Cell

Astrocytes: Powering Memory

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Creating long-term memory requires a cellular program in neurons involving gene expression, protein synthesis, and formation of new synaptic connections. Suzuki et al. (2011) show that astrocytes, glial cells of the brain, play a necessary role in this program by converting glycogen to lactate and transporting it to neurons.

Memory is a mechanism for retaining newly learned information. External events are represented in the brain as specific spatiotemporal patterns of neural activity, and this activity can affect the way neurons communicate with each other at specialized junctions called synapses. The physical location of memory storage thus occurs at synapses that undergo activity-dependent changes in synaptic efficiency. A key brain region for storage of explicit memories—that is, memories involving conscious recall of people, places, objects, or events—is the hippocampus, where synaptic connections exhibit activity-dependent plasticity changes such as long-term potentiation (LTP) (Kandel, 2001).

A memory role for astrocytes, glial cells strategically intercalated between blood vessels and synapses, has not been considered until very recently. Astrocytes are the main energy reservoirs of the brain. They accumulate glycogen and help fulfill the high-energy demands associated with neuronal activity (Attwell and Gibb, 2005; Rouach et al., 2008). However, their precise roles and mechanism of action remain unclear. Suzuki and colleagues (2011) now demonstrate a direct role for astrocyte metabolism in the memory process. Using an elegant combination of in vivo approaches in rats, the authors show that glycogenolysis, the breakdown of glycogen into glucose, occurs immediately after animals undergo a learning task and demonstrate that this metabolic event is required for consolidation of the learned paradigm (Figure 1).

Consolidation is the process by which memories, initially labile and highly sensitive to disruption, are stabilized and stored for a long time. At the cellular level, the early phase of memory (minutes to hours) relies on posttranslational modification of pre-existing proteins, whereas consolidation involves gene expression, new protein synthesis, and growth of new synaptic connections (Kandel, 2001) (Figure 1). Suzuki and colleagues show that pharmacological inhibition of glycogen metabolism during the initial phase of memory storage, but not at later stages, prevents retention of the learned task. This result suggests that glycogenolysis in astrocytes is necessary for triggering the conversion of memory from a transient short-term form to a more stable long-term one.

Why is glycogenolysis, and not another energy source, required for memory consolidation? Does the process require an initial extra-energy burst? Intriguingly, the authors find that the relevant metabolic product is not glucose but lactate, a downstream product of glycogenolysis. They show that extracellular lactate levels increase in the hippocampus immediately after rats engage in a learning task. Furthermore, when they block the endogenous release of lactate, administration to the animals of exogenous lactate prevents amnesia. Glucose administration, by contrast, even at doses that are higher calorie-wise, produces only a transient effect on memory formation.

Why do lactate and glucose have different effects? Perhaps different timing or location of production and delivery determine the outcome. Lactate transport among cells, for example, depends on the action of monocarboxylate transporters (MCTs), which do not transport glucose. Indeed, bilateral injection into the hippocampus of antisense oligonucleotides directed against specific MCT isoforms (MCT1, 2, and 4) affects memory consolidation in a way that resembles the effects of a blockade of glycogenolysis. The same effect is observed when targeting either astrocytic transporters (MCT4) or neuronal ones (MCT2). However, the memory defects caused by knockout of MCT4 (the astrocytic transporter) but not those caused by knockout of MCT2 (the neuronal transporter) can be rescued by addition of exogenous lactate. These results suggest that lactate is transported from astrocytes into neurons.

It is therefore likely that a specific shuttle system delivers lactate from astrocytes to neurons, as has been postulated long ago (Pellerin and Magistretti, 1994) but never directly proven. The shuttle system may be located strategically, allowing it to deliver lactate directly where it is needed, possibly in the neuronal dendritic spines that will undergo plastic transformation during memory consolidation. This hypothesis is consistent with the reported localization of MCT2 in dendritic spines at excitatory hippocampal synapses (Bergersen, 2007) (Figure 1). However, the authors find that knocking out MCT1, a transporter widely distributed in astrocytes, blood cells, and oligodendrocytes, also affects memory consolidation, which may argue against the specific shuttle hypothesis. Further studies will be needed to delineate the lactate transport route and the exact localization and specific function of each transporter in the process.

Another potential difference between lactate and glucose may be that lactate has not only purely energetic functions but also (or instead) signaling functions, in analogy to other neuroactive agents

released by astrocytes (gliotransmitters; Volterra and Meldolesi, 2005). This idea is consistent with recent studies implicating a role for lactate in the control of vessels by astrocytes. In this process, astrocytes release vasodilating prostaglandins and lactate acts as modulator of prostaglandin transport, not as an energy source (Gordon et al., 2008).

In the context of synaptic plasticity, unexpected roles are emerging for additional molecules released from astrocytes. For example, astrocyte-released TNF-α participates in synaptic scaling, a form of homeostatic plasticity that modulates the strength of an entire synaptic network depending on its activity history (Stellwagen and Malenka, 2006). On the other hand, astrocyte-released D-serine plays a role in the induction of long-term potentiation at hippocampal synapses by acting as an endogenous NMDA receptor coagonist (Henneberger et al., 2010). Interestingly, the D-serine study also suggested that LTP formation requires intact metabolic activity in astrocytes.

By showing that glycogenolysis and its product, lactate, are required for memory consolidation in vivo, Suzuki et al. enhance our understanding of the links between metabolic and memory processes. Nevertheless, several aspects of this system still await clarification. For example, we don't know what triggers glycogenolysis in astrocytes, the time of the signal, and whether it originates from presynaptic or postsynaptic neuronal activity. Likewise, the mechanism by which lactate acts in the neuronal cellular cascade leading to memory consolidation and the exact timing of its action remain unknown.
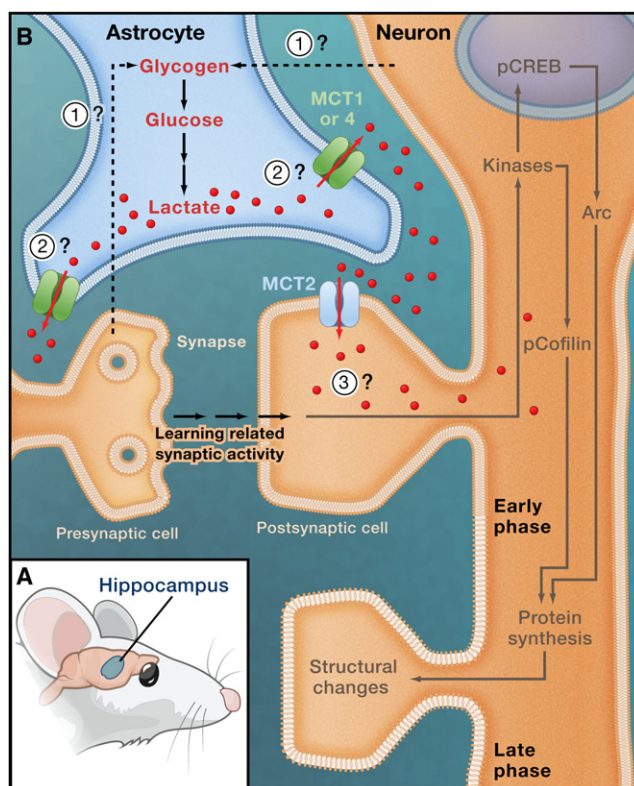
Figure 1. Astrocytes in Long-Term Memory Formation
Suzuki et al. (2011) show that glycogenolysis (the breakdown of glycogen) and the release of its downstream product lactate from astrocytes are required for memory consolidation in response to a learning paradigm.
(A) Rats participate in a learning task, creating a stable memory in the CA1 region of the hippocampus.
(B) Some of the key molecular and structural changes at CA1 synapses (brown) and neighboring astrocytes (light blue) that lead to the establishment of long-term memory.
The figure is based on the available literature and the new results by Suzuki et al. The learning task stimulates memory formation that, in the early phase, requires both glutamatergic synaptic activity in neurons and glycogen metabolism and lactate release in astrocytes. The memory program in the postsynaptic neuron triggers activation of protein kinases with subsequent phosphorylation of the nuclear transcription factor CREB and of cofilin (an actin-binding protein), as well as rapid expression of the activity-dependent gene Arc, all necessary steps for the establishment of long-term memory. In the late phase, new protein synthesis leads to structural changes and formation of new synapses. The authors' data suggest that lactate is exported from astrocytes via the monocarboxylate transporters MCT1 or MCT4 and imported into neurons via MCT2. Lactate transport is necessary for the expression of Arc and for the phosphorylation of CREB and cofilin. Question marks in the figure highlight the several issues that remain to be resolved: (1) the neuronal signal responsible for triggering glycogen metabolism in astrocytes; (2) the specific location of the different lactate transporters in astrocytes and neurons; (3) the mechanism by which lactate acts in the cascade of events leading to memory consolidation.

Another, more general question concerns the experimental approaches required for clarifying the above points. For instance, it is unclear whether Ca^{2+} imaging, the main current approach for real-time study of synapse-astrocyte communications, can be used to study the interplay between astrocytes and neurons that involves glycogenolysis. Other real-time methods may need to be developed.

These unresolved questions underline our present limited understanding of the modes of synapse-astrocyte interaction and the methodological challenges associated with their study. However, with more and more studies implicating astrocyte signaling in synaptic plasticity and now, directly, in memory processes, the Pandora's Box has been opened. Understanding neuron-glia interactions may well reveal new critical and unexpected aspects of the neurobiology of memory.

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