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Review

Neuron–glia metabolic coupling and plasticity

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Summary

The coupling between synaptic activity and glucose utilization (neurometabolic coupling) is a central physiological principle of brain function that has provided the basis for 2-deoxyglucose-based functional imaging with positron emission tomography (PET). Astrocytes play a central role in neurometabolic coupling, and the basic mechanism involves glutamate-stimulated aerobic glycolysis; the sodium-coupled reuptake of glutamate by astrocytes and the ensuing activation of the Na-K-ATPase triggers glucose uptake and processing *via* glycolysis, resulting in the release of lactate from astrocytes. Lactate can then contribute to the activity-dependent fuelling of the neuronal energy demands associated with synaptic transmission. An operational model, the 'astrocyte–neuron lactate shuttle', is supported experimentally by a large body of evidence, which provides a molecular and cellular basis for interpreting data obtained from functional brain imaging studies. In addition, this neuron–glia metabolic coupling undergoes plastic adaptations in parallel with adaptive mechanisms that characterize synaptic plasticity. Thus, distinct subregions of the hippocampus are metabolically active at different time points during spatial learning tasks, suggesting that a type of metabolic plasticity, involving by definition neuron–glia coupling, occurs during learning. In addition, marked variations in the expression of genes involved in glial glycogen metabolism are observed during the sleep–wake cycle, with in particular a marked induction of expression of the gene encoding for protein targeting to glycogen (PTG) following sleep deprivation. These data suggest that glial metabolic plasticity is likely to be concomitant with synaptic plasticity.

Key words: neuro-metabolic coupling, plasticity, astrocyte, glia, sleep–wake cycle.

Brain energy metabolism

Background

The energy requirements of the brain are amazingly high; indeed, while representing only 2% of the body mass, its oxygen and glucose utilization account for approximately 20% of those of the whole organism, almost ten times more than those predicted on a mass basis (Magistretti, 1999). A similar mismatch is observed for blood flow destined to the brain, which represents over 10% of cardiac output. In addition to these quantitative aspects, brain metabolism has other distinctive features, in particular its regional variability and the nature of its cellular determinants. At the macroscopic level, one regional variability is manifested by the difference in energy metabolism between grey and white matter (Clarke and Sokoloff, 1994). But a much finer feature of brain metabolism is that its regional variability is strongly determined by the ever-changing spatially and temporally specified levels of synaptic activity. Thus one of the founding principles of brain physiology is that metabolism and flow are tightly coupled with neuronal activity; this fact has been appreciated since the turn of the 19th century when Sherrington proposed that "*…the brain possess an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity*" (Roy and Sherrington, 1890).

The pioneering work of Louis Sokoloff and his colleagues in the 1970s and 1980s using the 2-deoxyglucose (2-DG) autoradiographic technique and its *in vivo* extension to humans with 18-fluoro-DG imaging of glucose utilization by positron emission tomography (PET) (Sokoloff et al., 1977), has clearly demonstrated a similar coupling between neuronal activity and glucose metabolism. Indeed, this tight relationship between neuronal activity with blood flow and metabolism has provided the basis for the functional brain imaging techniques that are now widely in use by cognitive neuroscientists and clinicians (Mazziotta et al., 2000). Thus local changes in glucose utilization, blood flow and oxygen utilization for PET and, mostly, variations in the level of hemoglobin oxygenation for functional magnetic resonance imaging (fMRI) during well-

defined behavioral tasks or mental states, are taken as indicators of the activity of specific neuronal pathways, allowing a novel and extremely fertile appraisal of the neural substrates of brain functions, in particular those at a higher level.

While being very appropriate and widely used for functional brain mapping, the cellular mechanisms that are at the basis of the coupling between neuronal activity and metabolism, and hence at the basis of the signals detected by functional imaging techniques, have only recently begun to be unraveled. Our group has contributed over the last ten years to the understanding of such cellular and molecular mechanisms (Pellerin and Magistretti, 1994).

Briefly we have identified a key role of astrocytes in coupling synaptic activity to glucose utilization, through molecular mechanisms that involve the sequential intervention of astrocyte-specific glutamate transporters and sodium-potassium ATPase, activation of glycolysis in astrocytes and monocarboxylate transporter-mediated exchange of lactate from astrocytes to neurons (Magistretti and Pellerin, 1999; Magistretti et al., 1999). The basic mechanism in neurometabolic coupling is astrocyte glutamate-stimulated aerobic glycolysis, such that the sodium-coupled re-uptake of glutamate by astrocytes and the ensuing activation of the Na-K-ATPase triggers glucose uptake and its glycolytic processing, resulting in the release of lactate from astrocytes. Lactate can then contribute to the activity-dependent fuelling of the neuronal energy demands associated with synaptic transmission (Magistretti and Pellerin, 1999). A large body of experimental evidence (for recent reviews, see Pellerin and Magistretti, 2003; Pellerin and Magistretti, 2004) led to the proposal of an operational model, the 'astrocyte–neuron lactate shuttle' (Bittar et al., 1996; Pellerin et al., 1998). Recently a series of results obtained by independent laboratories provided further support for this model (Kasischke et al., 2004; Loaiza et al., 2003; Serres et al., 2004). This body of evidence provides a molecular and cellular basis for interpreting data obtained with functional brain imaging studies. Thus the picture that emerges is that glucose metabolism is coupled to glutamate-mediated neuronal activity *via* molecular mechanisms that are largely, although possibly not exclusively, based on a coupling role of astrocytes (Fig. 1). A similar role of astrocytes in coupling neuronal activity to blood flow has also been recently suggested (Mulligan and MacVicar, 2004; Takano et al., 2006; Zonta et al., 2003).

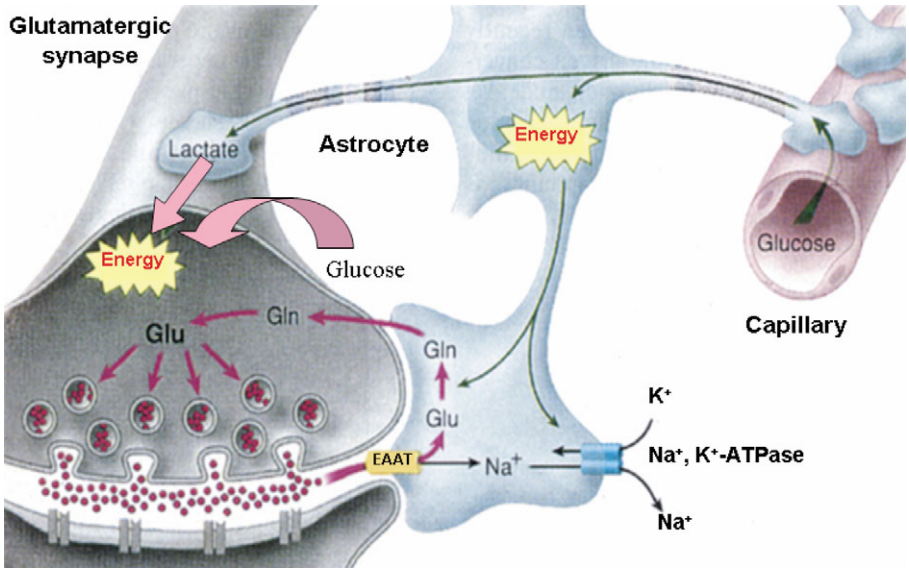

Fig. 1. Model for neuron–glia metabolic coupling (see text for details) (modified from Magistretti et al., 1999).

Activation vs baseline

The emphasis on glutamate as a determining coupling signal deserves some discussion. First it should be remembered that over 90% of synapses, at least in the cerebral cortex, use glutamate as their neurotransmitter (Braitenberg and Schuz, 1998). Second, the physiological studies concerned with neurometabolic coupling on one hand, and the main focus of functional imaging studies on the other, are centered around what we generally refer to as 'activation'. The idea is that a given behavioral task will involve the activation of a specific neuronal pathway resulting in glutamate release and in the temporally and spatially coupled metabolic and vascular responses that provide the signal detected with functional imaging techniques. The question is: '*How large is the increase in the metabolic or vascular response during "activation", when compared to "baseline" activity?*'. The answer is: '*Surprisingly small!*'. Indeed, there is a general consensus that during a given behavioral task, blood flow and glucose utilization increase by an average of 10% over baseline, at most by 20%, depending on the paradigm used, and oxygen consumption even less, possibly remaining under 5% increase (Raichle, 2003). It is worth noting here that these data indicate a partial uncoupling of glucose utilization and oxygen consumption, suggesting that during activation, the brain resorts to a transient glycolytic processing of glucose, a consideration consistent with the proposed cellular mechanisms of neurometabolic coupling pointing at a central role of glutamate-stimulated glycolysis in astrocytes (Fox et al., 1988; Magistretti and Pellerin, 1999).

The next questions then are: '*Why is basal brain activity so high and, more importantly from a physiological point of view, what kind of neural activity is occurring during baseline?*' The question about the nature of the mechanisms underlying baseline brain activity has attracted considerable attention recently both from the physiological angle and from the neuroimaging perspective, as the

intuition is that neurobiologically important information may have been overlooked by almost exclusively focusing on activation (Gusnard and Raichle, 2001). Indeed, baseline activity not only represents 90% of brain metabolism, but also appears to be dynamically regulated, varying under a variety of physiological and pathological conditions (Raichle, 2003; Reiman et al., 1996; Shulman et al., 1997).

Before briefly reviewing the instances during which baseline activity varies, it is important to address the issue of how baseline is defined. This issue has been tackled most lucidly by Marc Raichle in a series of illuminating articles (Raichle, 2003; Raichle and Gusnard, 2002; Raichle et al., 2001). As noted above, during activation, oxygen consumption does not increase commensurately with glucose utilization and blood flow (Fox and Raichle, 1986; Fox et al., 1988). Thus, during activation, oxygen delivery to the activated area increases (as a consequence of the increased arterial blood flow) while oxygen utilization does so only marginally. This implies that the fractional oxygen extraction is lower, meaning that what is referred to as the 'oxygen extraction fraction (OEF)', will decrease during activation. OEF has turned out to be a very useful variable to define baseline: it is very stable at rest because there is an excellent match between blood flow and oxygen utilization, and activation or deactivation (to be discussed below) of a given area can be defined in terms of its OEF. Thus an alternative way to define activation is an instance where and when an area shows a transient decrease in OEF in comparison to the mean OEF of the brain (Gusnard and Raichle, 2001; Raichle et al., 2001). Following this line of reasoning, an increase in OEF would imply a decrease in the activity, or deactivation, of a given area.

Thus the fact that a baseline can be defined, vastly increases the dynamic range of brain metabolism as an informative correlate of neural activity. Interestingly, a thorough analysis of a large number of PET studies has shown that decreases in activity could be observed in certain brain areas, notably postero-medial and -lateral cortices and ventral- and dorso-medial prefrontal cortices, during visual, auditory and motor tasks (for a review, see Gusnard and Raichle, 2001). Thus, this notion of baseline implies that during a particular task not only activation is observed (e.g. activation of primary visual cortex during visual stimulation) but also deactivation in certain areas. These data suggest that there are areas that are activated during goal-directed protocols (sensory-motor tasks for example), while others are actively engaged during the 'resting state'. The time constants of both types of activities are markedly different: indeed, while the typical activations are transient, the functional activity embedded in the baseline is sustained, suggesting the involvement of mechanisms related to processing of the information acquired during the transient activations. Available PET data indicate that these sustained activities may cease during task-dependent transient activations and resume during the intervening periods, thus providing a strong determinant of baseline metabolism (Gusnard and Raichle, 2001).

To summarize this important new dimension of brain metabolism and related imaging studies it appears that two modes with different temporal dimensions operate:

(1) The much studied activation mode, which is transient in nature, which relates to 'on-line processing of information' involving sensory, motor and possibly associative modalities, and which provides the signals that have attracted the attention of functional brain mapping studies. This mode involves a modest mobilization of energy resources, about 10% of baseline activity, representing in a way 'the tip of the iceberg of brain metabolism' (Raichle, 2003).

(2) A thus far barely explored mode, the sustained baseline activity mode, which quantitatively represents the bulk of brain energy metabolism, which may transiently decrease during modality-specific activations, and which may be related to a 'post-processing of information' mode.

Recognizing the potential significance of this task-independent activity mode obviously raises questions, for example: '*What is its function and which are its cellular and molecular determinants?*'. For the second question, potential answers are at hand, based on the current knowledge that we have about the cellular and molecular mechanisms of neurometabolic coupling. Indeed, glucose utilization, which is one of the variables measured in most of the PET studies that have resulted in the recognition of the sustained baseline activity mode, is largely determined by glutamate-mediated neurotransmission (Magistretti and Pellerin, 1999). This is not surprising, since, as noted earlier, 90% of synapses are glutamatergic. A bottom-up analysis of the energy budget of the cerebral cortex has indicated that most energy is devoted to action potential propagation and restoration of ion gradients at excitatory synapses (Attwell and Laughlin, 2001). In this analysis, only 15% of total brain energy consumption can be accounted for by maintenance of resting potential and glial cell activity. Similar results have been obtained using a radically different approach, namely magnetic resonance spectroscopy determination of glucose oxidation and glutamate cycling at different levels of anesthesia and the corresponding levels of cortical electrical activity (Hyder et al., 2002; Sibson et al., 1998). Also in this analysis, over 80% of glucose utilization was linearly correlated with glutamate-mediated neurotransmission. Thus, one is compelled to conclude from these data that synaptic activity at glutamatergic circuits operates during the task-independent baseline mode of activity reflected in the large glucose utilization that characterizes this state. The mechanisms that couple glutamate activity and glucose utilization are now largely known involving, as noted earlier, a central role of astrocytes (Magistretti et al., 1999; Pellerin and Magistretti, 2003).

In contrast, the answer to the first part of the question namely '*What is its (baseline activity) function..*', is much more elusive. One could suggest that in general terms it may correspond to a 'post-processing of information' mode. Terms that have been used include 'stimulus-independent thoughts' (Teasdale et al., 1995), 'stream of consciousness' (Andreasen et al., 1995), 'optimization of cognitive and behavioral serial

programs' (Ingvar, 1985) (for a review, see Gusnard and Raichle, 2001). Another formulation could be that this baseline mode reflects, at least in part, ongoing processes of synaptic plasticity. These processes have been the object of intense attention over the recent years (Bear, 2003; Grossman et al., 2002). A number of neurotransmitter-regulated mechanisms have been identified and have provided new insights into the cellular and molecular mechanisms of learning and memory (Malenka, 2003). In other words, it is conceivable that a sustained task-independent activity that is correlated with a high basal metabolic activity, does not simply correspond to 'neuronal noise' but actually reflects synaptic plasticity processes that are related to the post-processing of incoming information.

Synaptic plasticity and metabolic plasticity

Given the tight coupling that exists between synaptic activity and energy metabolism, it is likely that the processes that underlie synaptic plasticity may also be reflected at the energy metabolism level, resulting in correlated metabolic adaptations, which could be defined as 'metabolic plasticity'. The notion of metabolic plasticity has indeed found experimental validation. Thus evidence has been obtained in a restricted number of experimental paradigms for activity-dependent long-term metabolic adaptations (Barrett et al., 2003; Gonzalez-Lima and Garrosa, 1991; Hyden et al., 2000; Maviel et al., 2004; Room et al., 1989; Welker et al., 1992; Zhang and Wong-Riley, 1999). In this context, over the years our laboratory has gathered evidence that plasticity of energy metabolism is regulated by a restricted set of neurotransmitters. Such adaptations in metabolic pathways are mediated by transcriptional mechanisms that modulate the expression of genes involved in energy metabolism (Allaman et al., 2003; Allaman et al., 2000; Allaman et al., 2004; Debernardi et al., 2003; Pierre et al., 2003; Sorg and Magistretti, 1992). Most of the data on metabolic plasticity that our laboratory has collected relate to *in vitro* analyses at the molecular level. We have recently begun to explore the mechanisms of metabolic plasticity in a well-established paradigm of learning and memory, and during the sleep–wake cycle, two conditions for which we have preliminary evidence of such metabolic plasticity. Particular, although not exclusive, attention has been focused on the possible correlation between task-independent activity and metabolic plasticity.

Metabolic plasticity: the example of glycogen

A main line of research of our laboratory has been to explore the role of certain neurotransmitters on the metabolic fluxes of glucose, with particular reference to the regulation of glycogen metabolism in astrocytes. This line of research constituted our initial interest on long-term metabolic regulation, or in other words, metabolic plasticity. Thus, we have identified a number of neuroactive molecules, in particular adenosine, noradrenaline and certain cytokines, regulating the expression of key genes involved in glycogen metabolism (Fig. 2), in particular protein targeting to glycogen (PTG) (Allaman et al., 2000; Allaman et al., 2004; Cardinaux et al., 2000). Thus exposure to the above-mentioned transmitters results in the cyclic-AMP-dependent induction of expression of the transcription factor C/EBP, of glycogen synthase and of PTG. In search for an *in vivo* physiological condition in which a certain degree of metabolic plasticity could be identified, we explored the level of expression of the key enzyme in glycogen metabolism, PTG. We have identified a circadian rhythm for the expression of PTG mRNA and a reversible induction of its expression following sleep deprivation (Petit et al., 2002).

Brain energy metabolism during sleep–waking cycle

A proposed function for sleep is brain energy restoration. Numerous studies using glucose uptake measurements in

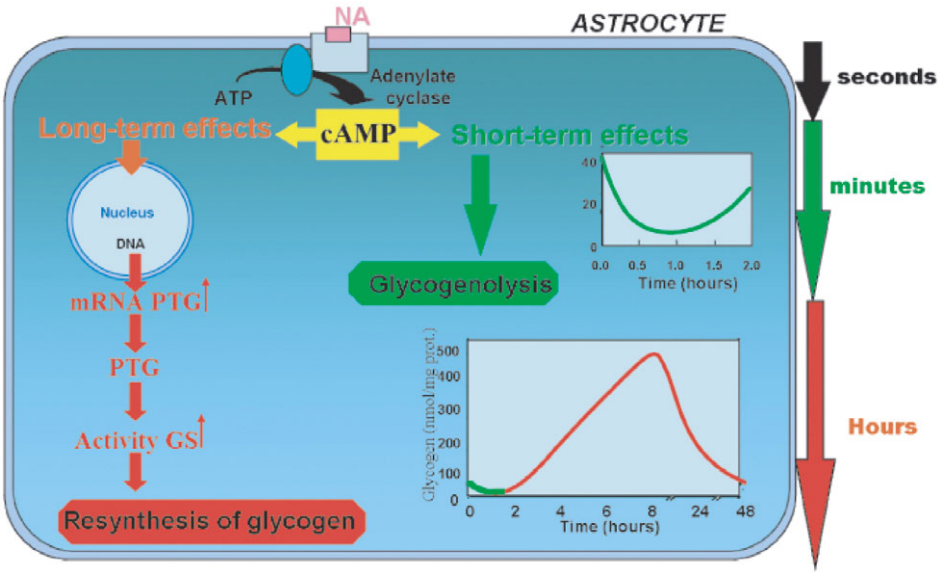

Fig. 2. Plasticity of glycogen metabolism in astrocytes. Activation of c-AMP-dependent intracellular signaling by a restricted set of neurotransmitters (noradrenaline, vasoactive intestinal peptide, adenosine) results in a short-term (seconds to minutes) effect, i.e. glycogenolysis, and in a delayed (hours) transcriptionally regulated action, i.e. glycogen resynthesis. This long-term plastic response triggers the induction of expression of a coordinated set of genes involved in glycogen resynthesis such as the transcription factors C/EBP, and the genes encoding for the enzymes glycogen synthase and protein targeting to glycogen.

mouse, rat and cat with the [^{14}C]2-deoxyglucose technique, have reported that energy metabolism exhibits a decrease during slow-wave sleep (SWS) and an increase during paradoxical sleep (PS), depending on the brain areas (for a review, see Franzini, 1992). It has also been reported that the synthesis of glycogen is increased during SWS with a 50–70% rise when compared to the preceding waking period (Karnovsky et al., 1983). Taken together these data suggest that SWS might be a period of energy saving while PS has a relatively high energy cost. More recently, investigations on brain gene expression during sleep and wakefulness in rat indicate that different genes encoding proteins involved in energy metabolism are modulated by sleep deprivation (Tononi and Cirelli, 2001). In particular, genes encoding subunit 1 of the cytochrome *c* oxidase and subunit 2 of the NADH dehydrogenase, which play a key role in oxidative metabolism, are induced by a short period of total sleep deprivation (TSD) during 3 h. After 8 h of sleep deprivation, other genes related to energy metabolism such as glucose transporter type 1 are also induced. These data suggest that a plasticity in the expression pattern of energy-metabolism genes can be revealed by manipulations affecting the sleep–wake cycle.

Glycogen metabolism and homeostatic regulation of sleep

The homeostatic regulation of sleep fits the brain energy restoration hypothesis, as suggested in its most recent formulation (Benington and Heller, 1995). According to this hypothesis, adenosine, a neurotransmitter with inhibitory properties, may be a link between sleep regulation and energy metabolism. Adenosine concentrations, which partly derive from the ATP degradation, rise during the spontaneous or forced-waking period and decrease following subsequent sleep period (Huston et al., 1996; Porkka-Heiskanen et al., 1997). The second aspect of the hypothesis is that sleep, and in particular SWS, might serve to replenish glycogen stores depleted during the waking period. Recent experimental results have failed to verify or falsify this hypothesis, since both (small) decreases and increases in brain glycogen levels have been observed following sleep deprivation (Franken et al., 2003; Gip et al., 2002; Kong et al., 2002).

In view of these *in vivo* and *in vitro* results and in consideration of the long-standing interest of our laboratory in the regulation of glycogen metabolism, we have explored the possibility that regulation of the expression of genes encoding enzymes involved in glycogen metabolism could take place during the sleep–waking cycle (Fig. 3). In order to test this hypothesis, we measured the variations of mRNA levels coding for three such enzymes, namely protein targeting to glycogen (PTG), glycogen synthase (GS) and glycogen phosphorylase (Gphos), throughout the sleep–waking cycle and at the end of 6 h of sleep deprivation (SD). In addition, in order to determine the functional impact of the regulation of these mRNAs on glycogen synthesis, we assayed the activity of GS in the cortex of mice after 6 h SD as well as 3 h later when animals had recovered sleep. The results of this study indicate that prolonged waking induces a twofold increase of PTG mRNA. Moreover, a parallel increase in GS activity suggests a functional role of the increase in PTG. Indeed, the induction of PTG during waking may set cortical glycogen metabolism in a ‘glycogen-synthesis mode’ and possibly set the appropriate metabolic conditions for sleep induction (Petit et al., 2002).

Metabolic plasticity in a learning and memory paradigm

It is now widely recognized that subtle mechanisms of neuronal plasticity, resulting in functional and structural modifications at the synaptic level, represent the cellular and molecular correlates of the processes of learning and memory. A variety of behavioural paradigms are available to explore the mechanisms of learning and memory in laboratory animals. Spatial learning is one of the best established of such behavioural paradigms; in addition the role of a particular brain area, the hippocampus in such spatial learning has been extensively characterized. Indeed, the hippocampus is involved in coding, consolidation as well as retrieval of spatial memory in rodents (O’Keefe and Nadel, 1978; Riedel et al., 1999). What is less clear, however, is whether such tasks are accomplished by the hippocampus as a uniform computational unit, or whether information processing occurs in discrete steps distributed throughout distinct subregions with evolving temporal patterns. Previous evidence from electrophysiology, partial hippocampal lesion studies and, more recently, human brain imaging have suggested the existence of functional specialization within the hippocampus (Jung et al., 1994; Lepage et al., 1998; Moser and Moser, 1998; Poucet and Buhot, 1994). In addition, studies in rodents have shown that markers of activity (in particular metabolic markers such as 2-deoxyglucose 2-DG), evolve spatially and temporally over the

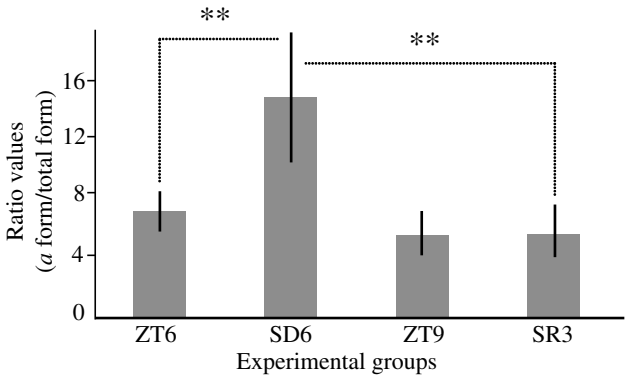

Fig. 3. Functional plasticity of glycogen metabolism during sleep–wake cycle. Glycogen synthase activity is induced by sleep deprivation and returns to normal levels after 3 h recovery. ZT6, undisturbed animals sacrificed 6 h after light onset; SD6, animals sacrificed at the end of a 6 h sleep deprivation period; ZT9, undisturbed animals sacrificed 9 h after light onset; SR3, sleep deprived animals sacrificed after 3 h of sleep recovery. Asterisks, $P<0.01$.

different phases of the learning paradigm, including during recall (Bontempi et al., 1999).

We have mapped glucose utilization at different phases of a well-established spatial learning task, the eight-arm radial maze. The results obtained obtained indicate that indeed, the metabolic demand during the various learning phases evolve spatially and temporally in the areas engaged by the task, in particular in the hippocampus. In keeping with the initial hypothesis, distinct patterns of metabolic activity were observed during the learning and recall phases. Analysis of the metabolic activity in the hippocampus revealed different patterns over the rostro-caudal axis in its three major subregions, the CA1, CA3 and dentate gyrus (DG). Thus, as learning proceeded, more areas of the CA1 and CA3 became engaged metabolically, moving from the posterior and intermediate parts toward the anterior level. In addition, during recall, increased metabolic activity could be observed only in the anterior parts of the dentate gyrus (Fig. 4B–D) (Ros et al., 2006). This set of data is in keeping with the notion that metabolic adaptations (plasticity) are occurring as a correlate of learning and recall.

Significance

Understanding the cellular and molecular determinants of brain energy metabolism is extremely relevant, not only to unravel basic mechanisms of brain physiology, but because it may also contribute to the understanding of pathophysiological mechanisms of a variety of neurological and psychiatric disorders. In addition, the main techniques of functional brain imaging such as PET and fMRI rely upon signals that are directly related to the coupling between neuronal activity and metabolic responses. A new dimension of brain metabolism, namely its relation to mechanisms of neuronal plasticity, is now being explored. We believe that this approach may also shed new light on the determinants of one of the most striking features of the mammalian brain, namely its capacity to adapt to the environment and to be determined by experience,

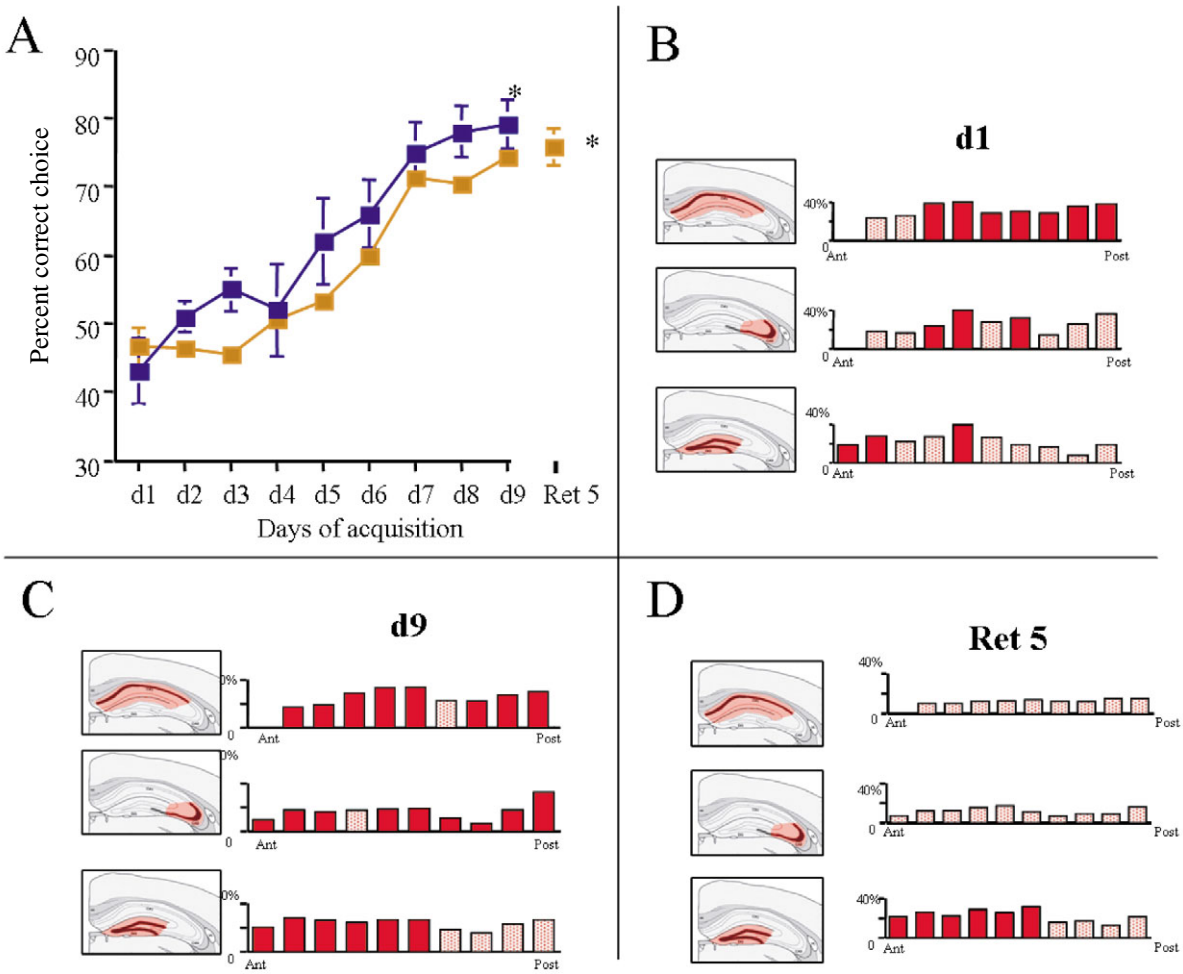

Fig. 4. (A) Spatial discrimination performance of mice. Animals were trained 9 days (squares) and retested 5 days later (Ret 5; last orange square). Values are means ± s.e.m. (*N*=6). (B–D) Changes in relative ^{14}C-deoxyglucose along the antero-posterior axis in CA1 (top), CA3 (middle) and dentate gyrus (DG; bottom) at (B) day 1, (C) day 9 and (D) 5 days after last test (retention, Ret 5).

through the mechanisms of neural plasticity to which metabolic aspects, at least in part based in glial cells, may participate.

List of abbreviations

2-DG	2-deoxyglucose
fMRI	functional magnetic resonance imaging
Gphos	glycogen phosphorylase
GS	glycogen synthase
OEF	oxygen extraction fraction
PET	positron emission tomography
PS	paradoxical sleep
PTG	protein targeting to glycogen
SD	sleep deprivation
SWS	slow-wave sleep
TSD	total sleep deprivation

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References

Allaman, I., Pellerin, L. and Magistretti, P. J. (2000). Protein targeting to glycogen mRNA expression is stimulated by noradrenaline in mouse cortical astrocytes. *Glia* **30**, 382-391.

Allaman, I., Lengacher, S., Magistretti, P. J. and Pellerin, L. (2003). A2B receptor activation promotes glycogen synthesis in astrocytes through modulation of gene expression. *Am J. Physiol.* **284**, C696-C704.

Allaman, I., Pellerin, L. and Magistretti, P. J. (2004). Glucocorticoids modulate neurotransmitter-induced glycogen metabolism in cultured cortical astrocytes. *J. Neurochem.* **88**, 900-908.

Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G. L., Ponto, L. L. and Hichwa, R. D. (1995). Remembering the past: two facets of episodic memory explored with positron emission tomography. *Am. J. Psychiatry* **152**, 1576-1585.

Attwell, D. and Laughlin, S. B. (2001). An energy budget for signaling in the grey matter of the brain. *J. Cereb. Blood Flow Metab.* **21**, 1133-1145.

Barrett, D., Shumake, J., Jones, D. and Gonzalez-Lima, F. (2003). Metabolic mapping of mouse brain activity after extinction of a conditioned emotional response. *J. Neurosci.* **23**, 5740-5749.

Bear, M. F. (2003). Bidirectional synaptic plasticity: from theory to reality. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **358**, 649-655.

Benington, J. H. and Heller, H. C. (1995). Restoration of brain energy metabolism as the function of sleep. *Prog. Neurobiol.* **45**, 347-360.

Bittar, P. G., Charnay, Y., Pellerin, L., Bouras, C. and Magistretti, P. J. (1996). Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. *J. Cereb. Blood Flow Metab.* **16**, 1079-1089.

Bontempi, B., Laurent-Demir, C., Destrade, C. and Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature* **400**, 671-675.

Braitenberg, V. and Schuz, A. (1998). *Cortex: Statistics and Geometry of Neuronal Connectivity*. New York: Springer.

Cardinaux, J.-R., Allaman, I. and Magistretti, P. J. (2000). Pro-inflammatory cytokines induce the transcription factors C/EBP b and C/EBP d in primary astrocytes. *Glia* **29**, 91-97.

Clarke, D. D. and Sokoloff, L. (1994). Circulation and energy metabolism of the brain. In *Basic Neurochemistry* (ed. G. J. Siegel, B. W. Agranoff, R. W. Albers and P. B. Molinoff), pp. 645-680. New York: Raven Press.

Debernardi, R., Pierre, K., Lengacher, S., Magistretti, P. J. and Pellerin, L. (2003). Cell-specific expression pattern of monocarboxylate transporters in astrocytes and neurons observed in different mouse brain cortical cell cultures. *J. Neurosci. Res.* **73**, 141-155.

Fox, P. T. and Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc. Natl. Acad. Sci. USA* **83**, 1140-1144.

Fox, P. T., Raichle, M. E., Mintun, M. A. and Dence, C. (1988). Nonoxidative glucose consumption during focal physiologic neural activity. *Science* **241**, 462-464.

Franken, P., Gip, P., Hagiwara, G., Ruby, N. F. and Heller, H. C. (2003). Changes in brain glycogen after sleep deprivation vary with genotype. *Am. J. Physiol.* **285**, R413-R419.

Franzini, C. (1992). Brain metabolism and blood flow during sleep. *J. Sleep Res.* **1**, 3-16.

Gip, P., Hagiwara, G., Ruby, N. F. and Heller, H. C. (2002). Sleep deprivation decreases glycogen in the cerebellum but not in the cortex of young rats. *Am. J. Physiol.* **283**, R54-R59.

Gonzalez-Lima, F. and Garrosa, M. (1991). Quantitative histochemistry of cytochrome oxidase in rat brain. *Neurosci. Lett.* **123**, 251-253.

Grossman, A. W., Churchill, J. D., Bates, K. E., Kleim, J. A. and Greenough, W. T. (2002). A brain adaptation view of plasticity: is synaptic plasticity an overly limited concept? *Prog. Brain Res.* **138**, 91-108.

Gusnard, D. A. and Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* **2**, 685-694.

Huston, J. P., Haas, H. L., Boix, F., Pfister, M., Decking, U., Schrader, J. and Schwarting, R. K. W. (1996). Extracellular adenosine levels in neostriatum and hippocampus during rest and activity periods of rats. *Neuroscience* **73**, 99-107.

Hyden, H., Rapallino, M. V. and Cupello, A. (2000). Unraveling of important neurobiological mechanisms by the use of pure, fully differentiated neurons obtained from adult animals. *Prog. Neurobiol.* **60**, 471-499.

Hyder, F., Rothman, D. L. and Shulman, R. G. (2002). Total neuroenergetics support localized brain activity: implications for the interpretation of fMRI. *Proc. Natl. Acad. Sci. USA* **99**, 10771-10776.

Ingvar, D. H. (1985). 'Memory of the future': an essay on the temporal organization of conscious awareness. *Hum. Neurobiol.* **4**, 127-136.

Jung, M. W., Wiener, S. I. and McNaughton, B. L. (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *J. Neurosci.* **14**, 7347-7356.

Karnovsky, M. L., Reich, P., Anchors, J. M. and Burrows, B. L. (1983). Changes in brain glycogen during slow-wave sleep in the rat. *J. Neurochem.* **41**, 1498-1501.

Kasischke, K. A., Vishwasrao, H. D., Fisher, P. J., Zipfel, W. R. and Webb, W. W. (2004). Neural activity triggers neuronal oxidative metabolism followed by astrocytic glycolysis. *Science* **305**, 99-103.

Kong, J., Shepel, P. N., Holden, C. P., Mackiewicz, M., Pack, A. I. and Geiger, J. D. (2002). Brain glycogen decreases with increased periods of wakefulness: implications for homeostatic drive to sleep. *J. Neurosci.* **22**, 5581-5587.

Lepage, M., Habib, R. and Tulving, E. (1998). Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* **8**, 313-322.

Loaiza, A., Porras, O. H. and Barros, L. F. (2003). Glutamate triggers rapid glucose transport stimulation in astrocytes as evidenced by real-time confocal microscopy. *J. Neurosci.* **23**, 7337-7342.

Magistretti, P. J. (1999). Brain energy metabolism. In *Fundamental Neuroscience* (ed. M. Zigmond, F. E. Bloom, S. Landis, J. Roberts and L. Squire), pp. 389-413. San Diego: Academic Press.

Magistretti, P. J. and Pellerin, L. (1999). Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **354**, 1155-1163.

Magistretti, P. J., Pellerin, L., Rothman, D. L. and Shulman, R. G. (1999). Energy on demand. *Science* **283**, 496-497.

Malenka, R. C. (2003). The long-term potential of LTP. *Nat. Rev. Neurosci.* **4**, 923-926.

Maviel, T., Durkin, T. P., Menzaghi, F. and Bontempi, B. (2004). Sites of neocortical reorganization critical for remote spatial memory. *Science* **305**, 96-99.

Mazziotta, J. C., Toga, A. W. and Frackowiak, R. S. J. (ed.) (2000). *Brain Mapping*. San Diego: Academic Press.

Moser, M. B. and Moser, E. I. (1998). Functional differentiation in the hippocampus. *Hippocampus* **8**, 608-619.

Mulligan, S. J. and MacVicar, B. A. (2004). Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature* **431**, 195-199.

O'Keefe, J. and Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press.

Pellerin, L. and Magistretti, P. J. (1994). Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proc. Natl. Acad. Sci. USA* **91**, 10625-10629.

Pellerin, L. and Magistretti, P. J. (2003). How to balance the brain energy budget while spending glucose differently? *J. Physiol.* **546**, 325.

Pellerin, L. and Magistretti, P. J. (2004). Empiricism and rationalism: two paths toward the same goal. *J. Cereb. Blood Flow Metab.* **24**, 1240-1241.

Pellerin, L., Pellegri, G., Bittar, P. G., Charnay, Y., Bouras, C., Martin, J. L., Stella, N. and Magistretti, P. J. (1998). Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. *Dev. Neurosci.* **20**, 291-299.

Petit, J.-M., Tobler, I., Allaman, I., Borbély, A. A. and Magistretti, P. J. (2002). Sleep deprivation modulates brain mRNAs encoding genes of glycogen metabolism. *Eur. J. Neurosci.* **16**, 1163-1167.

Pierre, K., Debernardi, R., Magistretti, P. J. and Pellerin, L. (2003). Noradrenaline enhances MCT2 expression in cultured mouse cortical neurons via a translational regulation. *J. Neurochem.* **86**, 1468-1476.

Porkka-Heiskanen, T., Strecker, R. E., Thakkar, M., Bjorkum, A. A., Greene, R. W. and McCarley, R. W. (1997). Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* **276**, 1265-1268.

Poucet, B. and Buhot, M. C. (1994). Effects of medial septal or unilateral hippocampal inactivations on reference and working spatial memory in rats. *Hippocampus* **4**, 315-321.

Raichle, M. E. (2003). Functional brain imaging and human brain function. *J. Neurosci.* **23**, 3959-3962.

Raichle, M. E. and Gusnard, D. A. (2002). Appraising the brain's energy budget. *Proc. Natl. Acad. Sci. USA* **99**, 10237-10239.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A. and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. USA* **98**, 676-682.

Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S. N. and Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N. Engl. J. Med.* **334**, 752-758.

Riedel, G., Micheau, J., Lam, A. G., Roloff, E., Martin, S. J., Bridge, H., Hoz, L., Poeschel, B., McCulloch, J. and Morris, R. G. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nat. Neurosci.* **2**, 898-905.

Room, P., Tielemans, A. J., De Boer, T., Tonnaer, J. A., Wester, J., Van den Broek, J. H. and Van Delft, A. M. (1989). Local cerebral glucose uptake in anatomically defined structures of freely moving rats. *J. Neurosci. Methods* **27**, 191-202.

Ros, J., Pellerin, L., Magara, F., Dauguet, J., Schenk, F. and Magistretti, P. J. (2006). Metabolic activation pattern of distinct hippocampal subregions during spatial learning and memory retrieval. *J. Cereb. Blood Flow Metab*. **26**, 468-477.

Roy, C. S. and Sherrington, M. B. (1890). On the regulation of the blood-supply of the brain. *J. Physiol. Lond.* **11**, 85-108.

Serres, S., Bezancon, E., Franconi, J. M. and Merle, M. (2004). Ex vivo analysis of lactate and glucose metabolism in the rat brain under different states of depressed activity. *J. Biol. Chem.* **279**, 47881-47889.

Shulman, G. L., Corbetta, M., Buckner, R. L., Raichle, M. E., Fiez, J. A., Miezin, F. M. and Petersen, S. E. (1997). Top-down modulation of early sensory cortex. *Cereb. Cortex* **7**, 193-206.

Sibson, N. R., Dhankhar, A., Mason, G. F., Rothman, D. L., Behar, K. L. and Shulman, R. G. (1998). Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proc. Natl. Acad. Sci. USA* **95**, 316-321.

Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M. H., Patlak, C. S., Pettigrew, K. D., Sakurada, O. and Shinohara, M. (1977). The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J. Neurochem.* **28**, 897-916.

Sorg, O. and Magistretti, P. J. (1992). Vasoactive intestinal peptide and noradrenaline exert long-term control on glycogen levels in astrocytes: blockade by protein synthesis inhibition. *J. Neurosci.* **12**, 4923-4931.

Takano, T., Tian, G. F., Peng, W., Lou, N., Libionka, W., Han, X. and Nedergaard, M. (2006). Astrocyte-mediated control of cerebral blood flow. *Nat. Neurosci.* **9**, 260-267.

Teasdale, J. D., Dritschel, B. H., Taylor, M. J., Proctor, L., Lloyd, C. A., Nimmo-Smith, I. and Baddeley, A. D. (1995). Stimulus-independent thought depends on central executive resources. *Mem. Cognit.* **23**, 551-559.

Tononi, G. and Cirelli, C. (2001). Modulation of brain gene expression during sleep and wakefulness: a review of recent findings. *Neuropsychopharmacology* **25**, S28-S35.

Welker, E., Rao, S. B., Dorfl, J., Melzer, P. and van der Loos, H. (1992). Plasticity in the barrel cortex of the adult mouse: effects of chronic stimulation upon deoxyglucose uptake in the behaving animal. *J. Neurosci.* **12**, 153-170.

Zhang, C. and Wong-Riley, M. (1999). Expression and regulation of NMDA receptor subunit R1 and neuronal nitric oxide synthase in cortical neuronal cultures: correlation with cytochrome oxidase. *J. Neurocytol.* **28**, 525-539.

Zonta, M., Angulo, M. C., Gobbo, S., Rosengarten, B., Hossmann, K. A., Pozzan, T. and Carmignoto, G. (2003). Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat. Neurosci.* **6**, 43-50.