Alternative Energy Substrates for the Brain

Lipids as Energy Substrates

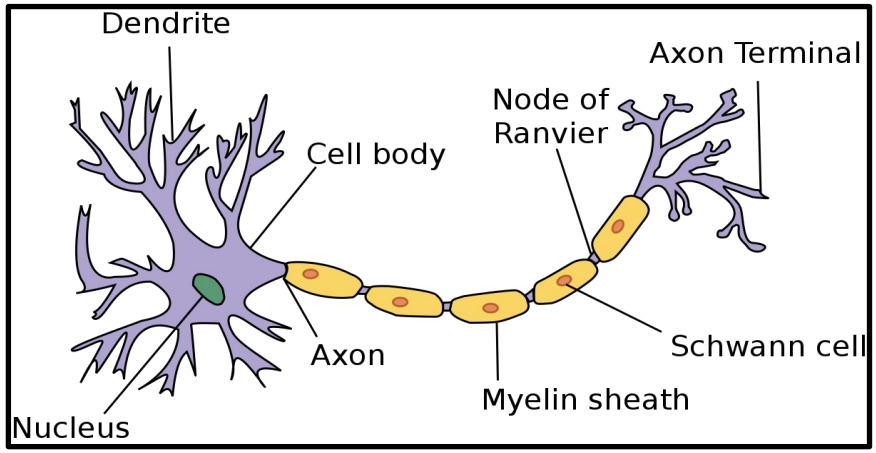
The brain is an incredibly energy-hungry organ.

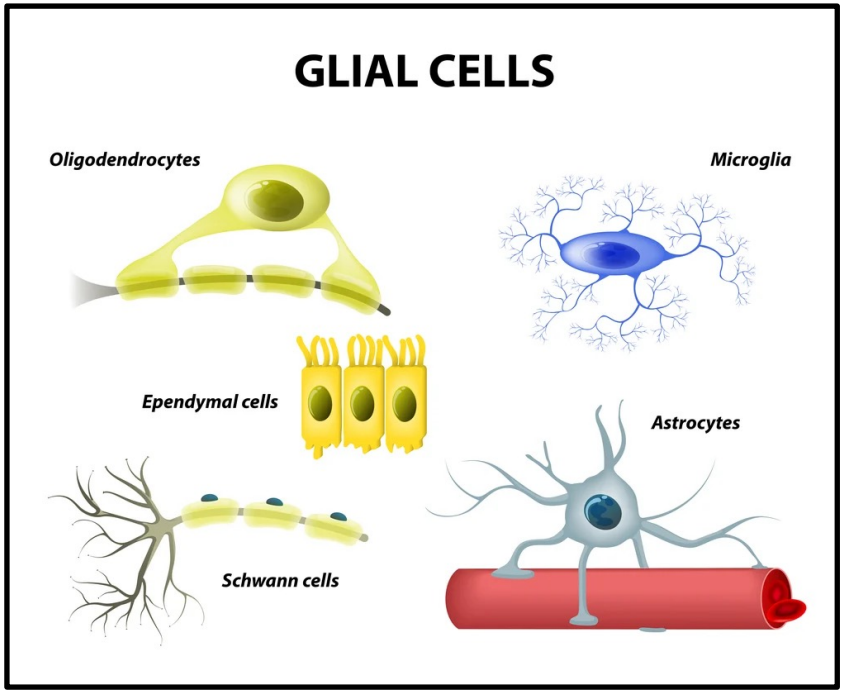
It requires a constant source of metabolites to maintain function.

The general consensus is that this energy requirement is almost entirely satisfied by glucose metabolism.

However, it has recently been shown that approximately 20% of the total energy requirement of the brain is met through the oxidation of fatty acids and that this fatty acid oxidation may take place entirely in astrocytes

- Virtually all cholesterol produced in the brain (>99.5%) remains unesterified, and the majority of this is present within myelin sheaths and plasma membranes of glial and neuronal cells.
- Lipid metabolism in the CNS is unique in that there is virtually no exchange of cholesterol and lipoproteins from the peripheral circulation, owing mostly to the impermeable nature of the BBB.

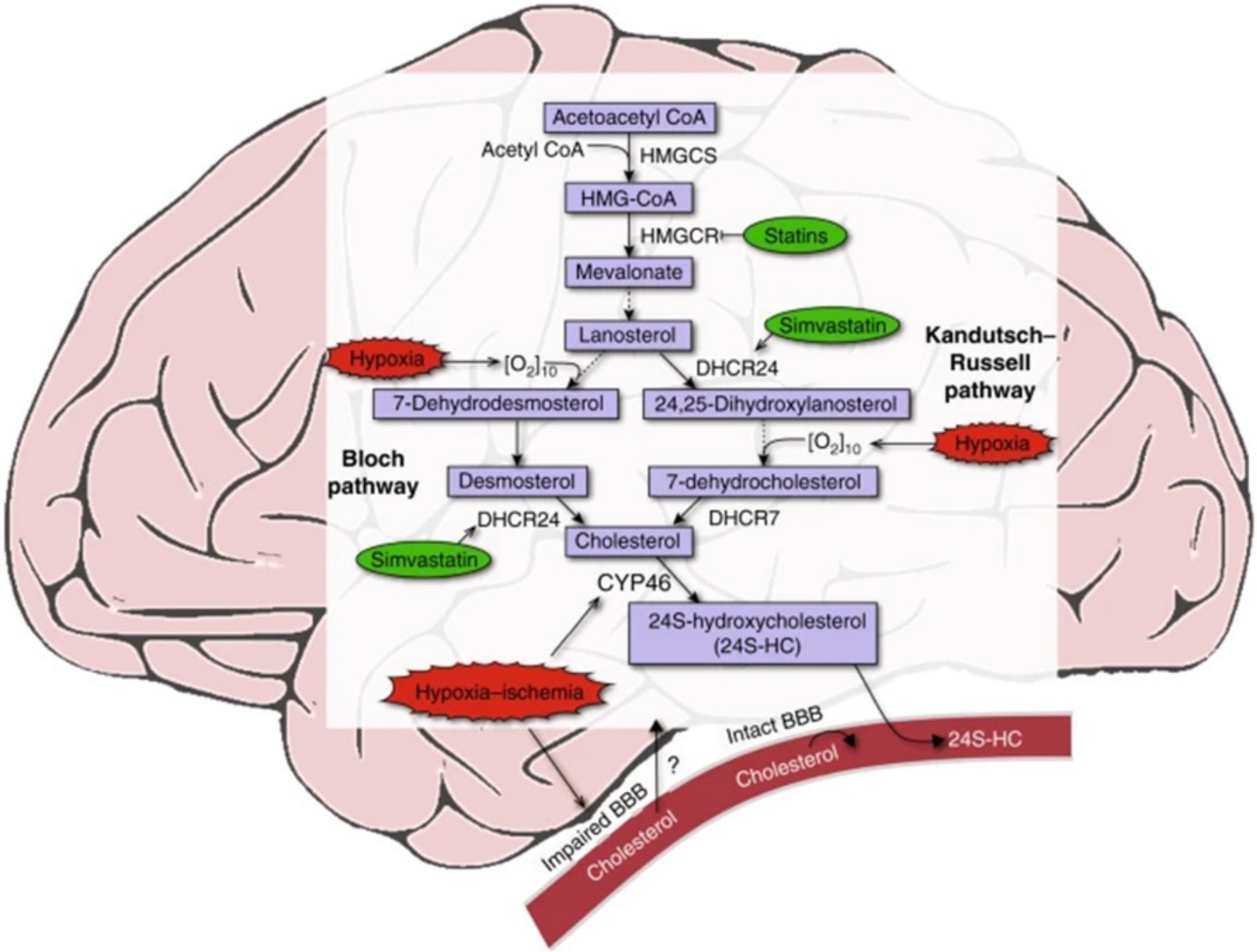




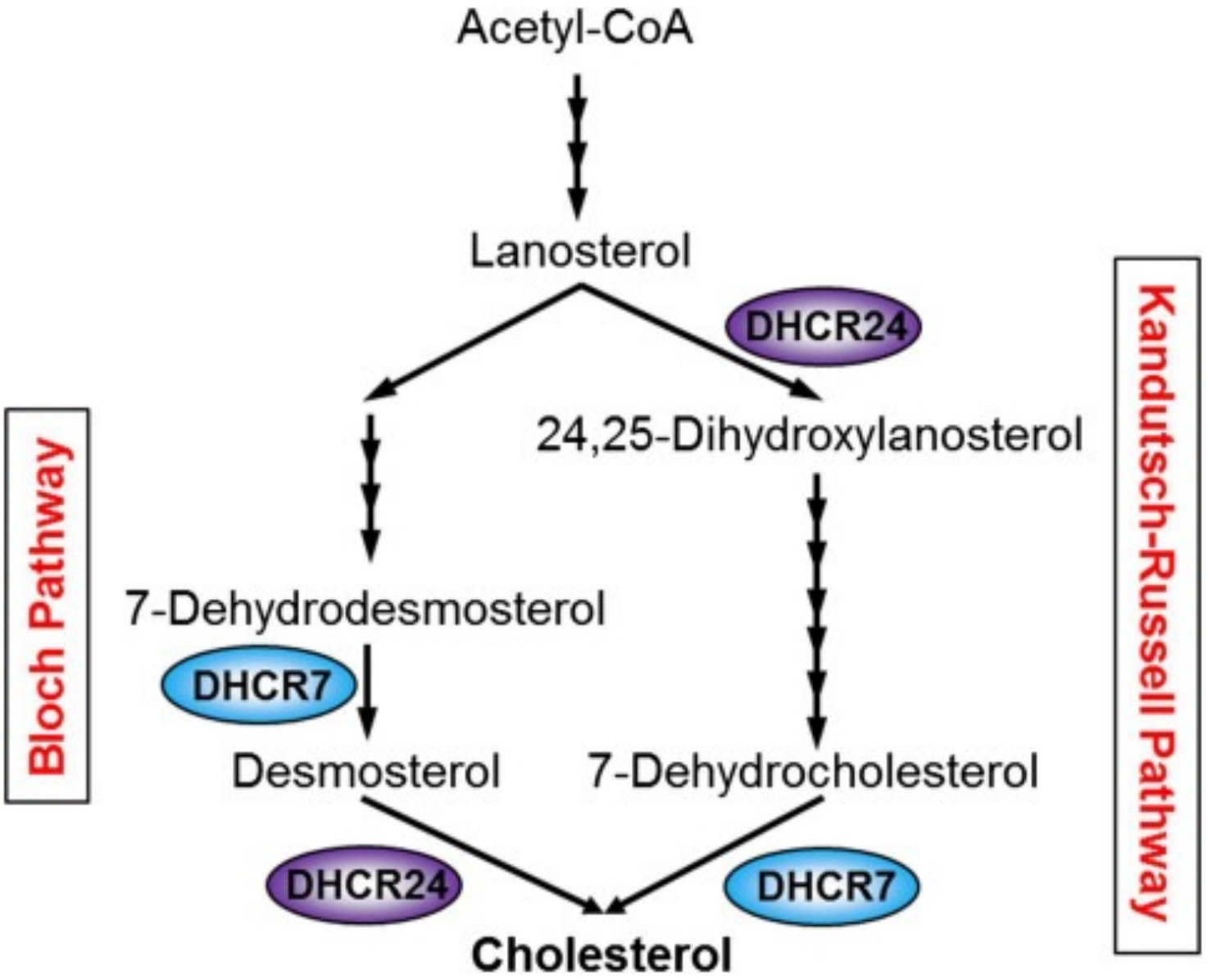
- Thus, cholesterol in the CNS exists in a compartment distinct from the rest of the body.
- This has been clearly demonstrated in numerous studies, where radio-labeled cholesterol injected into the periphery cannot be detected in the CNS.
- Thus, practically all cholesterol present in the CNS is synthesized *de novo* in brain cells, and is efficiently recycled within the CNS, having a half-life of between 1 and 5 years in comparison with a few hours in the periphery.
- Lipids in the brain are composed of cholesterol, sphingolipids, and glycerophospholipids.
- The majority of cholesterol in the central nervous system is concentrated in myelin (~80%) as well as in the membranes of neurons and glia.

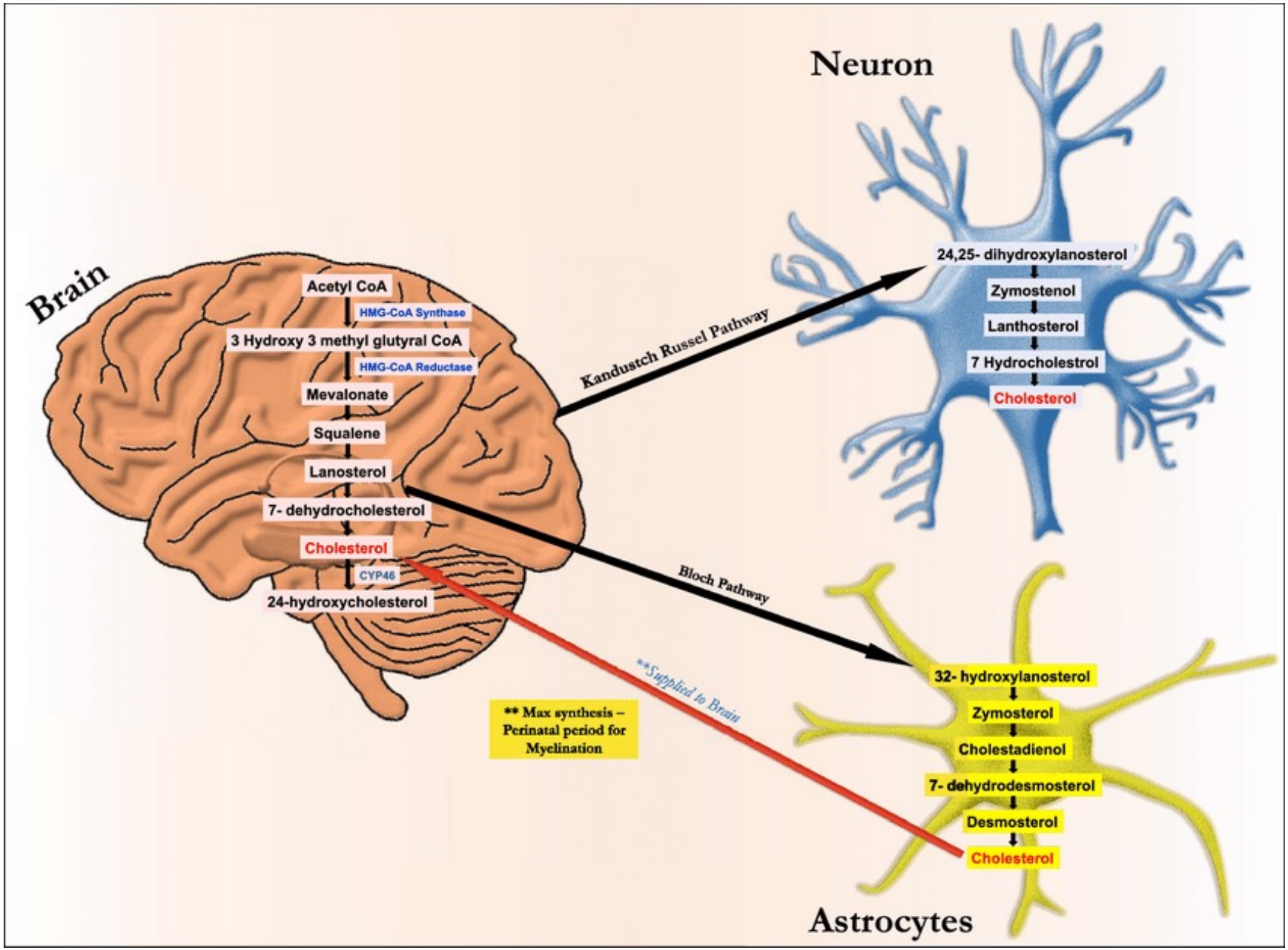
- Cholesterol homeostasis is dependent on balanced synthesis, absorption, and conversion to bile acids.
- The concentration of sterols in the central nervous system is higher than in other parts of the body
- The peripheral cholesterol is unable to cross the blood- barrier (BBB), so cholesterol synthesis in the brain is almost completely de novo.
- Cholesterol biosynthesis occurs from a series of reactions in the **Kandutsch–Russell, and Bloch pathways**.
- Neurons and astroglia use the Bloch pathway preferentially.
- Maintenance of adequate brain cholesterol levels is vital to neurodevelopment, and interruptions of any of the several steps of the cholesterol biosynthesis pathway may result in abnormal cholesterol levels, potentially affecting neurodevelopment.

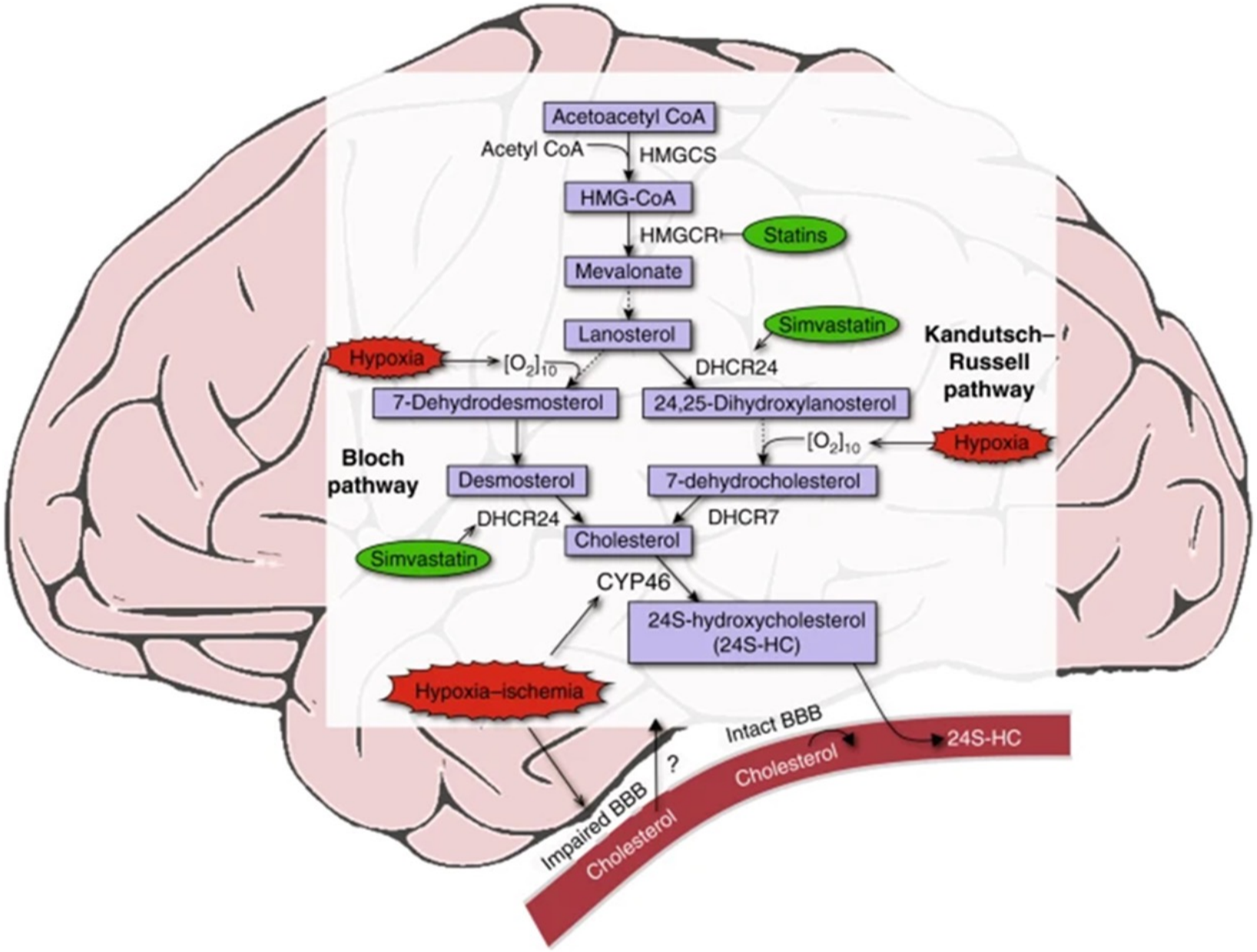
Central nervous system cholesterol metabolism



Kandutsch–Russell and Bloch pathways




Neuron
Brain
Acetyl CoA
HMG-CoA Synthase
3 Hydroxy 3 methyl glutyral CoA
HMG-CoA Reductase
Mevalonate
Squalene
Lanosterol
7- dehydrocholesterol
Cholesterol
CYP46
24-hydroxycholesterol
Kandustch Russel Pathway
24,25- dihydroxylanosterol
Zymostenol
Lanthosterol
7 Hydrocholestrol
Cholesterol
Bloch Pathway
** Max synthesis – Perinatal period for Myelination
**Supplied to Brain
32- hydroxylanosterol
Zymosterol
Cholestadienol
7- dehydrodesmosterol
Desmosterol
Cholesterol
Astrocytes


Acetoacetyl CoA
Acetyl CoA
HMGCS
HMG-CoA
HMGCR
Statins
Mevalonate
Lanosterol
Simvastatin
Hypoxia
$[O_2]_{10}$
DHCR24
Kandutsch–Russell pathway
7-Dehydrodesmosterol
24,25-Dihydroxylanosterol
$[O_2]_{10}$
Hypoxia
Bloch pathway
Desmosterol
7-dehydrocholesterol
DHCR24
DHCR7
Simvastatin
Cholesterol
CYP46
24S-hydroxycholesterol (24S-HC)
Hypoxia–ischemia
Intact BBB
24S-HC
Cholesterol
?
Impaired BBB
Cholesterol

Role of astrocytes in lipid metabolism
Most cholesterol synthesis occurs in astrocytes

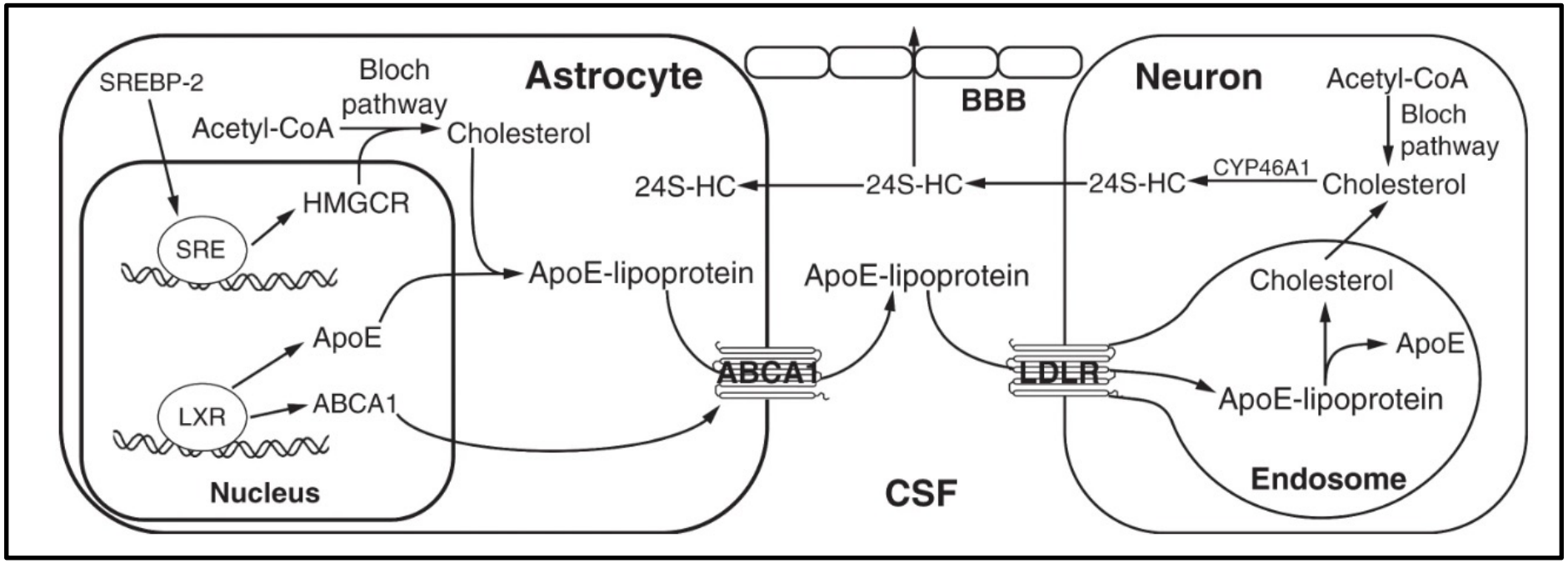
- Apoprotein E (apoE) is the major apolipoprotein of the CNS, where it is secreted by astrocytes.
- The ATP dependent transporter ABCA1, expressed by both astrocytes and neurons, promotes the formation of the apoE-stabilized high-density lipoprotein (HDL)–sized particles from astrocytic cholesterol
- apolipoprotein E (apoE) is a well-characterized 34 kDa protein that assists in the regulation of lipid metabolism.

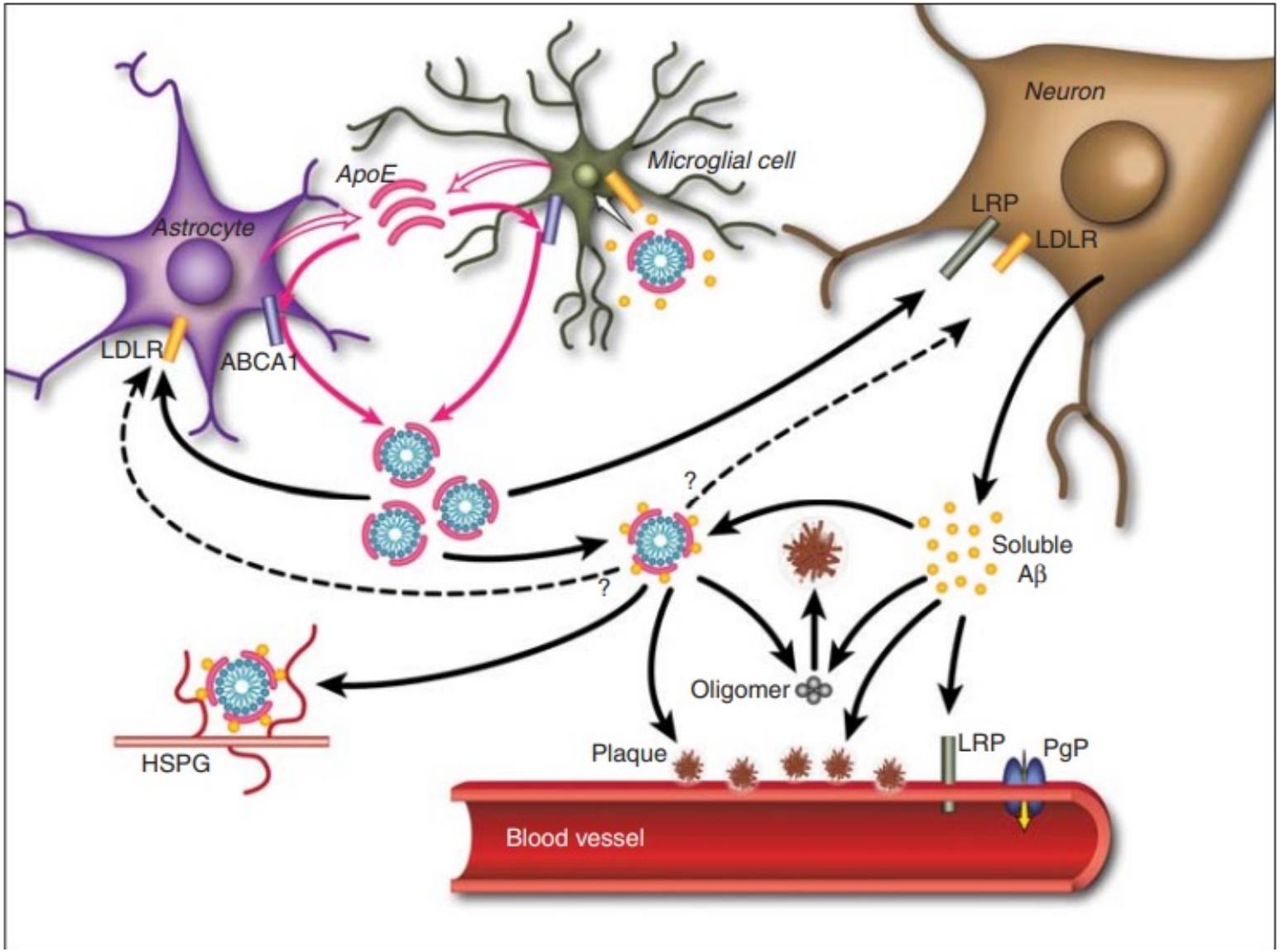
- ApoE is expressed throughout the brain and is produced by astrocytes that secrete apoE as part of a cholesterol-rich lipoprotein particle
- ApoE in the brain is derived from local synthesis with little contribution from the periphery

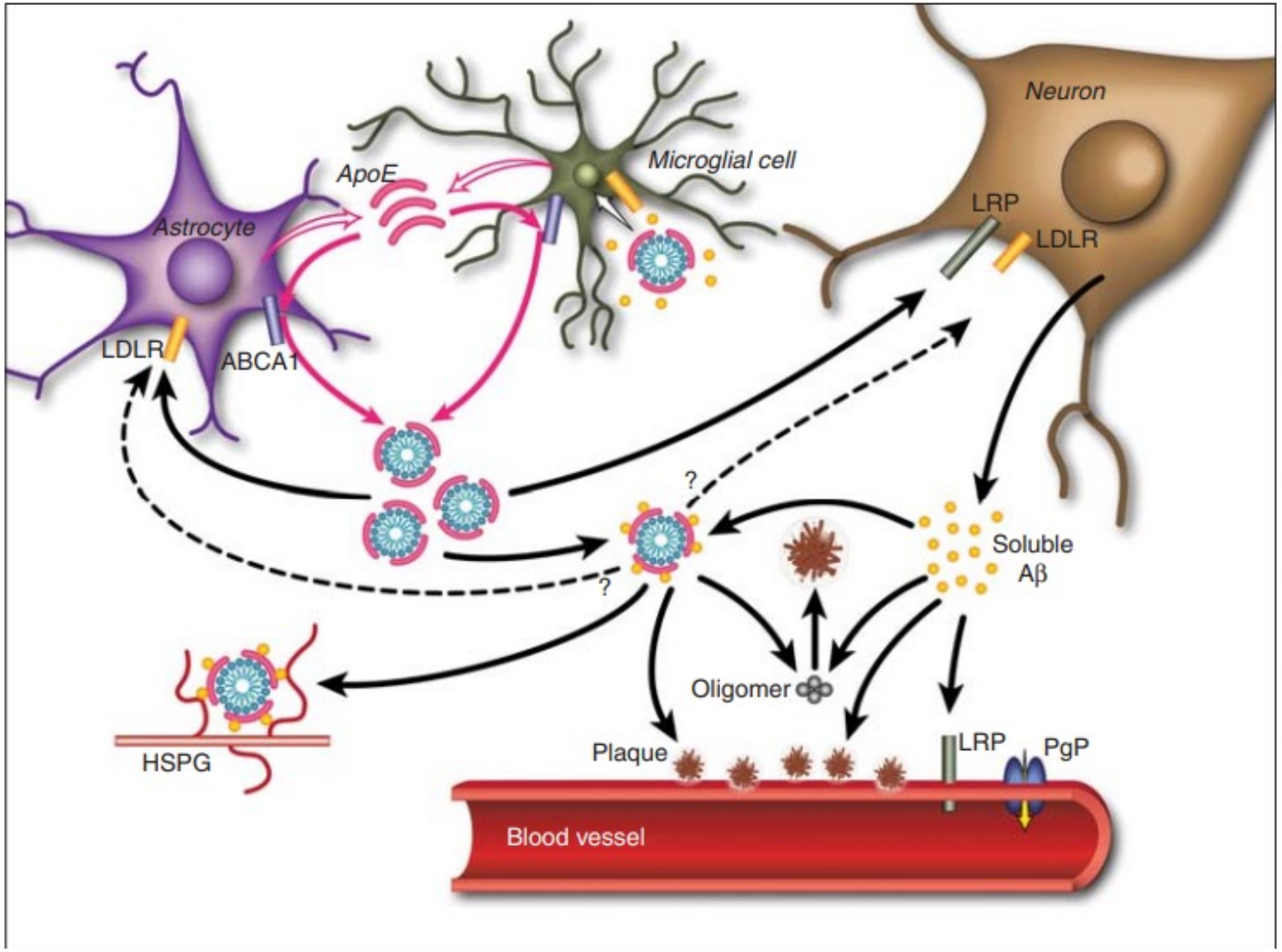
In humans, apoE has three major protein isoforms:

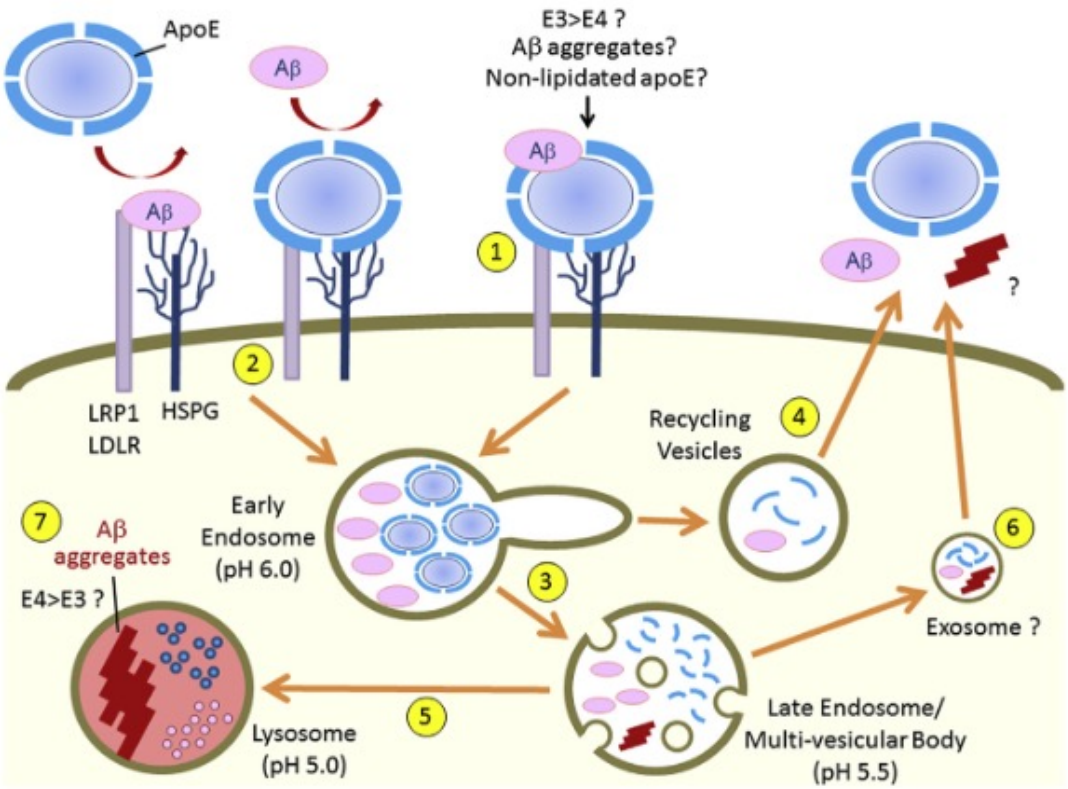
- apoE2 (cys112, cys158)
- apoE3 (cys112, arg158)
- apoE4 (arg112, arg158)
- The association of allele four of apoE (ε4) as a genetic risk factor for Alzheimer's disease (AD) has been well established, accounting for between 50–60% of the genetic variation in the disease

Cholesterol transport during development




Neuron
Microglial cell
ApoE
Astrocyte
LRP
LDLR
LDLR
ABCA1
?
?
Soluble
Aβ
Oligomer
HSPG
Plaque
LRP
PgP
Blood vessel


Neuron
Microglial cell
ApoE
Astrocyte
LRP
LDLR
LDLR
ABCA1
?
?
Soluble
Aβ
Oligomer
HSPG
Plaque
LRP
PgP
Blood vessel


ApoE
Aβ
E3>E4 ?
Aβ aggregates?
Non-lipidated apoE?
Aβ
Aβ
Aβ
?
1
2
LRP1
LDLR
HSPG
Recycling
Vesicles
4
Early
Endosome
(pH 6.0)
7
Aβ
aggregates
E4>E3 ?
3
6
Exosome ?
5
Lysosome
(pH 5.0)
Late Endosome/
Multi-vesicular Body
(pH 5.5)

Pathological alterations in cholesterol metabolism

1. Stroke

- Low levels are associated with intracerebral hemorrhage
- while high levels are associated with ischemic stroke.
- In addition to increasing the risk of stroke, excess cholesterol accumulation in peripheral vasculature induces an inflammatory response and a positive feedback loop that subsequently induces further cholesterol deposition.
- An increase in cholesterol has also been associated with an increase in leukocyte recruitment as well as the release of chemokines and proinflammatory cytokines.

2. Huntington's disease

- Huntington's disease (HD) has also been associated with aberrations of cholesterol metabolism.
- Expression of the mutant huntingtin protein, the protein involved in the development of HD, has been shown to lead to an accumulation of cholesterol and a reduction of cholesterol synthesis in cell culture.

Please Describe the mechanism that illustrates the association between Huntington's disease and cholesterol level?

3. Traumatic brain injury

TBI can affect patients of all ages and is a complex injury resulting from a combination of the primary impact and secondary injury mechanisms.

Secondary effects of TBI result from glial cell activation, leukocyte recruitment, upregulation of inflammatory mediators, and impairment of the BBB.

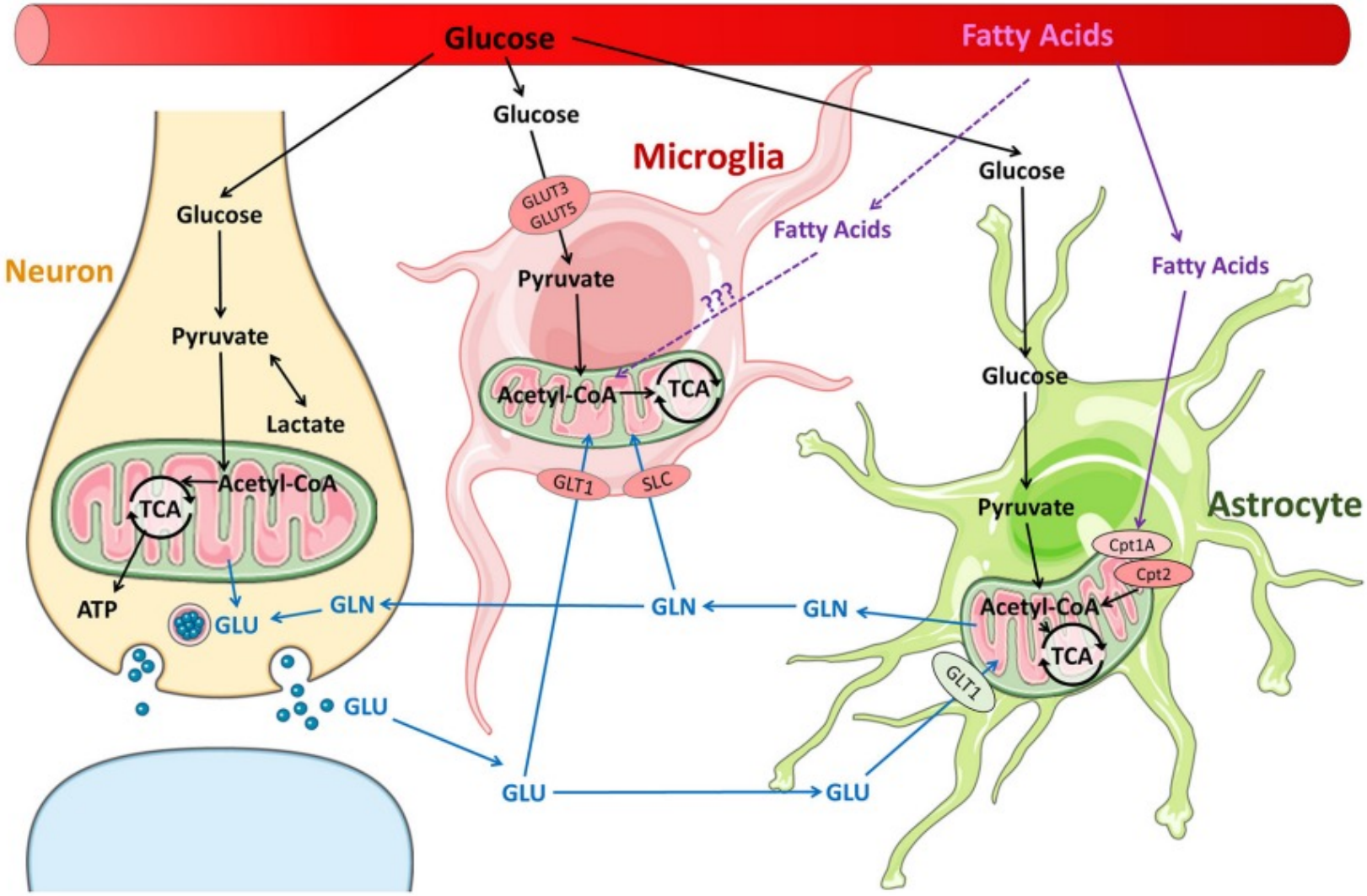
TBI is associated with changes in total cholesterol and phospholipid concentrations.

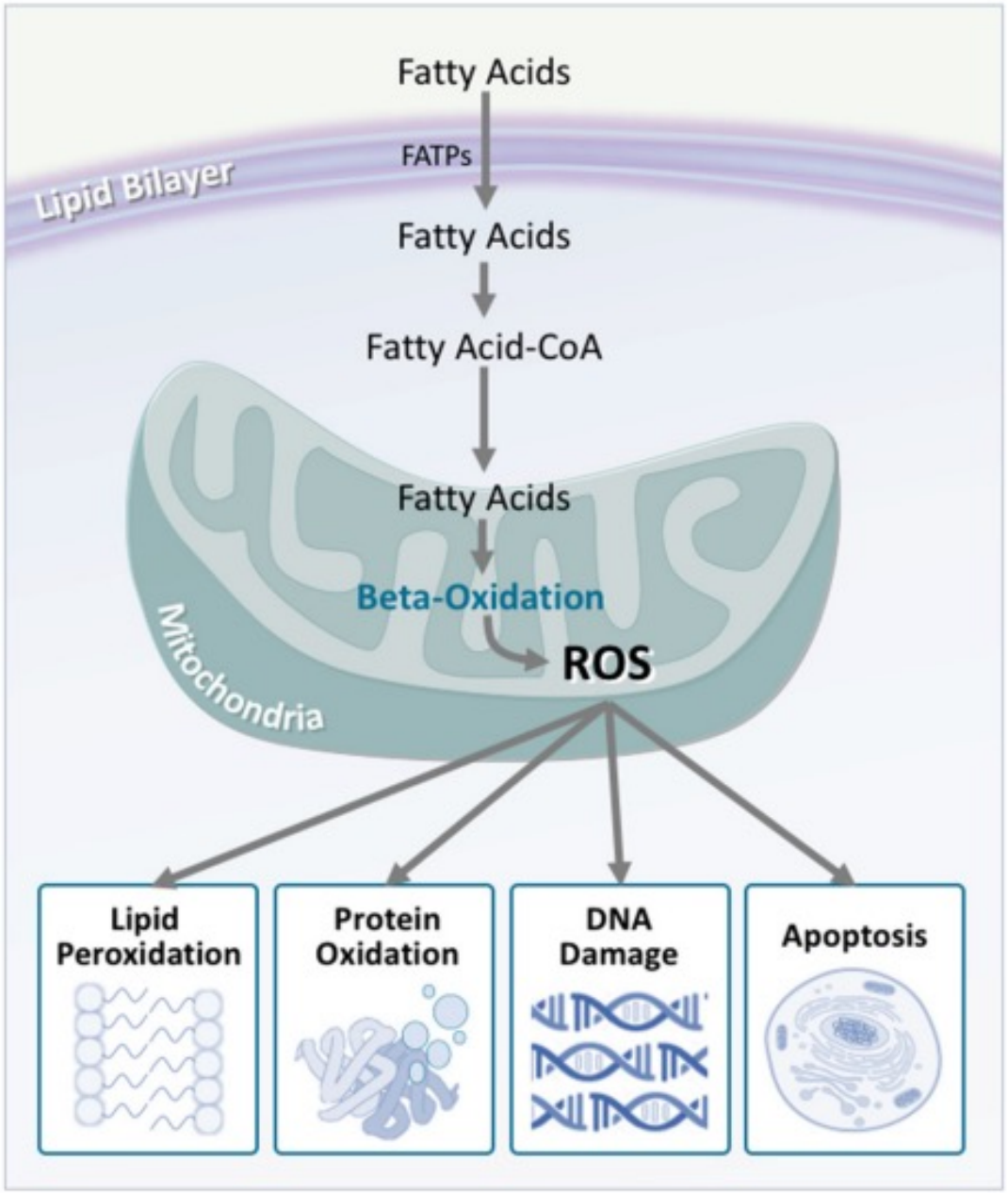
CYP46 activity is upregulated in the cortex and microglia 3 and 7 days after TBI injury, likely reflecting the injured brain's attempt at normalizing the increased cholesterol levels through lipid phagocytosis and increased efflux from the cells.

Fatty Acid Metabolism

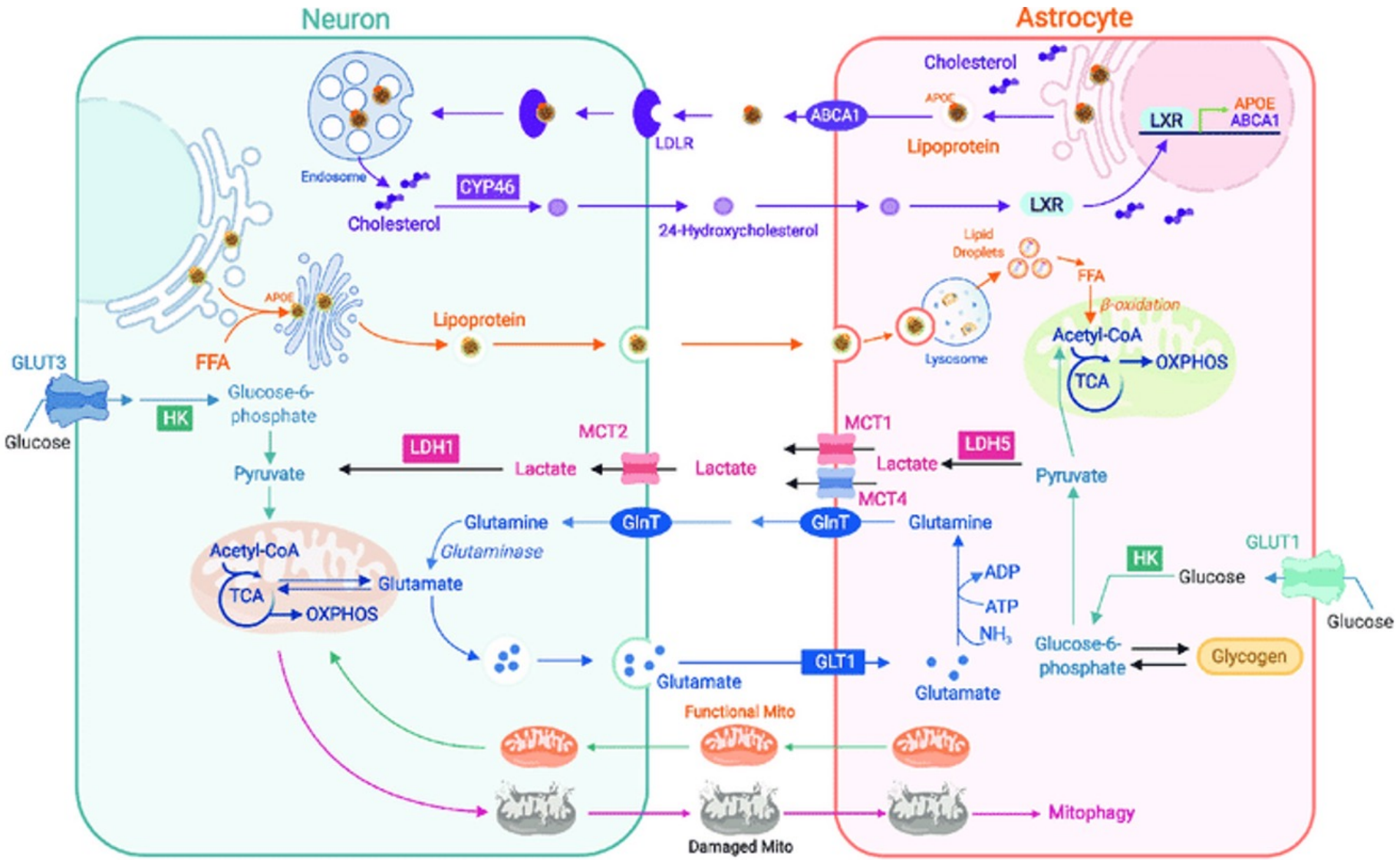
- The brain has a high expression of fatty acid transporters and fatty acid synthase, which enables extensive fatty acids uptake from the blood as well as synthesis de novo in the brain.
- Brain fatty acids are necessary for neurogenesis, synaptogenesis, and synaptic activity.
- The products of fatty acid synthase are important branch points for biosynthesis and the formation of complex lipids or for energy production.
- Fatty acid oxidation is carried out by neural progenitor cells and astrocytes.
- The long-chain acyl-CoAs are shuttled across the mitochondrial membranes via the carnitine palmitoyl transferases (CPTs), and are metabolized into acetyl-CoA by β-oxidation, which subsequently enters the TCA cycle.

Metabolic pathways of fatty acid in neurons and glia in the normal brain




Fatty Acids
FATPs
Lipid Bilayer
Fatty Acids
Fatty Acid-CoA
Fatty Acids
Beta-Oxidation
ROS
Mitochondria
Lipid Peroxidation
Protein Oxidation
DNA Damage
Apoptosis

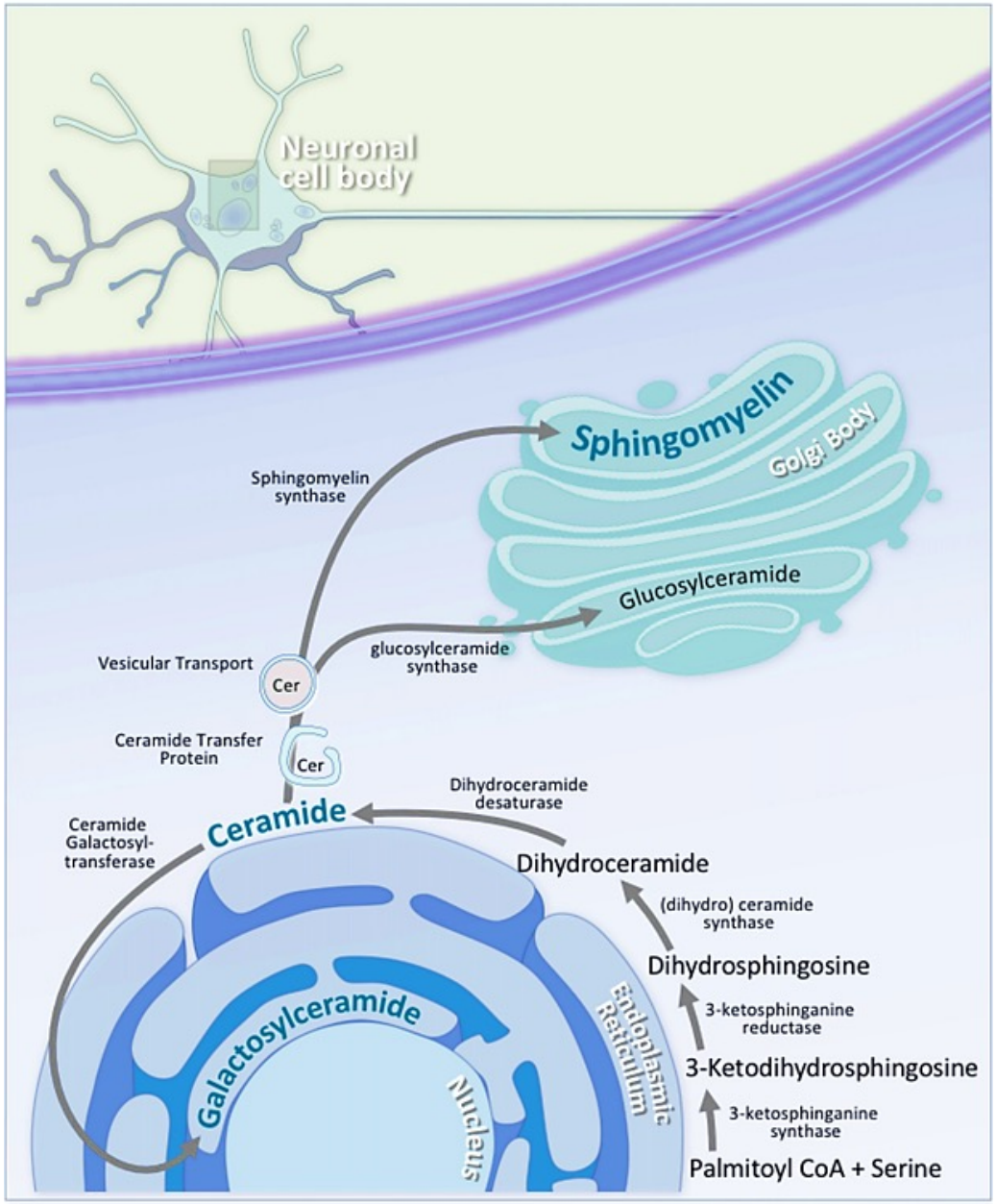
Neuron-astrocyte metabolic coordination



Sphingolipid synthesis

- Neuronal sphingolipid synthesis takes place across multiple cellular compartments.
- Sphingolipid synthesis begins at the cytosolic leaflet of the ER. Via a series of reactions, palmitoyl CoA and serine are converted to ceramide.
- A portion of this ceramide is transported to the luminal leaflet of the ER, where ceramide galactosyltransferase (CGT) converts the ceramide to galactosyl ceramide which is an essential neuronal sphingolipid.
- Another portion of this ceramide is transported to the Golgi complex, where it is converted to either glucosylceramide on the cytosolic side of the Golgi via glucosylceramide synthase, or to sphingomyelin on the luminal side by sphingomyelin synthase.
- Transport of ceramide from the ER to the Golgi complex is facilitated by either ceramide transfer protein (CERT) or vesicular transport.

Neuronal sphingolipid synthesis



Three major metabolic pathways of Sphingolipids :

- de novo pathway coming from saturated fatty acids
- salvage pathway
- sphingomyelin pathway

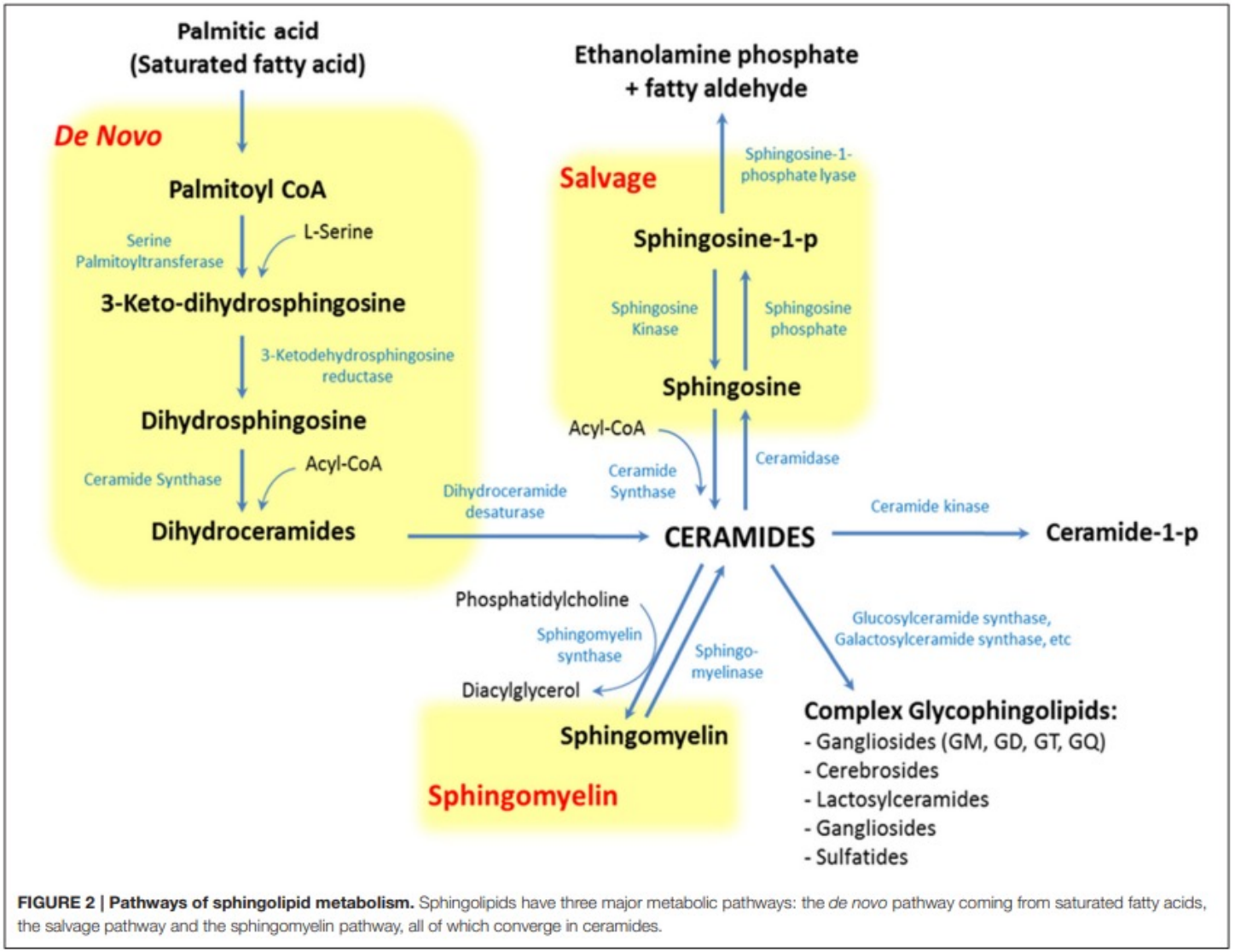
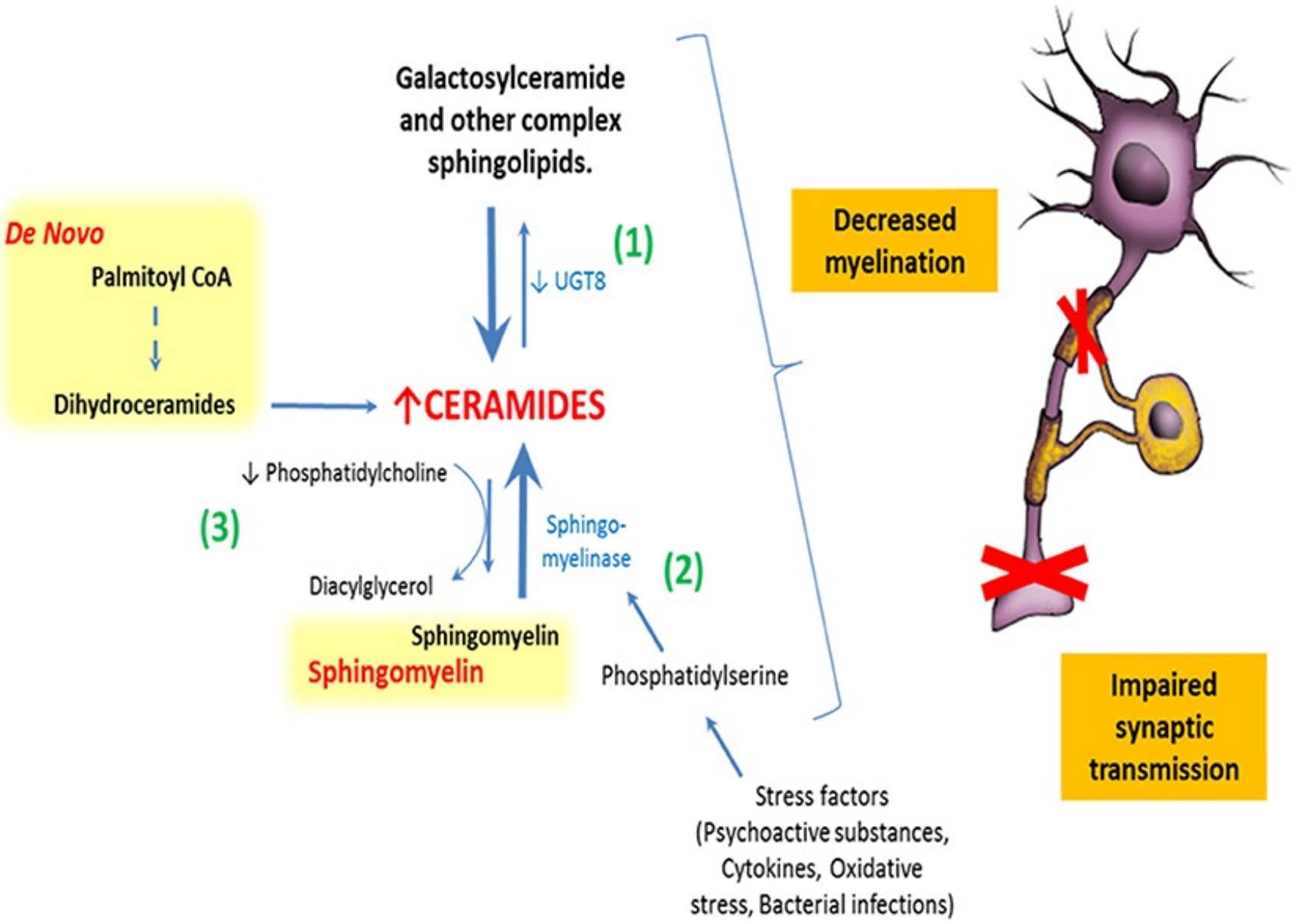


FIGURE 2 | Pathways of sphingolipid metabolism. Sphingolipids have three major metabolic pathways: the *de novo* pathway coming from saturated fatty acids, the salvage pathway and the sphingomyelin pathway, all of which converge in ceramides.

Mechanism of abnormal sphingolipids metabolism in the schizophrenia



Relationship between sphingolipids and schizophrenia. There are at least three different described ways by which abnormal sphingolipid metabolism could impair normal neural functioning in humans:

(1) By the abnormal expression of galactosylceramide synthase increasing ceramides and decreasing galactosylceramides in myelin sheaths.

(2) Stimulation of sphingomyelinase by stress factors, leading to a breakdown of sphingomyelins to ceramides.

(3) And finally, by decreased synthesis of phosphatidylcholine. All of these mechanisms impact normal lipid membrane properties and might induce the synaptic and axonal dis-connectivity seen in schizophrenia.

Please Describe the two following mechanism

1. **Lipid Signaling in the Pathology of Autism Spectrum Disorders?**
2. **Association between Huntington's disease and cholesterol level?**