Here, we present the perspective that lactate acts as a volume transmitter in brain tissue by distributing cellular signals that are relevant to the metabolic support of large neuronal ensembles. We interpret recent evidence to mean that lactate transmission serves the maintenance of network metabolism by two different mechanisms; one by regulation of neuronal cAMP formation through the lactate receptor GPR81, the other by adjusting the NADH/NAD+ redox ratios, both linked to the maintenance of brain energy turnover and possibly cerebral blood flow. The role of lactate as mediator of metabolic information rather than metabolic substrate answers a number of questions raised by the controversial oxidative nature of astrocytic metabolism and its contribution to neuronal function.

Keywords: lactate, lactate receptor, central fatigue, metabolic information, volume transmission
is prominent in adipose tissue, where it inhibits lipolysis, but it is known also to be expressed in a wider range of organs such as liver, kidney, skeletal muscle, spleen, and testis (Giunta et al., 1997; Ge et al., 2008; Liu et al., 2009; Rooney and Trayhurn, 2011). Evidence from in situ hybridization show a widespread distribution of GPR81 mRNA in the brain, predominantly in neurons, including the principal neurons in cortex, hippocampus (pyramidal and granule cells), and cerebellum (granule cells), while labeling of astrocytes cannot be excluded (The Allen Institute for Brain Science1, GENSTA T2, St. Jude Children’s Research Hospital3). The receptor's reported affinities for L-lactate range from 1.3 to 5 mM (Cai et al., 2008; Liu et al., 2009), which is consistent with the range of lactate concentrations measured in brain tissue in vivo (Abi-Saab et al., 2002). The binding of lactate to GPR81 attenuates the formation of cAMP, which in turn inhibits protein kinase A and hence glycogenolysis, leading to decreases of glucose-1-phosphate and glucose-6-phosphate (G6P) that affect glycolysis in the cytosol, as recently shown by kinetic modeling (D’Nuzzo et al., 2010). The decrease of G6P affects its role as allosteric regulator of hexokinase (HK), including the association of HK with the voltage dependent anion channel (VDMC) in the outer mitochondrial membrane, with important consequences for the efficiency of oxidative phosphorylation of ADP (Wilson, 2003; Malilou and Harper, 2011). The main thrust of this perspective is the importance of any physical separation of HK and pyruvate dehydrogenase (PDH) activities, which would lead to diffusion of lactate between the sites. As such, this concept is not limited to major compartments or cell types but applies equally well to subdivisions of cells, such as distal vs proximal dendrites and astrocytic processes vs cell bodies rather than to astrocyte/neuron differences (Figure 1).

**CYTOSOLIC AND MITOCHONDRIAL NADH/NAD+ REDOX RATIOS AND LACTATE DEHYDROGENASES**

Lactic and pyruvic acids interact through the actions of the cytosolic near-equilibrium lactate dehydrogenase (LDH) isozymes, which reflect the cytosolic NADH/NAD+ ratios in cytosol. The cytosolic and the mitochondrial redox states are linked through a network of redox reactions and inner membrane transport processes, but the exact relation between cytosolic and mitochondrial NADH/NAD+ ratios is not known. There are reports of mitochondrial LDH activity (Brooks, 2009) and therefore potential for coupling of lactate–pyruvate and NADH/NAD+ ratios in the mitochondrial matrix. Changes of the NADH/NAD+ redox ratios trigger several intracellular responses, including expression of genes by modification of histone deacetylases, which profoundly affect the regulation of protein synthesis. For example, sirtuins, gene-regulating histone deacetylases with effects on energy metabolism rather than metabolic substrate answer a number of questions raised by the aerobic glycolysis of astrocytes and its controversial contribution to neuronal function. (Cai et al., 2008; Liu et al., 2009), which is consistent with the range of lactate concentrations measured in brain tissue in vivo (Abi-Saab et al., 2002). The binding of lactate to GPR81 attenuates the formation of cAMP, which in turn inhibits protein kinase A and hence glycogenolysis, leading to decreases of glucose-1-phosphate and glucose-6-phosphate (G6P) that affect glycolysis in the cytosol, as recently shown by kinetic modeling (D’Nuzzo et al., 2010). The decrease of G6P affects its role as allosteric regulator of hexokinase (HK), including the association of HK with the voltage dependent anion channel (VDMC) in the outer mitochondrial membrane, with important consequences for the efficiency of oxidative phosphorylation of ADP (Wilson, 2003; Malilou and Harper, 2011). The main thrust of this perspective is the importance of any physical separation of HK and pyruvate dehydrogenase (PDH) activities, which would lead to diffusion of lactate between the sites. As such, this concept is not limited to major compartments or cell types but applies equally well to subdivisions of cells, such as distal vs proximal dendrites and astrocytic processes vs cell bodies rather than to astrocyte/neuron differences (Figure 1).

**NEAR-EQUILIBRIUM REACTIONS AND LACK OF COMPARTMENTATION**

Both the LDH isozymes and the monocarboxylic acid transporters (MCT) of the blood–brain barrier and cell membranes of brain tissue mediate near-equilibrium transfer of lactate (Bergersen et al., 2001; Bergersen, 2007) when unidirectional fluxes exceed net fluxes by several orders of magnitude. Therefore LDH and MCT proteins serve to dissipate lactate concentration differences across cell membranes and tissue volumes. Thus, changes of pyruvate and lactate concentrations in one place lead to similar changes of lactate concentrations across large volumes of brain tissue over long times. In turn, any effects of changes of lactate on the NADH/NAD+ ratio in one place lead to similar effects in widely distributed populations of cells (Cai et al., 2008; Ramírez et al., 2007; Rodrigues et al., 2009). In fact, the transfer of lactate is so efficient that it is difficult to observe any differences of lactate concentrations across cell membranes in brain tissue (Gjedde and Marrett, 2001; Ido et al., 2001, 2004; Gjedde et al., 2002), such that significant cellular compartmentation of lactate is unlikely to exist under normal conditions, except briefly. The high concentration of MCT2 at the PSD of fast excitatory synapses co-localized with glutamate receptors (Bergersen et al., 2002), the DNA binding of the transcription factor fos-fjun heterodimer AP-1 depends on a specific cysteine residue being in the reduced state (Abate et al., 1998), acting as a redox sensor. In addition, pyruvate, which interacts closely with lactate as dictated by the NADH/NAD+ ratio, is a gene regulator through histone deacetylase inhibition (Thangaraju et al., 2009; Rajendran et al., 2011).
tate spreads through the astroglial network in which individual
and MCT4, and by diffusion through the extracellular space, lac-
across plasma membranes of all cells through MCT1, MCT2,
addition to moving through brain tissue by facilitated transfer
synapses perhaps involved in volume transmission signaling. In
which at near-equilibrium is not yet understood (Ross et al., 2010;
Quasthoff and Grunnet, 2011; Ross, 2011), but may be related to
the proposed function of lactate as a volume transmitter in cytosol-
and perhaps mitochondrial environments with widely differing

NON-STeadY-STATES AND ACTIVATION

The purported changes of lactate concentrations and the conse-
quent redistribution of lactate happen whenever and wherever
sites of generation and metabolic conversion of pyruvate are
unaltered or physically separated. Pyruvate is the main end
product of aerobic glycolysis, which is controlled by the con-
certed action of the HK and phosphofructokinase (PFK) enzyme
complex, while the fate of pyruvate is determined by the PDH
complex in mitochondria. The two enzyme complexes are the
main flux-generating determinants of brain energy metabolism
as controlled by allosteric effectors, and both therefore define the
path that is open to the respective so-called "pathway substrates,"
glucose in the case of the HK–PFK complex, pyruvate in the case
of the PDH complex (Gjedde, 2007). The temporal and spatial
integration of these enzymes complexes is then the key to the dynamics of lactate inside and among the cells of
brain tissue. Both the oxygen–glucose index (OGI) and the oxygen
extraction fraction (OEF) decline during the temporary departures
from steady-state associated with functional activation of
brain regions, attributed to increased aerobic glycolysis (Madsen
et al., 1999; Schmalbruch et al., 2002). The declines are signs of
focal disintegration of the HK–PFK and PDH activities, resulting in
increased lactate–pyruvate ratios, redistribution of lactate and
adjustment of NADH/NAD+ ratios within the sphere of action of
the redistributed lactate. This process seems to be so efficient that
it leaves no oxygen deficit or abnormal ATP, ADP, or AMP levels,
even in seizures (Larach et al., 2011).

Extracellular lactate concentrations increase during neuronal
and synaptic activation in vivo, as determined by microdialy-
sis (Uehara et al., 2008; Bero et al., 2011), and proton magnetic
resonance spectroscopy minutes after stimulation (Priechard et al.,
1991; Sappey-Mariner et al., 1992; Maddock et al., 2006), follow-
ing a transient decrease 5 s after stimulation (Manjia et al., 2003).
These observations are consistent with adjustments that follow
the perturbation of an existing steady-state and the subsequent
return to a potential new steady-state, depending on conditions,
such as the intensity of the continuing neuronal activation. The
lactate dynamics are uniquely dependent on the shifts among
these steady- and non-steady-states of brain energy metabolism. The
observations that the OGI declines during the non-steady-
state of the early stages of functional brain activation, signifies
increased lactate production in the tissue as a whole, evidently due
to increased glucose consumption relative to oxygen consumption. The observations are consistent with changes of glucose consump-
tion that match the changes of blood flow during activation, while
changes of oxygen consumption generally do not (Gjedde et al.,
2002; Paulson et al., 2010). Recent evidence also shows that the
changes of glucose consumption exceed the changes of oxygen
consumption at specific regional locations (Vaishnavi et al., 2010),
rather than everywhere, creating the gradients of lactate concen-
tration that serve to redistribute lactate inside as well as outside
cells and across the blood-brain barrier. The regional variation of
the OGI (Vaishnavi et al., 2010) may possibly be related to different
ratios of cell types (low in cortex with numerous astrocytes, high
in cerebellum with numerous neurons). Any separation of the
sites of lactate generation and lactate metabolism inside or among
cells therefore must result in shuttling of lactate among its sites of
generation and metabolism. The fluxes alter the interactions with
enzymes and transporters that qualify as volume transmission. Thus,
the temporal and spatial mismatches of lactate generation and
metabolism arise because different cellular and subcellular
compartments react differently to activating stimuli (Gjedde et al.,
2000; Vaishnavi et al., 2010).

CENTRAL vs PERIPHERAL FATIGUE

Physical exertion generates considerable increases of lactate con-
centration in the circulation. It has been shown by MR spec-
troscopy that blood lactate is an efficient substrate for the brain,
and especially for neurons, both in rat (Bouzier et al., 2000; Has-
siel and Brübe, 2000) and in humans (Boumezeur et al., 2010).
The increased lactate also has effects on brain metabolism, which
are characterized by reduction of the cerebral OGI in the context
of a state known as "central fatigue" (Dalgaard, 2006; Dalgaard
and Secher, 2007; Rasmussen et al., 2010). Central fatigue pre-
cedes the muscle fatigue that also relates to increased lactate (van
Hall, 2010). The mechanism responsible for the onset of central
fatigue is not known with certainty but appears to be related to
decreased oxygen delivery, which in turn may be due to increased
lactate in brain tissue and possible effects on lactate's receptor
gPCR1 (Rasmussen et al., 2010; Gam et al., 2011). The down-
regulation of cAMP formation by binding of lactate to GPCR1
offers a novel explanation of central fatigue and “over-training”
distress (Lehmann et al., 1993), and possibly in part the authen-
tica seen in advanced cancer, a condition that is known to be
characterized by chronically increased blood lactate levels (Kop-
penol et al., 2011). Chronically increased lactate levels similarly
are held to be characteristic of old age and dementia, based on the
properties of a mtDNA mutator mouse model (Ross et al.,
2010). These effects contrast with the upregulation of cAMP by
noradrenaline with effects such as arousal and enhanced brain
performance (Berridge, 2008).

Many other observed effects of lactate on neuronal function
may result from enzyme- or receptor-mediated responses rather
than from the direct actions of lactate as a metabolic substrate.
For example, the observation that lactate administration pro-
tects against ischemia (Schurr et al., 1997, 2001; Careton et al.,
2010) has been ascribed to enhanced neuronal energy turnover.
However, this is not readily explained by metabolic effects, as
lactate metabolism cannot raise energy turnover under ischemic
conditions, although after ischemia and in the penumbra of vascu-
lar occlusion, the availability of lactate for oxidation may assist in
alleviating ischemia induced damage (Schurr et al., 2001; Berthet
et al., 2009). Similarly, the observed protective effect of lactate on
neuroglia toxicity in the brain (Ros et al., 2001) may be due to
receptor-mediated inhibition, rather than the simple satis-
faction of the metabolic demands for higher concentrations of glutamate (Schurr et al., 1999). In microdialy-
sis of the cerebral cortex, excitotoxic concentrations of glutamate
raised lactate at the expense of glucose in the dialysate. The
addition of l-lactate caused the lesion to become smaller and
abolished the decrease of glucose. Replacing l-lactate with the non-
physiological D-lactate isomer expanded the lesion and raised l-lactate in the dialysate above the level observed with glutamate
alone (Ros et al., 2001), consistent with the claim that endoge-
nously produced lactate is neuroprotective by means of receptor
interaction.

The suppression of noradrenaline and adrenaline releases by
blood lactate clamps at 4 mM (Tattor et al., 2005) also suggests
a receptor mechanism, consistent with the postulated reduc-
tion of AMP formation by GPRKI activation. Interestingly, also
β-adrenoceptor blockers, which presumably act by reducing intra-
cellular cAMP, are neuroprotective in stroke and other brain
injuries, and also lower extracellular glutamate levels, which may
further limit excitotoxic cell damage (Goyagi et al., 2011).

CONCLUSION

The proposed role of lactate as a mediator of information on
changing NAH/NAD⁺ ratios among the cells of brain tissue has
implications for the understanding of regulation of brain energy
metabolism, including the communication between cytosol and
mitochondria in large populations of cells (Xu et al., 2007). Lactate's
inhibition of AMP formation through G-protein-coupled
receptors may be a factor in the development of central fatigue.
An action of lactate may therefore be to "smooth" the non-steady-
states that underlie the mismatches of glycolysis and oxidative
phosphorylation, induced by needs for aerobic glycolysis that
satisfy the short time constants of ATP turnover required for
maintenance of rapid de- and repolarizations. The redistribution of lactate by the volume transmission is both temporal and spa-
tial and potentially reaches large volumes of tissue, aided by the
extended synecytium of astrocytic networks connected by gap-junc-
tions. The role of lactate as informant of metabolic states rather
than substrate of metabolism solves a number of puzzles that
contribute to the controversy surrounding the understanding of
astrocytic metabolism and its contribution to neuronal function.

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