Behavioural Brain Research 344 (2018) 91–102

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Fluctuations of extracellular glucose and lactate in the mouse primary visual cortex during visual stimulation

Alexandria Béland-Millar, Claude Messier*

School of Psychology, University of Ottawa, Canada

ARTICLE INFO

Keywords:
Brain metabolism
Visual cortex
Glucose
Lactate
Fructose
Novel object
Visual stimuli

ABSTRACT

We measured the extracellular glucose and lactate in the primary visual cortex in the CD-1 mouse using electrochemical electrodes. To gain some additional information on brain metabolism, we examined the impact of systemic injections of lactate and fructose on the brain extracellular glucose and lactate changes observed during visual stimulation. We found that simple stimulation using a flashlight produced a decrease in visual cortex extracellular glucose and an increase in extracellular lactate. Similar results were observed following visual stimulation with an animated movie without soundtrack or the presentation of a novel object. Specificity of these observations was confirmed by the absence of extracellular glucose and lactate changes when the mice were presented a second time with the same object. Previous experiments have shown that systemic injections of fructose and lactate lead to an increase in blood lactate but no change in blood glucose while they both increase brain extracellular glucose but they do not increase brain extracellular lactate. When mice were visually stimulated after they had received these injections, we found that lactate, and to a slightly lesser degree fructose, both reduced the amplitude of the changes in extracellular glucose and lactate that accompanied visual stimulation. Thus, neural activation leads to an increase in extracellular lactate and a decrease in extracellular glucose. Novelty, attentional resources and availability of metabolic fuels modulate these fluctuations. The observations are consistent with a modified view of brain metabolism that takes into account the blood and brain glucose availability.

1. Introduction

Compared to other organs, the brain specific resting metabolic rate appears to be only second to that of the heart and kidneys, and greater than the liver, muscles and adipose tissue [1–3]. Some questions remain as to the extent to, and the means by which the brain modulates its metabolic rate in response to increased neuronal activity as well as the metabolites it uses to sustain this activity. During physical exercise, there are significant increases in muscle metabolic use of both glucose and alternative substrates such as lactate [4–11]. Unfortunately, the same pattern is more difficult to ascertain in the brain [12–15].

Similar to muscles, an increase in neuronal activity is expected to generate localised increases in metabolic demand and therefore consumption of metabolites[1] [17,18]. A vast body of literature supports this assumption. Notably, there are important increases in cerebral blood flow following passive and active stimulation [17,19–22]. The increase in cerebral blood flow (CBF) raises the availability of glucose, alternative substrates and oxygen in active neuronal circuits – possibly increasing their consumption as a result of their increased perfusion. Research using fluorodeoxyglucose and positron emission tomography (FDG-PET) in humans demonstrated an increase in glucose uptake in auditory cortex following auditory stimulation [23] and verbal fluency testing [24]. A negative correlation between metabolic indices and performance is often reported indicating that better performance is also associated with either more efficient metabolism or more energetically efficient strategies. *In vivo* microdialysis in rat Purkinje cell layers demonstrated an increase in both extracellular lactate and glucose following stimulation [17]. Interestingly, the changes in extracellular glucose, lactate and cerebral blood flow were all attenuated when blocking AMPA receptors, suggesting a unique and connected pathway for the regulation and use of both glucose and lactate during activity.

The high energetic cost of neuronal activity is commonly believed to be a result of stimulation-induced increases in action potentials, membrane repolarisation and neurotransmitter release [25,26]. These

* Corresponding author: School of Psychology, University of Ottawa, 136 Jean-Jacques Lussier Room 2076A, Ottawa, Ontario K1N 6N5, Canada.
E-mail address: cmessier@uottwa.ca (C. Messier).

[1] Though neural activity can induce localized increases in metabolism, these changes are rarely large enough to induce changes in whole brain metabolism. This is due to the combined effect of an extremely metabolically active organ possessing a high metabolic resting rate and an efficient and flexible metabolic organ capable of reducing metabolic in one region to favor another [16].

https://doi.org/10.1016/j.bbr.2018.02.018
Received 29 December 2017; Received in revised form 12 February 2018; Accepted 14 February 2018
Available online 16 February 2018
0166-4328/ © 2018 Published by Elsevier B.V.

energetically costly processes [27] account for a large portion of increases in local cerebral metabolism and changes in cerebral blood flow during stimulation. Mechanisms associated with action potentials and neurotransmitter release are estimated to account for ~80% of the total energy required for excitatory signalling and that the increase of one action potential will raise "oxygen consumption by 145 mL/100 g grey matter/h" [28].

The visual cortex is no exception to the stimulation-induced increases in energy demand: increases in blood flow and metabolism are observed in the visual cortex when stimulated. Multiple techniques, such as NIRS [29], FDG PET [30,31] and fMRI [32], have all demonstrated increased metabolism and blood flow in the visual cortex following visual stimulation. This increase in CBF and glucose metabolism appears to be accompanied by a 2 to 3-fold increase in cerebral lactate [33,34]. Cerebral lactate appears to be closely linked to neuronal activity as its fluctuations are least partially regulated by neurotransmitter release [17]. Its cerebral increase has been suggested to be a result of increased glycolysis [34,35]. The stimulation-induced increase in metabolic activity of the visual cortex appears to be dependent on the complexity [36] as well as the subjects' expectation [37] of the stimuli.

The use of biosensors also demonstrated that visual stimulation induced increases in cerebral lactate [38,39]. However, the fate of cerebral glucose following stimulation is slightly more complex, with some results demonstrating an increase and others a decrease, likely due to the methodological differences between the studies [38,39]. Thus, it would appear neuronal activity increases glucose metabolism, as well as cerebral lactate. What still remains a question of interest in the field of cerebral metabolism is how this local increase in blood flow and nutrient delivery during increased stimulation is translated to functional use and transfer of metabolites.

Metabolite flux can occur in one of two ways: influx and efflux. However, the analysis of their relative contributions is challenging for a number of reasons. First, the fluctuation of various metabolites can vary independently of one another because they are modulated and influenced by a variety of external factors. For example, increasing extracellular glucose could be interpreted as either an increase in cellular/vascular efflux (cells exporting glucose or increased cerebral blood flow delivering more glucose), a decrease in cellular/vascular influx (cells could be importing less glucose thus causing an accumulation) or a variable combination of both. At this point, there is an agreement that during increased neuronal stimulation, there is a local increase in glucose use and lactate shuttling. There is, however, divergence of opinion when it comes to the directional flux of these metabolites. One position, the Astrocyte-to-Neuron Lactate Shuttle hypothesis (ANLS), proposes that glucose undergoes glycolytic metabolism within astrocytes and lactate issued from glycolysis is shuttled to activated neurons [40,41]. The opposing Neuron-to-Astrocyte Lactate Shuttle hypothesis (NALS), proposes that active neurons metabolize glucose and transfer the resulting lactate to astrocytes for disposal [42,43].

The approach used in the present report is to examine the impact of visual stimulation on extracellular glucose and lactate simultaneously when blood concentrations of metabolic substrates (lactate and fructose) are increased in the peripheral circulation. We then measured the resulting changes in extracellular glucose and lactate with biosensors when mice are presented with visual stimuli that vary in their complexity and nature. The present report is an extension of our finding that an increase in peripheral levels of lactate produced by fructose, lactate, beta-hydroxybutyrate and pyruvate all increase blood lactate but not blood glucose. These metabolites also all produce a significant increase in brain extracellular glucose suggesting that these metabolites can contribute to brain metabolism [44].

2. Materials and methods

2.1. Animals

Twelve, 18-week old, male CD1 mice (Charles River Canada, St-Constant, Québec, Canada) were individually housed with standard bedding (Teklad 7097 Corncob bedding, Envigo, Mississauga, Canada) and maintained on a reverse 12-h night/day cycle with lights on at 7 p.m. Mice had *ad libitum* access to standard chow (Teklad Global 18% Protein 2018, Teklad Lab Animal Diets, Envigo, Mississauga, Canada) and water, unless otherwise specified. All testing was conducted during the dark (active) phase of the cycle with the use of dim red lighting. All procedures in this study adhere to guidelines of the Canadian Council on Animal Care and were approved by the Animal Care Committee of the University of Ottawa.

2.2. Surgical procedure

Pre-surgical treatment included a 0.05 mg/kg subcutaneous (s.c.) injection of buprenorphine hydrochloride (Reckitt Benckiser Healthcare, Hull, North Humberside, UK) as well as 1 ml of 0.9% saline (Hospira, Montreal, Canada). Immediately prior to surgery, mice were anesthetised using 4–5% isoflurane (Fresenius Kabi Canada Ltd., Richmond Hill, ON) then secured in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA).

Mice were maintained under anesthesia during the surgery with 1–2.5% isoflurane and kept warm with a heated pad (TP650, Gaymar Industries, Orchard Park, NY, USA). Based on the stereotaxic atlas of Franklin and Paxinos (2008), two guide cannulas (BASi cannulas Bioanalytical Systems, West Lafayette, IN) were positioned above the left and right primary visual cortex. The target coordinates, from Bregma, were ± 0.25 mm lateral and −3 mm anterior. The cannulas were positioned 0.25 mm beneath the skull's surface so that the sensing cavity (1 mm) of the electrochemical electrode (inserted later, immediately prior to the testing phase) would be situated within the primary visual cortex of the mouse (Fig. 1). The guide cannulas were fixed using a UV-polymerized compound (CG3 & CG4, Clear Cure Goo, Southlake, TX, USA) and four 0.10-inch screws positioned anterior to the two guide cannulas. Post-surgical care included application of transdermal bupivacaine (Chiron Compounding Pharmacy Inc., Guelph, ON, Canada) and s.c. injections of buprenorphine hydrochloride (0.05 mg/kg) twice daily for 3 days. Mice were given 7–8 days to recover before testing.

2.3. Electrodes

The electrodes have been previously extensively described [45–48]. Briefly, extracellular brain levels of glucose and lactate are monitored using two platinum enzyme-linked electrodes (7005-Glucose-C and 7005-Lactate- C; Pinnacle Technology Inc., Lawrence, KS, USA). Sensors are prepared from Pt-Ir wire of 180 µm in diameter, wrapped concentrically with an AgCl reference electrode. Near the tip of the electrode, a 1 mm section is coated with either glucose or lactate oxidase. These enzymes oxidize the analytes of interest, resulting in a release of hydrogen peroxide (H_2O_2). H_2O_2 is subsequently detected and recorded as an amperometric oxidation current by the electrode [49]. The data was collected at 1 Hz, transmitted from a potentiostat to a computer and recorded with the Sirenia Acquisition Software (Pinnacle Technology Inc., Lawrence, KS, USA). In addition to the oxidase enzymes, the metabolite sensitive surface is also coated with a series of membranes to increase the specificity and selectivity of the electrodes. For example, the potential contribution of ascorbic acid is reduced with the presence of ascorbic acid oxidase. Ascorbic acid oxidase convert the electroactive ascorbate, which can interfere with the electrodes recordings, to non-electroactive dehydroascorbate and water [50].

Immediately prior to, and following *in vivo* testing, the electrodes

Download English Version:

https://daneshyari.com/en/article/8837853

Download Persian Version:

https://daneshyari.com/article/8837853

Daneshyari.com