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► **To cite this version:**

Didier F Pisani, Nicolas Blondeau. Deciphering the brain glucose metabolism: A gateway to innovative stroke therapies. *Journal of Cerebral Blood Flow and Metabolism*, In press, <10.1177/0271678x251346277>. <hal-05130005>

**HAL Id: hal-05130005**

**<https://hal.science/hal-05130005v1>**

Submitted on 25 Jun 2025

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# Deciphering the brain glucose metabolism: a gateway to innovative stroke therapies

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Short title: Glucose metabolism in normal and ischemic brain

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## Abbreviations

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5 Coenzyme Q (CoQ)  
6 Cytochrome c (Cyt c)  
7 Cytoplasmic superoxide dismutase (Cu/Zn-SOD)  
8 Deoxyhypusine hydroxylase (DOHH)  
9 Deoxyhypusine synthase (DHPS)  
10 Eukaryotic Translation Initiation Factor 5A (eIF5A)  
11 Ectoenzyme  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GT)  
12 Ecto-peptidase aminopeptidase N (ApN)  
13 Flavin adenine dinucleotide (FADH<sub>2</sub>)  
14 Glucose-6-phosphate dehydrogenase (G6PD)  
15 Glutathione oxidized (GSSG)  
16 Glutathione peroxidase (GPx)  
17 Glutathione reduced (GSH)  
18 Glutathione reductase (GR)  
19 N1-guanyl-1,7-diaminoheptane (GC7)  
20 Lactate dehydrogenase 1 (LDH1)  
21 Mitochondrial permeability transition (MPT)  
22 Mitochondrial pyruvate carrier (MPC)  
23 Mitochondrial superoxide dismutase (Mn-SOD)  
24 Monocarboxylate transporters (MCT)  
25 Nicotinamide adenine dinucleotide (NAD<sup>+</sup>)  
26 Nicotinamide adenine dinucleotide phosphate (NADPH)  
27 Nicotinamide adenine dinucleotide reduced (NADH)  
28 Oxygen glucose deprivation (OGD)  
29 Pentose phosphate pathway (PPP)  
30 Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ )  
31 Phosphoenolpyruvate (PEP)  
32 Pyruvate kinases (PK)  
33 Reactive oxygen species (ROS)  
34 Superoxide dismutase (SOD)  
35 Tissue plasminogen activator (tPA)  
36 Tricarboxylic acid cycle (TCA)  
37 Xanthine dehydrogenase (XDH)  
38 Xanthine oxidoreductase (XOR)  
39 Xanthine oxidase (XO)  
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## Abstract

Stroke is the leading cause of physical disability and death among adults in most Western countries. Consecutive to a vascular occlusion, cells face a brutal reduction in supply of oxygen and glucose and thus an energy failure, which in turn triggers cell death mechanisms. Among brain cells, neurons are the most susceptible to ischemia because of their high metabolic demand and low reservoir of energy substrates. In neurons, glycolysis uses glucose coming from blood or from glycogen stored in astrocytes, underlying the deep astrocyte-neuron metabolic cooperation. During ischemia, both the aerobic and anaerobic pathways and thus energy production are compromised, which disrupts proper cell functioning, notably  $\text{Na}^+/\text{K}^+$  ATPase and mitochondria. This results in altered  $\text{Ca}^{2+}$  homeostasis and overproduction of ROS, the latter being further exacerbated during the reperfusion phase. Consequently, the cerebral metabolism of glucose in the different populations of cerebral cells plays a central role in injury and recovery after stroke, and its therapeutic targeting has attracted recent interest. In this context, the overall objectives of this article are to review what are the interconnection between stroke and brain glucose metabolism and how its targeting may offer new therapeutic opportunities in addressing the global stroke epidemic.

**Keywords:** Cerebral ischemia, Reperfusion, Oxidative Stress, Glycolysis, Pentose Phosphate Pathway, Neuroprotective Agents

## 1. Stroke in brief.

In the context where there is currently no approach capable of simultaneously protecting against

Stroke is the leading cause of death and physical disability in adults. The number of people living with stroke as well as experiencing a first stroke is estimated to keep increasing in the next 30 years. It is mainly due to the aging of the population and improved survival rates, as well as the increase in its risk factors, which account for up to 80% of stroke incidence. Among modifiable risk factors of stroke, diabetes and obesity that are metabolic diseases are linked to alteration of glucose homeostasis. Obesity and diabetes mellitus, exhibiting an escalating prevalence within the population and yet inadequately addressed, share molecular and cellular similarities with each other and also demonstrate commonalities with stroke <sup>1</sup>. Consequently, apart from the imperative to address these conditions preventively, their inclusion in the search for novel treatments is essential to advance the field towards improved strategies for stroke treatment and recovery. Long-term recovery after stroke is also complicated by the juxtaposition of motor and cognitive impairments and frequent psychiatric complications, including dementia, anxiety disorders, and post-stroke depression. The size and location of the lesion, of which the sudden neurological deficit is the tip of the iceberg, are related to the vascular origin of stroke caused by cardiovascular deficiency, brain hemorrhage (vessel wall rupture) or vascular occlusion (atheroma, thrombosis). In all scenarios, it leads to regional or general oxygen and nutrient deprivation of the brain. Due to their high metabolic demand and low reservoir of energy substrates, among brain cells, neurons are the most susceptible to stroke.

Recent advances in understanding stroke-induced neuronal death, particularly potential therapeutic targets, have been extensively reviewed <sup>2</sup>. It includes glutamate excitotoxicity, accounting for early mechanisms of damage. This process starts with the drop in neuronal ATP and the Na<sup>+</sup>/K<sup>+</sup> pumps failure, leading to uncontrolled neuronal depolarization and glutamate leakage, occurring *via* reversal of uptake and other routes, from the intracellular space of both neurons and glia. This skyrockets the levels of the excitatory neurotransmitter glutamate in the extracellular space, that causes

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3 overwhelming  $\text{Ca}^{2+}$  influx primarily through the NMDA and AMPA sub-types of glutamate  
4 receptors, during and after reperfusion.  
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6 While a pharmacological treatment for brain cells in acute stroke patients remains  
7 elusive, therapeutic advancements have been realized specifically in the context of  
8 ischemic stroke, which arises from the formation of a clot in a cerebral blood vessel and  
9 constitutes approximately 80% of all stroke cases. The therapeutic strategy involves clot  
10 removal, executed through the administration of a clot-busting drug known as tissue  
11 plasminogen activator (tPA). However, the effectiveness of this treatment is constrained  
12 by a narrow therapeutic window, allowing administration only within 4.5 hours after the  
13 onset of stroke <sup>3</sup>. More recently, blood clot extraction has also been successfully  
14 performed by coupling neuroimaging with a mechanical device housed within a catheter  
15 inserted into the blood vessel. This represents both the latest advance in ischemic stroke  
16 and future in term of therapeutic <sup>4</sup>. Despite reperfusion, injury can still be significant as  
17 harmful biochemical processes counteract the benefits of restored oxygen and glucose  
18 supply for oxidative phosphorylation. Notably, oxidative stress has been linked to further  
19 damage following blood flow restoration <sup>5</sup>. Moreover, tissue response to reperfusion varies  
20 among patients, as evidenced by significant differences in brain metabolism.  
21 Spectroscopy indicates that increased brain metabolism after stroke correlates with better  
22 clinical outcomes <sup>6</sup>. Therefore, gaining insights into how the brain oxygen/glucose  
23 metabolism impacts stroke outcome and how targeting brain metabolism may offer novel  
24 therapeutic opportunity should be now considered as key areas of research in stroke.  
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## 41 **2. Brain metabolism in brief.**

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44 The brain, requiring a considerable energy input, is considered the most active organ  
45 from a metabolic point of view, as it requires a considerable energy supply.  
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48 This explains why cerebral metabolism, especially in relation to glucose, has been a  
49 subject of extensive study over the years (for further details on this aspect of brain biology,  
50 refer to reference <sup>7</sup>. Consequently, the subsequent sections of this review exclusively  
51 address the fundamental principles and concepts essential for understanding the role of  
52 glucose metabolism in the context of stroke.  
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3 While it represents only ~2% of the body's mass, brain accounts for approximately  
4 20% of the human body's oxygen and glucose consumption. This particular energy  
5 requirement of the brain is linked to several physiological characteristics facilitating the  
6 transport of energy substrates to this organ. Notably, the brain benefits from a substantial  
7 cerebral blood flow, accounting for more than 10% of the cardiac output specifically  
8 directed towards the central nervous system. Beyond these quantitative considerations,  
9 brain metabolism shows distinct variations depending on the specific region of interest  
10 and cell type examined <sup>8</sup>. Moreover, the synaptic activity that requires high-energy  
11 expense also leads to metabolic variations <sup>9</sup>. A fundamental characteristic of the brain is  
12 its regionalized functional specialization; thus, the activation of a specific region correlates  
13 with a temporally and spatially coordinated increase in brain metabolism. This notion of  
14 coupling between metabolism, blood flow and cerebral activity, is therefore crucial to  
15 understanding brain physiology.

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17 With few exceptions, glucose is the mandatory energy substrate of the brain. While  
18 glucose follows various metabolic pathways in any tissue, in the brain, glucose is almost  
19 entirely oxidized through its sequential processing by glycolysis, pentose phosphate  
20 pathway (PPP) and/or oxidative phosphorylation <sup>10</sup>. In specific situations, the brain can  
21 use substrates other than glucose. For example, the ketone bodies acetoacetate and D-  
22 3-hydroxybutyrate are synthesized by the liver from lipids and can be used by the brain <sup>11</sup>.  
23 This takes place in glucose distress conditions observed during periods of low or  
24 restrictive diets, as well as in Type 1 diabetes patients. Also, the brain can use  
25 monocarboxylate lactate as an alternative energy substrate <sup>12</sup>.

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27 The brain consumes energy mainly for the maintenance of ionic gradients across  
28 cell membranes through the ATP dependent activity of ionic pumps. The most important  
29 being Na<sup>+</sup>/K<sup>+</sup>-ATPase is present in all neural cells and involved in half of basal glucose  
30 oxidation in the brain. At the cell level, neurons consume ≈85% of the brain energy  
31 whereas glial cells account for ≈15% of the brain's energy expenditure <sup>13</sup>. In addition to  
32 basal cell metabolism and maintenance of ionic gradients, other energy-consuming  
33 processes take place in neural cells including neurotransmitter synthesis and axonal  
34 transport <sup>14</sup>.

### 3. Glucose metabolism in physiological condition.

Glucose, which is the main source of energy for activated neurons, is up-taken in the cells by glucose transporters of GLUT family and processed following the glycolytic process, which is a sequential pathway of oxidation and non-oxidation processes governed by specific enzymes (Figure 1). Through this pathway glucose is mainly oxidized in pyruvate. Under aerobic conditions, pyruvate is oxidatively decarboxylated in acetyl-coA by pyruvate dehydrogenase, which enters in the tricarboxylic acid cycle (TCA). Taking place in mitochondria TCA generates reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH<sub>2</sub>). NADH and FADH<sub>2</sub> are used by mitochondrial respiratory chain to generate thirty-six ATP molecules, a pathway known as oxidative phosphorylation. Differently, under anaerobic conditions when oxygen level does not allow the complete oxidation of pyruvate, pyruvate can be transformed into lactate by lactate dehydrogenase (LDH). This reaction regenerates nicotinamide adenine dinucleotide (NAD<sup>+</sup>), which is essential to maintain a continuous glycolytic flux.

In addition, after the first glycolytic step, glucose-6-phosphate can escape glycolysis to be redirected to 1) glycogenesis pathway to be stored under the form of glycogen mainly in astrocytes <sup>15</sup> and 2) the ubiquitous highly active PPP (Figure 1) also named hexose monophosphate shunt <sup>16</sup>. Through PPP, glucose oxidization leads to the main cytosolic source of reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is essential for redox balance of the cells <sup>17</sup> and to reductive biosynthesis reactions, including the synthesis of fatty acids that are components of myelin and plasma membrane. In addition, this anabolic pathway can lead to other macromolecule synthesis, like nucleotides, and can fuel back glycolysis at the glyceraldehyde-3-phosphate and fructose-6-phosphate level. These glycolytic intermediates are produced by transketolase, an enzyme involved in non-oxidative step of PPP (Figure 1) <sup>18</sup>.

The entry of glucose-6-phosphate in PPP is tightly regulated and irreversible, which is different of the next glycolysis step driven by the reversible phosphoglucose isomerase (or glucose-phosphate isomerase, GPI). The first step of PPP that is catalyzed by glucose-6-phosphate dehydrogenase (G6PD) is a rate-limiting step generating one NADPH and 6-phosphogluconolactone. G6PD is tightly regulated by phosphorylation and protein interaction, and activated through its allosteric site to NADP<sup>+</sup> <sup>18</sup>. Thus, NADPH/NADP<sup>+</sup>

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3 ratio governs G6PD activity and the entry of glucose 6-phosphate into PPP. In unstressed  
4 conditions, the cells present an elevated NADPH/NADP<sup>+</sup> ratio and the low level of NADP<sup>+</sup>  
5 prevents glucose-6-phosphate from entering the PPP. Under oxidative stress conditions,  
6 the oxidation of NADPH increases the availability of NADP<sup>+</sup>, which activates G6PD,  
7 redirects glucose flow to the PPP and thereby inhibits glycolysis <sup>19</sup>. G6P oxidation by the  
8 PPP is also modulated by ROS. This can be done either indirectly by an increase of  
9 NADP<sup>+</sup> which is produced during one of the sequential steps of ROS scavenging by  
10 glutathione peroxidase (GPx), or directly by controlling the activity of glycolytic enzymes  
11 through the direct oxidation of their thiol residue <sup>20</sup>.  
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19 Under physiological conditions, glucose metabolism is finely regulated and linked to  
20 the fate of neurons, which, for some populations display a restricted glycolytic rate even  
21 though they are considered as energy-demanding cells <sup>19</sup>. This restriction seems  
22 associated to the continuous degradation by proteasome of 6-phosphofructo-2-  
23 kinase/fructose-2,6-bisphosphatase-3 (PFKFB3), a pro-glycolytic enzyme leading to  
24 fructose-2,6-bisphosphate, an allosteric activator of the rate-limiting glycolytic enzyme  
25 phosphofructokinase. This original mechanism developed by neurons favours the flow of  
26 glucose into the PPP to increase their antioxidant capacities <sup>19</sup>. Under specific stimuli as  
27 activation, neuron could limit PFKFB3 degradation to promote glycolysis instead of PPP.  
28 Inversely, in some pathologic situations the stabilization of PFKFB3 activates the  
29 phosphofructokinase and thus glycolysis. This dampens PPP and also limits NADPH  
30 production, which by increasing ROS level will lead to neuron degeneration. In the same  
31 way, other mechanisms related to antioxidant defense, such as the Oxidation Resistance  
32 1 protein (OXR1) have been described to interact with glucose metabolism. Indeed, OXR1  
33 can inhibit GPI the second enzyme of the glycolysis cascade promoting its inactivation,  
34 and ultimately a redirection of glucose-6-phosphate to PPP <sup>21</sup>. The overexpression of  
35 OXR1 promotes resistance to oxidative stress while its depletion increases  
36 neurodegeneration induced by oxidative stress <sup>22</sup>. Along different functions related to  
37 antioxidant defence, this regulation of glucose metabolism by OXR1 could also account  
38 for the differences in neurons sensitivity to oxidative stress observed in various regions of  
39 the brain. Indeed, in addition to redox homeostasis sensing through NADPH/NADP<sup>+</sup> ratio,  
40 the inhibition of glycolytic enzymes helps the cell to redirect glycolytic flux into the PPP  
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3 pathway by supplying metabolites accumulating upstream of the inhibited glycolysis step  
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5 <sup>20</sup>. In these conditions, the switch from glycolysis to PPP allow glucose to be metabolized  
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7 while generating reducing equivalents and maintaining a sufficient NADPH/NADP<sup>+</sup> ratio  
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9 needed to counteract an acute oxidative challenge <sup>16</sup>.

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11 In conclusion, the different populations of brain cells as well as the various sub-  
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13 populations of neurons display multiple metabolic profiles. While neurons display oxidative  
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15 phosphorylation using pyruvate, originating from glucose or lactate hence modulating their  
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17 PPP activity, astrocytes exhibit a high glycolytic metabolism leading to lactate production,  
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19 and thus certainly a lowered PPP activity.

#### 20 21 22 **4. Metabolic interaction between neurons and non-neuronal cells in** 23 24 **physiological and ischemic conditions**

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27 The brain comprises diverse neuronal populations intricately intertwined with glial  
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29 cells, including astrocytes, oligodendrocytes, and microglia, each playing various roles in  
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31 glucose metabolism. As detailed below, the astrocytes regulate glucose uptake, storage,  
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33 and lactate shuttling to neurons, ensuring energy supply during both normal and ischemic  
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35 conditions. Oligodendrocytes support axonal function and myelination, relying on glucose  
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37 metabolism to sustain their high energy demands. Microglia modulate inflammatory and  
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39 metabolic response during injury. The blood-brain barrier (BBB) controls glucose transport  
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41 into the brain, ensuring a continuous, regulated supply of energy maintaining  
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43 homeostasis. The complex interplay between these cells and neurons is crucial for brain  
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45 function, and its disruption during stroke worsens energy deficits, oxidative stress, and  
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47 neuroinflammation, intensifying ischemic injury.

##### 48 **4.1. The Astrocyte-Neuron metabolic cooperation.**

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51 The monocarboxylate lactate can be used by neurons as an energy source  
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53 alternative or additional to glucose. When plasmatic concentrations of lactate are  
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55 elevated, it can represent up to 25% of the metabolic fuel for brain, where it is mainly  
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3 oxidized<sup>12</sup>. Several data demonstrated that lactate can sustain neuron functions including  
4 synaptic activity in absence of glucose. Lactate can also serve as a more efficient or  
5 preferable energy source than glucose for cortical neurons, even when glucose is  
6 available at low concentrations<sup>23</sup>. In the same way, lactate infusion protects neuron from  
7 ischemia or energy deprivation injury (see below)<sup>24, 25</sup>. Mechanistically, lactate enters  
8 neural cells through monocarboxylate transporters 2 (MCT2) where it is metabolized into  
9 pyruvate by lactate dehydrogenase 1 (LDH1). This LDH isoform is highly expressed by  
10 cells using lactate as an energetic substrate and is inactivated by pyruvate. Then, pyruvate  
11 is used by the mitochondria through oxidative phosphorylation to produce ATP.  
12 Conversion of lactate to pyruvate by LDH1 results in the formation of NADH from NAD<sup>+</sup>,  
13 and when the concentration in lactate is elevated, this can modify the availability of NAD<sup>+</sup>  
14 in the cells<sup>26</sup>. NAD<sup>+</sup>/NADH ratio is crucial for numerous enzymatic activities in the cells  
15 as TCA cycle and activity of glyceraldehyde 3-phosphate dehydrogenase (G3PDH) along  
16 glycolysis, and currently, the NADH produced by G3PDH is recycled/oxidized in NAD<sup>+</sup> by  
17 various ways including LDH5<sup>27, 28</sup>. We can suppose that the increased activity of LDH1  
18 at the detriment of LDH5 potentially limits G3PDH activity due in part to a low NAD<sup>+</sup>/NADH  
19 ratio, which could limit complete glucose oxidation by glycolysis in favor of the  
20 lactate/pyruvate way (Figure 1)<sup>29</sup>. Consequently, intermediate metabolites of glycolysis  
21 upstream to glyceraldehyde3-phosphate will accumulate and could push for an increase  
22 in the use of glucose-6-phosphate by the PPP to product NAPDH<sup>28</sup>.  
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38 Neurons do not seem to produce their own source of lactate but seem to uptake  
39 lactate produced by other cells<sup>9, 30</sup>. It underscores the importance of Astrocyte-Neuron  
40 metabolic coupling. Astrocytes, outnumbering neurons, possess cellular extensions that  
41 form bridges between neurons and blood capillaries. These connections facilitate the  
42 exchange of metabolites and play a crucial role in supporting neuron metabolism<sup>11</sup>.  
43 Astrocytes can recycle glutamate, released by neurons, in glutamine which is carried back  
44 to neurons to be metabolized again in glutamate, these two biosynthesis being driven by  
45 glutamine synthase (Figure 2)<sup>31</sup>. Glutamate is co-transported with Na<sup>+</sup> and thus requires  
46 proper functioning of Na<sup>+</sup>/K<sup>+</sup>-ATPase. This and glutamate conversion in glutamine reduce  
47 ATP levels in astrocytes, which in turn may activate anaerobic glycolysis generating  
48 lactate to restore ATP reserve<sup>30, 32</sup>. Accumulated lactate moves outward the astrocyte  
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3 through MCT4 and it can be finally uptake into the surrounding neurons *via* MCT2<sup>33</sup>, an  
4 exchange known as Astrocyte-Neuron Lactate Shuttle (ANLS). To note, astrocytes  
5 express LDH5, which is known to be specific to lactate-producing cells. The glucose  
6 utilized in glycolysis is derived either from the bloodstream or from glycogen stores  
7 maintained by astrocytes. These reserves become particularly vital during conditions of  
8 low environmental glucose<sup>34</sup> or heightened neural activity when neurons require  
9 additional energy substrates<sup>35</sup>. This dynamic enables the transfer of lactate from  
10 astrocytes to neighboring neurons<sup>10</sup>. It should be noted that lactate trafficking between  
11 astrocytes also exists and exceeds the shuttle to the neuron under physiological  
12 conditions<sup>36</sup>.

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Glycogenolysis is compromised during ischemia and reperfusion, primarily  
attributable to a decrease in enzymatic activity<sup>37, 38</sup> and leading to brain glycogen  
accumulation after reperfusion in ischemic stroke patients and primates. In addition,  
stimulation of glycogenolysis by insulin at the start of reperfusion limits stroke damage<sup>38</sup>.  
The accumulation of glycogen is linked to dysfunction in glycogenolysis within astrocytes,  
and the interest in glycogen metabolism within these cells has recently grown with the  
discovery of astrocyte subtypes<sup>39</sup>. Indeed, studies propose the categorization of  
astrocytes into A1-like and A2-like subtypes, where A1-like astrocytes exhibit neurotoxic  
properties, while A2-like astrocytes produce trophic factors and manifest protective  
properties<sup>39, 40</sup>. A1 astrocytes may be activated in response to inflammatory factors  
secreted by microglia during brain injury and neurodegenerative diseases<sup>39</sup>. During  
ischemia, metabolic switching from oxidative phosphorylation to anaerobic glycolysis  
seems crucial for neurotoxicity of A1-like astrocyte<sup>41</sup>. Activated astrocytes have a dual  
role during stroke are they are involved in neuroinflammation and blood brain barrier  
disruption<sup>39, 42</sup>, as well as in brain homeostasis restoration after reperfusion<sup>43</sup>.  
Interestingly, recent research has demonstrated that the activation of glycogenolysis  
during ischemia and reperfusion limits the formation of A1-like astrocytes in favor of A2  
neuroprotective astrocytes<sup>41, 44</sup>. This mechanism appears to be mediated by the decrease  
in ROS production due to increasing antioxidant defense which can be considered also  
as a therapeutic alternative<sup>44</sup>.

#### **4.2. Microglial cell metabolism and activation**

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Microglia serves as the resident immune cells within the central nervous system. These cells play a crucial role in sensing brain homeostasis and are actively engaged in the control of neuronal activity, neurogenesis, and the clearance of apoptotic and necrotic brain cells <sup>45</sup>. Microglia establishes interactions with the brain microenvironment through the secretion of various molecules, including chemokines and cytokines. The microenvironment, in turn, has the capability to modulate microglial function responsively <sup>45</sup>. Functionally and in terms of polarization/activation, microglial cells bear a resemblance to classic macrophages, although they exhibit distinct properties <sup>46, 47</sup>. Microglial cells can be activated into M1 and M2 subtypes. The M1 subtype is characterized by cytotoxic and pro-inflammatory properties, while the M2 subtype displays phagocytic, repair, and anti-inflammatory activities. However, despite their heightened phagocytic properties, the activation of M2 microglial cells into the M2-activated phenotype appears to be more circumscribed compared to macrophages <sup>46</sup>. The M2 phenotype can be further classified into three subtypes, namely M2a, M2b, and M2c <sup>46-49</sup>. Like to macrophages and others immune cells <sup>50</sup>, the activation of microglial cells involves and is regulated by modifications in energy metabolism. This process is contingent upon the availability of energy substrates, such as glucose, fatty acids, and amino acids <sup>51-53</sup>. M1-polarized microglial cells exhibit a preference for generating ATP through glucose and glycolysis, coupled with lactate production. On the other hand, M2 microglial cells utilize oxidative phosphorylation for ATP production, lacking real selectivity in the choice of energy substrate <sup>51-53</sup>. Given that microglial cells actively monitor brain homeostasis, they exhibit sensitivity to alterations in brain metabolism. Under physiological normoxic conditions, cells generate energy through glycolysis or oxidative phosphorylation, contingent upon their activated phenotype. In the absence of glucose, microglia demonstrate the capability to utilize free fatty acids or amino acids as alternative energy sources for oxidative phosphorylation <sup>51, 54</sup>, an adaptative phenomenon recently described in white matter microglia after stroke<sup>55</sup>. This metabolic adaptation ensures the preservation of the phagocytic and anti-inflammatory roles of microglial cells <sup>51</sup>.

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Furthermore, ketone bodies, produced by the liver during sustained hypoglycemia, such as extended or repeated fasting periods, possess the capability to inhibit microglial activation <sup>56</sup>. Ketone bodies can serve as an alternative energy substrate for oxidative

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3 phosphorylation in brain cells and are capable of activating membrane receptors. One  
4 crucial mechanism behind the inhibition of microglia activation appears to be the activation  
5 of the ketone receptor GPR109A <sup>57</sup>. Concept supported by the observation that a  
6 ketogenic mitigate stroke injuries in mice, and this protective effect is notably absent in  
7 mice lacking the *gpr109a* gene <sup>58</sup>.  
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12 In the ischemic brain, microglial cells undergo activation from the initial hours post-  
13 ischemia through the recovery phase following ischemic stroke <sup>59-62</sup>. Interestingly, the  
14 activation of microglial cells in the infarct zone exhibits a negative correlation with clinical  
15 outcome <sup>63</sup>. While M1-activated microglial cells appear detrimental for neuron survival  
16 post-ischemia, M2 type displayed neuroprotective properties <sup>64, 65</sup>. Depleting microglia  
17 after stroke results in an adverse outcome, underscoring the beneficial role of microglial  
18 cell activity in tissue repair <sup>66, 67</sup>. In hypoxic conditions, microglial cells transition to an M1  
19 phenotype, marked by a shift from oxidative phosphorylation to glycolysis. It is postulated  
20 that the inflammatory components, such as cytokines, and the presence of cellular debris  
21 resulting from ischemia, contribute to fostering this metabolic transition in microglial cells  
22 <sup>53, 65</sup>. Nevertheless, it is plausible to hypothesize that insufficient oxygen supply, as well  
23 as a deficit in energetic substrates could compromise oxidative phosphorylation, elevate  
24 anaerobic glycolysis, resulting in M1 activation, and thereby instigate brain inflammation.  
25 This scenario is observed in neurons and astrocytes during ischemia (see chapter 6).  
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37 Microglial cells exhibit essential functions during the ischemic stroke, depending  
38 on their polarization. Thus, they represent an intriguing target for the treatment of stroke,  
39 especially inhibition of their pro-inflammatory activation by modulating metabolism.  
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#### 44 **4.3. Interaction between neurons and oligodendrocytes to myelination maintenance**

45 Oligodendrocytes are specialized cells whose metabolism is uniquely tuned to  
46 support its functions. While oligodendrocytes and their precursors display high oxidative  
47 metabolism <sup>68</sup> and iron content <sup>69</sup>, and are able to use glucose or lactate to produce energy  
48 for myelination <sup>70, 71</sup>, mature oligodendrocytes shift to glycolytic metabolism to maintain  
49 myelination <sup>70</sup>. Oligodendrocytes are highly dependent on the metabolism of surrounding  
50 cells <sup>69, 71</sup>, but their direct involvement in overall brain metabolism remains less defined.  
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3 However, they play a crucial role in maintaining the functional integrity of the axons they  
4 surround by shuttling lactate and other trophic factors through myelinic channels <sup>72</sup>. Since  
5 oligodendrocytes can utilize lactate supplied by astrocytes, it is hypothesized that they  
6 contribute to the astrocyte-neuron lactate shuttle, acting as an intermediary in metabolic  
7 support for neurons <sup>70</sup>.  
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11 Oligodendrocytes function is highly sensitive to ischemia due to their high demand  
12 for O<sub>2</sub> and metabolite substrate, and also because their iron content can catalyze the  
13 conversion of H<sub>2</sub>O<sub>2</sub> produced during ischemia/reperfusion into highly reactive hydroxyl  
14 radicals OH<sup>-</sup> by Fenton reaction <sup>73, 74</sup>. This vulnerability is accentuated by their low  
15 antioxidant defense <sup>75</sup>. Moreover, oligodendrocytes are highly sensitive to glutamate  
16 toxicity found during brain ischemia/reperfusion which leads to their death and  
17 demyelination <sup>76</sup>. Subsequently, stroke leads to a loss of myelin integrity, which  
18 contributes to long-term morbidity, including cognitive and sensorimotor deficiencies <sup>77</sup>.  
19 This sensitivity to oxidative stress partly explains why antioxidant strategies represent an  
20 interesting approach to dampen stroke-induced damage in oligodendrocytes and support  
21 the regeneration of myelin following reperfusion, ultimately aiding in functional recovery.  
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#### **4.4. Blood-brain barrier, an essential component of brain metabolism and function.**

36 The BBB comprises endothelial cells, pericytes and basement membrane  
37 surrounded by astrocyte, along with neurons and microglia, forming a cellular interface,  
38 named neurovascular unit. With the support of tight junctions between endothelial cells,  
39 BBB constitutes both a physical and biochemical barrier, restricting passive diffusion and  
40 regulating molecular trafficking between the blood and the brain through active transport  
41 <sup>78</sup>. Under normal physiological conditions, it ensures a constant supply of oxygen,  
42 nutrients (such as amino acids, ketones and glucose), ions and proteins to brain cells,  
43 while also controlling inflammatory response by sensing local changes in its surrounding  
44 <sup>79</sup>. BBB protects the brain from toxins and other damaging materials circulating in the  
45 peripheral blood. Thus, BBB is crucial for maintenance of brain homeostasis to provide  
46 an optimal environment for neuronal function <sup>79</sup>. Relatively little is known about metabolic  
47 homeostasis and interplay between cells of the BBB. However recent studies showed that  
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3 the highly glycolytic endothelial cells metabolize blood glucose to produce significant  
4 lactate quantity, which is then secreted and taken up by pericytes <sup>80</sup>. While classic  
5 pericytes are glycolytic, brain pericytes use preferentially lactate as energetic substrate  
6 for oxidative phosphorylation even in presence of other nutrients. This endothelial cell-  
7 pericyte shuttle of lactate appears to be crucial for pericyte homeostasis and given  
8 pericytes key regulatory properties in vascular stability, permeability, and blood flow  
9 control to BBB maintenance <sup>80</sup>.

15 BBB remains effective only if all its cellular components function properly and  
16 maintain their structural integrity. BBB disruption begins immediately after vessel  
17 occlusion and persists for an extended period following a stroke. Indeed, oxidative stress  
18 and neuroinflammation generated during the ischemic period contribute to structural  
19 alterations of BBB, increasing its permeability <sup>81</sup>. Consequently, when the integrity of the  
20 BBB is compromised, it can result in ion imbalance, macromolecule intrusion and immune  
21 cell infiltration in the brain, ultimately leading to neuronal dysfunction and degeneration <sup>81</sup>.  
22 During ischemia, the disruption of oxidative phosphorylation and others sources of ROS  
23 production led to oxidative stress, which damage endothelial cells contributing to BBB  
24 disruption and vasogenic edema. Hence, ROS scavenging or the induction of antioxidant  
25 defense during stroke reduced BBB permeability <sup>82</sup>. Moreover, it was demonstrated that  
26 peroxiredoxin-4 is an endogenous protective antioxidant protein against endothelial  
27 dysfunction and BBB damage <sup>83, 84</sup>. Surprisingly, enhancing oxidative phosphorylation in  
28 endothelial cells by inhibiting pyruvate dehydrogenase kinase appears to protect BBB  
29 integrity and reduce stroke damage in a MCAO mouse model <sup>85</sup>. However, if inhibiting PDK  
30 promotes oxidative phosphorylation over glycolysis, which may enhance endothelial cell  
31 metabolism and BBB stability, the broader metabolic consequences of this intervention  
32 on other brain cells remain unclear. Finally, oxidative stress and inflammatory factors  
33 during stroke are also known to activate metalloproteinases (MMP-2 and MMP-9) which  
34 are proteolytic enzymes able to degrade basement membrane of BBB leading to its  
35 instability and permeability <sup>86, 87</sup>.

##### 53 **5. Dual role of glucose in neuronal oxidative stress.**

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3 More than in other organs, the high metabolism level maintained in the brain for  
4 generating large amounts of ATP through oxidative phosphorylation <sup>8</sup> generates harmful  
5 oxidative species, which are neutralized by reactions using mainly NADPH <sup>17</sup>. The  
6 synthesis of aerobic ATP is carried out *via* the mitochondrial respiratory chain that takes  
7 place in the mitochondrial inner membrane <sup>88</sup> (Figure 2). This chain is composed of 4  
8 complexes (I to IV), of electron transporters such as ubiquinone (coenzyme Q (CoQ)) and  
9 cytochrome c (Cyt c) and of ATP synthase considered as complex V. Reactions within  
10 complexes generate a flow of electrons from complex I to complex IV, which is coupled to  
11 the establishment of a proton gradient between the inter-membrane space and the matrix  
12 of the mitochondria. This gradient is finally used by the ATP synthase as energy for the  
13 synthesis of ATP. During transfer reactions across complexes, a part of the electrons  
14 escapes and are accepted by O<sub>2</sub> to result in the production of reactive oxygen species  
15 (ROS) <sup>88, 89</sup>. This production seems to be linked to a high membrane potential and/or to  
16 the redox state of the substrate <sup>90</sup>. For Complex I, a high NADH/NAD<sup>+</sup> ratio promotes the  
17 reduction of electron carriers and increases their movement into the complex. If the  
18 electron carriers are reduced, the production of superoxide anion increases <sup>91</sup>. For  
19 Complex III, the oxidation/reduction cycles of quinones generate unstable semiquinone  
20 intermediates that move freely in the complex allowing the electron escape towards O<sub>2</sub>  
21 and create ROS <sup>92</sup>. Usually, these ROS are eliminated by the antioxidant systems of the  
22 cell. The coordinated activity of two molecules is essential in protecting cells against ROS-  
23 mediated damage: NADPH and glutathione. The scavenging of ROS is ensured by the  
24 sequential action of superoxide dismutase (SOD) and glutathione peroxidase <sup>93</sup>. Two  
25 superoxide radical anions (O<sub>2</sub><sup>•-</sup>) are converted by SOD into the less reactive H<sub>2</sub>O<sub>2</sub>.  
26 Catalase (CAT) and glutathione peroxidases (GPx) degrade H<sub>2</sub>O<sub>2</sub> to water and molecular  
27 oxygen. GPx used reduced glutathione (GSH) to convert H<sub>2</sub>O<sub>2</sub> and produce oxidized  
28 glutathione (GSSG). GSH is regenerated by glutathione reductase (GR) in the presence  
29 of NADPH <sup>93</sup>. GSH is a major antioxidant molecule in brain cells. Catalase does not require  
30 cofactor for H<sub>2</sub>O<sub>2</sub> degradation but display an allosteric site for NADPH that maintains the  
31 enzyme in its active conformation <sup>18</sup>.  
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53 It is somehow surprising that while neurons displayed the highest oxidative activity  
54 in the brain, GSH seems mainly synthesized by astrocytes, which displayed in addition  
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3 the higher GSH content of the brain <sup>11, 94, 95</sup>. These probably make neurons more  
4 vulnerable to oxidative stress and highly dependent on astrocytes for their protection <sup>95</sup>.  
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6 <sup>96</sup>. Moreover, neurons appear to be unable to transport GSH and in consequence transfer  
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8 from astrocytes must require intermediate reactions. In astrocyte, GSH that is a tripeptide  
9 combining glutamate, cysteine and glycine is synthesized by the action of two enzymes,  
10 the  $\gamma$ GluCys synthase and the glutathione synthase. After its release by astrocyte, GSH  
11 could be sequentially cleaved by the ectoenzyme  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GT, from  
12 astrocyte) and the ectopeptidase aminopeptidase N (ApN, from neuron) to generate  
13 cysteine and glycine, which are two amino acids that can enter the neuron <sup>95</sup>. In this last,  
14  
15 cysteine, glycine and glutamate are used as substrates to generate GSH. Interestingly,  
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17 numerous studies demonstrated that glutamate is mainly provided again by the astrocyte  
18 in the form of glutamine <sup>31</sup>. Altogether, this underlines the crucial cooperation between  
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20 neuron and astrocyte.  
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## 27 **6. Glucose metabolism in ischemic condition.**

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29 Ischemic brain cells are deprived (partially or completely) of oxygen, glucose and  
30 more generally in energetic substrates. This compromises both oxidative phosphorylation  
31 (due to oxygen deficiency) and glycolysis (attributed to glucose scarcity) pathways for  
32 cellular energy synthesis. Consequently, the rate of ATP production falls below the rate  
33 of its utilization by many cellular reactions <sup>97</sup>. Reduction of cellular ATP inactivates all  
34 energy-dependent activity of the neuron, disrupting  $\text{Na}^+/\text{K}^+$  ATPase proper functioning  
35 and  $\text{Ca}^{2+}$  homeostasis. These changes lead to morphological and functional disruption of  
36 cellular organelles, especially mitochondria, promoting the opening of the mitochondrial  
37 permeability transition pore (MPTP) dissipating mitochondrial membrane potential. It  
38 exacerbates the energy dysfunction of brain cells and ultimately leads to cell death <sup>98</sup>.  
39 Furthermore, the drop in oxygen levels induces a severe alteration of both glycolysis and  
40 oxidative phosphorylation, resulting in oxidative stress through ROS production <sup>99, 100</sup>. This  
41 is particularly visible within the mitochondrial respiratory chain at Complexes I and III  
42 where ROS production occurs <sup>90</sup>.  
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53 Besides mitochondrial ROS, other sources of ROS exist but they appear to be less  
54 involved in the brain than in other tissues during ischemia <sup>101</sup>. This could be related to the  
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3 NMDA activation by glutamate excitotoxicity, which has been shown to be the major  
4 pathway for ROS production in neurons through activation of NADPH oxidase (NOX) <sup>102</sup>.  
5 Nevertheless, these results did not meet *in vivo* studies suggesting that NOX production  
6 of ROS take place mainly at reperfusion stage <sup>101, 103</sup>.  
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10 ROS are produced under physiological conditions, where they serve as secondary  
11 mediators, and their concentration is regulated by several antioxidant mechanisms. The  
12 most important in brain is composed of mitochondrial (Mn-SOD) and cytoplasmic (Cu/Zn-  
13 SOD) superoxide dismutases, which catalyze the transformation of  $O_2^{\cdot-}$  in  $H_2O_2$ . Then,  
14 CAT and especially GPx generates  $H_2O$  from  $H_2O_2$  a reaction possible thanks to GSH in  
15 the case of GPx <sup>93</sup>. During stroke, the balance between ROS production and detoxification  
16 is compromised by i) an excessive production of ROS resulting from reduced oxygen and  
17 nutrients availability, and ii) a decline in antioxidant capacity attributed in part to  
18 unavailability of glucose <sup>104</sup>. Indeed, GSH is regenerated from GSSG plus NADPH by  
19 glutathione reductase (GR), cytosolic NADPH coming primarily from the metabolization of  
20 glucose by PPP (Figure 3). Thus, when glucose availability decreased during stroke,  
21 NADPH is less synthesized and GSH cannot be regenerated despite the high  $NADP^+$  rate  
22 <sup>105</sup>. Moreover, the high glutamate exocytosis also contributes to GSH pool decrease in  
23 brain cells along stroke <sup>106</sup>. Indeed, the high quantity of extracellular glutamate appears  
24 to block the uptake of cystine (= di-cysteine) by the antiporter cystine/glutamate expressed  
25 by astrocytes. As cystine is a crucial substrate of GSH synthesis, this latter decreases  
26 <sup>106</sup>. This deficiency in defense systems leads to oxidative stress causing irreversible  
27 oxidation of biological molecules such as DNA, lipids and proteins, and ultimately cell  
28 death by apoxytosis/ferroptosis or apoptosis <sup>98</sup>. Ferroptosis is a central event in brain  
29 damage <sup>107</sup>, making it widely studied and a preferred target in the prevention of  
30 neurodegenerative disease and stroke <sup>108</sup>.  
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46 Oxygen deprivation involved a switch of cell metabolism from aerobic to anaerobic  
47 pathway <sup>99</sup>. In consequence, early after stroke glucose is used by glycolysis for generating  
48 lactate. Lactate is extruded by MCT from the cells with  $H^+$ , leading to lactate accumulation  
49 and mostly acidosis that turns being toxic for the cells <sup>109</sup>. If glucose becomes completely  
50 unavailable, the glycolysis is blunted leading to complete energy depletion including the  
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3 decrease in PPP, which also results in a decrease in NADPH production and a  
4 disturbance of macromolecules synthesis.  
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## 8 **7. Glucose metabolism in reperfusion condition.**

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11 Reperfusion after ischemia (Figure 3) normalizes tissue acidosis and restores the  
12 delivery to brain cells of oxygen and nutrients required for energy production. On one  
13 hand, neurons retrieve aerobic metabolism and should be able to immediately use the  
14 lactate accumulated in their environment during ischemia <sup>110</sup>. Lactate is metabolized into  
15 pyruvate that is used by mitochondria to produce ATP. On the other hand, glucose enters  
16 in glycolysis then shifts to PPP where it is used to nucleosides synthesis as well as  
17 production of NADPH, which in turn promotes GSH synthesis and thus antioxidant  
18 defense <sup>111</sup>. New analysis using metabolic imaging demonstrated that sustained lactate  
19 production was maintained 48 hours after stroke and normalized eleven days later.  
20 Interestingly, the same study shown that glutamine/glutamate synthesis was low 48 hours  
21 after stroke and did not increase eleven day later, suggesting a delayed glutamine  
22 oxidative metabolism which could be normalized the weeks after concomitantly to  
23 functional recovery <sup>112</sup>.  
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34 Nevertheless, it is well-known that tissue reperfusion itself is responsible, to some  
35 extent, for the damage. Indeed, the quick reactivation of aerobic metabolism alters the  
36 functioning of mitochondrial complexes and induces a critical increase in ROS production  
37 <sup>5</sup>. The production of ROS during brain reperfusion has long been described in rodent  
38 models of focal ischemia <sup>113</sup> or reversible middle cerebral artery occlusion <sup>114</sup>. Contrary to  
39 its involvement in ROS production from other tissues, in the brain NOX2 would be a major  
40 source of ROS during reperfusion, whereas during the ischemia phase its involvement  
41 seems trivial <sup>103</sup>. Indeed, the availability of glucose and oxygen is necessary for NOX2  
42 activity and the acidosis that occurs at the ischemic stage has an inhibiting action on its  
43 activity. During reperfusion there is a pH normalization reversing the inhibition of NOX as  
44 well as an influx of its substrates, especially glucose, which will produce NADPH by PPP  
45 <sup>115</sup>. In addition, NOX2 activation could be triggered by the sustained activation of the  
46 NMDA receptor due to glutamate excessive release <sup>116</sup>. Conversely, a study  
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3 demonstrated that NOX4, but not NOX2, is the main oxidase involved in ROS production  
4 during stroke <sup>117</sup>.

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6 Xanthine oxidase (XO) was described as another probable source of ROS during  
7 reperfusion. XO is one of the two forms of xanthine oxidoreductase (XOR), the other being  
8 xanthine dehydrogenase (XDH). The activities of XO and XDH catalyze the transformation  
9 of hypoxanthine in xanthine and then in uric acid. XO uses O<sub>2</sub> as an electron acceptor that  
10 generates O<sub>2</sub><sup>•-</sup> <sup>118</sup>. Under low oxygen availability, ADP can be metabolized by adenylate  
11 kinase in AMP plus ATP which is used as an alternative energy source by the brain.  
12 Residual AMP is metabolized in inosine and hypoxanthine resulting in depletion of the  
13 adenine nucleotide pool and hypoxanthine accumulation <sup>119</sup>. During reperfusion, when O<sub>2</sub>  
14 is available again, hypoxanthine is massively metabolized by XO and leads to ROS  
15 generation <sup>118</sup>.

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17 Nevertheless, the exact participation of these ROS in cerebral injury and  
18 macromolecules oxidation is still poorly understood, especially in human. In this context,  
19 an investigation conducted in post-stroke patients has proposed a marginal role of ROS  
20 generated during reperfusion. This study, encompassing 160 patients, indicated that  
21 ischemia would be linked to elevated lipid and protein oxidation resulting from ROS  
22 production, a process observed to end after thrombolysis <sup>120</sup>. If confirmed, this would  
23 mean that the collateral damage of thrombolysis, which is the unique clinical approaches  
24 available to limit stroke impact, is only minimally associated with ROS production by rapid  
25 reperfusion of the ischemic region by recanalization of the occluded artery and restoration  
26 of the blood flow. This would be contrary to current thinking in the field.

## 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 **8. The Janus face of Glucose in stroke**

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46 Glucose is a crucial energetic and molecular substrate of brain cells, and its  
47 deprivation is a highly deleterious situation leading to cerebral injuries. During ischemia,  
48 glucose could support oxygen independent glycolytic ATP production and/or maintain  
49 antioxidant defense through PPP. Thus, it was tempting to speculate that increasing  
50 glucose concentration in the ischemic brain would limit stroke injury. In this way, glucose  
51 perfusion was early tested experimentally in a rat model of brain ischemia-reperfusion in  
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3 the eighties <sup>121</sup>. Contrary to what was expected, moderate glucose injection resulted in  
4 more extensive brain injury and mortality in rats. This unfortunate outcome was linked to  
5 an increased glutamate release found after brain acute ischemia in glucose perfused rats  
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8 <sup>122</sup>. These pioneer results paved the way for understanding the detrimental impact of  
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10 hyperglycaemia and hypoglycaemia on stroke outcome, two recognized risk factors  
11 especially found in Type 2 and Type 1 diabetes patients.  
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14 The rapid amount of glucose supplied at reperfusion increases the anaerobic  
15 metabolism in astrocytes and thus to acidosis, a situation that will be exacerbated by  
16 hyperglycaemia <sup>123</sup>. While moderate acidosis can be neuroprotective <sup>124</sup>, more severe  
17 acidosis is deleterious in part by activating acid-sensing ion channels <sup>125</sup> and increased  
18 oxidative stress <sup>126</sup>. At the level of neurons, the rapid supply in substrate for aerobic  
19 metabolism (under the form of glucose or lactate) feeds the production of ROS within  
20 mitochondrial respiratory complexes <sup>5</sup>, a deleterious mechanism enhanced under high  
21 glucose concentration <sup>127</sup> and modulated in part by glucose-6-phosphate level and the  
22 inhibition of mitochondria-bound hexokinase <sup>128</sup>. Reperfusion also triggers an  
23 overproduction of ROS by NOX2. This is enhanced by the high availability of NADPH  
24 observed during reperfusion, which is generated primarily by the glucose metabolism  
25 through PPP. This paradoxical role of NADPH, which is mainly used for GSH regeneration  
26 in physiological conditions, is increased by hyperglycaemia <sup>115</sup>. Hyperglycaemia is well  
27 recognized as a significant risk factor for stroke, which has led to the clinical development  
28 of protocol to lower blood glucose level including the use of insulin therapy. The downside  
29 is that these treatments are associated with risks of hypoglycaemia, which is also  
30 deleterious during stroke <sup>1</sup>.  
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43 Aggravation of stroke outcome by hypoglycaemia was demonstrated in rodent model  
44 of Type 1 diabetes where sequential hypoglycaemia led to a worsening of ischemia  
45 injuries <sup>129, 130</sup>. Independently to an ischemic situation, severe, sustained, or repeated  
46 hypoglycaemia leads to brain cells energy failure that is detrimental for brain cells.  
47 Furthermore, the noxious effects of hypoglycaemia on stroke outcomes have been  
48 associated to mitochondrial dysfunction and its associated ROS production during the  
49 reperfusion stage <sup>130</sup>. Hypoglycaemia also impairs GSH production due to the low activity  
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of PPP and thereby contributes to exacerbate oxidative stress induced by reperfusion and mitochondrial dysfunction <sup>131</sup>.

## **9. Comorbidities and patient characteristics modulating brain glucose metabolism in stroke**

Several risk factors associated with alterations in brain glucose metabolism can exacerbate the occurrence and consequences of strokes. Predominantly, Type 1 (T1D) and Type 2 diabetes (T2D) elevate the risk of stroke by two to three times, with diabetic patients exhibiting higher age-adjusted levels of stroke mortality and morbidity <sup>132</sup>.

Common comorbidities of diabetes and obesity, such as elevated blood levels of cholesterol, triglycerides, and hypertension, are well-recognized risk factors for stroke <sup>133</sup>. To note, the hyperinsulinemia found during obesity increases the brain glucose uptake which could modify neural cell metabolites availability and dependance <sup>134</sup>. Consequently, therapeutic interventions aimed at normalizing these parameters in diabetic patients, including the use of hypotensive and hypolipidemic drugs, contribute to a reduction in stroke incidence <sup>135</sup>. Nevertheless, the hyperglycaemia seems play a central role in the increased incidence and aggravation of stroke affecting both diabetic and non-diabetic patients <sup>1</sup>. This is partly due to microvasculature change including diminished perfusion, abnormal endothelial proliferation, and increased permeability of the BBB, which can aggravate hemorrhagic event <sup>136</sup>. Accordingly, recent evidence indicates that elevated blood level of glycated haemoglobin (HbA1c), reflecting hyperglycaemia in the preceding months, is associated with an increased risk of stroke in both diabetic and non-diabetic patients <sup>137</sup>. Therefore, interventions aimed at reducing glycaemia are of interest in mitigating the occurrence and consequences of stroke. However, it is noteworthy that intensively treated or inadequately managed diabetic patients may experience hypoglycemic events, which pose additional risks <sup>138</sup> and are positively correlated to increase incidence of ischemic events including stroke <sup>139</sup>.

Sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like-peptide-1 receptor (GLP-1-R) agonists are a new generation of antidiabetic drugs able to limit hyperglycaemia without severe hypoglycaemic events <sup>140</sup>. SGLT2 inhibitors of the gliflozin

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3 family limit glucose reabsorption by the nephron and lead to blood glucose decrease.  
4 Interestingly, it seems that a compensation by SGLT1 takes place to limit hypoglycaemia.  
5 Incretin mimetics (GLP-1R agonist) stimulate insulin secretion and inhibit glucagon output  
6 in a glucose-dependent manner leading to better control of blood glucose. At the same  
7 time, they act on hypothalamus and promote satiety. Both drugs displayed anti-  
8 inflammatory and antioxidant capacity along with the ability to reduce blood pressure <sup>140</sup>.  
9 Management of diabetic patients using these two classes of drugs could be also highly  
10 interesting to limit associated pathologies as kidney failure, cardiovascular disease, and  
11 stroke. Stroke incidence in various clinical trials investigating the effect of SGLT2 inhibitors  
12 and GLP-1-R agonists in T1D and T2D patients have been retrospectively analysed. Both  
13 treatments appeared to reduce the occurrence of stroke in a significant portion of the trials  
14 <sup>140</sup>. The direct link between stroke protection and glycemic control, as well as the direct or  
15 indirect effect of GLP-1-R agonist, has yet to be fully demonstrated. However,  
16 experiments conducted in rodent have demonstrated antioxidant effects of incretin  
17 mimetics, which could also play a crucial in stroke prevention <sup>141</sup>.

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19 As explained previously, both hyper- and hypoglycaemia can induce ROS  
20 production, mitochondrial dysfunction and extracellular glutamate accumulation, and  
21 thereby aggravates stroke consequences <sup>122, 142</sup>. It occurs in both neural and non-neural  
22 cells, including oligodendrocytes, astrocytes and microglia. In these cells, ROS lead,  
23 among other things, to the activation of NFkB and subsequent inflammatory response,  
24 which exacerbates the damage <sup>62</sup>. For example, cytokines and other molecules secreted  
25 by the activated non-neuronal cells will damage the BBB, further upsetting the brain's  
26 metabolic and inflammatory balance <sup>143</sup>. It is noteworthy that various brain cells can  
27 compensate for a scarcity of glucose by shifting their metabolism to alternative energy  
28 resource, which helps maintaining their function. For instance, microglial cells <sup>51</sup> and  
29 astrocytes <sup>44</sup> can adapt by respectively using glutamine or glycogen instead of glucose for  
30 oxidative phosphorylation, thus supporting their anti-inflammatory capacity, as can  
31 oligodendrocyte progenitors lactate for remyelination <sup>144</sup>.

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33 In conjunction with comorbidities, various patient-specific attributes exert influence  
34 upon cerebral metabolism, thereby contributing to the incidence and severity of strokes.  
35 The prevalence of stroke is heightened within the elderly demographic, a population

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3 characterized by discernible modifications in cerebral glucose metabolism. Aging leads to  
4 human brain modification, including synaptic density decrease, brain volume loss, BBB  
5 alteration <sup>145</sup> and a drop in the connected glucose metabolism, oxygen consumption and  
6 cerebral blood flow <sup>146</sup>. The data generated from these observations suggest a decline in  
7 oxidative glucose metabolism within the aging brain. Recent investigations have  
8 substantiated this notion, revealing a reduction in brain metabolism during early adulthood  
9 relative to childhood. Interestingly, cerebral oxygen consumption and blood flow exhibit  
10 minimal alterations in subsequent years, while there is a continual decrease in glucose  
11 metabolism throughout the aging process <sup>147</sup>. In a different study, Goyal et al. elucidated  
12 that the age-related decline in glucose metabolism primarily stems from a reduction in  
13 glycolytic activity rather than impaired glucose oxidation by mitochondria <sup>146</sup>. Furthermore,  
14 a comprehensive analysis of previous datasets enabled to ascertain that the trajectory of  
15 glucose metabolism during aging exhibits topographical variations across distinct brain  
16 regions <sup>148</sup>, which can be related to differential gene expression and stress susceptibility  
17 as highlighted in mouse brain <sup>149, 150</sup>. It is conceivable that the diminished glycolytic activity  
18 observed in older individuals could potentially confer heightened vulnerability in the  
19 context of stroke. Specifically, alterations in glycolysis may result in a diminished  
20 production of NADPH and lactate, both of which play pivotal roles in preserving neurons  
21 and other brain cells against ischemia/reperfusion injuries.  
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36 Several investigations have explored gender differences in brain biology and  
37 function. Notably, analyses of brain metabolism reveal distinctions between young and  
38 elderly individuals, with the exception of the brain oxygen consumption rate. Interestingly,  
39 this rate remains comparable between women and men across all age groups. Moreover,  
40 these variations are contingent upon the specific brain regions assessed. For example,  
41 within the gyrus and cortex, young women demonstrated heightened cerebral blood flow  
42 compared to men, with these gender-related distinctions diminishing as age progresses  
43 <sup>147</sup>. Old investigations examining overall brain metabolism failed to observe gender-based  
44 differences in glucose metabolism, regardless of brain region or age <sup>151</sup>. In contrast,  
45 contemporary studies have revealed region-specific disparities in glucose metabolism.  
46 For instance, women in their sixties exhibited higher glucose metabolism in the  
47 hypothalamus, while men demonstrated elevated metabolism in the frontal lobe <sup>152</sup>.  
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3 Moreover, several gender differences in glucose metabolism within the brain, identified in  
4 young individuals, diminish with age <sup>153, 154</sup>. These gender disparities appear to be  
5 predominantly associated with factors such as brain size, laterality, and synaptic density  
6 and activity, which exhibit variability between men and women contingent upon age.  
7 Furthermore, given the pronounced dependence of these differences on specific brain  
8 regions, predicting their impact on the occurrence and consequences of strokes is  
9 challenging. Additionally, post-ischemic hyperperfusion may develop differentially in  
10 males and females as shown in MCAO rat by a recent paper suggesting its interest to  
11 predict gender-dependent outcome <sup>155</sup>.  
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## 20 **10. Lactate: waste or recycling?**

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24 Lactate has been considered for a long time as an end-product of anaerobic  
25 glycolysis, without any metabolic interest and deleterious at high concentration. Now, it is  
26 proposed as an essential energy substrate especially for neurons <sup>156</sup>. Then, major  
27 discoveries have shift lactate from waste molecules to key energetic substrate, including  
28 the characterization of monocarboxylate transporter (MCT) at the membrane of cells and  
29 of mitochondria <sup>157</sup>, and then MCT colocalization with the mitochondrial lactate  
30 dehydrogenase characterizing an oxidative mitochondrial complex <sup>158</sup>. Cumulative results  
31 about lactate oxidation have paved the way to the study of lactate as energy substrate  
32 and of lactate shuttle inside cell between organelles and between cells <sup>159</sup>. Indeed, lactate  
33 can be produced and released by cells and absorbed by others nearby or at a distance  
34 as lactate can shuttle between tissues and blood and vice versa. Of course, this is true in  
35 brain, where a lactate shuttle between neuron and glial cells has long been suspected <sup>160</sup>.  
36 This exchange has also been demonstrated between glial cells <sup>72</sup> and more recently  
37 between neurovascular endothelial cells and pericytes <sup>80</sup>. In addition of its energetic role,  
38 lactate emerged as signalling molecule able to activate receptor or modify proteins by  
39 binding lysine residue. This lactylation described for its involvement in histone activity <sup>161</sup>,  
40 could be of interest in stroke as it seems involved in cell viability <sup>162</sup> and astrocyte  
41 inflammatory phenotype <sup>163</sup> during stroke. Lactate is therefore an important energy  
42 substrate and signalling molecule, which is increasingly being incorporated into research  
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3 into brain pathophysiology <sup>156, 164</sup>. It is also important to note that blood lactate is not the  
4 preferential source of lactate for brain cell metabolism, as its uptake through BBB is  
5 relatively low in physiological conditions. This uptake increases only after BBB disruption  
6 or stress conditions <sup>165</sup>, suggesting that the main source of lactate used by brain cells is  
7 likely derived from glycolysis of their neighboring cells.  
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12 The demonstration of a deleterious effect of glucose infusion after stroke was  
13 deleterious <sup>122</sup> redirected attention the putative role of lactate during brain oxygen and  
14 glucose deprivation. Interesting results obtained in a rodent model of stroke revealed a  
15 significant neuroprotective effect of lactate <sup>166</sup>. Indeed, post-ischemic intracerebral or  
16 intravenous lactate injections resulted in reduced infarct size and better neurological  
17 outcomes. Subsequently, several studies in human have demonstrated the benefits of  
18 lactate infusion after traumatic brain injury <sup>25</sup>, that beneficial role of lactate was also  
19 validated in a clinical trial <sup>24</sup>.  
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27 Studies on neonatal ischemia, a leading cause of perinatal mortality and disability,  
28 reveal key molecular insights into lactate-induced neuroprotection. Firstly, injection of  
29 lactate after ischemia injury in new-born rat provided effective neuroprotection, even  
30 better compared to pre-treatment <sup>167</sup>. Secondly, only the injection of lactate, but not  
31 glucose or pyruvate, resulted in damage size reduction. Finally, the positive effect of  
32 lactate was blunted upon co-injection of oxamate, an LDH inhibitor. Since LDH is an  
33 enzyme converting lactate into pyruvate to fuel the mitochondria, it demonstrated that  
34 lactate-induced neuroprotection was related to its metabolic use <sup>167</sup>.  
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41 Altogether, these studies illustrate the increased interest in lactate for stroke  
42 treatment and more generally brain injury associated to hypoxia/ischemia events.  
43 Nevertheless, there may be a downside to the effect of lactate that is related to its use as  
44 energetic substrate in neurons, an event leading to elevated ROS production at the time  
45 of reperfusion. LDH activity due to forced availability of lactate may result in glycolysis  
46 inhibition and a shift of glucose to the PPP. This could allow an increase in GSH  
47 production balancing the antioxidant defense of the cells, or at the opposite an increase  
48 in NOX2-dependant ROS production. Investigations need to be engaged to clearly define  
49 the role of glucose in the case of lactate injection.  
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## **11. Neuroprotection targeting glucose metabolism.**

Recent advances highlight cell metabolism as key to stroke therapy. Glucose plays a central role in both injury and recovery, making each element involved in its metabolic pathways prime targets for intervention. Decades of research on brain glucose metabolism and ischemic injury have outlined crucial features for developing effective treatments. Concurrently, it is imperative firstly to minimize energy expenditure by brain cells during ischemia, thereby averting the production of ROS and reactive nitrogen species (RNS). Secondly, during reperfusion, it is imperative to reactivate PPP and augment lactate production by glial cells. Although the infusion of lactate represents a promising advancement in stroke medical care, it falls short in preventing injury arising from ischemia.

In the context where there is currently no approach capable of simultaneously protecting against lesions and the repercussions of reperfusion, there is a growing interest in novel pharmacological strategies targeting glucose metabolism. These emerging approaches, highlighted in preclinical studies and underscoring the ongoing efforts to explore and address the challenges and perspectives of targeting glucose metabolism for therapeutic opportunities in the context of stroke management, are the subject of a detailed chapter in the Online-Only Supplement.

## **12. Conclusion**

Despite impressive progress in understanding ischemia-induced cell death, including neuronal death, the development of clinically effective neuroprotective or even anti-ischemic agents for stroke patients remains a challenge. Stroke affects several mechanisms of cellular homeostasis, and disruption of glucose metabolism remains a central event in the alteration of cellular function leading to cell death.

The different chapters of this review underlined that momentum is building in the field with compelling demonstrations that targeting glucose homeostasis in the ischemic brain would be an excellent therapeutic strategy for stroke. While the observations presented in this review indicate that cerebral energy metabolism in the normal and

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3 ischemic brain involves more complex cellular and molecular mechanisms than previously  
4 thought, they also identify a list of elements that could be, or already are, the subject of  
5 therapeutic research.  
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8 Hence, at the cellular level, it is important not to underestimate the potential of  
9 astrocytes and microglia in mitigating the impact of stroke. At the subcellular level,  
10 targeting mitochondria may emerge as a pivotal therapeutic strategy for preventing ROS-  
11 induced damage following an ischemic insult. At the molecular level, exploring the  
12 enzymes and metabolites associated with glucose metabolism presents promising  
13 therapeutic avenues. Furthermore, a substantial portion of metabolic investigations in  
14 brain cells have been conducted on dissociated populations, lacking the intricate  
15 interconnection and diversity of cell lineages observed in vivo, which adapt their function  
16 and metabolism in response to external signals. There is a compelling need for concerted  
17 efforts to enhance the relevance of in vitro studies, thereby uncovering new shared  
18 mechanisms of interest. Therefore, we firmly believe that concerted efforts are essential  
19 to improve the relevance of in vitro studies, to reveal new common mechanisms of  
20 interest.  
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30 Certainly, additional mechanisms contribute to stroke injury and should be regarded  
31 as potential therapeutic targets to improve stroke outcomes. Notably, two of these  
32 mechanisms are linked to cellular energy metabolism, namely inflammation and  
33 mitochondrial dynamics <sup>168</sup>. Nevertheless, the mechanisms delineated in our review,  
34 along with those additional factors, exhibit interconnections, and several of the highlighted  
35 therapeutic targets above exert an impact across all these interconnected processes.  
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41 We hope this review inspires metabolism specialists to reengage in stroke research,  
42 refining molecular insights and therapeutic possibilities while advancing stroke  
43 pathophysiology knowledge and optimizing the search for novel treatments.  
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## 50 **Acknowledgements**

51 DFP is funded by Agence Nationale de la Recherche (ANR-19-CE18-0029 KIRI; ANR-23-  
52 CE18-0006 MOMI) and « Société Francophone du Diabète » (2022). DFP and NB were  
53 supported by CNRS and the French Government for the "Investments for the Future"  
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3 LabEx ICST #ANR-11 LabEx 0015". The authors thank Drs. Tauc, Rovère, Heurteaux,  
4 and Mazella and all our past and present team members and collaborators for continuous  
5 discussion about metabolism and ischemia/reperfusion.  
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### 10 **Conflict of interest**

11 The authors declare no conflict of interest.  
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## **Figure legends**

**Figure 1. Schematization of Glycolysis and Pentose phosphate pathways.** Enzymes involved in the different reactions are displayed in green, adenosine phosphate co-reactions in red and nicotinamide factors in blue. TCA, tricarboxylic acid cycle; MPC, mitochondrial pyruvate carrier. ATP, adenosine triphosphate; ADP, adenosine diphosphate; NADH/NAD<sup>+</sup>, Nicotinamide adenine dinucleotide reduced/oxidized; NADPH/NADP<sup>+</sup>, Nicotinamide adenine dinucleotide phosphate reduced/oxidized.

**Figure 2. Glucose metabolism in neuron and cooperative metabolic pathways with astrocyte.** Main pathways are differentiated by colours: glycolysis in orange, lactate metabolism in yellow, glutaminolysis in green, glutathione metabolism in blue. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MCT, monocarboxylate transporter; LDH, lactate dehydrogenase; GLUT, glucose transporter; PPP, pentose phosphate pathway; GR, glutathione reductase; GPx, glutathione peroxidase; GSH, glutathione; GSSG, oxidized glutathione; GS, glutathione synthetase;  $\gamma$ GCS, gamma-glutamylcysteine synthetase; ApN, aminopeptidase N;  $\gamma$ GT, gamma-glutamyl transpeptidase; GLS, glutamine synthetase; GluD, glutamate dehydrogenase;  $\alpha$ KG, alpha-ketoglutarate; GABA, gamma aminobutyric acid; MPC, mitochondrial pyruvate carrier; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle; ETC, electron transport chain. EAAT, excitatory amino acid transporter; CysGly, cysteine-glycine; ATP, adenosine triphosphate; ADP, adenosine diphosphate; NADH/NAD<sup>+</sup>, Nicotinamide adenine dinucleotide reduced/oxidized; NADPH/NADP<sup>+</sup>, Nicotinamide adenine dinucleotide phosphate reduced/oxidized; FADH<sub>2</sub>/FAD<sup>+</sup>, flavin adenine dinucleotide reduced/oxidized; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; Pi, inorganic phosphate.

**Figure 3. Difference in neuron glucose metabolism during ischemia and reperfusion situation.** Main modifications in metabolism pathways are indicated as well as main sources of reactive oxygen species production (in red) and antioxidant pathways (in blue). GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MCT, monocarboxylate transporter; LDH, lactate dehydrogenase; GLUT, glucose transporter; PPP, pentose

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3 phosphate pathway; GR, glutathione reductase; GPx, glutathione peroxidase; GSH,  
4 glutathione; GSSG, oxidized glutathione; MPC, mitochondrial pyruvate carrier; PDH,  
5 pyruvate dehydrogenase; TCA, tricarboxylic acid cycle; ETC, electron transport chain;  
6  
7 SOD, superoxide dismutase; AK, adenylate kinase; XOR, xanthine oxidoreductase; XDH,  
8 xanthine dehydrogenase; NOX, nicotinamide adenine dinucleotide phosphate oxidase;  
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10 ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine  
11 monophosphate; NADH/NAD<sup>+</sup>, Nicotinamide adenine dinucleotide reduced/oxidized;  
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13 NADPH/NADP<sup>+</sup>, Nicotinamide adenine dinucleotide phosphate reduced/oxidized;  
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15 FADH<sub>2</sub>/FAD<sup>+</sup>, flavin adenine dinucleotide reduced/oxidized; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide;  
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17 Pi, inorganic phosphate; O<sub>2</sub><sup>-</sup>, superoxide anion; OH<sup>-</sup>, hydroxyl radical.  
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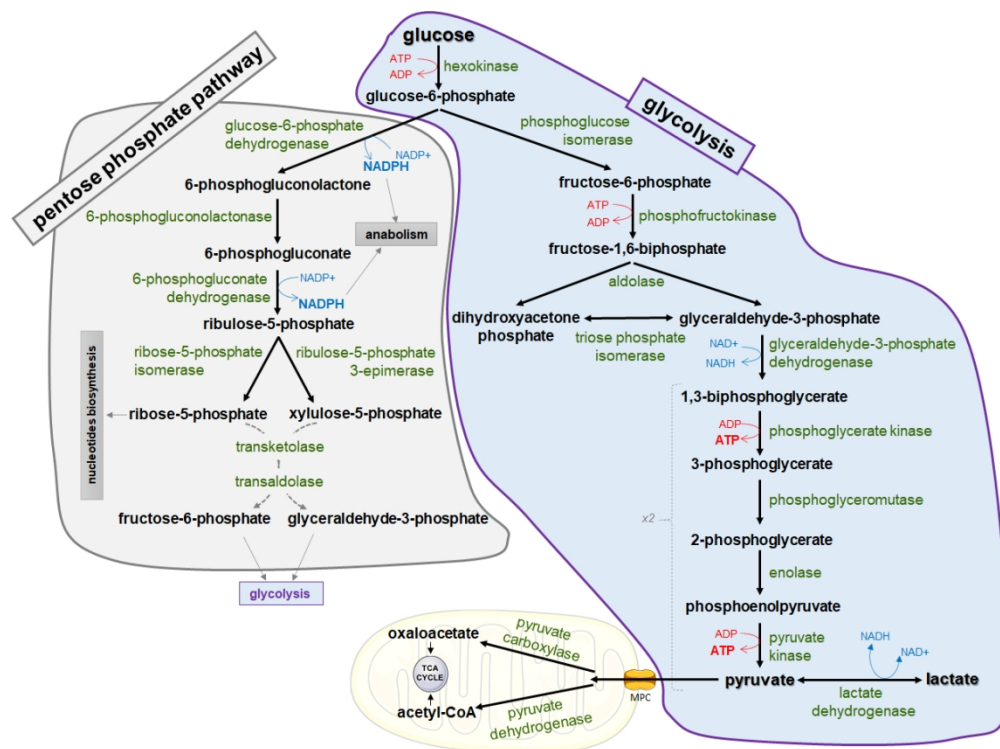


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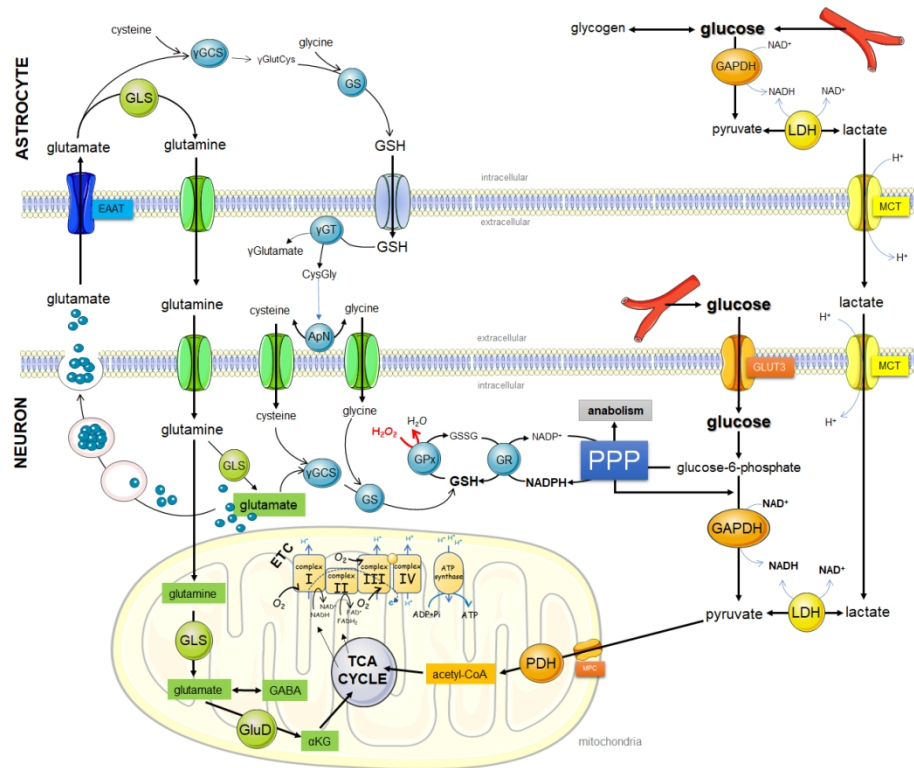


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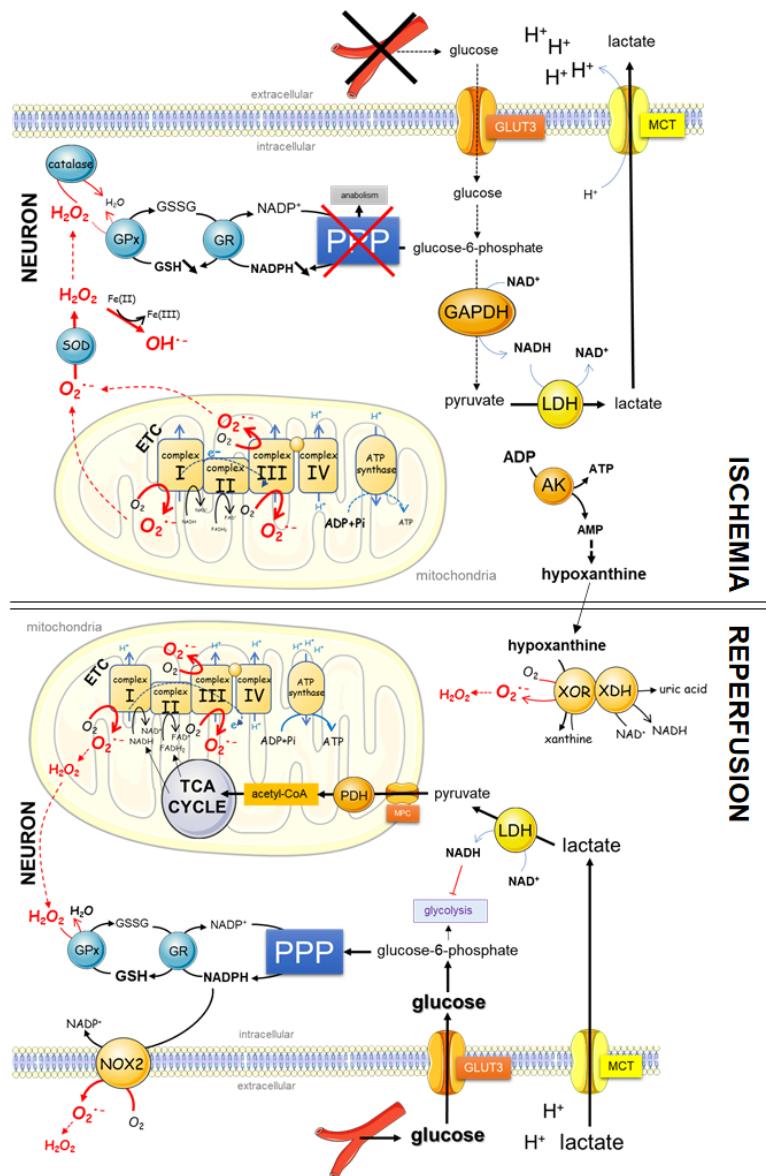


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