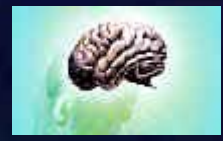
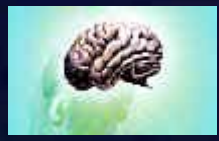


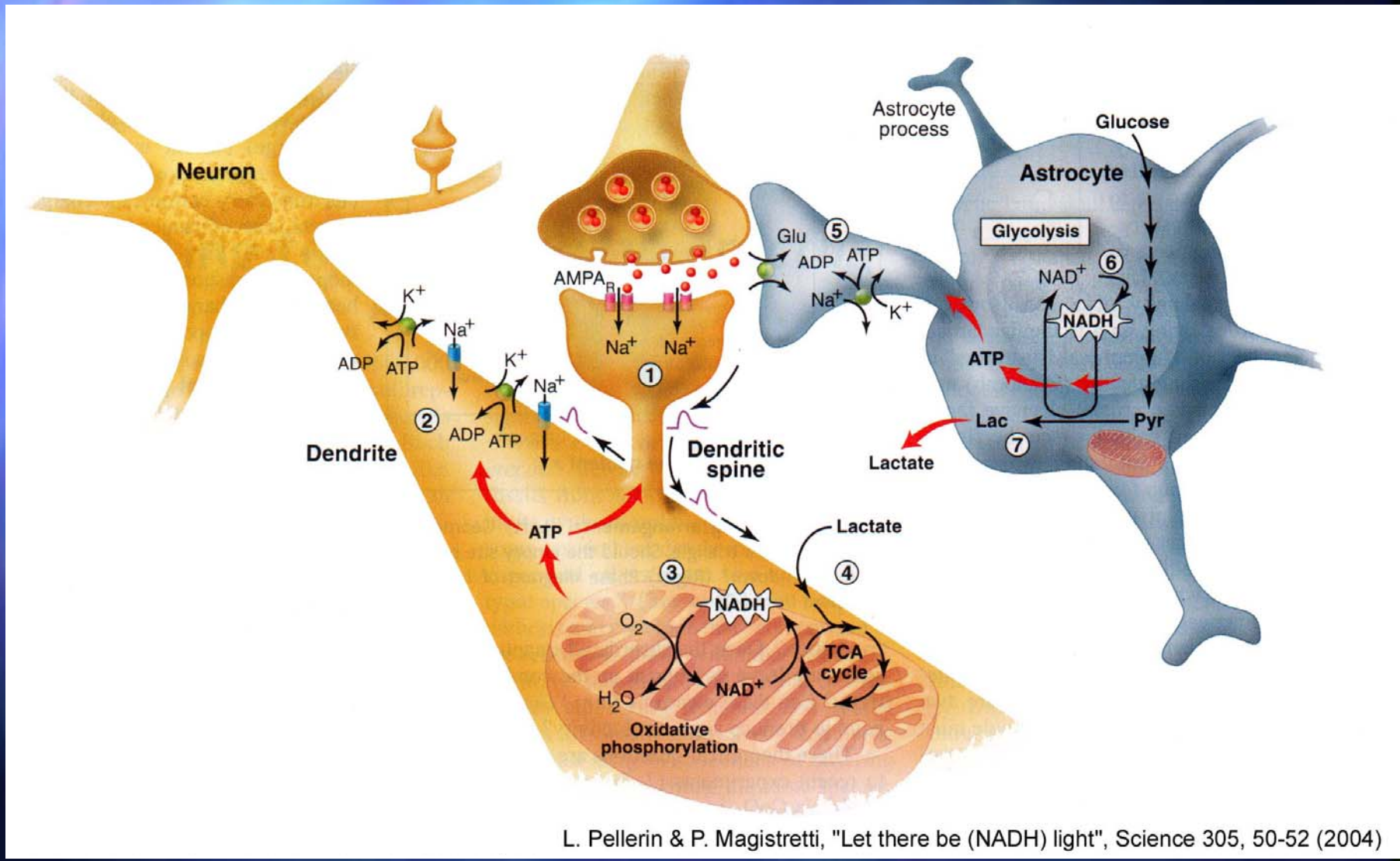
Constantes de temps différentes pour
l'activité synaptique et la réponse métabolique

Rôle de l'espace extracellulaire comme
tampon spatial et temporel

A unifying model for neurometabolic coupling[1,2]

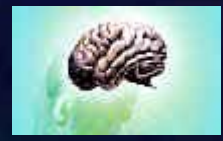


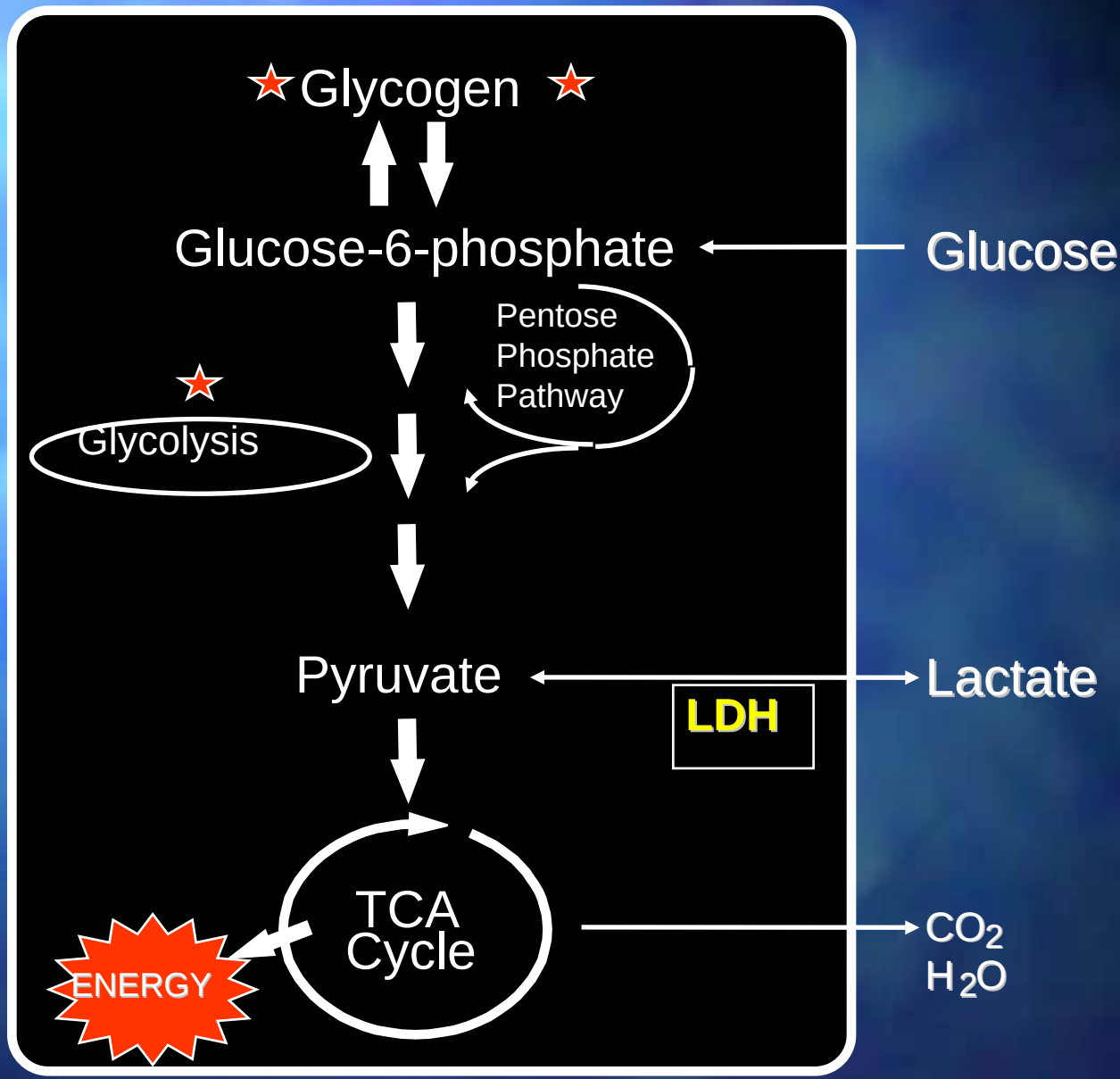
Early oxidative metabolism in neurons is sustained by late activation of glycolysis in astrocytes.



L. Pellerin & P. Magistretti, "Let there be (NADH) light", Science 305, 50-52 (2004)

Principales voies métaboliques du glucose





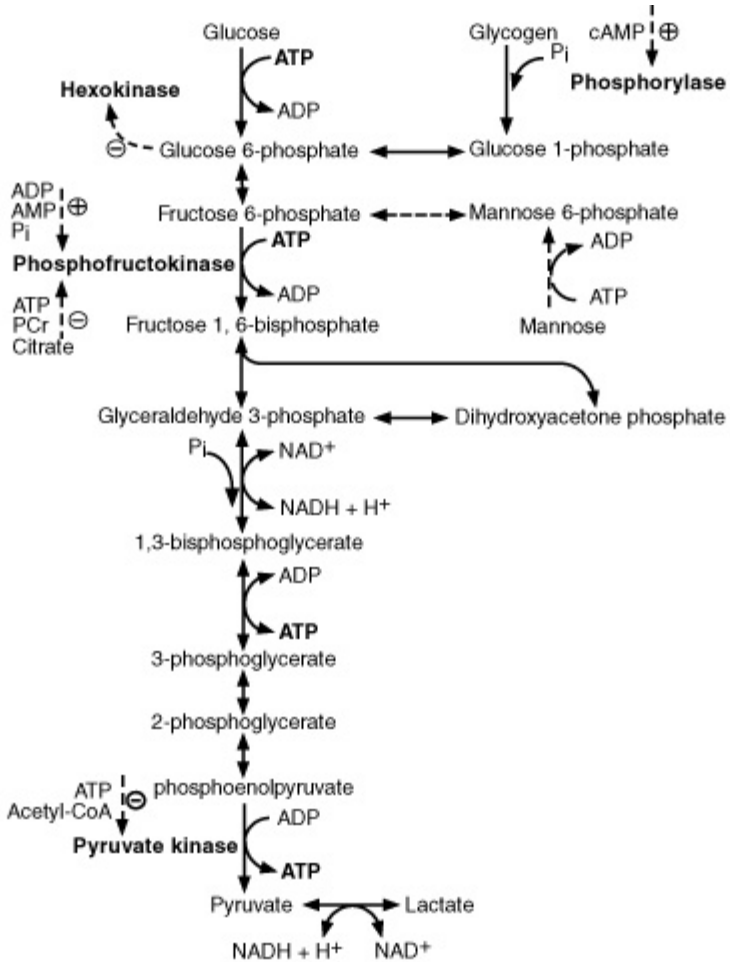


FIGURE 3.1 Glycolysis (Embden–Meyerhof pathway). Glucose phosphorylation is regulated by hexokinase, an enzyme inhibited by glucose 6-phosphate. Glucose must be phosphorylated to glucose 6-phosphate to enter glycolysis or to be stored as glycogen. Two other important steps in the regulation of glycolysis are catalyzed by phosphofructokinase and pyruvate kinase. Their activity is controlled by the levels of high-energy phosphates as well as of citrate and acetyl-CoA. Pyruvate, through lactate dehydrogenase, is in dynamic equilibrium with lactate. This reaction is essential to regenerate NAD^+ residues necessary to sustain glycolysis downstream of glyceraldehyde 3-phosphate. PCr, phosphocreatine.

FROM MOLECULES TO NETWORKS John H. Byrne, James L. Roberts

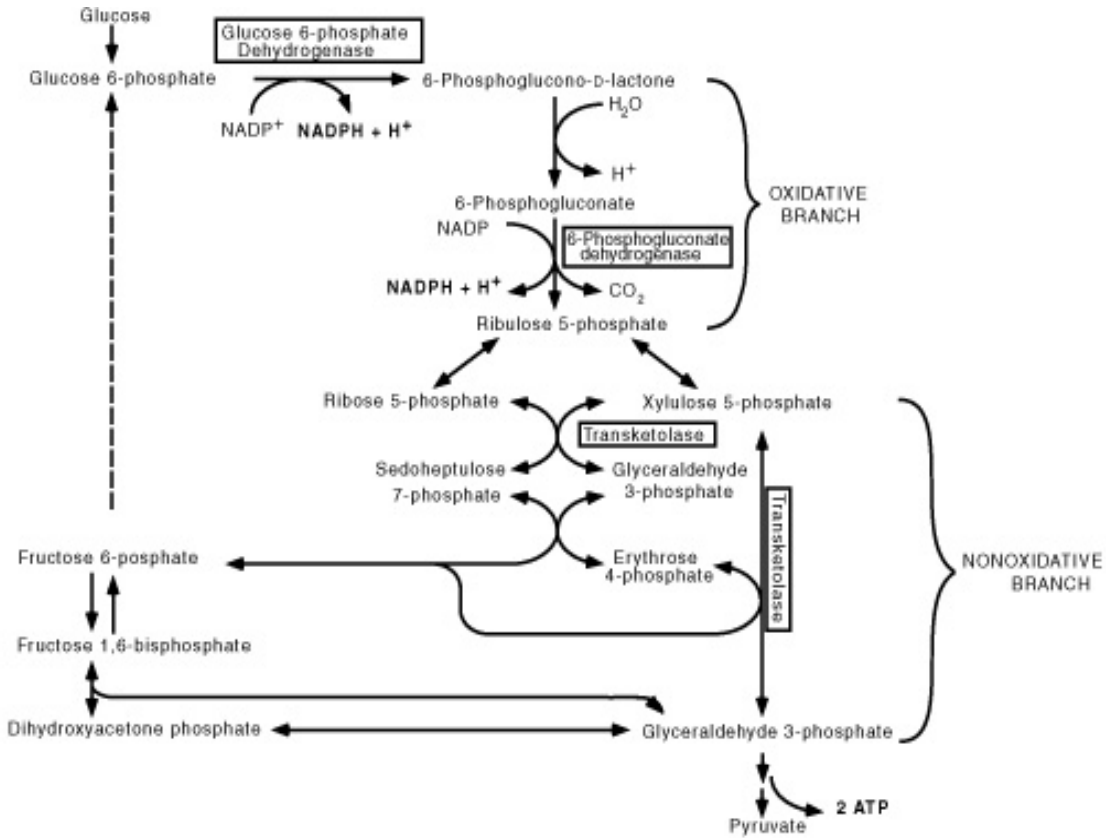


FIGURE 3.5 Pentose phosphate pathway. In the oxidative branch of the pentose phosphate pathway, two NADPH are generated per glucose 6-phosphate. The first, rate-limiting reaction of the pathway is catalyzed by glucose-6-phosphate dehydrogenase; the second NADPH is generated through the oxidative decarboxylation of 6-phosphogluconate, a reaction catalyzed by glucose-6-phosphogluconate dehydrogenase. The nonoxidative branch of the pentose phosphate pathway provides a reversible link with glycolysis, by regenerating the two glycolytic intermediates glyceraldehyde 3-phosphate and fructose 6-phosphate. This regeneration is achieved through three sequential reactions. In the first, catalyzed by transketolase, xylulose 5-phosphate and ribose 5-phosphate (which originate from ribulose 5-phosphate, the end product of the oxidative branch) yield glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate. Under the action of transaldolase, these two intermediates yield fructose 6-phosphate and erythrose 4-phosphate. The latter intermediate combines with glyceraldehyde 3-phosphate, in a reaction catalyzed by transketolase, to yield fructose 6-phosphate and glyceraldehyde 3-phosphate. Thus, through the nonoxidative branch of the pentose phosphate pathway, two hexoses (fructose 6-phosphate) and one triose (glyceraldehyde 3-phosphate) of the glycolytic pathway are regenerated from three pentoses (ribulose 5-phosphate).

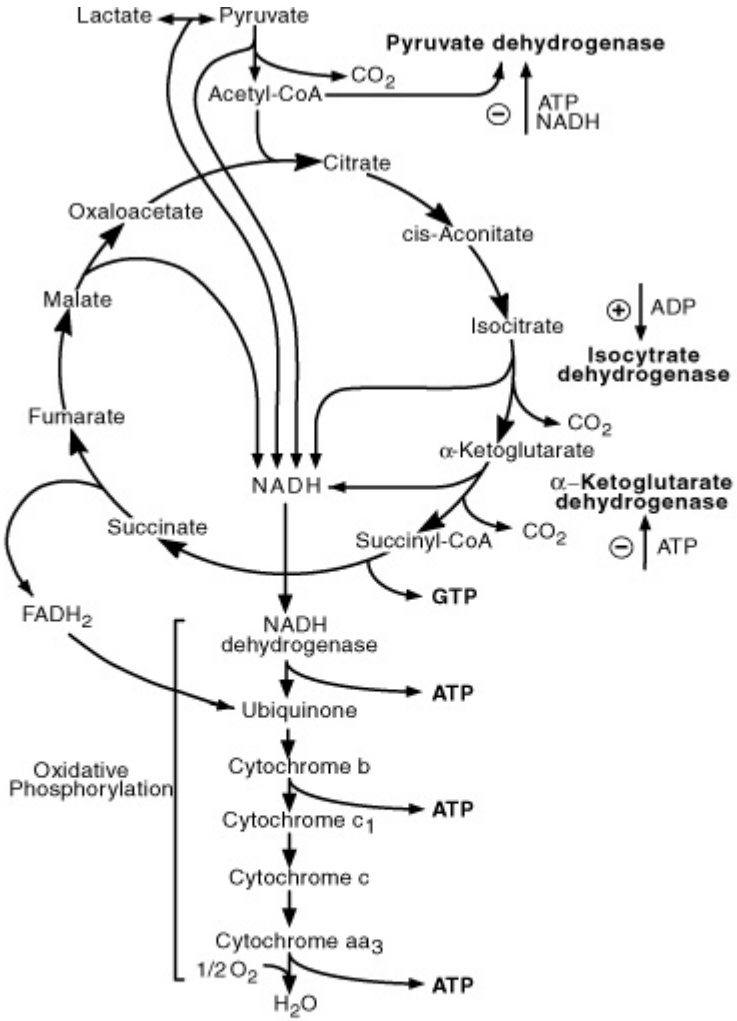


FIGURE 3.2 Tricarboxylic acid cycle (Krebs cycle) and oxidative phosphorylation. Pyruvate entry into the cycle is controlled by pyruvate dehydrogenase activity that is inhibited by ATP and NADH. Two other regulatory steps in the cycle are controlled by isocitrate and α-ketoglutarate dehydrogenases, the activity of which is controlled by the levels of high-energy phosphates.

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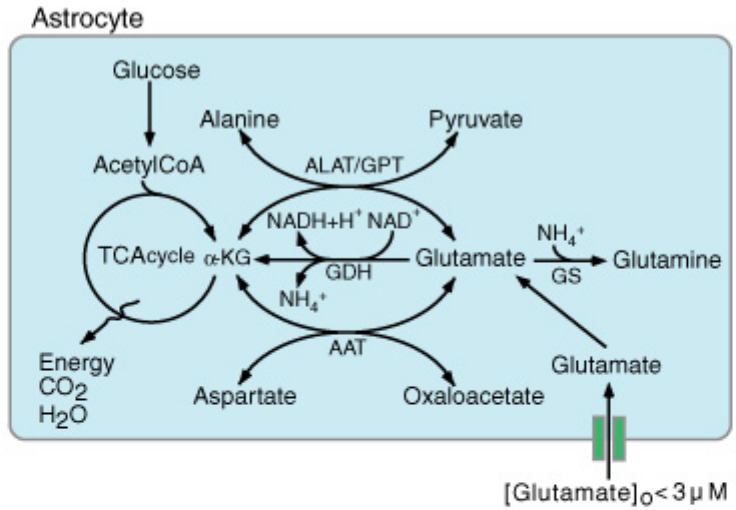

FIGURE 3.12 Metabolic fate of glutamate taken up by astrocytes. ALAT, alanine aminotransferase; GDH, glutamate dehydrogenase; GS, glutamine synthase; AAT, aspartate aminotransferase; GPT, glutamate dehydrogenase; α-KG, α-ketoglutarate.

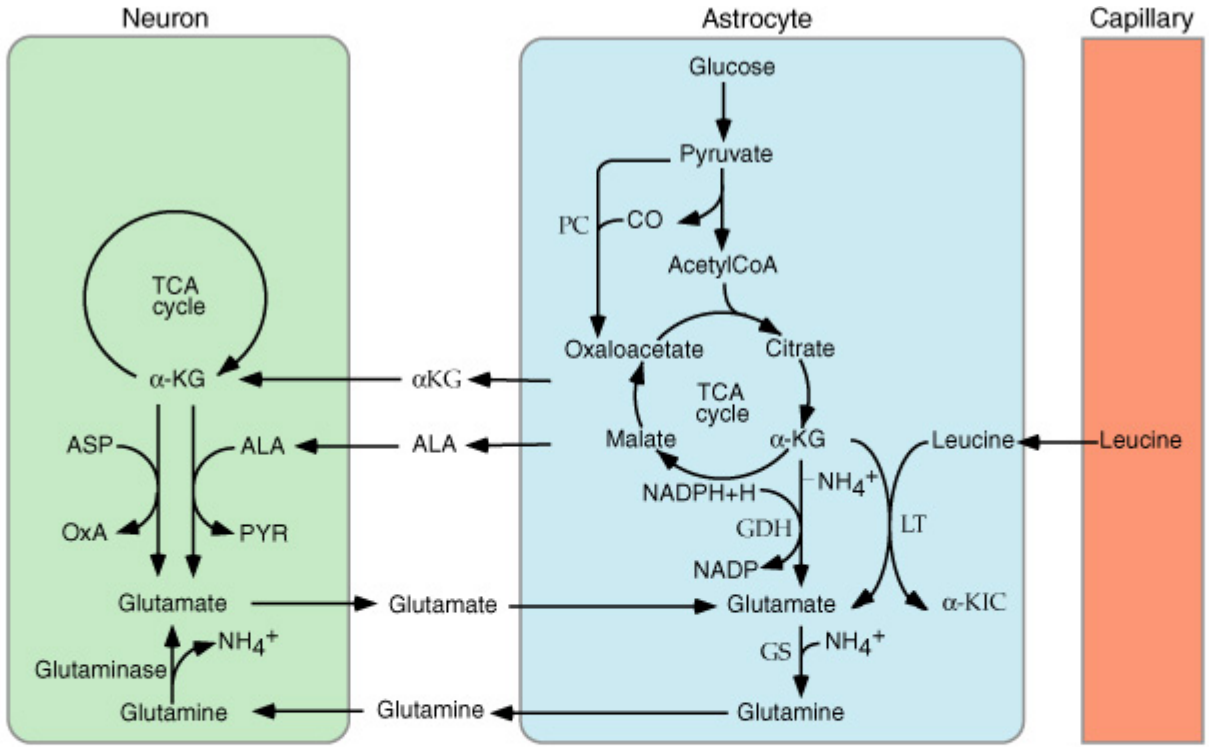

FIGURE 3.13 Metabolic intermediates are released by astrocytes to regenerate the glutamate neurotransmitter pool in neurons. Glutamine, formed from glutamate in a reaction catalyzed by glutamine synthase (GS), is released by astrocytes and taken up by neurons, which convert it into glutamate under the action of glutaminase. GS is an enzyme selectively localized in astrocytes. This metabolic cycle is referred to as the glutamate–glutamine shuttle. Other, quantitatively less important sources of neuronal glutamate are lactate, alanine, and α-ketoglutarate (α-KG). In astrocytes, glutamate is synthesized *de novo* from α-KG in a reaction catalyzed by glutamate dehydrogenase (GDH). The carbon backbone of glutamate is exported by astrocytes after conversion into glutamine under the action of GS; the conversion of leucine into α-ketoisocaproate (α-KIC), catalyzed by leucine transaminase (LT), provides the amino group for the synthesis of glutamine from glutamate. The carbons "lost" from the TCA cycle as α-KG is converted into glutamate are replenished by oxaloacetate (OxA) formed from pyruvate in a reaction catalyzed by pyruvate carboxylase (PC), another astrocyte-specific enzyme.

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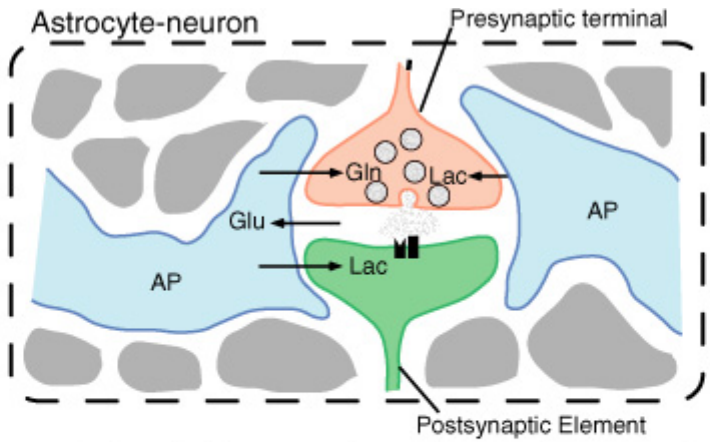

FIGURE 3.14 The astrocyte–neuron metabolic unit. Glutamatergic terminals and the astrocytic processes that surround them can be viewed as a highly specialized metabolic unit in which the activation signal (glutamate) is furnished by the neuron to the astrocyte, whereas the astrocyte provides the precursors needed to maintain the neurotransmitter pool (glutamine, lactate, alanine), as well as the energy substrate (lactate). AP, astrocyte process.

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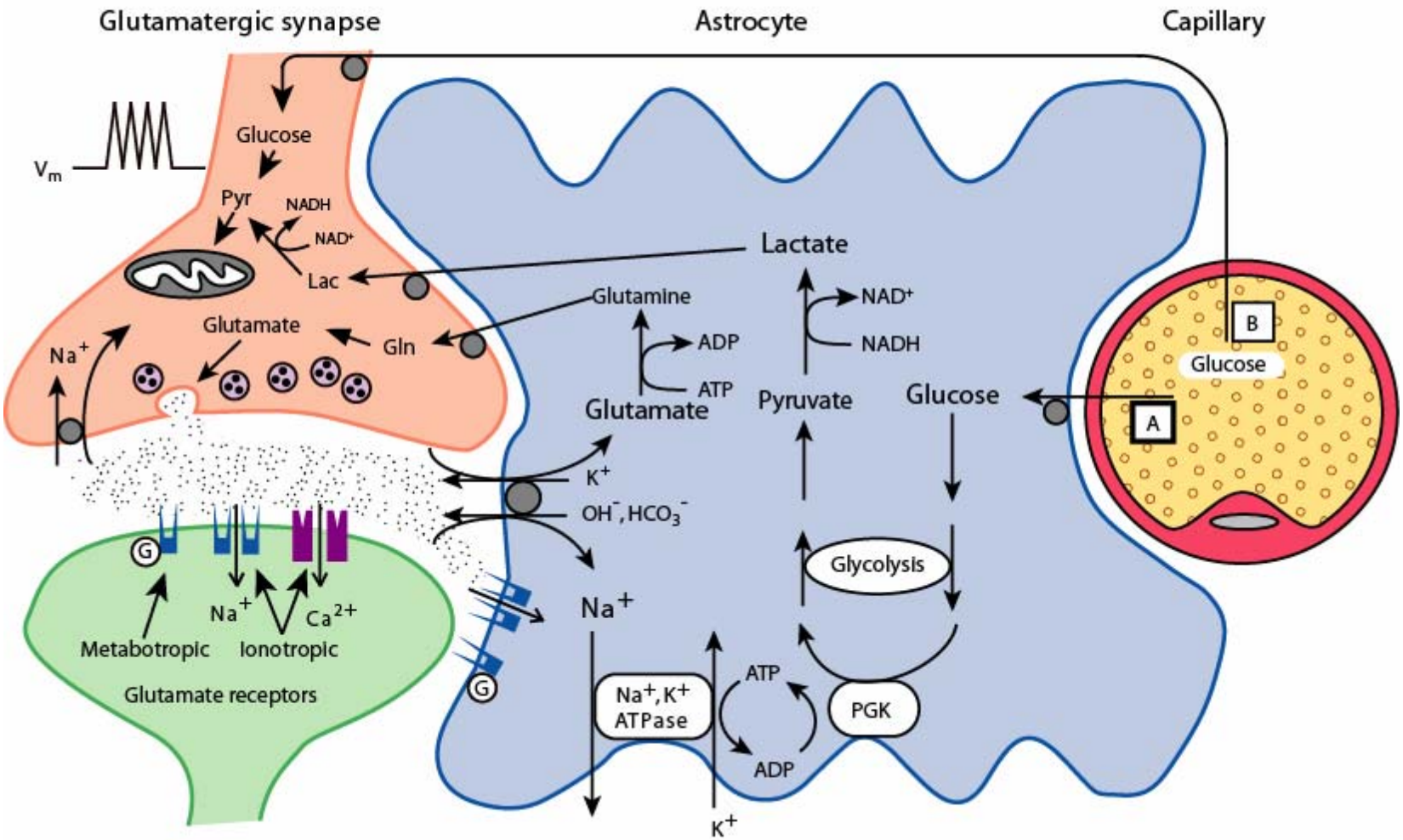
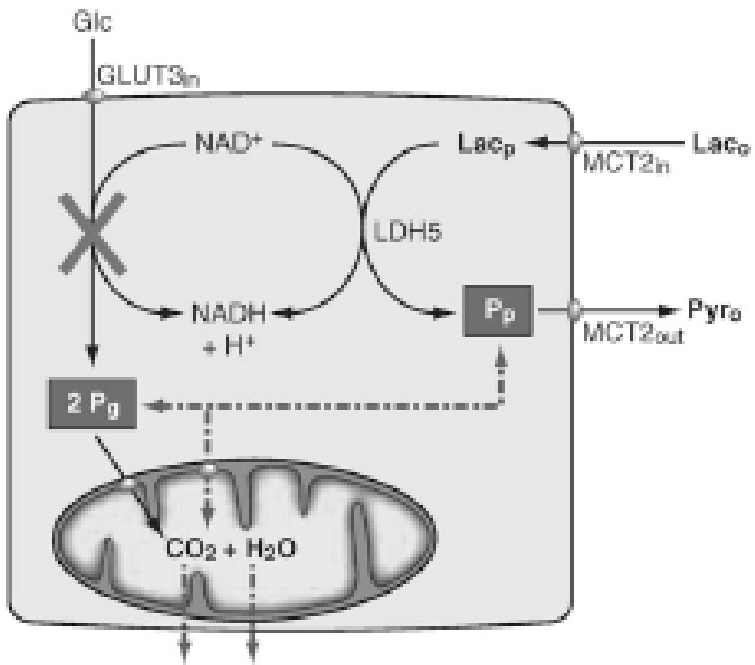

Glutamatergic synapse
Astrocyte
Capillary
V_m
Glucose
Pyr
NADH
NAD+
Lac
Lactate
Glutamine
ADP
ATP
Glutamate
Pyruvate
NAD+
NADH
Glucose
B
Glucose
A
Na+
Glutamate
Gln
K+
OH-, HCO3-
G
Na+
Ca2+
Metabotropic
Ionotropic
Glutamate receptors
Glycolysis
Na+
Na+, K+ ATPase
ATP
ADP
PGK
K+

Deux compartiments de pyruvate neuronal

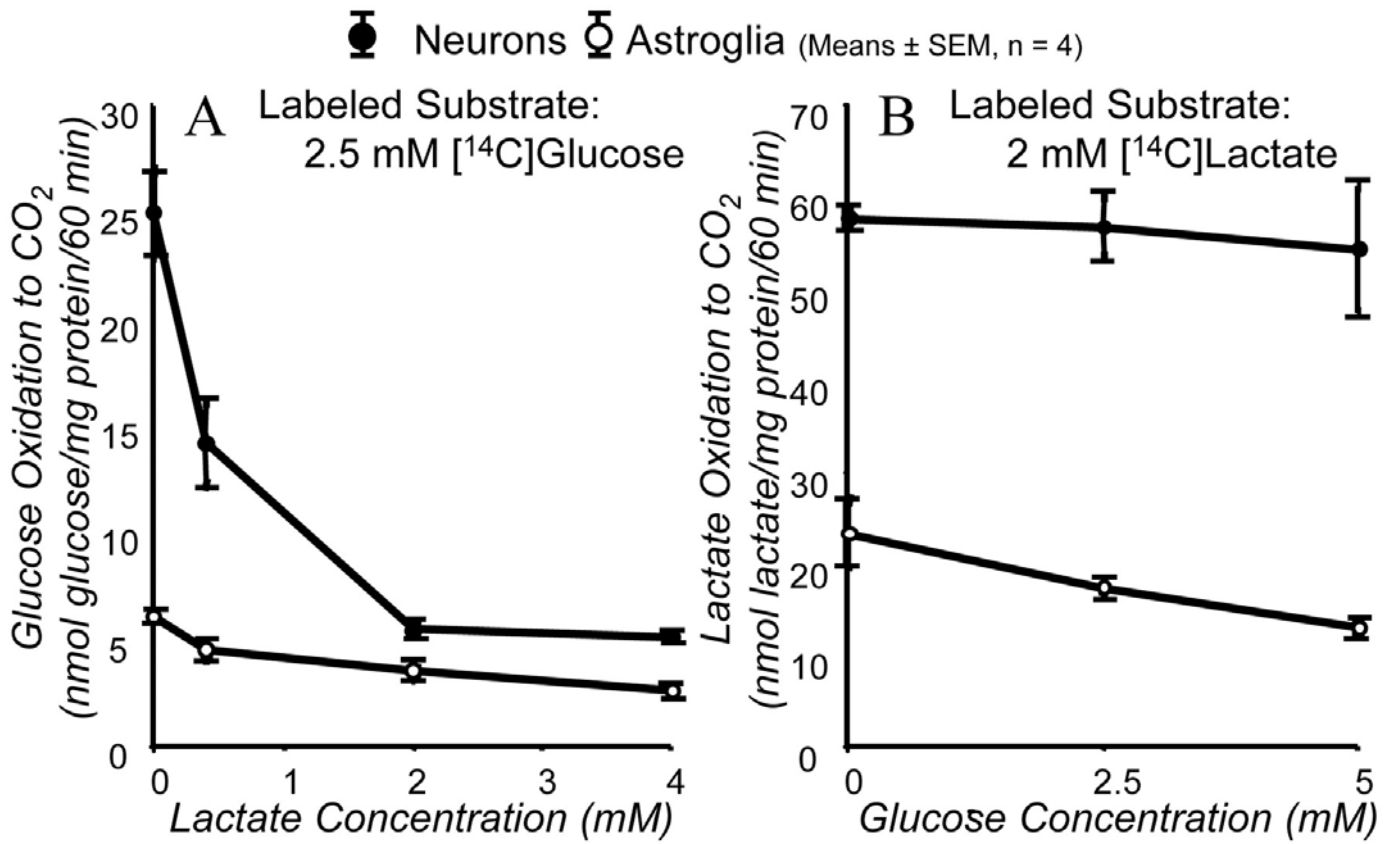


Cerdan et al. 2006

TABLE I. Apparent Kinetic Constants of Glucose and Lactate Consumption in Primary Cultures of Cortical Neurons in the Absence and Presence of the Corresponding Competitive Substrate

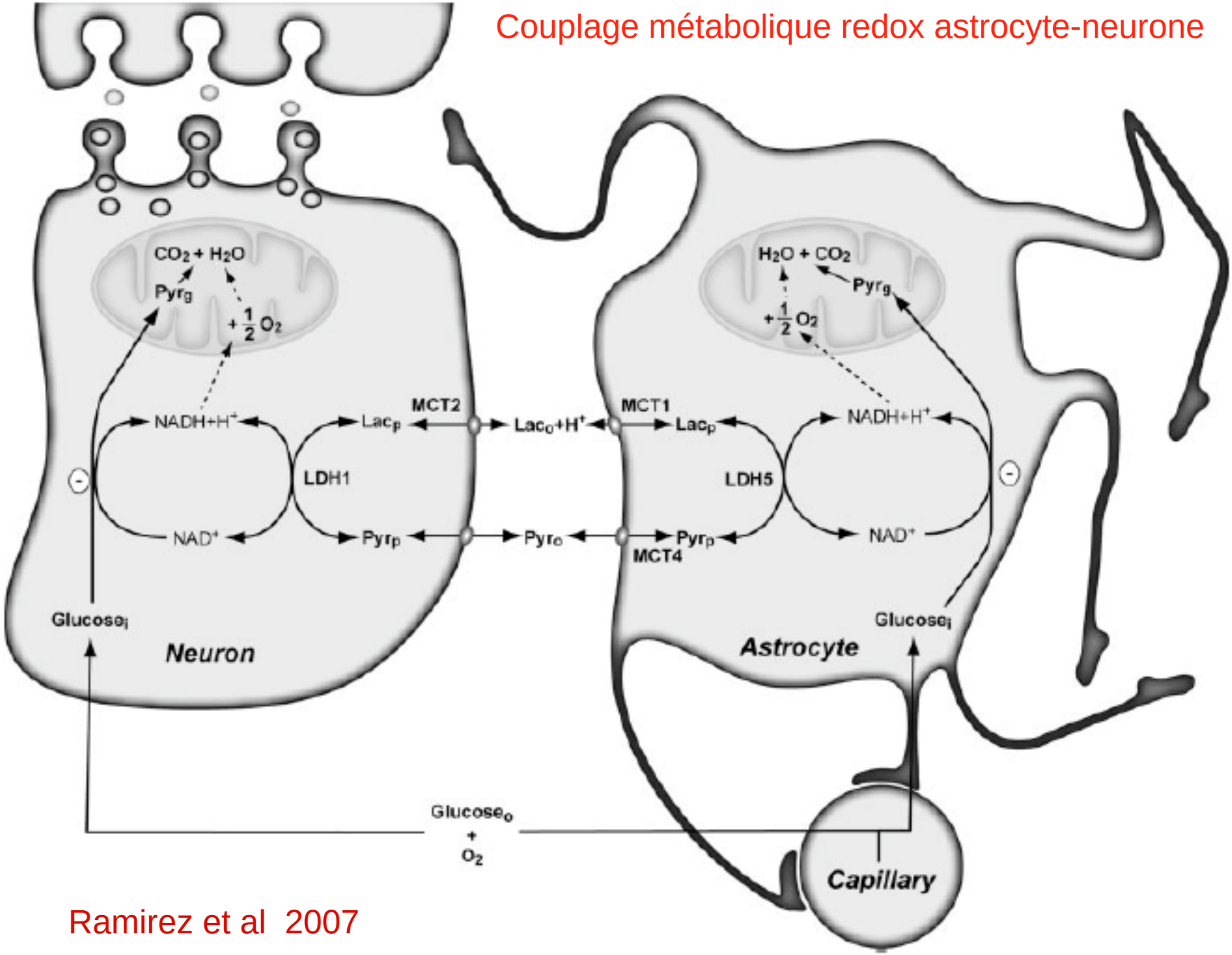
Process	Incubation condition	K_m (mM)[a]	V_{max} (nmol/mg/hr)[a]	K_i (mM)[b]
Glucose consumption	Glucose 0.25–5 mM	2.2 ± 0.2	600 ± 65	na
Glucose consumption in the presence of lactate	Glucose 0.25–5 mM and 5 mM lactate	3.6 ± 0.1	674 ± 54	3.6
Lactate consumption	Lactate 1–15 mM	7.8 ± 0.1	440 ± 3	na
Lactate consumption in the presence of glucose	Lactate 1–15 mM and 1 mM glucose	8.5 ± 0.1	451 ± 3	11.1

Ramirez et al, 2007



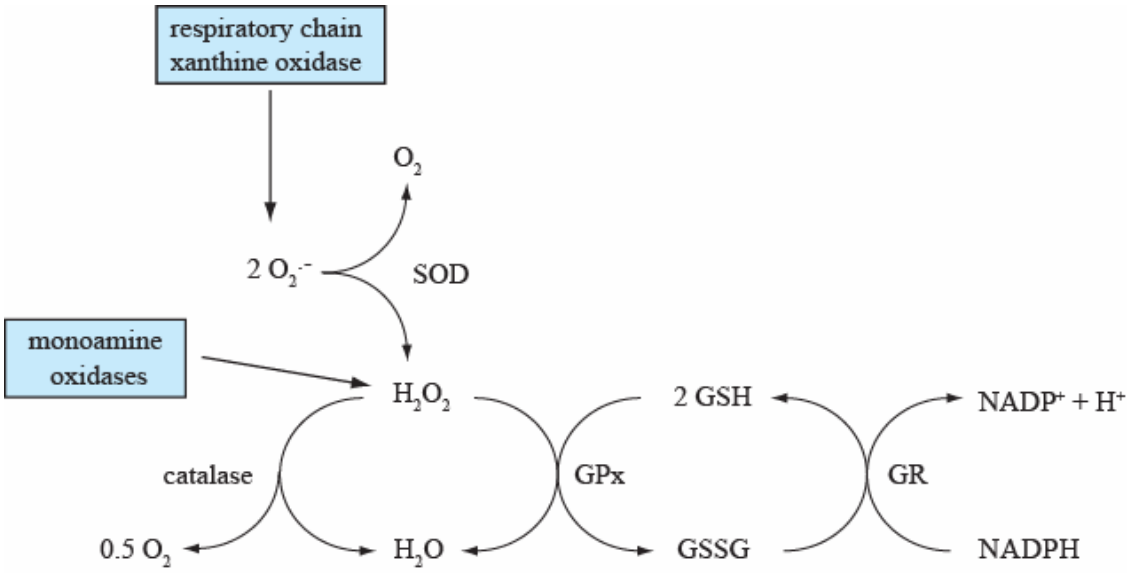
Itoh, Yoshiaki et al. (2003)

Couplage métabolique redox astrocyte-neurone

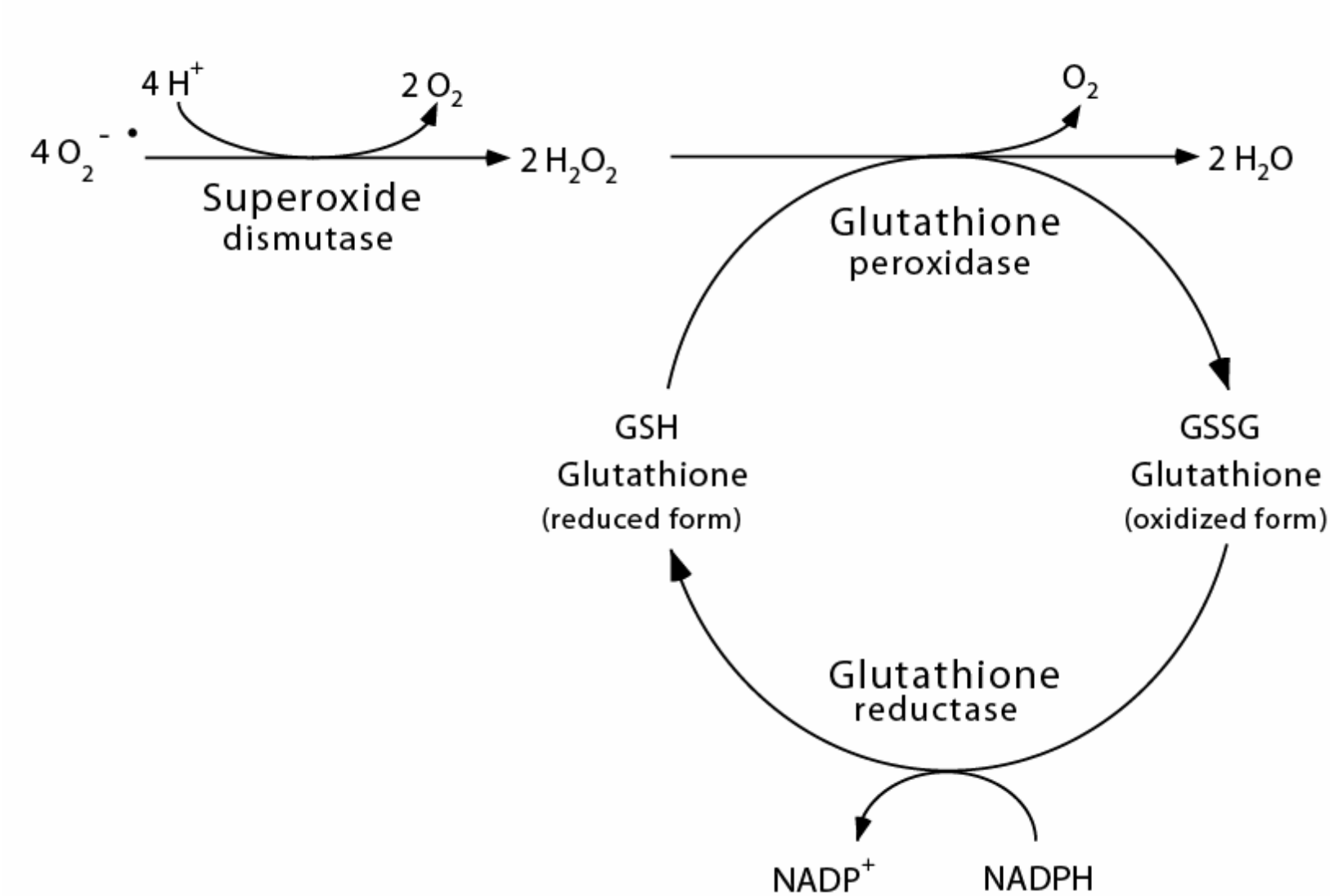


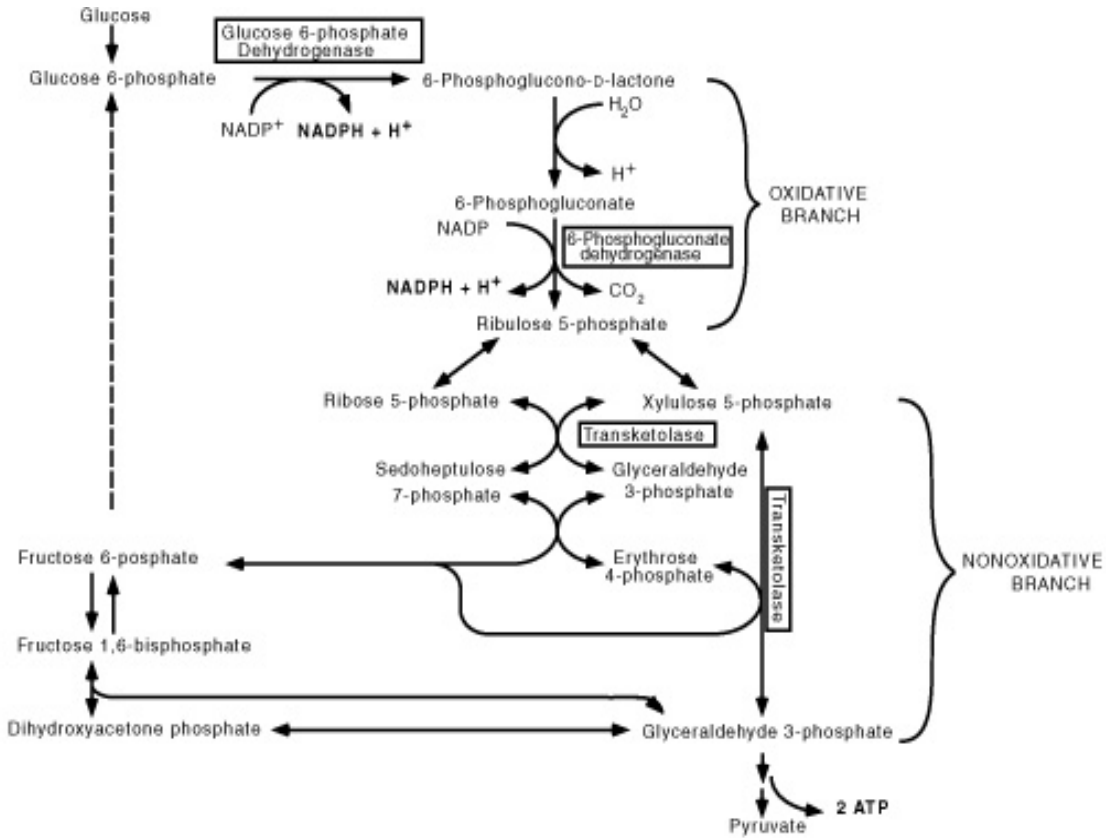
Ramirez et al 2007

Sources de radicaux libres et mécanisme de leur neutralisation



Rôle du glutathion et du NAPDH dans la neutralisation des radicaux libres





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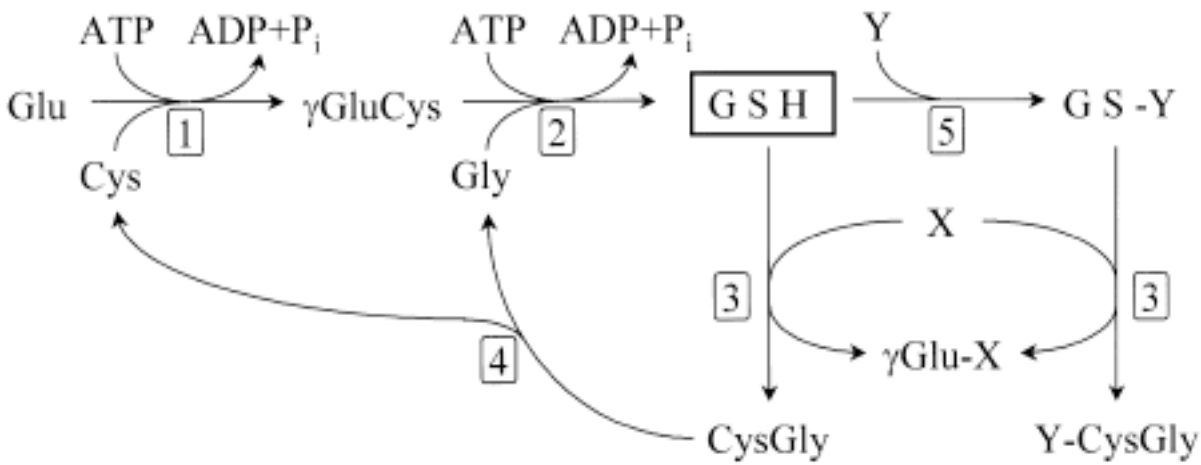
Voie de synthèse du glutathion



Couplage métabolique neurone-glie dans la synthèse du glutathion