Lactate in the brain: from metabolic end-product to signalling molecule

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Abstract | Lactate in the brain has long been associated with ischaemia; however, more recent evidence shows that it can be found there under physiological conditions. In the brain, lactate is formed predominantly in astrocytes from glucose or glycogen in response to neuronal activity signals. Thus, neurons and astrocytes show tight metabolic coupling. Lactate is transferred from astrocytes to neurons to match the neuronal energetic needs, and to provide signals that modulate neuronal functions, including excitability, plasticity and memory consolidation. In addition, lactate affects several homeostatic functions. Overall, lactate ensures adequate energy supply, modulates neuronal excitability levels and regulates adaptive functions in order to set the 'homeostatic tone' of the nervous system.

Pyruvate dehydrogenase (PDH). The first component enzyme of the pyruvate dehydrogenase complex; it converts pyruvate into acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle for cellular respiration.

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When studied at the organ level, brain energy metabolism can be considered as being almost fully oxidative: elegant studies pioneered in the 1940s and 1950s by Schmitt and Kety[1] and later by Sokoloff[2] showed that glucose is the obligatory physiological energy substrate of the brain and is metabolized to CO_2 and water to yield 32–36 ATP molecules per molecule of oxidized glucose[3]. Studies over the past 20 years have added a cellular resolution to these organ studies, demonstrating a cell-specific metabolism of glucose. Given the cellular heterogeneity of the brain, it is not surprising that different cell types have distinct metabolic profiles. In particular, the emerging view is that neurons are mostly oxidative, whereas glial cells — notably, astrocytes and oligodendrocytes — predominantly process glucose glycolytically, meaning that they produce lactate and pyruvate from glucose[4,5] (FIG. 1). Estimates of glucose uptake from the circulation indicate that, at the most, neurons take up an amount approximately equal to that taken up by astrocytes under basal conditions[6,7].

During functional activation, most of the increase in glucose uptake occurs in astrocytes[7–9]. As neurons use 80–90% of the total energy consumed by the brain[10], and as oxidative activity is the most efficient ATP-producing pathway (FIG. 1a), energy substrates such as pyruvate and lactate must be transferred from astrocytes to neurons, particularly during functional activation. This consideration is fully compatible with the original organ-level studies, because the sequential two-step glucose processing (that is, the transient glycolysis in astrocytes followed by oxidation in neurons) results in brain glucose oxidation.

Notably, under physiological conditions, the lactate:pyruvate concentration ratio is at least 10:1 (REF. [11]). Thus, when considering the intercellular transfer of a glycolytic substrate, lactate is the predominant substrate in the brain. This ratio can also massively increase under hypoxia, as decreases in the partial pressure of oxygen (pO_2) impair the oxidative capacity of the brain. Indeed, owing to this association with hypoxia, lactate has long been considered a metabolic end-product, at best a marker of pathology, if not a toxic molecule (BOX 1). However, many recent studies in various tissues and cell types under physiological and pathological conditions[12–14] now call for lactate to also be considered as an important signalling molecule. By acting through different molecular effectors, lactate contributes to several homeostatic processes (FIG. 2). This Review focuses on the emerging roles of lactate in brain function, with a particular focus on the modulation of neuronal excitability, neuronal plasticity and neuroprotection.

Lactate production and metabolism

Lactate is formed through glycolysis, one of the various metabolic pathways through which glucose can be processed to produce energy (FIG. 1a). With normal oxygen tension, ATP is mostly produced through the mitochondrial electron transport chain. Glucose is processed to pyruvate, which under the action of the enzyme pyruvate dehydrogenase (PDH) provides carbon atoms for the tricarboxylic acid (TCA) cycle. TCA-cycle products, such as NADH and $FADH_2$, feed the electron transport chain, resulting in the production of 32–36 ATP molecules. By contrast, under hypoxic or

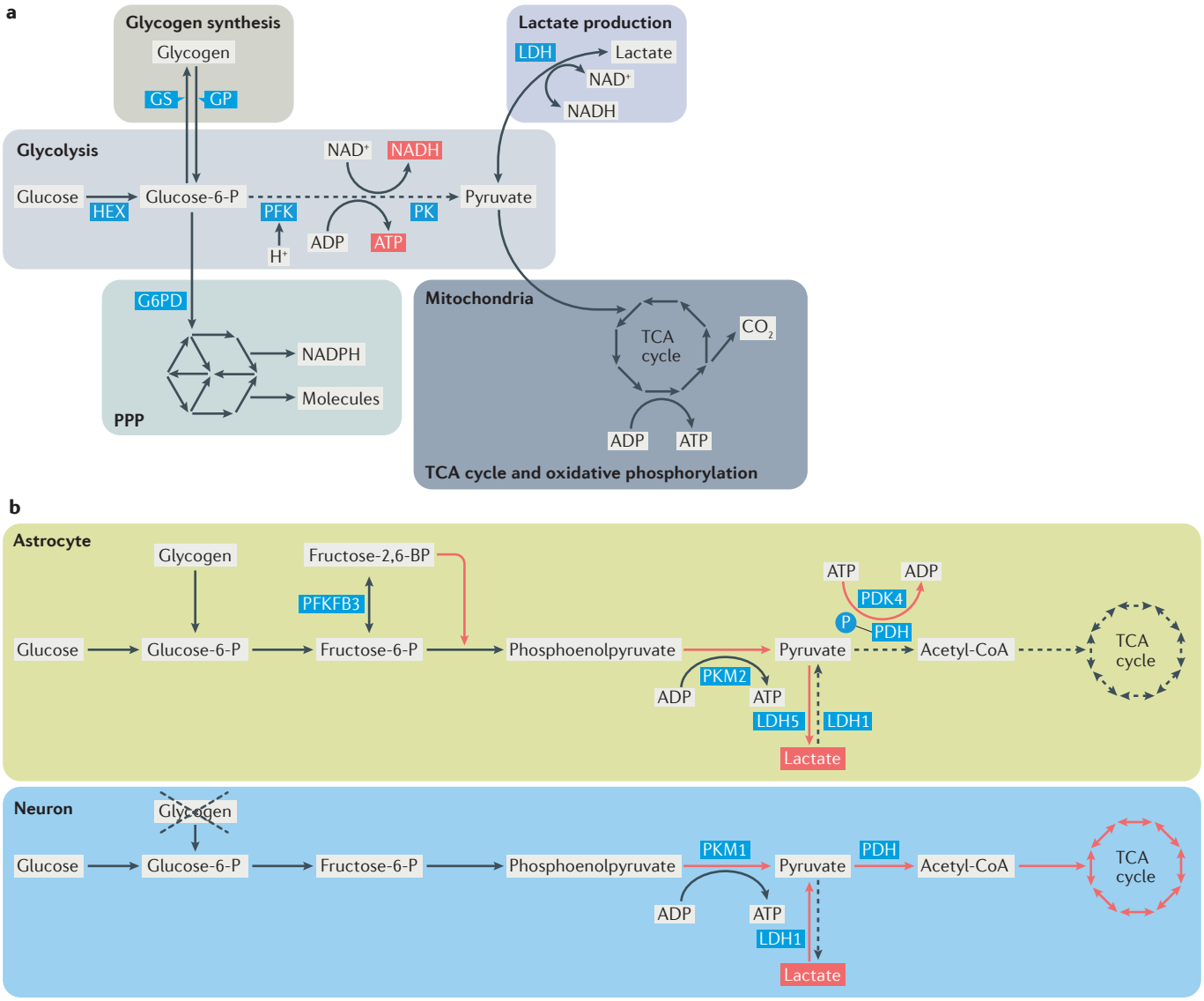


Figure 1 | **Glucose metabolism in astrocytes and neurons. a** | The processing of glucose by cells subserves several important functions: the storage of energy, the production of energy and the production of reducing equivalents and substrates for biosynthesis. Glucose is first phosphorylated by hexokinase (HEX) to glucose-6-phosphate (glucose-6-P), which has three fates that correspond to the three main functions of glucose. First, energy can be stored as glycogen through the action of glycogen synthase (GS). Glycogen can later be mobilized by glycogen phosphorylase (GP) and subsequently metabolized to pyruvate. Second, energy in the form of ATP can be produced by glucose-6-P entering glycolysis, supplying pyruvate for the tricarboxylic acid (TCA) cycle in the mitochondria and the associated oxidative phosphorylation. The main, and irreversible, steps of glycolysis are catalysed by phosphofructokinase (PFK) and pyruvate kinase (PK). Glycolysis produces ATP and NADH. Depending on the cell type, pyruvate can also be converted into lactate through the action of lactate dehydrogenase (LDH); in doing so, NAD^+ levels (which are necessary to maintain the glycolytic flux) are regenerated. Third, reducing equivalents in the form of NADPH are produced in the pentose phosphate pathway (PPP) through a reaction catalysed by the enzyme glucose-6-P dehydrogenase (G6PD). Pentose backbones produced by the PPP are used for various biosynthetic processes, including nucleotide and nucleic-acid synthesis. **b** | In the brain, the expression of different metabolic pathways for glucose is cell specific. Red arrows depict upregulated pathways; black dashed arrows depict pathways that are downregulated in these cell types. Glycogen storage and lactate production characterize astrocytes, whereas neurons use glucose predominantly in the PPP and use lactate, after its conversion to pyruvate, as their preferred mitochondrial energy substrate. Glycogen is almost exclusively present in astrocytes, where GS is permanently degraded by a ubiquitin–proteasome process[195]. In astrocytes, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) expression is high and produces fructose-2,6-bisphosphate (fructose-2,6-BP; a key positive modulator of glycolysis), whereas, in neurons, PFKFB3 is kept low through a proteasome-driven process[32]. PK expression is regulated in a cell-specific manner by differential splicing, resulting in expression of the M1 form (PKM1) in neurons and expression of the aerobic glycolysis-promoting form, PKM2, in astrocytes[34]. In astrocytes, pyruvate dehydrogenase kinase isoform 4 (PDK4) is highly expressed and phosphorylates pyruvate dehydrogenase (PDH), inhibiting its activity in these cells[20,34]. The opposite situation exists in neurons, resulting in high PDH activity and favouring entry of pyruvate into the TCA cycle. LDH5 — the LDH form that drives aerobic glycolysis — is expressed predominantly in astrocytes, whereas neurons express low levels of, if any, LDH5, but rather express LDH1 (REFS [25,208]). Taken together, these cell-specific expression and activity profiles confer to neurons a restricted potential for upregulating glycolysis and an active oxidative phosphorylation activity. By contrast, in astrocytes, the expression profiles favour aerobic glycolysis and limit oxidative activity.

anoxic conditions, only 2 ATP molecules are produced per glucose molecule. Under such conditions, pyruvate is converted to lactate (and NADH to NAD^+) by lactate dehydrogenase (LDH) in a process known as anaerobic glycolysis (FIG. 1a). The regeneration of NAD^+ is necessary to maintain a glycolytic flux, as NAD^+ enables reduction during the initial steps of glycolysis.

A third way to process glucose is aerobic glycolysis, which was initially described in cancer cells by Otto Warburg. In aerobic glycolysis, lactate is formed despite the presence of normal oxygen tension[15]. This metabolic processing of glucose is typical of astrocytes and is due to a cell-specific gene expression profile that favours the conversion of pyruvate to lactate rather than the use of pyruvate in the TCA cycle (FIG. 1).

Cell-specific metabolism of lactate

Cell-specific metabolic profiles exist in different organs and tissues. For example, in skeletal muscle, fast 'white' fibres are predominantly glycolytic, whereas slow 'red' fibres are oxidative[16]. Early studies in individually isolated neurons and astrocytes revealed that neurons produce CO_2 at a much higher rate than do astrocytes, indicating high oxidative activity in neurons, whereas the enzyme function profile of astrocytes is consistent with a predominance of glycolysis[17,18]. More extensive recent studies have confirmed these neuron-specific and astrocyte-specific metabolic profiles (reviewed elsewhere[5]). Not surprisingly, such cell-specific functional metabolic profiles are mirrored by the differential expression of enzymes that regulate metabolic fluxes (BOX 2; FIG. 1b).

Why do astrocytes produce lactate? A question that can be raised is: why do astrocytes, which are endowed with a considerable mitochondrial complement[19], produce lactate rather than using pyruvate to feed the TCA cycle and the energetically favourable respiratory chain to achieve a high yield of ATP? One reason may be that, in astrocytes, the enzyme PDH is highly phosphorylated and therefore shows lower activity, favouring the aerobic glycolytic profile[20]. Another characteristic of astrocytes

Box 1 | **A brief history of lactate in the brain**

The 'bad reputation' of lactate as a useless, if not toxic, metabolite dates back to the early 20th century from studies in muscle (reviewed elsewhere[179]). These studies concluded that lactate is formed by exercising muscles through anaerobic glycolysis (that is, when the glycolytic flux exceeds the availability of oxygen). In the 1930s, elegant studies by the Coris showed that some excess lactate could be recycled by the liver and produce glucose through gluconeogenesis (Cori cycle).

Interestingly, at that time, evidence already showed that, under physiological conditions, excess lactate could in fact be oxidized in certain organs, including the heart and brain, to produce pyruvate and could thus enter the tricarboxylic acid (TCA) cycle. Quite surprisingly, this fate of lactate was simply considered as a way to clear this unwanted or toxic metabolite rather than as a process through which lactate could produce energy. Only recently did it become clear that intercellular lactate shuttles exist whereby lactate is transferred from lactate-producing cells to lactate-consuming cells. Examples of such shuttles are those existing between fast and slow skeletal muscle fibres and, as explained in the main text, between astrocytes and neurons[5,16].

Studies by McIlwain in the 1950s demonstrated that lactate is a perfectly adequate energy substrate for neural cells: synaptic activity could be sustained in slices of human and monkey cerebral cortex maintained in vitro in artificial media in which glucose was replaced by lactate[180]. These observations were later confirmed in isolated dorsal root ganglia[181], hippocampal slices[182] and isolated optic nerve preparations[183]. Critics of these studies claimed that their relevance for a role of lactate in the brain was limited, as these results were obtained in the absence of glucose, suggesting that, at best, lactate could be considered as an alternative energy substrate to glucose in the case of glucose deprivation. However, a closer look at the literature shows that even in the presence of adequate glucose, lactate is a preferred substrate to sustain neuronal activity. These observations were made in vitro by monitoring the consumption by preparations that contained radioactively labelled glucose and lactate[184,185], as well as through analysis of metabolic fluxes by magnetic resonance spectroscopy (MRS)[46,138,186,187]. The preferential use of lactate has also been shown in vivo using MRS and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)[131,133,136]. In the latter studies, brain glucose utilization was decreased in individuals during intravenous perfusions of lactate, indicating that lactate could be preferentially used instead of glucose as an energy substrate[133,136]. In summary, studies over six decades by different investigators using various experimental approaches have established that lactate, particularly if formed within the brain, where its concentrations range between 2 and 5 mM (REFS [188–190]), can be an energy substrate for neurons and may even be their preferred substrate.

The preference for lactate as an energy substrate in the brain is particularly interesting when considered in the light of recent studies using ^{13}C-labelled metabolic substrates followed by flux analysis with MRS, which have revealed that glycolysis and the TCA cycle are uncoupled in peripheral tissues. Specifically, glucose is first processed though glycolysis, thus generating a pool of lactate in the circulation, and then this lactate is oxidized via the TCA cycle by most tissues, except muscle and brain[191]. In the brain, uncoupling of glucose processing occurs between astrocytes and neurons instead. Indeed, the transport of glucose across the blood–brain barrier occurs at more than tenfold the rate of lactate transport into the brain[192]. Thus, brain energetics do not depend on the uncoupling of glycolysis and the TCA cycle in the periphery; rather, the brain modulates, in an activity-dependent manner, its own supply of lactate, through the transient processing of glucose by aerobic glycolysis and glycogenolysis in astrocytes. Overall, this uncoupling between glycolysis and the TCA cycle adds considerable energetic flexibility both to peripheral tissues, which are supplied with circulating lactate, and to the brain, where lactate is formed by astrocytes.

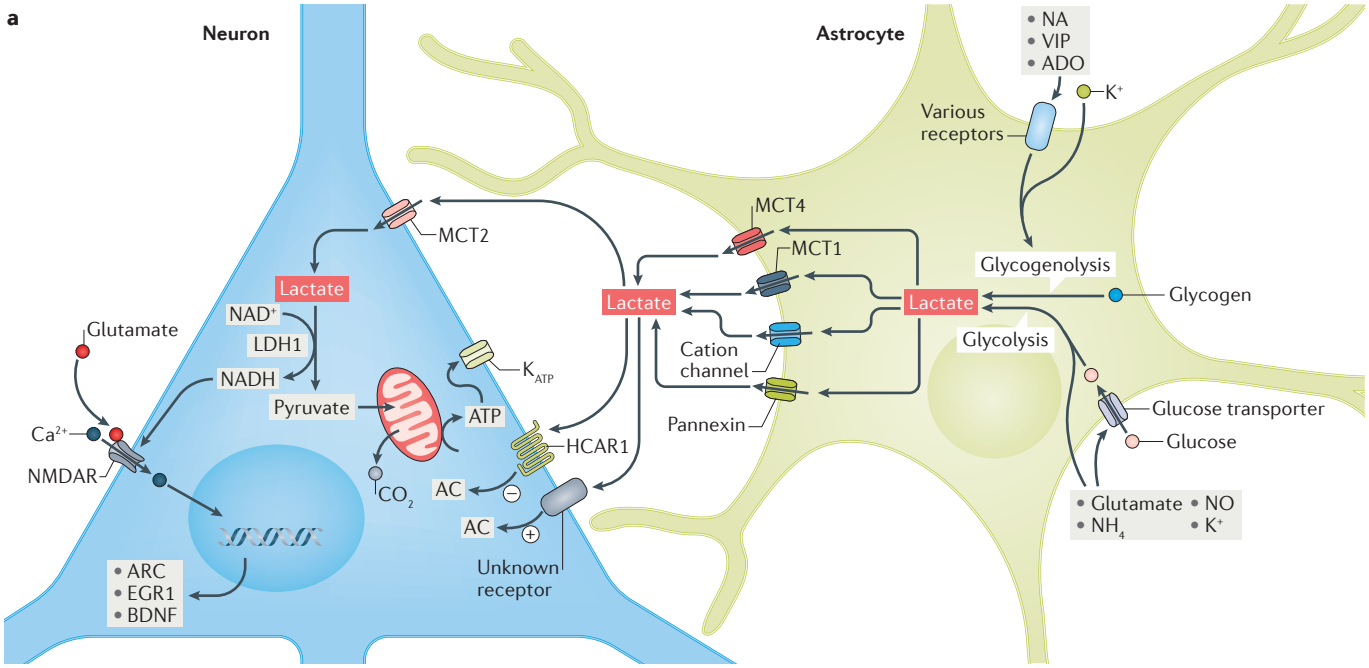
Glycolytic flux
The rate at which glucose and its metabolites proceed through the glycolytic pathway.

Flux analysis
A technique used to examine production and consumption rates of metabolites. It determines the transfer of moieties containing isotopic tracers from one metabolite into another using stoichiometric models of metabolism and mass spectrometry methods.

Mitochondrial respiratory chain (MRC) complexes
Complexes that operate the transfer of electrons from donors to acceptors via redox mechanisms, creating an electrochemical proton gradient that drives the synthesis of ATP.

is the particular organization of their mitochondrial respiratory chain (MRC) complexes. The organization of different MRC complexes (which are numbered I–IV) into macromolecular structures known as supercomplexes dictates the MRC electron flux and energy-producing efficiency. In astrocytes, most complex I is uncoupled from supercomplexes, resulting in poor mitochondrial respiration[21]. By contrast, in neurons, complex I is mostly embedded into supercomplexes, resulting in high mitochondrial respiration[21]. A striking illustration of the modest mitochondrial respiration in astrocytes was recently provided: mice in which cytochrome oxidase activity — and hence, mitochondrial respiration — was conditionally suppressed specifically in astrocytes for more than a year were phenotypically normal and did not present any signs of neurodegeneration[22].

The astrocyte–neuron lactate shuttle. The existence of such drastically different metabolic profiles between astrocytes and neurons suggests that dynamically regulated metabolic exchanges exist between lactate-producing cells and lactate-consuming cells.



b

Molecular interactions	Cellular mechanisms	Physiological processes
• MCTs • NADH/NAD+ • NMDARs • ATP • K_{ATP} channels • Lactate receptors • pH changes	• Neuronal plasticity • Axonal integrity • Neuronal excitability	• Learning and memory • Glucose sensing • Sodium sensing • Osmoregulation • pO_2 sensing • Ventilation • Arousal

Figure 2 | **Lactate-mediated metabolic coupling and signalling between neurons and astrocytes. a** | Lactate is formed by astrocytes through two pathways: glycogenolysis and glycolysis. Both processes are triggered by activity-dependent neuronal signals: noradrenaline (NA), vasoactive intestinal peptide (VIP), adenosine (ADO) and K^+ promote glycogenolysis, whereas glucose uptake and lactate production (aerobic glycolysis) are triggered by glutamate, ammonium (NH_4), nitric oxide (NO) and K^+ (REFS [24,30,41,43,81,88–90,92]). Lactate is released by astrocytes through three means: via transmembrane monocarboxylate transporters (MCT1 and MCT4), via a high-capacity cation channel and via pannexins[27,42,82]. Lactate exerts metabolic effects and activates signalling cascades in neurons through two main mechanisms: through transmembrane transport via MCT2 and by acting on specific receptors. A G protein-coupled receptor called hydrocarboxylic acid receptor 1 (HCAR1) has been identified that binds lactate and is negatively coupled to adenylyl cyclase (AC)[79]. A second, unidentified receptor type, positively coupled to AC, is present on noradrenergic neurons in the locus coeruleus[80]. The processing of lactate as a consequence of its uptake into the neuronal cytoplasm through MCT2 transporters results in the production of NADH and ATP. The conversion of lactate to pyruvate by lactate dehydrogenase 1 (LDH1) produces NADH, which affects the redox state of the neuron. The increase in NADH positively modulates the activity of NMDA receptors (NMDARs), resulting in enhanced Ca^{2+} currents, the activation of intracellular signalling cascades and the induction of the expression of plasticity-associated genes — for example, those encoding activity-regulated cytoskeleton-associated protein (ARC), early growth response protein 1 (EGR1) and brain-derived neurotrophic factor (BDNF)[113]. Pyruvate formed from lactate enters the mitochondria and fuels ATP production. ATP supports the energy demands of active neurons and provides a signal that modulates the activity of ATP-dependent potassium (K_{ATP}) channels, resulting in depolarization[122,123,146]. The possibility that pyruvate may act directly to activate K_{ATP} channels has been suggested[62]. **b** | The physiological processes involving lactate in the nervous system and the cellular mechanisms and molecular interactors through which lactate exerts these physiological effects (see text for details). pO_2, partial pressure of oxygen.

This is clearly the case in skeletal muscle, where lactate is shuttled between white and red fibres[12,13]. Intracellular lactate has also been described to shuttle between the cytosol and mitochondria[16,23].

More than two decades ago, studies showed that glutamate stimulated aerobic glycolysis in primary astrocyte cultures and triggered lactate release[24]. This effect was mediated by sodium-driven glutamate reuptake, a well-characterized function of astrocytes. Ex vivo analyses of protein expression and localization suggested that lactate is produced in astrocytes and transferred to neurons[25,26]. Specifically, neurons were found to express lactate dehydrogenase 1 (LDH1; the form present in lactate-consuming tissues such as the myocardium), whereas LDH5 (the form predominantly expressed in lactate-producing tissues such as skeletal muscle) is exclusively present in astrocytes[25]. Furthermore, the monocarboxylate transporters (MCTs) that operate transmembrane lactate transport showed a cell-specific distribution, with the low-affinity MCT1 and MCT4 present in astrocytes and the high-affinity MCT2 present in neurons[27]. This cell-specific distribution is not sufficient alone to argue for a predominant traffic of lactate from astrocytes to neurons, as the interconversion of lactate and pyruvate is driven by the redox state of cells. Astrocytes present a much higher NADH:NAD^+ ratio than do neurons[28], indicating that astrocytes have a highly reducing status, which thermodynamically favours the conversion of pyruvate to lactate in these cells.

Overall, these observations gave rise to the astrocyte–neuron lactate shuttle (ANLS) model, whereby synaptically released glutamate triggers glucose uptake and lactate production by astrocytes for the use of neurons[24,25] (FIG. 2). Over the following two decades, experiments from several laboratories have supported the ANLS model[7,9,22,24,28–51] (for reviews, see REFS [4,5,52–54]).

In further support of the ANLS model, the existence of a lactate gradient between astrocytes and neurons was recently demonstrated in vivo[44]. Two-photon microscopy of genetically encoded nanosensors was used to visualize changes in lactate levels. This approach revealed that, upon simultaneous transacceleration[55] of MCTs in both astrocytes and neurons, by adding exogenous pyruvate (see REFS [56,57] for details on transacceleration), lactate decreases in astrocytes and then, after a delay, increases in neurons. Furthermore, glutamate reuptake into astrocytes triggers activity-dependent glucose import from the circulation into the brain parenchyma both ex vivo and in vivo[8,9,58,59]. Electrophysiological evidence also indicates that lactate released by astrocytes and taken up by neurons is necessary to sustain neuronal activity[60–62] (see FIG. 3 for example).

Challenges to the ANLS. Until the ANLS was described, the unanimous view was that glucose was transferred directly from capillaries to neurons as their exclusive energy substrate. The ANLS model introduced: a mechanism for the coupling between neuronal activity and energy delivery; the first evidence that astrocytes take up

Box 2 | **Cell-specific expression of genes for glucose metabolism in the brain**

As demonstrated by the transcriptional profiling of astrocytes acutely isolated using fluorescence-activated cell sorting (FACS), these cells are characterized by high expression of glycolytic genes, such as the gene encoding 6-phosphofructo-2-kinase/fructose-2,6-bisphosphate 3 (PFKFB3), a key positive regulator of glycolysis[34]. Furthermore, the M2 form of pyruvate kinase (PKM2) is also highly expressed in astrocytes, as in cancer cells, where aerobic glycolysis predominates[193]. In fact, PKM2 is necessary to regulate glycogen fluxes to feed glycolysis in cells such as cancer cells and astrocytes that are metabolically defined as sites of the Warburg effect[193].

Furthermore, neurons express low levels of PFKFB3, implying a low glycolytic activity, and the M1 form of pyruvate kinase predominates in neurons, indicative of oxidative activity[19,34] (FIG. 1b). Another distinguishing metabolic difference is the relatively low activity of pyruvate dehydrogenase (PDH) in astrocytes compared with neurons[194], implying a lower flux of pyruvate into the tricarboxylic acid (TCA) cycle and a corresponding prevalence of lactate production in astrocytes (FIG. 1b). This low activity of PDH in astrocytes is due to its high degree of phosphorylation, which renders the enzyme less active[20,194]. Consistent with this observation, transcriptomic analysis indicates a high expression in astrocytes of pyruvate dehydrogenase kinase isoform 4 (PDK4), which phosphorylates PDH[20,34]. The reverse profile for both PDH and PDK4 is observed in neurons, consistent with a high flux of pyruvate into the TCA cycle and its associated oxidative phosphorylation in these cells[20,34] (FIG. 1b).

In addition, glycogen, the stored form of glucose, is contained almost exclusively in astrocytes[3]. Interestingly, neurons express the gene encoding glycogen synthase, a key enzyme in glycogen metabolism; however, the expressed glycogen synthase protein is continuously degraded by an ubiquitin–proteasome process, thus preventing glycogen accumulation in neurons[195]. Manipulations or pathological conditions in which glycogen accumulates in neurons lead to neuronal demise[195,196]. For example, Lafora body disease, a form of juvenile myoclonal epilepsy, is associated with a toxic accumulation of glycogen in neurons[197,198].

Interestingly, studies in cultured neurons and astrocytes showed that PFKFB3 undergoes a similar proteasome-driven degradation process in neurons, further highlighting the inability of neurons to upregulate glycolysis. In fact, glucose taken up by neurons is mainly processed through the pentose phosphate pathway (PPP) to generate reducing equivalents in the form of NADPH, which are used for scavenging reactive oxygen species produced by the intense oxidative activity of neurons[32] (FIG. 1). In testimony to the importance of glucose processing through the PPP rather than glycolysis in neurons, inhibition of the proteasome-mediated degradation of PFKFB3 results specifically in neuronal death by oxidative stress[32]. Indeed, this intervention reduces the flux of glucose through the PPP, thus decreasing the production of reducing equivalents such as NADPH[54].

Complex I
The first step in the mitrochondrial respiratory chain; it removes two electrons from NADH and operates their transfer to ubiquinone.

Transacceleration
A property of monocarboxylate transporters whereby the presence of extracellular monocarboxylates (such as pyruvate) stimulates transporter efflux of the substrate (for example, lactate).

Warburg effect
Also called aerobic glycolysis. The metabolic pathway of glucose that results in the production of lactate in the presence of physiological concentrations of oxygen.

Fast glucose transport
Facilitated transmembrane transport of glucose via specific transporters.

glucose and use it to produce lactate via aerobic glycolysis (reviewed elsewhere[5,52,53]); and support for the idea that lactate could adequately fuel neurons, as was already suggested by Henry McIlwain in the 1950s (BOX 1).

Nevertheless, as is often the case for new proposals in science, the ANLS model was met with a degree of scepticism by some, and over the years has been challenged, mostly on theoretical grounds[63–65]. Most resistance came from the interpretation that the ANLS implied that all circulating glucose enters exclusively into astrocytes and operates at all synapses; however, neither of these interpretations is correct. The original article describing the ANLS[24] shows that glucose also enters neurons. Moreover, it is unlikely that ANLS operates at all neurons; indeed, ANLS probably does not operate at GABAergic synapses. GABA reuptake into astrocytes does not promote aerobic glycolysis[66], and GABAergic neurons may instead rely on their own glycolytic activity to sustain their energy needs[67].

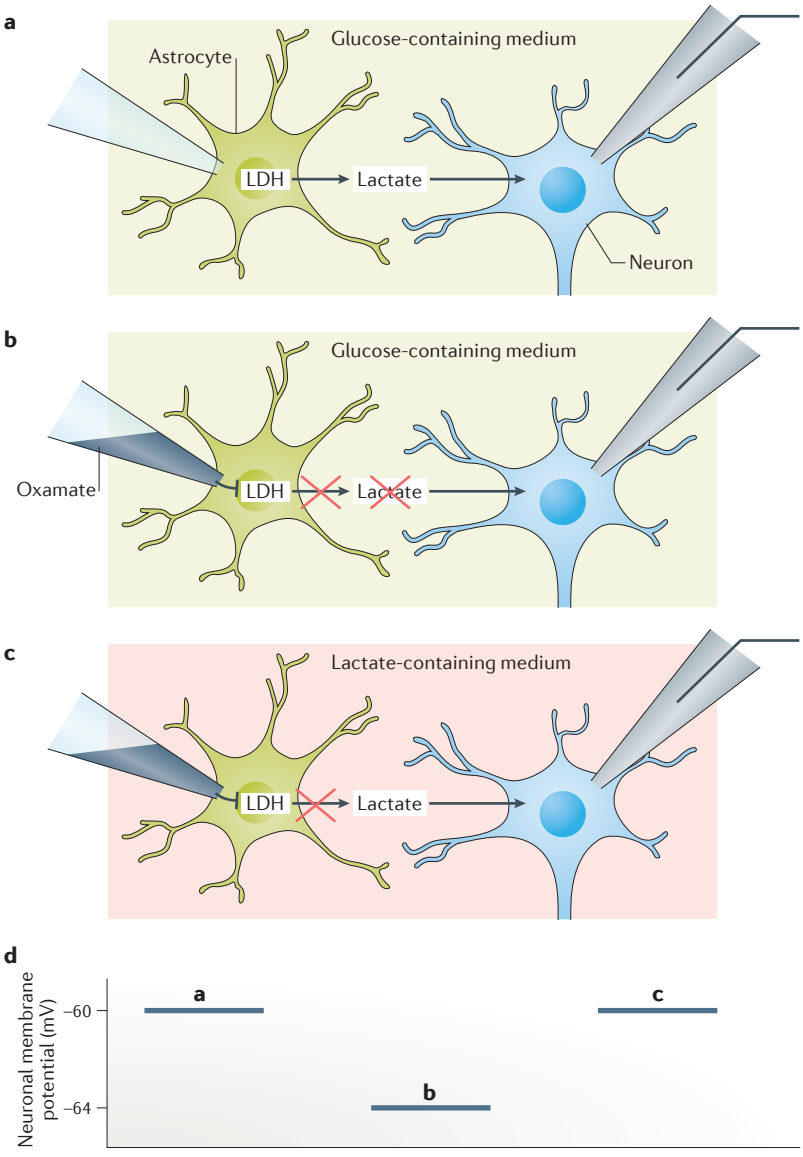


Figure 3 | **Lactate transfer from astrocytes to neurons modulates the excitability of pyramidal cells.** Double patch recordings from a pyramidal cell and a neighbouring astrocyte in the CA1 region of the hippocampus[62]. **a** | In a glucose-containing medium, lactate is formed and released by astrocytes. **b** | Inhibition of lactate dehydrogenase (LDH) activity in astrocytes by oxamate results in the hyperpolarization of the neighbouring pyramidal cell. **c** | In the presence of lactate in the medium, the same inhibition of LDH by oxamate does not affect the membrane potential of the pyramidal cell, as lactate is readily available. **d** | Approximate membrane potentials corresponding to the pyramidal cells shown in the other figure parts are schematized here.

Nevertheless, a few challenges have arisen from experimental reports that warrant discussion. For example, two reports have claimed that glucose is taken up preferentially, if not exclusively, by neurons. The first showed that a fluorescent glucose analogue, IR 2-deoxyglucose 800 (IRDye 800CW 2-DG; which has a molecular mass of ~1,300 Da, compared with 180 Da for glucose), was preferentially taken up by activated neurons[68]. Limiting the interpretation of this study, however, IRDye 800CW 2-DG has been shown to be endocytosed as a complex with the glucose transporter[69] — a process that is unrelated to fast glucose transport. In the second report, the phosphorylation of infused fluorodeoxyglucose (FDG) was used as a marker of glucose utilization[70]. The ratio of FDG-6-phosphate (FDG-6P) to *N*-acetylasparate (NAA; a neuronal marker) was compared between brain homogenate and a preparation of neuronal terminals from rats with or without injection of the epileptogenic agent bicuculline. The FDG-6P:NAA ratio in the nerve terminal preparation was similar to that in the brain homogenate (which contained neurons and glia). As such, the study's authors concluded that, during activation, neurons directly take up glucose, challenging the role of the ANLS. However, these observations would indicate that all glucose is taken up by neurons — a notion that is not supported experimentally[6,7]. Moreover, technical issues (such as the use of neuronal terminal preparations, which undergo membrane disruption and resealing followed by density gradient centrifugation during their preparation and thus are likely subject to changes in substrate concentrations) and the use of bicuculline, which does not reflect a physiological activation, make it difficult to draw firm conclusions from this study.

By contrast, the astrocytic reuptake of glutamate has been demonstrated to be required for glucose utilization (as predicted in the ANLS model) in the whisker–barrel cortex pathway in vivo. Downregulation of astrocyte-specific glutamate transporters markedly reduced glucose utilization[71] in the barrel corresponding to a mechanically stimulated whisker[58,72]. In the same system, and under basal conditions, glucose uptake (measured using the fluorescent, non-metabolizable glucose analogue, 6-deoxy-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-aminoglucose (6-NBDG), a probe validated as a marker of fast glucose transport)[73–75] by astrocytes and neurons occurred at the same rate. By contrast, during whisker stimulation, glucose uptake by astrocytes, but not by neurons, in the barrel rapidly increased[7]. Another in vivo imaging study showed that the ^{18}F-FDG positron emission tomography (PET) signal is driven by astroglial glutamate transport[9].

Furthermore, in hippocampal slices, 6-NBDG was taken up predominantly by astrocytes at a much higher rate than by neurons[29]. In primary mixed cultures, glutamate stimulated glucose uptake into astrocytes and, interestingly, also inhibited the transport of glucose into neurons by triggering an AMPA receptor-mediated influx of sodium into these cells[76]. This latter observation suggests that glutamate signalling may actually redistribute glucose towards astrocytes during activation. Together with the much higher cytosolic NADH:NAD^+ ratio (indirectly indicating higher glycolytic flux) observed in astrocytes relative to neurons in hippocampal slices, these results converge towards a predominant glucose uptake into astrocytes[28].

In another study in hippocampal slices, inhibitors of the neuronal lactate transporter MCT2, under basal conditions, lowered the neuronal NADH:NAD^+ ratio, implying lactate consumption in these cells[77]. Yet, during activation of hippocampal granule-cell synapses, the rise in the neuronal NADH:NAD^+ ratio was insensitive to MCT2 inhibition — an observation that was taken to suggest that the active neurons did not require imported lactate, challenging the ANLS[77]. However, the NADH:NAD^+ ratio in active neurons remained much lower than that in resting astrocytes[28,77], which is inconsistent with the notion that neurons exhibit glycolysis more than do astrocytes.

Another indirect argument against the ANLS is a stoichiometric one based on the theoretical notion that the energy for sustaining glutamate reuptake by astrocytes does not require glucose uptake, as glutamate can enter the TCA cycle and thus fuel its own uptake[64]. However, this contention is not consistent with experimental evidence. First, as noted above, impairing astrocytic glutamate uptake reduces glucose uptake into the brain in vivo[58,72]. Second, D-aspartate, a substrate that is taken up by astrocytic glutamate transporters but is not metabolized in the TCA cycle, stimulates glucose uptake into astrocytes just as glutamate does[24]. Third, glutamate uptake into astrocytes markedly decreases the energy charge of these cells[78]. Thus, glutamate uptake into astrocytes and glucose utilization are tightly linked.

In summary, the ANLS does not discount glucose utilization by neurons (particularly under basal conditions) and probably does not operate equally at all synapses of the brain. Some lactate produced is probably not used by neurons and may instead be released into the circulation[64]. Moreover, given that lactate receptors have been identified in the brain[79,80] (FIG. 2), lactate itself may in part act as a gliotransmitter on cognate receptors[5]. Finally, activated neurons might initially use and oxidize lactate from the extracellular space that is subsequently replenished through the ANLS[5].

Extending the ANLS model. Several more recent studies have provided further evidence for the ANLS and have even extended the model. In addition to glutamate, certain other neuron-derived agents promote glucose uptake, lactate production and lactate release by astrocytes (FIG. 2). Experiments using genetically encoded nanosensors demonstrated that K^+ and NH_4^+ ions, which increase in the extracellular space with neuronal activity, drive aerobic glycolysis in astrocytes[30,43]. Physiological concentrations of nitric oxide (NO), another signal released by neurons, were also recently shown to promote lactate release from astrocytes[81]. Cortical astrocytes of anaesthetized mice were also observed to release lactate rapidly in response to local field stimulation[42]. Similarly, there may be further conduits for lactate release beyond MCT1 and MCT4. Neuronal depolarization or physiological increases in extracellular K^+ induce rapid release of lactate through a lactate-permeable, high-capacity ion channel[42]. Moreover, pannexin and connexin hemichannels can also extrude lactate[82].

The ANLS seems to be evolutionarily conserved, as it has been demonstrated in vivo with cellular resolution in *Drosophila melanogaster*[36]. Indeed, inhibition of the ANLS by genetic knockout of selective glycolytic enzymes in glia results in neurodegeneration[36], suggesting that the ANLS is necessary for proper neuronal function in flies. Related to the evolutionary conservation of the ANLS, a well-coordinated transfer of lactate from astrocytes to neurons in *D. melanogaster* was recently shown to involve the formation of lipid droplets and to be important for neuroprotection. Briefly, the authors of the study showed that glial lactate fuelled neuronal lipogenesis when reactive oxygen species were formed in neurons owing to mitochondrial dysfunction. These neuronal lipids are subsequently transported and stored in glia as lipid droplets, and this neuronal lipogenesis and subsequent lipid storage in glia were found to be important for neuroprotection in flies[83,84]. Also in line with evolutionary conservation of the ANLS, a compartmentation between glia and neurons that enables metabolite exchange was reported in the honeybee retina in the 1980s[85].

The ANLS model has recently been extended to metabolic exchanges between oligodendrocytes and axons by in vivo studies showing that in mice, lactate released by oligodendrocytes is required to maintain axonal function[33,86]. Genetic disruption of lactate transfer from oligodendrocytes to axons resulted in axonal dysfunction. Furthermore, decreased expression of the glia-specific lactate transporter MCT1 has been observed in the spinal cord of mice expressing $SOD1^{G93A}$ (a model of amyotrophic lateral sclerosis (ALS)) as well as in the motor cortices of individuals with ALS[49,87].

Lactate production from astrocytic glycogen is another example of neuron–glia metabolic coupling. Neuron-derived molecules such as noradrenaline (NA), vasoactive intestinal peptide (VIP) and adenosine, as well as activity-dependent increases in extracellular K^+, all promote glycogen mobilization in astrocytes[41,88–92], where glycogen is exclusively localized within the brain[3] (FIG. 2). As described below, transfer of glycogen-derived lactate is critically involved in neuronal plasticity[39,40,93].

Overall, work by several groups over almost three decades has provided strong evidence of neuron–glia metabolic coupling. The transfer of lactate from astrocytes to neurons is one example of a larger palette of metabolic transactions between astrocytes and neurons that also includes the exchange of ATP and serine[94–97] as well as the release of agents that promote the reducing capacity of neurons[37,98,99] (the discussion of which is outside the scope of this Review).

Energy charge
An index that measures the energy status of cells. It is related to ATP, ADP and AMP concentrations.

Memory consolidation
A category of processes whereby a brain converts short-term memories into long-term memories (that is, stabilizing a memory trace after its initial acquisition).

Lactate as a signalling molecule

Lactate, neuronal plasticity and memory. Studies initiated in the 1990s by Gibbs and Hertz[100] showed that glycogenolysis was necessary for memory consolidation in a neonatal chick model of passive avoidance learning, which, in this species, involves the intermediate medial mesopallium (which corresponds to the cortex in mammals[100,101]). In addition to providing energy substrates for neurons, the breakdown of glycogen in astrocytes was proposed to produce glutamine as a precursor for glutamate and GABA neurotransmission[100]. Given the evidence identifying astrocytes as lactate producers, a possible role of lactate transfer from astrocytes to neurons in memory consolidation was investigated. In the rat hippocampus, pharmacological inhibition of glycogen phosphorylase using DAB (1,4-dideoxy-1,4-imino-D-arabinitol) inhibited the production of lactate, as determined by microdialysis, during single trial learning tasks including inhibitory avoidance[39]. Blockade of lactate production from astrocytic glycogen also inhibited in vivo hippocampal long-term potentiation (LTP) and memory consolidation. By contrast, co-injection of lactate with DAB (negating the inhibitory effects of DAB on lactate concentrations) rescued LTP and memory consolidation. Similarly, downregulation of the astrocytic MCTs (MCT1 and MCT4) using targeted antisense oligonucleotides prevented the transfer of lactate from astrocytes to neurons and resulted in amnesia that was rescued by lactate. Consistent with these findings, MCT1-deficient mice exhibit impaired memory in the inhibitory avoidance task[102]. By contrast, downregulation of the neuronal lactate transporter MCT2 also prevented learning but was not rescued by lactate, as it could not be transported into neurons[39]. Thus, the transfer of lactate from astrocytes to neurons is necessary for LTP and memory consolidation (FIG. 4).

Lactate has similarly been shown to be necessary for memory consolidation in other learning tasks in rodents, including spatial working memory[40] and conditioned place preference for cocaine (the latter behaviour involving the basolateral amygdala)[103–105]. Recently, astrocyte-derived L-lactate was shown to facilitate synchrony of the amygdala with the anterior cingulate cortex and decision making[106].

One of the physiological triggers for glycogenolysis in the brain is NA released by fibres originating in the locus coeruleus (LC)[107,108]. Activation of β-adrenergic receptors by NA has a key role in the consolidation of inhibitory avoidance memory; this type of memory consolidation is inhibited by bilateral hippocampal injection of the β-adrenergic antagonist propranolol[109]. Interestingly, the amnestic effect of propranolol is prevented by injecting lactate into the hippocampus[93], implicating NA-evoked glycogenolysis in memory consolidation. This implication is also consistent with the role of the LC–cortical noradrenergic projection in memory consolidation[110,111]. Using 3D immersive virtual reality constructed from electron microscopy stacks, more than 50% of the glycogen granules in astrocytic profiles were observed to localize near monoaminergic — probably noradrenergic — boutons, with the remaining 25% close to postsynaptic compartments. This intracellular distribution renders glycogen readily available to modulate synaptic functions[112].

Why is glycogen-derived lactate released by astrocytes necessary for neuronal plasticity and memory? A straightforward answer may be that lactate meets the increased energy demands of neurons undergoing plasticity processes such as cytoskeletal rearrangements, protein trafficking or increased gene expression.

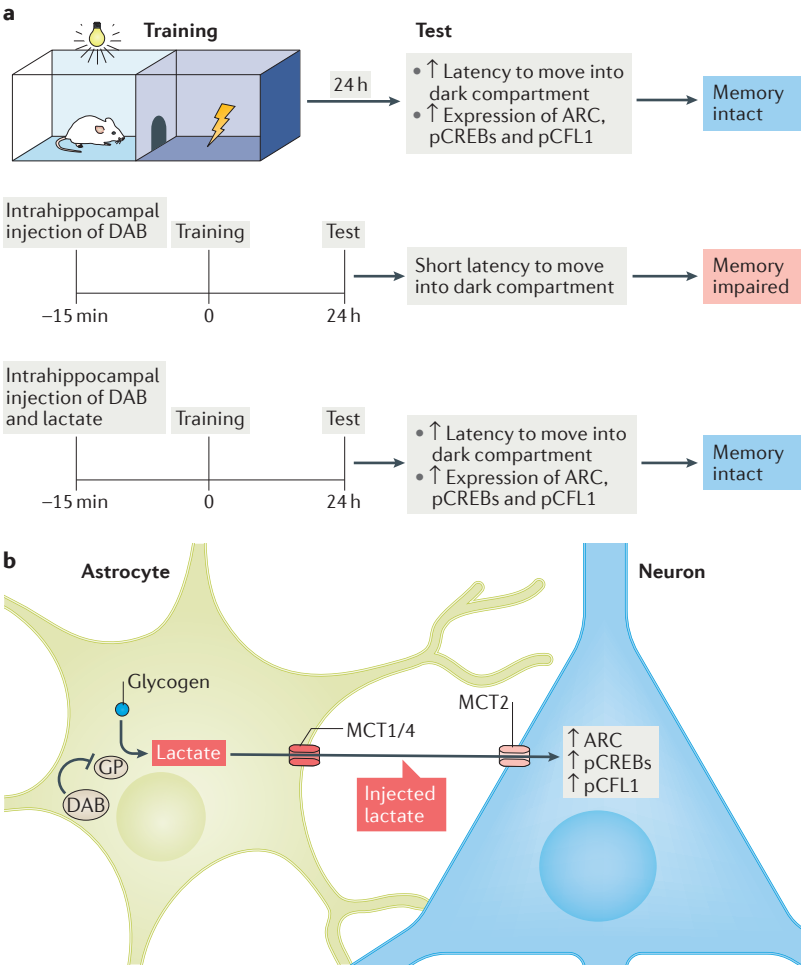


Figure 4 | **Lactate transfer from astrocytes to neurons in memory consolidation.** **a** | One-trial learning for inhibitory avoidance. Rats are placed in a box with two compartments: one well illuminated and one dark. Rodents rapidly move into the dark compartment. On the day of training, rodents receive a mild electric shock as they enter the dark compartment. After 24 hours, the animals are retested; their latency to move into the dark compartment is considerably longer, and the expression of molecules involved in plasticity (such as activity-regulated cytoskeleton-associated protein (ARC), phosphorylated cAMP-responsive element-binding proteins (pCREBs) and phosphorylated cofilin 1 (pCFL1)) is increased, suggesting that the memory of the trained shock is intact. When 1,4-dideoxy-1,4-imino-D-arabinitol (DAB), an inhibitor of glycogen phosphorylase (GP; the key enzyme involved in glycogenolysis), is injected bilaterally into the dorsal hippocampus 15 minutes before training, the latency to move into the dark compartment tested 24 hours later remains short, meaning that memory consolidation has been impaired[39]. If lactate is co-injected with DAB, thus bypassing the inhibition of DAB, memory consolidation is rescued[39]. **b** | A schematic summarizing the mechanisms underlying the results observed in the one-trial learning for inhibitory avoidance. The production of lactate in astrocytes can be blocked by DAB, and this impairs the formation of memories; however, injection of lactate directly into the hippocampus bypasses the need for lactate production and rescues memory formation. MCT, monocarboxylate transporter.

However, the observation that glucose only marginally rescues the effect of blocking glycogenolysis with DAB on memory consolidation suggests that lactate has an energy-independent function in this context[39].

Consistent with an energy-independent action of lactate on neuronal plasticity, lactate, but not glucose or pyruvate, induces the expression of several plasticity-related genes such *Arc*, *Egr1* and *Bdnf*[113] in cultured mouse cortical neurons. Lactate exerts this action starting at concentrations as low as 2.5 and 5 mM by amplifying NMDA receptor (NMDAR)-mediated currents and increasing intracellular calcium concentrations[113]. The molecular mechanism or mechanisms of this interaction between lactate and NMDARs are still unknown, but it relies on changes in neuronal redox state and the binding of glycine to its regulatory site on the NMDAR. For example, exposure of cultured neurons to NADH, which is formed by the intracellular conversion of lactate to pyruvate by LDH, mimics the effects of lactate on plasticity[113] (FIG. 2). Conversely, the oxidizing agent DTNB (5,5′-dithiobis(2-nitrobenzoic acid)) antagonizes the potentiating effect of lactate on NMDAR signalling[113].

Further supporting a role for lactate in plasticity, aerobic glycolysis is high throughout the human brain during early development (with a peak at around 5 years), when synaptic growth rate is prominent[114]. During adulthood, aerobic glycolysis becomes restricted to brain areas where expression of neotenic genes (that is, genes typically expressed during early development, such as those related to synapse formation and growth) persists, suggesting that aerobic glycolysis in the brain supports processes related to synaptic plasticity. Recently, a marked decrease in aerobic glycolysis was shown by brain PET imaging in humans during ageing[115], consistent with a decrease in plasticity with ageing[116].

Lactate and neuronal excitability. Experimental evidence suggests that lactate also strongly affects neuronal excitability[62]. In single neurons from the subthalamic nucleus, and in pyramidal cells in the CA1 hippocampal subregion, intracellular application of lactate depolarized the patched neurons. However, when oxamate, an inhibitor of LDH, was co-applied, neurons became hyperpolarized. By contrast, following application of pyruvate (a metabolite downstream of LDH; FIG. 1), oxamate had no effect. These results indicate that conversion of lactate to pyruvate is necessary for the depolarizing effect of lactate. Furthermore, double recordings from pyramidal cells and neighbouring astrocytes revealed that preventing lactate formation in astrocytes (by inhibiting LDH activity with oxamate) results in hyperpolarization of neighbouring pyramidal neurons, an effect that is rescued by extracellularly applied lactate, indicating that the hyperpolarization was due to a reduction in lactate release from astrocytes[62]. Therefore, lactate released by astrocytes modulates neuronal excitability (FIG. 3). Interestingly, these effects were not observed in inhibitory fast-spiking cells in the hippocampus, supporting the view that the astrocyte-to-neuron transfer of lactate may operate predominantly, if not exclusively, at excitatory synapses.

Consistent with these observations, preventing the intercellular trafficking of lactate (using carbenoxolone, which blocks connexin 30 and connexin 43 gap junctions) across the astrocytic network in mouse hippocampal slices inhibited excitatory synaptic activity[61]. A recent study showed that the delivery of lactate from the astrocytic network to orexin neurons is necessary to maintain the daily cycles of wakefulness[51], emphasizing the involvement of astrocyte–neuron metabolic coupling across the sleep–wake cycle[117]. Moreover, whole-cell recordings showed that lactate transport into neurons of the rat nucleus solitary tract constitutively supports excitatory synaptic transmission, even in the presence of glucose[118]. The researchers concluded that "[...]'on-site' astrocyte–neuron lactate transport to presynaptic and postsynaptic elements is necessary for the integrity of excitatory synaptic transmission" (REF. [118]).

Several other examples of the effects of lactate on the excitability of specific neuronal populations have been reported. One study showed that lactate is a necessary and sufficient energy substrate to maintain the spontaneous activity of orexin neurons in hypothalamic slices through a mechanism involving ATP-dependent potassium (K_{ATP}) channels[119]. Similarly, LC noradrenergic neurons are excited by lactate[80]. Unlike what is observed in orexin neurons, this effect does not depend on transport of lactate into LC neurons; rather, it seems to depend on an as-yet unidentified 'lactate receptor' that is positively coupled to cAMP formation[80]. This putative lactate receptor is distinct from another G protein-coupled receptor for lactate previously described in the nervous system: hydroxycarboxylic acid receptor 1 (HCAR1). However, HCAR1 is coupled to an inhibitory Gα subunit and therefore probably does not affect the excitatory action of lactate on LC neurons[79]. In fact, lactate reduces the excitability of cortical neurons in primary cultures (as monitored by calcium imaging), as demonstrated by a decrease in the basal spontaneous calcium spiking frequency, and pharmacological analysis has indicated that this action of lactate is mediated by HCAR1 (REF. [120]).

In summary, the excitability of several populations of neurons is modulated by lactate, with most results indicating that lactate increases excitability. Different responses to lactate probably depend on the signalling pathways that the monocarboxylate activates as well as on the intrinsic properties of the target neurons. Further studies are necessary to draw a definitive picture of the acute effects of lactate on neuronal excitability.

The truly novel message of these studies revealing roles of lactate in neuronal plasticity and neuronal excitability is that lactate should no longer be considered simply as an energy substrate for neurons, but rather as an important signalling molecule that can regulate cellular processes independent of its metabolic effects.

Lactate and integrated physiological responses. The brain can be considered as the ultimate organ for homeostatic regulations. It monitors a large number of physiological functions of the body through subtle processes that rely on efficient sensing mechanisms in various brain regions, particularly the hypothalamus and the brainstem.

Glycogen phosphorylase
The enzyme that catalyses the rate-limiting step in glycogenolysis.

Inhibitory avoidance
A behavioural task that is commonly used to investigate learning and memory processes in rodents and that is based on contextual fear conditioning.

Nucleus solitary tract
A major sensory nucleus in the dorsal medulla that receives cardiovascular, visceral, respiratory, gustatory and orotactile information.

Euglycaemia
Physiological concentration of glucose in the blood.

Ependymal cells
A glial cell type that lines the spinal cord and the ventricular system of the brain and that is involved in the creation, secretion and circulation of cerebrospinal fluid.

Subfornical organ
One of the highly vascularized circumventricular organs of the brain localized on the ventral surface of the fornix. It does not possess a blood–brain barrier.

Macrophage polarization
The process by which macrophages express different functional programmes in response to microenvironmental signals.

In turn, neuronal and neuroendocrine pathways operate counter-regulatory responses that ensure the maintenance of physiological variables. Recently, it has become clear that lactate — either in circulation or formed in the brain by glial cells — signals in several neuronal circuits involved in homeostatic functions. A detailed review of all these physiological processes is beyond the scope of this article, which instead focuses on physiological regulation involving the action of lactate on neuronal mechanisms. BOX 3 includes some details of how lactate and other metabolic intermediates signal in other cellular systems.

One of the main physiological variables relevant for energy homeostasis, food intake and reward is blood glucose[121]. Neurons in the ventromedial hypothalamus (VMH) are major sensors of circulating glucose levels and operate counter-regulatory neuroendocrine and metabolic responses[122]. However, VMH neurons do not only respond to glucose; VMH neurons that are sensitive to astrocyte-derived lactate and that contribute to the maintenance of systemic euglycaemia have also been identified[122–125]. The signalling mechanisms triggered by lactate in these neurons include changes in redox and cellular energy states, which are mediated by NADH and ATP, respectively.

Box 3 | **Signalling role of lactate in other cellular systems**

The role of lactate as a signalling molecule, in addition to serving metabolic functions, is well established in various cellular systems. For example, lactate regulates gene transcription in muscle cells[199], acts as a signalling molecule for cancer cell migration[200] and participates in immune and inflammatory responses and in stem cell differentiation[201–203] (reviewed elsewhere[204]).

At sites of inflammation, lactate is transported into $CD8^+$ T cells and $CD4^+$ T cells via monocarboxylate transporter 1 (MCT1) and the sodium-coupled monocarboxylate transporter 2 (SLC5A12; also known as SMCT2), respectively, and renders these immune cells unresponsive to various chemokines[202]. This action of lactate results in the accumulation of T cells at the inflammatory site. Lactate has additional modulatory effects on immune-competent cells: it inhibits the cytolytic function of cytotoxic $CD8^+$ T cells[205] and promotes the expression of interleukin-17, a pro-inflammatory cytokine, by $CD4^+$ T cells[204].

In tumours, lactate is taken up by tumour-associated macrophages, where it promotes macrophage polarization[201] and stabilizes the transcription factor hypoxia-inducible factor 1α (HIF1α), which in turn promotes expression of the angiogenic factor vascular endothelial growth factor (VEGF)[14]. In endothelial cells, the HIF1α-stabilizing effects require lactate uptake through MCT1. Lactate-evoked angiogenesis can be inhibited by targeting these transporters[206]. Lactate can also contribute to angiogenesis by promoting the differentiation of vasculogenic stem cells[203].

Lactate is not the only energy substrate that exerts signalling actions. Other intermediate metabolites, including succinate and α-ketoglutarate[204], regulate cellular functions by acting as intercellular signals, notably in the immune and vascular systems and in cell-differentiation processes. For example, succinate is angiogenic and, in equilibrium with α-ketoglutarate, influences the pluripotency of embryonic stem cells[207].

It is tempting to speculate that molecules produced by energy-related metabolic pathways that are vital for maintaining cell integrity evolved early on to become intercellular signalling molecules in simple cellular systems and maintained this function through evolution[204]. It must be hypothesized that the emergence of a role as intercellular signals for metabolic intermediates has been contingent upon the appearance of signal-transduction operators, such as specific receptors that could recognize them on target cells. Molecules such as glutamate, adenosine, lactate and ATP that are now established intercellular signalling molecules in the nervous system are also key molecular intermediates of energy metabolism.

Glial-cell-derived lactate also operates as a signalling molecule in the regulation of plasma osmolarity[126]. Astrocytes and ependymal cells in the subfornical organ are in direct contact with the cerebrospinal fluid at the surface of the fourth ventricle. They express Na_x channels, which monitor sodium levels in the cerebrospinal fluid. Increases in sodium transport through the Na_x channels activate the α2 subunit of Na^+/K^+-ATPase, which, in analogy with the ANLS[127], is fuelled by the glycolytic metabolism of glucose and results in lactate production[126,128]. A similar link between Na^+/K^+-ATPase activity and lactate formation has also been observed in injured peripheral nerves[129]. Here, endothelin receptor type B is coupled to a similar Na_x channel (as in the subfornical organ), resulting in endothelin-mediated activation of the Na^+/K^+-ATPase and lactate release, which promotes peripheral nerve regeneration[129].

Respiratory control is operated by subtle regulatory mechanisms, mainly through chemosensory neuronal circuits in the brainstem and in the carotid body that detect changes in pH and pO_2. Lactate seems to have a key signalling role in respiratory control. Pharmacological disruption of the transfer of lactate from astrocytes to neurons in the retrotrapezoid nucleus (RTN) of the rat brainstem increased minute ventilation, tidal volume and breathing frequency[130]. The signalling mechanism of lactate on RTN neurons involves a reduction in extracellular pH. These results were interpreted to indicate that astrocyte-derived lactate in the RTN contributes to the chemosensory signal that reflects ventilation[130].

Lactate levels in the circulation also increase during moderate-to-vigorous exercise and can reach concentrations close to 10 mM in humans[131]. MCTs are expressed on endothelial cells that make up brain capillaries[27], and lactate uptake into the brain parenchyma has been demonstrated by magnetic resonance spectroscopy (MRS)[132] and correlates with increasing plasma lactate levels[133–135]. In humans, the increase in plasma lactate that occurs during exercise or following intravenous administration is oxidized by the brain[131], and this is associated with a reduction in glucose utilization in the brain[135–137]. This observation suggests a preferential use of lactate as an energy substrate for the brain, also shown by MRS in vitro and in vivo[20,46,48,138] (reviewed elsewhere[139]). In vivo lactate use by the brain is related to neuronal activity[140]; for example, during whisker stimulation in rats, lactate produced from ^{13}C-labelled glucose infused in the circulation increases locally in the corresponding (active) somatosensory cortex[141].

These observations are particularly interesting when considered alongside the effects of lactate on neuronal plasticity and excitability reviewed above. For example, in rats, exercise results in increased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus[142]. In humans, increases in blood lactate levels during exercise increase excitability of the primary motor cortex as evaluated by a decrease in the motor threshold evoked by single pulses of transcranial magnetic stimulation[143,144]. Thus, the link between the beneficial effects of exercise, plasma levels of lactate and the actions of lactate on the nervous system deserves

further attention. A recent study in mice[145] pointed to a possible molecular mechanism for this link by showing that exercise stimulates cerebral expression of vascular endothelial growth factor (VEGF) and angiogenesis and that these effects are mediated through HCAR1 on pericyte-like cells around intracerebral microvessels.

Molecular mechanisms of lactate signalling. Our understanding of the molecular mechanisms through which lactate exerts its numerous effects in the brain is still at an early stage. A principal putative receptor has been identified: HCAR1, which is negatively coupled to cAMP production and decreases excitability[79,120]. The existence of second, as-yet unidentified receptor type that is positively coupled to cAMP formation and that increases excitability was hypothesized[80] (FIG. 2) on the basis that the effect of lactate on LC neurons is blocked by the adenylyl cyclase inhibitor, SQ22536 (REF. [80]).

Lactate can also signal by being transported through neuronal MCTs and converted to pyruvate by LDH. This process results in the formation of NADH and ATP. In turn, NADH and ATP can act as direct or indirect intracellular effectors by modulating redox-dependent and energy-dependent mechanisms, which affect the activation of NMDARs or K_{ATP} channels, respectively[113,122,123,146] (FIG. 2). In the cerebral cortex, lactate inhibits the reuptake of prostaglandin E2 — a mechanism that may account for the vasodilatory effects of lactate[147].

Beneficial effects of lactate

Excitotoxicity and ischaemia. Early experiments showed that lactate could be neuroprotective against excitotoxicity induced by exposure to high glutamate concentrations in the rat cerebral cortex[148]. More translationally relevant studies showed a neuroprotective effect of lactate in the transient middle cerebral artery occlusion model of stroke[149,150]. In these studies, infarcts were smaller and neurological scores improved in animals given intracerebroventricular or intravenous injections of lactate up to 1 hour after reperfusion. Interestingly, lactate and pyruvate sustain hippocampal synaptic function and morphological integrity during glucose deprivation in hippocampal slices[151,152]. Studies at the cellular level in cultured cortical neurons[146] indicate that lactate and pyruvate exert their neuroprotective effects by increasing energy availability and thus ATP production.

Traumatic brain injury. Brain microdialysis studies in individuals who have sustained a traumatic brain injury (TBI) allow the determination of various metabolites, including lactate. Brain lactate levels are generally increased in TBI. When these increased lactate levels occur in the presence of normal pO_2 — suggesting the existence of aerobic glycolysis and a capacity for lactate oxidation — a better clinical outcome is observed. By contrast, high lactate concentrations in the presence of low pO_2 — indicating that lactate is formed by anaerobic glycolysis[153,154] — are associated with poor outcome. This correlation was also found when circulating lactate was considered, leading to the proposal that brain pO_2 and high blood lactate levels are the best predictors of outcome after TBI[155]. Furthermore, MRS studies using peripherally administered ^{13}C-labelled lactate as a tracer showed that increases in lactate uptake and oxidation by the brain were associated with better clinical outcomes after TBI. These observations, made by several independent groups[155,156], suggested that additional studies testing the potential positive effects of the intravenous administration of hypertonic lactate solutions in TBI patients may be warranted. Initial clinical observations have supported this notion[155,157,158], although this view has been challenged[159].

Psychiatric disorders. There is increasing evidence for a role of glial cells in mood disorders such as depression[160–163], and epidemiological evidence in individuals with depression indicates a positive effect of exercise, which, among other effects, is expected to result in increased circulating lactate levels (reviewed elsewhere[164]). Complex patterns of brain glucose metabolism monitored by ^{18}F-FDG PET are observed in depression. For example, individuals with depression show decreases in glucose metabolism in the dorsolateral prefrontal cortex and increases in the amygdala and insula[165–167]. In vitro studies show that selective serotonin-reuptake inhibitor antidepressants increase glucose utilization, glycogenolysis and lactate release by astrocytes[168].

On the basis of these observations, the possible antidepressant effect of acute or chronic peripheral administration of lactate was recently explored in several rodent models of depression[169] and, intriguingly, such treatment produced antidepressant-like behavioural responses in each of the tested models[169]. Acute peripheral injection of lactate reduced immobility in the forced swim test (a test of depressive-like symptoms) to a similar extent as did desipramine, a classic antidepressant. The antidepressant response induced by acute lactate administration was accompanied by increases in hippocampal lactate concentration, as determined by electrochemical-based biosensors[169]. Lactate also induced antidepressant-like effects in two animal models that respond to chronic but not acute antidepressant treatment: the open-space forced swim test and the corticosterone model of depression. The antidepressant-like effects induced by chronic lactate administration were accompanied by increases in the expression of genes implicated in serotonin receptor trafficking, astrocyte function and neurogenesis, and decreases in the expression of genes involved in NO synthesis and cAMP signalling. Interestingly, a clinical report published in 1947 indicated positive effects of lactate administration in depression[170].

Notably, hypertonic (0.5 M) lactate infusions have been shown to elicit panic attacks in a subpopulation of individuals with anxiety disorder[171]. The lifetime prevalence of panic disorder is approximately 5% of the general population[172]. Some preclinical data suggested that the mechanism of this panic-inducing effect of lactate in this restricted subpopulation is through the activation of acid-sensing ion channels (ASICs) by lowered pH in the amygdala[173]. However, other data indicate that the hypertonic sodium used in these studies, and not the lactate itself, is actually the key stimulus provoking panic attacks[174,175].

Carotid body
A chemosensory organ at the carotid artery bifurcation that is the major sensor of blood oxygen in mammals.

Minute ventilation
The volume of gas inhaled or exhaled by the lungs per minute.

Excitotoxicity
The pathological process by which neurons are damaged or killed by excessive stimulation by glutamate or other excitatory neurotransmitters.

Middle cerebral artery occlusion
An experimental model of stroke based on focal cerebral ischaemia induced by permanent or transient occlusion of the middle cerebral artery in mice or rats.

Conclusions

Overall, lactate displays pleiotropic effects in the brain that can be related to a common physiological role in coupling neuronal activity to both energy metabolism and signalling[176–178] (FIG. 2). One form of coupling involves neurons responding to astrocyte-derived lactate that provides both energy and signals. In this context, lactate, along with other astrocyte-derived signalling molecules (such as ATP, adenosine and serine), represents an additional intercellular signalling pathway in the brain. The actions of lactate should be considered to occur at different temporal and spatial scales than neurotransmission, overall operating at longer timescales and more diffuse spatial domains[177]. The actions of lactate should be viewed as mainly setting the 'homeostatic tone' of the nervous system, by ensuring adequate energy supply, setting neuronal excitability levels and regulating adaptive functions, including memory, that are mediated by plasticity mechanisms.

Further studies on the role of lactate in the brain are undoubtedly necessary, in particular to better characterize the molecular mechanisms through which lactate affects the functions of neurons and possibly other brain cell types, such as oligodendrocytes, microglia, pericytes and capillary endothelial cells. A better understanding of such molecular mechanisms will also open the way to the development of novel molecules with therapeutic properties, particularly regarding neurodegenerative and other neuropsychiatric disorders.

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