Oxidation of fatty acids

Beta oxidation

- It is a catabolic pathway
- Sequential removal of two carbon units at a time
- Site : mitochondria (matrix)
- Precursor (substrate) : fatty acid
- Intermediates: present as CoA derivatives
- End product: acetyl CoA, FADH2, NADH
- Enzymes: 4 enzymes independent enzymes
- Co Enzymes: FAD and NAD
- Reactions: dehydrogenation,hydration, dehydrogenation,thiolysis
- Nutritional status of the cell: energy deprived

BETA OXIDATION

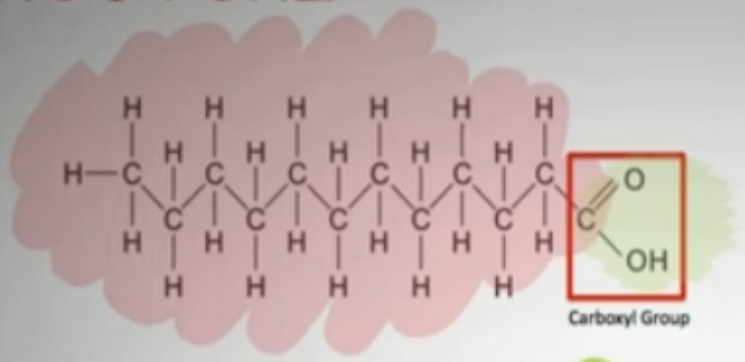
CATABOLIC PATHWAY OF FATS

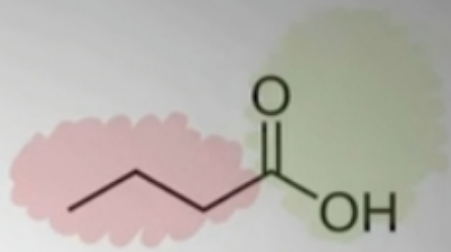
FREE FATTY ACIDS

ACETYL COA

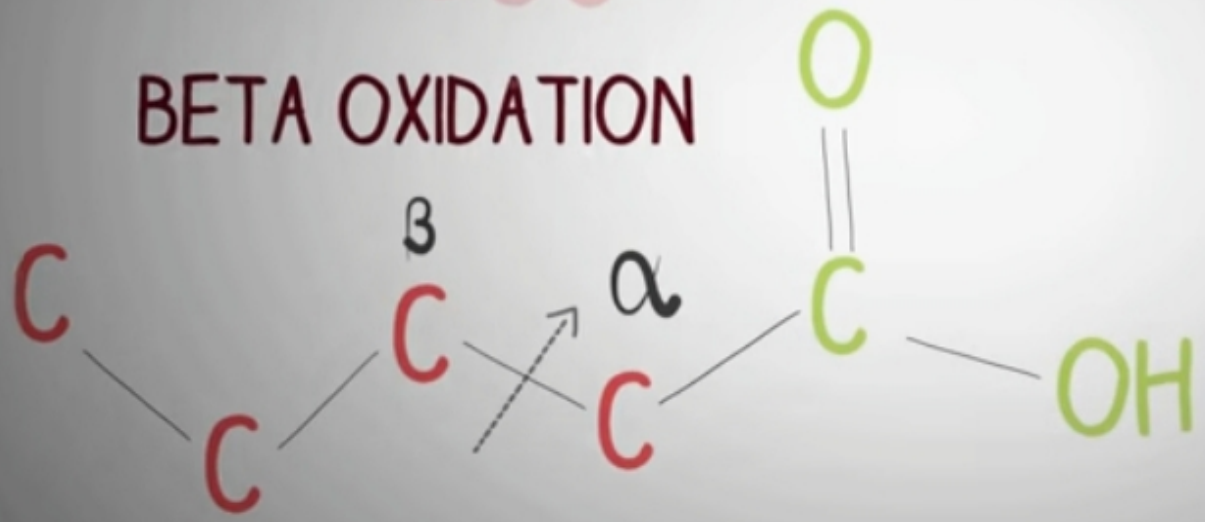
TRYGLYCERIDES

STRUCTURE





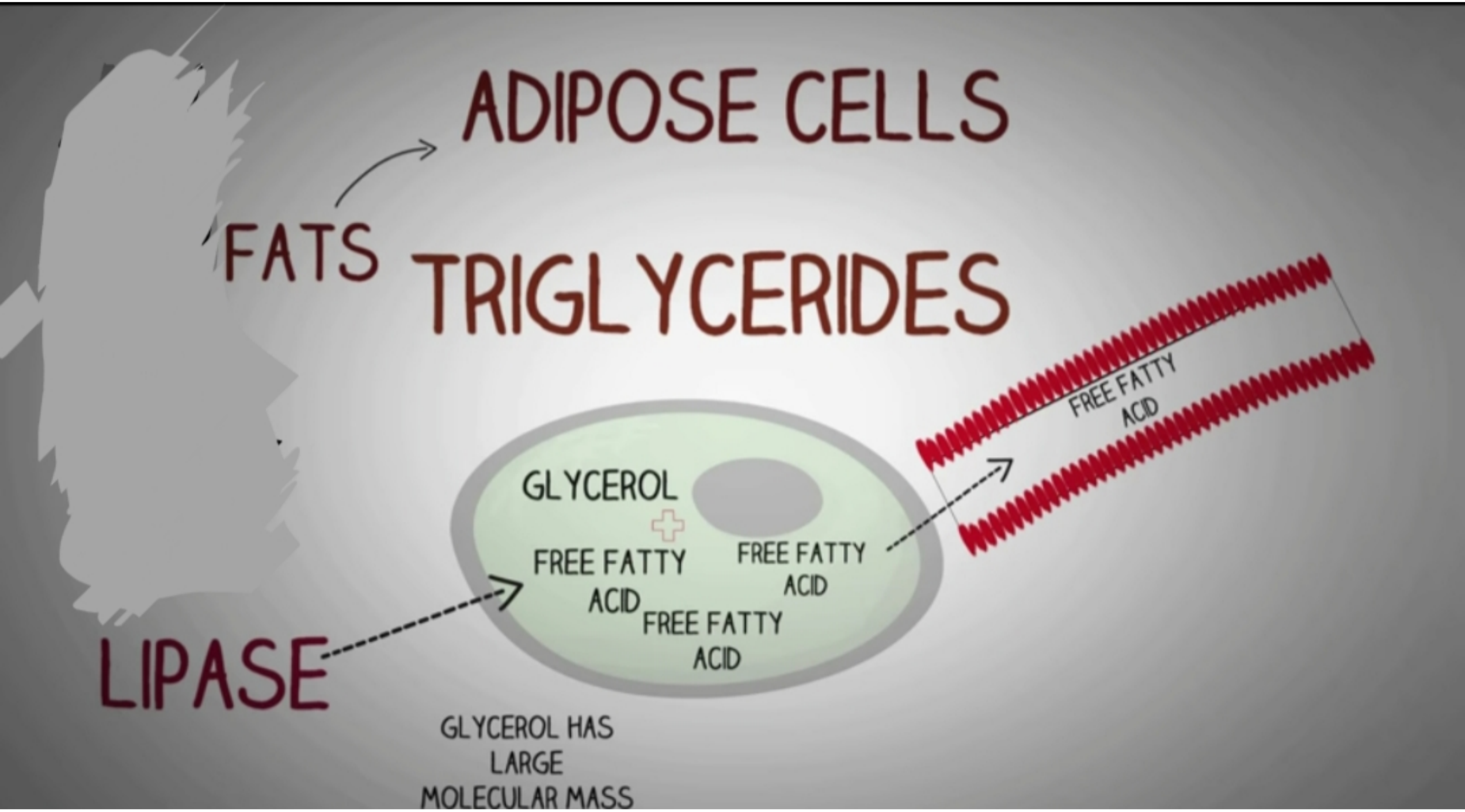
BETA OXIDATION

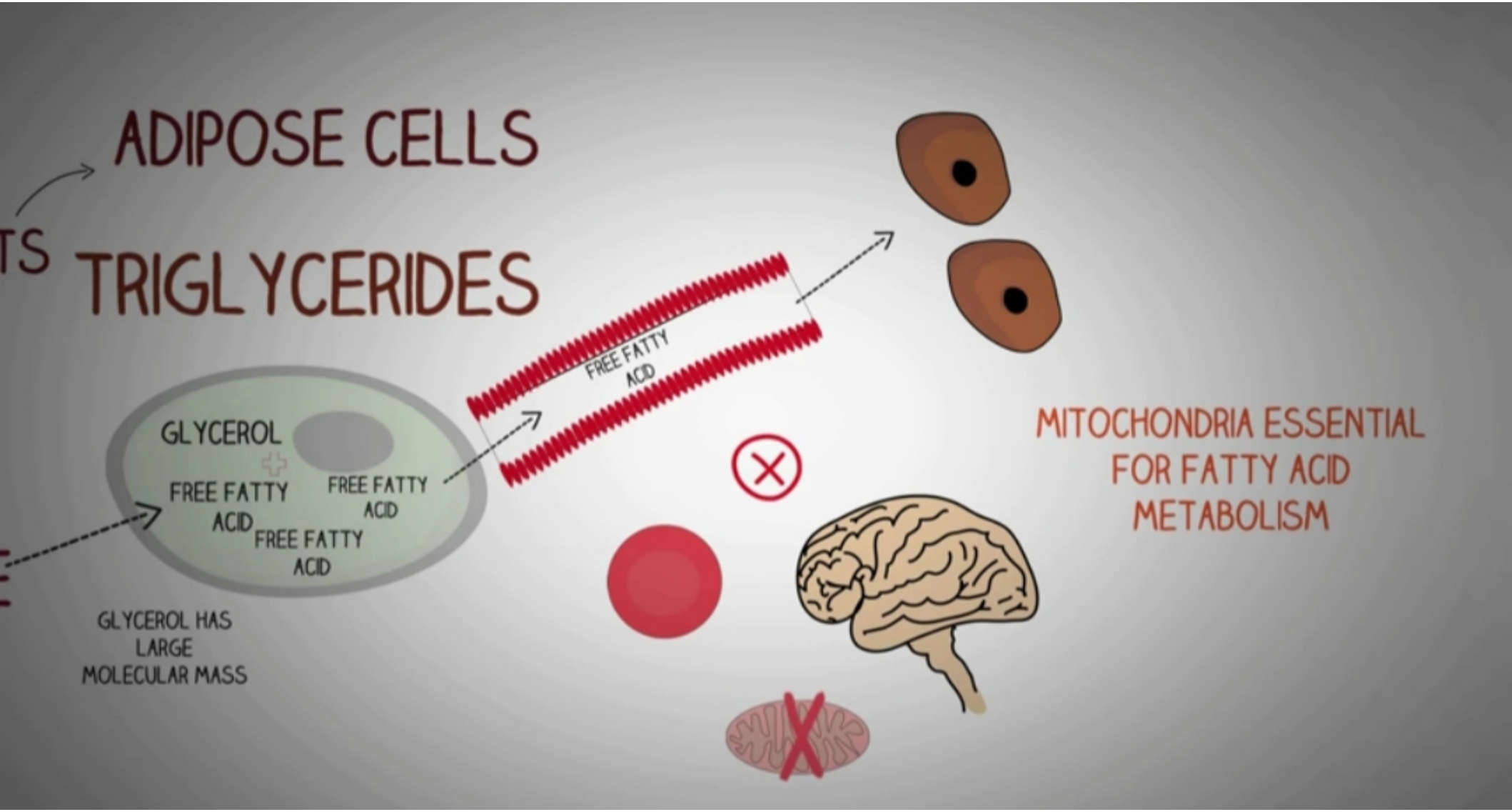


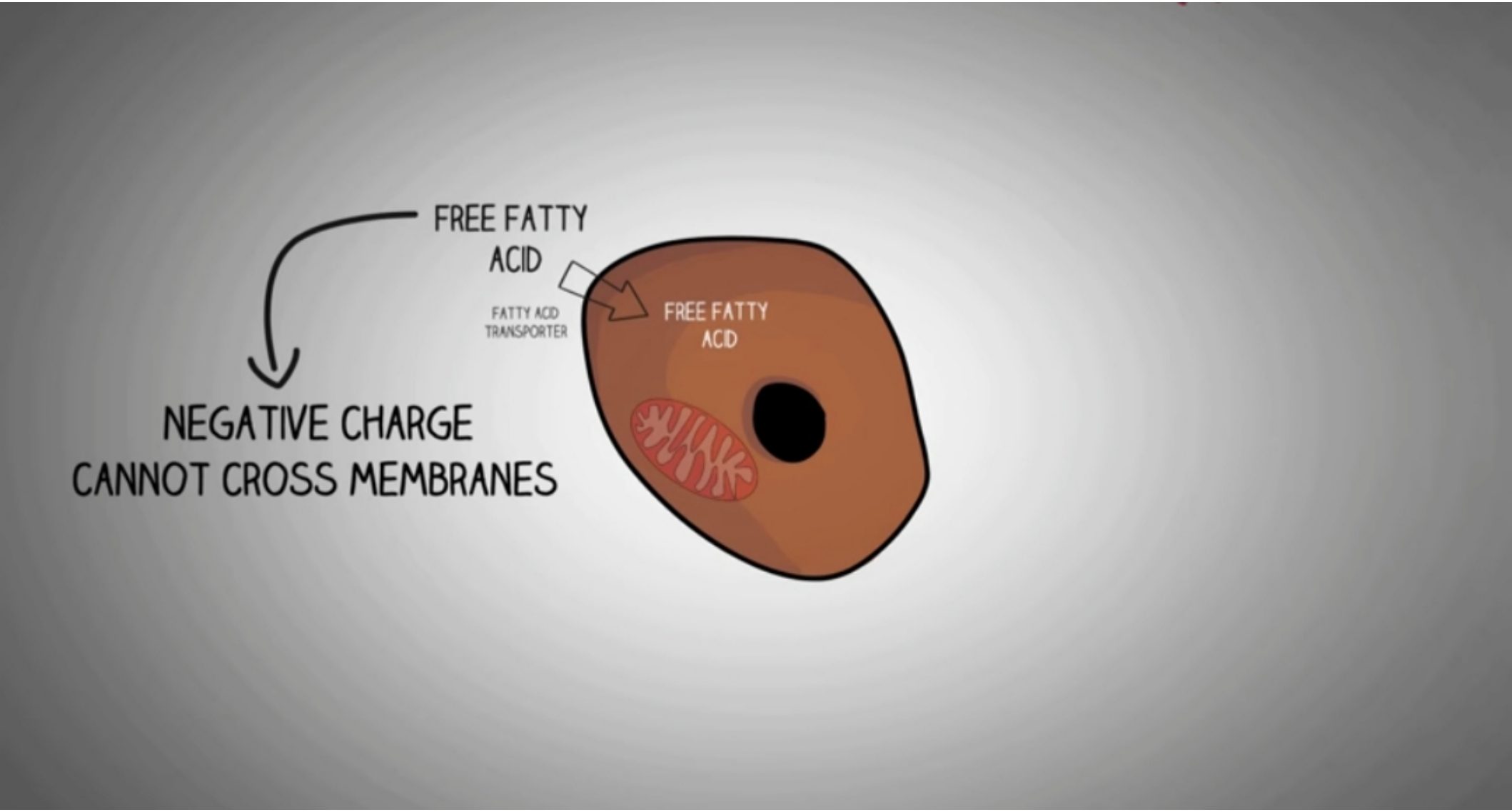
Stages of beta oxidation

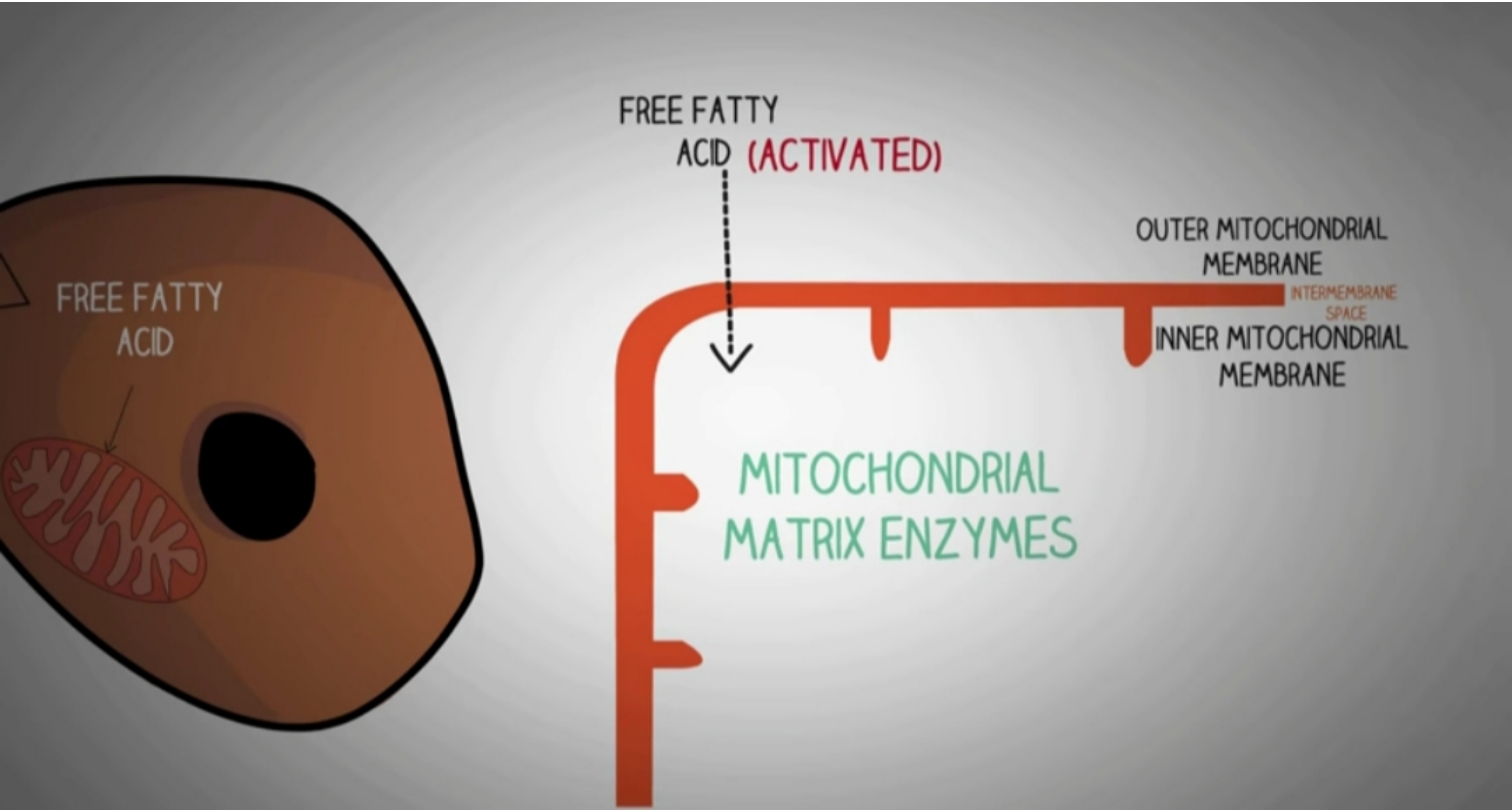
Three stages to beta oxidation:

1. Mobilization and transport of fatty acids to Target tissues
2. Activation and transport of fatty acids into mitochondria
3. Reactions of beta oxidation


ADIPOSE CELLS
FATS
TRIGLYCERIDES
FREE FATTY ACID
GLYCEROL
FREE FATTY ACID
FREE FATTY ACID
FREE FATTY ACID
LIPASE
GLYCEROL HAS LARGE MOLECULAR MASS


ADIPOSE CELLS
TS
TRIGLYCERIDES
FREE FATTY ACID
GLYCEROL
FREE FATTY ACID
FREE FATTY ACID
FREE FATTY ACID
GLYCEROL HAS LARGE MOLECULAR MASS
MITOCHONDRIA ESSENTIAL FOR FATTY ACID METABOLISM


FREE FATTY ACID
FATTY ACID TRANSPORTER
FREE FATTY ACID
NEGATIVE CHARGE
CANNOT CROSS MEMBRANES


FREE FATTY ACID
FREE FATTY ACID (ACTIVATED)
OUTER MITOCHONDRIAL MEMBRANE
INTERMEMBRANE SPACE
INNER MITOCHONDRIAL MEMBRANE
MITOCHONDRIAL MATRIX ENZYMES

OVERVIEW

A.

TRANSPORT FROM ADIPOSE TISSUE TO TARGET CELLS

B.

ENTRY INTO CYTOPLASM & MITOCHONDRIA

C.

OXIDATIVE CATABOLISM INSIDE MITOCHONDRIAL MATRIX

Activation of fatty acids

- Fatty acids inside the cell must be activated before proceeding through metabolism.
- Activation consists of conversion of the nonesterified fatty acid to its CoA derivative.
- The faty acyl CoA may then be transported into the mitochondrion for energy production. Transport across the mitochondrial membrane requires a carrier.

FATTY ACID ACTIVATION

ATP

AMP + PP

FREE FATTY ACID

ACYL COA

COA

ACYL-COA SYNTHETASE

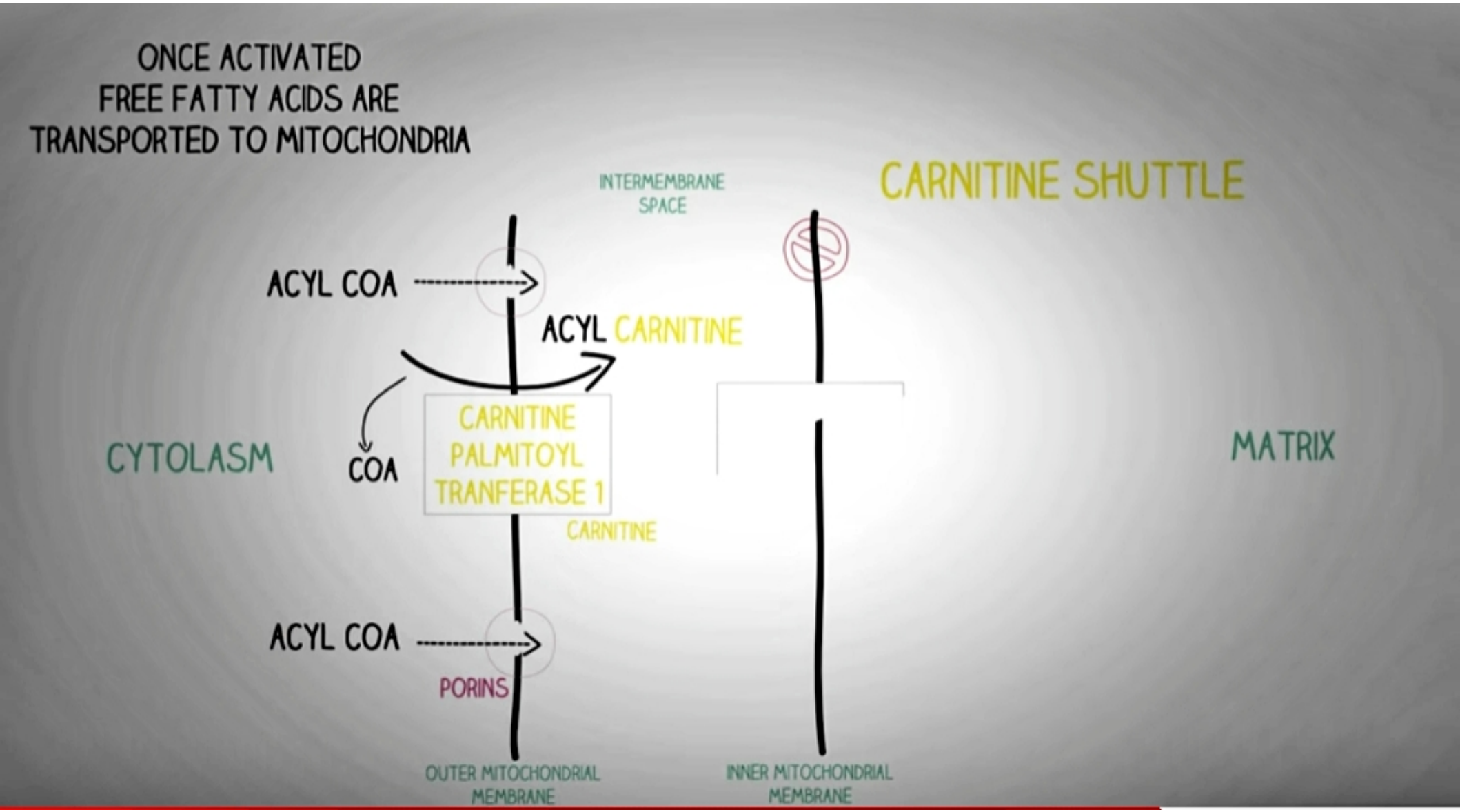
FATTY ACID ACTIVATION IS ESSENTIAL BECAUSE WITHOU IT FATTY ACIDS CANNOT BE UTILIZED IN THE MITOCHONDRIA

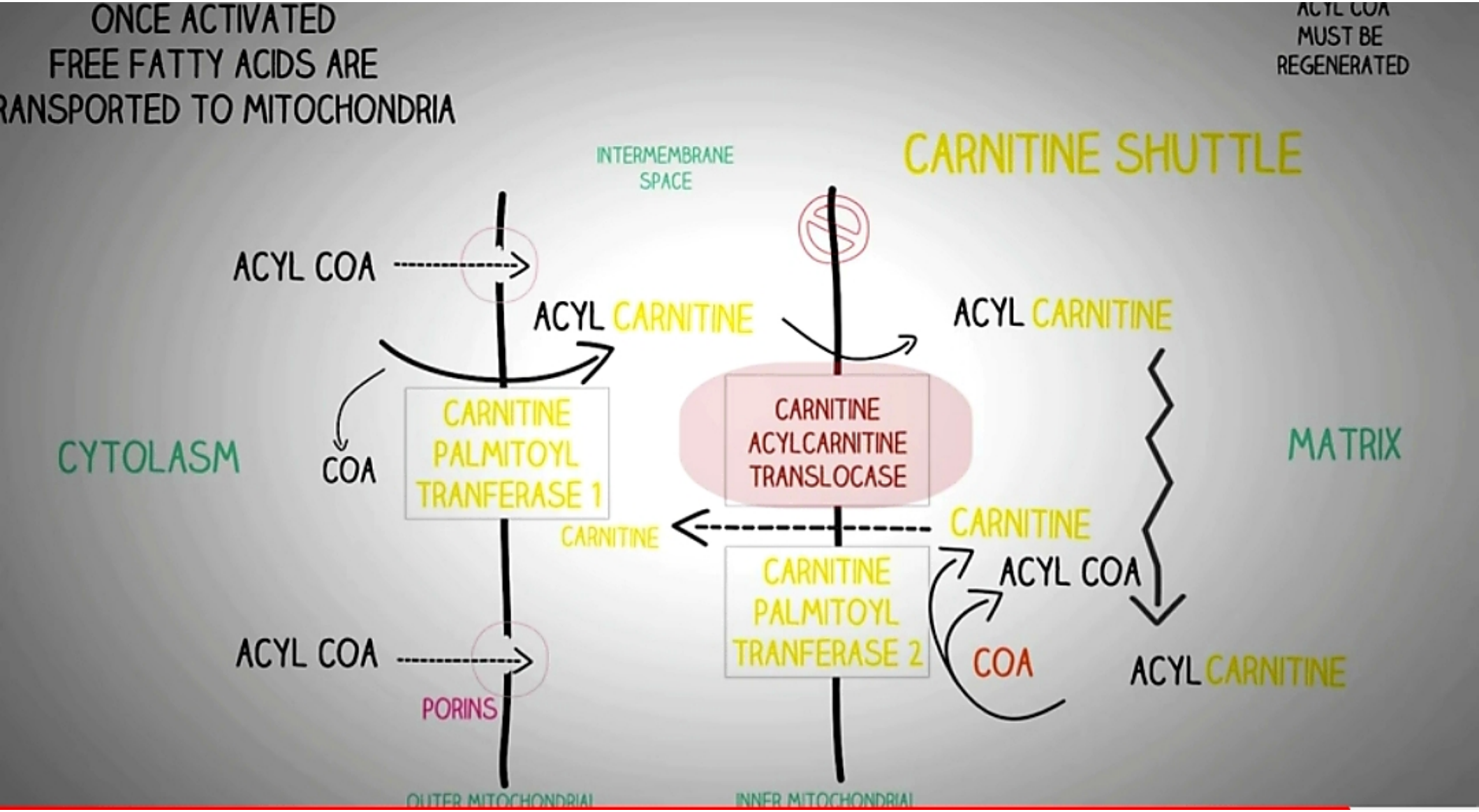
OUTER MEMBRANE MITOCHONDRIA

ENDOPLASMIC RETICULUM

PEROXISOMES

- Beta oxidation occurs in mitochondrial matrix
- Mitochondrial membrane is impermeable to CoA
- Specialized carrier is required to transport long chain acyl groups from cytosol to mitochondria
- This carrier is CARNITINE
- It is a rate-limiting transport process and is called CARNITINE SHUTTLE.


ONCE ACTIVATED
FREE FATTY ACIDS ARE
TRANSPORTED TO MITOCHONDRIA
INTERMEMBRANE
SPACE
CARNITINE SHUTTLE
ACYL COA
ACYL CARNITINE
CARNITINE
PALMITOYL
TRANFERASE 1
CYTOLASM
COA
MATRIX
CARNITINE
ACYL COA
PORINS
OUTER MITOCHONDRIAL
MEMBRANE
INNER MITOCHONDRIAL
MEMBRANE


ONCE ACTIVATED
FREE FATTY ACIDS ARE
RANSPORTED TO MITOCHONDRIA
ACYL COA
MUST BE
REGENERATED
CARNITINE SHUTTLE
INTERMEMBRANE
SPACE
ACYL COA
ACYL CARNITINE
ACYL CARNITINE
CARNITINE
PALMITOYL
TRANFERASE 1
CARNITINE
ACYLCARNITINE
TRANSLOCASE
CYTOLASM
COA
MATRIX
CARNITINE
CARNITINE
ACYL COA
CARNITINE
PALMITOYL
TRANFERASE 2
ACYL COA
COA
ACYL CARNITINE
PORINS
OUTER MITOCHONDRIAL
INNER MITOCHONDRIAL

- 1-In the intermembrane space of the mitochondria, fatty acyl CoA reacts with carnitine in a reaction catalyzed by carnitine acyltransferase I (CAT-I), yielding CoA and fatty acyl carnitine. The resulting acyl carnitine crosses the inner mitochondrial membrane.

- CAT-I is associated with the outer mitochondrial membrane.
- CAT-I reaction is rate-limiting;
- The enzyme is allosterically inhibited by malonyl CoA. Malonyl CoA concentration would be high during fatty acid synthesis. Inhibition of CAT-I by malonyl CoA prevents simultaneous synthesis and degradation of fatty acids.

- 2-Fatty acyl carnitine is transported across the inner mitochondrial membrane in exchange for carnitine by carnitine-acylcarnitine translocase.
- In the mitochondrial matrix fatty acyl carnitine reacts with CoA in a reaction catalyzed by carnitine acyltransferase II (CAT-II), yielding fatty acyl CoA and carnitine.
- The fatty acyl CoA is now ready to undergo beta-oxidation.

Sources of carnitine

- Diet- meat products
- Can be synthesized in liver and kidney from amino acids lysine and methionine.
- Skeletal and heart muscles cannot synthesize carnitine and depend on diet or endogenous synthesis.

Carnitine deficiencies

- PRIMARY CAUSES:-
- - Genetic CAT-I deficiency --- mainly affects liver. Liver cannot synthesize glucose in a fast , results in hypoglycemia, coma and death.
- - CAT-II deficiency ---- mainly affects skeletal and cardiac muscles.
- -Defect in renal tubular reabsorption of carnitine.
- - Defect in carnitine uptake by cells.

- SECONDARY CAUSES :---
- -liver diseases-----
- decreased endogenous synthesis.
- - malnutrition or strict vegetarian diet
- - increased metabolic demands - hemodialysis

Entry of short and medium chain fatty acids into the mitochondria

- Carnitine and CAT system not required for fatty acids shorter than 12 carbon length.
- They are activated to their CoA form inside mitochondrial matrix.
- Not inhibited by malonyl CoA.