



# Brain Energy Metabolism I



Dr. Nesrin Mwafi

Biochemistry & Molecular Biology Department  
Faculty of Medicine, Mutah University

# Central Nervous System

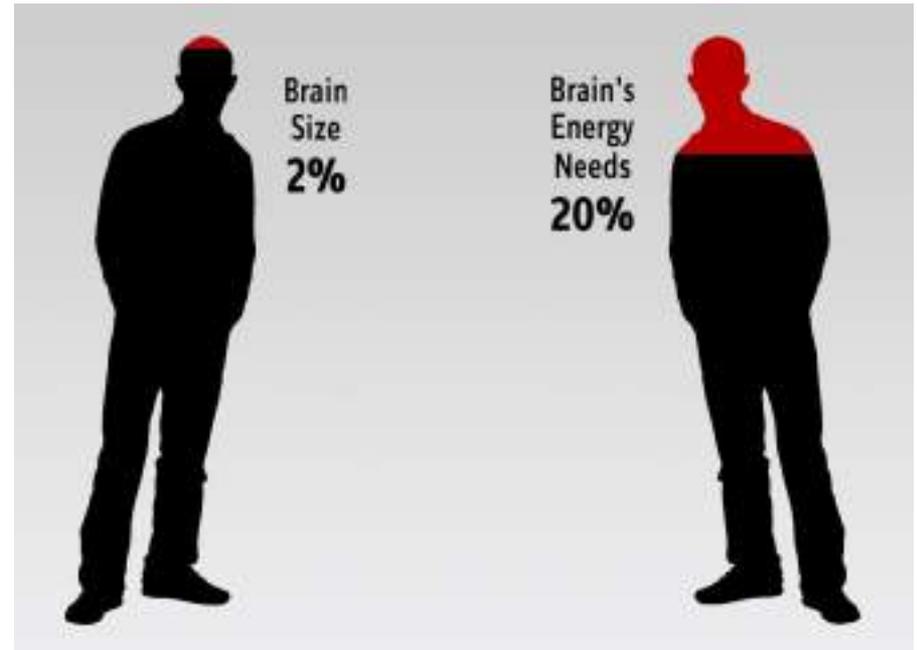


- Nervous system is that part of our body which coordinates all voluntary and involuntary missions and transmits signals to and from various parts of the body
- Nervous system is divided into two main parts: central nervous system (CNS) and peripheral nervous system (PNS)
- The **CNS** consists of *Brain* 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



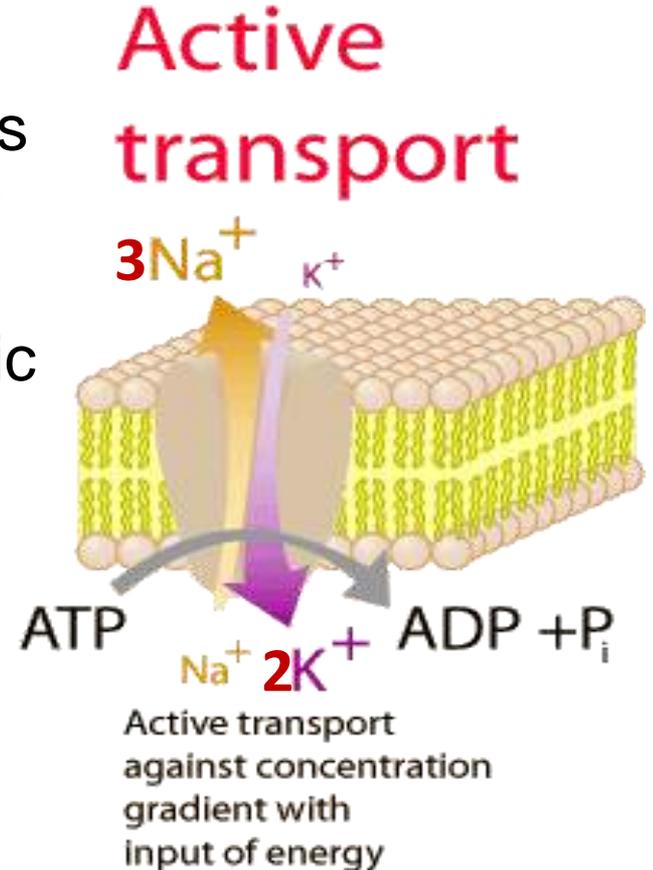
- Glucose is the primary energy substrate of the brain, where it is almost entirely oxidized to  $6\text{CO}_2$  and  $6\text{H}_2\text{O}$  through its sequential processing by glycolysis, tricarboxylic acid (TCA) cycle and the associated oxidative phosphorylation resulting in **30 ATP molecules/ glucose**



# Brain Energy Expenditure



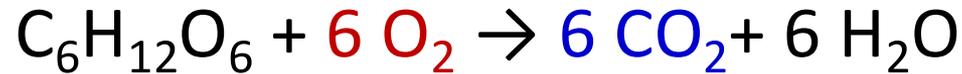
- $\text{Na}^+/\text{K}^+$ –ATPase pump: is an ATP-dependent transporter found in the membrane of neuronal and glial cells responsible for the active transport of 3  $\text{Na}^+$  out and 2  $\text{K}^+$  in
- The main energy-consuming process in brain (70%) is the maintenance of ionic gradients across the plasma membrane which is achieved by ionic pumps fueled by ATP, particularly  $\text{Na}^+/\text{K}^+$ –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

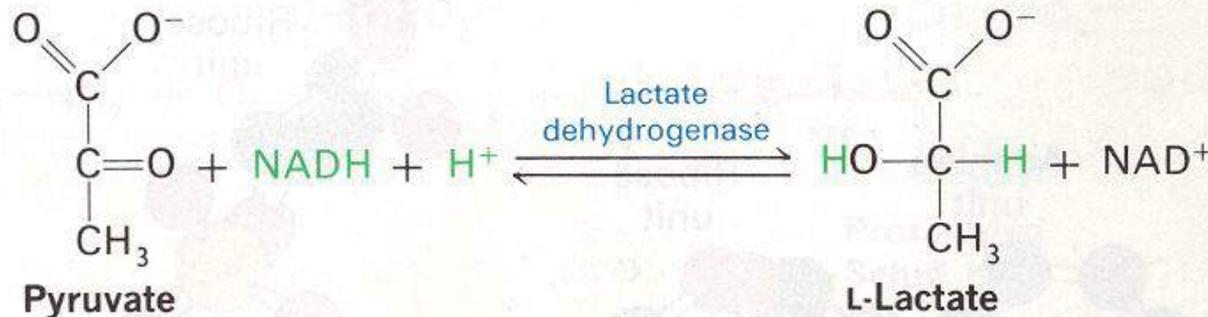


$$\begin{aligned}\text{Respiratory Quotient} &= v\text{CO}_2 / v\text{O}_2 \\ &= 6\text{CO}_2 / 6 \text{O}_2 \\ \text{RQ} &= 1\end{aligned}$$

# Oxygen-Glucose Uncoupling



- O<sub>2</sub> 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 predicted (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)

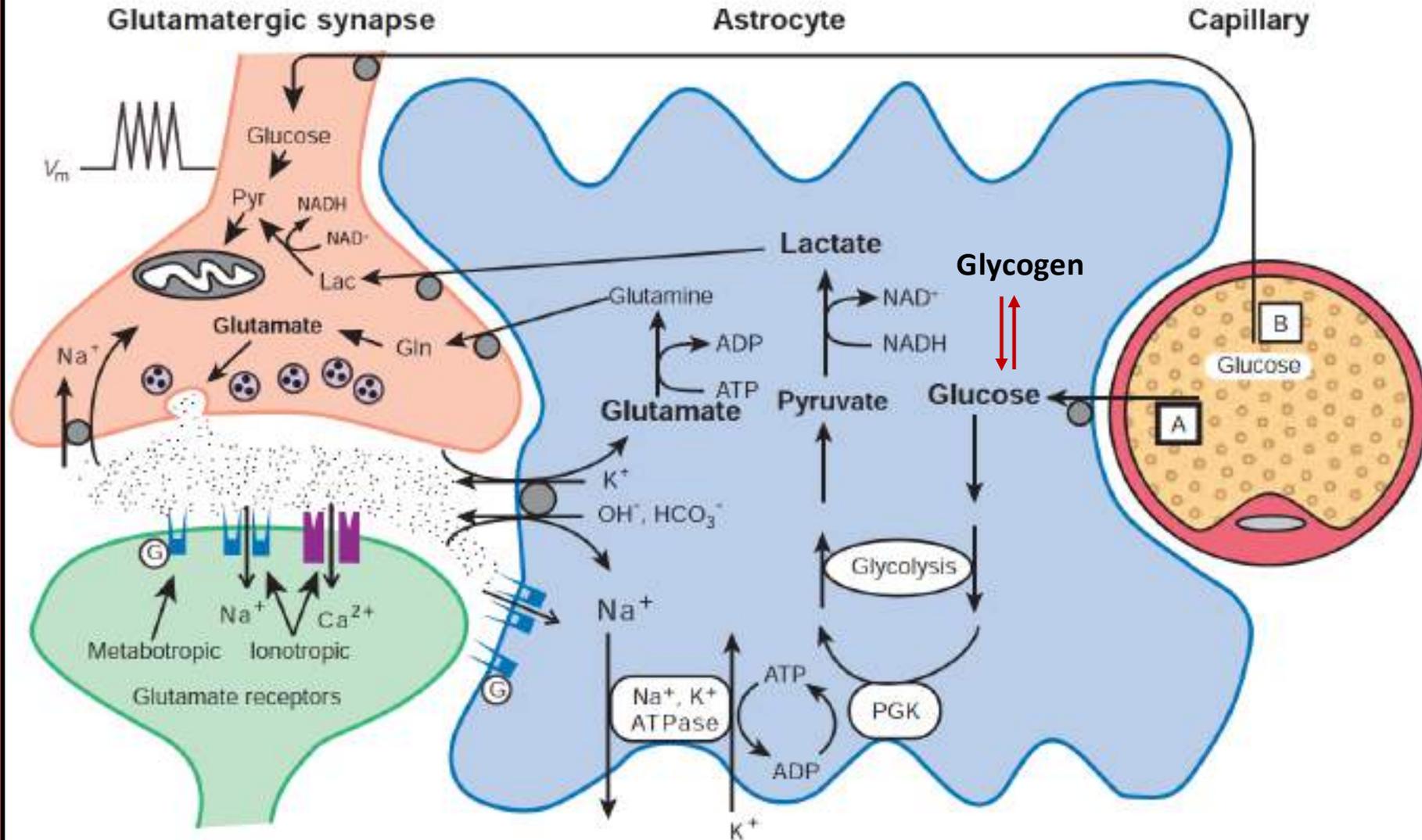


# Oxygen-Glucose Uncoupling



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<sub>2</sub> 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  $\text{Na}^+$  ions which increases intracellular  $\text{Na}^+$  concentration
  - This activates  $\text{Na}^+/\text{K}^+$  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

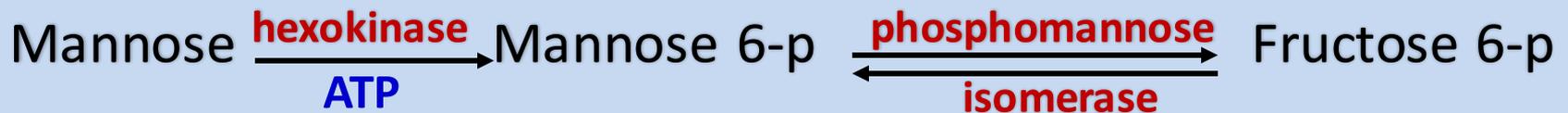


1. Glucose is the exclusive substrate for oxidative metabolism used to produce energy in the form of ATP molecules under aerobic conditions and very limited extent under anaerobic conditions (fermentation)
2. Ketone bodies particularly acetoacetate (AcAc) and 3-hydroxybutyrate (3-HB or  $\beta$ -HB) become energy substrates for the brain in particular circumstances:
  - Ketogenic conditions ( Starvation & Diabetes)
  - Breastfed neonates

# Energy Substrates for Brain



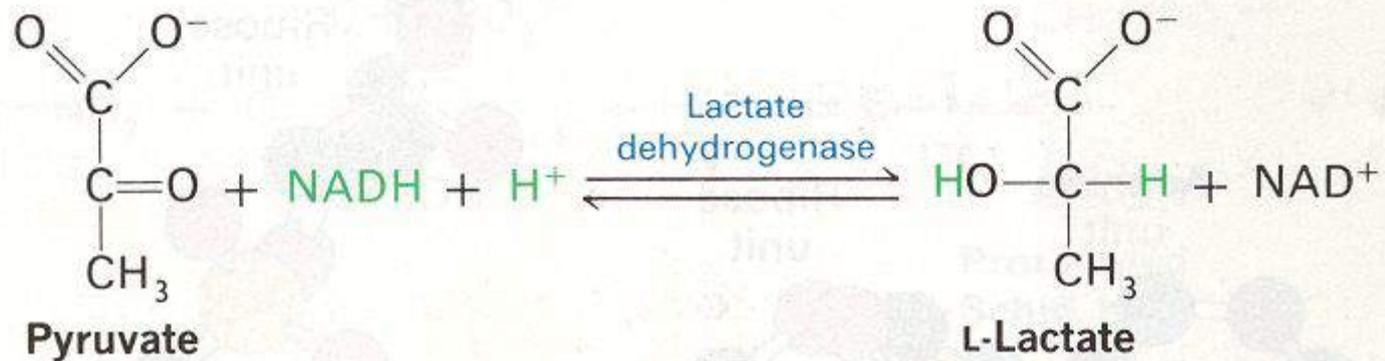
3. Other substrates like mannose, pyruvate and lactate have been tested as alternative substrates to glucose for brain energy metabolism:
  - **Mannose:** it can cross BBB readily but is not normally present in the blood so it has no physiological significance



# 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



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## Review Article

### Fuelling cerebral activity in exercising man

Mads K. Dalgaard

Department of Anaesthesia and The Copenhagen Muscle Research Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

The metabolic response to brain activation in exercise might be expressed as the cerebral metabolic rate (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 0, 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'.

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**Keywords:** amino acids; brain activation; cerebral blood flow; glycogen; lactate

## Introduction

Daily activities such as walking and cycling become automated to an extent where they are executed without mental awareness. In contrast, a mentally demanding activity would be expected to require comparatively more brain activity and already Larsson [1799] reasoned that such enhanced mental effort should be measurable. In this context, physical exercise is not only a ubiquitous part of daily living, but might be considered as an intensive and complex stimulus to the brain. Thus, exercise involves a diversity of cerebral functions, including cognitive and sensorimotor aspects, and the magnitude of the stimulus might be modulated by the intensity of the task. Furthermore, exercise is often accompanied by shifts in the supply of fuel to the brain, for example, high arterial lactate, and an elevated levels of systemic hormones. As a paradigm

of cerebral activation, uniquely, exercise marks motor neural output and thereby neuronal function. Notably, a decline in motor neural output contributes to the involuntary decrease in force of contraction and divides fatigue into factors within the muscle and those within the central nervous system, termed 'central fatigue' [830] and Secher, 2004).

Assessment of brain activity hinges on the currently recognised relationships between its physiologic basis, that is, propagation of action potentials and release of neurotransmitters with perturbation and restoration of membrane potentials and of the extracellular milieu, and the need for enhanced cerebral blood flow (CBF) and consumption of oxygen. However, the brain-imaging techniques applied to gauge these variables are employed with difficulty during exercise and, accordingly, the cerebral metabolic response is assessed as that of the whole brain by arterial-venous jugular venous differences [A-V]. This paper reviews brain metabolism in exercise, expressed by the reduction in the cerebral metabolic rate (MR) of  $O_2$  versus substrate. Such disproportionate cerebral uptake of substrate relative to that of  $O_2$ , is provoked during demanding exercise as it characterises cerebral activation in general. Focus centres on the aspects of exercise that decrease MR and on the energy sources besides glucose that fuel metabolism, particularly lactate,

## The FASEB Journal • Review

### Lactate fuels the human brain during exercise

Bjorn Quistorff,\* Niels H. Secher,<sup>†‡</sup> and Johannes J. Van Lieshout<sup>§¶</sup>

\*Department of Biomedical Sciences, †Department of Anaesthesiology, and ‡The Copenhagen Muscle Research Centre, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark, and §Department of Internal Medicine, MedStar Care Unit, and Laboratory for Clinical Cardiovascular Physiology, Center for Heart Failure Research, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

**ABSTRACT** The human brain releases a small amount of lactate at rest, and even an increase in arterial blood lactate during anaesthesia does not provide a net cerebral lactate uptake. However, during cerebral activation associated with exercise involving a marked increase in plasma lactate, the brain takes up lactate in proportion to the overall concentration. Cerebral lactate uptake, together with glucose uptake, is larger than the uptake accounted for by the concomitant  $O_2$  uptake, as reflected by the decrease in cerebral metabolic rate (CMR) [the cerebral metabolic rate  $O_2$ /glucose + 1/2 lactate] from a resting value of 0 to <0. The CMR also decreases when plasma lactate is not increased, as during prolonged exercise, cerebral activation associated with mental activity, or exposure to a stressful situation. The CMR decrease is prevented with combined  $\beta_1$ - and  $\beta_2$ -adrenergic receptor blockade but not with  $\beta_1$ -adrenergic blockade alone. Also, CMR decreases in response to apinephrine, suggesting that a  $\beta_2$ -adrenergic receptor mechanism enhances glucose and perhaps lactate transport across the blood-brain barrier. The pattern of CMR decrease under various forms of brain activation suggests that lactate may partially replace glucose as a substrate for oxidation. Thus, the notion of the human brain as an obligatory glucose consumer is not without exceptions—Quistorff, B., Secher, N. H., and Van Lieshout, J. J. Lactate fuels the human brain during exercise. *FASEB J.* 22, 3448–3449 (2008).

**Key Words:** energy metabolism • glucose • oxygen

REGULATION OF BLOOD FLOW to the activated brain is different from regulation of flow to working skeletal muscles. When the brain is activated (1), as during exercise (2), the increment in cerebral blood flow (CBF) enhances cerebral oxygenation while muscle oxygenation progressively decreases with work rate. Thus, increased activation leads to hyperemia in the brain but not in the muscle. The cerebral hyperperfusion may be an important precursor because brain function deteriorates when its oxygenation is reduced by more than 10% from the resting level (3–5). During exercise, reduced cerebral oxygenation precedes development of so-called central fatigue (6). In contrast, skeletal muscles tolerate  $O_2$  desaturation down to 10% (7). It is well established that increased activation of

skeletal muscle results in lactate output, but uptake of lactate by skeletal muscle may also occur as demonstrated during maximal whole body exercise, during which leg muscles take up lactate (8).

Lactate uptake in the brain is less established, but during exhaustive physical exercise with intense activation of large muscle groups, during which anaerobic metabolism prevails and arterial lactate is elevated, the brain takes up lactate in amounts that may approximate the uptake of glucose (9). Thus, lactate uptake may be on the order of 1 mmol min<sup>-1</sup> and glucose uptake on the order of 0.5 mmol min<sup>-1</sup>.

The conventional view of the liver as the organ that clears the blood of lactate is explained by the Cori cycle (10) should be extended to also include lactate uptake by brain and muscle, limiting distribution of carbohydrate energy to the body and saving on glucose. During exhaustive exercise the cerebral metabolic rate for carbohydrate, defined as  $O_2$ /glucose + 1/2 lactate, can decrease to 3 or even lower, whereas the  $O_2$ /glucose ratio decreases somewhat less (11, 12). This decrease in the uptake rate indicates a surplus or nonoxidative carbohydrate uptake by the activated brain, the fate of which remains unknown. Presumably, lactate and glucose are metabolized in the brain, because they do not accumulate in the cerebrospinal fluid (3, 13) or within the brain tissue, at least not to a level above the detection of proton magnetic resonance spectroscopy (14). Only after prolonged (45 min) exercise is there a small increase in lactate in the cerebrospinal fluid (3.1 ± 3.1 mM at rest to 1.2 ± 0.1 mM; mean ± SE) (unpublished results). This assumption is in agreement with animal data (15), and preliminary data from human studies with 15-<sup>3</sup>C-lactate infusion confirm that lactate taken up by the brain is fully decarboxylated (17). Thus, externally supplied lactate serves as a substrate for the brain (5, 14, 18) and probably, as suggested by studies performed on mice culture systems, for rest (19).

Glucose uptake by the brain follows saturation kinetics, primarily mediated by the glucose-transporter

† Correspondence: Department of Internal Medicine, MedStar Care Unit, Room F205, Academic Medical Center, University of Amsterdam, PO Box 22000, 1100 DE Amsterdam, The Netherlands. E-mail: j.j.vanlieshout@amc.uva.nl  
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Correspondence: Dr M.K. Dalgaard, Department of Anaesthesia, The Copenhagen Muscle Research Centre, University of Copenhagen, Rigshospitalet 2641, Blegdamsvej 3, DK-2100 Copenhagen, Denmark. E-mail: madd@rnk.hi.hi.dk

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