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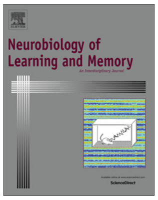

Training-induced elevations in extracellular lactate in hippocampus and striatum: Dissociations by cognitive strategy and type of reward

Lori A. Newman [a], Claire J. Scavuzzo [b], Paul E. Gold [a], Donna L. Korol [a,*]

[a] Department of Biology, Syracuse University, Syracuse, NY 13224, USA
[b] Department of Psychology, University of Alberta, Edmonton, Alberta T6G 2E9, Canada

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ABSTRACT

Recent evidence suggests that astrocytes convert glucose to lactate, which is released from the astrocytes and supports learning and memory. This report takes a multiple memory perspective to test the role of astrocytes in cognition using real-time lactate measurements during learning and memory. Extracellular lactate levels in the hippocampus or striatum were determined with lactate biosensors while rats were learning place (hippocampus-sensitive) or response (striatum-sensitive) versions of T-mazes. In the first experiment, rats were trained on the place and response tasks to locate a food reward. Extracellular lactate levels in the hippocampus increased beyond those of feeding controls during place training but not during response training. However, striatal lactate levels did not increase beyond those of controls when rats were trained on either the place or the response version of the maze. Because food ingestion itself increased blood glucose and brain lactate levels, the contribution of feeding may have confounded the brain lactate measures. Therefore, we conducted a second similar experiment using water as the reward. A very different pattern of lactate responses to training emerged when water was used as the task reward. First, provision of water itself did not result in large increases in either brain or blood lactate levels. Moreover, extracellular lactate levels increased in the striatum during response but not place learning, whereas extracellular lactate levels in the hippocampus did not differ across tasks. The findings from the two experiments suggest that the relative engagement of the hippocampus and striatum dissociates not only by task but also by reward type. The divergent lactate responses of the hippocampus and striatum in place and response tasks under different reward conditions may reflect ethological constraints tied to foraging for food and water.

1. Introduction

Neuroendocrine responses to an experience can regulate brain processes involved in learning and remembering that experience (Gold, 2014; Gold & Korol, 2014). In particular, release of the hormone epinephrine into blood from the adrenal medulla enhances learning and memory across many tasks and species (Gold, 1995; Gold & Korol, 2012). Although circulating epinephrine does not readily cross the blood-brain barrier to enter the brain (Axelrod, Weil-Malherbe, & Tomchick, 1959), the hormone's peripheral actions, largely at the liver, increase blood glucose levels. The increase in blood glucose levels is both necessary and sufficient for the enhancement of learning and memory by epinephrine (Gold, 2014; Gold & Korol, 2014). Glucose itself enhances learning and memory when administered by systemic administration or by direct brain injections (Gold, 2001; Gold & Korol, 2012; Korol, 2002; Korol & Gold, 2007; Messier, 2004; Messier, Desrochers, & Gagnon, 1999; Morris & Gold, 2013; Smith, Riby, van Eekelen, & Foster, 2011; van der Zwaluw, van de Rest, Kessels, & de Groot, 2015).

Of particular interest here, brain lactate may function downstream from glucose to modulate learning and memory. According to this view, glucose enters astrocytes where it can be converted to lactate, which is subsequently used under conditions of heightened activation such as during cognitive processing (Newman, Korol, & Gold, 2011). Like glucose, direct intrahippocampal injections of lactate enhance working memory (Newman et al., 2011) and memory for inhibitory avoidance training (Suzuki et al., 2011). Interfering with lactate transport into neurons by pharmacological or gene expression manipulations impairs memory and attenuates the ability of lactate or glucose to enhance memory (Newman et al., 2011; Suzuki et al., 2011), suggesting that glucose may enhance

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* Corresponding author at: Syracuse University, Department of Biology, Life Sciences Complex, Syracuse, NY 13244, USA.

E-mail address: dlkorol@syr.edu (D.L. Korol).

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memory by conversion to lactate in astrocytes for delivery to neurons.

Past findings indicate that extracellular glucose levels in the hippocampus are diminished by spatial working memory testing (McNay, Fries, & Gold, 2000; McNay & Gold, 2001; McNay, McCarty, & Gold, 2001; Newman et al., 2011), with the magnitude of reduction corresponding to the cognitive load of the task (McNay et al., 2000, 2001). The decrease in extracellular glucose levels in the hippocampus during working memory testing is mirrored by an increase in extracellular lactate levels during testing (Newman et al., 2011). The reciprocal changes in hippocampal extracellular glucose and lactate levels are consistent with the idea that lactate may serve as a supplementary energy substrate to neurons during a time of heightened energy utilization (Brown & Ransom, 2015; Magistretti, Pellerin, Rothman, & Shulman, 1999; Pellerin, 2003; Pellerin & Magistretti, 2012). The use of lactate as an energy source is one of several roles lactate may perform to support cognitive functioning (Fryer & Brown, 2015), such as contributions to astrocytic energy needs, particularly to support glutamate and potassium clearance (Dienel & McKenna, 2014; Sonnewald, 2014), glia-neuronal signaling (Barros, 2013; Bergersen & Gjedde, 2012; Bozzo, Puyal, & Chatton, 2013; Tang et al., 2014), and regulation of neurovascular coupling (Gordon, Choi, Rungta, Ellis-Davies, & MacVicar, 2008; Lauritzen et al., 2013), that in turn may regulate delivery of energy substrates and nutrients to the brain during demanding tasks.

Extensive evidence indicates that different cognitive attributes are subserved by the activity of multiple memory systems. In particular, place (spatial) and response (habit) learning are particularly sensitive to perturbations of functions in the hippocampus and striatum, respectively (Chang & Gold, 2003a, 2004; Gold, Newman, Scavuzzo, & Korol, 2013; Kathirvelu & Colombo, 2013; Korol, 2004; Korol & Pisani, 2015; Packard & Goodman, 2013; Packard & McGaugh, 1992; Poldrack & Packard, 2003; White & McDonald, 2002; White, Packard, & McDonald, 2013). Support for participation of the hippocampus and striatum in these different cognitive attributes comes from demonstrations of double dissociations of task by brain area using lesions or pharmacological interference (Dagnas, Guillou, Prevot, & Mons, 2013; Kosaki, Poulter, Austen, & McGregor, 2015; McDonald & White, 1994; Soares, Oliveira, & Ferreira, 2013), direct injections of glutamate (Packard, 1999), glucose (Canal, Stutz, & Gold, 2005; Pych, Kim, & Gold, 2006; Stefani & Gold, 2001), and estradiol (Korol & Pisani, 2015; Zurkovsky, Brown, Boyd, Fell, & Korol, 2007; Zurkovsky, Serio, & Korol, 2011) in these brain areas.

Several neurochemical and neurophysiological measures of activity in the hippocampus and striatum also exhibit task-specific differences (Chang & Gold, 2003b; Colombo, 2004; Gold, 2004; McIntyre, Marriott, & Gold, 2003; Mizumori & Jo, 2013; Pleil, Glenn, & Williams, 2011; Pych, Chang, Colon-Rivera, Haag, & Gold, 2005; Rubio, Begega, Mendez, Méndez-López, & Arias, 2012). In particular, contrasting the response in the hippocampus, extracellular glucose in the striatum does not decline, and may actually rise, during working memory testing (McNay et al., 2001). Thus, the striatum may have metabolic requirements and responses to experiences that differ from those in the hippocampus. Regional differences in the glucose response to memory testing may also reflect the varying contributions of different brain areas to different types of cognition. These regional differences in physiological responses to experience together with the important role of lactate provisions from astrocytes in modulating hippocampus-sensitive learning and memory (Newman et al., 2011; Suzuki et al., 2011), suggest that, when compared to the hippocampus, the striatum may demonstrate a very different pattern of lactate responses to training on tasks that have selective cognitive attributes.

To test the task and regional specificity of metabolic responses to learning, the present experiments examined fluxes in extracellular lactate levels in the hippocampus and striatum while rats were trained on place and response versions of mazes designed to tap the function of each of these brain regions. The first experiment measured extracellular lactate concentrations in the hippocampus and striatum while rats learned to find food in mazes that rely on those neural systems. Because food intake *per se* increased lactate levels in the brain, perhaps obscuring training-related changes, we also examined extracellular lactate concentrations in a parallel second experiment in which rats were trained using water as the reward to solve the same mazes. The lactate responses to training in hippocampus and striatum dissociated not only by learning strategy, but, unexpectedly, also by the reward used during training.

2. Methods

All procedures described in this report were approved by the University of Illinois Urbana-Champaign and the Syracuse University Institutional Animal Care and Use Committees, and were consistent with the Guide for Care and Use of Laboratory Animals. The animal facilities at both universities are accredited by the Association for Assessment and Accreditation of Laboratory Care.

2.1. Experiment 1: hippocampal and striatal lactate responses to maze training with a food reward

This experiment monitored lactate levels throughout training on place and response versions of a food-motivated plus-shaped maze. These versions of the maze are sensitive to hippocampus and striatum manipulations, respectively (Chang & Gold, 2003a, 2004; Korol, Gold, & Scavuzzo, 2013; Zurkovsky, Brown, & Korol, 2006; Zurkovsky et al., 2007, 2011).

2.1.1. Experimental design

Three-month-old male Sprague-Dawley rats (Harlan Laboratories) were housed in individual cages and were maintained on a 12:12 h light-dark cycle. The rats had free access to food and water until food restriction procedures were started. All rats received unilateral implantation of guide cannulae for lactate biosensor probes (Pinnacle Technology Inc., Lawrence, KS) under stereotaxic control and were allowed at least one week to recover after surgery. Seven days before training, rats were placed on a food restriction regimen, which reduced body weights and maintained the rats' weights at 80–85% of baseline. During food restriction, rats received a small allotment of food reward (Frosted Cheerios®) in their home cages for several days prior to training to familiarize the rats with the reward used during training. Rats were handled for 3 min each day for 5 consecutive days prior to training.

Rats with lactate biosensor probes placed into the dorsal hippocampus or dorsolateral striatum were trained on either a place or response learning task. Extracellular hippocampal and striatal lactate levels were also obtained in a separate control group of food-restricted rats that were not trained but received the food reward every 90 s while kept in a holding cage, i.e., on a schedule that approximated the reward schedule of trained rats. This feeding group controlled for eating- vs. training-related effects on brain neurochemical measures. Thus, there were six experimental groups: hippocampus-place (N = 5), hippocampus-response (N = 5), hippocampus-untrained-fed (N = 4), striatum-place (N = 5), striatum-response (N = 5), striatum-untrained-fed (N = 5), reflecting a 2 (brain site) × 3 (training conditions) experimental design.