Metabolism of the brain and Metabolic aspects of Neuron-Oligodendrocyte-Astrocyte interactions

Brain Energy

Most of what the brain does is accomplished by synaptic transmission between neurons, and by calling upon the information encoded by past transmissions across synapses.

The brain accomplishes this task with the help of a collection of parallel processing systems or neural networks.

The neural networks allow humans to accomplish three things:

- Think (cognition)
- Attach value to things (emotions)
- Set and achieve goals (motivation)

total energy cost: the brain uses 20% of the energy generated in the body.

Brain does not store energy

- The brain cells have no backup energy sources (except a small amount of glycogen in astrocytes) such as creatine phosphate (CP) that muscle cells have.
- Thus, the brain depends on the second supply of oxygen and glucose from the blood.

Energy metabolism in the brain

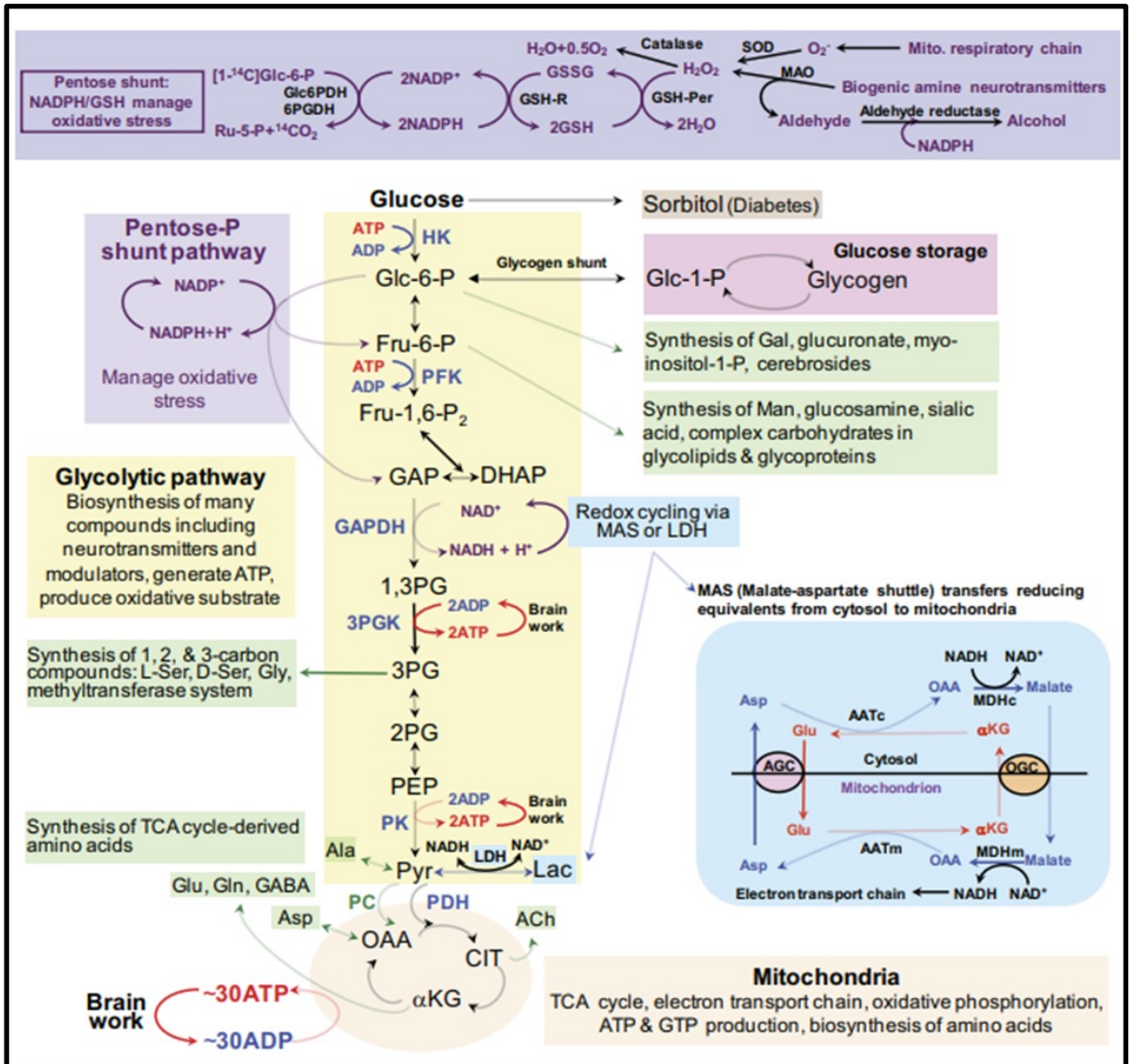
- **Continuous cerebral circulation is required to sustain brain function.**

Since the amount of O2 and glucose stored in the brain is extremely small compared with rates of utilization, the brain requires a continuous fuel supply from the circulation, and disruption of glucose or O2 delivery quickly leads to decrements in brain function and consciousness.

Glucose is the main obligatory substrate for energy metabolism in the adult brain

metabolism in the brain is highly compartmentalized; Over the past few decades, it has become quite clear that the metabolism of neurons and glial cells is interrelated and that these cells function in an integrated fashion. Several important enzymes, e.g., pyruvate carboxylase and glutamine synthetase, are selectively localized in astrocytes, and many transporters (e.g., for glucose, monocarboxylic acids, glutamate, and glutamine) are differentially distributed on neurons and glial cells

Glucose fulfills many critical roles for brain function, including that of a substrate for inositol biosynthesis and glycogen formation. Moreover, its carbon skeleton is incorporated into acetylcholine, lactate, glutamate, glutamine, aspartate, GABA, alanine, serine, glycine, and lipids).

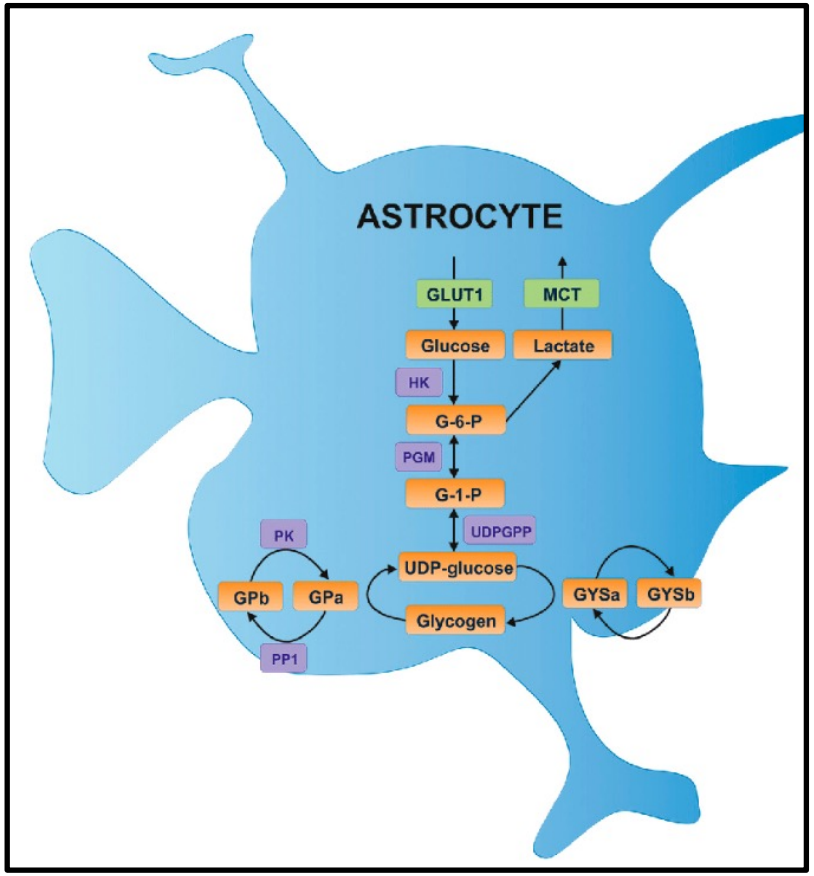


Glycogen is actively synthesized and degraded in astrocytes

- Brain glycogen concentration (6–12 μmol)
- glycogen is the only energy reserve in the brain.
- Glycogen and its enzymes are compartmentalized in adult human, where glycogen is located predominantly, but not exclusively, in astrocytes; in immature human, glycogen is found in both astrocytes and some neurons

- Glucose entry and glycogen formation in astrocytes.
- Glucose is transported via glucose transporter 1 (GLUT1) and possibly insulin-sensitive glucose transporter 4 (GLUT4).
- Glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate (G-6-P), which is subsequently converted to glucose-1-phosphate (G-1-P) by phosphoglucomutase (PGM) and then to (Uridine diphosphate glucose)UDP glucose by UDP glucose pyrophosphate (UDPGPP).
- The UDP glucose continues to glycogen synthesis via the actions of glycogen synthase (GYS), which can exist in two forms:

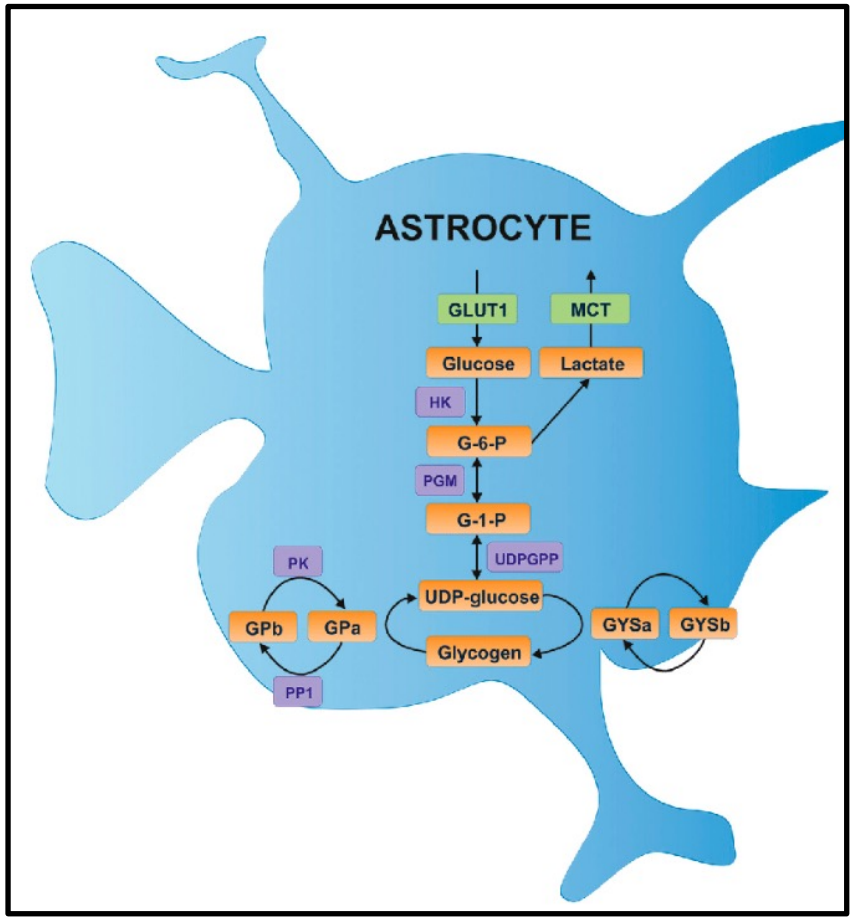
the active phosphorylated form (GYSa) or the inactive dephosphorylated form (GYSb).



- Protein phosphatase 1 (PP1) converts GYSb to active GYSa via the regulatory subunit Protein Targeting to Glycogen (PTG), resulting in glycogen formation.
- Glycogen is broken down by glycogen phosphorylase (GP), which similar to glycogen synthase exists in two forms:

the active phosphorylated form(GPa), or the inactive dephosphorylated form (GPb). Phosphorylase kinase (PK) dephosphorylates GPb to the active form.

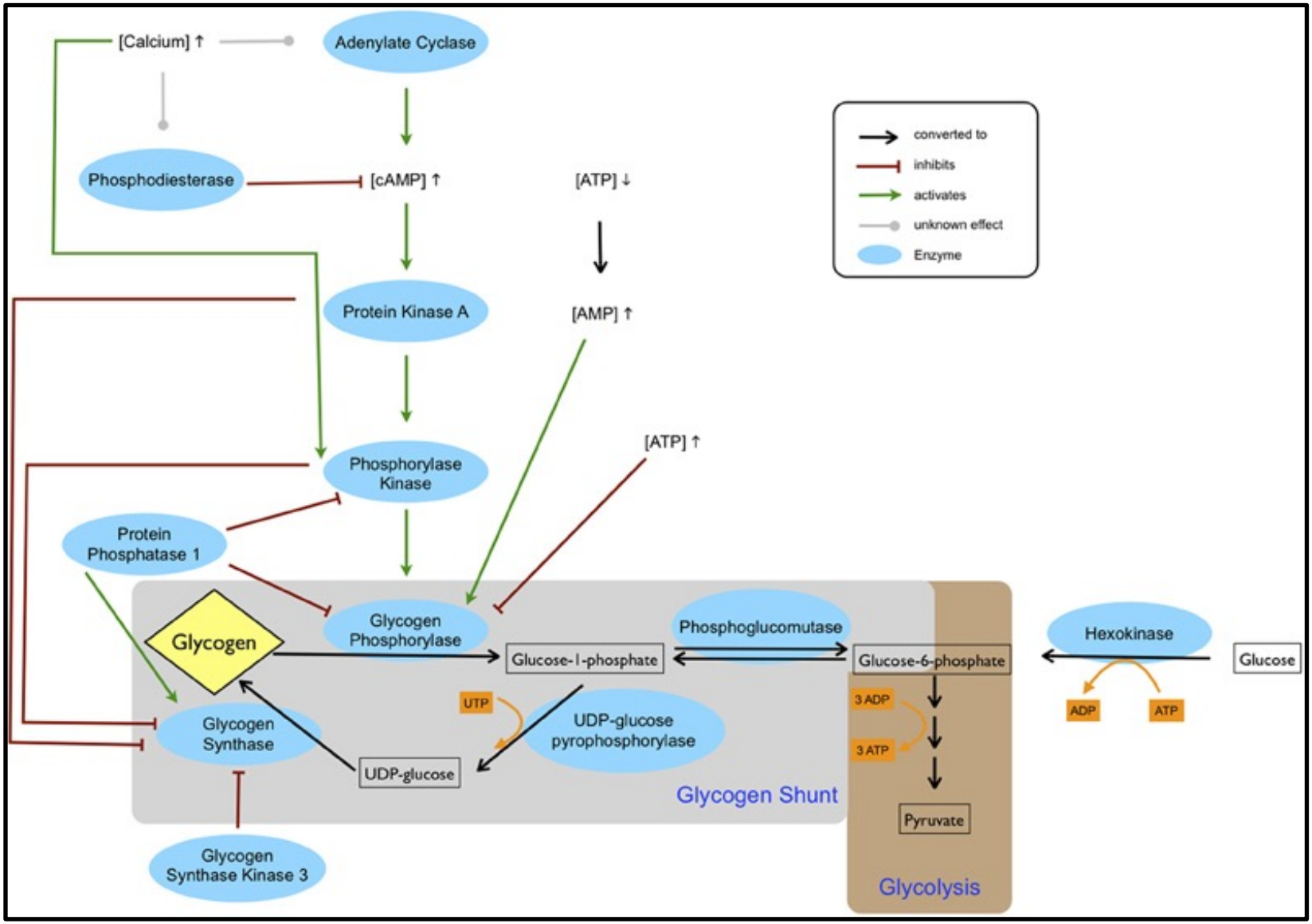
- A major glycogen-derived product is lactate, which is transported into the extracellular space via monocarboxylate transporters (MCT).



The steady-state concentration of glycogen is regulated by the coordination of separate degradative and synthetic enzymatic processes

Glycogen is a large, complex glucose polymer with a heterogeneous, branched structure comprised of glucose molecules linked in 1,4- and 1,6-linkages. This structure gives the glycogen phosphorylase, the degrading enzyme, multiple sites for attack and rapid degradation.

steady-state concentration of glycogen



Brain does not transport energy

- Human-made systems usually use a central energy source connected with the energy consumers by conductors (like the electric grid).
- In contrast, the brain uses a decentralized model where in the energy is produced at the site of utilization (in-house power plant model).
- Because the brain does not store or transport energy, the energy source (metabolism) and work (information processing) are one and the same and occur in the same cellular system

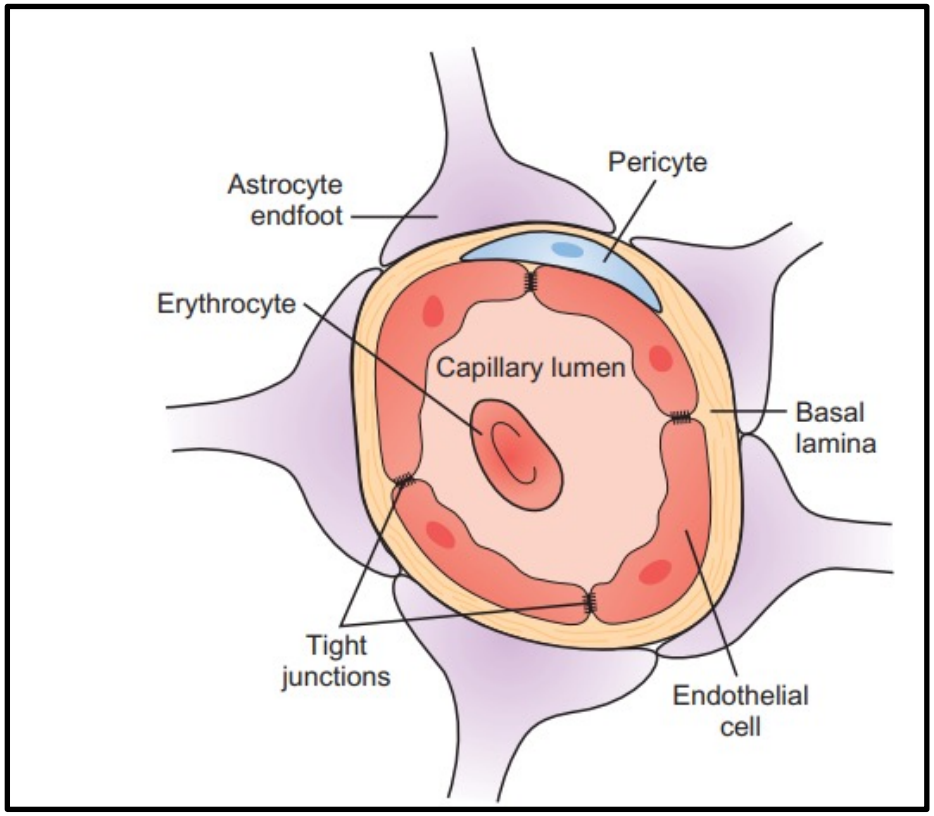
Advantage of local Energy supply

No wiring is necessary for energy transport, which means that the brain can utilize wiring exclusively for information processing.

If a region of the brain is lost due to trauma or disease there will be no energy blackout in the rest of the organ(the brain can function even if large areas are turned Off.

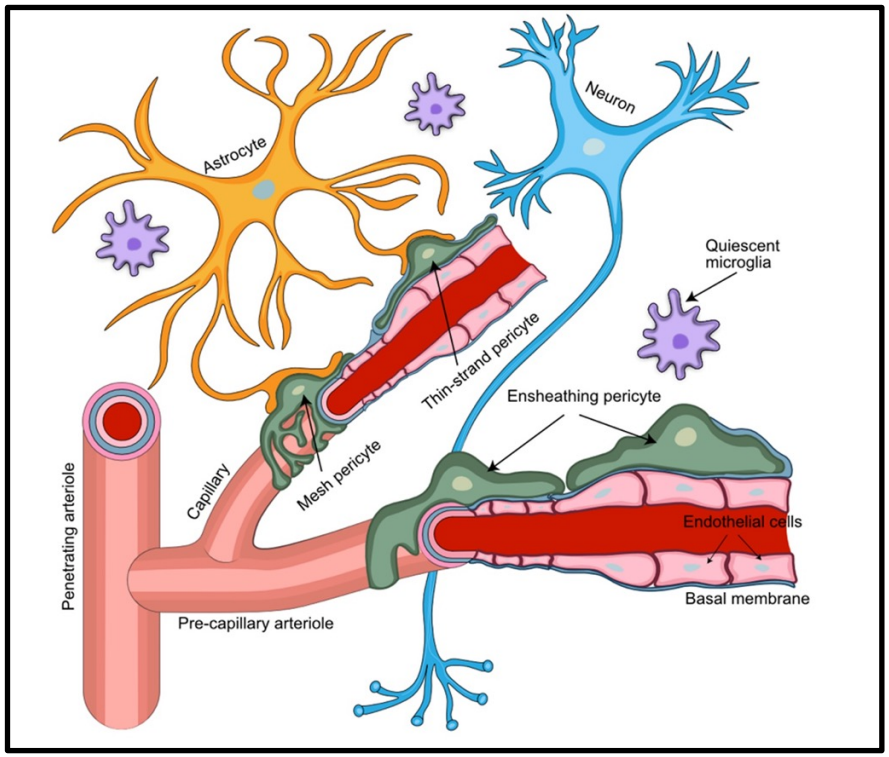
Neurovascular unit

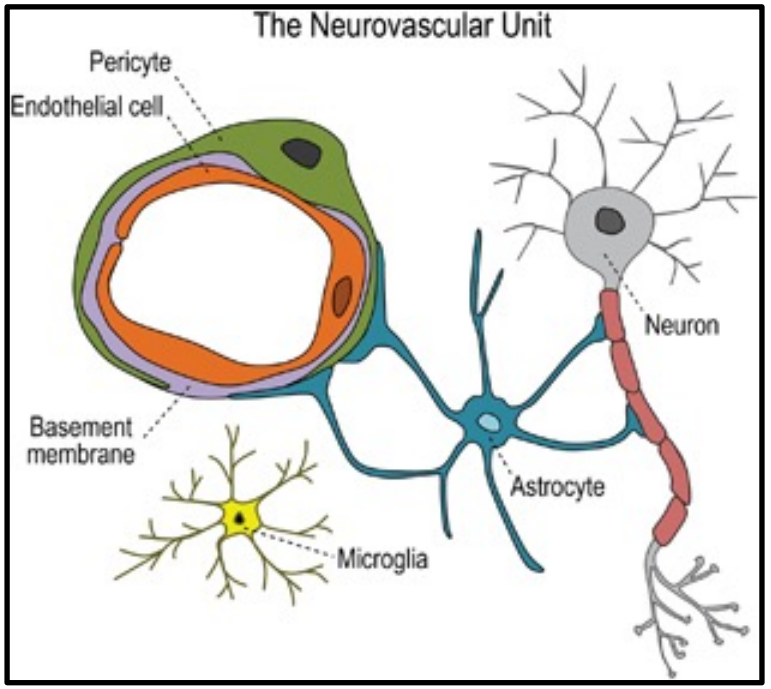
- Brain capillaries are lined by specialized endothelial cells, which are intermingled with pericytes and surrounded by a basal lamina. Astrocytic end feet surround the basal lamina.



The structure of NVU

- A brain capillary with endothelial cells and pericytes -Astrocytes and microglia -Neurons and interneurons -The surrounding extracellular matrix





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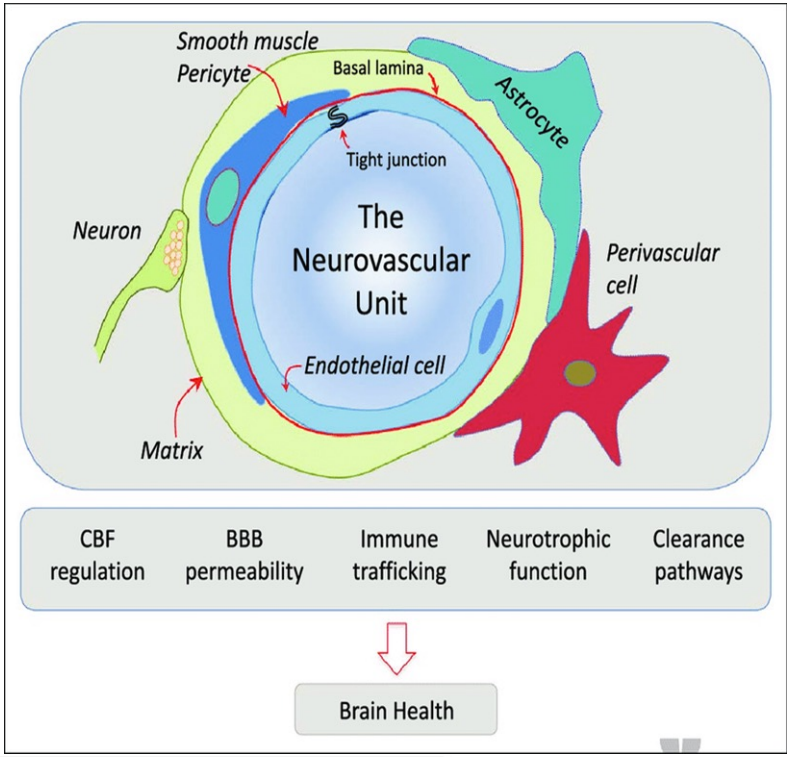
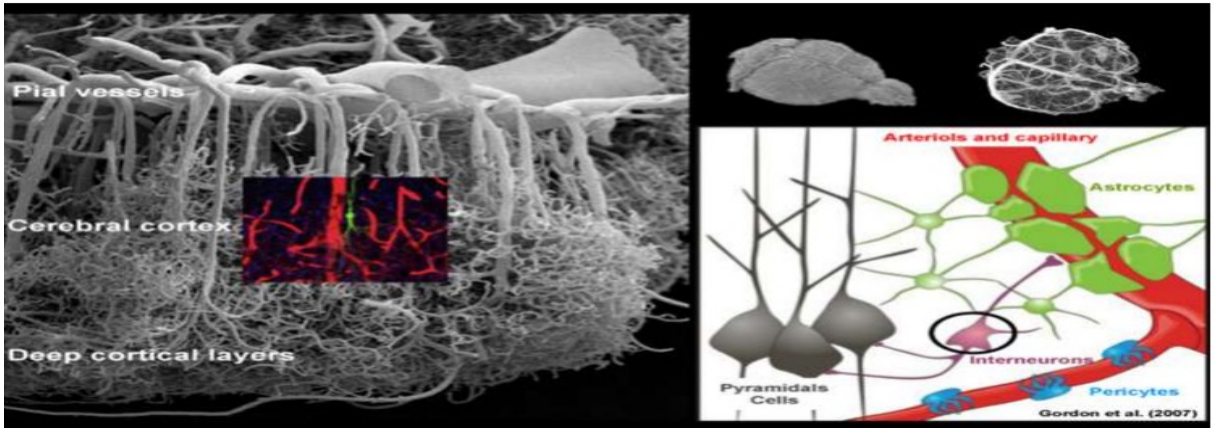
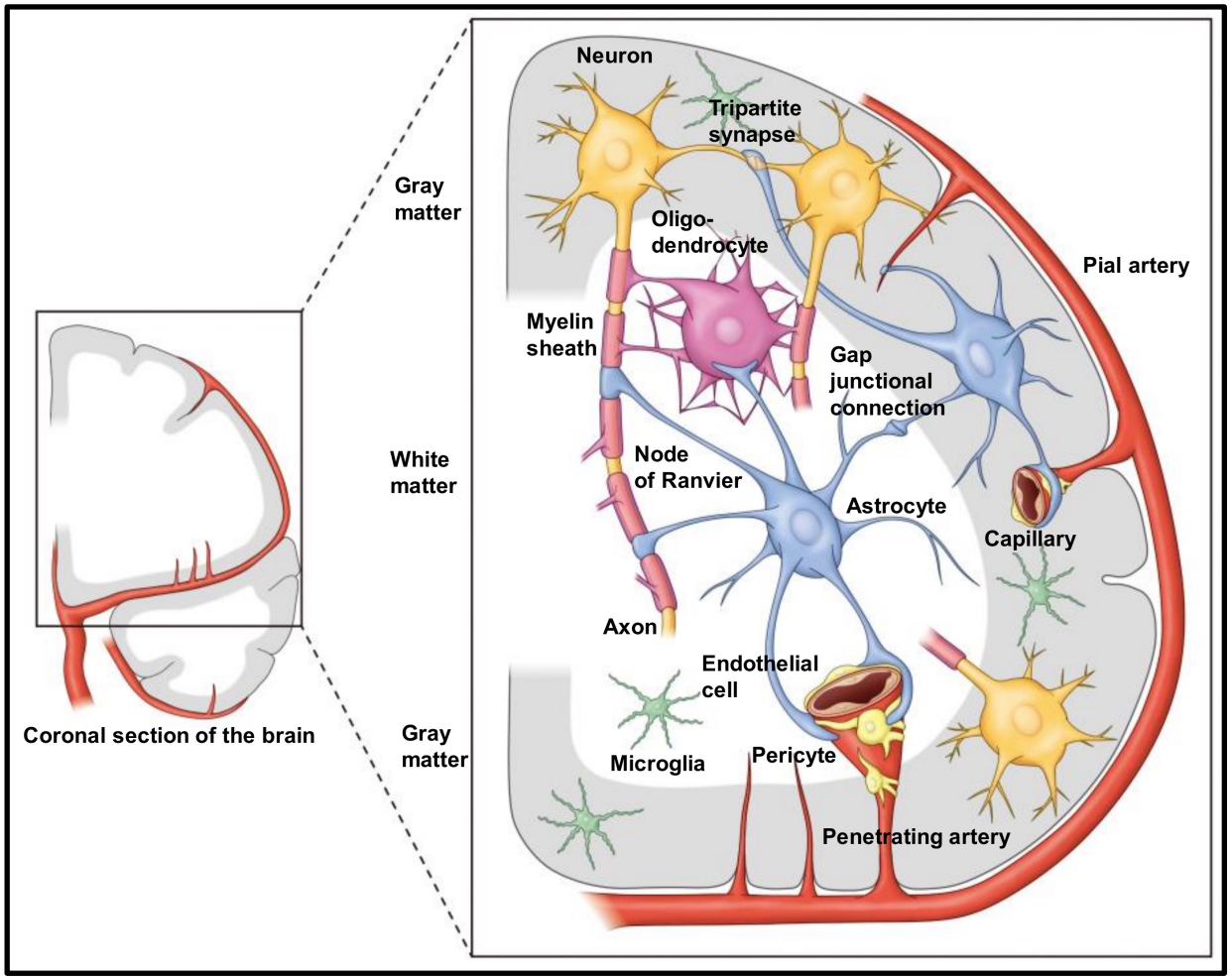
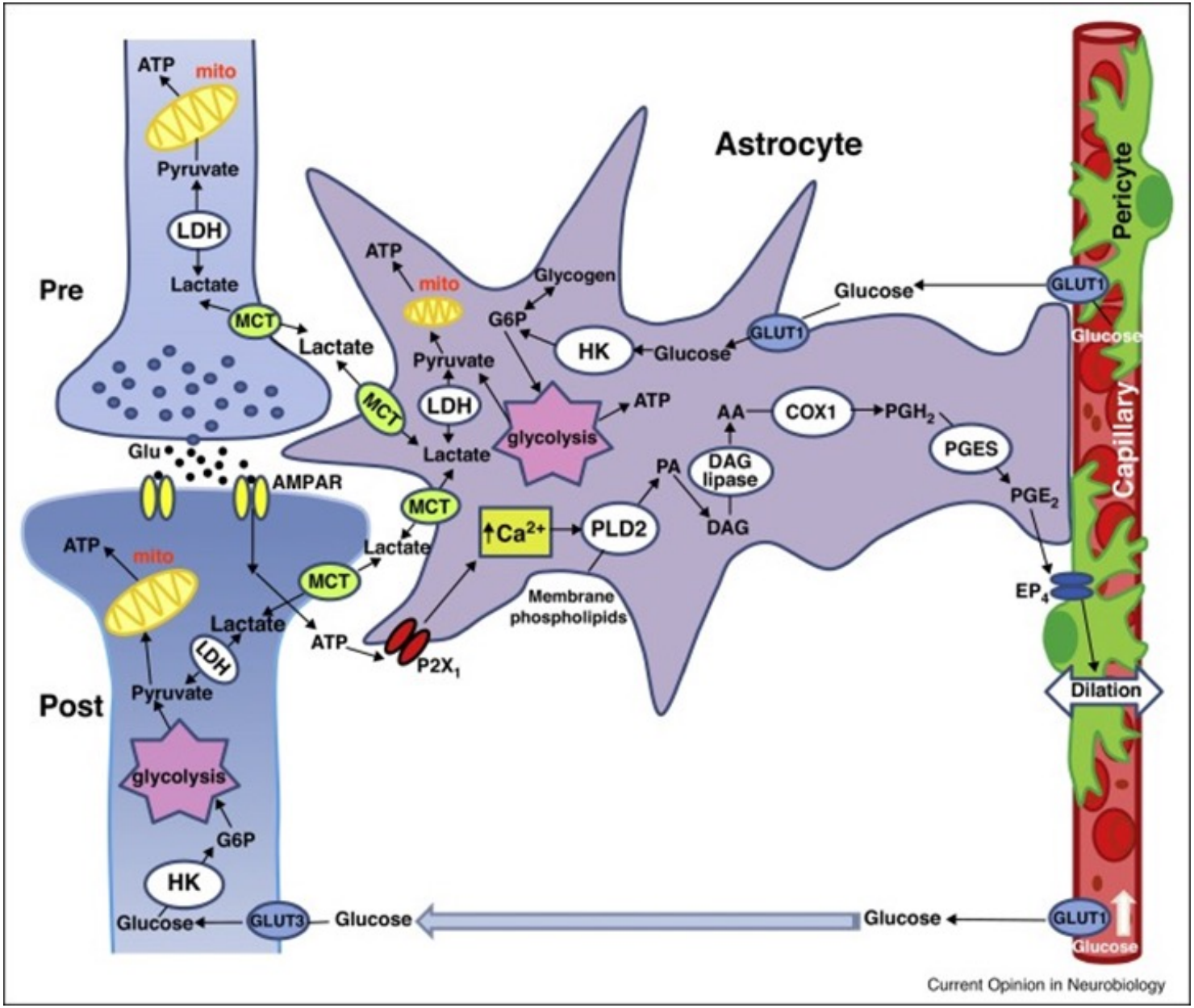




NVU Is The Electro-Metabolic System Of The Brain

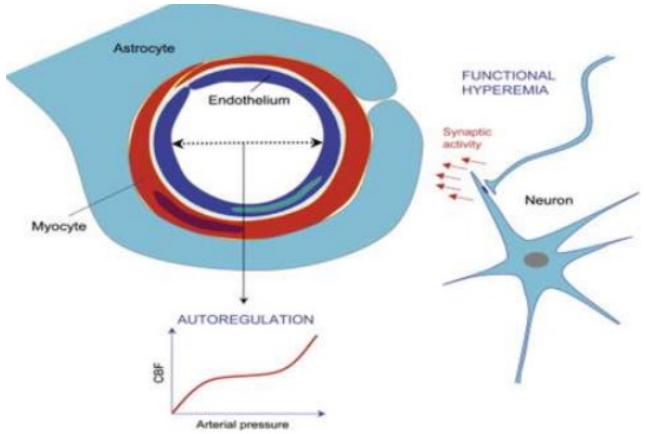
- The function of the NVU is local generation of energy in the form of ATP used by the synapse for information processing.




Astrocyte
Pre
Post
Pericyte
Capillary
ATP
mito
Pyruvate
LDH
Lactate
MCT
Glu
AMPAR
Glycogen
G6P
HK
Glucose
GLUT1
glycolysis
ATP
AA
COX1
PGH2
PGES
PGE2
DAG lipase
PA
DAG
↑Ca2+
PLD2
Membrane phospholipids
P2X1
EP4
Dilation
GLUT3
Current Opinion in Neurobiology

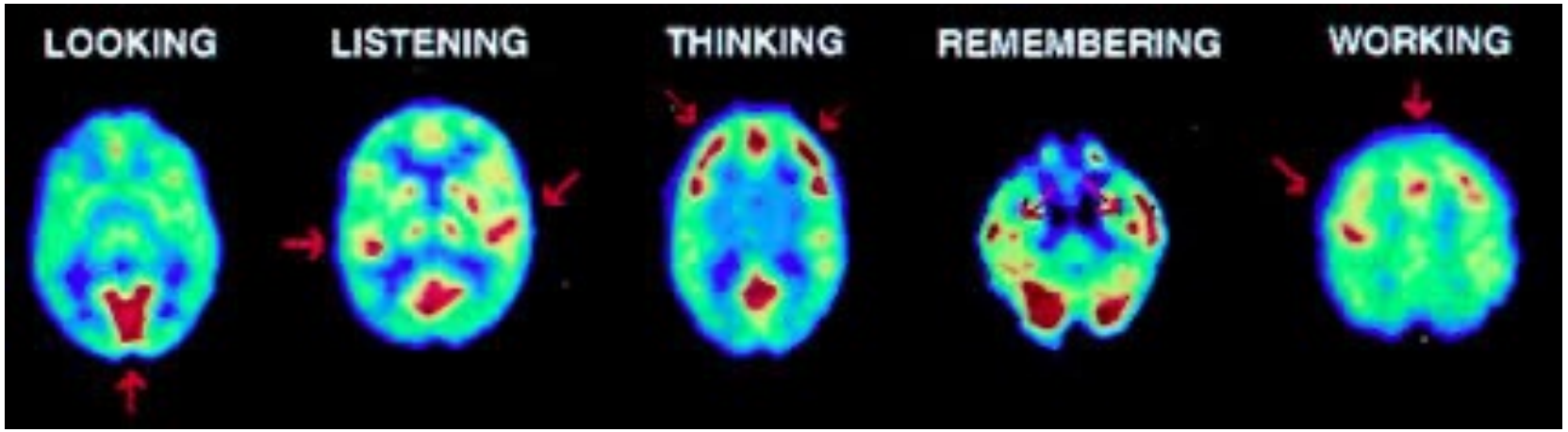
Intermittent Local Hyperemia

At the local level, when **brain** activity increases, blood flow to that region rises, supplying active neurons with sufficient nutrients. This increase in local blood flow in response to neuronal activity is termed functional Hyperemia. The NVU has an auto-regulatory mechanism for functional hyperemia. Microvasculature dilates temporarily in response to local neural activity to meet the increased demand for blood flow and oxygen (energy on demand).



Cognitive Tasks or Sensory Stimuli Result in Immediate Local Functional Hyperemia

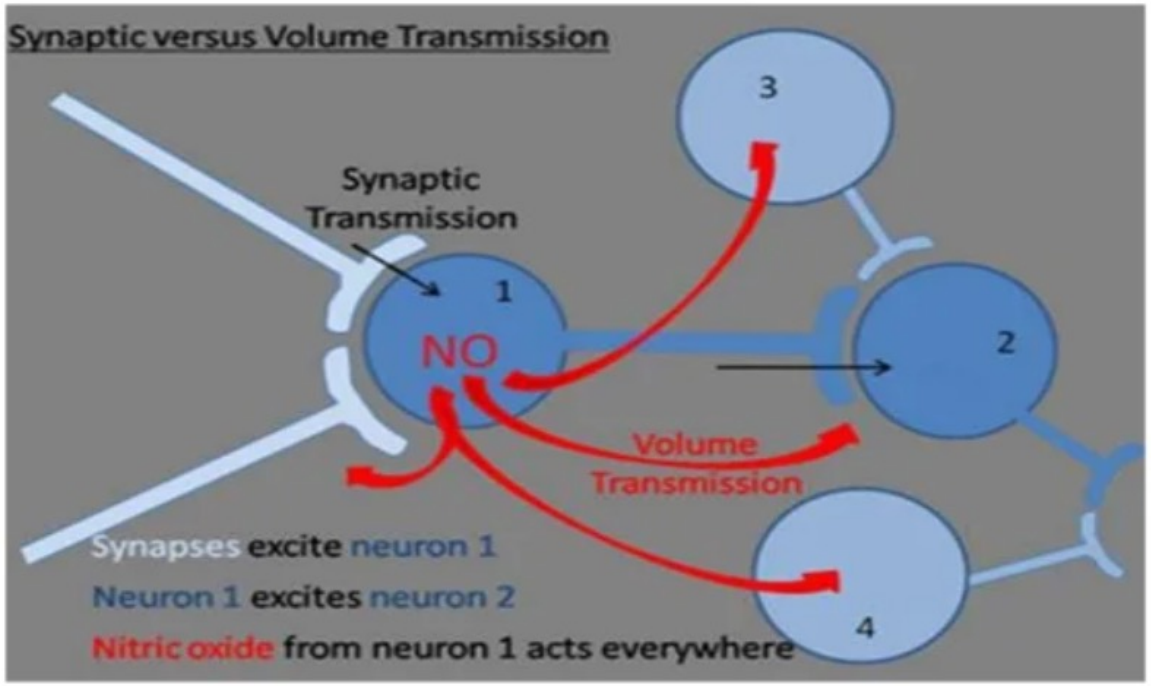
Within seconds after the onset of brain activity there is the increase in local blood flow and metabolism



Local neural activity (during a cognitive task) triggers the release of vasoactive mediators in the extracellular fluid (matrix) whose end result is local hyperemia.

Role of NO in brain

- Nitric oxide (**NO**) is a key signaling molecule in the regulation of cerebral blood flow.
- Nitric oxide depletion in ischaemic **brain** tissue plays a pivotal role in the development of subsequent morbidity and mortality through microcirculatory disturbance and disordered blood flow regulation.

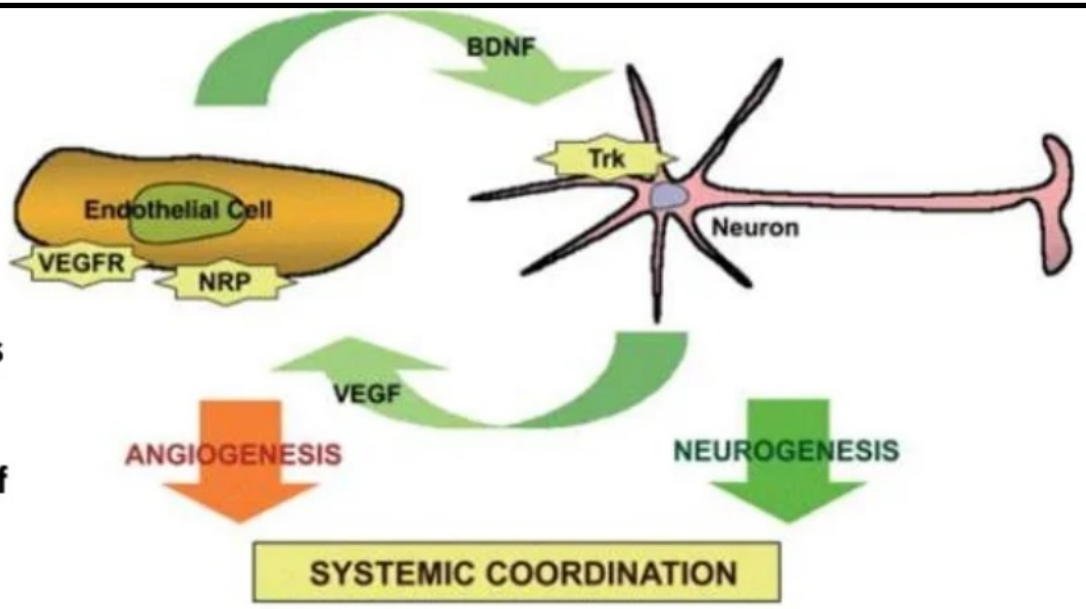


Local Hyperemia and volume transmission

- Although synaptic transmission is an important means of communication between neurons, neurons also communicate among themselves and with glia by extra-synaptic “volume transmission”, which is mediated by diffusion in the extracellular fluid (matrix)
- There is synchronization between local neuronal activity and the density of the capillary bed.
- neuronal activation over longer periods of time triggers the release of vasoactive substances that stimulate angiogenesis resulting in increased capillary density.
- Conversely, a constant decrease in neuronal activation reduces the area capillary density.

Systemic Coordination Among NVU Cellular System Occurs By Volume

During development neurons express vascular endothelial growth factors (VEGF) that induce proliferation of endothelial cells through its receptors (VEGFR and/or NRP).

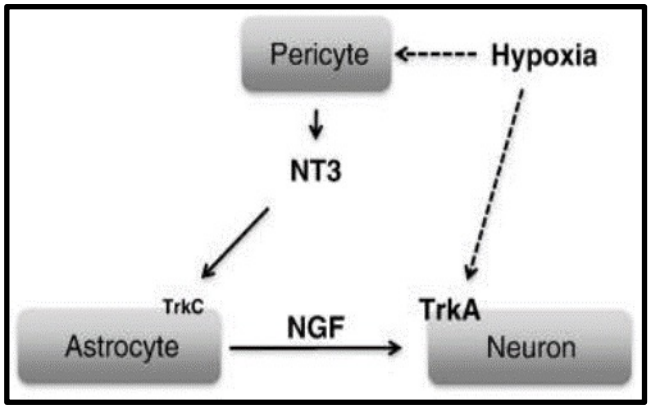


Conversely, endothelial cells produce brain derived neurotrophic factor (BDNF), which binds with Trk on nerve cells, and stimulate neurite growth.

Jeong-Ae Parka, Kyu-Sil Choia, Soo-Young Kima, b, Kyu-Won Kim; Coordinated interaction of the vascular and nervous systems: from molecule- to cell-based approaches; Biochemical and Biophysical Research Communications Volume 311, Issue 2, 14 November 2003, Pages 247–253

Neuroprotective Role of Pericytes

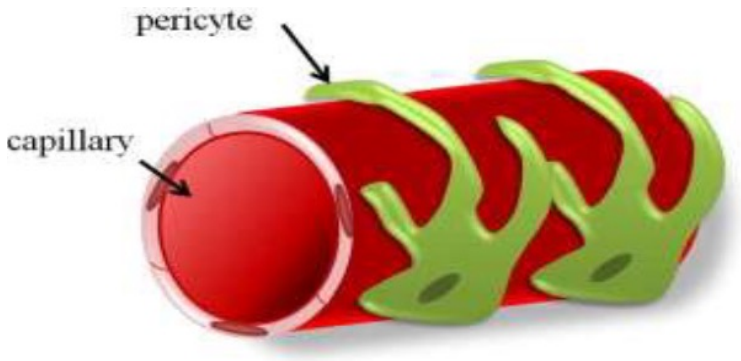
Recent studies suggest that pericytes produce neuroprotective mediators such as neuronal growth factor (NGF) and neurotrophin-3 (NT-3).



Pericytes Are Contractile Cells That React To Glutamate

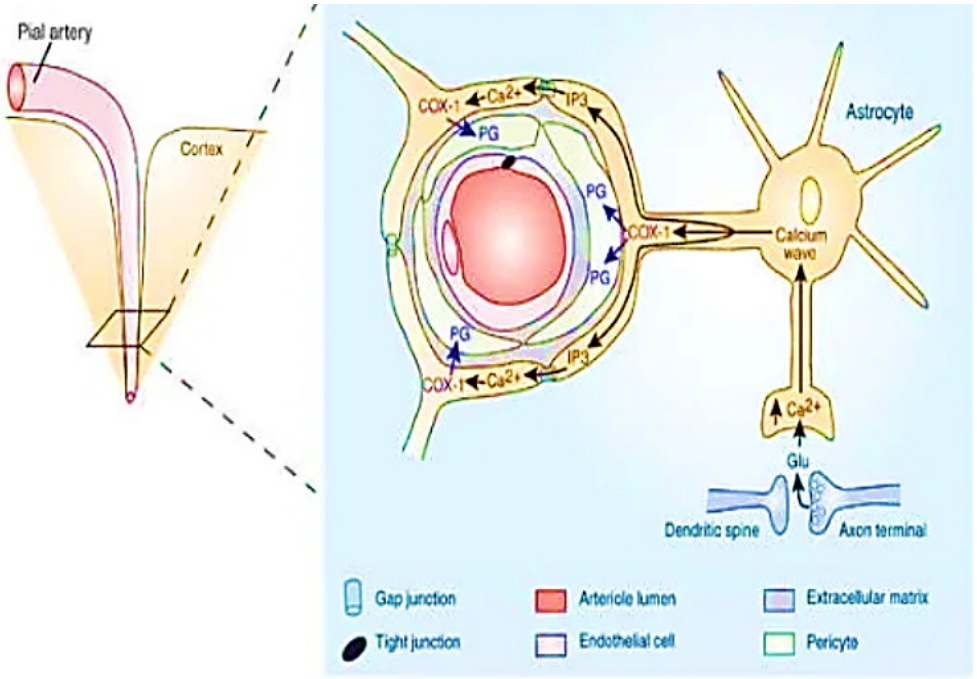
Capillaries lack smooth muscle but in places are surrounded by Pericyte contraction and relaxation is the mechanism of local hyperemia (in addition to arterioles).

Pericytes relax in response to glutamate (this action decreases Cerebral vascular resistance).



The Molecular mechanism of Hyperemia

- Increased neural activity leads to increased glutamate in the synapse.
- Excess glutamate is released into the extracellular space.
- Extracellular glutamate is taken by the astrocyte(to be recycled into glutamine)
- The intra- astrocytic glutamate creates a calcium wave
- calcium wave triggers A cascade of vasodilators
- Glutamate-induced calcium waves in the astrocyte trigger NO, prostaglandins, arachidonic acid, adenosine and potassium that directly alter blood vessel tone causing pericyte relaxation(vasodilation)



Pericytes endothelial cells communication

Pericytes communicate with endothelial cells of the brain capillaries by means of both direct physical contact and paracrine signaling(volume transmission)

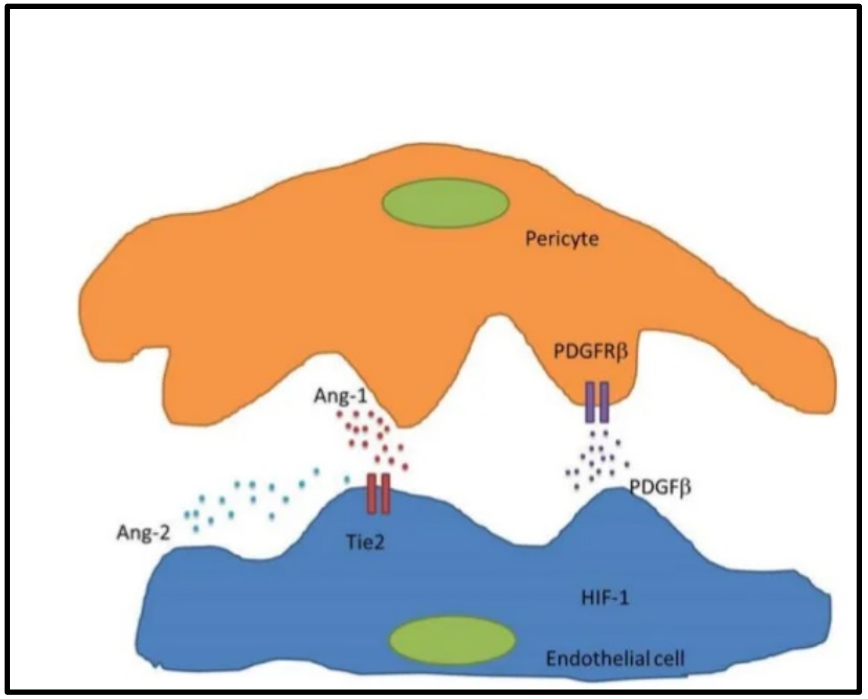
Such as:

HIF1: Hypoxia-inducible factor 1-alpha,

PDGFR beta Platelet-derived growth factor receptor-β

Ang 2: Angiopoietin-1

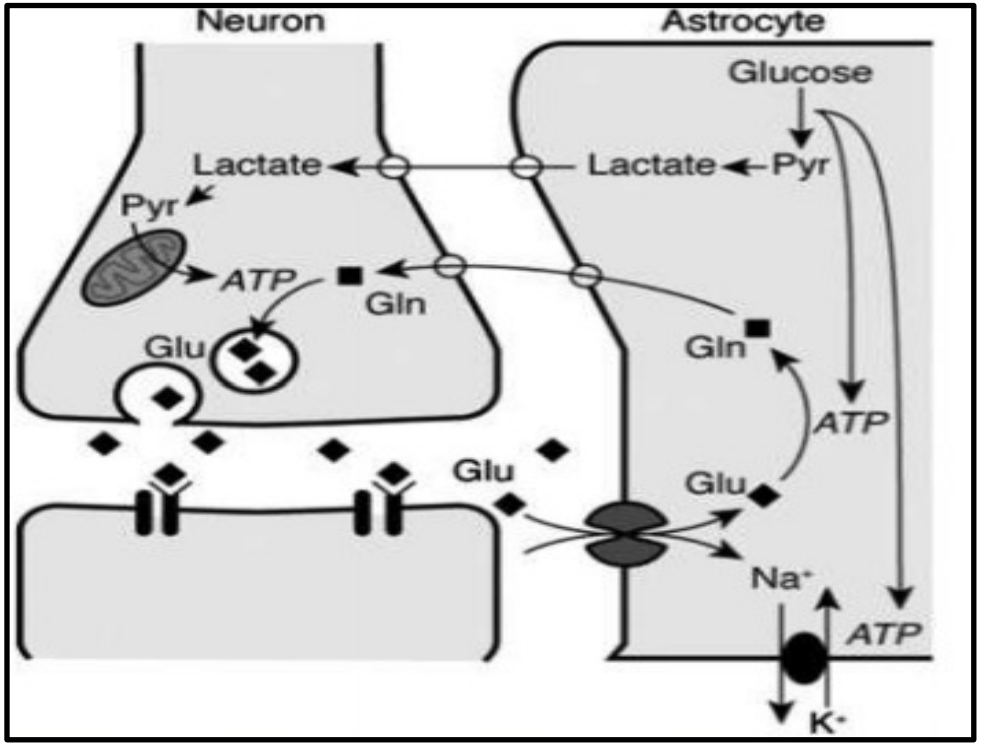
Ang 2 Angiopoietin-2



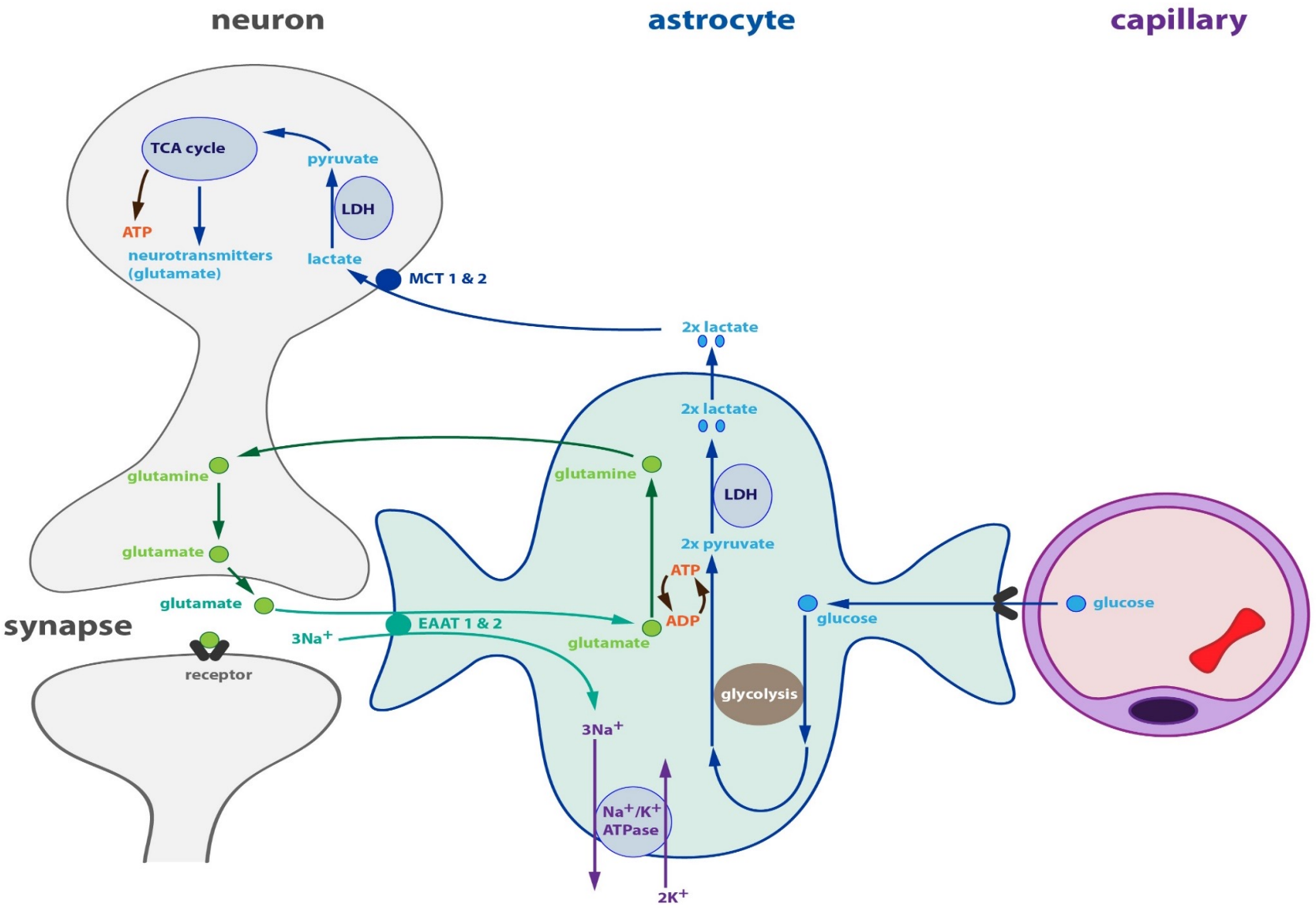
Cytological Relationships between Neurons and Astrocytes

“fuel injector” of lactate into the combustion chamber of the synapse (lactate shuttle).

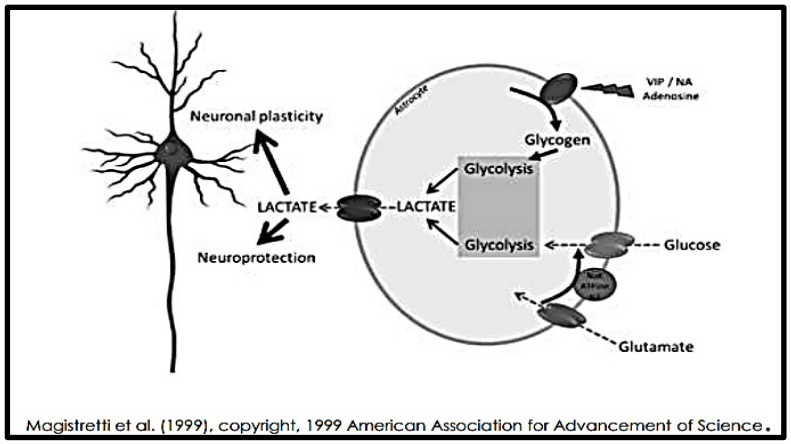
-“house keeper” of the combustion chamber – recycles left over glutamate from the synapse.



Astrocyte as a powerhouse

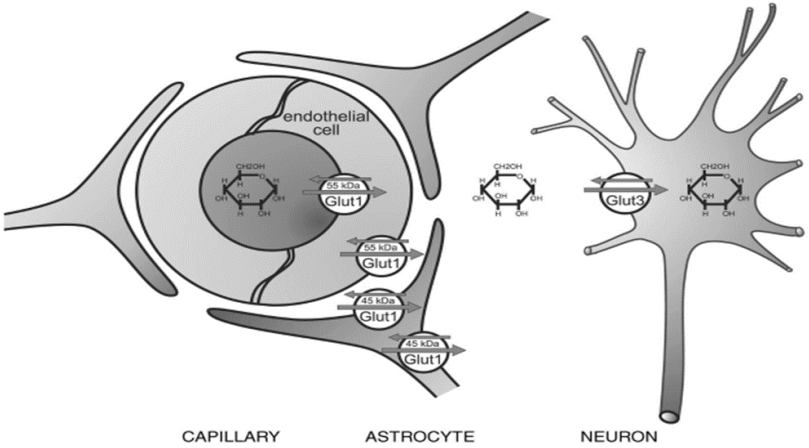


- Glycogenolysis in astrocytes and transport of the released lactate into neurons play a vital role in memory formation via support of synaptic plasticity processes as well as neuroprotection of neurons under stress conditions (e.g., excitotoxicity).



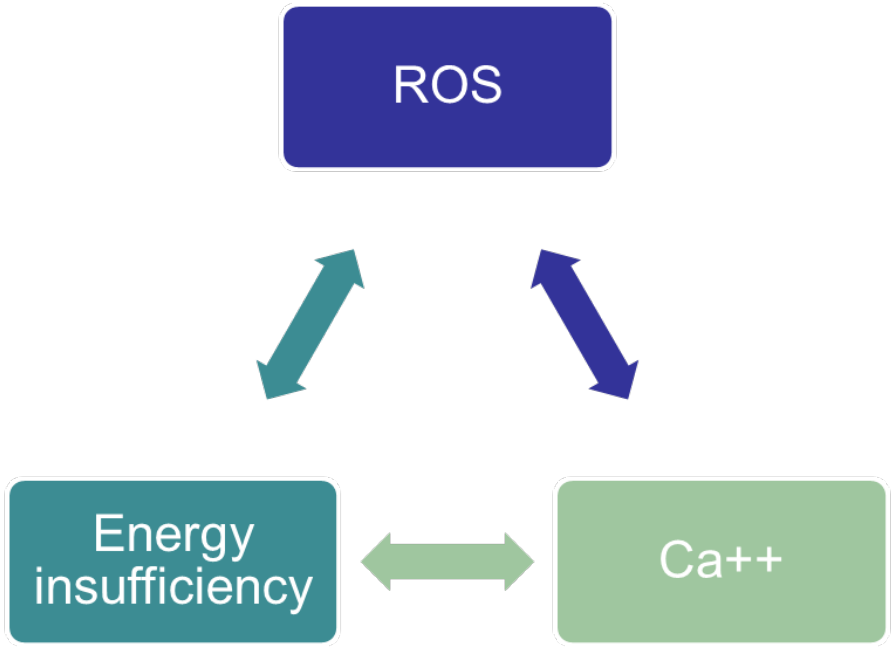
Magistretti et al. (1999), copyright, 1999 American Association for Advancement of Science.

- Location of different glucose transporter isoforms in brain. Glut 55KD is found in endothelial cells while 45Kd is found in astrocytes. Glu3 is found in neurons, Both Glu1 and 3 are insulin independent. Only traces of other Glut receptors are found in the brain.

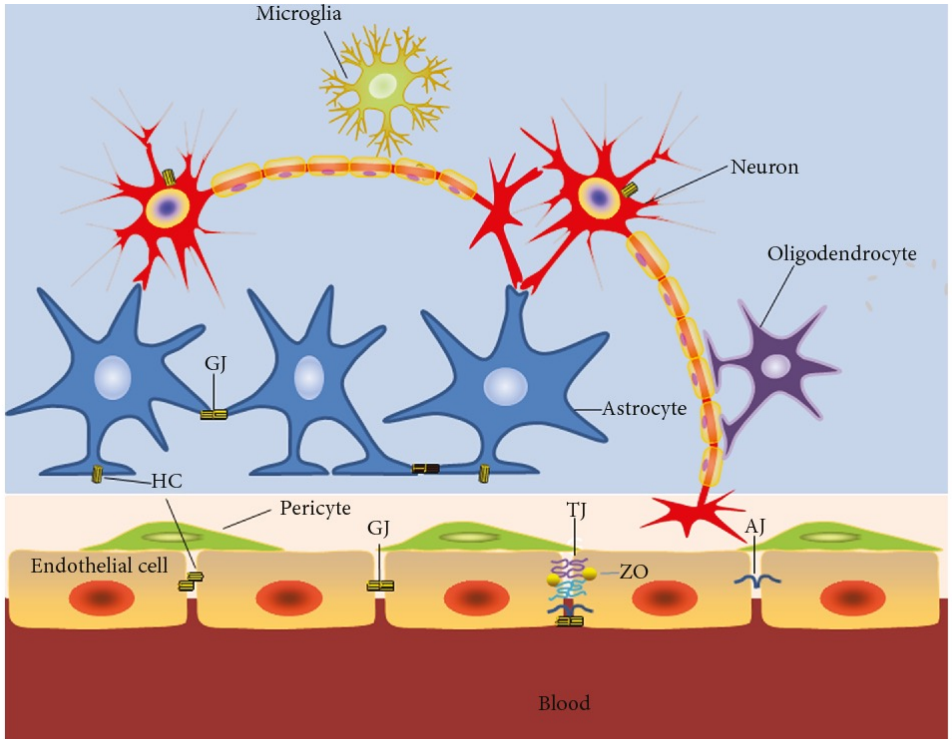


Energy depletion cause of neurodegeneration

Impairments of energy metabolism, alterations in cellular calcium homeostasis, and excess free radicals (ROS) interact with each other in mitochondria; inducing any one of them leads to abnormalities in the other two.



Metabolic aspects of Neuron-Oligodendrocyte-Astrocyte interactions

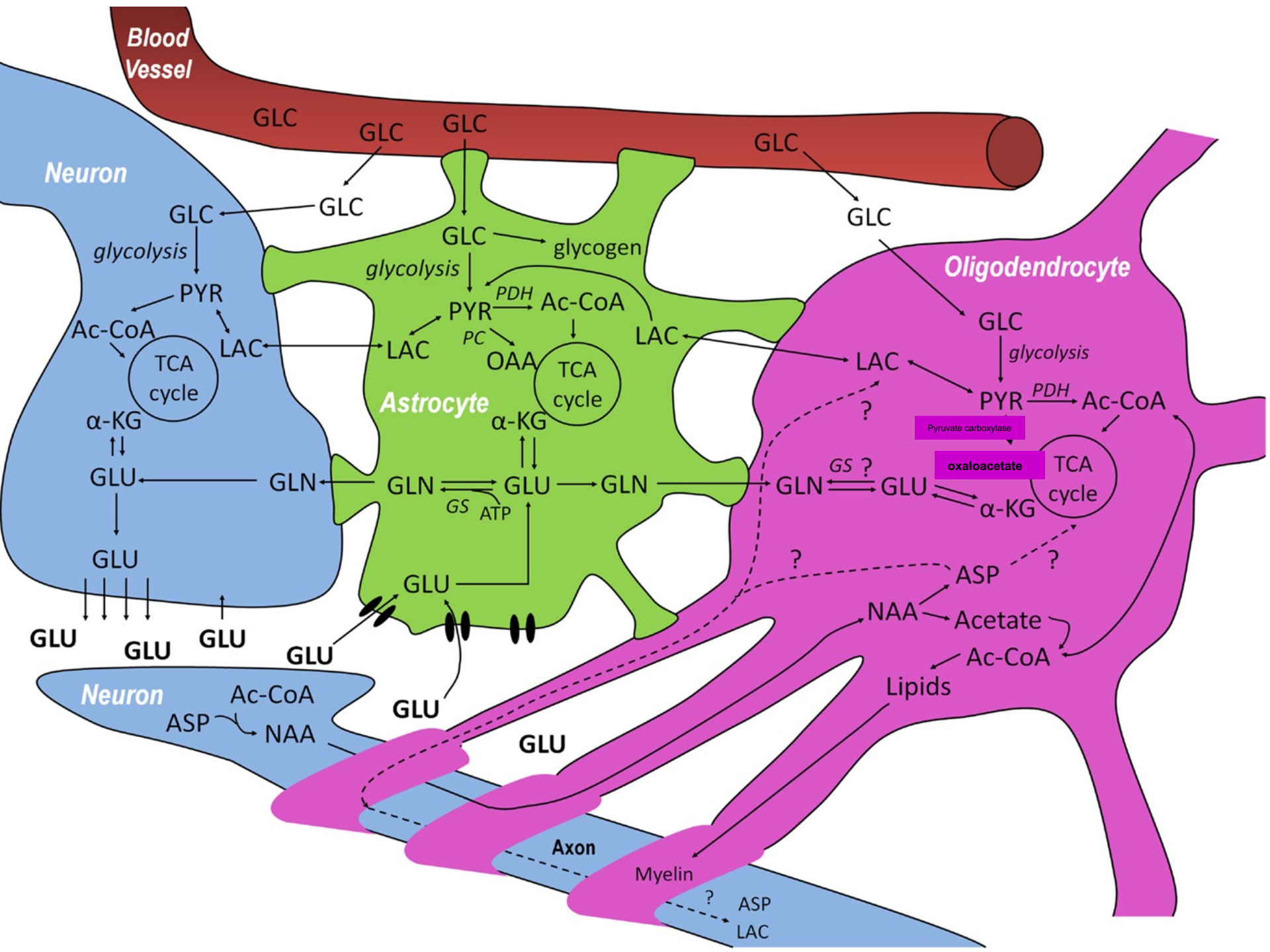


Review Article:

Ana I. Amaral,ToreW. Meisingset, Mark R. Kotter and Ursula Sonnewald. Metabolic aspects of Neuron – Oligodendrocyte - Astrocyte interactions. *Frontiers in Endocrinology. May 2013*

- Neurons are in continuous, dynamic interaction with several types of glial cells (astrocytes, oligodendrocytes, microglia).
- The interactions between neurons and astrocytes characterized by the glutamate–glutamine (–GABA) shuttle have received considerable attention since its discovery in the 1970s (van den Berg and Garfinkel, 1971).
- This shuttle is necessary since neurons cannot make their amino acid neurotransmitters glutamate (excitatory, 90% of synapses), GABA (most abundant inhibitory), and aspartate without glutamine from astrocytes.

- In this interplay, glucose has a central role as the major (or exclusive) source of energy for the adult brain and the molecules used to synthesize glutamine and thus glutamate, GABA, and aspartate (McKenna et al., 2011).


Blood Vessel
GLC
GLC
GLC
GLC
Neuron
GLC
GLC
glycolysis
PYR
Ac-CoA
LAC
TCA cycle
α-KG
GLU
GLN
GLU
GLU
GLU
GLU
GLU
Neuron
Ac-CoA
ASP
NAA
GLC
glycogen
glycolysis
PYR
PDH
Ac-CoA
LAC
LAC
PC
OAA
TCA cycle
Astrocyte
α-KG
GLN
GLU
GLN
GS
ATP
GLU
GLU
GLC
Oligodendrocyte
GLC
glycolysis
LAC
PYR
PDH
Ac-CoA
?
Pyruvate carboxylase
oxaloacetate
TCA cycle
GS ?
GLN
GLU
α-KG
?
?
ASP
?
NAA
Acetate
Ac-CoA
Lipids
GLU
Axon
Myelin
?
ASP
LAC

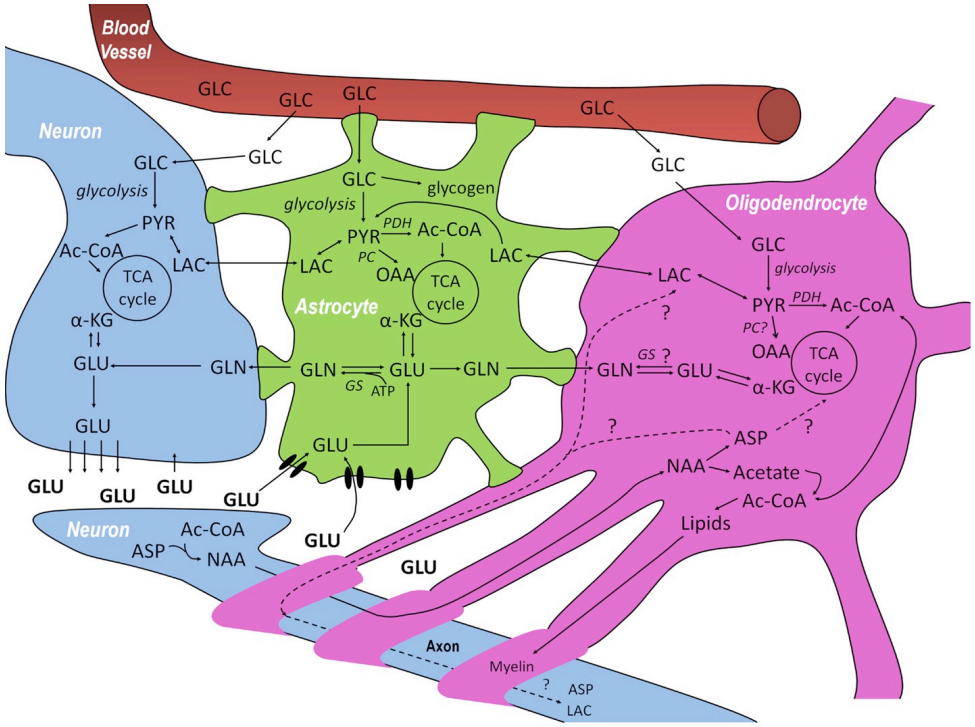
Gliotransmitters

- Astrocytes can release **gliotransmitters** (like glutamate) by exocytosis to send signals to neighboring neurons.
- Each astrocyte has its own territory (they don't overlap), and each may interact with several neurons and hundreds to thousands of synapses to properly integrate information
- End-feet" connect to blood vessels in the brain. By signaling blood vessels to expand or narrow, astrocytes regulate local blood flow to provide oxygen and nutrients to neurons in need

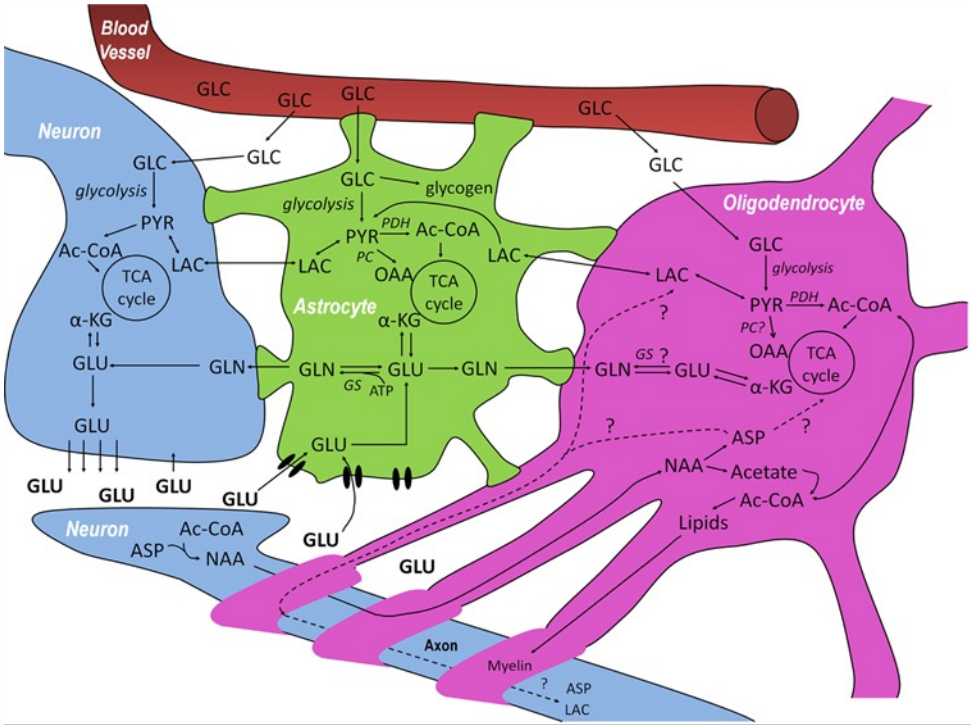
Alternative action potential

- Astrocytes generate signals that are chemical rather than electrical. Astrocytes are somehow activated when the level of calcium ions increases inside the cell.
- This change in concentration signals the release (typically by exocytosis) of what is now called "gliotransmitters". These small molecules travel to a neighbouring cell and deliver their message in a process very similar to that used by neurotransmitters.
- Knowing more about astrocytes will also shed light on diseases in which communication between astrocytes and neurons is altered, including Alzheimer's disease, AIDS, brain cancer, and ALS (amyotrophic lateral sclerosis).

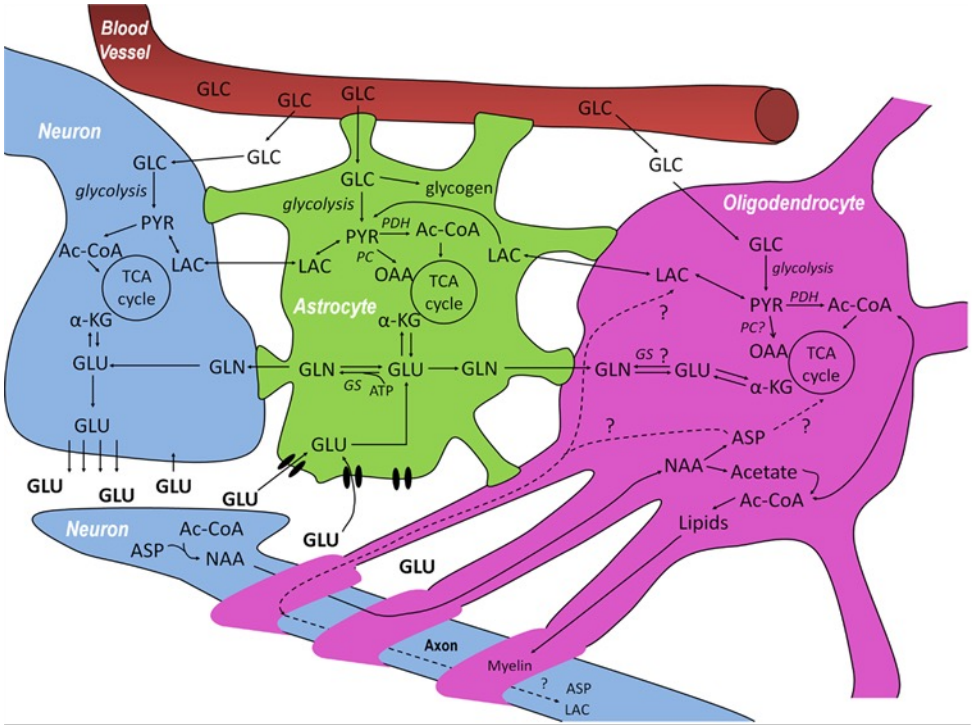
- Glucose (GLC) from the blood is taken up by neurons, astrocytes, and oligodendrocytes and can be metabolized via glycolysis, giving rise to pyruvate (PYR). In astrocytes, GLC can also be stored in the form of glycogen.
- PYR, the end product of glycolysis can be reduced to lactate (LAC) which can be released and taken up by cells with lower lactate concentration, be converted into alanine (not shown) or be converted into acetyl-CoA (Ac-CoA) and subsequently oxidized in the tricarboxylic acid (TCA) cycle.



- After the synaptic release of glutamate (GLU) by neurons, astrocytes are responsible for most of its uptake via specific high-affinity glutamate transporters to prevent neuronal excitotoxicity, although some pre-synaptic re-uptake can also occur.
- GLU taken up by astrocytes can be converted to glutamine (GLN) by glutamine synthetase (GS) which can be transferred to neurons where it is transformed into GLU, making it available again for neurotransmission and, in this way, closing the GLU-GLN cycle.



- The close association between GLU, GLN, and TCA cycle metabolism is indicated in the three cell compartments: GLU can be additionally converted into α-ketoglutarate (α-KG) and be subsequently oxidized.
- Even though there are reports on the absence of glutamine synthetase and pyruvate carboxylase (PC) in oligodendrocytes, it is not totally clear whether or not they are capable of synthesizing GLN and performing anaplerosis.



- Finally, neurons are known to synthesize *N*-acetyl-aspartate (NAA) from aspartate (ASP) and Ac-CoA. NAA is thought to be transferred to oligodendrocytes where it is metabolized into ASP and acetate.
- Whereas the resulting acetate is thought to be extensively used for the synthesis of myelin lipids, the fate of the ASP , it can either be metabolized in oligodendrocytes or transported back to neurons, closing another potentially important metabolic cycle in the brain.