

Metabolic Recruitment in Brain Tissue

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Keywords

neurons, astrocytes, glucose, lactate, oxygen, glycolysis, mitochondria

Abstract

Information processing imposes urgent metabolic demands on neurons, which have negligible energy stores and restricted access to fuel. Here, we discuss metabolic recruitment, the tissue-level phenomenon whereby active neurons harvest resources from their surroundings. The primary event is the neuronal release of K^+ that mirrors workload. Astrocytes sense K^+ in exquisite fashion thanks to their unique coexpression of NBCe1 and $\alpha 2\beta 2 Na^+/K^+$ ATPase, and within seconds switch to Crabtree metabolism, involving GLUT1, aerobic glycolysis, transient suppression of mitochondrial respiration, and lactate export. The lactate surge serves as a secondary recruiter by inhibiting glucose consumption in distant cells. Additional recruiters are glutamate, nitric oxide, and ammonium, which signal over different spatiotemporal domains. The net outcome of these events is that more glucose, lactate, and oxygen are made available. Metabolic recruitment works alongside neurovascular coupling and various averaging strategies to support the inordinate dynamic range of individual neurons.

ANLS:

astrocyte-to-neuron lactate shuttle; a model of brain metabolic coupling in which glutamate released by neurons stimulates astrocytic glycolysis and lactate production

NKA: Na^+/K^+

ATPase; a pump that modulates glycolysis and mitochondrial respiration by unknown mechanisms

INTRODUCTION

The metabolic rate is the speed at which cells live. It varies from cell to cell and from one moment to the next. It drops during sleep and rises when tissues are active, for example, during exercise for muscle, heart, and brain, or during food processing for the gut, liver, and fat. Every cell is equipped with homeostatic devices that adjust adenosine 5'-triphosphate (ATP) production to workload. This coupling may be so smooth that excitable cells may raise their work rate without detectable ATP depletion (1–3).

In relatively homogeneous organs such as heart and skeletal muscle, adjacent cells play similar roles. In the brain, adjacent cells behave differently. Neurons transit time and again between resting and activity and, in the process, are forced to deal with incremental energy demands that reach orders of magnitude (4, 5). Neurons do not have sizable energy stores and must constantly be supplied with fuel. Interposed between them and blood-borne nutrients are astrocytes (6, 7), which store glycogen, a polymer of glucose that is the organ's main energy reservoir (8, 9). In brain tissue the metabolic response is not just the algebraic sum of individual cell adaptations, but a higher-order phenomenon involving the division of labor between cell types (10–13). An early example of metabolic cooperation between cells is the astrocyte-to-neuron lactate shuttle (ANLS), the stimulation of astrocytic glucose consumption and lactate production mediated by the Na^+ /glutamate cotransporter (14, 15). The ability of glutamate, acting via its transporter, to impact the metabolism of astrocytes is modest compared to that of K^+ . Only three Na^+ ions enter the cell with each glutamate, a small number relative to the 150 Na^+ ions that are extruded per glutamate in exchange with K^+ at the astrocytic Na^+/K^+ ATPase (NKA), as detailed below. Another shortcoming of extracellular glutamate as a metabolic signal is poor correlation with workload. The extracellular concentration of glutamate may be a good proxy of the energy demand of synaptic boutons, but because of variable inhibitory input, it does not correlate well with the activity of dendrites and somata, where most of the energy is consumed (5, 16, 17), or with the metabolic demand at nonglutamatergic excitatory synapses. A third limitation is reach. Glutamate is extremely local, sensed by a single astrocyte (18); there is also the issue of speed. The glycolytic effect of glutamate on astrocytes takes minutes to kick in (19), too late to cater to the ATP demand of neurons, which peaks seconds after neurotransmission (1, 20, 21).

In this review, we argue that active neurons harvest glucose, lactate, and oxygen from astrocytes and neurons located beyond the active zone and that the main signal driving this fast metabolic recruitment is extracellular K^+ ($[\text{K}^+]_e$). The case for potassium-mediated recruitment rests on five pillars: (a) Elevated $[\text{K}^+]_e$ is a mirror of workload across the brain; (b) elevated $[\text{K}^+]_e$ reaches astrocytes beyond the active zone; (c) astrocytes are uniquely endowed to sense $[\text{K}^+]_e$; (d) the metabolism of astrocytes is acutely modulated by $[\text{K}^+]_e$; and (e) the metabolism of astrocytes and neurons is modulated by lactate, which serves as a secondary recruiter.

$[\text{K}^+]_e$ MIRRORS WORKLOAD

The excitatory postsynaptic potential, the main electric signal employed by neurons to pass information, is mediated by the influx of Na^+ and Ca^{2+} through α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) ionotropic glutamate receptors. Most of the Ca^{2+} load is swiftly transformed into a Na^+ load by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, and the Na^+ gradient is then restored by the NKA, the dominant energy sink of brain tissue (5, 16). In comparison, the energy consumption of axons and glial cells has been deemed modest (17; but see 22). What is sometimes overlooked is that AMPA and NMDA receptors conduct K^+ and that additional K^+ is released by active neurons through Ca^{2+} - and voltage-gated K^+ channels (23). In fact, electroneutrality dictates that the release of K^+ matches the entry of

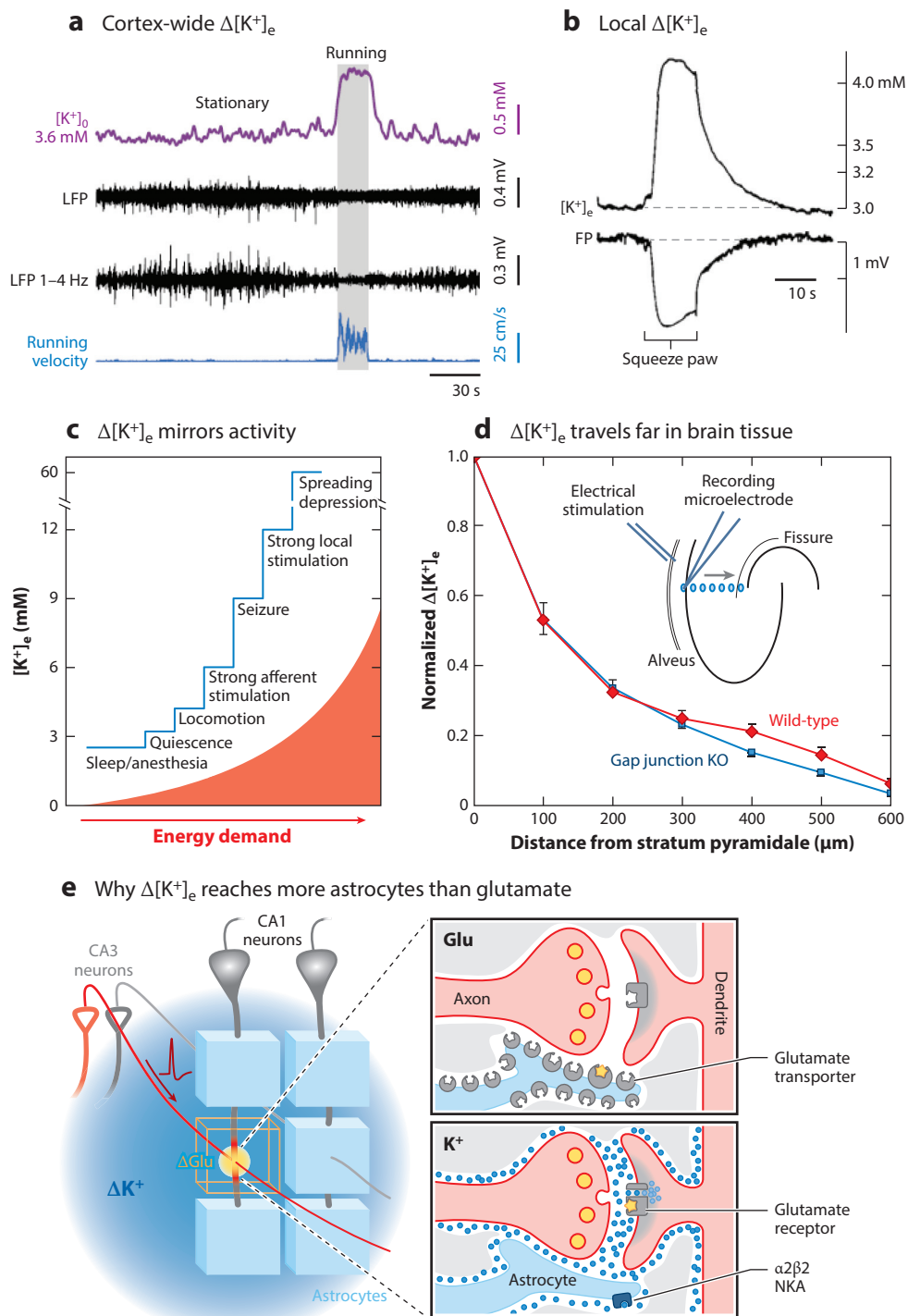
Na⁺ at approximately 100 ions per exocytosed glutamate (5). Therefore, [K⁺]_e amplifies the glutamate signal by two orders of magnitude, and because K⁺ efflux is inextricably coupled to the entry of Na⁺ that will be pumped out later on, the transformation of a presynaptic glutamate signal into an amplified postsynaptic extracellular K⁺ signal proceeds only if neurons require energy. This obligatory link existing between release and workload distinguishes K⁺ from glutamate. If glutamate fails to evoke a postsynaptic current because of coincident inhibitory input like gamma-aminobutyric acid (GABA) or ATP-sensitive potassium channel (K_{ATP}) activation, there will be no Na⁺ entry and workload, but astrocytes will still have to deal with the glutamate and GABA. Resting [K⁺]_e concentration is low, and therefore the release of K⁺ can cause a significant elevation of [K⁺]_e.

The dynamics of [K⁺]_e in brain tissue have been extensively characterized with microelectrodes and microdialysis probes, *ex vivo* and *in vivo*, most recently in awake animals (24–26). The blood–brain barrier permits autonomous regulation of brain [K⁺]_e, shielded from plasma fluctuations induced by exercise and food absorption. At 2.5–3 mM, the lowest [K⁺]_e is observed during deep sleep and anesthesia, ~40% lower than in plasma. Awakening elevates [K⁺]_e by 0.4–0.7 mM (27), and the transition from quiescence to locomotion adds an additional 0.7–1 mM, detected not just in motor cortex but in all cortical areas tested (26). These elevations occur within seconds and correlate with increased network activity (**Figure 1a**). Confirming a synaptic source, pharmacological blockage of excitatory neurotransmission inhibited the rise of [K⁺]_e induced by locomotion. On top of these cortex-wide state-dependent plateaus, transient [K⁺]_e elevations have been induced by a variety of paradigms (**Figure 1b**). For physiological stimuli, surges amount to 0.2–3 mM, reaching up to 12 mM during seizures, and a maximum of 60 mM in spreading depression (**Figure 1c**). A recent study based on genetically encoded voltage indicators indicates that local [K⁺]_e may reach up to 10 mM around perisynaptic astrocytic processes (28).

ELEVATED [K⁺]_e REACHES DISTANT ASTROCYTES

Over the sluggish timescale of metabolic events, glutamate and K⁺ may be said to arrive in the synaptic cleft simultaneously, but after that, their dynamics depart dramatically. While glutamate is removed within 1 ms, K⁺ diffuses for approximately 1–10 s (24, 29). Considering tissue tortuosity, diffusion coefficient, and diffusion half-time (24), K⁺ is estimated to travel 80–100 μm on average. This calculation fits the [K⁺]_e profile recorded with an electrode stepped through the hippocampus (**Figure 1d**). The removal of glutamate within 0.5–1 μm of the synaptic cleft (18) permits synaptic autonomy and is made possible by the combination of vanishingly low resting extracellular glutamate concentration and massive expression of Na⁺/glutamate cotransporters in astrocytes. These transporters are slow (70 ms per cycle) but they remove efficiently by trapping their ligand like sticky fly paper. Their resting occupancy is near zero, and there are enough of them around each synapse to handle the maximum speed of glutamate exocytosis (30). In contrast, K⁺ leaves the synaptic region unscathed. Whereas 100 K⁺ ions are released per glutamate, the astrocytic NKA, which is the main mechanism clearing synaptic and axonal K⁺ (31–35), is 100 times less abundant than the glutamate transporter (30, 36), a compounded factor of 10,000!

The strikingly different dynamics of glutamate and K⁺ are reflected in the behavior of astrocytic Na⁺. The three Na⁺ ions imported per glutamate by the Na⁺/glutamate cotransporter are very few compared to the 150 Na⁺ ions that would need to be extruded if all synaptic K⁺ ions were pumped by the NKA in the same local astrocyte that took up the glutamate. Nonetheless, in hippocampal astrocytes and cerebellar Bergmann glia exposed to glutamatergic activity, intracellular Na⁺ increases, a rise mediated by the Na⁺/glutamate cotransporter (37, 38). This observation confirms that, in the cells that take up all the glutamate, the NKA captures very little of the K⁺.



(Caption appears on following page)

Figure 1 (Figure appears on preceding page)

Extracellular K^+ ($[K^+]_e$) dynamics in nervous tissue. (a) Motor cortex $[K^+]_e$, local field potential (LFP), and velocity of a mouse before, during, and after running on a treadmill. Panel adapted with permission from Reference 26; copyright 2019 Elsevier. (b) Spinal cord $[K^+]_e$ and field potential (FP) in response to a noxious stimulus in an anesthetized cat. Panel adapted from Reference 132 (CC BY 4.0). (c) $[K^+]_e$ correlates with the degree of neural activity and the energy demand of the tissue across physiological to pathophysiological conditions. (d) Antidromical axonal K^+ release was triggered by electrical stimulation of the hippocampal alveus in the presence of synaptic blockers. $[K^+]_e$ was measured with a recording microelectrode stepped at 100- μ m intervals from the stratum pyramidale to the hippocampal fissure. Note the minor impact of connexin 30 and 43 genetic deletion [gap junction knockout (KO)] versus wild-type on the diffusion profile. Panel adapted from Reference 53; copyright 2006 Society for Neuroscience. (e) Representation of the hippocampal neuropil, where Schaffer collateral axons from CA3 pyramidal neurons make synaptic contact with dendrites from CA1 pyramidal neurons. While extracellular glutamate (Glu) is cleared by a small part of a single astrocyte (orange box), the $[K^+]_e$ rise reaches many astrocytes (blue boxes). (e, inset) Glu (top) is quickly captured by astrocytic Glu transporters. When an ionotropic glutamate receptor is engaged, $\sim 100 K^+$ ions are released for each Glu that is exocytosed (bottom). Astrocytes have ~ 100 times fewer Na^+/K^+ ATPase (NKA) pumps than glutamate transporters. The compounded 10,000 factor explains why glutamate is captured locally while most K^+ diffuses away.

Thus, while all the glutamate released at a given synapse is captured by the astrocyte that wraps that synapse, most K^+ is handled by distant astrocytes (Figure 1e).

EXQUISITE $[K^+]_e$ SENSING BY ASTROCYTES

Seconds after successful excitatory neurotransmission, a wave of K^+ reaches the surface of astrocytes. High expression of constitutively open K^+ channels and a lack of other significant ion permeabilities makes these cells virtual Nernstian electrodes (24, 25, 39) (Figure 2a). The ensuing depolarization of the astrocytic plasma membrane engages the NKA and the Na^+ /bicarbonate cotransporter.

The clearance of synaptic K^+ by astrocytes instead of neurons is explained by NKA subtype allocation (33, 40–42) (Figure 2b). The neuronal NKA ($\alpha 3\beta 1$) does not respond well to K^+ because its high-affinity site is permanently saturated, but it is sensitive to intracellular Na^+ . Conversely, the major astrocytic NKA ($\alpha 2\beta 2$) is substantially saturated by intracellular Na^+ and ready to respond to $[K^+]_e$, for which it has low affinity. Moreover, $\alpha 2\beta 2$ is sensitive to depolarization, whereas $\alpha 3\beta 1$ is not (33, 42), and the astrocytic membrane potential is four times more sensitive to $[K^+]_e$ than that of neurons (43). The compounded result is that the astrocytic NKA is 18 times more sensitive to $[K^+]_e$ than the neuronal NKA (22). Synaptic activity causes astrocytic swelling (34), which is largely explained by the influx of Na^+ and bicarbonate via the electrogenic Na^+/HCO_3^- cotransporter 1 (NBCe1) and by metabolic stimulation (44, 45). Part of the Na^+ for the NKA may be provided by voltage-sensitive Na^+ channels, transient receptor potential (TRP) channels, and the Na^+/Ca^{2+} exchanger (46–48).

Another mechanism of K^+ clearance is spatial buffering, with the diffusion into astrocytes and other glial cells facilitated by constitutively open Kir4.1 potassium channels (49). Spatial buffering is considered relevant in the highly polarized retina (50) but no longer relevant in brain tissue. The main roles of Kir4.1 in astrocytes and oligodendrocytes are to set the membrane potential, to limit the amplitude of the $[K^+]_e$ rise under high frequency stimulation, and to mediate the delayed release of K^+ , which is then captured by neurons to complete the K^+ cycle (31, 35, 48, 51–53). Worth noting is that a buffering role for Kir4.1 channels was sometimes deduced upon sensitivity to Ba^{2+} , but given the membrane potential sensitivity of $\alpha 2\beta 2$ (Figure 2b), the astrocytic effects of Ba^{2+} might also be explained by NKA modulation. The $Na^+-K^+-2Cl^-$ cotransporter, once deemed to be a significant K^+ clearance mechanism, plays a role in developing astrocytes, glioma

NBCe1: electrogenic Na^+/HCO_3^- cotransporter 1; abundant in astrocytes, it transduces $[K^+]_e$ into cytosolic pH

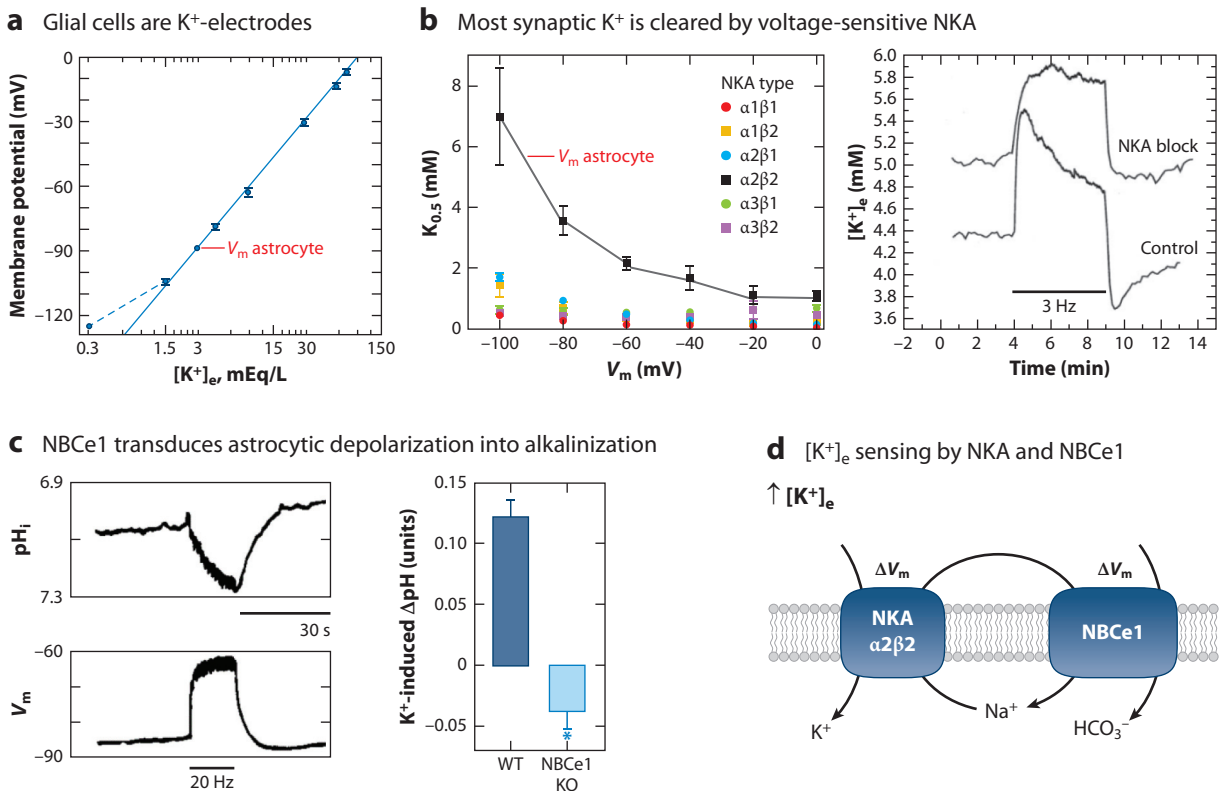


Figure 2

Extracellular K^+ ($[K^+]_e$) sensing by astrocytes. (a) Relation between $[K^+]_e$ and the glial membrane potential in the optic nerve of *Necturus*. The solid line has a slope of 59 mV according to the Nernst equation for a K^+ -selective electrode. The typical resting membrane potential (V_m) of astrocytes is indicated. Panel adapted from Reference 39 (CC BY 4.0). (b, left) Voltage dependence of the K^+ half saturation constant ($K_{0.5}$) of rat Na^+/K^+ ATPase (NKA) isoform combinations expressed in *Xenopus laevis* oocytes, with $\alpha 2\beta 2$ being the type found in mature astrocytes. The typical resting V_m of astrocytes is indicated. Panel adapted with permission from Reference 33; copyright 2014 Wiley. (b, right) Effect of neuronal stimulation (3 Hz) on hippocampal $[K^+]_e$, before (control) and during incubation with the NKA blocker dihydro-ouabain (5 μ M). Panel adapted from Reference 31 (CC BY 4.0). (c, left) Effect of surface brain stimulation (20 Hz) on the V_m and intracellular pH (pH_i) of cortical astrocytes measured with microelectrodes. Panel adapted with permission from Reference 54; copyright 1989 Society for Neuroscience. (c, right) Effect of elevated $[K^+]_e$ (3 to 15 mM) on the pH of astrocytes cultured from control wild-type (WT) and Na^+/HCO_3^- cotransporter (NBCe1) knockout (KO) mice. Panel adapted from Reference 57. (d) Elevated $[K^+]_e$ is sensed by astrocytes, directly via the K^+ -transport site at the NKA $\alpha 2\beta 2$, and indirectly via the voltage sensitivity of both the NKA $\alpha 2\beta 2$ and the NBCe1. Na^+ entering through the NBCe1 is recycled by the NKA.

cells, and optic nerve but not in adult gray matter (35, 48). The revised role of the astrocytic NKA, versus Kir4.1 channels, in the clearance of synaptic K^+ means that astrocytes take a much larger share of the brain's energy budget than anticipated (22).

The second astrocytic surface sensor with metabolic significance is the NBCe1. This protein, which is abundantly expressed in astrocytes and equivalent glial cells from nematodes to mammals, mediates the simultaneous translocation of one Na^+ and two HCO_3^- . In resting astrocytes, the NBCe1 is close to thermodynamic equilibrium and therefore catalytically silent. Upon depolarization by elevated $[K^+]_e$, the NBCe1 takes up Na^+ and HCO_3^- . Na^+ is recycled by the NKA, and the HCO_3^- causes intracellular alkalinization (54–57) (Figure 2c). The NBCe1 works in parallel with the NKA $\alpha 2\beta 2$ to transduce elevated $[K^+]_e$ into a metabolic response (Figure 2d).

PRIMARY METABOLIC RECRUITMENT

Early Dismissal of $[K^+]_e$ as a Metabolic Signal

Whereas the importance of local K^+ in neurovascular coupling has been recognized (48, 58–60), acceptance of its metabolic role has lagged. Ever since Louis Sokoloff and colleagues introduced brain mapping with isotopic 2-deoxyglucose (61, 62), questions were asked about the mechanisms underlying activity-dependent metabolism and their relationship with information processing. A first clue was the observation that in vitro electrical stimulation of the axon-rich neurohypophysis led to deoxyglucose-6-phosphate accumulation, which was abolished by ouabain (63). Pushed to its limit by means of tissue section tractography, the 2-deoxyglucose method showed similar rates of glucose consumption in neurons and astrocytes (64), a surprising result given the ostensibly larger energy demand of neurons. Neurons do not thrive in isolation, and astrocytes are easier to culture and may be passaged to obtain the large numbers required by isotopic measurements; hence, the metabolism of astrocytes is better known than that of neurons. Applied to astrocyte cultures, the 2-deoxyglucose method showed that glucose consumption is sensitive to NKA inhibition. Significantly, the astrocytic NKA was found to respond well to intracellular Na^+ but little, or not at all, to $[K^+]_e$, even at pathophysiological levels observed in seizures and spreading depression (65–68). At the same time, Pellerin & Magistretti (14) observed substantial stimulation of 2-deoxyglucose uptake in cultured astrocytes that was mediated by glutamate via the Na^+ /glutamate cotransporter, intracellular Na^+ accumulation, and NKA activation. The glutamate experiment was soon reproduced by Sokoloff and colleagues, who concluded that “the stimulation (of glycolysis) is due not to increased $[K^+]_e$ but rather to another mechanism, such as the release of glutamate and/or possibly other neurotransmitters that promote Na^+ entry into the cells” (67, p. 4620). As elsewhere, the astrocytic NKA was assumed to be driven by intracellular Na^+ , with K^+ being dismissed as a permissive cofactor; hence, its still popular short name is Na^+ pump, as opposed to K^+ pump.

Acute Modulation of Astrocytic Energy Metabolism by $[K^+]_e$

There is now evidence that the reported insensitivity of astrocytic metabolism to K^+ was an artifact. Astrocytes cultured in the absence of neurons, as required for the 2-deoxyglucose assay, fail to express $\alpha 2\beta 2$ (69, 70), which is the type of NKA that confers sensitivity to $[K^+]_e$ and to depolarization (33, 40–42). In addition, the trophic presence of neurons is required for the correct metabolic maturation of astrocytes (71, 72), and for practical reasons some studies used 5.4 mM as resting $[K^+]_e$ instead of the 2.5–3 mM prevalent in brain interstice. Thus, these resting astrocytes were already stimulated by K^+ . Demonstration of the metabolic importance of $[K^+]_e$ had to wait for real-time assays capable of probing astrocytic transport and metabolism in the presence of neurons. Förster or fluorescence resonance energy transfer (FRET) microscopy used with a genetically encoded FRET sensor for glucose (73; see the sidebar titled Visualizing Metabolism)

VISUALIZING METABOLISM

Genetically encoded fluorescent sensors are giving fresh impetus to the study of metabolism and its regulation. These sensors are fusion proteins composed of one or two fluorescent proteins and a ligand-binding protein, typically a bacterial periplasmic protein or transcription factor. Binding of the ligand, e.g., glucose, induces a change in fluorescence that is detected by microscopy. Usually expressed by means of viral vectors, these minimally invasive tools can monitor metabolite levels within identified cells and subcellular organelles in real time, in vitro and in vivo. A comprehensive review of the more than 50 metabolite sensors that have been validated in mammalian cells, as well as their strengths and pitfalls, is available (148). Once the turf of biochemists, metabolism is becoming a subject of interest for cell physiologists.

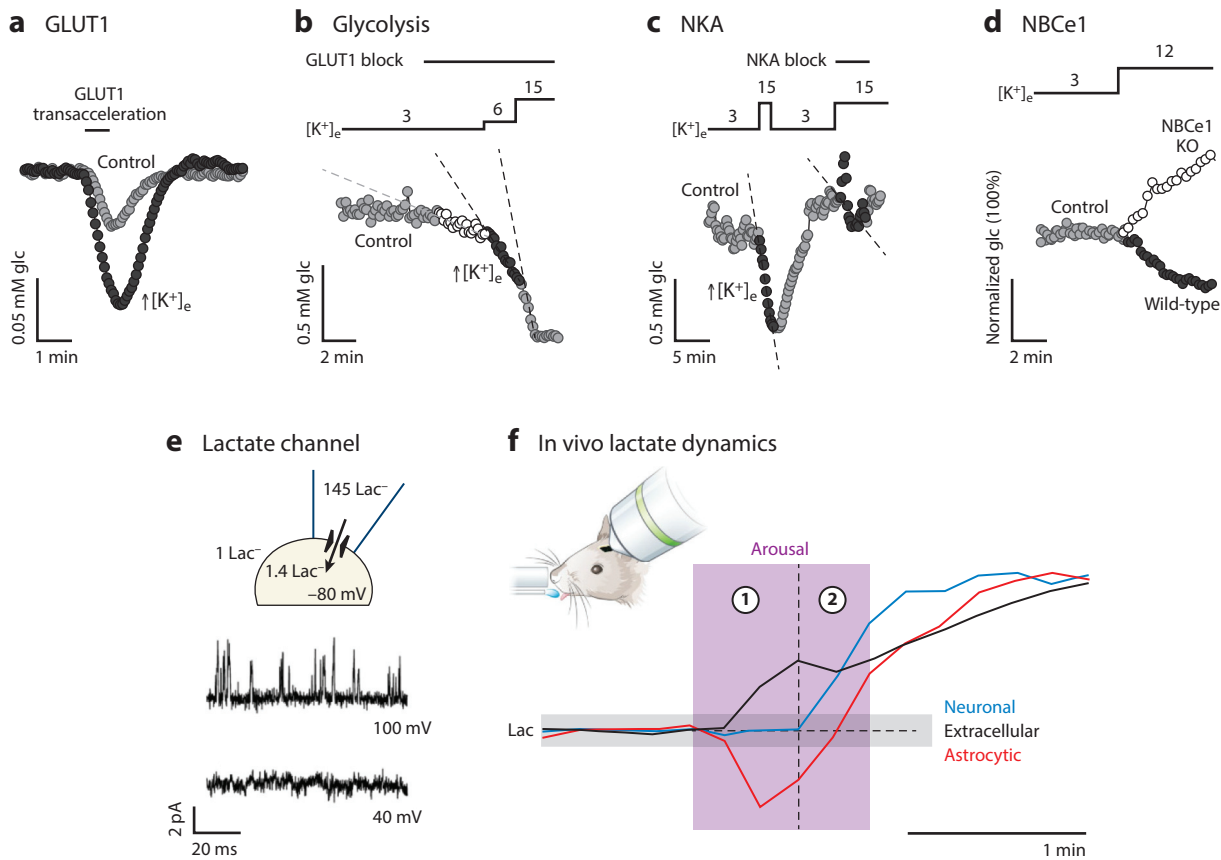


Figure 3

Metabolic effectors of elevated extracellular K⁺ ([K⁺]_e) in mouse astrocytes. (*a*) Glucose transporter isoform 1 (GLUT1) permeability, estimated as the rate of glucose transacceleration (accelerated exchange) induced with 3-*O*-methylglucose, was stimulated when [K⁺]_e was increased from 3 mM (*gray circles*) to 12 mM (*black circles*). Cytosolic glucose (glc) was measured with a genetically encoded Förster or fluorescence resonance energy transfer (FRET) sensor for glucose. Panel adapted from Reference 74. (*b*) The speed of glycolysis was measured in a cultured mouse astrocyte with the same sensor used in panel *a* as the rate of glc depletion induced by GLUT1 blockage with cytochalasin B (20 μM). Exposure to elevated [K⁺]_e (in mM) stimulated glucose consumption in a dose-dependent manner. Panel adapted from Reference 19. (*c*) The stimulation of glycolysis in a cultured mouse astrocyte caused rapid glucose depletion, which was curtailed in the presence of the Na⁺/K⁺ ATPase (NKA) blocker ouabain (1 mM). Panel adapted from Reference 19. (*d*) Glucose depletion induced by elevated [K⁺]_e in wild-type mice reverted to a glucose rise in Na⁺/HCO₃⁻ cotransporter (NBCe1) knockout (KO) mice. Panel adapted from Reference 57. The rise is likely explained by unopposed GLUT1 stimulation (74). (*e*) Cell-attached patch-clamp recording of an astrocyte showing lactate (Lac) currents. Panel adapted from Reference 99. (*f*) Astrocytic, neuronal, and extracellular lactate were measured in the somatosensory cortex of an awake mouse using a genetically encoded FRET sensor for lactate and a microelectrode. Arousal induced by an isoflurane pulse (1.5%) led to astrocytic lactate depletion and extracellular lactate accumulation, which were followed by neuronal lactate accumulation. Panel adapted from Reference 83.

and in a minimally invasive protocol based on substrate transacceleration showed that elevated [K⁺]_e stimulated the astrocytic glucose transporter 1 (GLUT1) (74) (**Figure 3a**). Whether or not astrocytes control the delivery of blood-borne glucose to neurons is not clear, as it is determined by how much of the capillary is covered by astrocytic endfeet (75, 76), a measurement that has been challenging (7, 77). Glycolysis can also be studied with a FRET glucose sensor. In this case, cells are first exposed to a GLUT1 blocker, leading to a steady decrease in cytosolic glucose as

hexokinase phosphorylates the hexose (78). Applying this transport-stop assay, researchers found that elevated $[K^+]_e$ stimulated the glycolytic rate of cultured astrocytes by more than 300% within seconds (19, 57, 79) (**Figure 3b**). Confirmed in brain tissue slices (79–81) and associated with rapid lactate fluctuations in awake animals (82, 83), the astrocytic effect of K^+ is a strong candidate to explain the intriguing phenomenon of aerobic glycolysis (84, 85).

$[K^+]_e$ Is Transduced into a Metabolic Signal by the NKA and NBCe1

Consistent with NKA involvement, the stimulation of astrocytic glycolysis by K^+ is blocked by ouabain (19) (**Figure 3c**). The mechanistic link between the pump and glycolytic machinery is not obvious. According to classic biochemistry, glycolysis is primarily regulated by adenine nucleotides, and ATP is indeed depleted in glutamate-treated astrocytes (80, 86, 87). However, in astrocytes exposed to elevated $[K^+]_e$, ATP levels actually rise (80, 88), which means that adenine nucleotides are not the signal between the astrocytic NKA and K^+ -stimulated glycolysis. This nagging knowledge gap between the transduction of extracellular signals at the cell surface and the metabolic machinery is also present in neurons (1, 89). In addition to NKA $\alpha 2\beta 2$ engagement, the stimulation of astrocytic glycolysis by $[K^+]_e$ requires coactivation of the NBCe1, as demonstrated in culture and tissue slices by functional, pharmacological, and genetic means (57, 79) (**Figure 3d**). The strong glycolytic response to cytosolic alkalization by means other than K^+ (57), the exquisite in vitro pH sensitivity of phosphofructokinase (90), and the alkalization of astrocytes in response to neural activity recorded in vivo (54, 91) suggest that pH may have an important role in the stimulation of glycolysis by elevated $[K^+]_e$. A recent in vivo study showed that subpopulations of cortical astrocytes may be defined based on whether they respond to physiological afferent stimulation with alkalization or with acidification (92). $[K^+]_e$, acting via the NBCe1 and the HCO_3^- -responsive soluble adenylyl cyclase, was proposed to mobilize glycogen (93), but the pharmacology that supports this possibility has been challenged (94). Glycogen mobilization by cAMP requires a coincidental Ca^{2+} rise (95, 96), which is not present in K^+ -stimulated astrocytes (48), so the soluble adenylyl cyclase pathway may perhaps be more relevant in glutamate-stimulated astrocytes, which do mobilize Ca^{2+} . The metabolic role of the NBCe1 goes beyond K^+ , as the rise in cytosolic NADH elicited by glutamate and ATP is also sensitive to functional and pharmacological inhibition of NBCe1 (81).

The Astrocytic Lactate Reservoir Is Mobilized by $[K^+]_e$

Astrocytes maintain higher steady-state lactate levels than neurons (97), a gradient also observed between glial cells and neurons in *Drosophila* (98). In cultured astrocytes, this lactate reservoir is acutely mobilized by elevated $[K^+]_e$, via a 37-pS, lactate-permeable anion channel that is gated by depolarization and extracellular lactate (99) (**Figure 3e**). The lactate channel, which is yet to be identified at the molecular level, moves lactate 1,000 times faster than monocarboxylate transporter 1 (MCT1) and 4 (MCT4), the isoforms of the H^+ -lactate symporter identified in astrocytes. Unlike MCTs, which are electroneutral, the lactate channel is capable of extruding lactate against a tenfold concentration gradient, using the membrane potential as a driving force. Expression of the channel may explain how mature astrocytes can export lactate efficiently despite the lack of detectable MCT4 messenger RNA (mRNA) expression (100) and the insensitivity of tissue lactate release to MCT blockers (101). A 1-mM rise in $[K^+]_e$ was sufficient to cause a lactate dip via the lactate-permeable channel (99), thereby releasing the tonic inhibition of glycolysis by the metabolite (102). Lactate may also be released by astrocytes via pannexin hemichannels in an activity-dependent fashion and in response to hypoxia (101). In awake mice under two-photon microscopy, the astrocytic lactate dip elicited by arousal was found to coincide with the

GLUT1: glucose transporter 1 is an isoform of the facilitative glucose transporter expressed in astrocytes, oligodendrocytes, and endothelial cells; neurons mainly express GLUT3

Crabtree effect:

inhibition of mitochondrial respiration by glucose, which in astrocytes is triggered by high $[K^+]_e$

extracellular lactate surge that accompanies neural activity (82, 83, 103). These immediate responses were followed by sequential increases in astrocytic and neuronal lactate, respectively explained by glycolytic stimulation in astrocytes and lactate influx in neurons (**Figure 3f**).

Mitochondrial Modulation by $[K^+]_e$

The most recently identified metabolic target of $[K^+]_e$ is the mitochondrion (80). Within seconds of exposure, the oxygen consumption of cultured astrocytes was reduced by 30% alongside a parallel reduction in mitochondrial pyruvate consumption. In hippocampal slices preincubated with tetrodotoxin to block the neuronal response, the inhibition of astrocytic respiration was evident as a rise in tissue oxygen level in response to elevated $[K^+]_e$. Consistently, experiments *in vivo* have shown that genetic ablation of astrocytic NBCe1 transformed the activity-dependent oxygen rise into an oxygen dip (104).

In longer observation periods *in vivo*, astrocytic mitochondrial metabolism was reported to increase (105). The acute reduction in mitochondrial oxygen consumption was found to be secondary to the NBCe1-dependent stimulation of glycolysis described above, possibly acting via a reduced cytosolic ADP/ATP ratio. This type of aerobic glycolysis may be understood as a regulated variant of the Crabtree effect (**Figure 4**), a phenomenon present in yeast and tumor cells in which mitochondria are suppressed by the glycolytic flux. This differs from the Warburg effect, where a primary change in mitochondria leads to augmented glycolysis (106).

Additional Primary Recruiters

Other intercellular signals capable of exerting acute metabolic effects on astrocytes are ammonium (NH_4^+) and nitric oxide. Neurons produce as much NH_4^+ as glutamate, a stoichiometry dictated

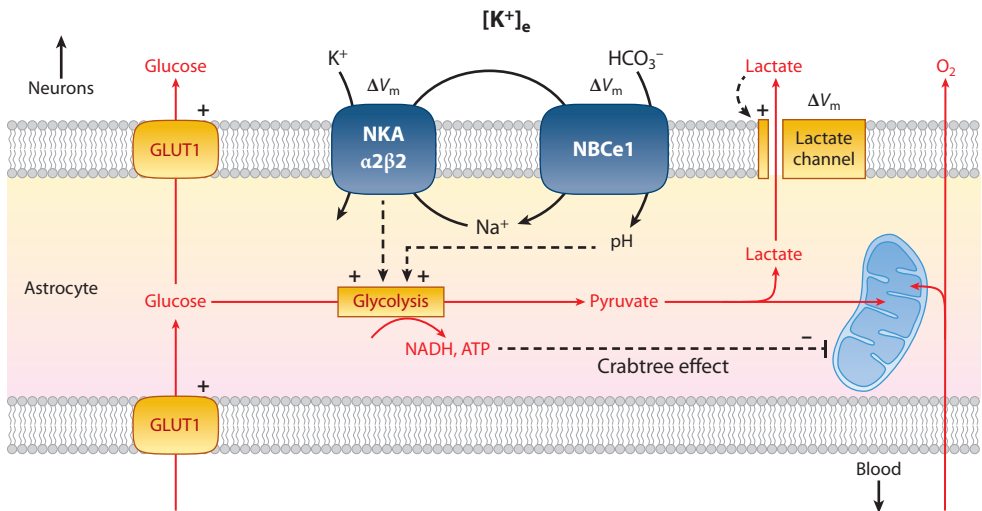


Figure 4

Modulation of astrocytic energy metabolism by extracellular K^+ ($[K^+]_e$). Glycolysis is stimulated by high $[K^+]_e$ via Na^+/K^+ ATPase (NKA) and Na^+/HCO_3^- cotransporter 1 (NBCe1). Elevated $[K^+]_e$ also stimulates glucose transporter 1 (GLUT1) via an unknown mechanism, while triggering the opening of a lactate channel via depolarization and gating by extracellular lactate. The increased production of glycolytic ATP and NADH results in reduced oxygen consumption by mitochondria, a variant of the Crabtree effect. Overall, the metabolic effect of high $[K^+]_e$ on astrocytes is to increase the availability of lactate, glucose, and oxygen.

by the glutamate-glutamine cycle (107). It was once thought that the NH_4^+ resulting from the neuronal conversion of glutamine into glutamate might return to astrocytes in the form of amino acids, but that possibility has been challenged (108), whereas a substantial increase in neural tissue NH_4^+ is measured within seconds of stimulation (109–111). An important albeit neglected subject is the neuronal release of NH_4^+ , via possible mechanisms such as its corelease with glutamate by synaptic vesicle fusion and its release via NH_4^+ -permeable ion channels (112). NH_4^+ is similar in size and charge to K^+ and is a good substrate for the NKA, K^+ channels, and transporters (113, 114). The metabolic impact of NH_4^+ was recently studied with genetically encoded sensors in cultured cells and tissue slices. At physiological concentrations NH_4^+ was found to inhibit the uptake of pyruvate by astrocytic mitochondria, resulting in augmented lactate production, thus contributing to aerobic glycolysis (115). Nitric oxide is also capable of inhibiting astrocytic respiration (116), acutely and at physiological levels (117). Nitric oxide interferes directly with complex IV of the mitochondrial respiratory chain, resulting in augmented lactate production. Because the strongest source of nitric oxide in brain tissue is in the vascular endothelium, nitric oxide may contribute to refilling the astrocytic lactate reservoir while increasing the availability of oxygen for cells situated deeper in the parenchyma (117, 118). Future research will clarify how NH_4^+ and nitric oxide articulate with K^+ and glutamate, as well as with slow-acting factors like Wnt (119), brain-derived neurotrophic factor (120), and cannabinoids (121), to account for the complex metabolic changes required for sustained brain tissue performance and plasticity (82, 122–124).

In summary, the unique combination of strong NKA $\alpha 2\beta 2$ and NBCe1 expression in astrocytes makes glycolysis in these cells exquisitely sensitive to elevated $[\text{K}^+]_e$. In addition, elevated $[\text{K}^+]_e$ supports the glycolytic flux at both ends by delivering glucose via GLUT1 activation and by removing lactate via opening of the lactate channel. The result is accumulation of ATP and NADH, inhibition of mitochondrial respiration, and sparing of oxygen. This may be understood as a feed-forward regulatory mechanism whereby neurons use $[\text{K}^+]_e$ to recruit lactate, glucose, and oxygen when their energy demand is highest (**Figure 4**). The occurrence of aerobic glycolysis (84), i.e., glucose consumption in excess of oxygen consumption, may seem counterintuitive, as glycolysis is 15 times less efficient at producing ATP than oxidative phosphorylation. But the turnover time of oxygen is about 1 s, whereas that of glucose and lactate is measured in minutes (125). Aerobic glycolysis is not an efficient way to metabolize glucose but makes sense as a strategy to procure oxygen for active neurons. Consistent with this view, the local rise in tissue oxygen level that is observed during neural activity (126) reverted into an oxygen dip in NBCe1 knockout mice (104).

SECONDARY METABOLIC RECRUITMENT

Astrocytes located beyond the direct reach of high K^+ are also recruited. Neural activity decreases extracellular glucose (82, 127), creating a diffusional sink. If astrocytic glucose were also depleted, as suggested by results in culture and in tissue slices (19, 57, 79), additional glucose may be drawn in via gap junctions (128–130), a possibility awaiting the experimental demonstration of interastrocytic glucose gradients in vivo. Lactate may also be recruited. The astrocytic depletion of lactate near the active zone, which has been observed in culture, in slices and in awake animals, is predicted to create a sink. Lactate is negatively charged, and therefore its mobility toward the active zone should be further facilitated by the voltage gradient between resting astrocytes and depolarized astrocytes. The role of gap junctions in the delivery of lactate to support synaptic transmission and plasticity was found to be compromised by acute stress (131).

Lactate itself behaves as a secondary signal for metabolic recruitment. Lactate is released in a much wider region than K^+ and diffuses in the interstice for minutes instead of seconds (83, 132), so its distribution volume is much larger. When coincident with elevated $[\text{K}^+]_e$, lactate is actively

extruded from astrocytes (83, 99), which fosters their aerobic glycolysis by feedback derepression of glycolysis (102). In resting areas, i.e., beyond the reach of K^+ , lactate reduces astrocytic and neuronal glucose consumption (1, 102), saving sugar for the active zone. Further sparing of fuel and oxygen may result from inhibition of neuronal activity through the G protein-coupled receptor HCAR1 (133–135). In contrast, the firing of active neurons is stimulated through positive modulation of the NMDA receptor by cytosolic NADH (136) and by spike facilitation mediated by the K_{ATP} channel (137). In addition, lactate was found to induce synapse-specific potentiation on cornu ammonis (CA3) pyramidal cells of the hippocampus through a cascade involving surface lactate receptors, G protein $\beta\gamma$ subunits, inositol-1,4,5-trisphosphate 3-kinase, protein kinase C, and Ca^{2+} /calmodulin protein kinase II (CaMKII) (138).

A HIERARCHY OF METABOLIC COUPLING

Metabolic recruitment may be understood in the wider context of neurometabolic coupling (Figure 5). The lowest echelon is the intrinsic, cell-autonomous neuronal response, whereby

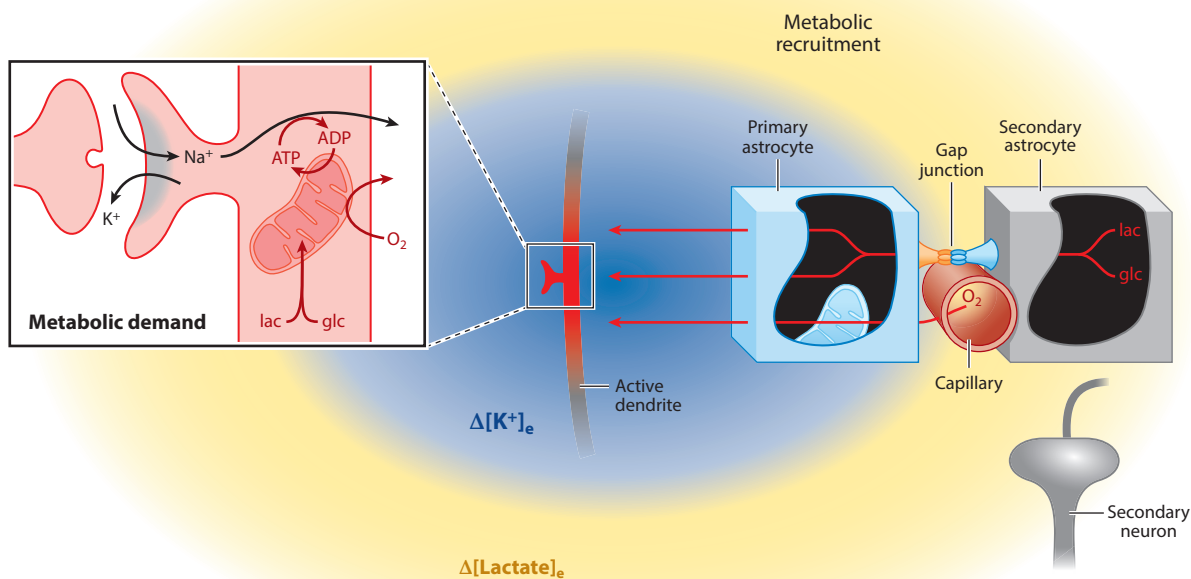


Figure 5

Primary and secondary metabolic recruitment. Excitatory postsynaptic potentials cause somatodendritic Na^+ accumulation and metabolic demand. Meanwhile, K^+ is released to the extracellular space. Elevated extracellular K^+ ($[K^+]_e$) modulates the metabolism of astrocytes, increasing the availability of lactate (lac), glucose (glc), and oxygen (primary recruitment). Lactate released by primary astrocytes inhibits the consumption of glucose by resting astrocytes and neurons and reduces the electrical activity of nonstimulated neurons (secondary recruitment). Reactive hyperemia further increases oxygen availability.

mitochondrial ATP production is quickly adjusted to the demand imposed by glutamate receptor ion channels via intracellular Na^+ and the NKA (1, 139) (see the inset in **Figure 5**). Superimposed to the neuronal response is metabolic recruitment. Here, postsynaptic neurons use K^+ acutely to harvest glucose, lactate, and oxygen from multiple astrocytes located beyond the active zone (primary recruitment). Depending on the neuronal compartment activated, K^+ is released via ionotropic receptors and/or K^+ channels. Distant resting astrocytes and neurons that lie beyond the reach of K^+ are recruited by lactate (secondary recruitment). The extended reach and short time course of metabolic recruitment are similar to those of the local vasodilation that underlies the blood-oxygen-level-dependent (BOLD) phenomenon and functional magnetic resonance imaging (126), in which $[\text{K}^+]_e$ is also a major player (48, 58–60). Minutes after these fast responses are over, glutamate transporter–mediated ANLS delivers lactate for long-lasting neuronal fueling and plasticity (14, 15, 19) (**Figure 5b**). Similarly, the stimulation of the NMDA receptor of oligodendrocytes by glutamate caused GLUT1 translocation to the cell surface and augmented intracellular glucose with a half time of several minutes (140).

The energy consumption of the brain is remarkably flat, a difference of just 15% between deep sleep and wake. Nonetheless, individual neurons are known to increase their metabolic demand by several orders of magnitude. Macroscopic stability in the face of microscopic dynamism has been explained by several instances of averaging over space and time. One of them is lateral inhibition, where neurons actively inhibit neighboring neurons (141). A related concept is limited processing capacity (142), where the activation of a neuronal network is balanced by the inactivation of another. A near-infrared spectroscopy study in human subjects has provided a metabolic underpinning to this idea by showing that increased mitochondrial oxidative metabolism triggered by visual attention concurs with a reduction in mitochondrial metabolism associated with a parallel nonattended task (143). In view of the metabolic effects of K^+ and lactate, it seems reasonable to speculate that these signals may also be involved in setting the limits of brain tissue performance. Another strategy to cope with the large dynamic range of neurons is sparse coding, whereby information is encoded by only a few neurons at any given time (144, 145). And of course, there is neurovascular coupling, which recruits oxygen and fuel from the greater body reservoir (48, 58–60). Metabolic recruitment may be understood as a fundamental averaging strategy, working in parallel with lateral inhibition, competing network inactivation, sparse coding, and neurovascular coupling to sustain the ample dynamic range of individual neurons.

PERSPECTIVES

Following the mapping of the metabolic network in the heyday of classic biochemistry, radio-labeled metabolites helped to understand the gross compartmentation of metabolism and its idiosyncrasies in brain tissue (146, 147). The advent of genetically encoded fluorescent sensors and parallel progress in viral vector delivery and time-lapse microscopy have made it possible to monitor glucose, ATP, NADH, lactate, pyruvate, and other metabolites in identified cells and in real time (148). These tools have helped to unveil some of the rapid events described in this review, but we have not yet started to exploit their capabilities to investigate regional specializations (149), the behavior of subtypes of neurons and astrocytes (150), and the more subtle signaling events that evolve over prolonged periods of time (119–121). Even less is known about other types of glia and the many ways in which brain cells become dysfunctional (151, 152). Sensors for other metabolic pathways are being developed, and existing sensors are being improved, now built smaller for easier subcellular targeting and made of various colors for multiplexing (148). These technical developments herald an exciting era of metabolic physiology.

SUMMARY POINTS

1. Metabolic recruitment endows active neurons with the capability of harvesting fuel and oxygen from resting areas beyond the active zone.
2. The primary signal driving metabolic recruitment is elevated extracellular K^+ ($[K^+]_e$), which mirrors workload.
3. The energy metabolism of astrocytes is acutely modulated by $[K^+]_e$ via the Na^+/K^+ ATPase (NKA) and the Na^+/HCO_3^- cotransporter (NBCe1), proteins that are enriched in these cells.
4. Lactate released by astrocytes via ion channels serves as a secondary recruiter, impacting the function and metabolism of resting astrocytes and neurons.
5. Glutamate, ammonium (NH_4^+), and nitric oxide play supplementary roles over different spatiotemporal domains.
6. Metabolic recruitment works in parallel to other averaging strategies like lateral inhibition, competing network inactivation, sparse coding, and neurovascular coupling.

FUTURE ISSUES

1. What are the signaling pathways linking the NKA and NBCe1 to the metabolic machinery? This question reflects a more general knowledge gap about the control of metabolic pathways, including mitochondrial respiration.
2. What is the molecular identity of the astrocytic lactate channel? Are pannexin hemichannels active under physiological conditions?
3. NH_4^+ dynamics in brain tissue remain to be characterized; e.g., how and when do neurons release the NH_4^+ generated by the conversion of glutamine into glutamate?
4. In brain tissue, the capillary endothelium is a permeability barrier that controls the passage of glucose and lactate to the parenchyma. We know little about the regulation of brain endothelial glucose transporter 1 (GLUT1) and monocarboxylate transporters by neural activity.
5. Is there cellular and subcellular metabolic heterogeneity in neurons and glial cells?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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RELATED RESOURCES

Brain RNA-Seq: <https://www.brainrnaseq.org/>. User friendly interface to access cell type-specific transcriptomic data from human and mouse brain, provided by the Barres Lab. It also contains information about aging astrocytes, peritumor astrocytes, and microglia.

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Errata

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