygen and glucose to function.
- Cerebral hypoxia can lead to irreversible neuronal damage after about 5 minutes. also, severe hypoglycemia kills the neurons.

Insights on Brain Energy

1. What are the energy substrates?
2. How does the brain generate its own energy from these substrates?
3. How is the generated energy expended?

Brain Energy Expenditure

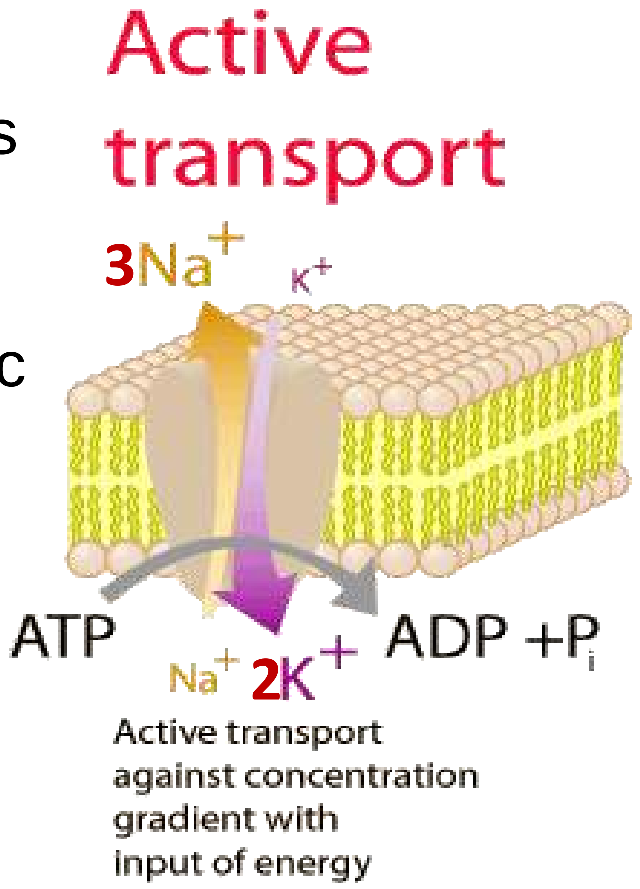
- Glucose is the primary energy substrate of the brain, where it is almost entirely oxidized to $6CO_2$ and $6H_2O$ through its sequential processing by glycolysis, tricarboxylic acid (TCA) cycle and the associated oxidative phosphorylation resulting in **30 ATP molecules/ glucose**

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

Brain Energy Expenditure

- Na^+/K^+– ATPase pump: is an ATP-dependent transporter found in the membrane of neuronal and glial cells responsible for the active transport of 3 Na^+ out and 2 K^+ in

- The main energy-consuming process in brain (70%) is the maintenance of ionic gradients across the plasma membrane which is achieved by ionic pumps fueled by ATP, particularly Na^+/K^+– ATPase pump



Oxygen-Glucose Uncoupling

- The respiratory quotient of brain (**RQ**) is very close to 1. This means that the brain metabolism utilizes almost exclusively carbohydrate sources, particularly glucose

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

Respiratory Quotient= vCO_2 / vO_2

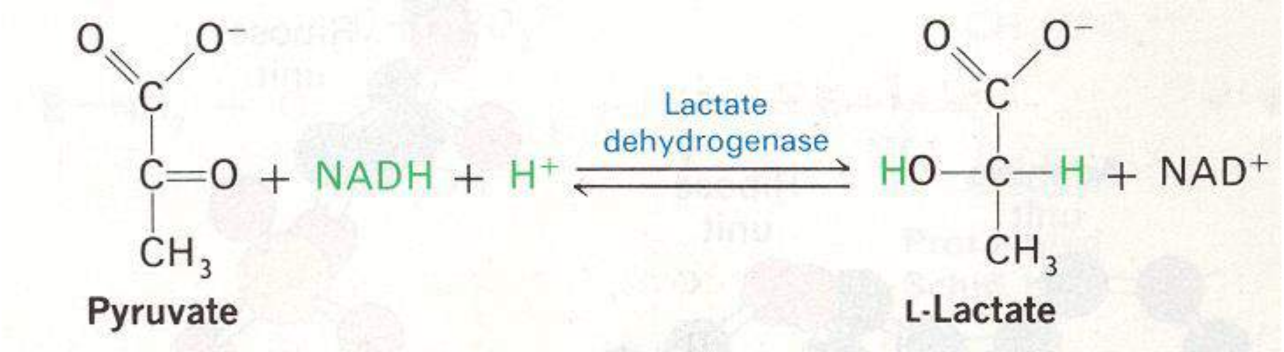
$= 6CO_2 / 6\ O_2$

RQ $= 1$

Oxygen-Glucose Uncoupling

- O_2 consumption rate of brain is 160 mmol /100 g/min but the **measured (actual) glucose** utilization rate is **31** mmol /100 g/min which is slightly higher than **the predicated (calculated)** value of **26.6** mmol /100 g/min
- The fate of the excess **4.4 mmol** of glucose:

1. Stored as **glycogen** in astrocytes
2. Limited amount of glucose is metabolized only by glycolysis where the pyruvate is converted to lactate via **anaerobic fermentation** process (particularly in astrocytes)

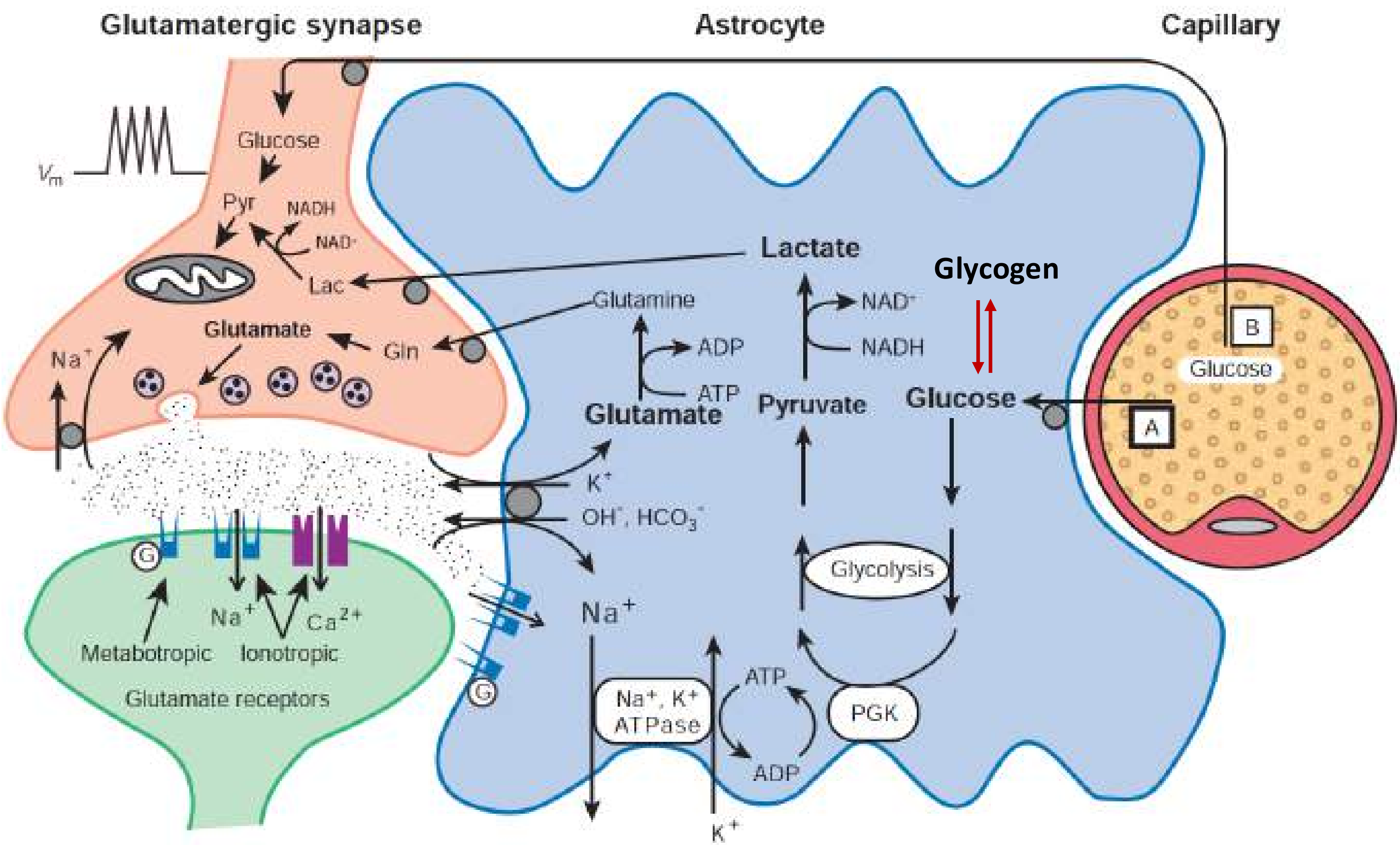


Oxygen-Glucose Uncoupling

3. Essential constituent of **glycolipids** and **glycoproteins** present in neural cells
4. Utilized in the synthesis of brain neurotransmitters: **glutamate**, **GABA** and **acetylcholine**

- **There is uncoupling between O_2 consumption and glucose utilization in cerebral tissue**
  - This indicates that metabolic needs of brain tissue are partially met by non-oxidative metabolism of glucose
  - Different active areas in brain tissue are associated with high level of lactate

Cell-Specific Glucose Uptake and Metabolism



Glycolysis is mediated by Glutamate Reuptake

- The basal rate of glucose utilization is high in astrocytes than in neurons
- In astrocytes, glucose utilization is mediated by glutamate reuptake via specific transporters
  - Glutamate is co-transported with Na^+ ions which increases intracellular Na^+ concentration
  - This activates Na^+/K^+ ATPase pump and consequently induces glycolysis
- Hence, neuronal activity is coupled with glucose utilization in brain
- Indeed, during activation there is an increase in lactate release by astrocytes to be utilized by neurons

Energy Substrates for Brain

1. Glucose is the exclusive substrate for oxidative metabolism used to produce energy in the form of ATP molecules under aerobic conditions and very limited extent under anaerobic conditions (fermentation)

2. Ketone bodies particularly acetoacetate (AcAc) and 3-hydroxybutyrate (3-HB or β-HB) become energy substrates for the brain in particular circumstances:

    - Ketogenic conditions (Starvation & Diabetes)
    - Breastfed neonates

Energy Substrates for Brain

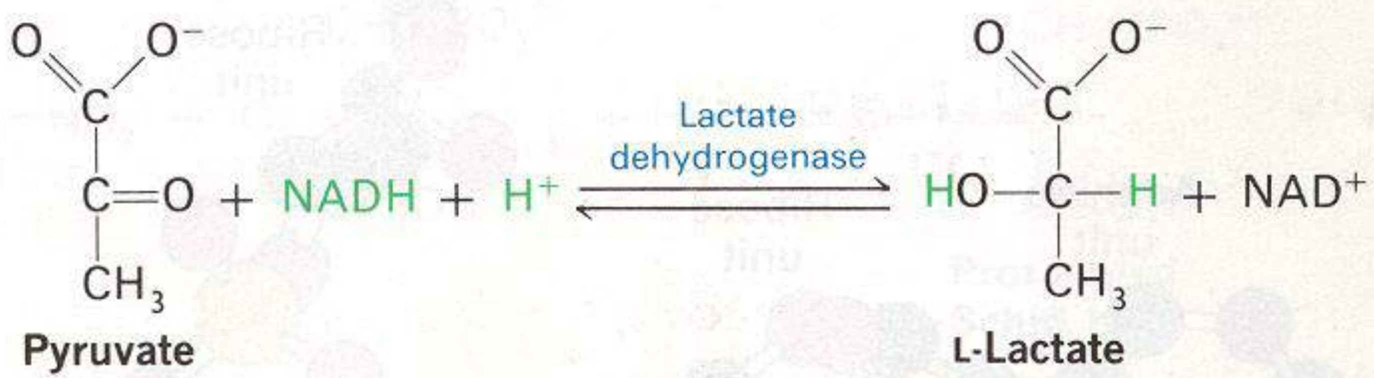
3. Other substrates like mannose, pyruvate and lactate have been tested as alternative substrates to glucose for brain energy metabolism:

- **Mannose:** it can cross BBB readily but is not normally present in the blood so it has no physiological significance

$$\text{Mannose} \xrightarrow[\text{ATP}]{\text{hexokinase}} \text{Mannose 6-p} \underset{\text{isomerase}}{\overset{\text{phosphomannose}}{\rightleftharpoons}} \text{Fructose 6-p}$$

Energy Substrates for Brain

- **Pyruvate and lactate**: when these monocarboxylate molecules are formed within cerebral tissues from the glucose that has been crossed the BBB, pyruvate and lactate in fact become the preferential energy substrates for activated neurons.



Energy Substrates for Brain

- Until recently, circulating pyruvate and lactate was thought that they have limited permeability across BBB thus circulating pyruvate and lactate can't serve as substrates for brain energy metabolism (several contradictory studies ???)
- For example, vigorous exercise resulting in increased blood lactate level which is then taken up by the brain and fully oxidized by the brain cells **(Dalsgaard, 2006)**. So, the circulating lactate can be utilized as energy substrate for human brain

Circulating Lactate as Substrates for Brain

Journal of Cerebral Blood Flow & Metabolism (2006) 26, 731–750

Review Article

Fuelling cerebral activity in exercising man

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The metabolic response to brain activation in exercise might be expressed as the cerebral metabolic ratio (MR: uptake O_2/glucose + 1/2 lactate). At rest, brain energy is provided by a balanced oxidation of glucose as MR is close to 6, but activation provokes a 'surplus' uptake of glucose relative to that of O_2. Whereas MR remains stable during light exercise, it is reduced by 30% to 40% when exercise becomes demanding. The MR integrates metabolism in brain areas stimulated by sensory input from skeletal muscle, the mental effort to exercise and control of exercising limbs. The MR decreases during prolonged exhaustive exercise where blood lactate remains low, but when vigorous exercise raises blood lactate, the brain takes up lactate in an amount similar to that of glucose. This lactate taken up by the brain is oxidised as it does not accumulate within the brain and such pronounced brain uptake of substrate occurs independently of plasma hormones. The 'surplus' of glucose equivalents taken up by the activated brain may reach ~10 mmol, that is, an amount compatible with the global glycogen level. It is suggested that a low MR predicts shortage of energy that ultimately limits motor activation and reflects a biologic background for 'central fatigue'.

Journal of Cerebral Blood Flow & Metabolism (2006) **26**, 731–750. doi:10.1038/sj.jcbfm.9600256; published online 14 December 2005

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Introduction

The FASEB Journal • Review

Lactate fuels the human brain during exercise

Bjørn Quistorff, Niels H. Secher, and Johannes J. Van Lieshout