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Astrocyte glycogen and lactate: new insights into learning and memory mechanisms

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Abstract

Memory, the ability to retain learned information, is necessary for survival. Thus far, molecular and cellular investigations of memory formation and storage have mainly focused on neuronal mechanisms. In addition to neurons, however, the brain comprises other types of cells and systems, including glia and vasculature. Accordingly, recent experimental work has begun to ask questions about the roles of non-neuronal cells in memory formation. These studies provide evidence that all types of glial cells (astrocytes, oligodendrocytes, and microglia) make important contributions to the processing of encoded information and storing memories. In this review, we summarize and discuss recent findings on the critical role of astrocytes as providers of energy for the long-lasting neuronal changes that are necessary for long-term memory formation. We focus on three main findings: first, the role of glucose metabolism and the learning- and activity-dependent metabolic coupling between astrocytes and neurons in the service of long-term memory formation; second, the role of astrocytic glucose metabolism in arousal, a state that contributes to the formation of very long-lasting and detailed memories; and finally, in light of the high energy demands of the brain during early development, we will discuss the possible role of astrocytic and neuronal glucose metabolisms in the formation of early-life memories. We conclude by proposing future directions and discussing the implications of these findings for brain health and disease.

Keywords

glucose; metabolism; glia; glycolysis; glycogenolysis; emotional arousal; development

Long-term memory and its underlying neuron-centric biological mechanisms

Memories can be classified according to their duration as *short-term memories*, which last for seconds to minutes, or *long-term memories*, which last for hours to years, and potentially throughout the entire lifetime. Formation of long-term memories is key for survival because it allows an organism to benefit from previous experience and respond adaptively to its changing environment. Short-term memories are distinct from long-term memories in terms

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of their underlying biological mechanisms and circuitry. Although long-term memories generally require *de novo* gene expression, short-term memories rely on post-translational protein modifications (Alberini 2009; Alberini and Kandel 2014; Squire and Dede 2015).

Memories can also be divided into different categories on the basis of the type of information encoded and stored. For example, one major distinction classifies memories as explicit (also known as declarative in humans) or implicit (non-declarative) (Squire 2004). Explicit memories retain information about facts, people, places, and things (also known as memories of what, where, who, and when, or wwww memories), and include episodic and semantic memories. Implicit memories, which are recalled in an unconscious/automatic manner, retain information about learned automatic responses, and include priming, procedural memories (memories of how to do things), and simple reflexes (Tulving 1972; Squire and Wixted 2011). Explicit and implicit memories recruit distinct systems (network of regions) for their encoding, consolidation, and storage. Both clinical and animal studies have revealed that explicit memories are processed by the medial temporal lobe, within which one critical region is the hippocampus, whereas implicit memories are processed elsewhere and can operate in the absence of an intact explicit system (Eichenbaum 2006; Kim and Fanselow 1992; Scoville and Milner 1957; Squire and Wixted 2011). Thus, explicit memories are also referred to as *hippocampus-dependent memories*. Although implicit and explicit memory systems can be functionally dissociated, under normal healthy conditions they cooperate to process and store complex information (Kim and Baxter 2001; McDonald et al. 2004).

Studies aimed at elucidating the biological bases of long-term memories have mainly focused on hippocampus-dependent memories. However, most of our understanding of the cellular and molecular mechanisms underlying memory formation and storage initially arose from investigations of simple forms of learning, such as the gill-withdrawal reflex of *Aplysia californica* and olfactory learning in *Drosophila melanogaster* (Yin et al. 1994; Dubnau and Tully 1998; Davis 2011; Kandel 2012). In *Aplysia*, these studies uncovered a great deal of information about the molecular and cellular pathways activated and recruited to implement long-term modifications of synaptic strength or long-term synaptic plasticity. These data converged with genetic and behavioral results obtained in *Drosophila*. Guided by this knowledge from these two invertebrate systems, studies on mammalian memory paradigms revealed that similar molecular pathways are also necessary in the more complex mammalian memory, including hippocampus-dependent memories. Ultimately, numerous studies in the last 30 years on many species converged on the conclusion that evolutionarily conserved biological mechanisms underlie long-term synaptic plasticity and long-term memory formation (Alberini 2009; Kandel 2012; Kandel et al. 2014). One classical example, which has been extensively investigated, is the evolutionarily conserved role of the cyclic adenosine monophosphate (cAMP)-dependent pathway and the functionally linked activation of the cAMP response element-binding protein (CREB)-dependent cascade of gene expression (Kida and Serita 2014; Lonze and Ginty 2002; Silva et al. 1998) (Figure 1).

Numerous mammalian models of different types of short- and long-term memory, particularly in rodents, have been employed to investigate the complexity of mammalian memory processing in a variety of brain regions. These studies revealed that the expression

and post-translational regulation of many classes of genes, RNAs, and proteins are required for long-term memory formation and storage; these include immediate-early genes (e.g., c-Fos, Zif268, NPAS4 and Arc/Arg3.1) (Bramham et al. 2008; Guzowski 2002; Loebrich and Nedivi 2009; Sun and Lin 2016; Veyrac et al. 2014), metabotropic and ionotropic receptors for various neurotransmitters (e.g., AMPA, NMDA, Kainate, GABA, and metabotropic glutamate receptors) and neuromodulators (e.g., dopaminergic and serotoninergic receptors), neurotrophic factors (e.g. tyrosine receptor kinase) (Fanselow et al. 1994; Gonzalez-Burgos and Feria-Velasco 2008; Kandel 2001; Makkar et al. 2010; Morris 2013; Purcell and Carew 2003; Riedel 1996; Riedel et al. 2003), kinases (e.g., ERK, CamKIIα, PKA, PKC, PKMζ, and MAPK) (Bejar et al. 2002; Kandel 2012; Lisman et al. 2002; Mayford 2007; Pastalkova et al. 2006; Rahn et al. 2013), transcription factors (e.g., CREB, C/EBP, NFkB, AP1, NPAS4, Zif268, NR4a, and SRF) (Alberini 2009; Alberini and Kandel 2014; Jones et al. 2001; Sun and Lin 2016), epigenetic regulators (e.g., MSK1, RSK2, NFkB, DNMT, HATs, and HDACs) (Day and Sweatt 2011; de la Fuente et al. 2015; Franklin and Mansuy 2010; Rudenko and Tsai 2014), microRNAs (e.g., miR-124, miR-132, miR-128b, and miR-134) (Bredy et al. 2011; Nudelman et al. 2010; Saab and Mansuy 2014), and a number of effector proteins engaged in structural changes, such as cell-adhesion molecules (e.g., neurexin and neuroligin) (Murase and Schuman 1999; Rose 1996; Ye et al. 2017; Bailey et al. 2015) (Figure 1).

These molecular investigations have been paralleled by electrophysiological studies, which showed that the cellular mechanisms underlying long-term memory involve long-term synaptic functional changes, and in particular long-term increases or decreases in synaptic transmission known as long-term potentiation (LTP) and long-term depression (LTD), respectively (Bliss and Collingridge 1993; Malenka and Bear 2004). Additional electrophysiological changes in the brain that have been implicated in long-term memory formation include electroencephalogram (EEG) coherence, i.e., phase synchronization of field potential oscillations, which coordinates the timing of neuronal spiking to promote synaptic plasticity across distributed brain regions (Corcoran et al. 2016; Zanto et al. 2011). Notably, this system-level communication among brain regions is controlled by sharp wave ripples (SPW-Rs) (Buzsáki 2015), a synchronous population pattern in the hippocampus that engages in crosstalk with a wide area of the cortex and several subcortical nuclei. SPW-Rs occur in “off-line” states of the brain during waking and in non-REM sleep, and are believed to consolidate episodic memories across the hippocampal-cortical system (Buzsáki 2015; Inostroza and Born 2013). These system-wide activities provide a possible mechanistic explanation for why hippocampus-dependent memories, which are fragile during the initial period when they are engaging a network of both hippocampal and cortical regions, become more stable and exclusively hippocampus-independent over time. This redistribution of memory representations and storage is known as *system-level consolidation* (Dudai et al. 2015; Squire et al. 2015; Frankland and Bontempi 2005).

Although these studies provided a great deal of information about the biological bases of learning and memory, they focused on neuronal mechanisms, and consequently generated conclusions mostly limited to neurons and neuronal functions. However, in addition to neurons, the brain comprises many types of cells and systems, including glia and vascular systems. Recent investigations have begun to assess the role of non-neuronal cells in long-

term memory, and provided clear evidence that all glial cell types (i.e. astrocytes, oligodendrocytes and microglia) play critical roles in memory processing (Adamsky and Goshen 2017; Fields 2008; Gibbs et al. 2008; Lee et al. 2014; Moraga-Amaro et al. 2014; Parkhurst et al. 2013; Suzuki et al. 2011).

Astrocytes are particularly well equipped to influence neuronal functions involved in memory formation (Haydon and Nedergaard 2014; Moraga-Amaro et al. 2014): they are excitable through calcium fluctuations and respond to neurotransmitters released at synapses; they synchronize via calcium waves and release their own gliotransmitters, which are essential for synaptic plasticity; they communicate with blood vessels thus coupling circulation (blood flow) to local brain activity; and finally, they regulate energy metabolism in support of neuronal functions, including those required for memory formation (Henneberger et al. 2010; Pannasch and Rouach 2013; Perea et al. 2009; Bazargani and Attwell 2016). In regard to this metabolic role, astrocytes are perfectly positioned to balance the metabolism of glucose in the brain: on one side, the astrocytic endfeet directly contact the layers of the blood vessel that import glucose from the blood via the selective glucose transporter GLUT1, and on the other side, these cells extend processes that wrap around the pre- and post-synaptic compartments of neurons (Falkowska et al. 2015; Morgello et al. 1995) (Figure 2).

In this review, we will specifically discuss the critical contribution of astrocytes, acting as regulators of glucose metabolism, to memory formation and storage.

Glycogen and glucose metabolisms play critical roles in memory formation

Studies by Paul Gold and colleagues identified systemic glucose as an intermediary of the memory-enhancing effect of norepinephrine (Gold and Korol 2012). Memories encoded in arousal states are remembered better (i.e., for longer periods and with greater detail), and arousal is well known to regulate the release of epinephrine from the adrenal glands. Epinephrine binds adrenergic receptors (ARs) on hepatocytes and initiates the breakdown of glycogen, a polymer of glucose stored in the liver (Sutherland and Rall 1960), leading to release of glucose into the bloodstream. Systemic glucose injections at doses comparable to those found in the blood after epinephrine treatment are sufficient to enhance memory, whereas low liver glycogen storage, as in food-deprived or aged rats, is associated with a lack of memory enhancement following epinephrine treatment (Morris et al. 2010; Talley et al. 2000). Conversely, peripherally blocking adrenergic receptors blocks the ability of epinephrine to enhance memory and increase blood glucose. Collectively, these studies support the conclusion that a major mechanism underlying the actions of epinephrine released by arousal is the increase in blood glucose.

The effect of glucose as a memory enhancer has been observed with both systemic and intracerebral injections, and it has been linked to the regulation of either norepinephrine or acetylcholine release. Ragozzino and colleagues showed that both systemic and intra-hippocampal injections of glucose, like injections of epinephrine, enhance spontaneous alternation, a form of spatial working memory, and increase the release of acetylcholine in the hippocampus (Ragozzino et al. 1998; Ragozzino et al. 1996).

The understanding of the role of glucose on memory modulation was considerably advanced by the observation that when rats are tested on a spontaneous alternation task, the levels of extracellular glucose in the hippocampus decrease significantly. Hence, it was suggested that learning and memory consume glucose, presumably to support the energy demands of the brain as it processes the new experience and stores the important information (McNay et al. 2000; McNay et al. 2001; McNay and Sherwin 2004).

Indeed, the brain consumes high levels of energy: the adult brain uses on average about 20% of total body energy, despite accounting for only 2% of total body weight. Glucose, the major source of energy entering the brain from the circulation, can either be directly metabolized or stored in the form of glycogen. In the mature brain, glycogen is stored mostly in astrocytes (Brown et al. 2004; Brunet et al. 2010; Cali et al. 2016; Cataldo and Broadwell, 1986; Maxwell and Kruger 1965; Petersen 1969; Pfeiffer-Guglielmi et al. 2003; reviewed in Waitt et al. 2017), and, under conditions of high energy demand such as glucose deprivation or intense neural activity, can be catabolized to rapidly deliver metabolic substrates (i.e., pyruvate and lactate) (Brown and Ransom 2015). Although neurons possess the enzymatic machinery to store and break down glycogen, under physiological conditions they suppress glycogen storage through a series of mechanisms. In fact, glycogen storage in neurons is observed only in severe neurological diseases such as progressive myoclonus epilepsy or Lafora disease, a brain disorder characterized by recurrent seizures (epilepsy) and a decline in intellectual function (Vilchez et al. 2007). Thus, glucose, either directly metabolized via glycolysis or supplied by astrocytic glycogenolysis, may fuel the high energy demands associated with the cellular changes underlying learning, memory formation, and memory storage.

One long-debated question is whether neurons directly import glucose entering the brain from the blood and use it immediately to provide the energy required to support their functions. An alternative model, suggested by Pellerin and Magistretti (Pellerin and Magistretti 1994), proposes that the high energy demands of stimulated neurons are supported by astrocytes, which supply the neurons with lactate produced via aerobic glycolysis, thereby providing the energy required for the activity-induced neuronal functions; hence, in the case of learning, for the changes involved in processing and storing memories. It is also possible that both mechanisms are utilized, perhaps in response to specific conditions.

The model proposed by Magistretti and Pellerin has been highly debated. These debates are complex and likely reflect the intricacy of metabolic regulations in different conditions. Given the variety of these conditions and systems, we will not be able discuss the points of the debate in this manuscript, thus we refer to several reviews reporting them (Chih et al., 2001; Chih and Roberts, 2003; Dienel and Hertz, 2001; Pellerin and Magistretti, 2003, 2012; Aubert et al., 2005; Dienel, 2010, 2017; DiNuzzo et al., 2010; Steinman et al. 2016). We will, however, discuss the literature important for the findings about the roles of glycogen, glucose and lactate in learning and memory as well as in brain plasticity.

Several studies reported that stimulation of brain areas increases glycogenolysis and glycolysis, as well as glucose uptake, in astrocytes, consistent with the idea that astrocytic

glycogen and glucose metabolism are needed to sustain activity-dependent processes. For example, NMR spectroscopy, which allows measurement of lactate *in vivo*, revealed an elevation of lactate in the human visual cortex during physiologic photic stimulation (Prichard et al. 1991), and microsensor-based measures revealed an increase in extracellular lactate concentration in the dentate gyrus of the rat hippocampus after electrical stimulation of the perforant pathway (Hu and Wilson 1997). Moreover, whisker stimulation in the awake rat leads to rapid glycogen breakdown in layer IV of the somatosensory cortex (Swanson et al. 1992) and results in preferential increase in glucose uptake into astrocytes in comparison with neurons in the somatosensory cortex *in vivo* (Chuquet et al., 2010), although more mechanistic details need to be understood (Dienel and Cruz 2015). The physical position of astrocytes, between the blood flow on one side and neurons on the other, further supports the idea that astrocytic regulation of glucose metabolism subsidizes the energy requirements of activity, plasticity, learning, and memory formation.

In accordance with this view, metabolic profiling of astrocytes and neurons revealed distinct features indicating that glycolysis occurs mainly in astrocytes. For example, cultured neurons produce CO_2 at a much higher rate than astrocytes, and their respective enzymatic profiles are consistent with the relative predominance of glycolysis in glial cells and oxidation in neurons (Bélanger et al. 2011; Hamberger and Hydén 1963; Hydén and Lange 1962). In addition, acutely isolated, FACS-purified astrocytes exhibit a primarily glycolytic profile (Lovatt et al. 2007; Zhang et al. 2014). Finally, the enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (Pfkfb3), which promotes glycolysis, is active in astrocytes but constantly subjected to proteasomal degradation in neurons (Bolaños et al. 2010; Herrero-Mendez et al. 2009), once again supporting the idea that astrocytes are the primary sites of glycolysis. Thus, a large body of evidence converges on the conclusion that astrocytes are predominantly glycolytic cells, whereas neurons are not, and instead exhibit high oxidative activity.

The first demonstration that astrocytic glycolysis is critical for learning and memory came from studies performed by Leif Hertz, Marie Gibbs, and colleagues, who showed that glycogenolysis is necessary for memory formation. Using taste avoidance training in a day-old chick, they showed that intracranial injection of an inhibitor of glycogen phosphorylase, 1,4-Dideoxy-1,4-imino-d-arabinitol (DAB), impaired memory in a dose-dependent manner, and concluded that glycogenolysis is a critical requirement for long-term memory storage (Gibbs et al. 2006). In agreement with this conclusion, breakdown of glycogen in the brain increases significantly during sensory activation in rats (Cruz and Dienel 2002; Swanson et al. 1992), and later studies detailed below demonstrated that glycogen contributes to several types of memory formation in rats and mice. In addition to glycogenolysis, aerobic glycolysis may also be necessary for memory formation, as revealed by experiments in which the glycolysis inhibitor 2-deoxyglucose was injected into the brains of 1 day-old chicks at training, resulting in long-term memory impairment (Gibbs et al. 2007). Thus, several studies have converged on the conclusion that glycogenolysis and aerobic glycolysis, resulting in the production of lactate, are critically linked to memory formation. This raises several questions: How exactly does this regulation occur? How are astrocytes functionally coupled to neurons? What are the target mechanisms that consume high levels of energy upon learning and allow memory consolidation to occur?

Astrocytic glycogenolysis, aerobic glycolysis, and lactate are critical for long-term memory formation in several brain regions

A model proposed by Pellerin and Magistretti (Pellerin and Magistretti 1994), known as the astrocyte–neuron lactate shuttle (ANLS), suggests that astrocyte glycolysis and neuronal oxidation play coordinated roles in long-term memory formation via transport of lactate. This model predicts that excitation, and hence glutamate release, stimulates the uptake of glutamate by astrocytes, which is converted into glutamine (glutamate–glutamine cycle), eventually sustaining synaptic release of glutamate. This cycle requires energy from astrocytes, which would therefore activate glucose uptake from the blood and metabolize it into lactate. Lactate, released by astrocytes via monocarboxylate transporters (MCTs), can enter other types of cells using similar transporters, which operate on the basis of concentration gradients of protons and monocarboxylate across the plasma membrane (Halestrap 2013; Pierre and Pellerin 2005). MCTs are proton-linked plasma membrane transporters that carry molecules containing one carboxylate group (hence the term monocarboxylates), such as lactate, pyruvate, and ketone bodies, across plasma membranes. MCT1 is expressed in astrocytes, ependymocytes, oligodendrocytes, and endothelial cells of blood vessels, whereas MCT4 is selectively expressed by astrocytes and enriched at synaptic sites (Pierre and Pellerin 2005; Rinholm et al. 2011; Suzuki et al. 2011). MCT2, on the other hand, is selectively expressed by neurons (Debernardi et al. 2003).

Thus, lactate, released by astrocytes via MCT4 and MCT1 is transported by MCT2 into neurons, where it is converted to pyruvate that is subsequently metabolized through oxidative phosphorylation in mitochondria to produce 14–17 ATPs per lactate molecule (Figure 2). This lactate supply from astrocytes to neurons provides an explanation for how neurons might handle the high-energy requirements evoked by active processes in response to stimuli.

The first studies that described the ANLS were performed *in vitro,* and questions were raised about whether these mechanisms occurred *in vivo* (Chih and Roberts 2003; Dienel and Cruz 2004; Gjedde et al. 2002). However, studies by Hertz and Gibbs in the chick described above suggested that glycogenolysis is involved in memory formation (for review see Gibbs 2016). In these studies, the chicks were exposed to two beads, one red and one blue, and trained to avoid pecking the red bead by association with an aversive taste. During the retention test, the ratio between the number of pecks of red and blue beads was measured, revealing an increase in avoidance of pecking red beads; the change in the discrimination ratio was indicative of memory (Hertz et al. 1996). The initial results showed that glycogen levels in the forebrain decreased 30 minutes after learning, concomitant with an elevation of glutamate, suggesting *de novo* synthesis of glutamate from glycogen to support memory consolidation (Hertz et al. 2003; O'Dowd et al. 1994). A few years later, the same group showed that DAB impairs taste aversion memory in day-old chicks when infused into the multimodal forebrain association region, the intermediate medial mesopallium (IMM), a brain region required for memory consolidation (Gibbs et al. 2006; Gibbs and Hertz 2008). They then found that glutamine was sufficient to rescue memory, and hence proposed that glycogenolysis was critical for the glutamate/glutamine shuttle, which may also be affected

by DAB. A subsequent study from the same authors demonstrated that L-lactate is also sufficient to rescue chick taste aversion memory after treatment with an inhibitor of either glycogenolysis (DAB) or glycolysis (2-deoxyglucose) (Gibbs et al. 2007). Furthermore, administration of D-lactate, the competitive non-biologically active form of lactate, impaired chick taste aversion memory with a time delay that suggested it was inhibiting L-lactate metabolism and not uptake, leading the authors to conclude that astrocytic metabolism through glycogenolysis and lactate metabolism is critical for memory formation (Gibbs and Hertz 2008). These findings supported the idea that learning in the neonatal chick relies on the breakdown of glycogen for glutamate synthesis in astrocytes (Gibbs et al. 2007).

However, an additional interpretation is that lactate produced by glycogenolysis is transported into neurons for their use, thus contributing to support neuronal modifications critical for memory formation. We tested this hypothesis *in vivo* in mammalian brains, focusing specifically on whether mechanisms of glycogenolysis, astrocytic lactate release and transport into neurons are involved in memory consolidation, the process that stabilizes a newly formed, initially fragile memory into a long-lasting stable representation (Alberini 2009, Dudai 2004).

Using adult rats trained in an inhibitory avoidance (IA) task, in which the animals learn to avoid a context previously paired with a foot-shock (a contextual response to threat), we demonstrated that lactate transported from astrocytes to neurons in the hippocampus plays a critical role in long-term memory consolidation (Suzuki et al. 2011). Specifically, we found that hippocampal astrocytic glycogenolysis is required for memory consolidation, *in vivo* hippocampal long-term potentiation, and learning-induced increases in synaptic and cellular macromolecular changes, including expression of the immediate early gene (IEG) activity–regulated cytoskeleton-associated protein (Arc or Arg3.1) and phosphorylation of the transcription factor CREB and of the actin-severing protein cofilin, all of which are markers of long-term synaptic plasticity. In fact, DAB injected bilaterally in the dorsal hippocampus before or immediately after IA training persistently disrupted memory retention, and this disruption was prevented by co-injection of L-lactate, but not equicaloric concentrations of glucose. In addition, after IA training the hippocampal extracellular concentration of lactate, measured by *in vivo* microdialysis, significantly increased and remained elevated for more than 1 hour, returning to baseline by approximately 90 minutes post-training. This increase in lactate was completely abolished by bilateral DAB injection into the hippocampus, suggesting that it was the result of astrocytic glycogenolysis.

Furthermore, we found that hippocampal injection of the inactive isomer D-lactate before training also blocks long-term memory retention, suggesting that lactate metabolism is critical for long-term memory formation. Similar effects on memory retention were observed following knockdown of the lactate transporters (MCTs). Notably, although the memory impairments induced by the knockdown of lactate transporters expressed in astrocytes (MCT1 and MCT4) was rescued by addition of L-lactate, the impairment induced by knockdown of the transporter expressed in neurons (MCT2) was not, consistent with the idea that the transport of lactate out of astrocytes and into neurons is critical for memory formation. In accordance with this interpretation, a lactate gradient between astrocytes and neurons was recently observed and characterized at high resolution *in vivo* using two-photon

microscopy (Machler et al. 2016). Therefore, we concluded that glycogenolysis and astrocyte–neuron lactate transport critically supports neuronal functions required for long-term memory formation. A more recent investigation further supported the role of astrocytic lactate in memory formation by showing that IA training induces hippocampal expression of molecules involved in astrocytic-neuronal transport, such as MCTs and the expression of lactate dehydrogenase (LDH) A and B, the enzymes that catalyze the interconversion of lactate and pyruvate (Tadi et al. 2015).

Similar conclusions were reached by Newman et al. (2011), who employed sensitive bioprobes to measure brain glucose and lactate levels in the hippocampus of rats while they underwent a spatial working memory task. They found that while extracellular glucose decreased, lactate levels increased during task performance, and intrahippocampal infusions of L-lactate enhanced memory in this task. In addition, pharmacological inhibition of astrocytic glycogenolysis with DAB impaired memory, and this impairment was reversed by either L-lactate or glucose, both of which can provide lactate to neurons in the absence of glycogenolysis. In this study, as in ours, blockade of the MCTs responsible for lactate uptake into neurons impaired memory, and this impairment was not reversed by either glucose or L-lactate, again supporting the idea that lactate uptake by neurons is necessary to support memory formation. The authors concluded, as we did, that astrocytes regulate memory formation by controlling the provision of lactate to sustain neuronal functions.

Additional studies based on genetic approaches support these conclusions. Delgado-Garcia and colleagues found that knockout of glycogen synthase in the nervous system of mice impairs both hippocampal LTP and associative learning (Duran et al. 2013). In addition, Boury-Jamot et al. (2016) and Zhang et al. (2016) reported that the consolidation and reconsolidation of appetitive conditioning using drugs of abuse (i.e., cocaine-conditioned place preference or self-administration) are also dependent on glycogenolysis and the directional transport of lactate from astrocytes to neurons via MCTs in the basolateral amygdala (BLA) of rats. Furthermore, extracellular lactate, as measured by *in vivo* microdialysis, is elevated in the BLA after IA training and retrieval (Sandusky et al. 2013).

Consistent with the results of these studies, we found that BLA glycogenolysis is critical for IA memory formation, as demonstrated by the fact that bilateral injection of DAB into the BLA 15 minutes prior to IA training severely and persistently disrupted memory retention in rats. This impairment was not rescued by a reminder shock delivered in a different context, a protocol that re-instates extinguished memories (Inda et al. 2011), suggesting that blocking glycogenolysis in the amygdala before training disrupts the consolidation process. Co-administration of L-lactate with DAB in the amygdala rescued the memory impairment, confirming the importance of the roles of glycogenolysis and lactate in diverse brain areas for IA memory consolidation (Figure 3).

The target functions fueled by lactate and/or glucose metabolism are still largely unknown. Brain energy is needed to support the electrical pulses required for neuronal communication, and for many housekeeping activities, including protein synthesis, phospholipid metabolism, neurotransmitter cycling, and transport of ions across cellular membranes (Du et al. 2008). As shown by the studies described above, lactate metabolism supports long-term memory

formation and the training-dependent increase in expression of several molecules related to activity and plasticity, including Arc, cFos, and Zif268 (Gao et al. 2016; Suzuki et al. 2011; Yang et al. 2014). These effects are NMDA receptor–dependent, implying that lactate-dependent changes are linked to activity and/or plasticity (Yang et al. 2014). *In vivo*, lactate is sufficient to maintain neuronal activity (Wyss et al. 2011) and recent data showed that interstitial K^+ elevations can activate a channel on the astrocyte membrane through which astrocytic lactate can flow into the interstitium, in parallel with the established transport via MCTs (Sotelo-Hitschfeld et al., 2015). This route for astrocytic lactate release is coupled to the membrane potential and allows lactate release against a concentration gradient, whereas the MCT is electro-neutral and net flux is governed by the trans-membrane concentrations of H^+ and lactate. Furthermore, an astrocytic mechanism via bicarbonate-responsive soluble adenylyl cyclase leading to glycogen breakdown, enhanced glycolysis, and the release of lactate into the extracellular space, which is subsequently taken up by neurons for use as an energy substrate has been demonstrated (Choi et al. 2012). Collectively these studies support the conclusion that lactate delivery by astrocytes to neurons can be regulated in many ways in response to activity and studies are needed to understand whether parallel or selective mechanisms occur *in vivo* upon learning. Nevertheless it emerges that lactate is needed to support not only ionic membrane homeostasis after depolarization, but also numerous other neuronal functions required for long-term modifications associated with memory formation and storage.

Glycogenolysis and lactate are important in arousal/stress-mediated memory consolidation

An event is well remembered for a long time if it is embedded in emotions. Emotional arousal leads to more detailed and long-lasting memories, and the stress hormones adrenaline (also known as epinephrine) and cortisol (corticosterone in rodents) are sufficient to mediate and modulate memory consolidation (McGaugh 2015).

Because epinephrine does not freely pass the blood–brain barrier (BBB), it may modulate memory consolidation by activating β-adrenergic receptors located peripherally on vagal afferents projecting to the nucleus of the solitary tract in the brainstem. Noradrenergic projections from this region influence neuronal activity in other brain regions, including the amygdala and hippocampus (Miyashita and Williams 2004; Williams et al. 2000). Consistent with this, increases in noradrenaline (NA) levels in the hippocampus have been observed *in vivo* in rats as early as 20 minutes after peripheral epinephrine injection, peaking one hour after application, and this effect is completely blocked by lidocaine injection into the nucleus of the solitary tract (Miyashita and Williams 2004). Importantly, neurons arising from the nucleus of the solitary tract project to the locus coeruleus, an area that releases NA upon stimulation and arousal (Gibbs et al. 2010; Lopes et al. 2016; Sara 2009; Sara et al. 1994).

In mammalian brains as well as in cultured astrocytes, NA stimulates glycogenolysis (Magistretti 1988; Quach et al. 1988; Subbarao and Hertz 1990). Application of NA is sufficient to modulate memory consolidation through the activation of α- and β-adrenergic

receptors (βARs) present in brain regions, such as the amygdala and the hippocampus (Roozendaal and McGaugh 2011). Because βAR blockers such as propranolol have been reported to interfere with memory consolidation and strengthening in rodents as well as in humans (Cahill et al. 1994; Dornelles et al. 2007; Przybyslawski et al. 1999), and have also been proposed as potential treatments for anxiety disorders, such as panic disorder and post-traumatic stress disorder (Ravaris et al. 1991; Vaiva et al. 2003), the action of NA through these receptors is of particular interest.

In the rat hippocampus, which is required for the consolidation of explicit/episodic memories, β1ARs predominate; both β2ARs and β3ARs are also present, although they are distributed differently (Milner et al. 2000; Rainbow et al. 1984; Summers et al. 1995), suggesting that the two types of receptors may have distinct roles. A variety of experiments with NA or βAR antagonists (e.g., propranolol) suggested that βARs play roles in memory encoding, modulation, and retrieval in humans and in rodents (Cahill et al. 1994; Przybyslawski et al. 1999; Summers et al. 1995). Studies of mice lacking β1ARs or treated with selective β1AR agonists or antagonists revealed critical roles of this receptor subtype in both synaptic plasticity and memory, with particular emphasis on memory retrieval (Murchison et al. 2004; Ramos et al. 2005; Winder et al. 1999). On the other hand, genetic deletion of β2ARs in mice impairs memory modulation by stress or corticosterone, and also impairs hippocampal plasticity, consistent with a role of β2ARs in the amygdala and its modulatory effects on the hippocampus and prefrontal cortex (Roozendaal and McGaugh 2011; Schutsky et al. 2011; Zhou et al. 2013).

In general, the functional contributions of βARs to memory processes are thought to result mainly from their effects on neurons, and have therefore been studied largely in neuronal/synaptic models (O'Dell et al. 2015). However, in addition to being expressed in pre- and postsynaptic compartments of neurons, βARs are also found in other cell types, particularly in astrocytes (Catus et al. 2011; Mantyh et al. 1995; Shao and Sutin 1992; Zhu and Kimelberg 2004). More specifically, it has been suggested that β2ARs in the nervous system are expressed predominantly in glia (Cash et al. 1986; Catus et al. 2011; Mantyh et al. 1995; Waeber et al. 1991), whereas β1ARs are found primarily in neurons, at synaptic junctions (Cash et al. 1986; Mantyh et al. 1995; Waeber et al. 1991). This suggestion raises the questions of which βAR subtype (β1AR or β2AR) and which βAR-expressing cells mediate hippocampal memory consolidation.

Moreover, β2adrenergic receptors (β2AR) play critical roles in memory consolidation in the avian cortex, and pharmacological experiments combining antagonists or agonists of βARs led Hertz and Gibbs to conclude that glycogenolysis stimulated by β2ARs is necessary for memory formation (reviewed in Gibbs 2016).

In recent studies, we sought to determine whether the contribution of βARs in the hippocampus to memory consolidation involves mechanisms related to glycogenolysis and astrocytic metabolism. Using our IA paradigm in young adult rats, we found that bilateral injections of propranolol into the dorsal hippocampus significantly impaired long-term memory, and that this impairment was not reversed following a reminder shock delivered in a different context, indicating that βARs in the hippocampus are required for memory

consolidation. Propranolol also blunted the learning-evoked induction of plasticity mechanisms such as induction of pCREB, pCamKIIα, and Arc. Both the behavioral and molecular disruptions were rescued by L-lactate, but not by an equicaloric concentration of glucose. These results suggested that production of astrocyte-derived lactate (i.e., lactate derived from glycogenolysis in astrocytes) is targeted by propranolol. To determine which of the β1- and β2ARs might be involved in the training-dependent behavioral and molecular changes, we systemically injected either the β2AR-selective antagonist ICI-118,551 or the β1AR-selective antagonist betaxolol before training, and then conducted hippocampal microdialysis experiments. The results revealed that both training-dependent lactate release and memory retention were significantly blocked by antagonists of β2ARs, but not β1ARs. Likewise, bilateral injections of the same antagonists into the dorsal hippocampus confirmed that antagonists of β2ARs, but not β1ARs, impaired memory retention. The effects on memory retention persisted. Collectively, these data indicated that β2ARs, rather than β1ARs, in the hippocampus contribute to IA memory consolidation, and that they do so by engaging mechanisms that control elevation of lactate levels in the extracellular space of the hippocampus upon training. Our previous experiments showing that learning-evoked lactate increase is blocked by DAB (Suzuki et al. 2011) led us to conclude that the β2AR-dependent increase in lactate level evoked by training derives from glycogenolysis.

Using autoradiography of ligand binding (in the absence of specific antibodies, for which we extensively screened, but could not find), we found that the distribution of β2AR in the hippocampus overlapped to a great extent with the distribution of the astrocyte marker glial fibrillary acidic protein (GFAP) visualized by immunohistochemistry, again supporting the idea that β2ARs are enriched in astrocytes rather than neurons (Gao et al. 2016). Employing astrocyte- or neuron-selective adeno-associated virus (AAV) under the control of either a modified GFAP or a synapsin-specific promoter, we expressed antisense or short hairpin (shRNA) sequences to significantly downregulate β2AR expression in either astrocytes or neurons. We found that astrocytic, but not neuronal, knockdown of β2AR led to persistent memory disruption. This disruption was fully rescued by L-lactate, providing evidence for the conclusion that β2ARs expressed in hippocampal astrocytes -via lactate production-, but not β2ARs expressed neurons, are critical for long-term memory formation.

It is interesting to note that also in chicks β2ARs had been previously described as the critical βAR subtype involved in glycogenolysis, despite the fact that the distribution of βAR subtypes does not correlate in chick and mammalian brains (Hutchinson et al. 2007), suggesting that β2ARs expressed by astrocytes may have a conserved role in regulating glycogenolysis. In agreement with the general role of β2ARs in glycogenolysis, lactate production from aerobic glycolysis coupled to β2AR stimulation has also been identified in muscle during shock states associated with reduced or maintained blood flow (Levy et al. 2008).

It remains to be determined whether the lactate is produced solely from glycogenolysis and/or also from glucose import and directly entering glycolysis. Regardless, our data implicating hippocampal β2ARs, rather than β1ARs, in memory consolidation, in conjunction with the observation that supplying lactate rescues the IA memory impairment caused by hippocampal astrocytic β2AR knockdown, strengthens the conclusion that lactate

produced by astrocytes is a key mediator of memory formation under arousal conditions (Suzuki et al. 2011).

Similar conclusions were provided by Jensen et al. (2016) who generated inducible astrocyte-specific β2AR knock-out mice by crossing homozygous β2AR floxed mice (Adrb2flox) and mice with heterozygous tamoxifen-inducible Cre recombinase-expression driven by the astrocyte specific L-glutamate/L-aspartate transporter promoter (GLAST-CreERT2). This study did not find any differences in physical health or motor functions between the knock-out mice and controls; however, it reported deficits in the ability of aged, but not young adult mice, in the water maze task. The study also found LTP impairment in hippocampal brain slices of aged knock-out mice maintained in low glucose media. The lack of effects on young mice may be due to the level of arousal of the task employed and future studies are needed to address this question.

In light of all these findings, we agree with Hertz and Gibbs (Hertz and Gibbs 2009) in suggesting that the level of arousal evoked by an experience may dictate whether glycogenolysis and/or glycolysis are recruited to promote memory consolidation. Further, we propose that if only memories of arousing experiences recruit the astrocytic β2AR mechanism, this may represent a distinct mechanistic signature of this type of memories. This would suggest that under physiological conditions glycogen acts to provide supplemental substrates when glucose is unable to support function during increased energy demand (Waitt et al. 2017). Again, future experiments should seek to address these important issues.

Notably, reminiscent of the effects of the glycogenolysis inhibitor DAB (Suzuki et al. 2011), direct supply of equicaloric concentrations of glucose into the hippocampus along with pharmacological blockers of β2AR failed to replicate the effect of lactate, and only at higher glucose concentrations were the memory impairments caused by β2ARs disruption transiently rescued. Although further experiments are needed to interpret this result, one possible explanation is that activity-dependent processes promote blood glucose entry into astrocytes rather than directly into neurons. Glucose then would be metabolized by astrocytes and, at least in part, converted into lactate, which would ultimately be transported from astrocytes to neurons (Magistretti and Pellerin 1999).

Mounting evidence indicates that astrocytic regulation of metabolism plays a role in many neurodegenerative diseases and brain-related pathologies, including Alzheimer’s disease, Huntington disease, multiple sclerosis, and amyotrophic lateral sclerosis (Maragakis and Rothstein 2006). For example, patients with multiple sclerosis exhibit dysregulated expression of glycolytic enzymes in both active and inactive lesions, and elevated levels of the lactate-producing enzyme LDHA in astrocytes within inactive lesions (Nijland et al. 2015). Furthermore, brain samples from patients with Alzheimer’s disease exhibit increases in both β2- and β1ARs, and β2 antagonists have yielded promising potential therapeutic results in mouse models (Fu and Jhamandas 2014; Dong et al. 2012). Further study will be required to fully understand the involvement of astrocytic β2ARs in neurodegenerative diseases. We suggest that disruption of the metabolic activation via astrocytic β2ARs in regions supporting cognitive functions may contribute to the pathological features of those

diseases. Hence, targeting astrocytic β2AR mechanisms may help prevent or repair these disorders and/or prevent their precipitation by stress.

How is lactate used to promote learning and memory?

The involvement of astrocyte-derived lactate in long-term memory formation shifts the view within the field from a neurocentric model of learning and memory to one in which multi-cell type cooperation plays a key role. An important question that remains to be addressed is: What does the lactate do?

Lactate, as found in other systems (i.e. muscle) (Brooks 2007; Brooks 2011; Brooks 2016) can be used as energy substrate. Based on the evidence for a critical role of MCT2 in long-term memory formation (Newman et al. 2011; Suzuki et al. 2011), our studies and those of several other laboratories mentioned above suggested that the major role of lactate might be metabolic, in support of the energy-intensive processes induced by learning. MCT2s are enriched in synapses, as showing by synaptoneurosomal (Suzuki et al. 2011) and electron microscopy studies which revealed their localization in both axons and spines (Bergersen et al. 2001; Bergersen et al. 2005). The idea that lactate entering activated synapses plays a metabolic role would be consistent with the high energy demands of membrane and cellular processes essential for long-term synaptic plasticity and memory, which include—to mention only a few—cytoskeletal remodeling, receptor trafficking, synaptic release, and local mRNA translation (Basu et al. 2007; Fukazawa et al. 2003; Harris et al. 2012; Lamprecht and LeDoux 2004; Malinow and Malenka 2002; Santini et al. 2014; Shi et al. 1999; Sudhof 2013; Xu et al. 2012).

In addition to its role as a metabolite and energy substrate, lactate has been shown to signal via changes in the NADH/NAD+ ratio, and hence redox regulation (Brooks 2009), a mechanism found to be important in long-term plasticity and memory (Knapp and Klann 2002; Massaad and Klann 2011). In fact, using cultured cortical neurons, Yang et al., (2014) reported that L-lactate application enhances intracellular NADH levels, promotes plasticity-related gene expression, and potentiates NMDA receptor signaling. These authors also found that although application of NADH recapitulated the effects induced by L-lactate on NMDA activation, application of pyruvate was insufficient to induce these changes, leading them to conclude that lactate is more than just an energy substrate.

Several studies have focused on other types of lactate signaling mechanisms. For example, lactate also signals via prostaglandin action and contributes to vasomotor regulation (Gordon et al. 2008). In addition, lactate was recently shown to signal through a specific G-protein–coupled receptor, GPR81/HCAR1, which is distributed in neurons (enriched in synaptic compartments), astrocytes, and vasculature cells, possibly linking neurotransmission, neurovascular coupling, and brain energy metabolism (Lauritzen et al. 2014; Morland et al. 2015). As described and discussed in an excellent review by Linda Hildegard Bergersen (Bergersen 2015), HCAR1 is mostly concentrated in neurons, on the synaptic membrane and intravesicular organelles. This distribution led Bergersen to propose the intriguing hypothesis that intravesicular lactate could contribute to lactate signaling. Moreover, in C2C12 myotube muscle cells, lactate application induced the expression of the lactate

receptor HCAR1 and of lactate transporters (MCT1/4), perhaps indicative of a positive feedback system, whereas pyruvate did not replicate this effect (Sun et al. 2016). In sum, our understanding of how lactate provides critical support for long-term memory formation is still in its infancy, and we cannot exclude the possibility that lactate plays multiple necessary roles in this process (Steinman et al. 2016).

Role of astrocyte–neuron metabolic coupling in memory formation during development

The metabolic demands of the developing brain are very high. Human brain glucose demand peaks during childhood (at an age of around 5 years) when glucose used by the brain represents approximately 60% of total body energy, compared to approximately 20% in adulthood (Kuzawa et al. 2014). This significant difference in energy requirements between the adult and developing brain may be reflected in differing roles of astrocyte and neuron metabolism in memory formation during development versus adulthood.

Astrocytes are critical for brain development. Due to their active contribution to several developmental processes, including neurogenesis, angiogenesis, axonal outgrowth, synaptogenesis, and synaptic maturation and pruning, dysfunction of astrocytes may contribute to the onset of neurodevelopment disorders, which could lead to learning and memory disabilities during adulthood (Clarke and Barres 2013). Although some astrogenesis has been reported in adults (Zhao et al. 2007), most astrocytes in the rodent brain are generated postnatally during the first 3 weeks of life, concurrently with the end of the initial neurogenic wave (Bandeira et al. 2009; Molofsky and Deneen 2015; Reemst et al. 2016). Astrocytes are distributed over all areas of the CNS, and likely migrate to their final destination shortly after their birth, leading to similar distributions between the neonatal and adult brains (Taft 2005; Tsai et al. 2012).

Therefore, given the extensive gliogenesis that greatly changes the cellular composition of the postnatal brain (Nedergaard et al. 2003), astrocytes in early development could either differentially influence memory processes, or remain uninvolved due to their functional immaturity. It would be interesting to determine whether astrocyte–neuron lactate metabolic coupling is necessary for memory formation during early development, as it is in adulthood.

Astrocyte–neuron metabolic interactions differ in several ways between the neonatal and adult brain (Brekke et al. 2015). For example, in the adult brain under normal conditions, glucose is the main energy substrate. By contrast, during the first three weeks following birth, the neonatal rat brain is characterized by reduced glucose utilization, coincident with lower expression of glucose transporters (GLUT) (Vannucci 1994; Vannucci et al. 1994; Vannucci and Simpson 2003) and the utilization of other substrates, such as ketone bodies, as energy sources (Hawkins et al. 1971; McKenna 2012). Indeed, during consumption of high-fat milk, ketone bodies provide a substantial fraction of the energy required by the neonatal brain (Dombrowski et al. 1989; Nehlig 2004). These nutrients are moved across the BBB through monocarboxylate transporters (MCTs) (Newman and Verdin 2014) whose expression decreases quickly after weaning, whereas expression of glucose transporters increases (Vannucci and Simpson 2003).

Even if the neonatal brain relies on alternative energy sources, glucose is indispensable for normal development. Using ^{13}C-labeled glucose and ^{13}C-labeled acetate, Morken and colleagues (2014) probed glycolysis, the pentose phosphate pathway (PPP), pyruvate carboxylation, and metabolic interactions between astrocytes and neurons in the 7-day-old rat brain, and compared these parameters to those of adult rats. In the immature brain, they observed lower transfer of glutamate from neurons to astrocytes, coupled to higher transfer of glutamine from astrocytes to neurons, indicating that much less glutamate-glutamine cycle is operating in the brain during early development. This reduction in the level of glutamate available for glutamine synthesis is partly compensated by an increase in pyruvate carboxylation in comparison with in the adult brain. Moreover, in the neonatal brain a relatively larger fraction of glucose is metabolized via the PPP and pyruvate carboxylation than by the glycolysis pathway, which is less active than the adult brain (Brekke et al. 2015; Morken et al. 2014).

The glucose, preferentially processed by the PPP, plays a key role during the rapid growth that occurs during the first postnatal weeks (Bandeira et al. 2009) by providing the substrates required for nucleotide and lipid synthesis, myelination, and production of NADPH, a crucial cofactor involved in cellular defenses against oxidative stress (Yager and Ashwal 2009). Thus, a high PPP-to-glycolysis ratio may explain the ability of the neonatal brain to more efficiently protect itself against oxidative stress.

Why is there a lower rate of glycolysis during early development? Moreover, does glycolysis play any role in memory formation at those early ages? Very few studies have described if and how glucose metabolism and astrocyte–neuron metabolic interactions contribute to the formation of long-term memory, and to cognitive functions more generally, during development. The first descriptions of such a contribution to memory formation during development were those of Gibbs and Hertz, described above, who used neonatal chicks in their studies and found that they require the breakdown of glycogen for glutamate synthesis in astrocytic memory mechanisms (Gibbs et al. 2007). Moreover, these authors reported mechanisms of glycogen-derived L-lactate (and/or pyruvate) transport between astrocytes and neurons in day-old chicks: in fact, either injection of D-lactate or pharmacological inhibition of MCT with α-cyano-4-hydroxycinnamate (4-CIN) inhibits their memory. Furthermore, glycogen breakdown and re-synthesis during learning and memory at this early developmental age were reported to be regulated by noradrenaline, serotonin, and ATP (Gibbs 2016). More specifically, it was shown that inhibition of β2-adrenergic, serotoninergic (5-HT2B), and purinergic P2Y1 receptors, all of which stimulate glycogenolysis, or of α2-adrenergic receptors, which favor glycogen synthesis, results in memory impairment in neonate chicks (Gibbs 2016).

In mammalian model systems (i.e., rodents) and humans, most studies have focused on the effect of glucose on memory. The essential finding of the last 20 years is that glucose, administered shortly before or after learning, or prior to memory retrieval, improves memory performance (Messier 2004). A similar effect has been observed at in 17- and 18-day-old rats, an age that corresponds to the period of infantile amnesia (Flint and Riccio 1999; Flint and Riccio 1997). Infantile amnesia refers to the inability of adults to remember early

memories. In humans as in non-human animals memories formed during the age of infantile amnesia are very rapidly forgotten (Li et al. 2014; Madsen and Kim 2016).

Recently, we showed that IA experiences in infant rats, although apparently forgotten, are actually stored over the long-term in a latent form, as these memories can be reinstated later in life if reminders are experienced (Travaglia et al. 2016a). Contrary to what had been suggested previously, we found that the infant hippocampus (at postnatal day 17, PN17) is highly responsive and engaged in learning, and makes a necessary contribution to the formation of the latent, long-lasting memories by recruiting molecular mechanisms typical of critical periods (Travaglia et al 2016a and b). Hence, we suggested that, as in other brain functions and systems, the episodic learning system undergoes a critical period, during which the hippocampal system acquires functional competence through experience (Alberini and Travaglia 2017).

Two studies have shown that infantile amnesia in rats can be attenuated by administration of glucose at the time of memory retention testing (Flint and Riccio 1997) or the time of learning (Flint and Riccio 1999). In the first study, 17-day-old rats were subjected to IA conditioning; 24 hours later, the animals were injected systemically with either saline or glucose immediately before testing. The saline-injected rats exhibited weak memory performance, suggesting rapid forgetting, whereas this memory loss was significantly attenuated in glucose-injected rats (Flint and Riccio, 1997). In a following study, the same authors exposed 18-day-old-rats to an immediate post-training subcutaneous injection of glucose; these rats performed significantly better than saline-injected control animals on a retention test given 24 hours after training (Flint and Riccio, 1999). The mechanisms by which glucose attenuates infantile amnesia remain unknown, and a better understanding of the functional implication of glucose metabolism and astrocyte-neuron metabolic coupling in memory formation during development could provide important insights into how the memory system develops, as well as suggesting potential clinical applications for learning disabilities.

Conclusions

Although most previous studies on the biological mechanisms of memory formation and storage have centered on neuronal mechanisms, attention has recently been given to the roles of other brain cell types, and in particular glia. Here, we reviewed the evidence for the role of astrocytes in regulating glycogen and glucose metabolisms, and their functional coupling to neurons via lactate transfer, which is necessary for memory formation. Furthermore, we discussed studies performed in different species revealing the critical role of astrocytic βARs in regulating the consolidation and modulation of memory. We suggest that astrocytic glycogenolysis and/or glycolysis in conjunction with astrocytic–neuronal lactate shuttling, provide a mechanistic explanation for a critical role of astrocytes in memory formation and storage. These findings offer only an initial understanding of the metabolic cooperation between astrocytes and neurons in memory; future studies shall elucidate the functions of glycogenolysis and lactate in many other important and complex brain functions. Many questions remain to be addressed. In the context of memory research, the outstanding issues include whether the lactate-mediated metabolic coupling is a general mechanism engaged in

different types of learning and memory, or only in memories encoded under arousal states. Other important outstanding questions include: Are these mechanisms common to any brain region in response to activity? Are they providing metabolic fuel or also cellular signaling? Which target mechanisms and cellular function do they support? How do these metabolic mechanisms mature during development, when the brain consumes the highest amount of energy? And finally, what are the implications when these mechanisms fail? These questions should be addressed in the near future, and the answers will greatly advance our understanding of the cooperative roles of different cell types in learning and memory processes.

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Main Points

Astrocyte glycogenolysis and lactate play a critical role in memory formation. Emotionally salient experiences form strong memories by recruiting astrocytic β2 adrenergic receptors and astrocyte-generated lactate. Glycogenolysis and astrocyte–neuron metabolic coupling may also play critical roles in memory formation during development, when the energy requirements of brain metabolism are at their peak.

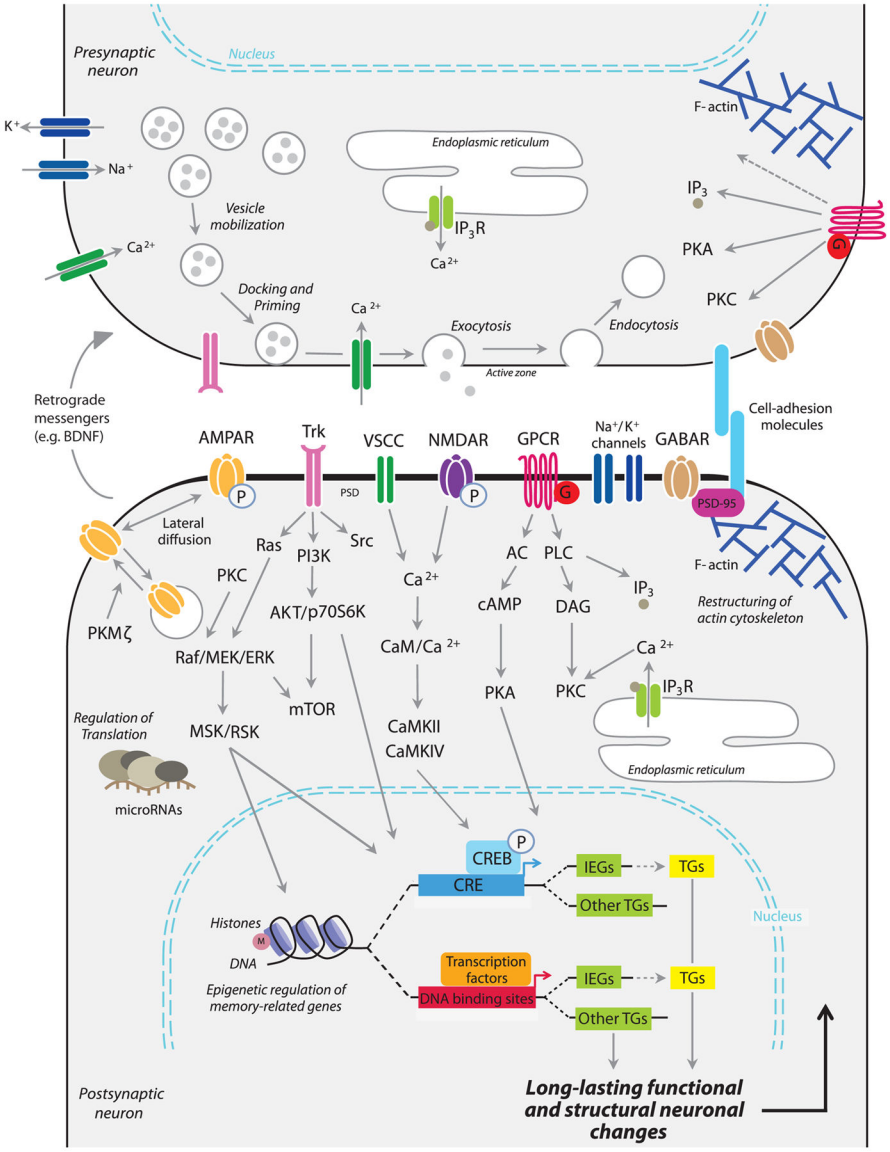

Figure 1. Schematic example of neuron-centric molecular pathways underlying long-term memory formation

Most literature's figures available thus far illustrating molecular mechanisms underlying learning and memory depict only pre and postsynaptic neurons and relative mechanisms of interest. One example is the following: learning-induced release of neurotransmitters (e.g. glutamate) and of neuronal growth factors (e.g. BDNF) activate different families of receptors, enabling the recruitment of various intracellular signaling pathways involving second messengers (e.g. Ca^{2+}, cAMP) and protein kinases (e.g. CamKII, PKA). These signaling pathways regulate: 1) post-translational modifications [e.g., phosphorylation (P) of postsynaptic glutamatergic receptors]; 2) activation of a CREB-regulated gene cascade leading to the expression of target genes, including IEGs (e.g., C/EBP, c-Fos, Zif268), which in turn regulate the expression of late response genes critical for long-lasting functional (e.g., membrane translocation of new receptors) and structural neuronal changes (e.g., dendritic

spine morphological changes). This gene expression is regulated by epigenetic mechanisms [e.g. histone acetylation and/or methylation (M), DNA methylation] as well as by several post-transcriptional and translational mechanisms including the mTOR pathway and microRNAs. Abbreviations: AC (adenylyl cyclase); AKT (protein kinase B or Akt); AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor); BDNF (brain-derived neurotrophic factor); CaM (calmodulin); CaMKII/IV (Ca++-calmodulin kinase II/IV); cAMP (cyclic adenosine monophosphate); C/EBP (CCAAT/enhancer binding protein); CRE (cAMP response element); CREB (cAMP response element binding protein); DAG (diacylglycerol); GPCR (G protein–coupled receptors); IEGs (immediate early genes); IP_3 (inositol trisphosphate); IP_3R (inositol trisphosphate receptor); MSK (mitogen and stress activated protein kinase); mTOR (mammalian target of rapamycin); NMDAR (N-methyl-D-aspartate receptor); p70S6K (ribosomal protein S6 kinase beta-1); PI3K (phosphoinositide 3-kinase); PKA (protein kinase A); PKC (protein kinase C); PKMζ(protein kinase M zeta); PLC (phospholipase C); PSD-95 (post-synaptic density 95); RSK (ribosomal s6 kinase family); Src (proto-oncogene tyrosine-protein kinase); TGs (target genes); Trk (tyrosine receptor kinase); VSCC (voltage-sensitive calcium channel). Notably, multiple cell types in the brain express many of these mechanisms.

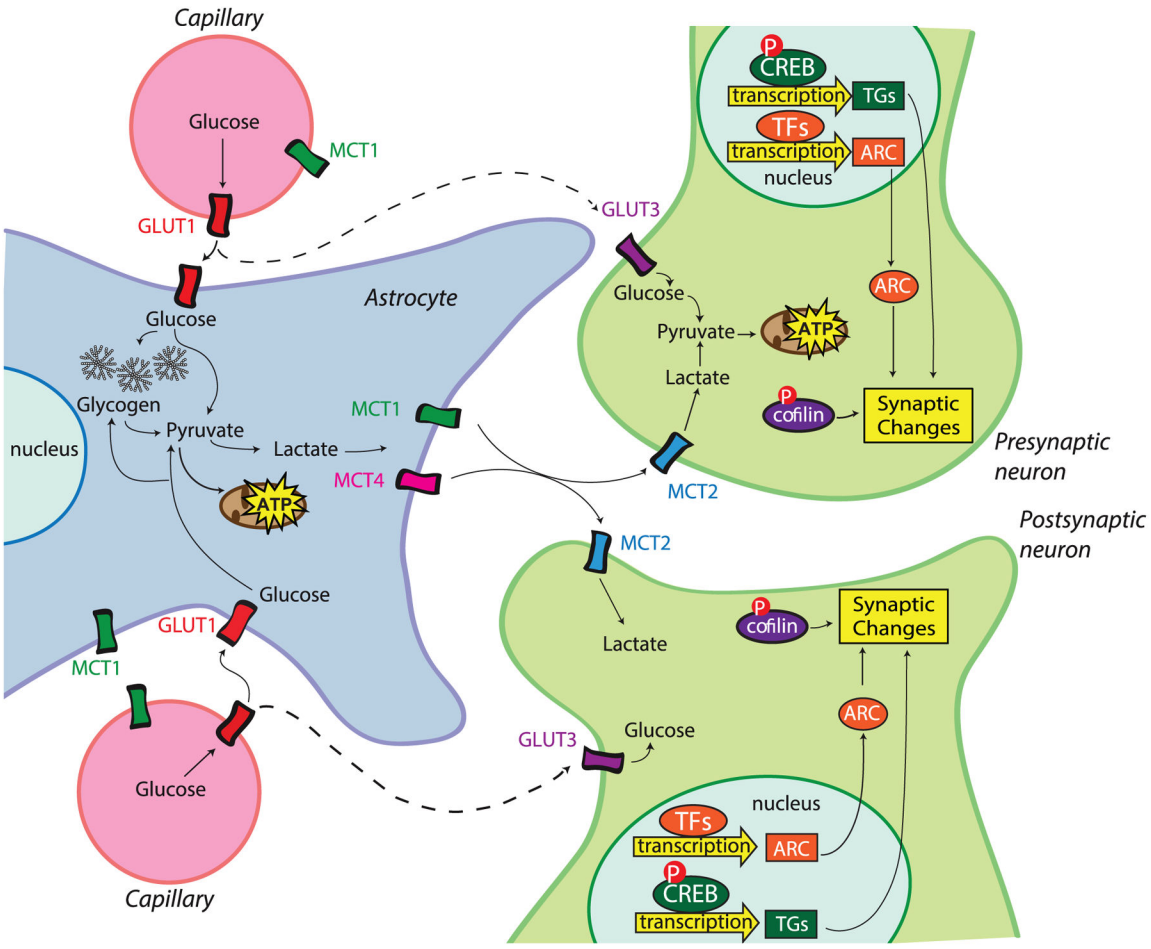

Figure 2. Astrocyte–neuron lactate coupling in long-term memory formation

Glucose is taken up by astrocytes from surrounding capillaries via glucose transporters (GLUT1). Glucose can then be stored as glycogen in astrocytes or undergo glycolysis to become pyruvate. In astrocytes, pyruvate can be transported into the mitochondria or converted to lactate, which can be exported out of the astrocyte by the monocarboxylate transporter 1 or 4 (MCT1/4) and transported into neurons via MCT2. In neurons, astrocytic-derived lactate is converted back into pyruvate and transported into the mitochondria to generate ATP. Glucose may also be transported from the capillaries into neurons through the glucose transporter (GLUT3). In Suzuki et al. 2011, we showed that the astrocytic-derived lactate from glycogenolysis is critical for long-term memory formation in rats and for the underlying regulation of molecular changes required for long-term memory formation. These changes include the phosphorylation of the transcription factor CREB, the expression of target genes (TGs), the expression of immediate early genes such as Arc, and the phosphorylation of the actin-binding protein cofilin. Whether glucose transport into neurons through GLUT3 is important for memory formation remains to be determined.

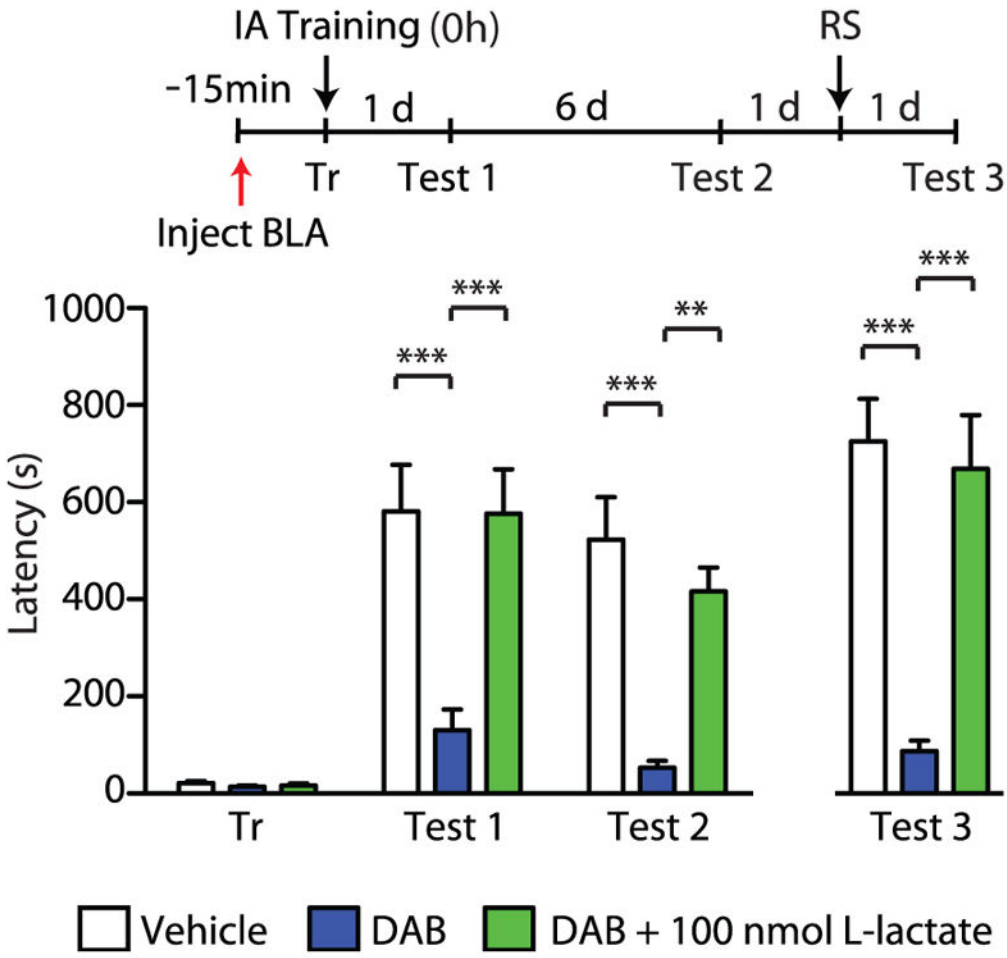

Figure 3. Blocking glycogenolysis in the basolateral amygdala impairs long-term memory

Long-term memory retention, expressed as mean latency values ± SEM in seconds (s), tested 1 day (d) after training (Test 1), 6 d later (Test 2), and after a reminder shock given in a distinct context (RS, Test 3). Vehicle, DAB (300 pmol), or DAB (300 pmol) + L-lactate (100 nmol) was injected bilaterally into the basolateral amygdala (BLA) 15 min prior to inhibitory avoidance (IA) training (red arrow). Statistical significance was assessed by two-way ANOVA followed by Bonferroni's post hoc tests compared to vehicle (**$p < 0.01$; ***$p < 0.001$; n = 7–8/group).