Lactate muscles its way into consciousness: fueling brain activation

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THE ENERGETICS OF NEURON-ASTROCYTE interactions during brain activation is an exciting but controversial topic because the idea that lactate might be a significant supplemental fuel challenges the long-held consensus that brain is strictly dependent on glucose as its obligatory fuel. Thus a “cellular menu” comprised of “sweet and sour food for thought” could be envisaged in which the traditional sweet brain foods, glucose and glycogen, might be combined with a sour ingredient, lactate, which is derived from glycolytic metabolism of glucose either within the brain, as proposed by studies described below, or by muscles during vigorous exercise, as reported in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology by Dalsgaard and colleagues (12). The uptake by brain of muscle-derived lactate during intense physical activity extends the “cell-cell and intracellular” lactate shuttle concepts recently reviewed by Brooks (4), in which lactate is recognized not as simply a dead-end metabolite formed during hypoxic-anoxic conditions, but rather, as an energy-rich intermediate or a precursor for gluconeogenesis that can be transferred within and among in normal, normoxic body tissues to maximize overall energy efficiency. Thus the flow of glucose-derived carbon through the glycolytic and oxidative pathways need not be continuous in a given cell, tissue, or organ. Instead, glycolysis might predominate in some subcellular structures, cells, regions, or conditions, whereas oxidative metabolism and resynthesis of glucose from circulating lactate might prevail in others. The possibility of activity-dependent and temporal-spatial partitioning of brain metabolism is an idea that has been evolving over time as different types of studies help elucidate the functional and interactive architecture of the brain’s cellular, neurotransmitter, and enzymatic systems (1, 3, 6–8, 14–16, 20, 21, 26, 35, 36).

It is well established that blood-borne glucose is the obligatory fuel for brain and, to satisfy the moment-to-moment changes in energy demand during information processing, the local rates of blood flow and glucose utilization are closely linked to the activities of brain cells; this coupling provides a means to measure functional activity under normal and pathophysiological conditions by metabolic imaging techniques (40). Because the blood-brain barrier restricts transfer of material from blood into brain, many compounds that are readily metabolized by cultured brain cells or brain slices, including lactate, cannot be transported into adult brain in vivo in sufficient quantities to compensate for inadequate levels of glucose and support the brain’s high and continuous energy demand. For this reason, the possibility that lactate synthesized within the brain might have an important role as an energy source during brain activation has received a lot of attention. This interest has been spurred by many types of studies, including support of synaptic function by lactate in brain slices (38); substrate transport and metabolism studies in cultured astrocytes and neurons carried out in many laboratories; and by a model, the key elements of which are derived from studies in cultured astrocytes, that portrays an astrocyte-neuron metabolic unit in which excitatory glutamatergic neurotransmission is linked to shuttling of lactate produced by astrocytes to neurons for oxidation (31, 35, 36). However, there are many critical unresolved issues related to this model (6, 14–16, 20, 21), especially two major concerns. First, metabolic responses to glutation exposure by astrocyte cultures grown in different laboratories are not consistent in magnitude or direction, suggesting differences in oxidative capacity or other properties of various astrocyte preparations and uncertainties of extrapolation of data obtained in vitro to characterize astrocytes that mature in vivo and function in their natural environment. Second, there is no direct experimental evidence for a targeted transfer of significant quantities of lactate specifically from one cell type to another in normal working brain in vivo. Furthermore, the disproportionate increase in the rate of utilization of glucose (CMRglc) compared with oxygen (CMRO2) in working brain in vivo (see below) demonstrates that there cannot be a tight spatial-temporal relationship between lactate synthesis and its oxidation in neighboring brain cells because oxygen consumption fails to match glucose utilization during activation. There are, however, normal physiological conditions in which lactate produced outside the brain can be a significant fuel, and an interesting series of studies designed, in part, to evaluate the energy cost of mental effort and central fatigue in human brain during and after vigorous physical activity by the Secher laboratory (reviewed in Ref. 34) has put a spotlight on muscle-derived lactate as a brain energy substrate during physical exertion.

A striking and unexpected finding during exhaustive exercise in humans, which causes blood lactate levels to rise markedly, is that uptake of lactate into brain is consistently associated with a substantial downward shift in the ratio of oxygen to carbohydrate utilization (10, 11, 34). Because lactate is an oxidative fuel and brain is generally considered to be a highly oxidative organ, uptake and metabolism of lactate derived from peripheral sources would be expected to raise oxygen consumption in proportion to the carbohydrate taken up into brain. Instead, as shown by Dalsgaard and colleagues (12) in this issue, the respiratory quotient is about one during both rest and exercise, indicating that carbohydrate is the major brain fuel, and the metabolic ratio, calculated as (oxygen/[glucose + 1/2 lactate]) from measured arteriovenous differences across the brain, falls from a resting value of about six (the theoretical maximum) to about three during forceful exercise; conceivably, this ratio might be reduced further if pyruvate released to blood by working muscle (24) is also taken up by brain. Despite its substantial uptake, lactate was previously shown not to accumulate in brain tissue or cerebrospinal fluid (11), suggesting that it is oxidized, perhaps sparing glucose for other uses. The quantity of the glucose taken up in...
excess of oxygen is large and similar in magnitude in subjects with or without β1-adrenergic blockade to attenuate cardiovascular response, reduce work capacity, and increase the “difficulty” of physical work; the “surplus” (i.e., nonoxidized) glucose approximates reported levels of brain glycogen concentration (12). However, the metabolic fate of lactate and excess glucose and the partitioning of these substrates among different types of brain cells are unknown.

In contrast to the endurance exercise studies described above, most investigations of brain activation involve stimulation of somatosensory pathways (e.g., touch, visual, auditory) or mental information processing (e.g., mental tests or tasks). In these studies, the experimental subjects are physically inactive, so their blood lactate levels would be low and net lactate transport into brain negligible or small. Nevertheless, disproportionate increases in the rate of glucose compared with oxygen utilization (i.e., a phenomenon sometimes called “aerobic glycolysis”) are observed during focal (19) or global (20) activation of normal, normoxic human brain. The stimulation paradigm, intensity, and sensory modality can influence the metabolic response to stimulation (21), but most studies observe a mismatch in the stoichiometry of oxygen-glucose utilization, particularly in the eye, which is highly glycolytic (15). When the basis for aerobic glycolysis that was induced in conscious rats by generalized somatosensory stimulation was examined, lactate uptake into brain was quite small and lactate accumulation in brain could account for only about half of the “excess” glucose (17, 30). Detailed analysis of metabolic changes during brain activation led to the discovery that resting glycogen levels in brain of carefully handled rats are three- to fourfold higher than generally recognized, 10–12 μmol/g (9), and similarly high brain glycogen levels are obtained by others (25). When the magnitude of brain glycolysis was included along with glucose in calculation of the oxygen/carbohydrate metabolic ratio during stimulation, the resulting value fell from ~5.2 to 3.5 (14, 15). Brain glycogen is synthesized and stored mainly in astrocytes, and in cultured astrocytes glycogen is degraded to lactate and released to the culture medium (18). However, the ultimate fate of the glycogen catabolized during sensory stimulation in brain in vivo is unknown; it cannot be accounted for by oxygen utilization, lactate efflux from brain to blood, or lactate accumulation in activated tissue. The lack of a stoichiometric rise in CMR₉, corresponding to glycolgenolysis indicates that the pyruvate/lactate derived from glycogen was probably not oxidized in neighboring neurons or astrocytes and suggests that the glycogen was used to supply energy to the working astrocytes, followed by rapid release and clearance of lactate from the activated tissue by unidentified routes (14–16).

Compartmentation of the cytosolic glycolytic pathways involved in glycolgenolysis and glucose utilization in working brain introduces more complexity into analysis of energetics of brain work. For example, the specific activity of lactate purified from rat brain after metabolic labeling with 6-[^14]C]glucose during sensory stimulation was one-half that of glucose, indicating that the lactate that accumulated in brain during activation was derived from blood-borne glucose, and the unlabeled pyruvate/lactate pool derived from glycolgenolysis did not mix with and dilute the ^14C-labeled lactate/pyruvate pool derived from blood-borne glucose (14, 15, 17). Segregation of glycogen and glucose metabolism is not unique to brain, and was first reported two decades ago in studies of vascular smooth muscle (27, 28). The two glycolytic pathways can operate simultaneously in smooth muscle and are differentially regulated; of special interest is the finding that glycogenolysis is associated with oxidative metabolism and CO₂ production, whereas lactate production from glucose is linked to Na⁺/K⁺-ATPase activity in K⁺-activated muscle (22, 23, 27, 28). In brain, the basis for glycogen-glucose compartmentation is not known but one could speculate that the separate glycolytic pathways might support different functions, perhaps in different cell types (neurons or astrocytes) or subcellular structures, such as astrocytic filopodia and endfeet. Fine processes (filopodia) of astrocytes surround synaptic structures and contain glutamate transporters, Na⁺/K⁺-ATPase, and glutamine synthetase but they are very thin processes with little cytoplasm and are devoid of mitochondria (13); filopodia are likely to be predominately glycolytic regions of the astrocyte. On the other hand, astrocytic endfeet surround the cerebral vasculature and should have preferential access to glucose and other substrates, such as lactate, entering brain from the blood. How astrocytes partition their fuel usage in subcellular structures is a difficult, unresolved issue, but astrocyte activation and the utilization and restoration of glycogen, the brain’s major energy reserve, appear to have key roles in the oxygen-glucose mismatch in working brain.

To summarize, lactate is an energy-rich compound that is “muscling its way into consciousness as food for thought,” as well as becoming a factor to be included in the design of new experiments by neuroscientists. The oxygen/carbohydrate metabolic ratio falls during brain activation in both sedentary and vigorously exercising subjects. During somatosensory activation of brain function, the CMR₀/CMR₉ ratio is reduced further by including glycogen with the quantity of carbohydrate consumed, whereas during intense muscular activity the lactate taken up into brain drives the metabolic ratio to a low level; if glycolgenolysis during severe exercise could be assayed in working human brain the true metabolic ratio might be well below 3. The basis for a stoichiometric mismatch is not well understood and appears to be linked, at least in part, to lactate production, trafficking, and oxidation at different sites in the brain and body.

The possibility that working astrocytes have a major role in energetics of brain activation and metabolic brain imaging is important because astrocytes are increasingly recognized as having critical roles in normal brain function, including regulation of the extracellular environment, synapse formation, microcirculation, and even neurotransmission (2, 32, 33, 37, 39, 41, 42). A single astrocyte in the hippocampal neuropil is likely to be in close proximity to more than 100,000 synapses (5), and astrocytes require ATP to respond to neuronal activity and interact with neurons and other astrocytes via signaling and metabolic pathways. Analysis of the cellular basis of functional metabolic activation in brain in vivo is an especially difficult problem due to the heterogeneity, compartmentation, and inaccessibility of brain structures and the requirement for comprehensive quantitative metabolic balance studies at a local level. It is obviously not sufficient just to measure changes in the levels of a few selected metabolites, and the contributions of other types of brain fuel, e.g., the monocarboxylic acids acetate and octanoate, which are preferentially oxidized by astrocytes, need to be included in the analysis.
The reactions and regulation of metabolic pathways are well established and glucose is clearly the essential fuel for brain, but the details of cellular and subcellular specialization that can confer local predominance of glycolytic and oxidative metabolism in specific domains of astrocytes and neurons as they interact are not well understood. In vivo assessment of brain activation in conscious subjects reveals previously undetected complexity of metabolism in brain and underscores the importance of functional studies within the normal environment of the living brain and active body. A challenge to researchers in this field is to devise new approaches for analysis of the functions and sites of lactate production, trafficking, and utilization in working brain in vivo, and these studies will undoubtably help understand the cellular physiology and biochemistry of astrocyte-neuron and brain-body interactions.

REFERENCES

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