Food for thought: the importance of glucose and other energy substrates for sustaining brain function under varying levels of activity

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Abstract

The brain requires a constant and substantial energy supply to maintain its main functions. For decades, it was assumed that glucose was the major if not the only significant source of energy for neurons. This view was supported by the expression of specific facilitative glucose transporters on cerebral blood vessels, as well as neurons. Despite the fact that glucose remains a key energetic substrate for the brain, growing evidence suggests a different scenario. Thus astrocytes, a major type of glial cells that express their own glucose transporter, play a critical role in coupling synaptic activity with glucose utilization. It was shown that glutamatergic activity triggers an enhancement of aerobic glycolysis in this cell type. As a result, lactate is provided to neurons as an additional energy substrate. Indeed, lactate has proven to be a preferential energy substrate for neurons under various conditions. A family of proton-linked carriers known as monocarboxylate transporters has been described and specific members have been found to be expressed by endothelial cells, astrocytes and neurons. Moreover, these transporters are subject to fine regulation of their expression levels and localization, notably in neurons, which suggests that lactate supply could be adjusted as a function of their level of activity. Considering the importance of energetics in the aetiology of several neurodegenerative diseases, a better understanding of its cellular and molecular underpinnings might have important implications for the future development of neuroprotective strategies.

Keywords: Lactate; Glucose; Substrates; Ketone bodies; Astrocyte; Neuron; Monocarboxylate transporters; Review

Résumé

Alimenter sa pensée : de l’importance du glucose et des autres substrats énergétiques pour soutenir l’activité cérébrale en fonction de son niveau

Le cerveau demande un apport énergétique constant et soutenu pour subvenir à ses besoins. Depuis plusieurs décennies, le glucose a été considéré comme la principale, voire la seule source d’énergie pour les neurones. Cette idée est renforcée par la présence de transporteurs du glucose spécifiques exprimés par les vaisseaux cérébraux ainsi que par les neurones. Malgré le fait que le glucose demeure un substrat énergétique-clé pour le cerveau, de nombreuses données suggèrent une vision différente. En effet les astrocytes, type important de cellules gliales qui expriment leur propre transporteur du glucose, ont un rôle prépondérant dans le couplage entre activité synaptique et utilisation de glucose. Il a été montré que l’activité glutamatergique stimulait la glycolyse aérobique dans ces cellules. Ce processus permet de fournir du lactate aux neurones en guise de substrat énergétique supplémentaire. En fait, il avait déjà été démontré que le lactate pouvait devenir un substrat énergétique préférentiel pour les neurones dans certaines conditions. Une famille de transporteurs connue sous le nom de transporteurs des monocarboxylates a été décrite et certains de ses membres sont exprimés de manière spécifique sur les cellules endothéliales, les astrocytes et les neurones. De plus, ces transporteurs semblent régulés de manière fine, que se soit leur niveau d’expression ou leur localisation, ce qui suggère que l’approvisionnement en lactate pourrait être ajusté en fonction du niveau d’activité neuronale. Etant donné l’importance de la neuroénergétique dans l’étiologie des maladies neurodégénératives, une meilleure compréhension de ces mécanismes moléculaires et cellulaires pourrait avoir des implications importantes pour le développement de stratégies visant une neuroprotection.

Mots clés : Lactate ; Glucose ; Substrats ; Corps cétoniques ; Astrocyte ; Neurone ; Transporteurs des monocarboxylates ; Revue générale

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1. Introduction

The brain makes up only 2% of the total body weight, but it receives 15% of the total blood flow provided by the cardiovascular system; in addition, it consumes at least 25% of all circulating glucose and 20% of the oxygen available in the body under resting conditions [1]. Such crude estimates give an idea of the importance of energy supply for brain function. A deficit in the sequence of events allowing neurons to be adequately supplied with the necessary energy to accomplish their tasks could have dramatic consequences, as is the case after cerebral ischemia or in Alzheimer’s disease. To understand how such energy supply is provided and ensured under all circumstances constitute one of the main goals of the emerging field known as neuroenergetics.

2. Glucose: an essential energy substrate for the brain

For decades, glucose has been considered as the main, if not exclusive, energy substrate for the adult brain [2]. Such a view is based notably on the classic work of McIlwain in the 1950’s on brain slices demonstrating that apart from glucose, few physiological substrates could sustain metabolic and electrical activities of the nervous tissue [3,4]. However, there are situations in which alternative substrates can contribute significantly to sustain brain energy needs. First of all, this is the case in early development. Immediately after birth, blood lactate levels are elevated and it has been shown that the brain uses this source of energy in the first few hours of life. Then, once the newborn begins breastfeeding in mammals, the levels of circulating ketone bodies, i.e. acetoacetate and β-hydroxybutyrate, become elevated as fatty acids contained in the lipid-rich maternal milk are converted by the liver. It has been shown that during the entire breastfeeding period, the brain utilizes ketone bodies to fulfil a significant part of its energy requirement. Such an observation is corroborated by a transient enhancement in the expression of monocarboxylate transporters, essential ketone body carriers, both on endothelial cells forming cerebral blood vessels as well as on parenchymal cells [5]. As soon as the newborn animal switch to a solid diet however, plasmatic levels of ketone bodies drop (as does the expression of monocarboxylate transporters), and glucose becomes from that moment and throughout life the most significant energy substrate used on a regular basis. More recently, another alternative has been exposed. Under resting conditions, blood lactate levels have been shown to satisfy about 10% of the brain energy needs [6]. However, this proportion could increase significantly if circulating lactate levels rise. Indeed, during moderate to intense exercise, plasmatic levels of lactate rise to significant values. In such circumstances, it has been clearly shown that the adult brain takes up and utilizes blood lactate, at the expense of glucose [7,8]. Nevertheless, even under such conditions, glucose remains the main cerebral energy substrate, and the contribution of circulating lactate to cerebral energy supply is only transient.

Glucose must cross several membranes before becoming available for use as an energy substrate by different brain cells. In order to do so, it requires the presence of several facilitative glucose transporters belonging to the GLUTs family [9]. Glucose leaves the blood (where its concentration is around 5 mM) to enter the brain parenchyma (with a concentration of approximately 1 mM), following its concentration gradient. Its passage through endothelial cells that form cerebral blood vessels is made possible by the expression of GLUT1 55 KDa, one specific isofrom of this glucose transporter. Uptake of glucose by each brain cell type is also mediated by specific glucose transporters. Thus, neurons exhibit a high affinity glucose transporter, GLUT3, which allows them to directly take up and use glucose provided by the circulation. Although glucose has long been considered the essential and unrivalled energy substrate for sustaining neuronal activity, recent data call this view into question. For example, experiments performed on cultured cortical neurons have shown that glucose uptake (mediated by GLUT3) decreases and does not increase, as would be expected, when neurons are stimulated with glutamate [10]. Moreover, as shown in the cerebellum, it seems that neurons do not massively take up glucose, but it is rather the glial cells that do so [11]. More recently, it has been shown that neurons lack an important regulatory component of glycolysis, which prevents them from enhancing their glycolytic flux [12]. But more surprisingly, it appears that most glucose consumed by neurons is metabolized through the pentose phosphate pathway and serves to maintain antioxidant status rather than participate in bioenergetic activity. Such observations raise at least two important questions. If neurons are not the main glucose consumers in the brain, what is the other cerebral cell type that would require so much glucose? And if neurons do not depend so much on glucose, what is the other substrate providing the energy necessary for neuronal function?

3. The astrocyte: a key element between blood vessels and neurons

Astrocytes belong to a category of non-neuronal brain cells known as glial cells. They are quantitatively the most important group of glial cells, which is also comprised of oligodendrocytes, microglial cells and tanyctyes. Astrocytes are also often more numerous than neurons themselves, as they can outnumber them by a factor of ten in certain human brain areas. Moreover, they occupy ~30% of the brain volume. But one aspect that is quite remarkable about astrocytes is their morphology and location. Astrocytes exhibit a stellate shape (hence their name) with multiple processes. Some of these projections, called astrocytic end-feet, abut onto blood vessels. In fact, 99% of the surface of cerebral blood vessels is covered by astrocytic end-feet. There is a specific glucose transporter on the membrane of end-feet facing blood vessels, an isofrom of GLUT1 known as GLUT1 45 KDa [13]. Because of such characteristics, end-feet constitute a preferential site for glucose...
uptake as it leaves the blood to enter the brain parenchyma. On the other hand, astrocytes have several projections that come in close contact with neurons, more specifically in the peri-synaptic area where they ensheathe this structure of communication between neurons. Because astrocytes express on these projections the receptors and transporters for most neurotransmitters used by neurons, they can be permanently informed of the level of activity of neurons and, concomitantly, on their energy needs.

This particular localization of astrocytes between blood vessels, which are the source of essential energetic substrates for the brain, and the important energy consumers that are neurons did not escape the attention of the first neuroanatomists that describe them at the end of the nineteenth century. Indeed, Camillo Golgi and his associates, on the basis of their morphological observations, suggested that astrocytes could play a critical role in the regulation of energetic supply to neurons. However, almost a century was required, together with the development of isolated cell culture models, before a precise mechanism implicating the astrocytes in such a function could be described. Now we know that astrocytes respond specifically to glutamate, the main excitatory neurotransmitter in the central nervous system, which triggers a particular metabolic response [14]. Thus, every time a particular brain region is activated, glutamate is released by glutamatergic neurons within that area. This glutamate is “detected” by astrocytes located nearby. As part of their homeostatic functions, astrocytes take up this glutamate and convert it to glutamine as part of a recycling of the neurotransmitter glutamate that has been well described. In doing so, glutamate uptake activates a cascade of molecular events that leads to the enhancement of glucose utilization by the astrocytes (Fig. 1). Recent observations made with the fluorescent glucose analog 6-NBDG have confirmed the predominant uptake by astrocytes in vivo following neuronal activation [15]. But quite importantly, this glucose is not oxidized entirely within the astrocyte. In fact, the astrocyte metabolises glucose into lactate, a metabolic intermediate with a high energetic value, and releases it into the extracellular space, making it available for energy-demanding neurons. This mechanism of energy supply on demand is known as the astrocyte-neuron lactate shuttle [16].

4. Lactate: supplemental and alternative energy substrate to glucose for neurons

Lactate is known as the end product of glycolysis under anaerobic conditions (or conditions of insufficient oxygen supply). This is the case in muscles that produce large amounts of lactate from glucose during brief, high intensity bouts of activity. Nonetheless, even for muscles, it has been demonstrated that lactate can be produced (and consumed locally by neighbouring muscle cells) even in the presence of adequate oxygen levels. In the brain, despite the fact that lactate has long been considered a metabolic waste and potentially toxic compound, it is now recognized not only as a valuable energy substrate for neurons but even possibly as a preferential source of energy under certain circumstances [17].

As mentioned earlier, it has been known for some time that the brain can use energy substrates other than glucose to satisfy its energy needs under particular conditions. Ketone bodies as well as lactate belong to this category. However, their supply to the adult brain remains limited, both quantitatively and over time, partly due to the limited expression of specific transporters known as monocarboxylate transporters on endothelial cells of cerebral blood vessels. The astrocyte-neuron lactate shuttle mechanism provides a different source of lactate, as it is produced from circulating glucose within the brain parenchyma. The uptake of glucose in astrocytes triggered by glutamate is facilitated by an enhancement of GLUT1 45 KDa-mediated glucose transport [18]. Lactate produced by astrocytes from glucose is released in the immediate surroundings of neurons, thus becoming directly available for metabolism. As both lactate and glucose are available in the extracellular space at similar concentrations (~1 mM), one may wonder to what extent neurons will use each of these substrates to fulfil their energy needs. Experiments performed on isolated cultured...
cell populations provide a clear answer. It has been shown under conditions where both substrates were present at the same concentration that at least 75% of oxidative metabolism in neurons is supported by lactate [19, 20]. Such a result is consistent with observations suggesting that neurons have a limited capacity to use glucose and rather use it mainly for other purposes than energy production.

5. Monocarboxylate transporters: essential highways for the lactate shuttle

Lactate as well as ketone bodies are physiological members of the family of compounds known as monocarboxylates. Since they are hydrophilic molecules, they cannot cross cellular membranes by simple diffusion. Thus, specific transporters are required for these compounds to be both released and taken up by different cell types. A family of proton-linked carriers has been identified in recent years and are collectively known as the monocarboxylate transporters or MCTs [21]. Up to now, fourteen members have been identified essentially by sequence homologies but only seven have been functionally characterized. Among them, only four have been shown to be true monocarboxylate transporters: MCT1, MCT2, MCT3 and MCT4. Their tissue distribution varies but only MCT1, MCT2 and MCT4 have been found to be expressed in the central nervous system. Their cellular distribution within the brain is quite specific. MCT1 is found on endothelial cells that compose blood vessels, where it plays an essential role in the entry of circulating lactate and ketone bodies within the brain. Astrocytes express MCT1, but they also exhibit MCT4 [22]. Both transporters are most likely involved in the release of lactate by astrocytes. However, these two transporters differ in their affinity for lactate, MCT1 displaying a lower \( K_m \) than MCT4 for this substrate (3.5 vs. 34.7 mM, respectively). Thus, it is possible that they play a distinct role depending on the metabolic state of the astrocytes (constitutive lactate release vs. activated production). To observe the expression of MCT4 on astrocytes comes as no surprise, since in the periphery MCT4 is expressed by tissues exhibiting a high glycolytic rate with significant lactate production (e.g. some muscle fibres). In contrast, a large majority of neurons have been found to express the high affinity transporter MCT2 (\( K_m = 0.7 \text{ mM} \)) [23]. Such a distribution is entirely consistent with the concept of a lactate transfer between astrocytes and neurons.

Interestingly, monocarboxylate transporters are subject to specific regulations in brain cells. For example, it has been shown that MCT2 expression can be upregulated in cultured cortical neurons by the neurotransmitter noradrenaline, the hormone insulin, as well as the trophic factors insulin-like growth factor (IGF-1) and brain-derived neurotrophic factor [24-27]. In all cases, it has been shown to involve a translational regulation mediated by activation of the PI3K/Akt/mTOR/S6 pathway. In addition to change in protein expression levels, it was also demonstrated that the localization of MCT2 at the plasma membrane can be either enhanced or reduced by various neuroactive substances [28]. In contrast to glucose transporters, it appears that expression and localization of monocarboxylate transporters are much more finely regulated by various signals originating from neuronal activity. Such observations suggest that the supply of monocarboxylates as energy substrates to neurons could be more easily adapted to the level of activity than could be the case with glucose.

6. Perspectives

The study of brain energy metabolism in recent years has highlighted the critical role played by astrocytes in the energetic supply of neurons. The canonical view that glucose is the only valuable energy substrate for sustaining neuronal activity has changed and has been replaced by a different concept. Although glucose remains an essential energy source for the brain, its distribution and metabolism by brain cells is more complex than previously thought and involves metabolic interactions between astrocytes and neurons. Moreover, other metabolic intermediates, lactate in particular, have emerged as additional energy substrates for neurons that may even be preferred over glucose in certain circumstances. Further understanding of these aspects and the specific regulations occurring under various conditions might be of prime importance. Indeed, several neurodegenerative diseases (e.g. Alzheimer’s disease) exhibit metabolic deficits that appear to precede the first symptoms. Thus, it may be that improving neuroenergetics at an early stage could provide at least partial neuroprotection.

7. Conflict of interest

None related to the content of this article.

References


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