

Special metabolism of brain

*By
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* 3 type of cell [Astrocyte, oligodendrocyte, neuron & microglia]
metabolism of this microglia
neuron and brain..

Neuron

Oligodendrocyte

Astrocyte

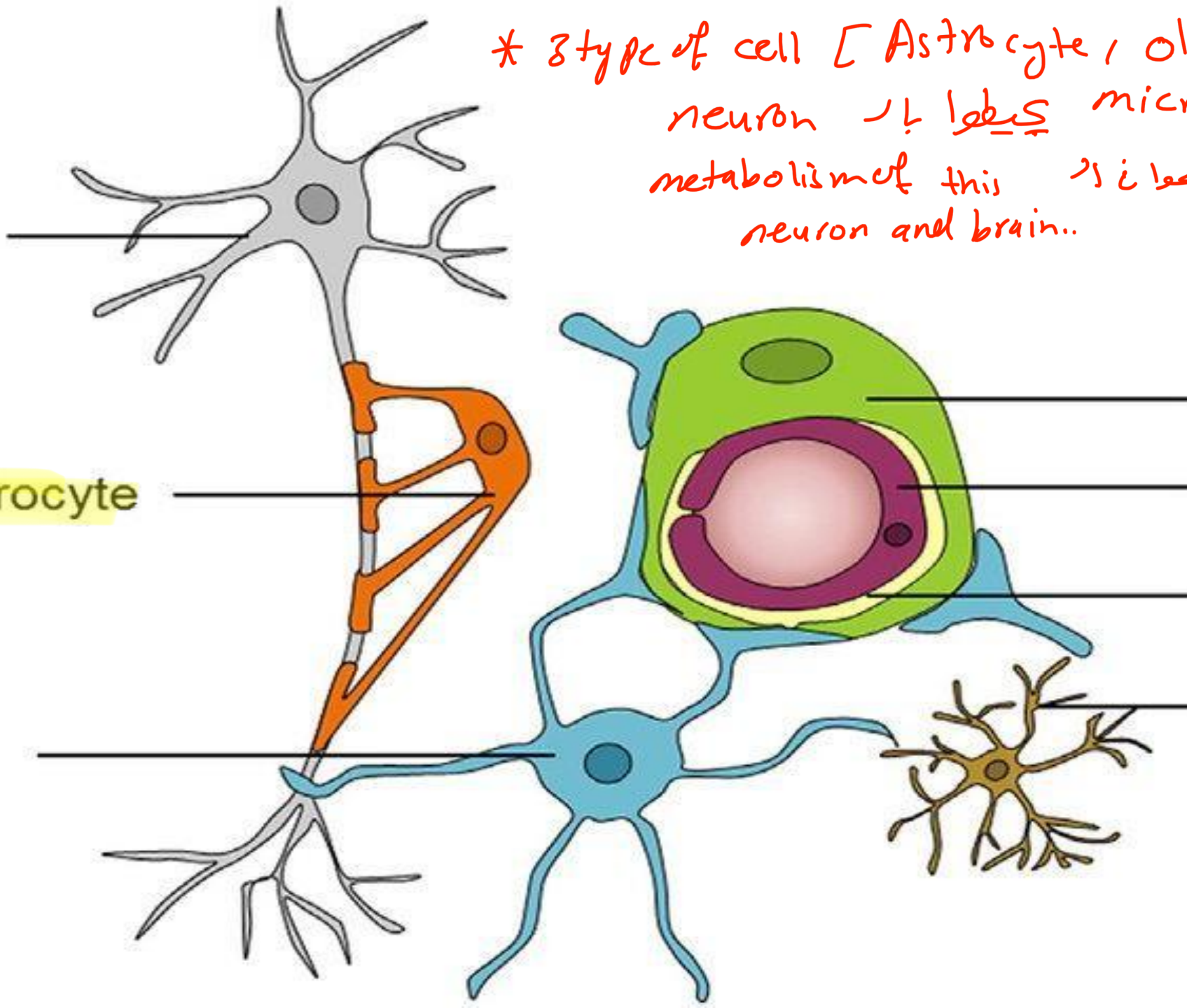
Pericyte

Endothelium

Basement
membrane

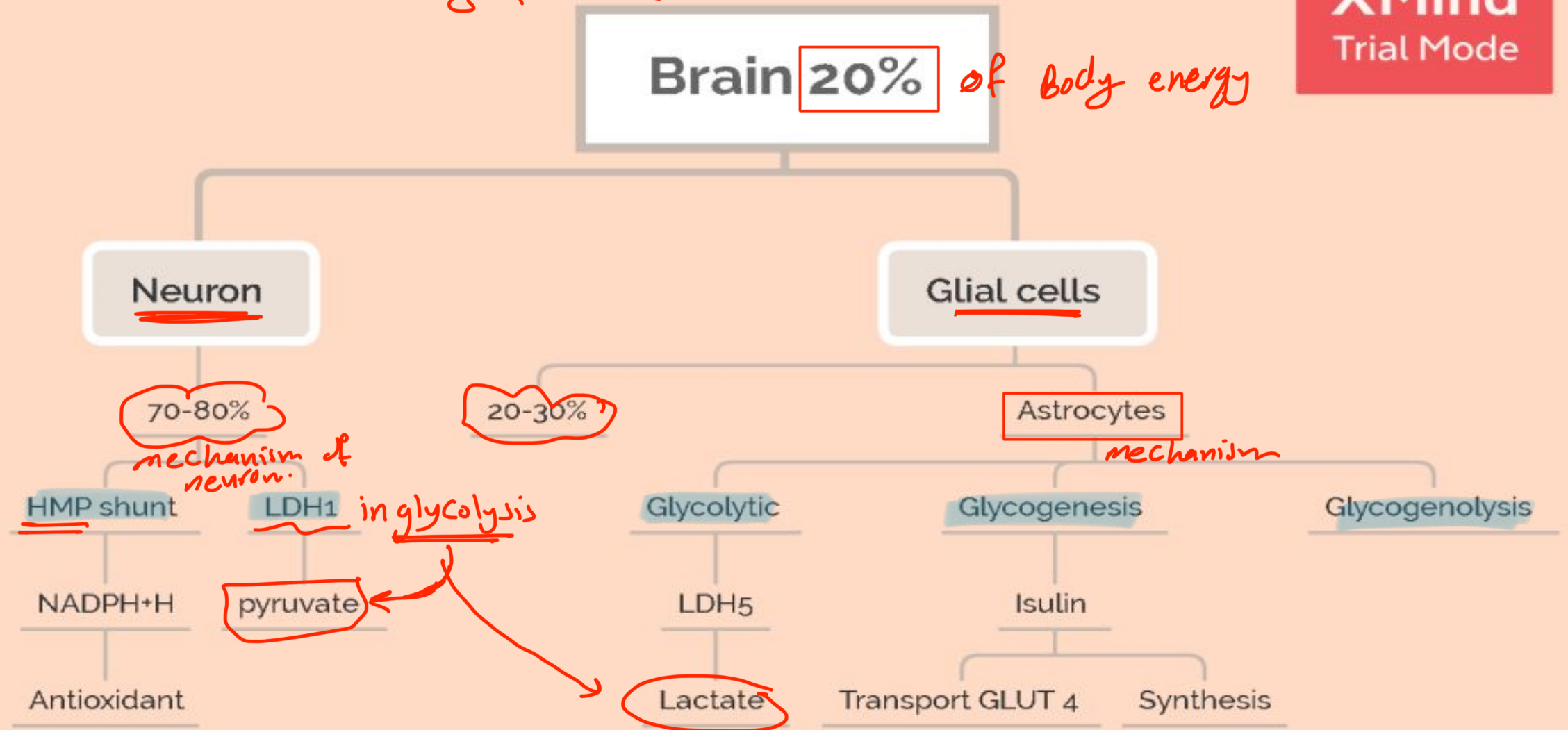
Microglia

↳ macrophage.



* the HMP in the purine [alternative pathway of glycolysis] release NADPH and ribose-5-phosphate..
↳ البديل

XMind
Trial Mode



* hyper polarization
نقطه انحطاط العصب

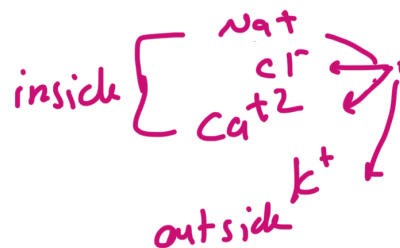
The brain uses 20% of the total energy used in the body at rest :

1. Neurons use 70-80 % of the total energy)used by the brain(:

a. To restore neuronal membrane potentials following **depolarization**

- opening of ion channels in the neuronal membrane and the subsequent influx of sodium ions (Na^+) or Ca^{++} and efflux of potassium ions (K^+).
[ion pump need ATP Energy.]
- The response of a neuron to ion channel receptor activation by either the neurotransmitter or a drug is rapid and brief

b. Other neuronal functions such as vesicle recycling, neurotransmitter synthesis



نقل الـ N.T. لا يصير فجأة لا channels عبي الـ electrolyte
to make the balance this called depolarization.

نقل الـ N.T. متى يتم نقطة انحطاط العصب

بقايا الطاقة

2. The remaining is used by glial cells (astrocytes, oligodendrocytes, microglia). provide support and protection to the neurons (nerve cells), and forming myelin

→ in myelination formation
→ in phagocytosis [defense]... etc

*the metabolism need energy so any defect in metabolic pathway lead to N.T disease.

- ❖ Decrease glucose and oxygen metabolic rates of brain cells occur during normal aging and are further exacerbated in disorders as Alzheimer's (AD), Parkinson's (PD) N.T disease

Energy sources of the brain

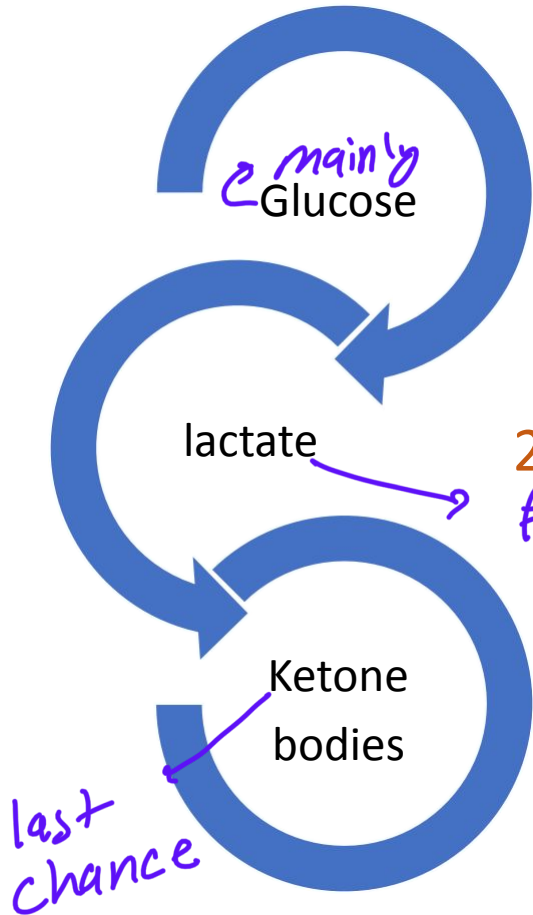
glucose lactate ketone body

Brain metabolism is mostly

1- Neurons in the adult brain dependent mostly on glucose as an energy source.

2- utilization is increased during intense physical activity
from pyruvate [alternative pathway of glucose]
[anaerobic condition] → we use the lactate

3- are utilized during brain development and in the adult during
prolonged fasting periods
or starvation



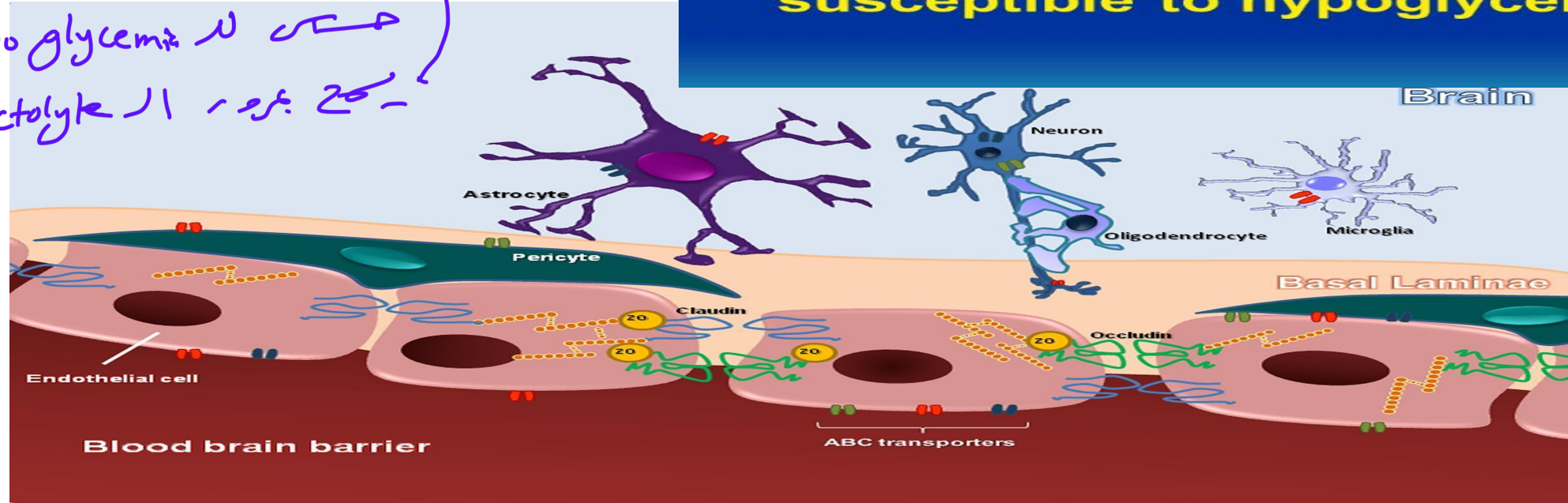
2 Barriers of Brain

Blood brain barrier

Brain
 یسج عروہ اسکر ذللہ ار
 hypoglycemia
 یسج عروہ ار electrolyte ..

من فہلہ یفہلہ
 ار nutrition
 یسج ار Brain
 یفہلہ

- **Glucose** crosses Blood Brain Barrier (BBB) by facilitated diffusion (**insulin-independent**)
- Therefore, brain is very **susceptible to hypoglycemia**



- ❖ surrounds most of the blood vessels in the brain. It is a structure that is formed primarily due to the establishment of **tight junctions between endothelial cells**
- ❖ highly selective semipermeable border of endothelial cells that **prevents** solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system where neurons reside

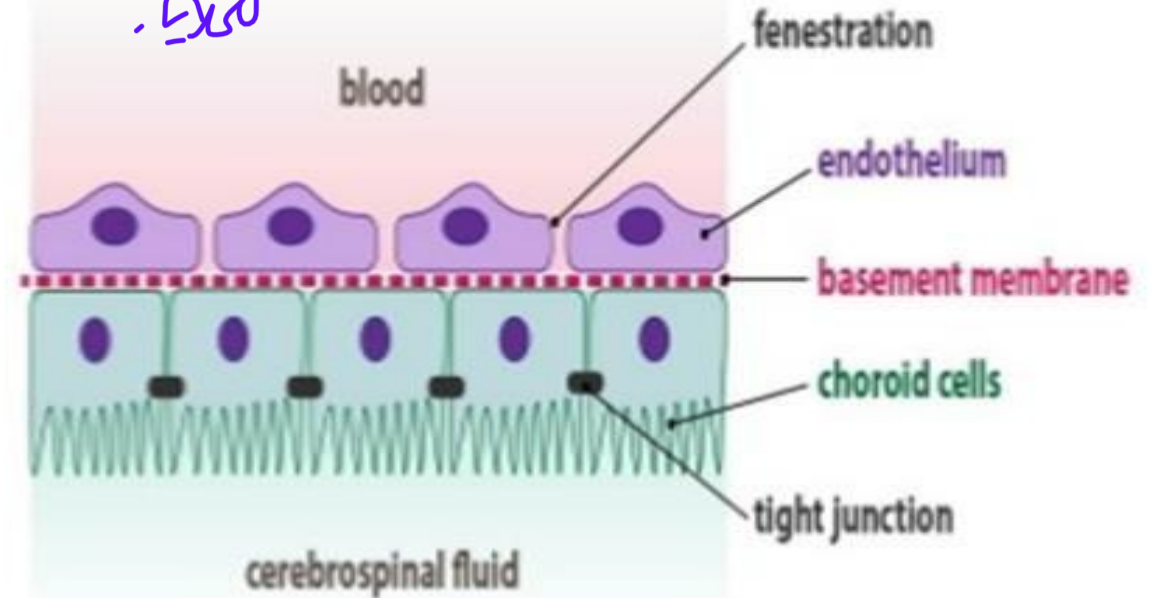
glucose
 electrolyte > demand
 selective
 عروہ

2

BLOOD -CSF BARRIER

- It exists at the level of epithelial cells that make up the choroid plexus.
- Responsible for carrier mediated active transport.

electrolyte / الجلوكوز / B-CSF B
 [active transport] ← المواد في حجرة الخلايا

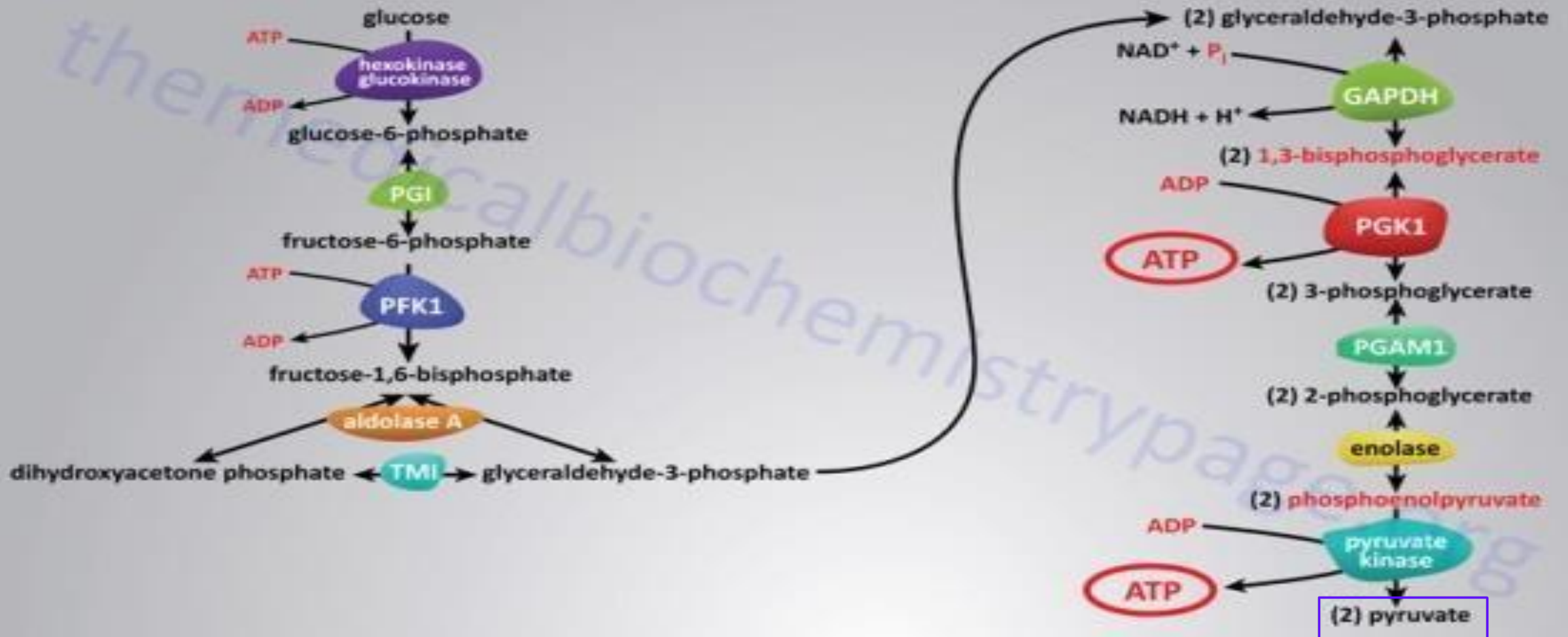


Fate of Glucose:

- 1- Glycolysis & lactate formation in the astrocytes.
- 2- Glycolysis & Krebs' cycle in neurons.
- 3- Glycogen synthesis in astrocytes.
- 4- HMP shunt.

Glycolysis & lactate formation in the astrocytes:

pyruvate $\rightarrow$ Acetyl CoA $\rightarrow$ ATP



- ❖ Astrocytes display a very high glycolytic activity.
Astrocytic metabolism is glycolytic.

لا مع ١٥
neurons

- ❖ Glucose → G-6-P → by glycolysis gives pyruvate. Astrocytes contain lactate dehydrogenase-5 (LDH-5) which makes lactate from pyruvate.

in cardiac muscle

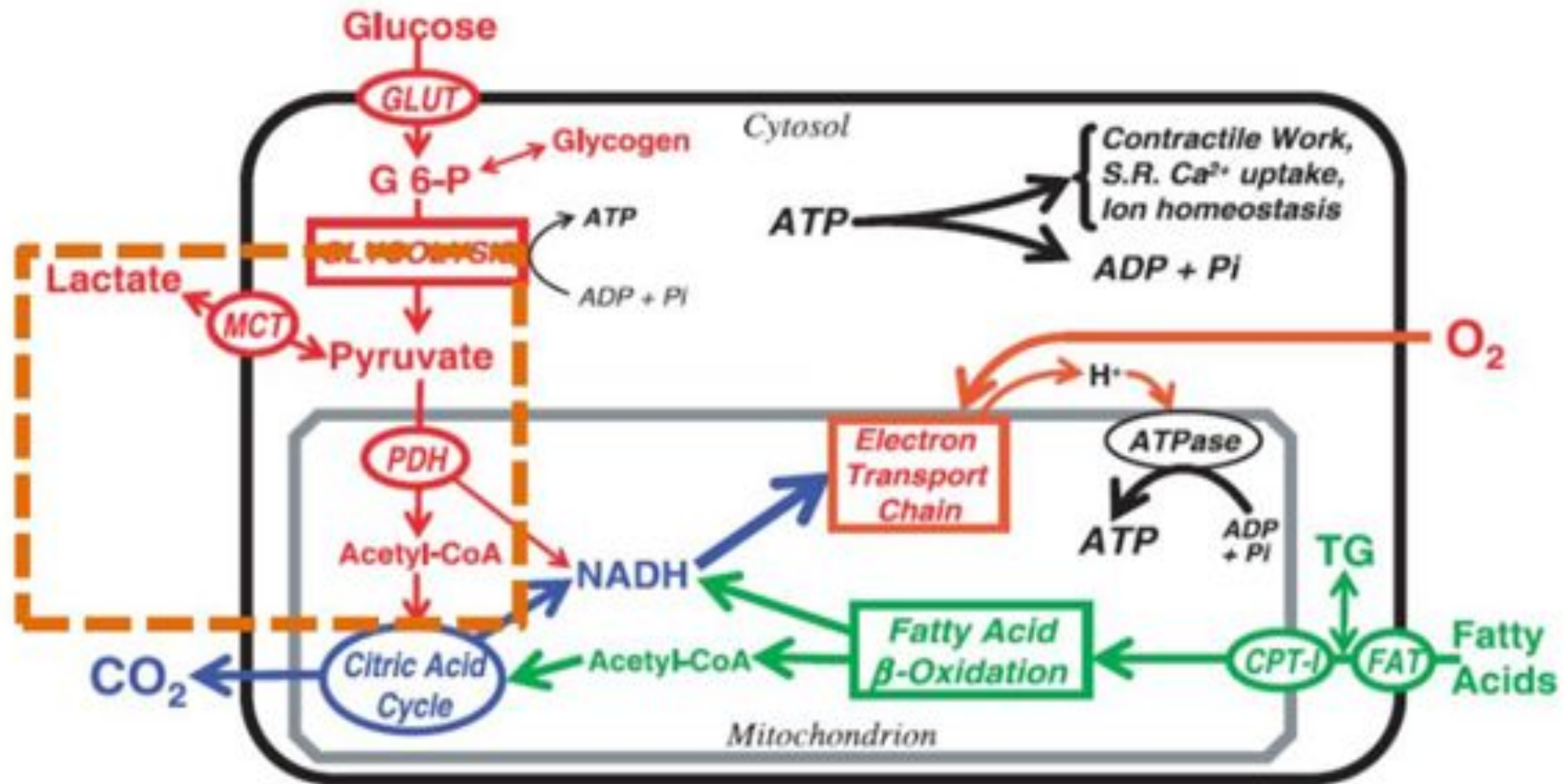
* glucose → form of glucose storage in the cells.

- ❖ Most astrocytic lactate is obtained from anaerobic metabolism of glucose and small amounts from G-6-P obtained from

has iso enzyme help in G6P → lactate [alternative pathway of energy]

↑ glucose → glycogen storage
↓ O₂ → lactate pathway.

- ❖ Astrocytic lactate is used as a source of energy for neurons.



Glycogen synthesis in astrocytes:

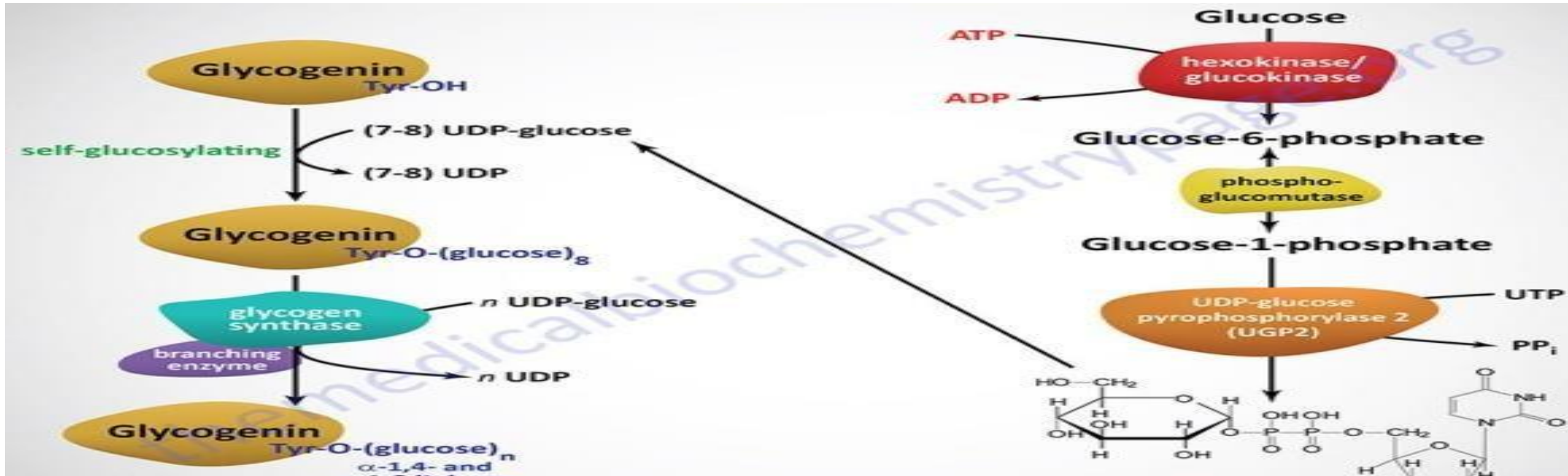
بقیم ذخیره بار neuron حیوانی طبیعتاً و لا

Glycogen is a complex glucose polymer found in a variety of tissues, including brain, liver **localized primarily in astrocytes**. The small quantity found in brain compared to **hypoglycemia** has led to the understanding that brain glycogen is merely used during

.or ischemia

← ذخیره ای است در گلوکز
.. liver

- Brain **glycogen stores are small** (about **1/10th** of muscle)



* there is 12 GLUT classes
[Glucose 7]

Astrocyte up to transporter

- ❖ Glucose enters the astrocytes via GLUT1 and GLUT4 (GLUT 4 not entering glucose in the cell without insulin stimulator).

M. N. 12

- ❖ Glucose is phosphorylated by hexokinase (HK) to G-6-P, which is subsequently converted to G-1-P by phosphoglucomutase (PGM) and then to UDP glucose by UDP glucose pyrophosphate (UDPGPP). The UDP glucose continues on to glycogen synthesis via the actions of glycogen synthase (GYS), which is activated by dephosphorylation (GYSb → active dephosphorylated GYSa) using protein phosphatase-1 (PP-1).

- ❖ Glycogenolysis: Glycogen is broken down by glycogen phosphorylase (GP) which is activated by phosphorylation (inactive GPb → active phosphorylated form GPa) using phosphorylase kinase (PK).

* when we need glucose → the glycogenolysis occur.

HMP shunt:

Glucose may be oxidized via HMP shunt, **highly important not only for neurons** but also for many other brain cells. This pathway contributes to the production of **NADPH** and 5-carbon sugar.

Reducing agent [نتائج] [نتائج]

NADPH + H⁺ is reducing agent important for: - ∴ neurons ∼ NADPH - [نتائج]

a. **Synthesis of lipids** and **nucleic acids**. Therefore, HMP shunt is of great importance in a developing brain compared to a mature brain, e.g. in terms of lipogenesis and myelination in the nervous system.

* support the neuron [myelination sheath].

②

promotes b. Metabolizing neurotransmitters In this way, NADPH also regeneration of antioxidant glutathione. Therefore, high HMP shunt activity can also be found in the mature brain

→ metabolism

← antioxidant for the cell

VC

c. Ascorbic acid is taken up by neurons to protect themselves from oxidant species (ascorbic acid is oxidized in neurons). Oxidized ascorbic acid (dehydroascorbic acid) is released from neurons and taken up by astrocytes. Oxidized ascorbic acid is reduced via

NADPH+H⁺ to ascorbic acid.

reduced form oxidized form is VC → VC → NADPH →

Brain Metabolism

Glucose

Lactate

Neuron

fructose-2,6-bisphosphate

transporter

MCT2s

High A and Low T

MCT4s

Low A and High T

Ketone Bodies

last chance

Lactate metabolism by the brain

Lowest transporter called mono carboxylate transporter..

1. Neurons exhibit a slower rate of glycolysis than astrocytes ^{more in Astrocyte than neuron.}
due to low production of fructose-2,6-bisphosphat, which is the strongest activator of phosphofructokinase, a key enzyme of glycolysis.
^{↓ phospho- fructose kinase the enzyme of glycolysis in the neuron.}

2. Excessive activation of glycolysis in neurons leads to oxidative stress. (excess free radicals : ^{accumulation. lead to Apoptosis} not paired electron can build up in cells and have avital role but in increase cause damage to other molecules, such as DNA, lipids, and proteins) and apoptosis of neurons ^{synthesis}

لذلك راح يدي كيتي بدسايهها. //

* the AMP shunt more in the neuron than Astrocyte
...NADPH لا كيتي بدسايهها

- This suggests that neurons cannot afford to maintain a high rate of glycolysis. ↑glucose concentration
- At the same time, it has been shown that starts the HMP shunt in neurons.
من مانتقصر الخلية + تطلز دار NADPH جاية بييد
- The **balance between the glycolysis and HMP shunt** must be strictly maintained in neurons to meet their energy needs, while retaining their antioxidant status.
- The use of lactate as a substrate may be a source of an oxidant to produce large amounts of ATP, apart from the glycolysis, which can save neurons glucose

The diagram illustrates the metabolic coupling between a post-synaptic neuron, an astrocyte, and a capillary. The post-synaptic neuron releases neurotransmitters (red dots) into the synaptic cleft. Glutamate (Glt) is taken up by the neuron and converted to Glutamine (Gln) in the astrocyte. Lactate (Lac) is also taken up by the astrocyte. The astrocyte then releases Gln back to the neuron and Lac to the capillary. The capillary releases Glucose (Glc) to the astrocyte. The astrocyte also shows the TCA cycle and Acetyl-CoA (Ac) production.

The hypothesis of astrocyte-neuron lactate shuttle:

- Glucose is transported from blood to astrocytes.
- After entering the astrocyte via GLUT1, part of the glucose is metabolized to lactate via pyruvate by the isoenzyme of lactate dehydrogenase (LDH5).
- Then lactate is transported outside the astrocyte through the MCT transporter and is captured by neurons, also via the MCT.

Monocarboxylate transporters

(MCTs): 3 types

- It transport monocarboxylic acids (monocarboxylates) as lactate.
 - Different types of MCTs are found in different cells in the brain:
1. **MCT1s**: It is found in oligo-dendrocytes, have an intermediate affinity for lactate, and tend to export lactate from a cell.
 2. **MCT2s**: It is found in neurons, have a high affinity for lactate, allowing neurons to bring in lactate as fuel efficiently even in substrate-poor conditions.
 3. **MCT4s** : It is found in astrocytes, have a low affinity but high transport rate to lactate

Ketone bodies metabolism by the brain:

↳ from fatty acid

last chance of Brain

- In the absence of glucose, the brain has alternative energy sources, including ketones derived from fatty acid metabolism taking place mainly in the liver. These include

- ① β -hydroxybutyrate (BHB),
- ② acetoacetate, and
- ③ acetone.

- Ketone bodies are metabolized to acetylCoA, then transferred to the Krebs' cycle (TCA) and oxidized in an amount sufficient to satisfy the high metabolic requirements of the brain.

glucose / fatty acid → Ketone Body → acetyl CoA → Krebs cycle.
 * الحاجة لأكسجين
 Ketone body ← fatty acid
 [prolonged starvation]
 كيتون بادي ← حمض دهني
 [طول فترةOrange starvation]

Lipid Metabolism

ريزنت موقه ريس
ريافت
• **Lipids** ← myeline
عليها
ديك
بها..

- **Lipids** store energy as triglycerides, but **NOT** in the **BRAIN** (almost **no** triglycerides there)
- Lipids function as **messengers** (steroid hormones, eicosanoids)

طالو دور خ (metabolism)

- **Triglycerides** and free fatty acids constitute only a very small percent
- The lipids are incorporated into membrane structures and are especially rich in myelin
- Cholesterol is the only sterol in the brain in significant amounts

دو [precursor of the neurotransmitter or to the steroid]