Review

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Sugar for the brain: the role of glucose in physiological and pathological brain function

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The mammalian brain depends upon glucose as its main source of energy, and tight regulation of glucose metabolism is critical for brain physiology. Consistent with its critical role for physiological brain function, disruption of normal glucose metabolism as well as its interdependence with cell death pathways forms the pathophysiological basis for many brain disorders. Here, we review recent advances in understanding how glucose metabolism sustains basic brain physiology. We synthesize these findings to form a comprehensive picture of the cooperation required between different systems and cell types, and the specific breakdowns in this cooperation that lead to disease.

> 'Nobody realizes that some people expend tremendous energy merely to be normal.' Albert Camus, Notebooks 1942–1951.

Glucose metabolism: fueling the brain

The mammalian brain depends on glucose as its main source of energy. In the adult brain, neurons have the highest energy demand [1], requiring continuous delivery of glucose from blood. In humans, the brain accounts for approximately 2% of the body weight, but consumes approximately 20% of glucose-derived energy, making it the main consumer of glucose (approximately 5.6 mg glucose per 100 g human brain tissue per minute [2]). Glucose metabolism provides the fuel for physiological brain function through the generation of ATP, the foundation for neuronal and non-neuronal cellular maintenance, as well as the generation of neurotransmitters. Therefore, tight

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Glossary

Autophagy: an intracellular 'recycling' pathway that can be activated under conditions of metabolic stress to inhibit cell death. It involves the lysosomal degradation of cytoplasmic proteins or entire organelles for catabolic regeneration of nutrient pools [61].
Blood–brain barrier (BBB): the permeability barrier arising from tight junctions between brain endothelial cells, restricting diffusion from blood to brain. Entry into the brain is limited to molecules that can diffuse across membranes (e.g., oxygen and other gases, or lipid-permeable compounds) or have transporter molecules (e.g., glucose transporters). Neuroactive compounds (e.g., glutamate or adrenalin) in the blood are restricted from entering into the brain.
Functional activation: a response by the brain to a specific stimulus (e.g., sensory stimulation) that increases cellular activity and metabolism above the 'resting' and/or baseline value before onset of the stimulus. Brain activation has the same meaning but is a more general term that includes increased activity during abnormal or disease states.
Glutamate–glutamine cycle: the release of the neurotransmitter glutamate from excitatory neurons, its sodium-dependent uptake by astrocytes, its conversion to glutamine by glutamine synthetase in astrocytes, the release of glutamine and uptake into neurons followed by the conversion to glutamate by glutaminase and its repackaging into synaptic vesicles.
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH): a glycolytic enzyme that reduces NAD^+ to NADH and converts D-glyceraldehyde-3-phosphate to 1,3-bisphospho-D-glycerate, an intermediary metabolite in the generation of pyruvate.
Glycolysis: a cytoplasmic pathway for metabolism of one molecule of glucose to produce two molecules of pyruvate, with phosphorylation of 2 ADP to form 2 ATP and reduction of 2 NAD^+ to 2 NADH. Cytoplasmic oxidation of NADH can be achieved by conversion of pyruvate to lactate by the LDH reaction or via the MAS (see Figure 2A in main text). The MAS is required to generate pyruvate for oxidation in the TCA cycle, whereas LDH removes this substrate from the cell. Net production of lactate in the presence of adequate levels and delivery of oxygen is sometimes termed 'aerobic' glycolysis, contrasting the massive production of lactate under hypoxia or anoxia ('anaerobic' glycolysis).
Hexokinase (HK): the enzyme catalyzing the first step in glucose metabolism: the irreversible conversion of glucose to Glc-6-P in an ATP-dependent reaction. The brain has different HK isoforms that have specific functions. HKI is the major isoform in brain for the glycolytic pathway; it has a broad substrate specificity and is feedback-inhibited by Glc-6-P. HKII is a minor, hypoxia-regulated isoform in the brain that controls neuronal survival depending on the metabolic state. HKIV (glucokinase, GK) is a minor isoform of hexokinase in the brain that has an important role in glucose-sensing neurons; it is specific for glucose and is not inhibited by Glc-6-P.
Ketogenic diet: a diet that has a high fat and low carbohydrate content so that plasma levels of ketone bodies (acetoacetate and β-hydroxybutyrate) increase and serve as alternative oxidative fuel.
Metabolic coupling: a synergistic interaction between different cells or cell types in which compounds produced in one cell are used by another cell.
Neurovascular unit: groups of neurons, astrocytes, endothelial cells, vascular smooth muscle cells, and pericytes that are involved in local signaling activities, metabolic interactions, and regulation of blood flow.
Tricarboxylic acid (TCA) cycle: a mitochondrial pathway for oxidation of pyruvate to produce 3 CO_2 and generate $FADH_2$ and NADH that are oxidized via the electron transport chain with conversion of oxygen to water and formation of approximately 32 ATP per glucose molecule. This ATP yield is less than the theoretical maximum due to proton leakage across the mitochondrial membrane.

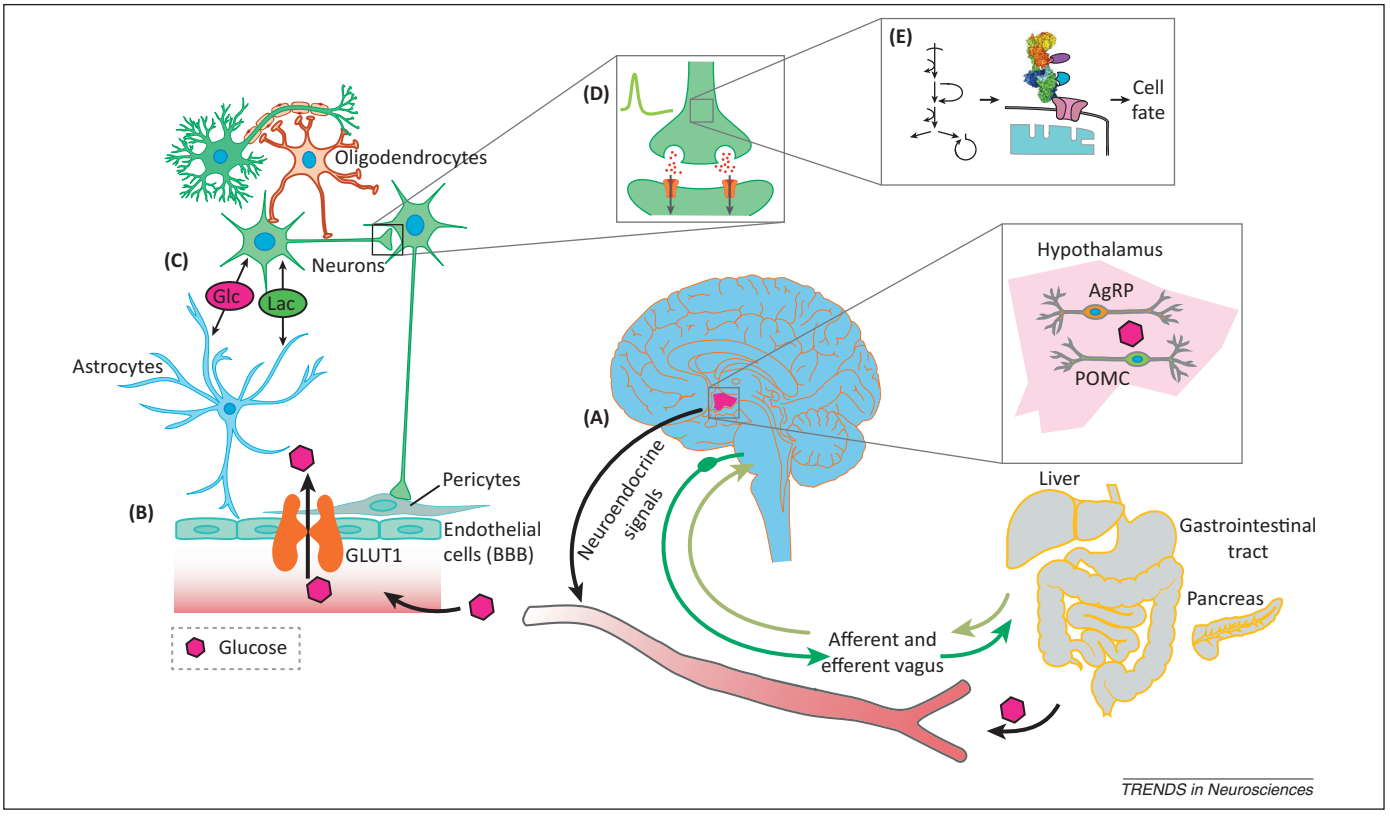

Figure 1. The role of glucose in brain function. Glucose (Glc) is the main source of energy for the mammalian brain. **(A)** Specialized centers in the brain, including pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons in the hypothalamus, sense central and peripheral glucose levels and regulate glucose metabolism through the vagal nerve as well as neuroendocrine signals. **(B)** Glucose supply to the brain is regulated by neurovascular coupling and may be modulated by metabolism-dependent and -independent mechanisms. Glucose enters the brain from the blood by crossing the blood–brain barrier (BBB) through glucose transporter 1 (GLUT1), and **(C)** glucose and other metabolites (e.g. lactate, Lac) are rapidly distributed through a highly coupled metabolic network of brain cells. **(D)** Glucose provides the energy for neurotransmission, and **(E)** several glucose-metabolizing enzymes control cellular survival. Disturbed glucose metabolism on any of these levels can be the foundation for the development of a large variety of disorders of the brain (see section on 'Disease mechanisms').

regulation of glucose metabolism is critical for brain physiology and disturbed glucose metabolism in the brain underlies several diseases affecting both the brain itself as well as the entire organism.

Here, we provide a comprehensive overview of the functional implications and recent advances in understanding the fundamental role of glucose metabolism in physiological and pathological brain function. Although brain energy metabolism has been investigated for decades, certain aspects remain controversial, in particular in the field of energy substrate consumption and utilization. It is beyond the scope of this review to resolve these controversies; rather, it is our aim to highlight conflicting concepts and results to stimulate discussion in key areas. To this end, we review the bioenergetics of neurotransmission, the cellular composition of a metabolic network, the regulation of cerebral blood flow (CBF), how peripheral glucose metabolism and energy homeostasis are sensed and controlled by the central nervous system (CNS), and the tight regulation of cellular survival through glucose-metabolizing enzymes.

Glucose is required to provide the precursors for neurotransmitter synthesis and the ATP to fuel their actions, as well as the energy demands of the brain that are not related to signaling. Cellular compartmentation of glucose transport and metabolism is intimately related to local regulation of blood flow, and glucose-sensing neurons govern the brain–body nutrient axis. Glucose metabolism is connected to cell death pathways by glucose-metabolizing enzymes. Thus, disruption of pathways of glucose delivery and metabolism leads to debilitating brain diseases. We highlight the multifaceted role and complex regulation of glucose metabolism in the CNS as well as the physiological and pathophysiological consequences of balanced and disturbed glucose metabolism (Figure 1).

Glucose metabolism: the bioenergetic basis for neurotransmission

The largest proportion of energy in the brain is consumed for neuronal computation and information processing [3]; for example, the generation of action potentials and postsynaptic potentials generated after synaptic events (Figure 1D), and the maintenance of ion gradients and neuronal resting potential [1,4]. Additionally, glucose metabolism provides the energy and precursors for the biosynthesis of neurotransmitters (for a comprehensive overview, see [5]). Importantly, astrocytic glycogen seems to be directly relevant for learning [6]. Furthermore, the glycolytic end-product lactate appears to have a role in long-term memory formation [7], although the exact mechanism has not yet been established. Lactate injections [7] alter the intracellular redox state and pH due to co-transport of H^+ with lactate, and lactate receptors may also have a role in linking brain energy metabolism and neurotransmission [8,9]. However, oxidative metabolism in both neurons and astrocytes appears to contribute to sustained learning effects after training, and glycogen can supply carbon for synthesis of glutamate during learning [6].