Biochemistry

5. Bio-Energetics & ATP

5.2b) Cellular Metabolism & Energetics

Prof. Dr. Klaus Heese

Brain Energy

The nervous system, compared with other organs, is the greatest consumer of oxygen and glucose.
The fact that, in a resting adult, about 40 % of the total energy consumption is required for ion pumping in the CNS accounts for the exquisite sensitivity of the brain to damage from oxygen deprivation.
Brain: 2% of body weight but 25% of total body glucose utilization.

----> brain: 2% of body weight only

----> 15% of cardiac output

----> 700ml/minute or ~57ml/100g of brain tissue/minute

----> 25% of total glucose consumption

----> 20% of total oxygen consumption of the whole organism (~160μmol/100g brain tissue/min)

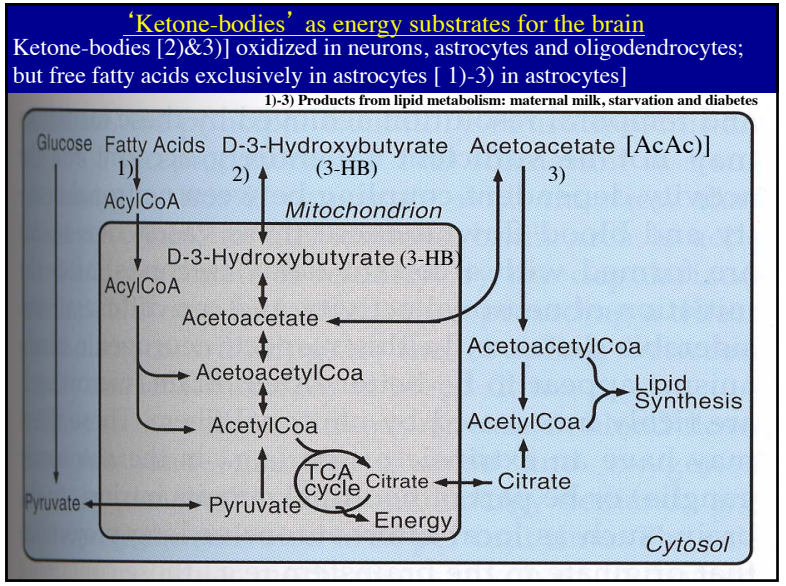
----> 40% of the total energy consumption is required for ion-pumping in the CNS

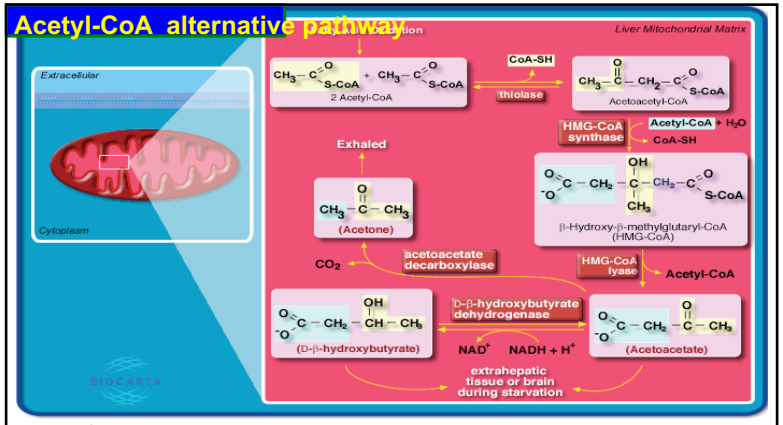
----> respiratory quotient = O_2-consumption/CO_2-production ~1

----> carbohydrates, glucose are the exclusive substrates for oxidative metabolism

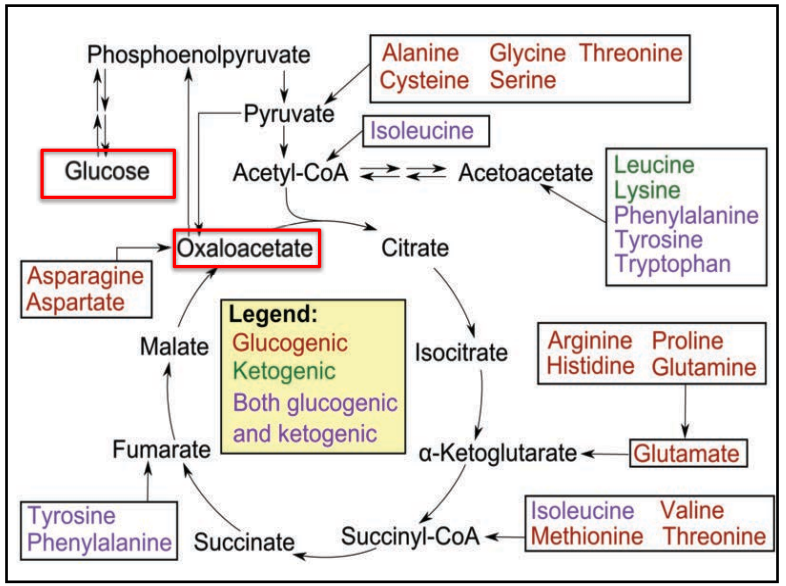
Ketone Bodies

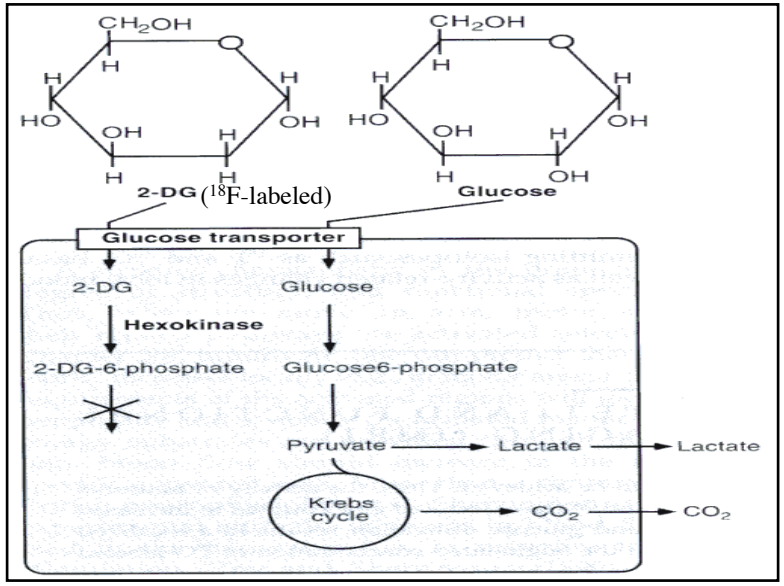
- Use of fatty acids in the citric acid (Kreb's) cycle requires carbohydrates (CHO) for the production of oxaloacetate (OAA) – 'fat burns in CHO flame'.
- During starvation or diabetes, OAA is used to make glucose
  - Fatty acids are then used to make ketone bodies (acetoacetate and D–3–hydroxybutarate)

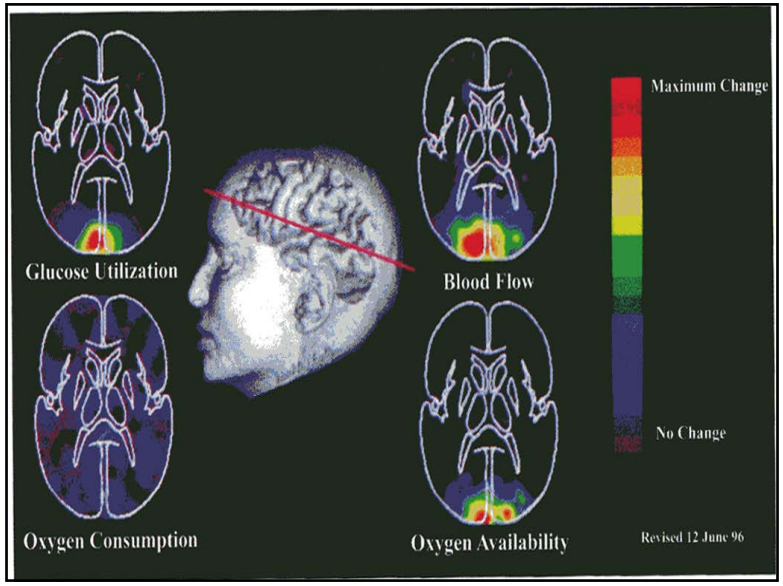




The acetyl-CoA produced by mitochondrial beta-oxidation of fatty acids enters the Kreb's cycle to produce energy, but that is not the only fate of acetyl-CoA. In liver mitochondria, some acetyl-CoA is converted to acetoacetate, beta-hydroxybutyrate, and acetone, collectively called ketone bodies. Ketone bodies are transported to other tissues such as brain, muscle or heart where they are converted back to acetyl-CoA to serve as an energy source. The brain normally uses only glucose for energy, but during starvation ketone bodies can become the main energy source for the brain. In the metabolic condition called ketosis, ketone bodies are produced faster than they are consumed by tissues and the smell of acetone can be detected on a person's breath. The smell of acetone is one indication that a person may have diabetes. The consumption of high-fat/low carbohydrate diets has been used as a weight loss program by many, intentionally inducing ketosis to consume fat stores, but these ketogenic diets can cause unwanted side effects related to increased urea production resulting from protein intake and risk of heart disease from increased cholesterol and fat intake.







Mediators of coupling Neuronal Activity to CBF

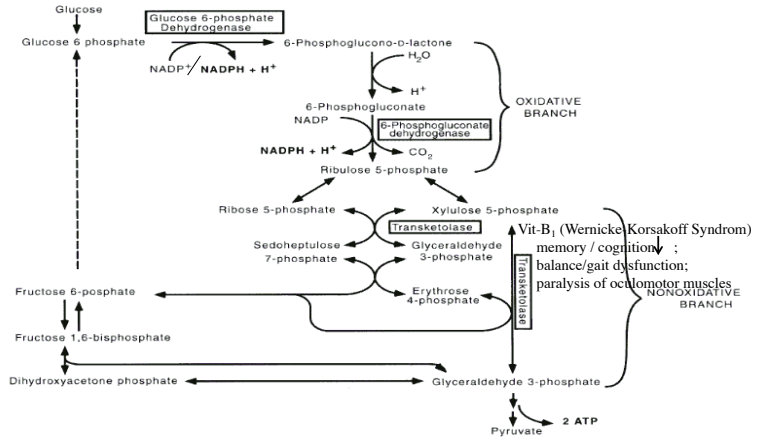
1) - K^+, adenosine, lactate, pH,
2) - Neurotransmitters: NE, 5-HT, ACh
3) - Peptides: neuropeptide-Y (NPY),
vasoactive intestinal peptide (VIP)
calcitonin gene-related peptide (CGRP),
substance-P (SP),

[2), 3) = *neurogenic mechanisms*]
and:
- NO

Regulation of cerebral blood flow is achieved mainly by control of the tone or the degree of constriction, or dilation, of the cerebral vessels. This in turn is controlled mainly by local chemical factors such as: $PaCO_2$, PaO_2, pH, …

$PaCO_2 \uparrow$, $PaO_2 \downarrow$, pH $\downarrow$ ---> dilate the blood vessels --->blood flow $\uparrow$

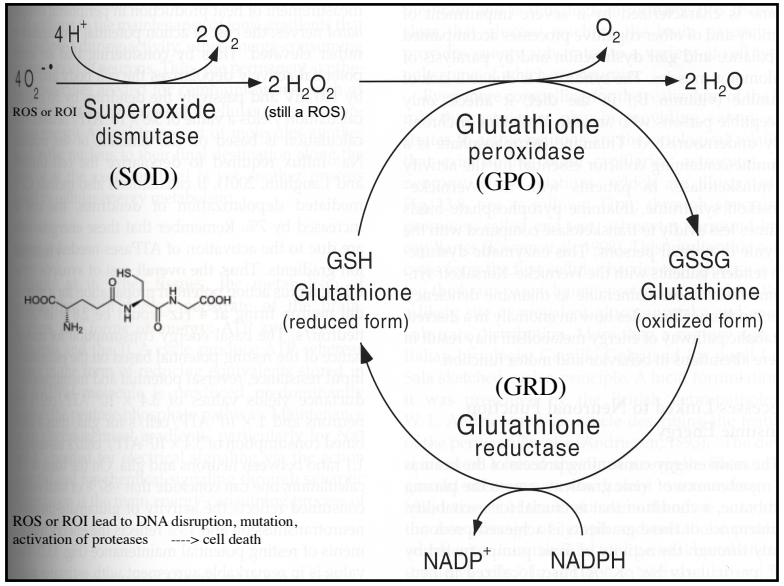
In cells of the brain (as in other organs) reducing energy power is needed and provided by the reduced form of NADPH. The processing of glucose through the Pentose Phosphate pathway produces NADPH which is needed, e.g., for synthesis of free fatty acids from acetyl-CoA, which are components of myelin and other neuronal structural elements



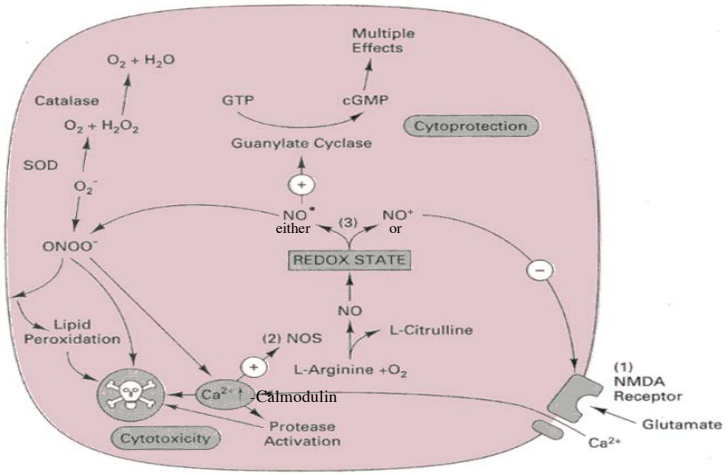
NADPH is also needed for the scavenging of reactive oxygen species (ROS)

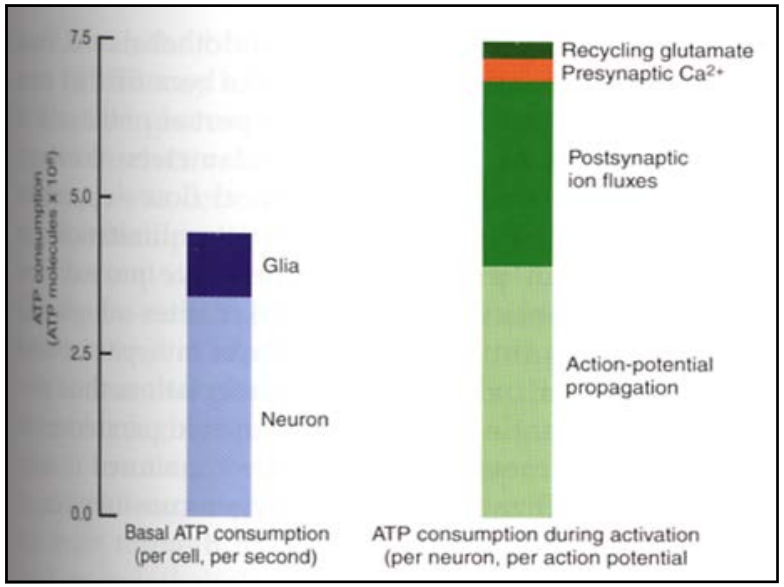
Superoxide anion, hydrogen peroxide, hydroxy radical generated as 'by-products' of certain physiological cellular processes:
Oxidative phosphorylation and activities of:
monoamine oxidase (MAO), tyrosine hydroxylase (TH),
nitric oxide synthase (NOS), cyclooxygenase (COX), lipoxigenase (lox)

(regeneration of NAD+ from NADH must be accomplished through the conversion of pyruvate to lactate and a hydrogen ion via lactate dehydrogenase. Because this pathway is inefficient - yielding 2 molar equivalents of ATP of each mole of glucose consumed versus ~30-38 mol ATP generated under aerobic conditions - ATP production falls as levels of lactate and hydrogen ions rise and local pH levels drop.)



Postulated mechanism whereby NO causes cytotoxicity or cytoprotection in nervous tissue



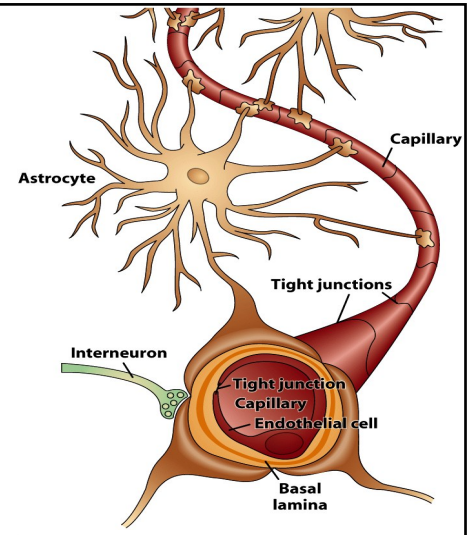


40 % energy consumption in resting body for ion-pumping in the CNS.
Na^+/K^+-ATPase in neurons/glia
The main energy consuming process of the brain is the maintenance of ionic gradients across the plasma membrane, a condition that is crucial for excitability.
Activity of these pumps accounts for approximately 50% of basal glucose oxidation in the nervous system.
Other energy-consuming processes:
neurotransmitter synthesis, axonal transport, …

Oxidases/oxygenases/hydroxylases (e.g.: TH), utilize O_2 and incorporate it into hydroxyl groups; or MAO which deaminates oxidatively monoamine neurotransmitters to aldehydes.

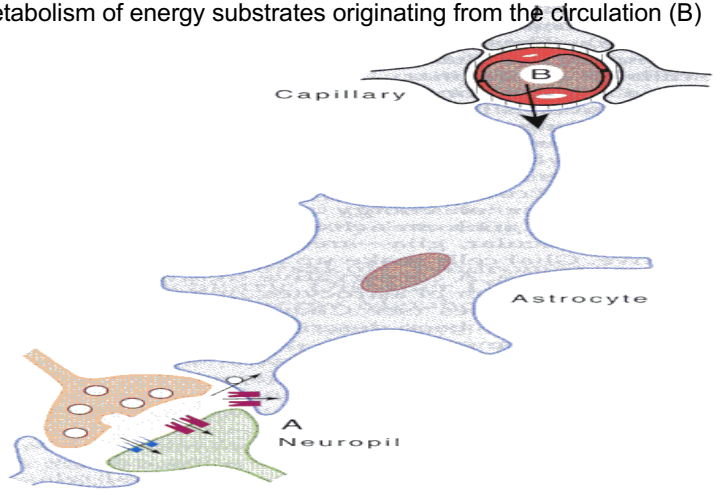
Pentose phosphate pathway provides reducing power (NADPH) for (e.g.) scavenging of ROS. … Wernicke-Korsackoff syndrome.

Astrocytes as mediators between capillaries and neuropil



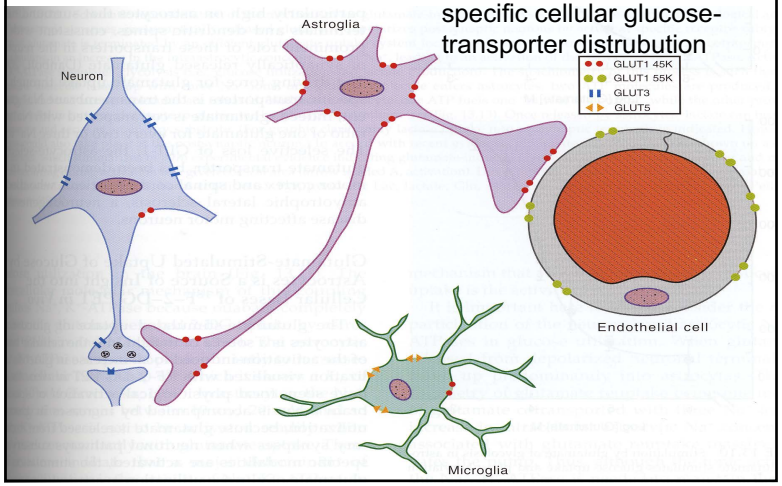
Astrocytes as mediators between capillaries and neuropil

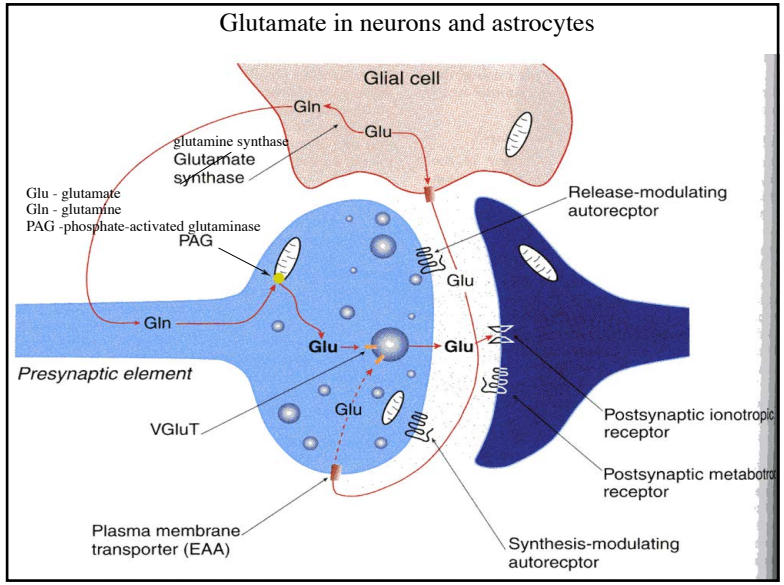
Astrocytes sense synaptic activity (A) and couple it with uptake and metabolism of energy substrates originating from the circulation (B)

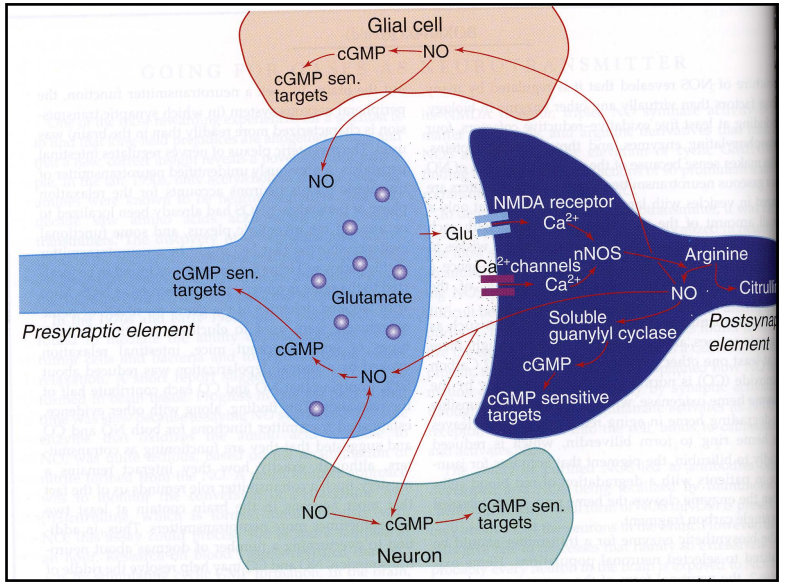


in brain: ~ 0.5-2.0 mM glucose in extracellular space; basal rate of glucose utilization is higher in astrocytes than in neurons, with values of about 20 and 6 nmol per milligram of protein per minute, respectively.

specific cellular glucose-transporter distrubution







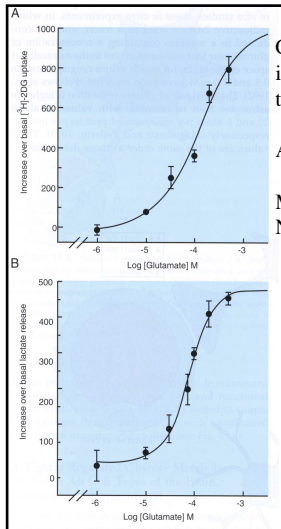
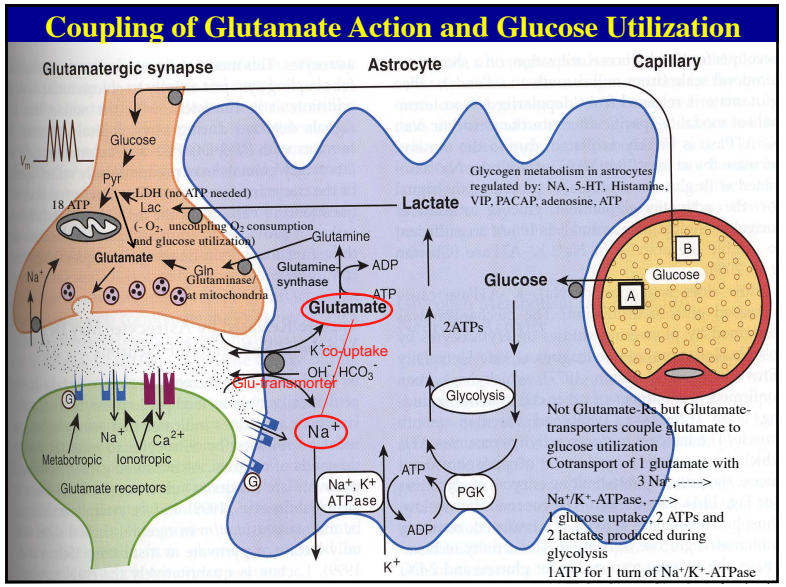


FIGURE 13.10 Stimulation by glutamate of glycolysis in astrocytes. Glutamate stimulates glucose uptake and phosphorylation (A) and lactate production (B) in astrocytes. This effect is concentration dependent with an EC_{50} of ~60 mM.

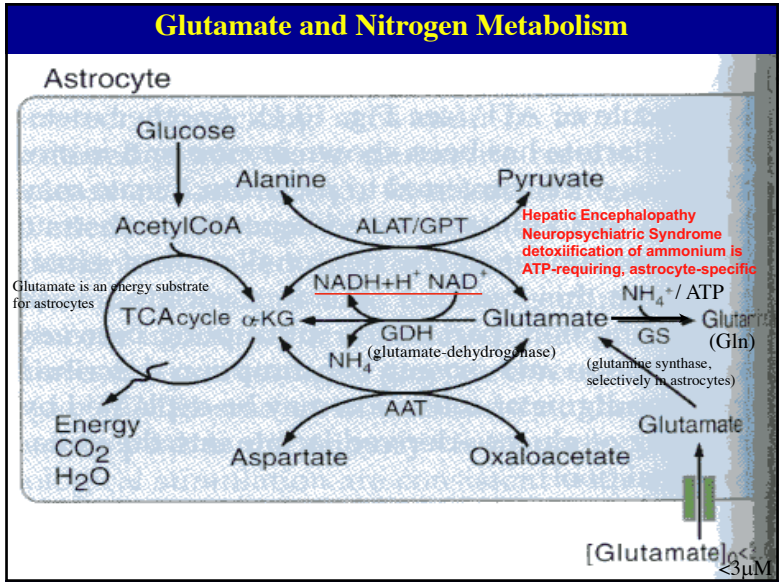
Glutamate stimulates glucose uptake and phosphorylation in a dose-dependent manner mediated by glucose-transporters.

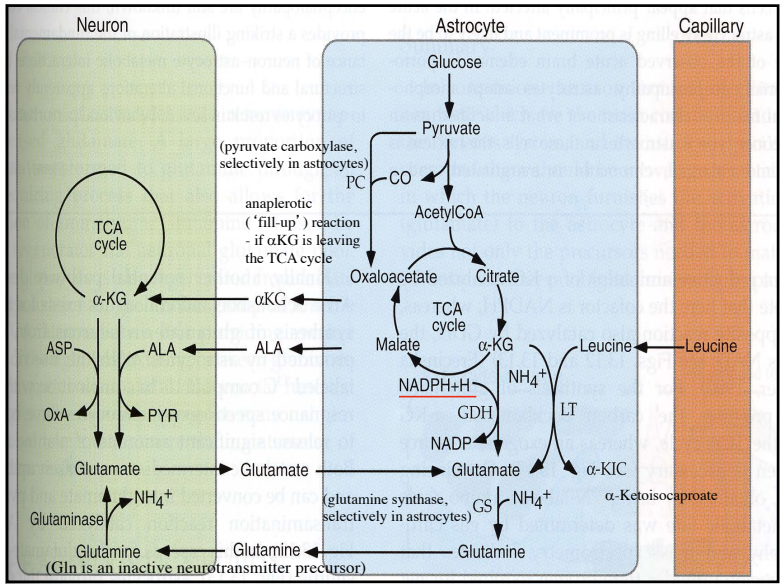
Additional functions of astrocytes:

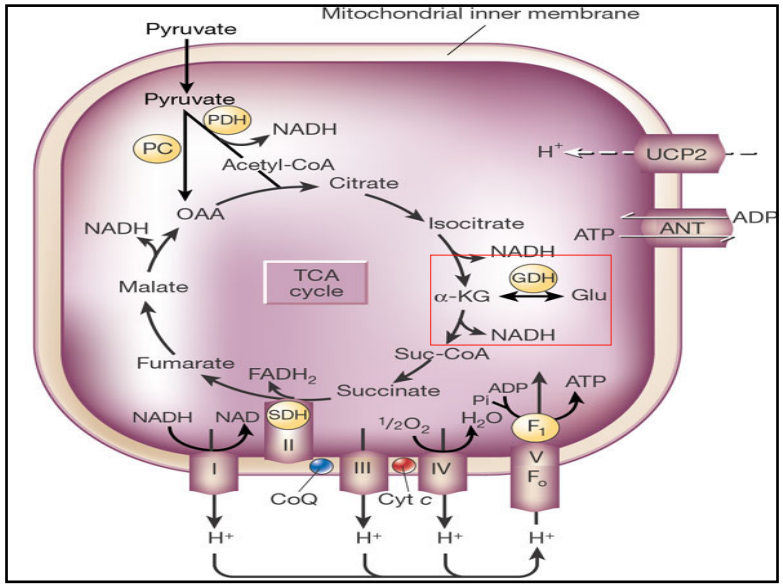
Maintenance of extracellular K^+-homeostasis
Neurotransmitter-uptake



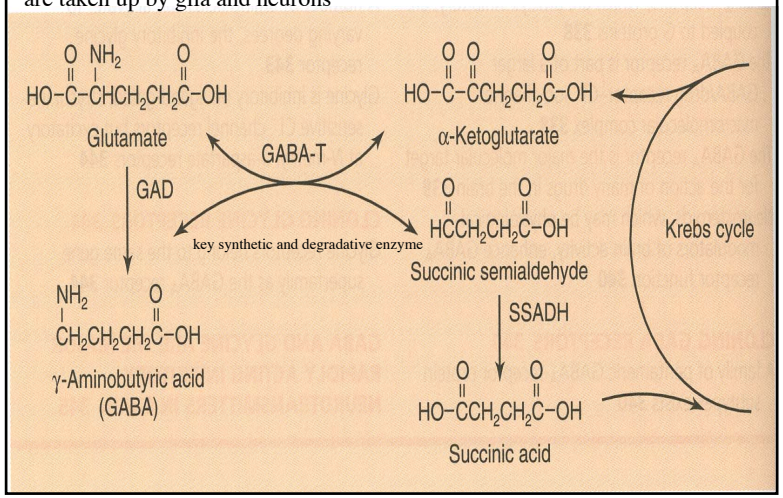
lactate formed within the brain parenchyma (e.g., through glutamat-activatcd glycolysis in astrocytes) can fulfill the energetic needs of neurons. Lactate, after conversion into pyruvate by a reaction catalyzed by lactate dehydrogenase (LDH), can provide, on a molar basis, 18 ATP through oxidative phosphorylation. Conversion of lactate into pyruvate does not require ATP, and, in this regard, lactate is energetically more favorable than the first obligatory step of glycolysis in which glucose is phosphorylated to glucose 6-phosphate at the expense of one molecule of ATP. Another metabolic fate for lactate has been shown *in vitro* and *in vivo* by MRS. Thus, once converted to pyruvate, lactate may enzymatically yield glutamate and hence be a substrate for the replenishment of the neuronal pool of glutamate. Because this reaction is not associated with oxygen consumption, part of the uncoupling between glucose utilization and oxygen consumption described in certain paradigms of activation may be explained by the processing of glucose-derived lactate into the glutamate neuronal pool.







Major difference between catecholamines and amino acid neurotransmitters
the latter are derived from glucose metabolism and
are taken up by glia and neurons



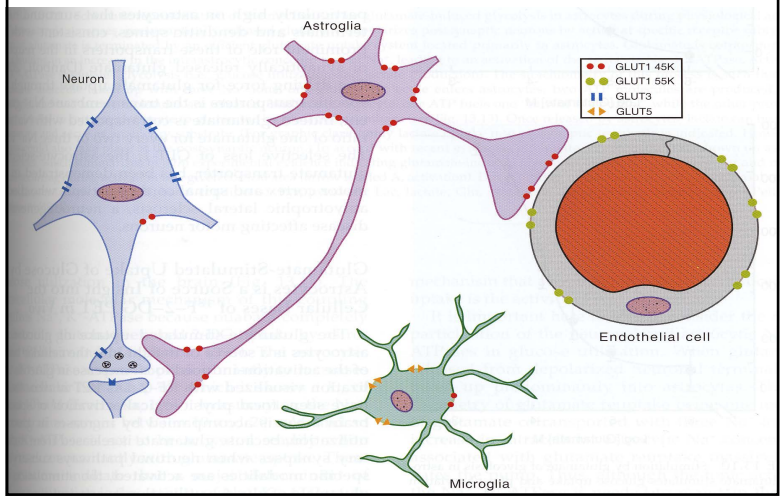
Taking home message:

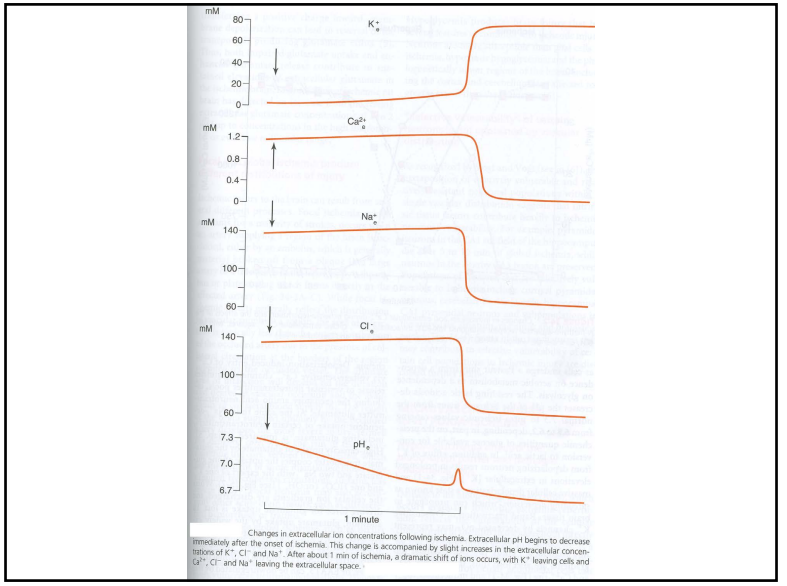
- main energy consuming process of the brain is?
- Wernicke-Korsackoff syndrome
- Coupling of Glutamate Action and Glucose Utilization

Ischemia

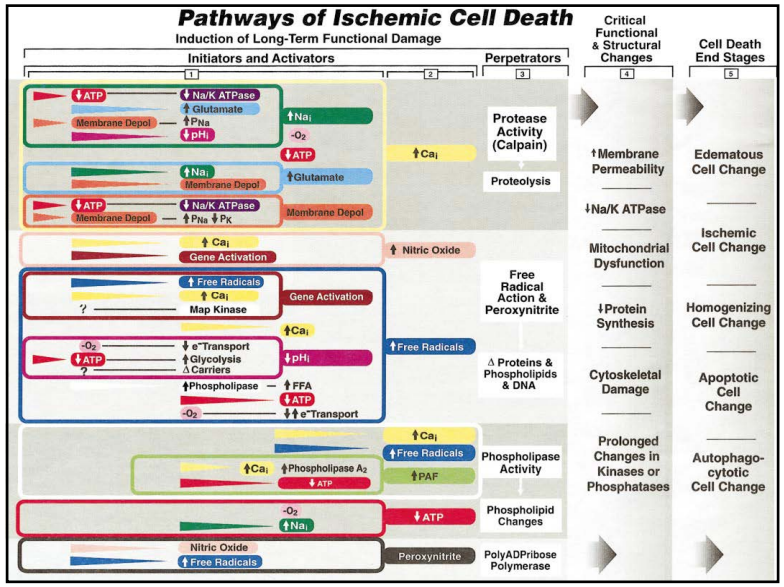
Q) Which mechanisms may contribute to ischemia-mediated neurodegeneration in the brain?

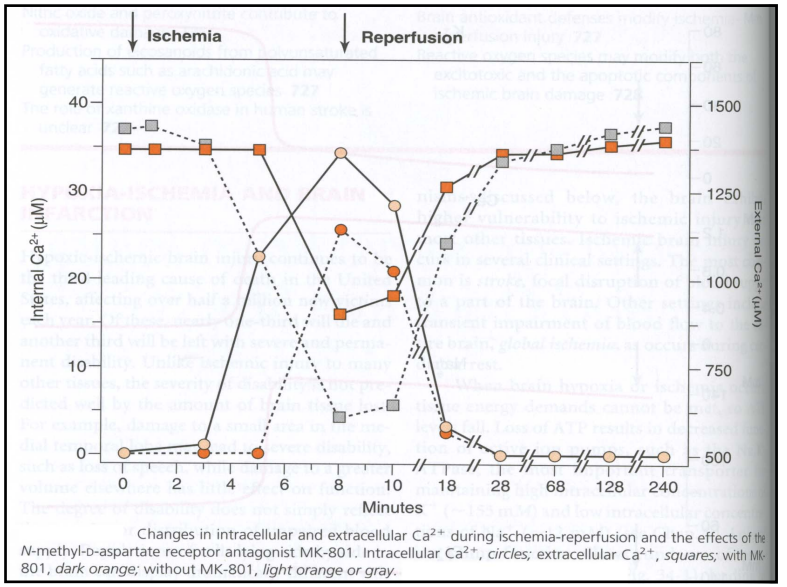
in brain: ~ 0.5-2.0 mM glucose in extracellular space; basal rate of glucose utilization is higher in astrocytes than in neurons, with values of about 20 and 6 nmol per milligram of protein per minute, respectively.



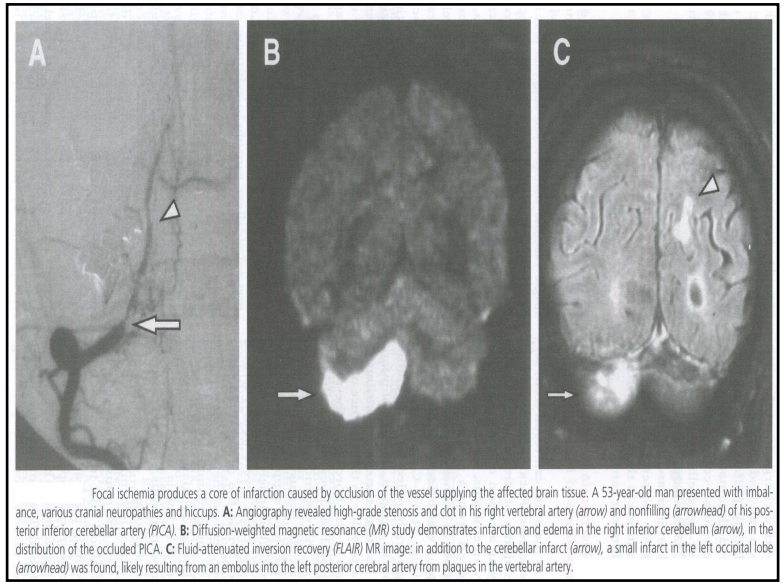


Changes in extracellular ion concentrations following ischemia. Extracellular pH begins to decrease immediately after the onset of ischemia. This change is accompanied by slight increases in the extracellular concentrations of K^+, Cl^- and Na^+. After about 1 min of ischemia, a dramatic shift of ions occurs, with K^+ leaving cells and Ca^{2+}, Cl^- and Na^+ leaving the extracellular space.

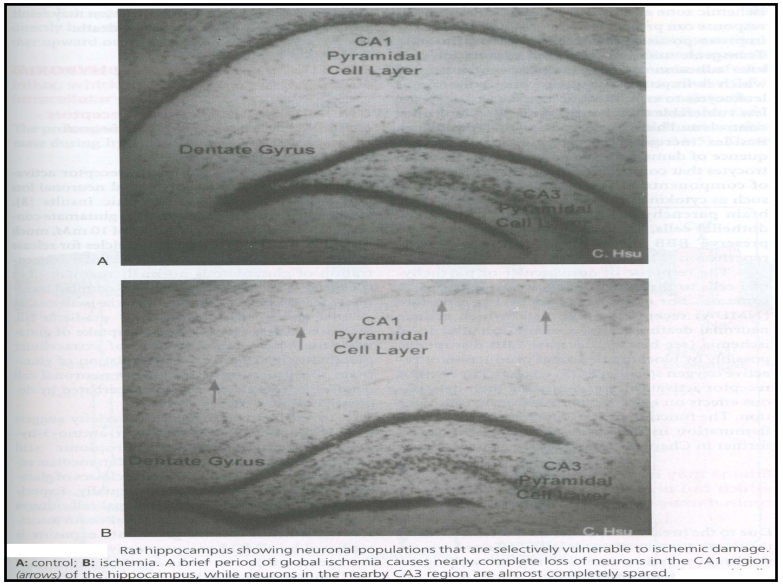




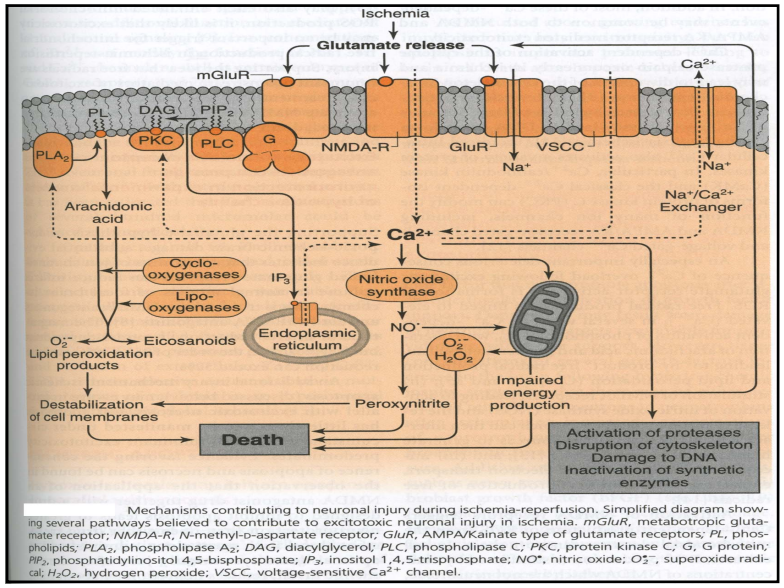
Changes in intracellular and extracellular Ca^{2+} during ischemia-reperfusion and the effects of the *N*-methyl-D-aspartate receptor antagonist MK-801. Intracellular Ca^{2+}, *circles;* extracellular Ca^{2+}, *squares;* with MK-801, *dark orange;* without MK-801, *light orange or gray.*



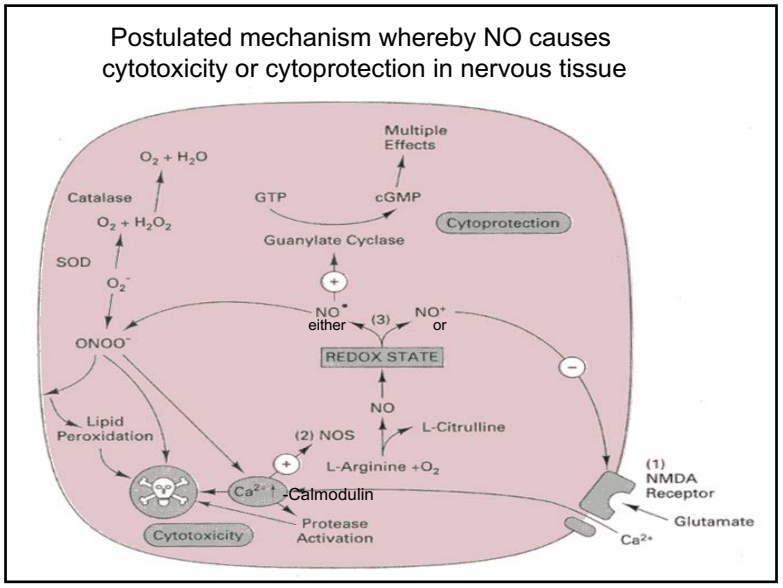
Focal ischemia produces a core of infarction caused by occlusion of the vessel supplying the affected brain tissue. A 53-year-old man presented with imbalance, various cranial neuropathies and hiccups. **A:** Angiography revealed high-grade stenosis and clot in his right vertebral artery *(arrow)* and nonfilling *(arrowhead)* of his posterior inferior cerebellar artery *(PICA)*. **B:** Diffusion-weighted magnetic resonance *(MR)* study demonstrates infarction and edema in the right inferior cerebellum *(arrow)*, in the distribution of the occluded PICA. **C:** Fluid-attenuated inversion recovery *(FLAIR)* MR image: in addition to the cerebellar infarct *(arrow)*, a small infarct in the left occipital lobe *(arrowhead)* was found, likely resulting from an embolus into the left posterior cerebral artery from plaques in the vertebral artery.

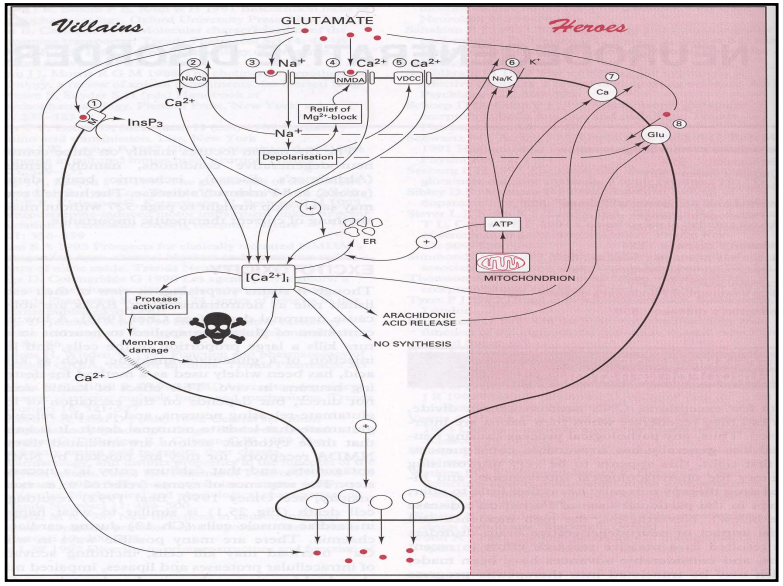


Rat hippocampus showing neuronal populations that are selectively vulnerable to ischemic damage. **A:** control; **B:** ischemia. A brief period of global ischemia causes nearly complete loss of neurons in the CA1 region *(arrows)* of the hippocampus, while neurons in the nearby CA3 region are almost completely spared.



Mechanisms contributing to neuronal injury during ischemia-reperfusion. Simplified diagram showing several pathways believed to contribute to excitotoxic neuronal injury in ischemia. *mGluR*, metabotropic glutamate receptor; *NMDA-R*, *N*-methyl-D-aspartate receptor; *GluR*, AMPA/Kainate type of glutamate receptors; *PL*, phospholipids; PLA_2, phospholipase A_2; *DAG*, diacylglycerol; *PLC*, phospholipase C; *PKC*, protein kinase C; *G*, G protein; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; $NO^{\bullet}$, nitric oxide; $O_2^{\bullet-}$, superoxide radical; H_2O_2, hydrogen peroxide; *VSCC*, voltage-sensitive Ca^{2+} channel.




Villains
Heroes
GLUTAMATE
Na+
Ca2+
Ca2+
K+
Na/Ca
NMDA
VDCC
Na/K
Ca
Glu
Ca2+
InsP3
Relief of Mg2+-block
Na+
Depolarisation
ATP
ER
MITOCHONDRION
[Ca2+]i
Protease activation
Membrane damage
Ca2+
ARACHIDONIC ACID RELEASE
NO SYNTHESIS