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Review

Lactate production and neurotransmitters; evidence from microdialysis studies

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ABSTRACT

Recent studies have found that lactate metabolism plays a significant role in energy supply during acute neural activation in the brain. We will review evidence from microdialysis studies for a relationship between neurotransmitters and lactate production, as revealed in studies of the effects of psychotropic drugs on stress-induced enhancement of extracellular lactate concentrations.

Glutamate enhances stress-induced lactate production via activation of N-methyl-D-asparate receptors, and is affected by uptake of glutamate through glutamate transporters. Findings from microdialysis studies suggest that major neurotransmitters, including norepinephrine, dopamine, serotonin, and GABA (via benzodiazepine-receptors) affect lactate production, depending on brain areas, especially during stress. Among these neurotransmitters, glutamate may principally contribute to the regulation of lactate production, with other neurotransmitter systems affecting the extracellular lactate levels in a glutamate-mediated manner.

The role for anaerobic metabolism in the supply of energy, as represented by lactate dynamics, deserves further clarification. Monitoring with intracerebral microdialysis is a reliable method for this purpose. Research into this area is likely to provide a novel insight into the mode of action of psychotropic drugs, and the pathophysiology of some of the stress-related mental disorders as well.

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Contents

1. Introduction

Microdialysis is an analytical technique suitable for measuring unbound fluid concentrations of molecules in tissues and organs. It is based on sampling of soluble molecules from the interstitial space

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fluid by means of a semipermeable membrane at the tip of a probe (Muller, 2002). The strength of this method is the ability to monitor changes in the composition of extracellular fluid in the brain of anesthetized or freely moving animals (Obrenovitch and Zilkha, 2001). Microdialysis is widely used to measure not only neurotransmitters/modulators, including amino acids, catecolamines, and peptides (Horn and Engelmann, 2001; Parent et al., 2001), but also energy substrates, such as glucose, lactate and local blood flow (Li et al., 2006). Moreover, this method is advantageous to study local pharmacodynamics, as it allows systemic or local administration of drugs (Li et al., 2006).

The brain requires continuous supply of oxygen and energy-yielding substrates, such as glucose (McKenna et al., 2006). Recent investigations have found that lactate metabolism also plays a significant role in the brain energy supply, especially during acute neural activation (Aubert and Costalat, 2007; Pellerin et al., 2007) or pathological conditions (e.g., ischemia) (Bergersen, 2007). It is generally assumed that energy production is obtained from both glucose and lactate under various conditions, e.g., acute neural activation, insufficient glucose supply from blood flow, and so on.

In this review we will present an overview on (1) the significance of extracellular lactate concentrations during neural activity, (2) dynamics of lactate production based on evidence from microdialysis studies, and (3) the effects of various stressors on lactate levels. Also, (4) the role for several neurotransmitters in lactate synthesis in relation to neural activation will be discussed.

2. Energy metabolism and neural activity

2.1. Energy metabolism under basal conditions and during neural activation

Postsynaptic dendrites consume a considerable proportion of the total energy production associated with synaptic currents and action potential propagation in the brain (Attwell and Laughlin, 2001). In other words, a large part of energy consumed by the brain fuels the Na^+/K^+ pumps, which maintain electrochemical gradients (Edwards et al., 1989; Erecinska and Dagani, 1990). Moreover, a certain amount of energy is required to sustain basic cellular functions. According to the conventional view (Fig. 1-A), the brain is fuelled almost entirely by oxidative metabolism of glucose, and production of lactate during neural activity is considered to be a result of glycolytic processes that occurs when energy demands transiently exceed the rate of oxidative metabolism (Chih and Roberts, 2003; Prichard et al., 1991). On the other hand, it is less clear how lactate behaves under basal (physiological) conditions. The conventional view precludes that lactate has to undergo a reuptake process by brain cells after activation is terminated (Chih et al., 2001). In fact, previous studies report that lactate exists in the extracellular space under basal conditions (Kuhr and Korf, 1988a; Takita et al., 1992; Uehara et al., 2006, 2007a). Moreover, glucose not only functions as an energy substrate but also fulfills many roles, including glycogen formation (McKenna et al., 2006). Glycogen can provide energy to neurons, presumably in the form of lactate, when the glucose concentration is low in the brain (McKenna et al., 2006).

In recent years, many investigations have found that lactate also plays a significant role in energy supply, especially during acute neural activation (Pellerin, 2003) or pathological conditions (e.g., ischemia) (Bergersen, 2007). The astrocyte-neuron lactate shuttle (ANLS) hypothesis (Pellerin, 2003; Pellerin and Magistretti, 1994; Tsacopoulos and Magistretti, 1996) was proposed to explain how glucose supplied from the circulation is converted to lactate by astrocytes following uptake of glutamate by these cells. Lactate is then released to the extracellular space, and is taken up by active neurons to fuel neuronal oxidative metabolism (Pellerin, 2003; Pellerin et al., 1998) (Fig. 1-B).

Since the proposal of the ANLS hypothesis, the role of lactate as an important energy substrate for brain cells has been the subject of intense debate (Chih and Roberts, 2003; Korf, 2006; Pellerin, 2003). Some researchers insisted that the distribution of monocarboxylate transporters (MCTs) do not support the concept of a directed flux of lactate from astrocytes to neurons (Hertz and Dienel, 2005), whereas others support the ANSL hypothesis (Bergersen, 2007). According to the ANLS hypothesis by Pellerin et al. (Pellerin, 2003; Pellerin et al., 2007), it is predicted that this mechanism solely accounts for the energy metabolism of neurons during activation, and that ANLS occurs at basal conditions. Pellerin et al. (2007) also emphasized that the ANLS hypothesis supports the role for glucose as a substrate for neural energy, and that neurons consume both glucose and lactate. The authors hypothesized that lactate is used by neurons as an aerobic substrate under precise circumstances (Pellerin et al., 2007). According to this proposal, lactate behaves differently depending on the phase of neural activation (early or late), its intensity, and length of stimulation (Gjedde et al., 2002; Pellerin et al., 2007). Moreover, Aubert and Costalat (2007) "compartmentalized" brain energy metabolism in neurons and glia using mathematical modeling. According to this model, no contribution of the ANLS was identified at rest, whereas the ANLS occurred, at least, during the first ten seconds of sustained neural activation and during the poststimulus period. Therefore, the conventional view and ANLS hypothesis may not be conflicting opinions.

2.2. Lactate metabolism and microdialysis technique

Microdialysis is a catheter-based sampling technique. The level of a substrate in dialysate samples is a net result of the interaction between release into and removal from the extracellular space (Parent et al., 2001). Therefore, extracellular lactate concentrations monitored by microdialysis depend on: (1) lactate exchange between cells (neurons, astrocytes) and the extracellular space via the MCTs, and (2) exchange across the blood-brain barrier (Aubert and Costalat, 2007).

Combination of sampling technique with off-line analysis of consecutive dialysate samples is the popular approach (Gardenfors et al., 2004). The advantage of off-line sampling is the ability to analyze some endogenous substances of interest in one sample simultaneously, e.g., lactate and glucose (Gardenfors et al., 2004). However, the off-line sampling is limited in terms of time resolution (Obrenovitch and Zilkha, 2001). In the late 1980s, the combination of in vivo microdialysis technique with enzyme reactor/fluorometric detector enabled researchers to measure extracellular lactate levels on-line (Kuhr and Korf, 1988a; Schasfoort et al., 1988). This methodology allows continuous sampling from the extracellular space, enzymatic conversion of lactate, and on-line detection of fluorescent NADH (Schasfoort et al., 1988). The advantage of this method is that it provides temporal information, nearly real-time nature, as well as quantitative information, about the fluctuations in the concentration of lactate in the extracellular fluid (Korf and de Boer, 1990; Kuhr and Korf, 1988a). Using this technique, we have conducted a series of studies on the effects of psychotropic drugs on lactate metabolism in the rat brain (Uehara et al., 2003a, 2005, 2006, 2007a,b).

Time resolution provided by flow enzyme analysis is still suboptimal, because of dispersion of reagent-dialysate solution during its transit from the dialysis probe outlet to the fluorometer (Obrenovitch and Zilkha, 2001). Also, it is difficult to detect changes of extracellular lactate concentrations, which occur in the second order. It should be noted that the site of extracellular lactate production cannot be identified by microdialysis technique. For example, it is not possible to identify the origin of lactate (neurons or astrocytes) during neural activation as proposed by the ANLS. However, on the basis of the Aubert's model (Aubert and Costalat, 2007), a part of lactate in dialysates is shown to originate from astrocytes.

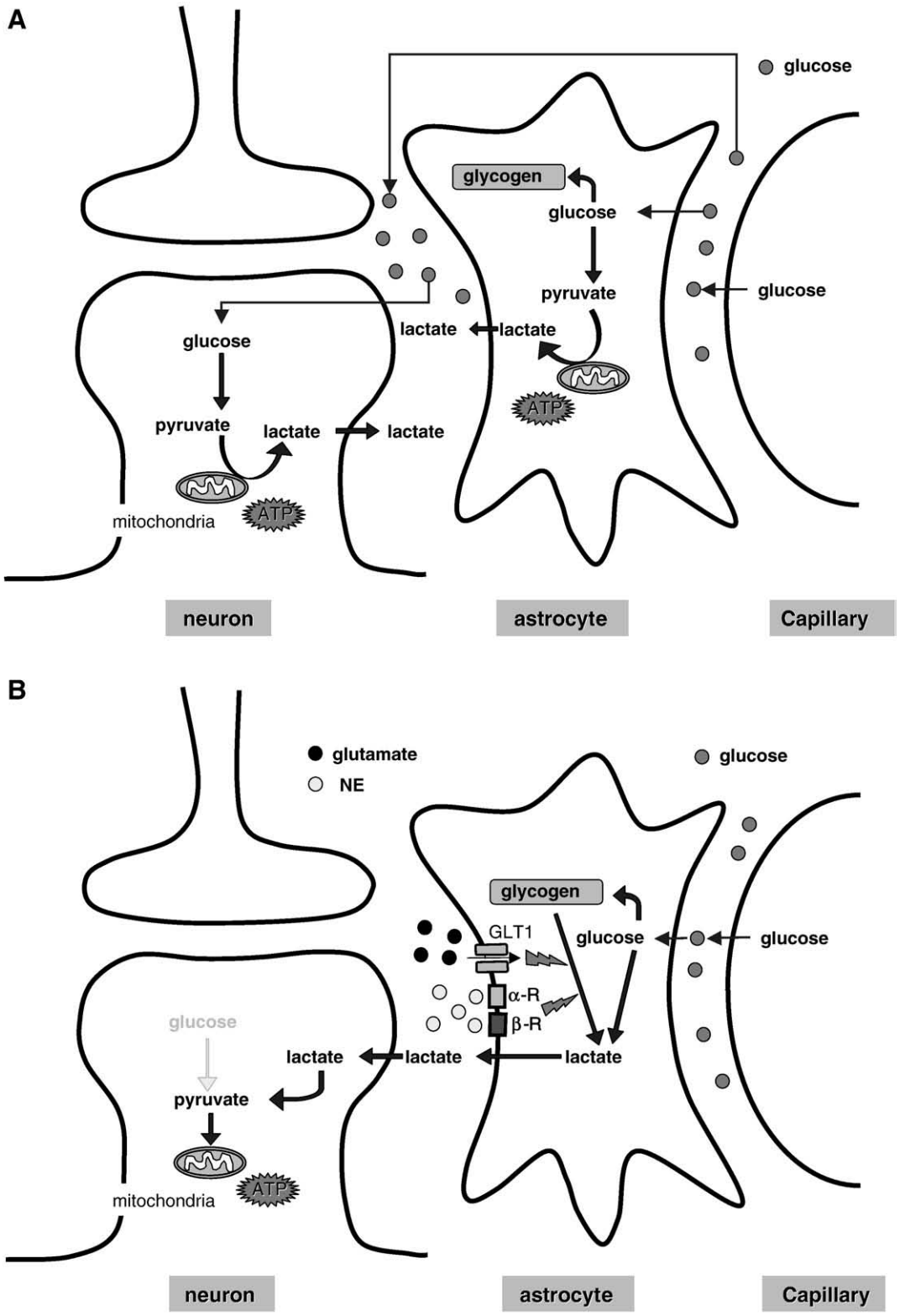


Fig. 1. Schematic diagrams of lactate production based on (A) the conventional hypothesis and (B) the astrocyte-neuron lactate shuttle (ANLS) hypothesis. (A) Glucose is used by neurons and astrocytes to maintain basic cellular functions. Increased energy demands (ATP use) activates the glycolytic pathway and increases oxidative glucose metabolism in both neurons and astrocytes. In this case, glucose is transported into neurons and astrocytes, and is mainly metabolized aerobically. Lactate is considered to be produced as a result of glycolytic activity when energy demand transiently exceeds the rate of oxidative metabolism during neural activation. (B) The ANLS postulates that neural activity promotes lactate production by astrocytes in a glutamate- or adrenergic receptor-mediated manner. Lactate is then released to the extracellular space and taken up by neurons to fuel neuronal oxidative metabolism. Abbreviations and symbols: GLT1, glutamate transporter 1; NE, norepinephrine; α-R, α-adrenergic receptor; β-R, β-adrenergic receptor; shaded circle, glucose; closed circle, glutamate; open circle, NE.

In the microdialysis technique, semipermeable membrane consists of a small probe (typically 1–3 mm) that is inserted into a specific brain region. Therefore, it measures the environment over a radius of several hundred microns. This technique is reliable for the measurement of micro-environmental events, which makes it an attractive tool for local pharmacodynamic research (Li et al., 2006). Estimation of

the effect of drugs on extracellular lactate concentrations at their sites of action reveals synaptic function within distinct brain areas.

3. Lactate production during neural activation

3.1. Correlations between glucose metabolism and lactate production

The addition of 2-deoxyglucose (2-DG) to dialysis perfusate results in an immediate decrease in extracellular glucose and lactate concentrations (Kuhr and Korf, 1988a; Takita et al., 1992; Uehara et al., 2007a). These findings demonstrate that extracellular lactate concentrations are coupled to glucose metabolism. The immediate decrease in levels of lactate following 2-DG perfusion suggests that lactate is produced incessantly even under basal conditions. Local application of tolbutamide (1 mM applied through the dialysis probe), which selectively blocks the ATP-sensitive potassium channel, caused a substantial decrease in basal lactate levels and a gradual decrease in extracellular glucose levels in the hippocampus (Fellows et al., 1993a). This suggests that high ATP concentrations in neural cells attenuate lactate production rather than glucose uptake. Paradoxically, lactate, as an energy substrate, is likely to meet energy demands in acutely activated neurons.

Extracellular glucose levels were increased following inactivation of neurons by TTX (10 μM) perfusion, whereas enhancement of neural activity by veratridine (50 μM) or K^+ (100 mM) perfusion decreased glucose concentrations in the nucleus accumbens (NAC). By contrast, lactate concentrations were increased by veratridine or K^+ perfusion, but were unaltered by TTX perfusion (Uehara et al., 2007a). In the same way, the addition of 1 μM TTX to the perfusion increased glucose levels in the striatum (Fellows et al., 1992). TTX prevents the generation of action potentials by blocking the voltage-gated sodium channel, whereas veratridine causes neuronal depolarization by persistently opening this channel at resting membrane potentials (Catterall, 1984). Thus, extracellular glucose represents a balance between supply from blood and cellular utilization, two events closely related in the brain (Cremer et al., 1983). Extracellular glucose concentrations in the brain are also influenced by blood levels. Thus, glucose levels in the hippocampus increase following intravenous glucose infusion (van der Kuil and Korf, 1991). These findings indicate that the changes of extracellular glucose concentrations are not specific to the intensity of neural activity, but rather reflect the balance between neural activity and energy demands. On the basis of these considerations, the observed decrease in glucose levels following veratridine or K^+ perfusion is thought to reflect enhanced glucose use by neurons. By contrast, reduction in neural activity by TTX perfusion may make the energy balance into the opposite direction.

By contrast, extracellular lactate concentrations are thought to be independent of such external milieu (Kuhr et al., 1988), because little lactate pass through the blood-brain barrier unlike glucose. Therefore, lactate is considered to be an important alternative substrate for energy metabolism in the absence of sufficient glucose. Brain tissues shift immediately to receiving energy supply from lactate in the face of acute neural activation (Hu and Wilson, 1997). It is proposed that lactate is produced by astrocytes and released into the extracellular space to form a pool readily available for neurons in case of high energy demands (Pellerin, 2003; Pellerin et al., 2007). This may be a mechanism by which neural activation by veratridine or K^+ perfusion is accompanied by increased extracellular lactate levels. Especially, K^+ released from axons as a consequence of action potential propagation mobilizes glycogen in astrocytes, producing lactate for use by neighboring neurons (Pellerin, 2003). TTX perfusion does not influence extracellular lactate in the basolateral amygdala (BLA) (Uehara et al., 2003a) and nucleus accumbens (NAC) (Uehara et al., 2007a). These findings indicate prolonged lactate production in the absence of energy demand. This is compatible with an opinion that lactate is produced during poststimulus period (Aubert and Costalat, 2007).

3.2. Stress-induced enhancement of lactate production

Various types of physical (e.g., tail pinch, immobilization, footshock) and emotional stressors have been shown to increase extracellular lactate concentrations in some brain regions. Table 1 demonstrates a summary of the stress effect on extracellular lactate levels in the rat brain. In the medial prefrontal cortex (mPFC), extracellular lactate concentrations were increased by tail pinch, immobilization (Takita et al., 1992), and footshock (Uehara et al., 2006) stress. Footshock stress also enhanced lactate production in the BLA (Uehara et al., 2006, 2005). Prolonged immobilization stress (40 to 90 min) induced a transient increase in lactate release in the mPFC and BLA, followed by a gradual decrease to basal levels during continued exposure to stressors (Takita et al., 1992; Uehara et al., 2003a). These findings indicate that immobilization stress induces transient increment of lactate, suggesting that enhancement of lactate production was due to acute neural activation, possibly representing an adaptation response. The second lactate response to tail pinch or immobilization stress was shorter than the initial response induced by the same stimulus after intervals, eliciting habituation (Takita et al., 1992; Thompson and Spencer, 1966).

Physical stress enhances lactate production also in the hippocampus. Thus, handling, immobilization, cold exposure, or tail pinch increased extracellular lactate concentrations (De Bruin et al., 1990; Dijk et al., 1991; Fellows et al., 1993b; Krugers et al., 1992; Schasfoort et al., 1988). The degree of lactate increment does not differ among these physical stressors (Schasfoort et al., 1988). Habituation to pre-exposed immobilization was also seen in the hippocampus (Schasfoort et al., 1988). On the other hand, tail pinch for 5 min increased extracellular lactate concentrations (Fellows et al., 1993b), whereas immobilization for 5 min did not affect lactate levels (De Bruin et al., 1990) in the striatum.

Only a few studies have demonstrated the effect of emotional stress on lactate production in the brain. Emotional stress evoked by placement of rats on the platform in a swimming pool increased extracellular lactate concentrations in the hippocampus but not striatum (De Bruin et al., 1990). Psychological stress, by means of communication box, also enhanced extracellular lactate levels in the BLA (Uehara et al., 2005). The communication box method designed by Ogawa and Kuwahara (1966) has been used to investigate the physiological events in response to sociopsychological stressors. Findings by this method have revealed that animals exposed to physical stress such as footshock can induce sociopsychological response by way of an interspecies emotional communication (Ishikawa et al., 1992; Uehara et al., 2003b).

Table 1
Stress-induced changes of extracellular lactate levels in the rat brain as evaluated by microdialysis technique

	Hippocampus	Striatum	mPFC	BLA
physical stress				
Foot shock			↑ (9)	↑ (8)(9)
IMB	↑ (1)(2)(4)(5)	↑ (2)(3) *or* → (1)	↑ (6)	
Prolonged IMB			↑ ~ → (6)	↑ ~ → (6)
Tail pinch	↑ (3)	↑ (3)	↑ (6)	
Cold exposure	↑ (5)			
Handling	↑ (5)			
emotional stress				
Psychological				↑ (7)
Platform	↑ (1)	→ (2)		

mPFC;medial prefrontal cortex, BLA; basolateral cortex, IMB; immobilization, platform placement on platform. ↑; increase, →; no change, ↑ ~ →; immediate increase followed by decrease to basal levels

(1) De Bruin et al., 1990 (2) Dijk et al., 1991 (3) Fellows et al., 1993b
(4) Krugers et al., 1992(5) Schasfoort et al., 1998 (6) Takita et al., 1991
(7) Uehara et al., 2003a (8) Uehara et al., 2005(9) Uehara et al., 2006.

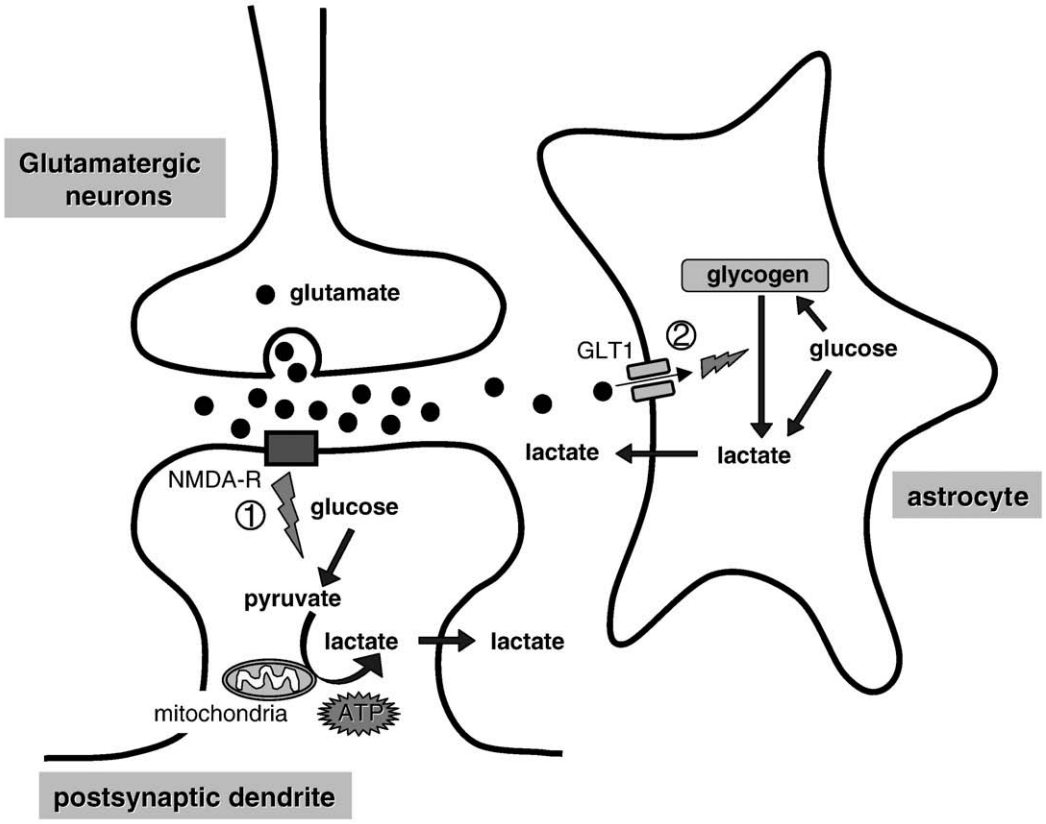


Fig. 2. Schematic diagram of the putative enhancement of lactate production induced by glutamatergic neurotransmission. Glutamate released into the synaptic cleft stimulates NMDA receptors on postsynaptic dendrites, and subsequently, is captured by glial-type Na^+-coupled glutamate transporters (GLT1, GLAST). First, stimulation of NMDA receptors activates glucose metabolism, in part anaerobically, in postsynaptic dendrites (①) or astrocytes. For graphic clarity, only the event in postsynaptic dendrites is indicated. Second, reuptake of glutamate into astrocytes through glutamate transporters enhances glycolytic process, resulting lactate production (②). Shaded circles represent glutamate. Abbreviations: NMDA-R, NMDA receptor; GLT1, glutamate transporter 1; GLAST, glutamate-aspartate transporter.

3.3. Activity-dependent production of lactate in astrocyte

When the ANLS is functioning, lactate is produced in an activity-dependent and glutamate-mediated manner by astrocytes, and is then transferred to and used by active neurons (Aubert and Costalat, 2007; Pellerin, 2003; Pellerin et al., 2007). Glutamate taken up into astrocytes through glutamate transporters (GLTs) after synaptic release stimulates astrocytic glycolysis and lactate production. In this process, glutamate uptake into astrocytes and the resulting increase in intracellular Na^+ have been identified to facilitate coupling of excitatory neural activity and increased glucose utilization (Chatton et al., 2000; Magistretti et al., 1999). Accordingly, it was shown that excitatory amino acids, such as glutamate, stimulate aerobic glycolysis, i.e. glucose consumption and lactate production, in cortical astrocytes (Pellerin and Magistretti, 1994; Takahashi et al., 1995). Moreover, a stoichiometric relationship exists between glutamate-neurotransmitter cycling flux and oxidative glucose metabolism (Sibson et al., 1998). Na^+ entry into astrocytes resulting from glutamate transport activates Na^+/K^+ ATPase, which in turn stimulates glucose use and lactate production, leading to rapid supply of ATP through the astroglial pump (Magistretti and Chatton, 2005; Pellerin and Magistretti, 1997).

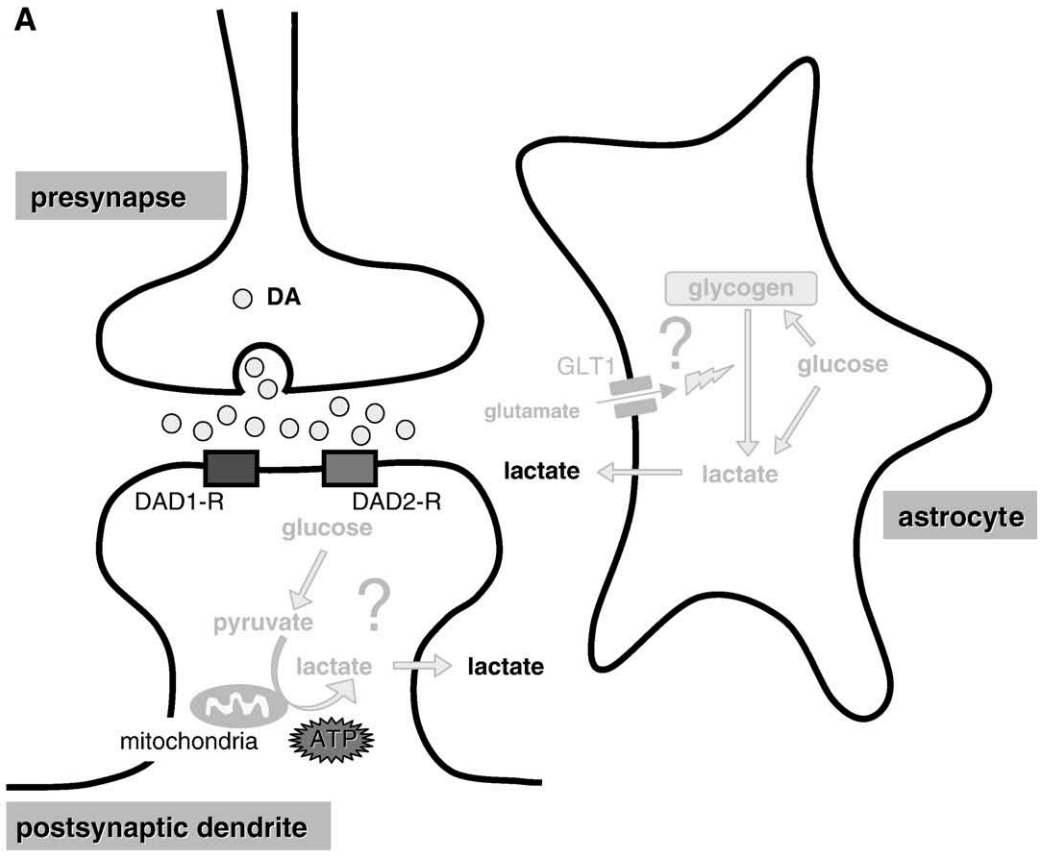
Glutamate transporters on astrocytes consist of GLT-1 and the glutamate-aspartate transporter (GLAST) (Robinson, 1999). Specifically, glutamate taken up into astrocytes through GLT-1 regulates lactate production during neural activation (Uehara et al., 2007b). We observed that inhibition of glutamate re-uptake by dihydrokainate (DHK, 0.1 mM), a non-transportable inhibitor of the GLT-1 (Johnston et al., 1979; Tan et al., 1999), attenuated a foot shock stress-induced increase in extracellular lactate concentrations both in the mPFC and BLA of rats (Uehara et al., 2007b). Thus, in glycolytic process in astrocytes, the ability of GLTs to activate Na^+/K^+ ATPase via glutamate is important for acute energy supply.

On the other hand, extracellular glutamate levels are increased by inhibition of glial TCA activity with fluorocitrate (Largo et al., 1996; Paulsen et al., 1987; Rodriguez Diaz et al., 2005). Fluorocitrate, which is selectively taken up by glial cells through MCT-1, inhibits aconitase, leading to inhibition of glial ATP production (Fonnum et al., 1997). Hirose et al. (2007) reported that inhibition of glial ATP production enhanced 2-fluoro-2-deoxyglucose (FDG) uptake into the striatum and cerebral cortex of rats, which was almost completely abolished by pretreatment with MK-801 (1. 0 mg /kg, i.v.), a noncompetitive NMDA blocker. These findings indicate a substantial contribution of NMDA-mediated signal transmission to the increase in glucose utilization induced by inhibition of glial energy metabolism, while it is unclear whether the increased glucose metabolism is due to anaerobic glycolysis or oxidative metabolism. Zielke et al. (2007) examined the effect of fluorocitrate on lactate and glucose oxidation using the microdialysis technique. The authors demonstrated that astrocytes oxidize about half of the interstitial lactate and about 35% of glucose, indicating that neurons metabolize a maximum of 50% of interstitial lactate and 65% of glucose.

4. Neurotransmitters and lactate production

4.1. Role of glutamate and GABA

Activation of NMDA or kainate receptors immediately increases extracellular lactate concentrations (Kuhr and Korf, 1988b; Schasfoort et al., 1988). These authors reported that infusion of NMDA (10 mM) or


A
presynapse
DA
DAD1-R
DAD2-R
glucose
pyruvate
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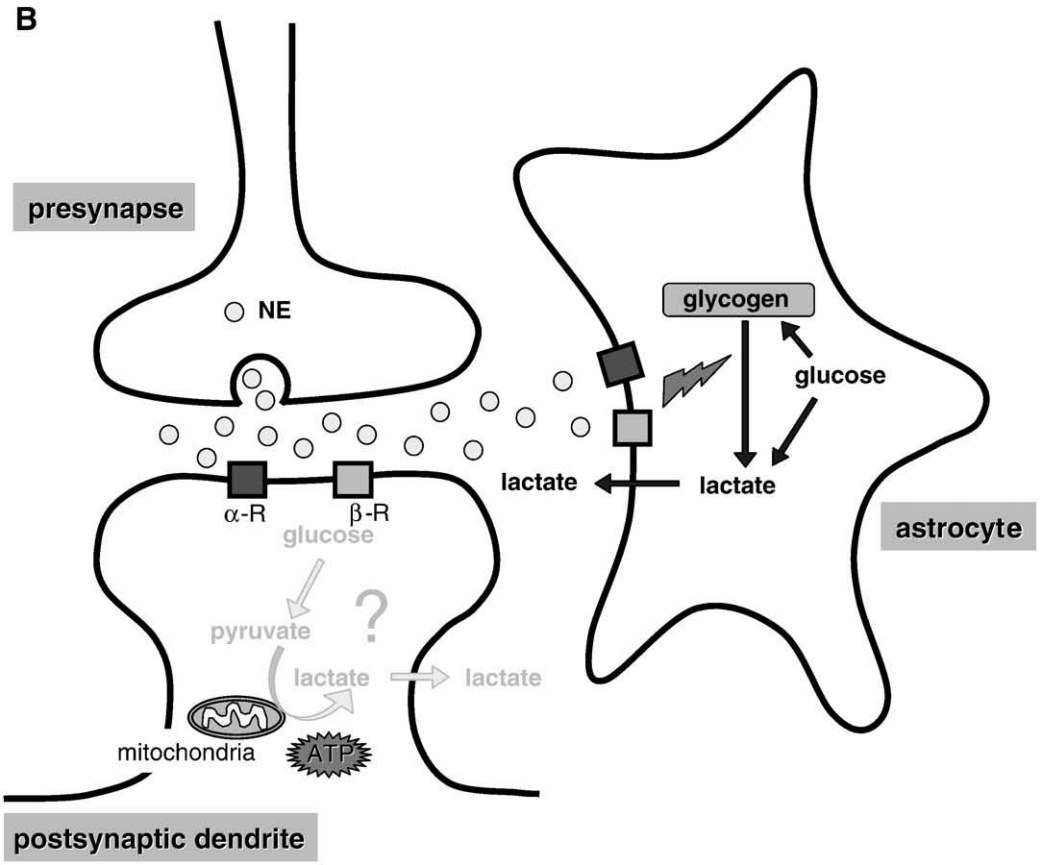
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kainic acid (0.5 mM) for 1 min resulted in an transient increase in extracellular lactate concentrations, which lasted several minutes longer than the drug administration period in the striatum and hippocampus. During acute neural activation, blockade of NMDA receptors attenuates the increase in extracellular lactate concentrations. Local administration of 2-amino-5-phosphonopentanoic acid (AP-5, 2 mM) or 2-amino-7-phosphonopentanoic acid (AP-7, 2 mM), competitive NMDA receptor antagonists, reduces the increase in lactate levels in the striatum following electroconvulsive shock (Kuhr and Korf, 1988b) and in the hippocampus following immobilization (Schasfoort et al., 1988). Moreover, the immobilization stress-induced increase in lactate concentrations has also been shown to be attenuated by MK-801 in the hippocampus (Korf et al., 1991). However, local infusion of MK-801 did not affect a tail pinch-induced increase in lactate efflux in the striatum (Fellows et al., 1993b).

On the other hand, local perfusion of 1.0 mM DHK, a non-transportable inhibitor of the GLT-1, increased extracellular lactate concentrations in the mPFC and BLA, whereas 0.1 mM DHK produced no effect (Uehara et al., 2007b). Local application of DHK has been shown to produce a concentration-dependent increase in basal glutamate efflux in the ventral tegmental area, which occurs gradually during DHK perfusion (Wolf et al., 2000). These findings lead to the possibility that the increase in extracellular glutamate concentrations induced by DHK perfusion enhances glucose uptake and anaerobic metabolism of glucose. GLTs also play an important role in stress-induced lactate productions. Thus, perfusion of DHK (0.1 mM) attenuated footshock stress-induced increment of extracellular lactate concentrations in the mPFC and completely prevented it in the BLA (Uehara et al., 2007b). These findings indicate that the mechanisms underlying the enhancement of lactate productions during stress include activation of NMDA receptors and uptake of glutamate through the GLTs (Fig. 2).

It is of note that glutamate is likely to enhance lactate production in several ways. As mentioned above, the stress-induced increase in extracellular lactate originate not only from astrocytes but also from neurons. Excessive activation of glutamatergic receptors, including NMDA receptors, leads to brain injury through a process known as 'excitotoxicity' (Robinson, 1999). Lactate has been shown to protect neurons from glutamate-induced neurotoxicity (Ros et al., 2001). The mechanism underlying the neuroprotective effect of lactate may be related to its ability to meet increased energy demands resulting from high levels of glutamate (Ros et al., 2001).

Benzodiazepines are widely prescribed therapeutic agents in psychiatric practice, and have anxiolytic, anticonvulsant, sedative/hypnotic, and amnestic properties. The pharmacological actions of benzodiazepines are mediated through allosteric modulation of γ-aminobutylic acid $(GABA)_A$ receptors. Benzodiazepine-binding sites reside on the alpha subunit of these receptors. The alpha-1 subunit of $GABA_A$ receptors may mediate sedative effects (Rudolph et al., 2001), while the alpha2 subunit may be responsible for anxiolytic effects of benzodiazepines (Low et al., 2000). Systemic administration of FG7142, an inverse agonist at benzodiazepine receptors, led to an increase in extracellular lactate concentrations in the BLA, which was attenuated by pretreatment with diazepam (1.0 mg/kg, ip), an agonist at benzodiazepine receptors (Uehara et al., 2005). These findings suggest that inhibition of GABAergic transmission regulates lactate synthesis under basal conditions. On the other hand, systemic administration of diazepam (1.0 mg/kg, ip) attenuated immobilization stress-induced lactate increment in the BLA, which was blocked by co-administration of flumazenil (15 mg /kg, ip), an antagonist at benzodiazepine receptors (Uehara et al., 2003a). Enhanced lactate efflux induced by footshock or psychological stress was also attenuated by pretreatment with diazepam (Uehara et al., 2005). On the basis of these findings, activation of GABAergic neurotransmissions is assumed to attenuate stress-induced lactate increment in the extracellular space.

4.2. Catecholamines and lactate production

Catecholamines (e.g., dopamine, DA; norepinephrine, NE) have been shown to enhance lactate production in rat brain. Thus, local perfusion of DA or NE increased extracellular lactate levels in the mPFC (Takita et al., 1992). Pretreatment with reserpine, which interferes with vesicular storage of catecholamines, did not prevent an increase in extracellular lactate levels induced by apomorphine (0.5 mg/kg sc), a mixed D1/D2 receptor agonist, or isoproterenol (20 mg /kg sc), a β-adrenergic agonist (Takita et al., 1992). These findings indicate that stimulation of catecholamine receptors enhances lactate efflux, although more precise mechanisms underlying a possible link between lactate production and catecholamine-mediated neurotransmissions has yet to be determined.

Administration of low-dose apomorphine (0.05 mg/kg, ip) did not affect extracellular lactate concentrations, whereas a higher dose (0.5 mg/kg ip) increased them in NAC (Uehara et al., 2007a). Apomorphine (0.5 mg/kg sc) also induced an increase in extracellular lactate concentration in the mPFC (Takita et al., 1992). On the other hand, bromocriptine (20 mg/kg, ip), a selective D2 receptor agonist, did not change extracellular lactate concentrations (Uehara et al., 2007a). Presynaptic DA autoreceptors are 5–10 times more sensitive to apomorphine than postsynaptic DA receptors, as has been shown in behavioral, biochemical, and electrophysiological studies (Cooper et al., 2003). Bromocriptine, at 20 mg/kg, has been suggested to selectively stimulate postsynaptic D2 receptors in the NAC (Uehara et al., 2007a). These findings indicate that simultaneous stimulation of D1/D2 postsynaptic DA receptor subtypes is necessary to enhance lactate production in the mPFC and NAC (Fig. 3-A). Haloperidol (0.5 mg/kg ip), a selective D2-receptor antagonist, increased basal lactate levels both in the striatum and hippocampus, whereas pretreatment with haloperidol abolished immobilization stress-induced lactate increment in these regions (Dijk et al., 1991). Thus, blockade of D2 receptor produces opposite effects on lactate efflux depending on the presence or absence of stressors.

Nomifensine, a selective DA uptake inhibitor, produces an increase in extracellular glutamate concentrations in the striatum of freely moving rats, which is attenuated by either the D1 antagonist SCH23390 or D2 antagonist sulpiride (Exposito et al., 1999). These results give rise to the possibility that DA transmission regulates lactate metabolism indirectly by modulating glutamatergic tone.

NE regulates glycogen levels in astrocytes via adrenergic receptors (Magistretti et al., 1994). When applied to primary astrocyte cultures prepared from neonatal mouse brain, NE promoted rapid and concentration-dependent glycogen breakdown (Sorg and Magistretti, 1991). Thus, NE is assumed to directly activate glycogenolysis in astrocytes followed by lactate production (Fig. 3-B). However, it is unclear whether stimulation of postsynaptic NE receptors enhances lactate production.

4.3. Effect of 5-HT_{1A} agonists on lactate production

The involvement of altered serotonin (5-HT) transmission in a variety of psychiatric disorders is highlighted by successful use of 5-HT-modulating drugs in the treatment of generalized anxiety, panic disorder, obsessive compulsive disorder, depression, and schizophrenia

Fig. 3. Schematic diagrams of putative enhancement of lactate production induced by catecholamines. (A) Simultaneous stimulation of both D1/D2 postsynaptic DA receptor subtypes is necessary to increase lactate production. DA transmission regulates lactate metabolism, possibly through the action of glutamate. (B) NE directly activates glycogenolysis in astrocytes which is mediated by adrenergic receptors. It is not clear whether stimulation of *postsynaptic* NE receptors enhances lactate productions. Abbreviations: DA, dopamine; DAD1-R, dopamine D1 receptor; DAD2-R, dopamine D2 receptor; NE, norepinephrine; α-R, α-adrenergic receptor; β-R, β-adrenergic receptor.

(Graeff, 2002; Graeff et al., 1996; Sumiyoshi et al., 2001a,b, 2007). Specifically, 5-HT_{1A} receptors have drawn attention because the azapirones, e.g., buspirone and tandospirone, which are partial agonists at these receptors (New, 1990), possess anxiolytic activity (Handley and McBlane, 1993). In basal conditions, systemic administration of tandospirone, a selective 5-HT_{1A} partial agonist, produced a significant increase in extracellular lactate levels in the mPFC, whereas it did not show such effect in the BLA (Uehara et al., 2006). This finding is consistent with clinical observations that 5-HT_{1A} partial agonists, e.g. tandospirone and buspirone, improve impaired performance on cognitive tasks related to frontal lobe functions in patients with schizophrenia (Sumiyoshi et al., 2001a,b, 2007). However, 8-OH-DPAT (a 5-HT_{1A} full agonist), RU 24969 (a 5-HT_{1B} agonist), and DOI (a 5-$HT_{2A/2C}$ antagonist/agonist) did not affect lactate efflux in the mPFC during administration of reserpine that decreases lactate release (Takita et al., 1992). These findings revealed that stimulation of 5-HT_{1A} receptors may enhance lactate production indirectly, perhaps through catecholamines transmission. This concept is supported by microdialysis studies that found 5-HT_{1A} agonists increased NE release in the prefrontal cortex of awake rats (Barnes and Sharp, 1999). On the other hand, stimulation of 5-HT_{1A} receptors attenuated a footshock stress-induced increase in extracellular lactate concentrations in the mPFC and BLA (Uehara et al., 2006). Furthermore, tandospirone markedly reduced the increment of extracellular lactate concentrations during footshock stress, which was reversed by pretreatment with WAY-100635, a 5-HT_{1A} antagonist (Uehara et al., 2006). 5-HT_{1A} agonists have been shown to inhibit potassium-evoked glutamate release in vitro (Mauler et al., 2001). Therefore, 5-HT_{1A} agonists are likely to reduce glutamate release during neural activation. It is thus speculated that the ability of tandospirone to attenuate footshock stress-induced increase in extracellular lactate levels is due to inhibition of glutamate release by stimulation of 5-HT_{1A} receptors.

5. Conclusions

Since the proposal of the ANLS hypothesis, lactate has attracted considerable attention as an energy substrate for neurons during neural activation. In this review, we have provided emerging pharmacological evidence for neurotransmitter regulation of extracellular lactate levels in discrete brain sites, especially during stress. Findings from microdialysis studies suggest that major neurotransmitters, including norepinephrine, dopamine, serotonin, glutamate, and GABA (via benzodiazepine-receptors) affect lactate production, depending on brain area. Among these neurotransmitters, glutamate may principally contribute to the regulation of lactate production, with other neurotransmitter systems affecting extracellular lactate levels in a glutamate-mediated manner. In spite of findings summarized in this review, the correlation between neurotransmission and dynamics of lactate metabolism in the brain remains largely unclear. It is possible that other neurotransmitters and/or neuropeptides, e.g., vasoactive intestinal peptide (Magistretti et al., 1994; Pellerin, 2003), are related to lactate synthesis in the brain. Clarification of these issues is important for understanding the more precise nature of brain energy metabolism. Monitoring lactate levels with the intracerebral microdialysis technique provides a useful tool to further clarify the contribution of lactate metabolism to a variety of brain functions.

Finally, further efforts are expected to study lactate metabolism in humans with psychiatric disorders. So far, neuroimaging methods, such as proton magnetic resonance spectroscopy (^{1}H-MRS) and positron emission tomography has mainly focused on glucose and oxygen metabolism. Only recently, some researchers have begun to measure lactate responses during neural activation in men using ^{1}H-MRS (Maddock et al., 2006). This kind of study is expected to help elucidate the more mechanisms by which psychotropic drugs act on the central nervous system. Further, research into interactions between neurotransmitters and lactate metabolism may provide a novel view of the pathophysiology of some stress-related disorders, e.g., mood disorder, anxiety disorder, and post-traumatic stress disorder.

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