LIPID DEFINITION CLASSIFICATION METABOLISM OF LIPID OXIDAT SECOND STAGE

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LIPID METABOLISM FULL SUMMARY

lipids are hydrophobic organic

molecules essential for energy storage, cellular structure
and hormonal regulation, and their metabolism imbalances can lead to

major health issues like atherosclerosis and obesity.

Classification of Lipids

lipids can be classified into several categories based on their structure and function:

Simple Lipids:

Triglycerides: composed of glycerol and three fatty acids; serve as energy storage.

Compound Lipids:

Phospholipids: contain glycerol, fatty acids, and a phosphate group; essential for cell membranes.

Derived Lipids:

Fatty Acids: carboxylic acids with long hydrocarbon chains; can be saturated or unsaturated.

Steroids: four fused carbon rings; include hormones like cholesterol and testosterone.

Other Classes:

Sphingolipids: composed of a sphingosine backbone; play roles in cellular signaling.

Lipoproteins: complexes of lipids and proteins; transport lipids in the bloodstream.

Summary: lipids are vital for numerous biological processes, ranging from energy

storage to membrane structure. their classification encompasses simple lipids

compound lipids, derived lipids, and other specialized forms, highlighting

their functional diversity in living organisms

Fatty Acid, Triacylglycerol, and Ketone Body Metabolism

OVERVIEW: Fatty acids (FFA) exist in the body both as free molecules and as esters in triacylglycerols (TAGs). while low levels of FFA are found in various tissues, significant amounts can circulate in plasma during fasting primarily transported via serum albumin.

they serve multiple functions, including energy provision through oxidation in the

liver and muscle, structural roles in membrane lipids, and as precursors for

hormone-like prostaglandins. esterified fatty acids stored in white adipose tissue

represent the body's primary energy reserve, and disruptions in their

metabolism are linked to obesity and diabetes.

FATTY ACID STRUCTURE:

a fatty acid comprises a hydrophobic hydrocarbon chain and a terminal carboxyl group with a pKa of

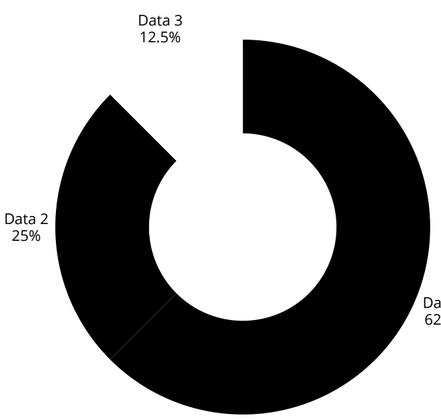
approximately 4.8. at physiological pH, this carboxyl group ionizes to form an anionic group (-COO-)

contributing to the amphipathic nature of the molecule. despite its hydrophilic head, long-chain fatty

acids (LCFA) are primarily hydrophobic and are poorly soluble in water. consequently, they are transported in

circulation, predominantly as fatty acid esters in lipoprotein particles, with free fatty acids bound to

serum albumin, the most abundant serum protein.



Structure of a fatty acid:

the carbon next to carbonyl group is designated as alpha (α). the next carbon is the beta carbon (β). when the chain is longer, the last carbon in the chain is designated as the ω carbon.

Fatty Acid Saturation:

fatty acid chains can either be saturated, containing no double bonds, or unsaturated, featuring one or more double bonds. in humans, most fatty acids are saturated or monounsaturated, and when double bonds are present, they predominantly occur in the cis configuration, which introduces a bend in the chain. multiple double bonds are typically spaced at three-carbon intervals. the presence of double bonds lowers the melting temperature of fatty acids while increased chain length raises it, contributing to the fluidity of membrane lipids that often contain long-chain fatty acids.

Fatty acid chain length and double-bond positions:

in humans, fatty acids of physiologic importance predominantly feature an even number of carbon atoms

particularly 16, 18, or 20, with longer fatty acids (>22) occurring in the brain. fatty acids are numbered starting

with the carbonyl carbon, with the format X:Y(Z1,Z2, ..) indicating the total carbon count, the number of double

bonds, and their positions. for instance, arachidonic acid is specified as 20:4(5,8,11,14) and is identified as an ω-6 fatty

acid due to its terminal double bond being six carbons from the methyl end. Essential fatty acids include linoleic acid

(18:2(9,12)) as an ω-6 and α-linolenic acid (18:3(9,12,15)) as an ω-3 fatty acid.

Arachidonic acid:

arachidonic acid, 20:4(5,8,11,14), illustrating the position of the double bonds.

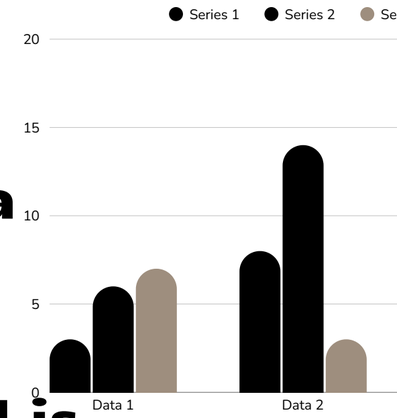
A: Arachidonic acid is an ω-6 fatty acid because the first double bond from the ω end

is 6 carbons from that end. B: it is also referred to as an n-6 fatty acid because the

last double bond from the carboxyl end is 14 carbons from that end: 20 - 14 = 6 = n. thus the

“ω” and “n” designations are equivalent.

Essential Fatty Acids:



linoleic acid is essential in human diets as it serves as a precursor to ω-6 arachidonic acid

crucial for prostaglandin synthesis, while α-linolenic acid is vital for growth and

development as a precursor to ω-3 fatty acids. humans cannot synthesize carbon-

carbon double bonds beyond the ninth carbon from the methyl (ω) end

necessitating the intake of these fatty acids from plant sources. should linoleic acid be

deficient, arachidonic acid becomes essential.

Essential Fatty Acid Deficiency:

essential fatty acid deficiency (rare)
can result in a dry, scaly dermatitis
as a result of an inability to
synthesize molecules that provide
the water barrier in skin.

FATTY ACID DE NOVO SYNTHESIS :

excess dietary carbohydrates and proteins can be converted into fatty acids through de novo

synthesis, primarily in the liver and lactating mammary glands. this endergonic and reductive

cytosolic process utilizes acetyl coenzyme A (CoA), ATP, and NADPH to elongate the fatty acid

chain. additionally, dietary triacylglycerols (TAG) contribute to fatty acid supply.

Cytosolic acetyl CoA production:

acid synthesis begins with the transfer of acetate units from mitochondrial acetyl

CoA to the cytosol via citrate. acetyl CoA condenses with oxaloacetate to form

citrate, which is transported out of the mitochondria when citrate levels are

elevated, often due to ATP accumulation. in the cytosol, ATP citrate lyase cleaves

citrate into acetyl CoA and oxaloacetate, signaling a favorable environment for

fatty acid synthesis.

Acetyl CoA carboxylation to malonyl CoA:

in fatty acid synthesis, the energy for carbon-to-carbon condensations is derived

from the carboxylation and subsequent decarboxylation of acyl groups. acetyl CoA

is converted to malonyl CoA by Acetyl CoA Carboxylase (ACC), which catalyzes this

ATP-dependent reaction using bicarbonate as a carbon source. biotin acts as a

coenzyme, covalently attached to ACC facilitating the transfer of the activated

carboxyl group to acetyl CoA.

Acetyl CoA carboxylase short-term regulation:

carboxylation of acetyl CoA to malonyl CoA is the rate-limiting and regulated step in fatty

acid synthesis, with Acetyl CoA Carboxylase (ACC) being activated by citrate and inactivated

by palmitoyl CoA. short-term regulation occurs through reversible phosphorylation by AMP-

activated protein kinase (AMPK), which is activated by AMP and influenced by hormones

like epinephrine and glucagon, leading to ACC's inactivation in contrast to insulin's effect

which promotes ACC activation.

Acetyl CoA carboxylase long-term regulation:

excess caloric intake, particularly from high-carbohydrate diets, elevates ACC synthesis and

fatty acid synthesis, while low-calorie or high-fat diets reduce ACC activity. ACC regulation is

influenced by carbohydrates and insulin through transcription factors like ChREBP and SREBP-1c

Metformin, used for type 2 diabetes, activates AMPK, thereby inhibiting ACC and fatty acid

synthase expression and enhancing glucose uptake in muscle.

Allosteric regulation:

allosteric regulation of malonyl coenzyme A (CoA) synthesis by acetyl CoA carboxylase. the carboxyl group

contributed by bicarbonate (HCO_3^-) is shown in blue. Pi = inorganic phosphate; ADP = adenosine diphosphate.

Eukaryotic fatty acid synthase:

fatty acid synthesis in eukaryotes is driven by the multifunctional enzyme Fatty Acid

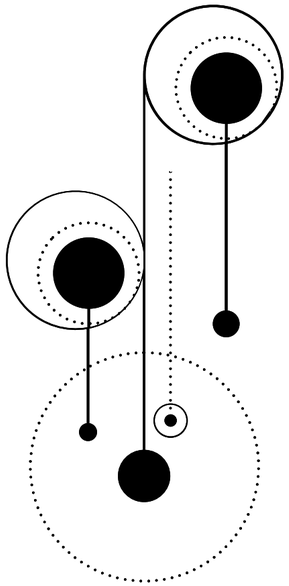
Synthase (FAS), which is a homodimeric polypeptide containing six enzymatic

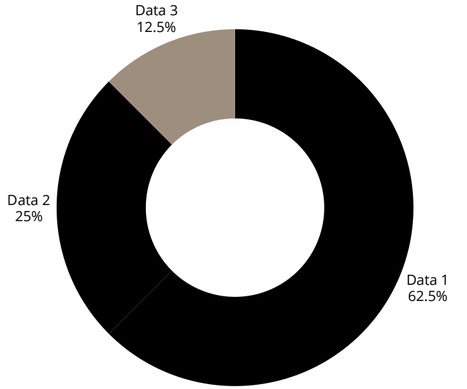
domains and an acyl carrier protein (ACP) domain that includes 4'-phosphopantetheine. this cofactor

derived from pantothenic acid, carries acyl units and facilitates their transfer to the catalytic domains

during synthesis. thus, FAS plays a crucial role in the sequential addition of two-carbon units from

malonyl CoA to acyl acceptors.





Reductant sources:

synthesis of one molecule of palmitate requires 14 NADPH, primarily sourced

from the pentose phosphate pathway, which generates two NADPH per glucose

6-phosphate. additionally, cytosolic malic enzyme converts malate to

pyruvate, producing NADPH via the oxidation and decarboxylation of

malate. this interrelationship emphasizes the links between glucose

metabolism and palmitate synthesis.

Further elongation:

palmitate (16:0), the primary product of fatty acid synthesis, can be elongated in

the smooth endoplasmic reticulum by adding two-carbon units using malonyl

CoA as the donor and NADPH for reducing power. this elongation process relies on a

distinct set of enzymes rather than a single multifunctional enzyme

additionally, the brain has specialized mechanisms to produce very-long-chain

fatty acids (over 22 carbons), essential for brain lipid synthesis.

Chain desaturation:

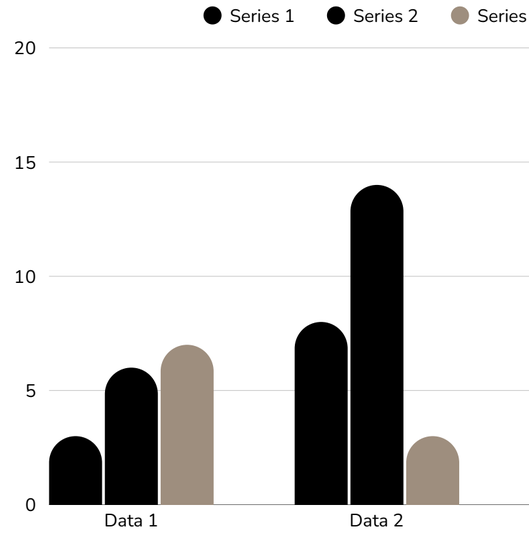
fatty acyl CoA desaturases in the smooth endoplasmic reticulum (SER) introduce cis double

bonds into long-chain fatty acids (LCFAs) by utilizing oxygen, NADH, cytochrome b5

and FAD-linked reductase. the initial double bond is typically added between carbons 9 and 10

yielding primarily oleic acid (18:1(9)) and minor amounts of palmitoleic acid (16:1(9)). further

desaturation and elongation can produce a variety of polyunsaturated fatty acids.



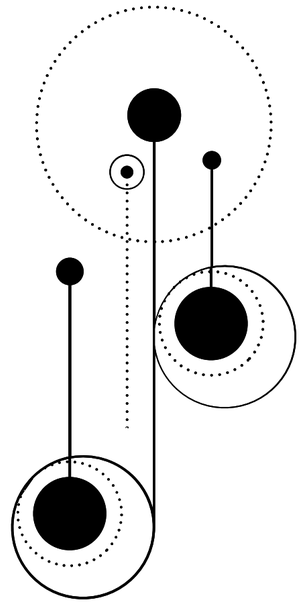
Note:

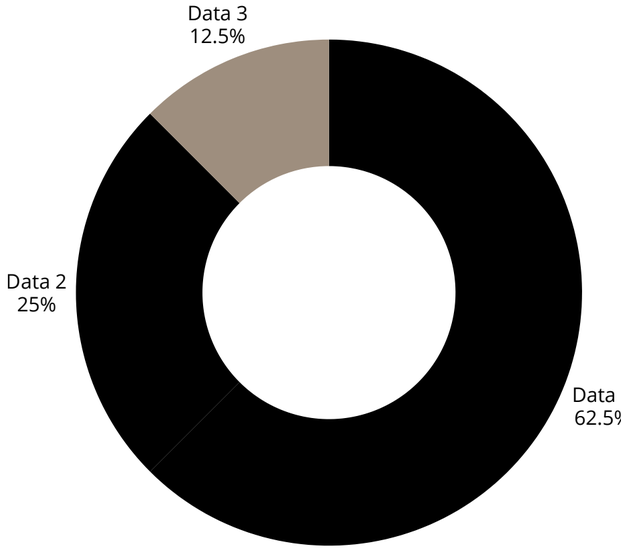
humans have carbon 9, 6, 5, and 4 desaturases but lack the ability to

introduce double bonds from carbon 10 to the ω end of the chain. this is

the basis for the nutritional essentiality of the polyunsaturated

ω-6 linoleic acid and ω-3 linolenic acid.





Triacylglycerol (TAG)

a triacylglycerol with an unsaturated fatty acid on carbon orange denotes the hydrophobic portions of the molecule.

STORAGE AS TAG COMPONENTS:

MONO-, DI-, AND TRIACYLGLYCEROLS ARE FORMED BY ESTERIFYING ONE, TWO

OR THREE FATTY ACID MOLECULES TO GLYCEROL, RESULTING IN THE LOSS OF

NEGATIVE CHARGE AND THE FORMATION OF NEUTRAL FATS. AT ROOM

TEMPERATURE, SOLID ACYLGLYCEROLS ARE TERMED FATS, WHILE LIQUID ONES

ARE CLASSIFIED AS OILS.

Arrangement:

in triacylglycerols (TAGs), the three esterified fatty acids are typically

different types: the fatty acid on carbon 1 is usually saturated

carbon 2 contains an unsaturated fatty acid, and carbon 3 may be

either the presence of unsaturated fatty acids lowers the melting temperature (Tm) of the lipid.

Triacylglycerol storage and function:

due to their low water solubility triacylglycerols (TAGs) coalesce in white adipocytes to form large, nearly anhydrous lipid droplets, serving as the body's primary energy reserve. in contrast, TAGs stored in brown adipocytes contribute to heat production via nonshivering thermogenesis.

Glycerol 3-phosphate synthesis:

glycerol 3-phosphate is the initial acceptor of fatty acids in triacylglycerol (TAG) synthesis

produced primarily in the liver and adipose tissue from glucose via the glycolytic pathway

which generates dihydroxyacetone phosphate (DHAP) that is then reduced to glycerol 3-

phosphate. additionally, in the liver, free glycerol can be converted to glycerol 3-

phosphate by glycerol kinase, while adipocytes are limited in glycerol phosphate

synthesis when plasma glucose levels are low due to insulin dependence on GLUT-4.

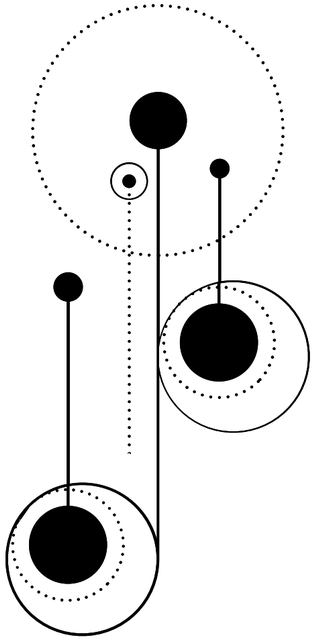
Fatty acid activation:

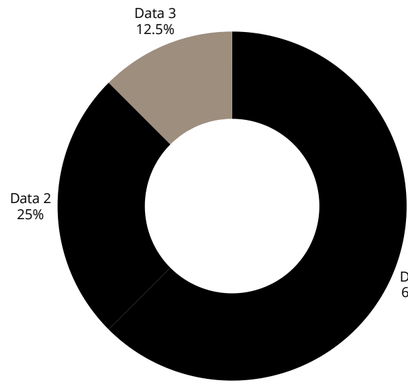
a FFA must be converted to its activated form (bound to CoA

through a thioester link) before it can participate in metabolic

processes such as TAG synthesis this reaction, is catalyzed by a family of

fatty acyl CoA synthetases (thiokinases).





TRIACYLGLYCEROL SYNTHESIS:

THIS PATHWAY FROM GLYCEROL 3-PHOSPHATE INVOLVES FOUR

REACTIONS. THESE INCLUDE THE SEQUENTIAL ADDITION OF

TWO FATTY ACIDS FROM FATTY ACYL COA, THE REMOVAL OF

PHOSPHATE, AND THE ADDITION OF THE THIRD FATTY ACID.

Triacylglycerol fate in liver and adipose tissue:

in white adipose tissue (WAT), triacylglycerols (TAG) are stored as nearly anhydrous fat

droplets coated with perilipins, which protect TAG from lipolysis until needed for energy

excessive TAG storage in healthy liver is minimal, as most is exported in the form of

very-low-density lipoproteins (VLDL) to deliver endogenously derived lipids to peripheral

tissues. in contrast, chylomicrons transport dietary lipids.

FAT MOBILIZATION AND FATTY ACID OXIDATION:

FATTY ACIDS STORED IN WAT, IN THE FORM OF NEUTRAL TAG, SERVE AS THE BODY'S MAJOR FUEL

STORAGE RESERVE. TAGS PROVIDE CONCENTRATED STORES OF METABOLIC ENERGY BECAUSE THEY ARE

HIGHLY REDUCED AND LARGELY ANHYDROUS THE YIELD FROM THE COMPLETE OXIDATION OF FATTY

ACIDS TO CO2 AND H2O IS 9 KCAL/G FAT (AS COMPARED TO 4 KCAL/G PROTEIN OR

CARBOHYDRATE).

Fatty acid release from fat:

the mobilization of stored fat involves the breakdown of triglycerides (TAGs)

into free fatty acids (FFAs) and glycerol through a process called lipolysis this

process is facilitated by proteins such a s perilipins and enzymes known as

lipases. it starts with adipose triglyceride lipase (ATGL), which converts

TAGs into diacylglycerol, the preferred substrate for hormone-sensitive lipase

(HSL). HSL then further breaks down diacylglycerol into monoacylglycerol

(MAG), which is subsequently acted upon by MAG lipase to complete the

degradation.

The regulation of perilipins and hormone-sensitive lipase (HSL):

the regulation of perilipins and hormone-sensitive lipase (HSL) involves

phosphorylation by protein kinase A (PKA), which is activated by cAMP. this

cAMP is produced when catecholamines like epinephrine, bind to β-adrenergic

receptors on adipocytes, activating adenylyl cyclase. phosphorylation of

perilipin by PKA facilitates the binding of active HSL to lipid droplets.

conversely, high insulin levels promote the dephosphorylation and

inactivation of HSL while also suppressing the expression of adipose

triglyceride lipase (ATGL). this dual mechanism ensures that when cAMP

signaling is active, fatty acid synthesis is inhibited, and

triglyceride degradation is promoted.

Fate of glycerol:

during triglyceride (TAG) degradation, glycerol is released but cannot be metabolized by adipocytes due to their lack of glycerol kinase

instead, glycerol is transported to the liver, where it undergoes phosphorylation to form glycerol 3-phosphate. this compound can then

be utilized to synthesize TAG in the liver or converted to dihydroxyacetone phosphate (DHAP) via the reversal of the glycerol 3-

phosphate dehydrogenase reaction. DHAP can enter either glycolysis or gluconeogenesis, facilitating energy production or glucose synthesis.

FATE OF FATTY ACIDS: FREE FATTY ACIDS (FFA) RELEASED FROM

ADIPOCYTES ENTER THE BLOODSTREAM, BIND TO SERUM ALBUMIN, AND ARE

TRANSPORTED TO VARIOUS TISSUES, SUCH AS MUSCLES, WHERE THEY ARE ACTIVATED TO THEIR COA DERIVATIVES AND OXIDIZED

FOR ENERGY IN MITOCHONDRIA. HOWEVER, RED BLOOD CELLS (RBCS)

CANNOT USE PLASMA FFA AS FUEL BECAUSE THEY LACK MITOCHONDRIA

WHILE THE BRAIN MINIMALLY USES FATTY ACIDS FOR ENERGY, THE REASONS FOR

THIS ARE NOT WELL UNDERSTOOD.

notably, over 50% of released fatty acids are reesterified to glycerol 3-phosphate, produced via glyceroneogenesis, since adipose tissue

does not express glycerol kinase.
this process involves converting pyruvate to oxaloacetate and then to

phosphoenolpyruvate, which is then converted to dihydroxyacetone phosphate (DHAP) and reduced to glycerol 3-phosphate

this mechanism helps decrease plasma FFA levels, which are associated with insulin resistance in type 2 diabetes and obesity.

fatty acid β-oxidation

the major pathway for catabolism of fatty acids is a mitochondrial pathway called β-oxidation, in which two-carbon

fragments are successively removed from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and FADH2.

long-chain fatty acid transport into cytosol and mitochondria:

the uptake of fatty acids can occur through several mechanisms, including passive diffusion and the action of lipid transport proteins

such as fatty acid translocase (FAT), fatty acid-binding protein (FABP), and fatty acid transport protein (FATP).

long-chain fatty acids (LCFAs) are specifically taken up by FATP
once inside the cell, LCFAs are converted to their CoA derivatives by

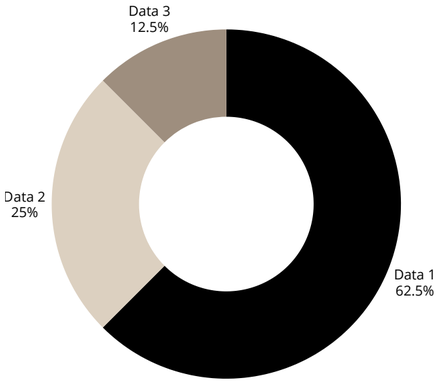
long-chain fatty acyl CoA synthetase, an enzyme located on the outer
mitochondrial membrane.

since β-oxidation occurs in the mitochondrial matrix, fatty acids need to be transported across the

inner mitochondrial membrane, which is impermeable to CoA.

this transport is facilitated by carnitine via the carnitine shuttle, which serves as a specialized carrier for the long-chain acyl

groups, making this transport process rate-limiting for fatty acid metabolism.



carnitine shuttle

carnitine shuttle. the net effect is that a long-chain (LC) fatty acyl coenzyme A (CoA) is transported from the outside to the inside of mitochondria.

AMP = adenosine monophosphate; PPi = pyrophosphate.

translocation steps:

the transport of long-chain fatty acids into the mitochondria involves a couple of key steps.

acyl group transfer: the acyl group is transferred from CoA to carnitine by carnitine palmitoyltransferase I (CPT-I, also known as CAT-I), an enzyme located on the outer mitochondrial membrane.

this reaction produces acylcarnitine and releases free CoA.

transport into mitochondrial matrix: the acylcarnitine is then transported into the mitochondrial matrix through a specific carrier

called carnitine-acylcarnitine translocase, which exchanges acylcarnitine for free carnitine.

regeneration of CoA:
inside the mitochondrial matrix, carnitine palmitoyltransferase II (CPT-II or CAT-II), found in the inner mitochondrial membrane, catalyzes

the transfer of the acyl group from carnitine back to CoA, regenerating free carnitine for reuse in the transport process.

this entire mechanism facilitates the entry of fatty acids into the mitochondria for subsequent β-oxidation.

carnitine shuttle inhibitor:
summary of fatty acid regulation:

malonyl CoA plays a crucial role in inhibiting carnitine palmitoyltransferase I (CPT-I).

this inhibition prevents long-chain acyl groups from entering the mitochondrial matrix for β-oxidation.

bumconnection to fatty acid synthesis:

the presence of malonyl CoA indicates ongoing fatty acid synthesis in the cytosol (e.g., synthesis of palmitate).

as a result, newly synthesized fatty acids cannot be transferred into mitochondria for degradation

DIFFERENT ISOZYMES:

MUSCLE TISSUE CONTAINS THE MITOCHONDRIAL ISOFORM OF ACETYL-COA CARBOXYLASE (ACC2), ALLOWING IT TO REGULATE FATTY ACID OXIDATION.

THE LIVER CONTAINS BOTH ACC ISOZYMES (ACC1 AND ACC2), WHICH CONTRIBUTE TO FATTY ACID METABOLISM.

acetyl CoA/CoA ratio:

fatty acid oxidation is also influenced by the acetyl CoA/CoA ratio.

an increase in this ratio leads to a decrease in the thiolase reaction, which is necessary for fatty acid oxidation.

conclusion:

the regulation of fatty acid metabolism is interconnected, with malonyl CoA serving a pivotal role in inhibiting fatty acid

oxidation during synthesis, and the acetyl CoA/CoA ratio further influencing the metabolic pathways involved

this regulatory mechanism ensures that fatty acid synthesis and degradation are balanced according to cellular energy needs.

carnitine sources:
summary of carnitine metabolism:

carnitine is primarily obtained from the diet, especially from meat products.

synthesis:

it can also be synthesized in the liver and kidneys from the amino acids lysine and methionine.

this enzymatic pathway is not present in skeletal or cardiac muscle tissue.

dependence on uptake:

skeletal and cardiac muscles are entirely dependent on the uptake of carnitine from the bloodstream, which can come from either dietary sources or endogenous synthesis.

distribution:

approximately 97% of the total carnitine in the body is found in skeletal muscle.

conclusion:

carnitine plays a crucial role in energy metabolism, particularly in muscle tissues, and is sourced both through diet and endogenous synthesis.

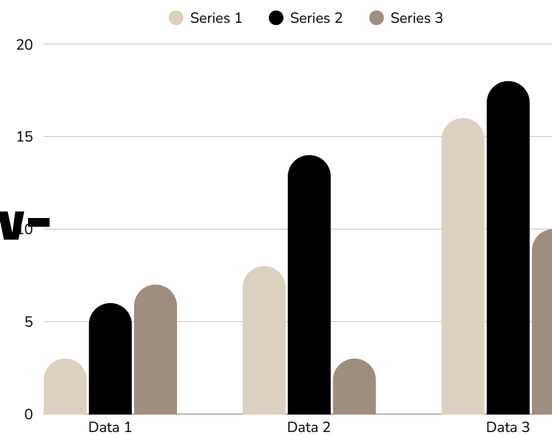
summary of carnitine transport and deficiency
cell entry:

bumcarnitine enters cells via specific transporters.

in heart, muscle, and kidney tissues, the high-affinity transporter responsible for carnitine uptake is organic cation transporter novel 2 (OCTN2).

liver transport:

the liver utilizes a different carnitine transporter, which is low-affinity but high-capacity, to manage carnitine levels.



primary carnitine deficiency:

a genetic defect in OCTN2 can lead to primary carnitine deficiency.

this condition results in the urinary loss of carnitine and consequently low levels of carnitine in both serum and cells.

conclusion:

carnitine transport is critical for cellular uptake, particularly in muscle and heart tissues. deficiencies in the transport mechanism can lead to significant metabolic issues due to inadequate carnitine levels.

THANK YOU

For your attention