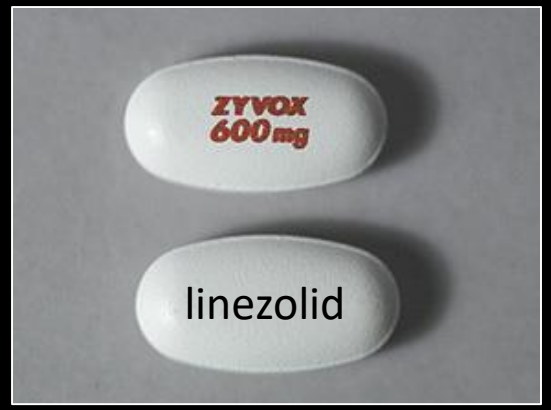
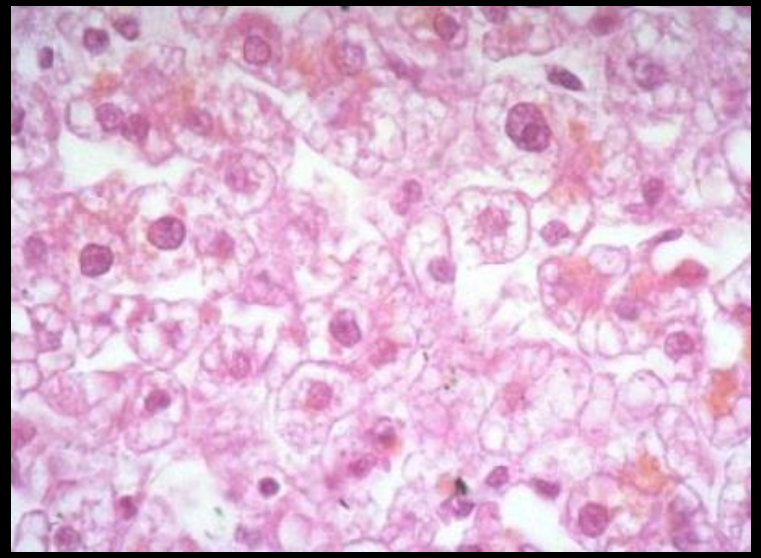
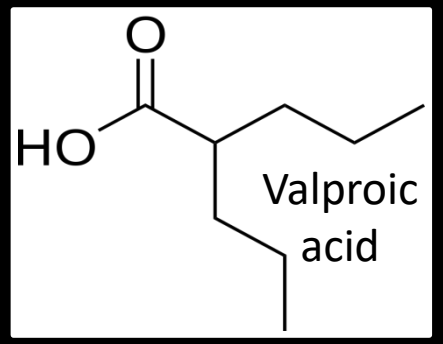
Drug- and Toxin-Induced Liver Disease
Microvesicular Steatosis
Mitochondrial Failure

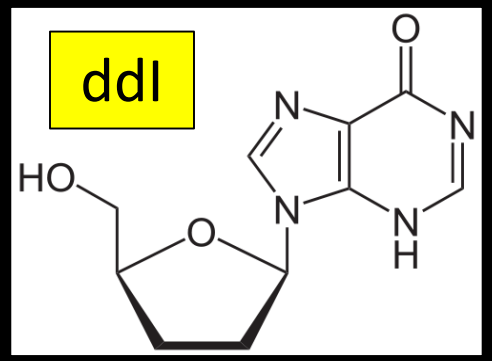
Steven Curry, M.D.
Department of Medical Toxicology
Banner – University Medical Center
Phoenix, AZ

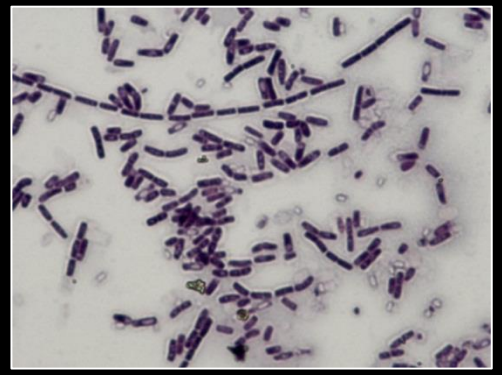
HMS Bounty











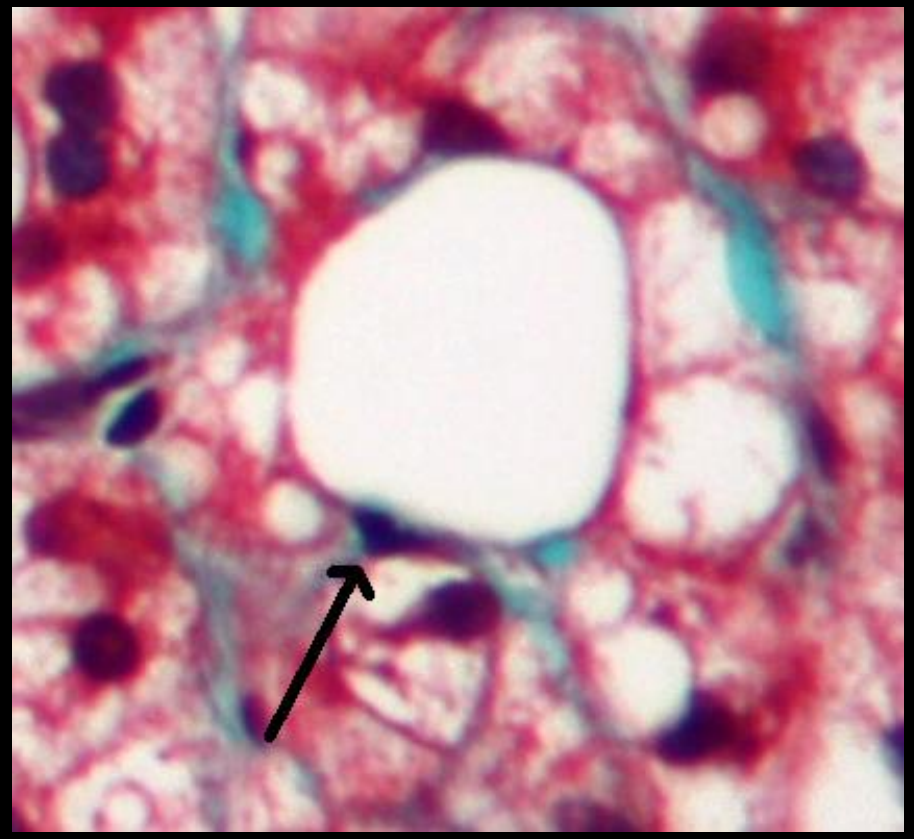
Drug- and Toxin-Induced Liver Injury

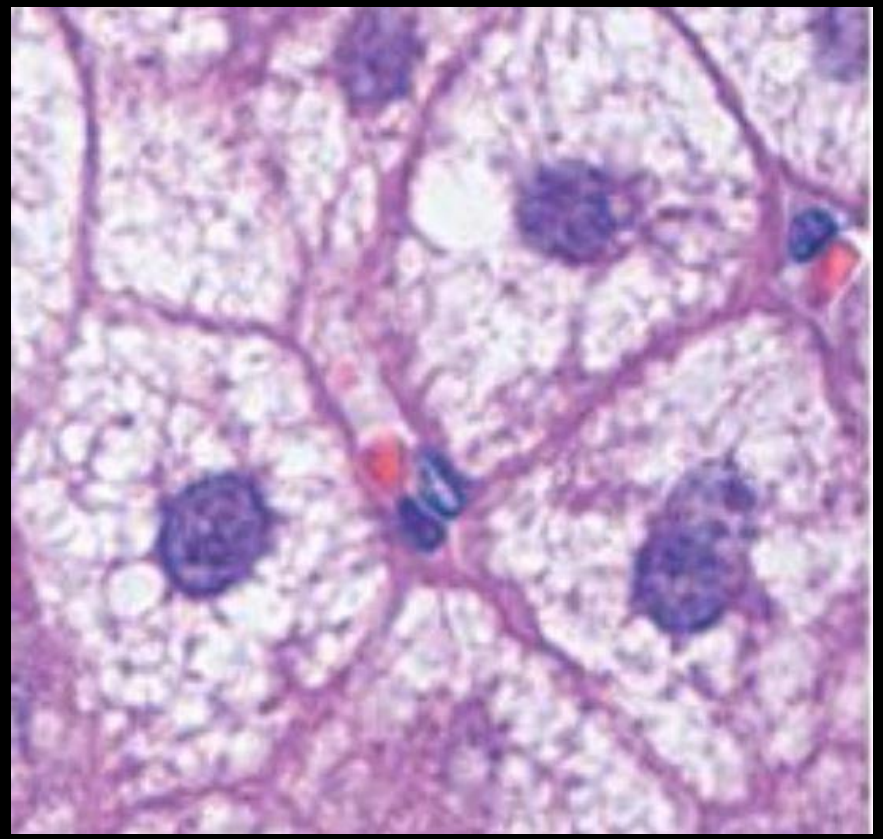
Examples of syndromes and patterns

- acute hepatitis
- cholestasis
- cetrilobular necrosis
- autoimmune
- granulomatous
- cholangitis
- peliosis hepatis
- veno-occlusive disease
- sinusoidal fibrosis
- macrovesicular steatosis
- microvesicular steatosis

macrovesicular steatosis

microvesicular steatosis





Objectives

- Microvesicular steatosis results from mitochondrial failure/dysfunction and sometimes appears with macrovesicular steatosis. Onset over hours to weeks.
- Two major mitochondrial pathogeneses:

Primary impaired β oxidation of fatty acids

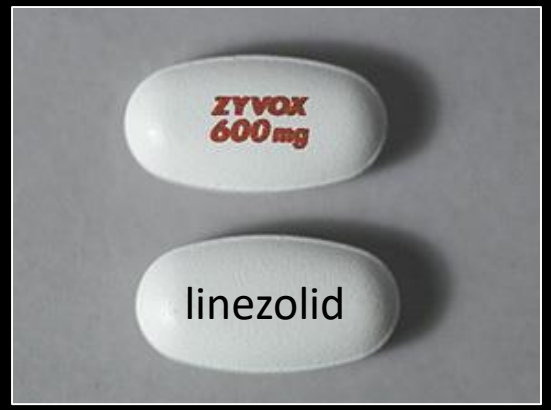
Primary impaired oxidative phosphorylation

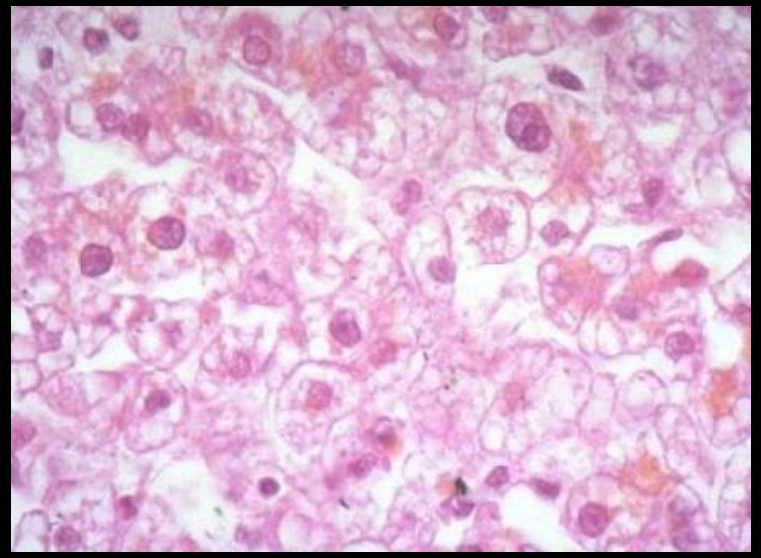
- AST & ALT nl to ~ 600 IU/L
- hyperammonemia
- hypoglycemia
- low ketones
- metabolic acidosis

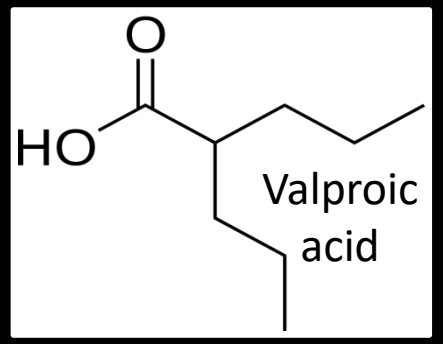
- ketones commonly low or absent
- hypoglycemia more common

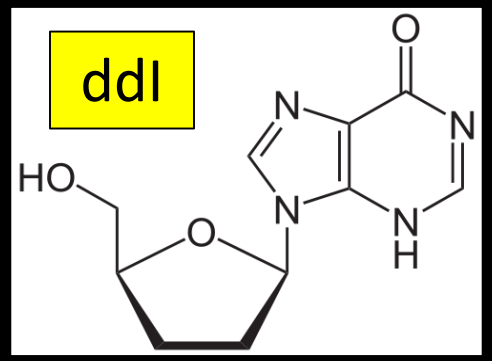
- significant lactic acidosis more common
- higher AST & ALT with necrosis, when present

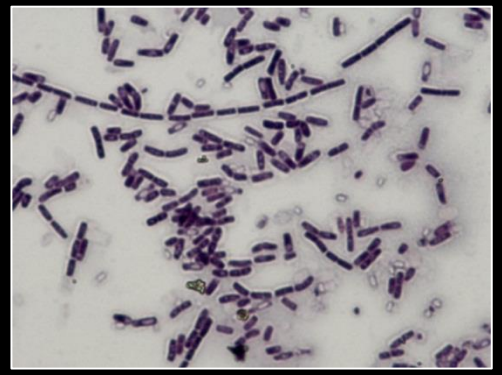
HMS Bounty





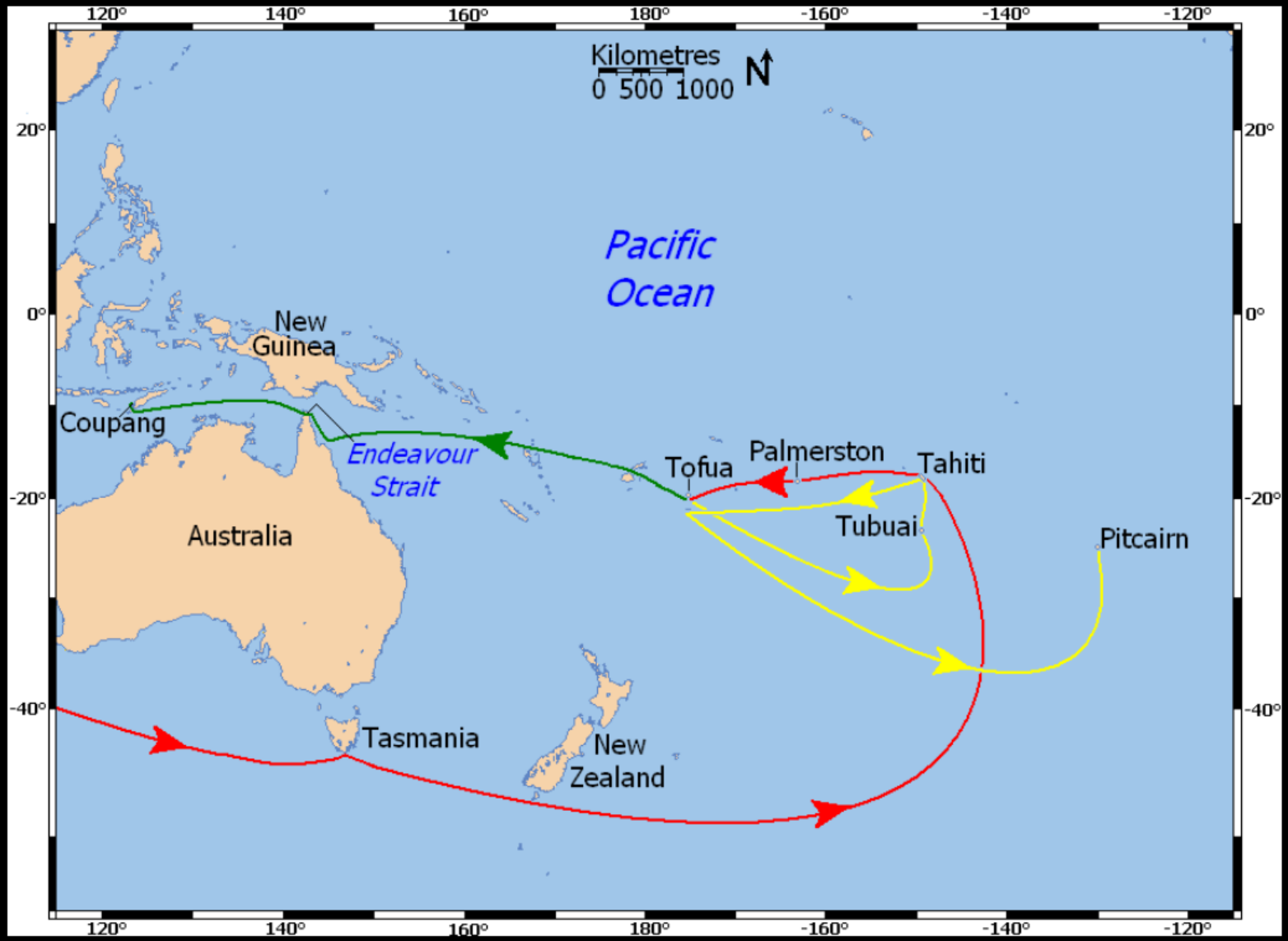







William Bligh
1754 - 1817


BOUNTY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-40°
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Ocean
New
Guinea
Coupang
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Strait
Australia
Tofua
Palmerston
Tahiti
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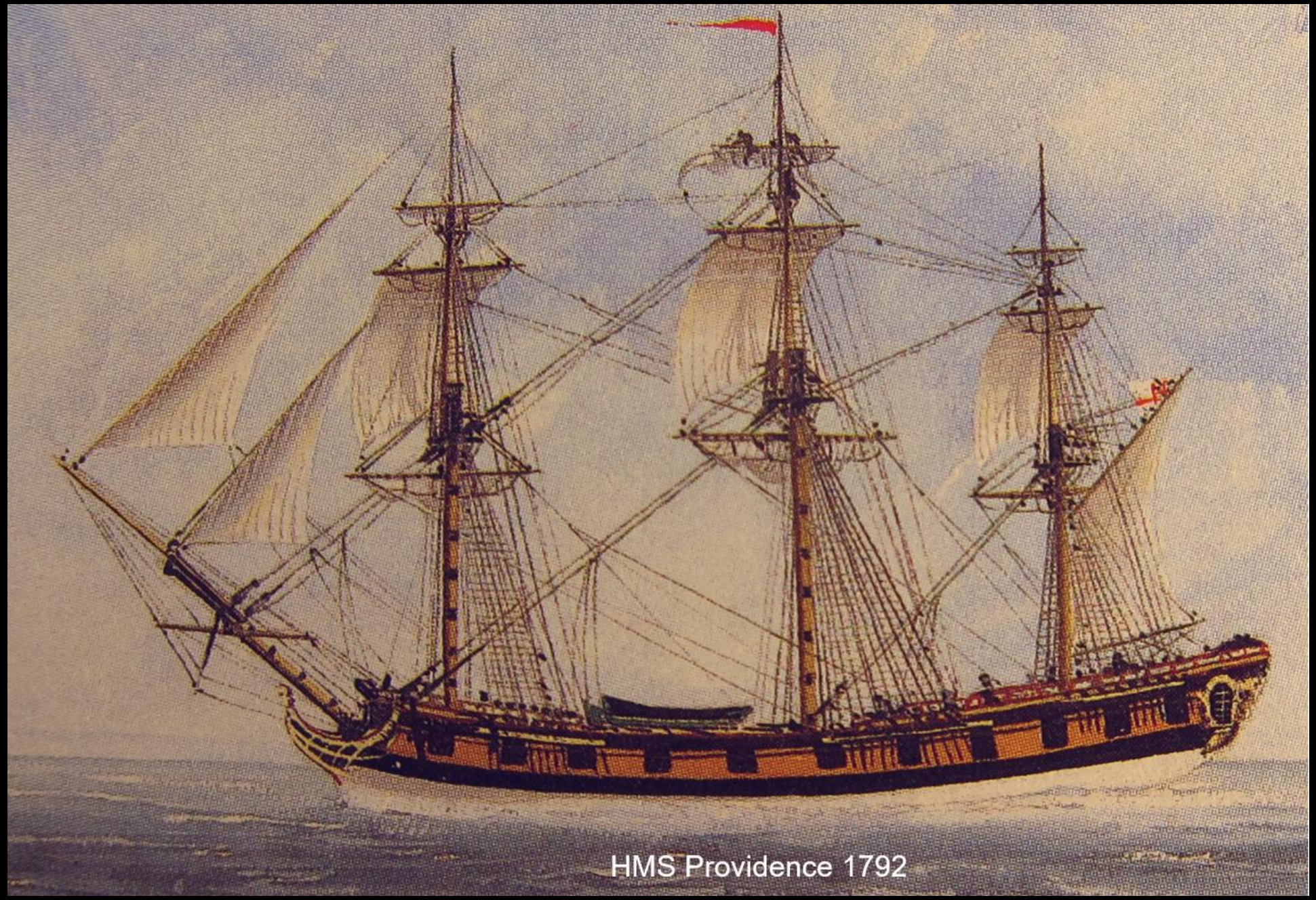
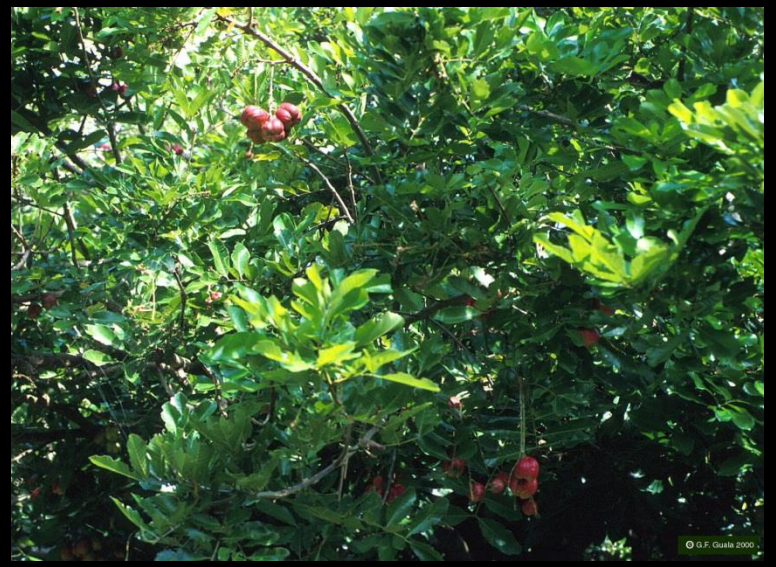
Pitcairn
Tasmania
New
Zealand

1789



HMS Providence 1792

William Bligh 1754 - 1817



Ackee fruit tree introduced to Jamaica in 1778 from Africa.

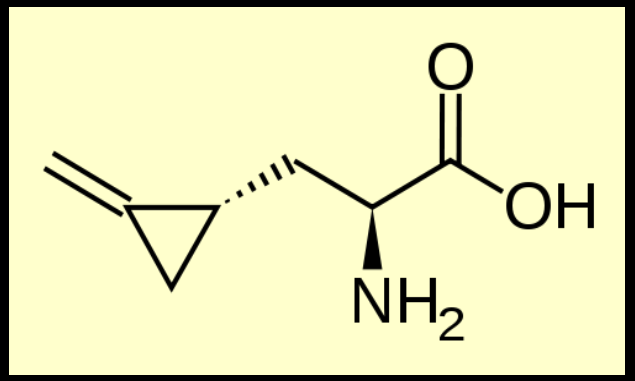
1791 – 1793 transports ackee trees from Jamaica to London.

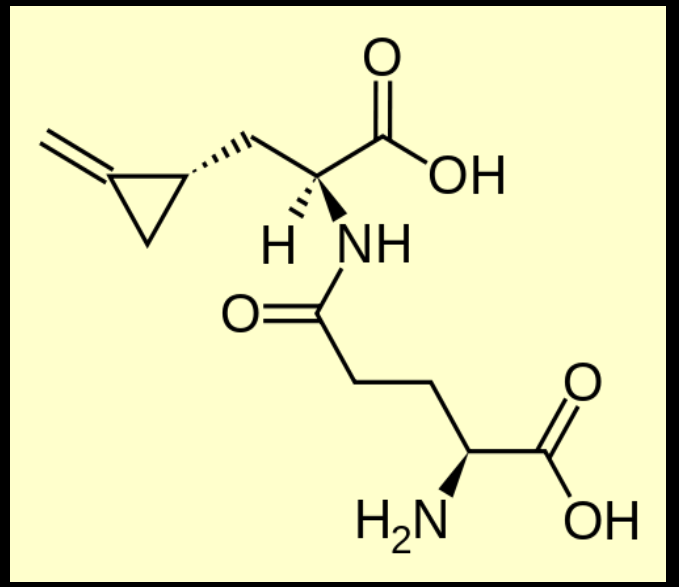
→

The Royal Society names the tree *Blighia sapida*.

Jamaican vomiting sickness reported in Jamaica as early as 1875. Vomiting, coma, seizures, death.

Hypoglycin A and B isolated in 1955 and linked to vomiting sickness in 1976.

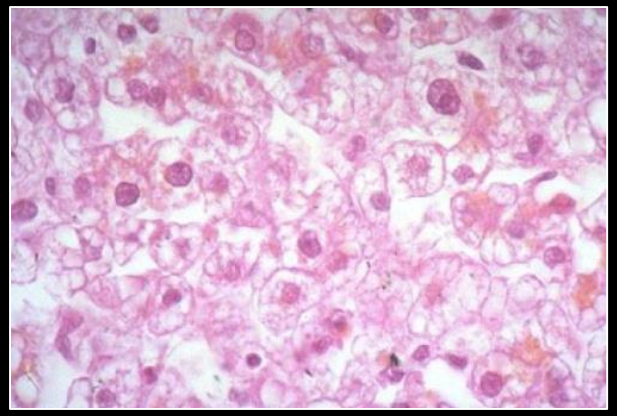




Jamaican vomiting sickness

- vomiting; mild transaminase elevation
- metabolic acidosis
- hypoglycemia
- hyperammonemia
- coma, death

microvesicular steatosis

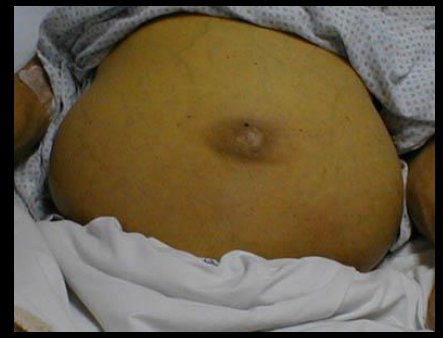


Acute Yellow Atrophy of the Liver in Pregnancy

H.J. Stander, M.D. and J.F. Cannden, B.S., New York, N.Y.

Am J Obstet Gynecol 1934; 28:61-69

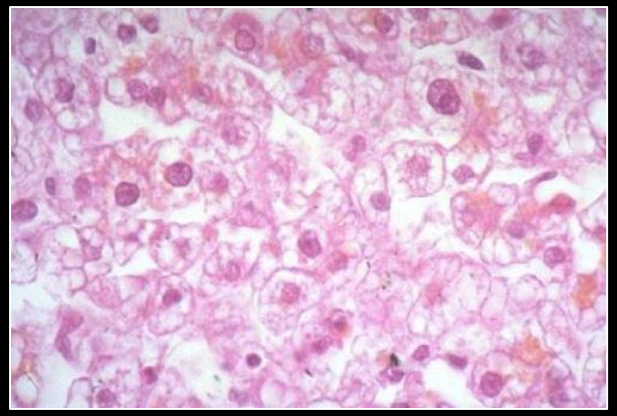
1934: First detailed report of fatty liver of pregnancy



Fatty Liver of Pregnancy

- vomiting; mild transaminase elevation
- jaundice
- metabolic acidosis
- hypoglycemia
- hyperammonemia
- coma, death

microvesicular steatosis



A. M. A.
ARCHIVES OF INTERNAL MEDICINE
VOLUME 88 SEPTEMBER 1951 NUMBER 3

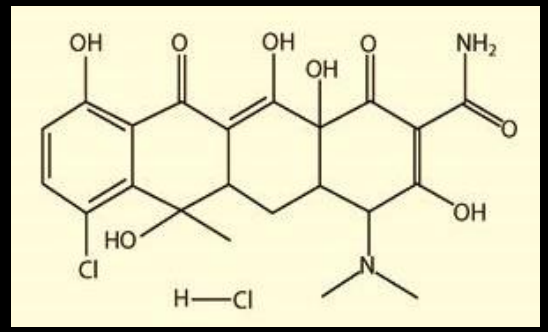
EFFECT OF LARGE DOSES OF AUREOMYCIN ON HUMAN LIVER

MARK H. LEPPER, M.D.
CHICAGO
CHARLES K. WOLFE, M.D.
HYMAN J. ZIMMERMAN, M.D.
ESTON R. CALDWELL Jr., M.D.
AND
HAROLD W. SPIES, M.D.
WASHINGTON, D. C.
AND
HARRY F. DOWLING, M.D.
CHICAGO

103 patients treated with IV chlortetracycline

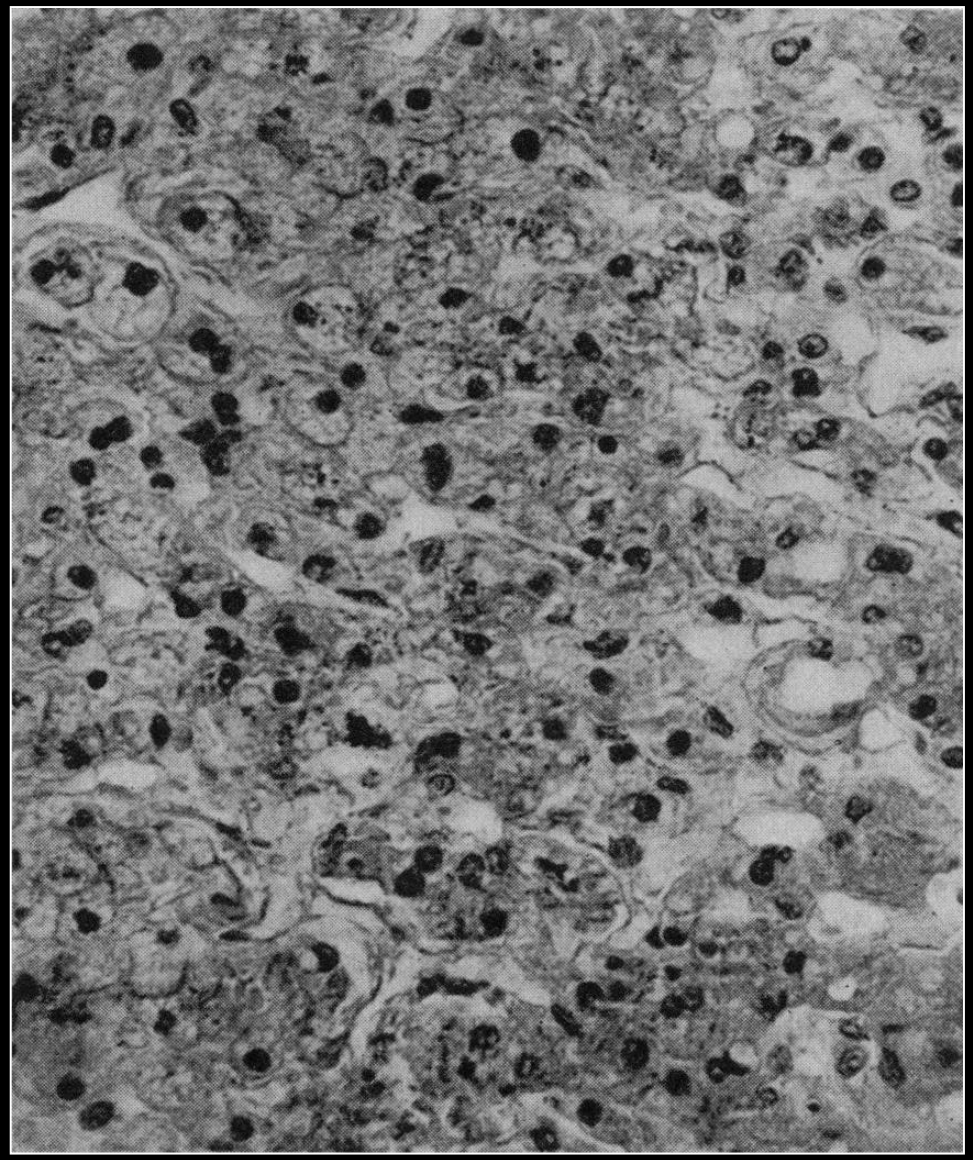
14 received concurrent oral and IV dosing

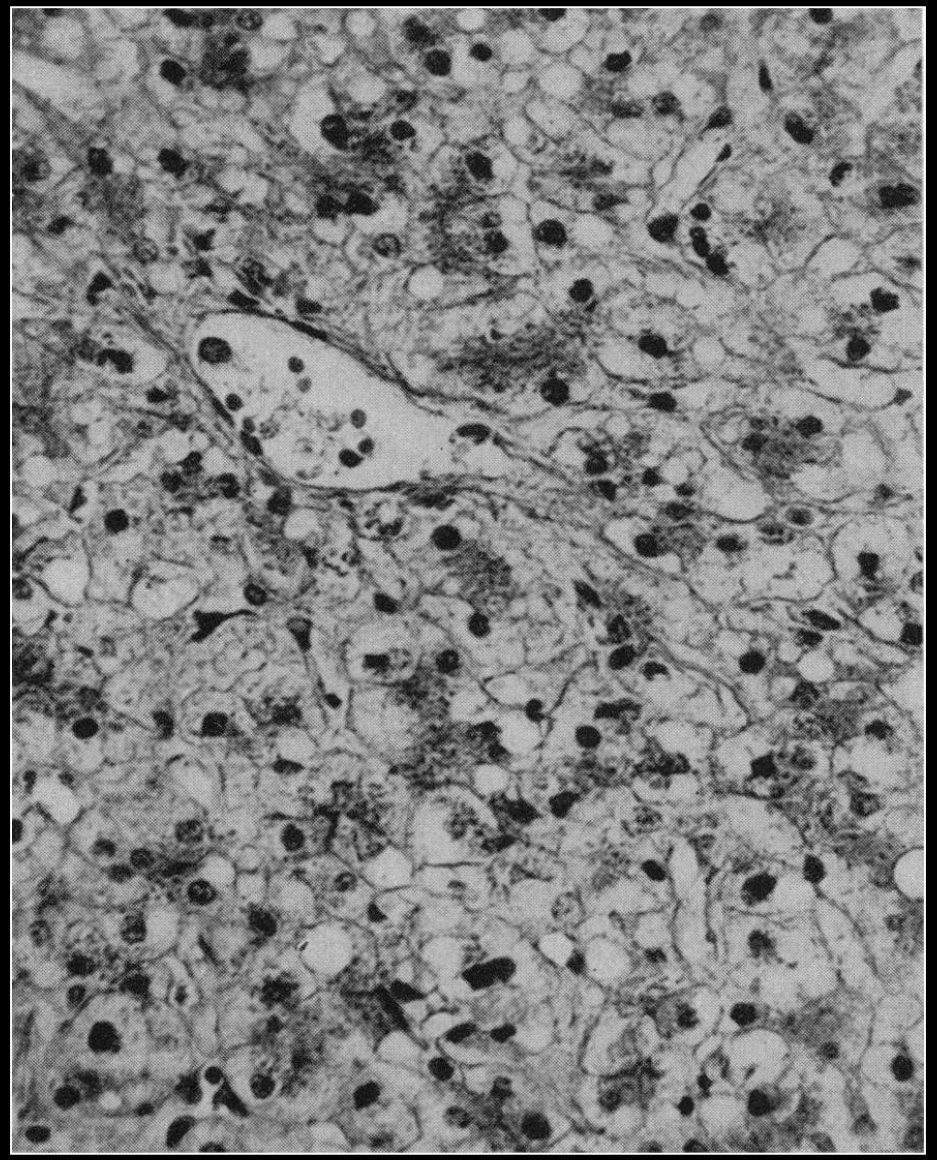
7 developed hepatotoxicity

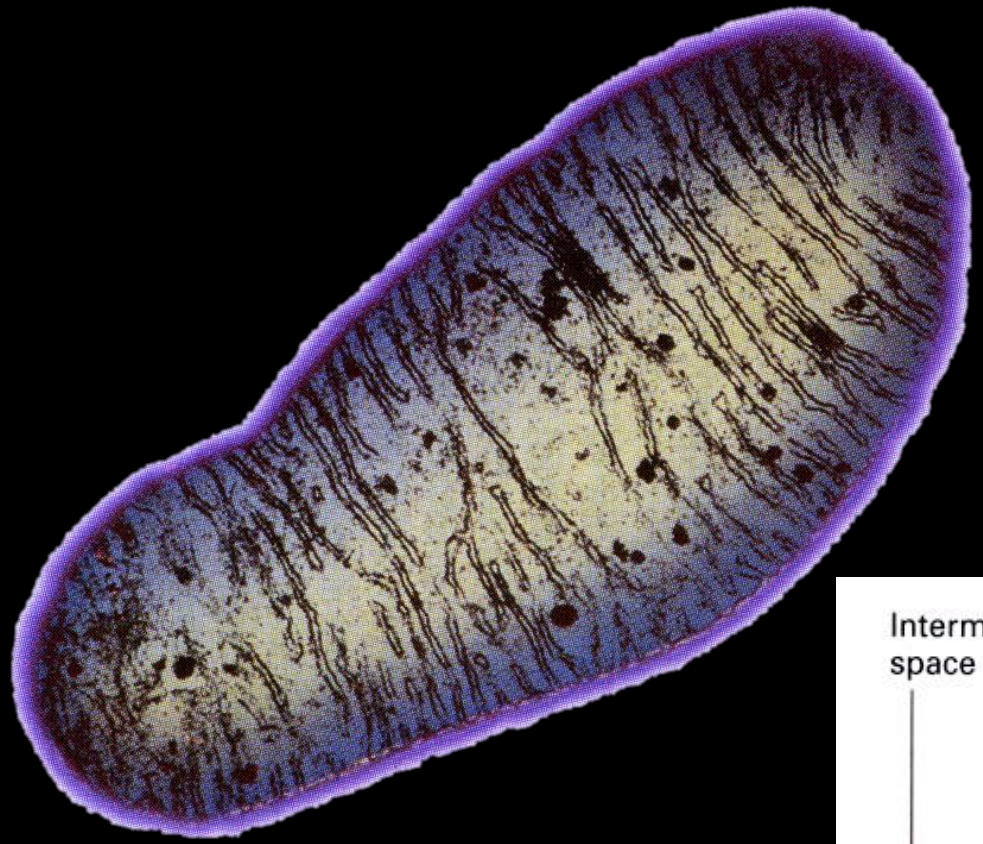


chlortetracycline

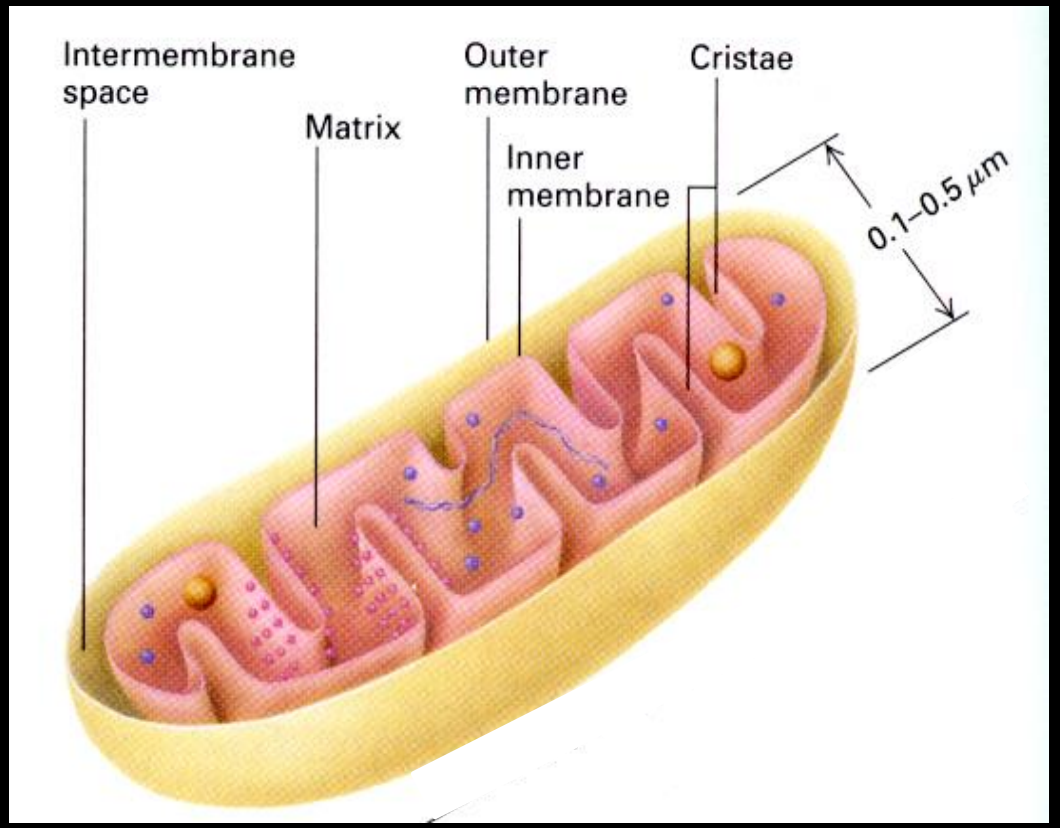
5 died; biopsy on 6th patient

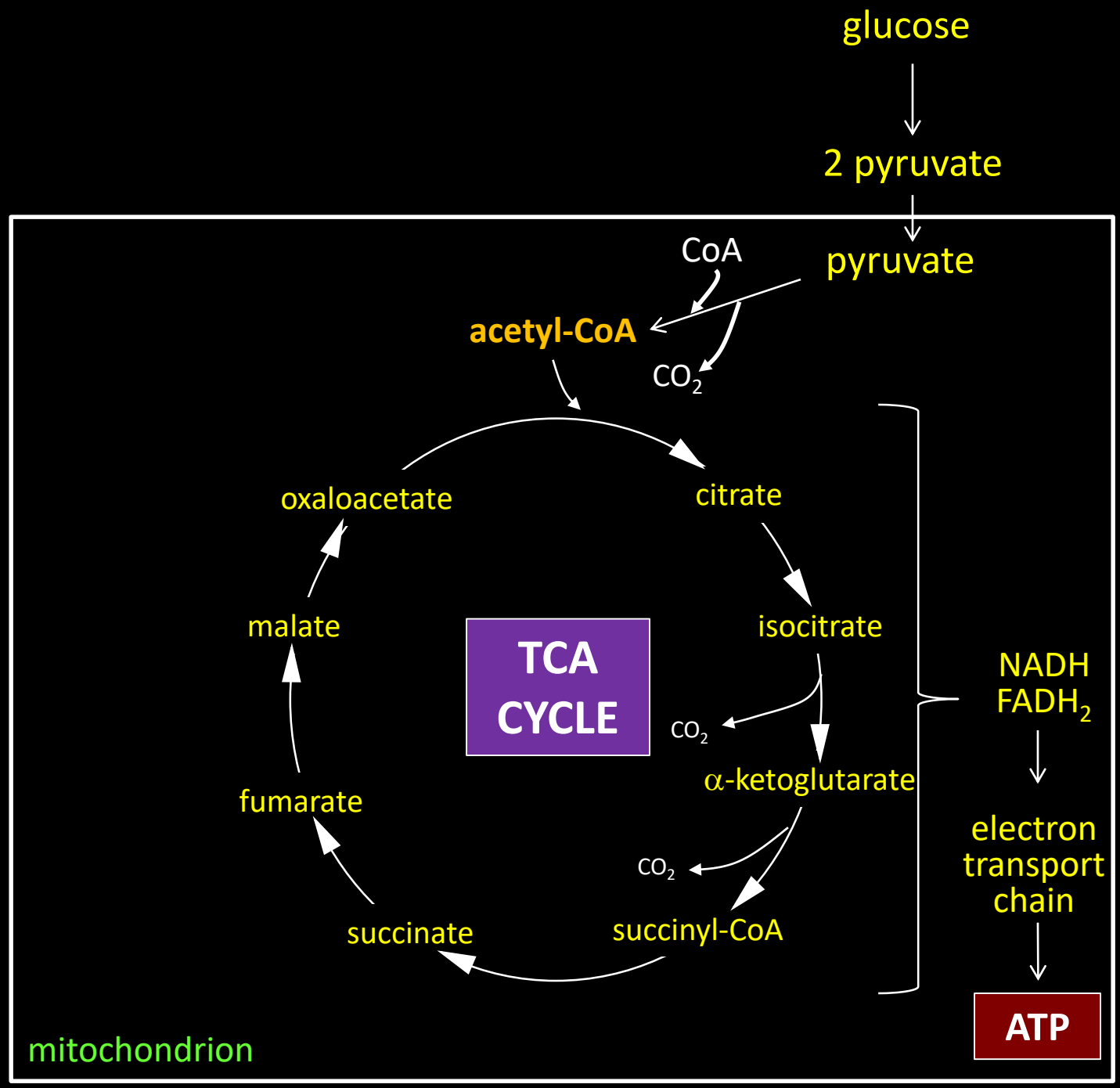






The Mitochondrion

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2 pyruvate
pyruvate
CoA
acetyl-CoA
CO_2
oxaloacetate
citrate
isocitrate
CO_2
α-ketoglutarate
CO_2
succinyl-CoA
succinate
fumarate
malate
TCA CYCLE
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electron transport chain
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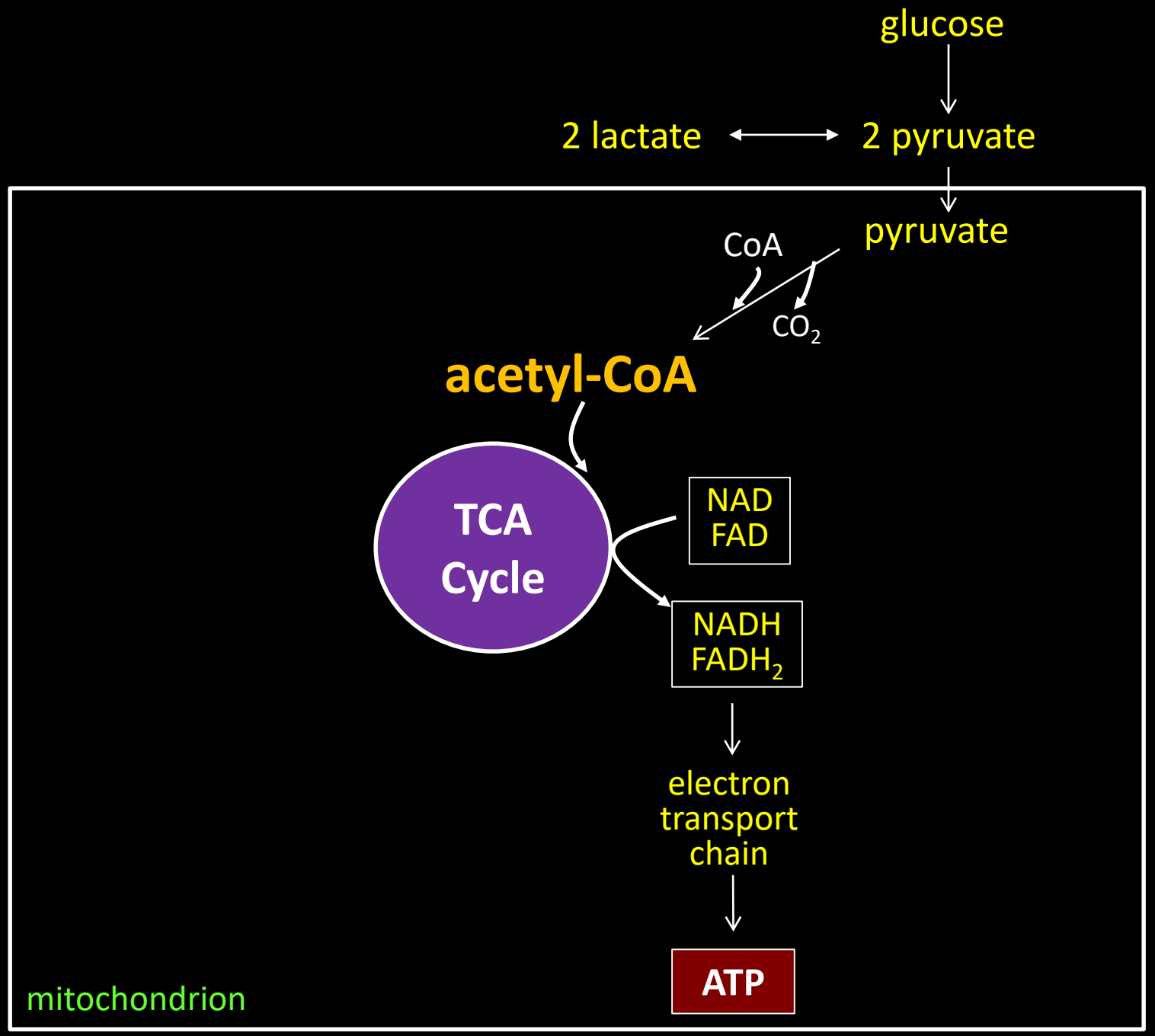
glucose
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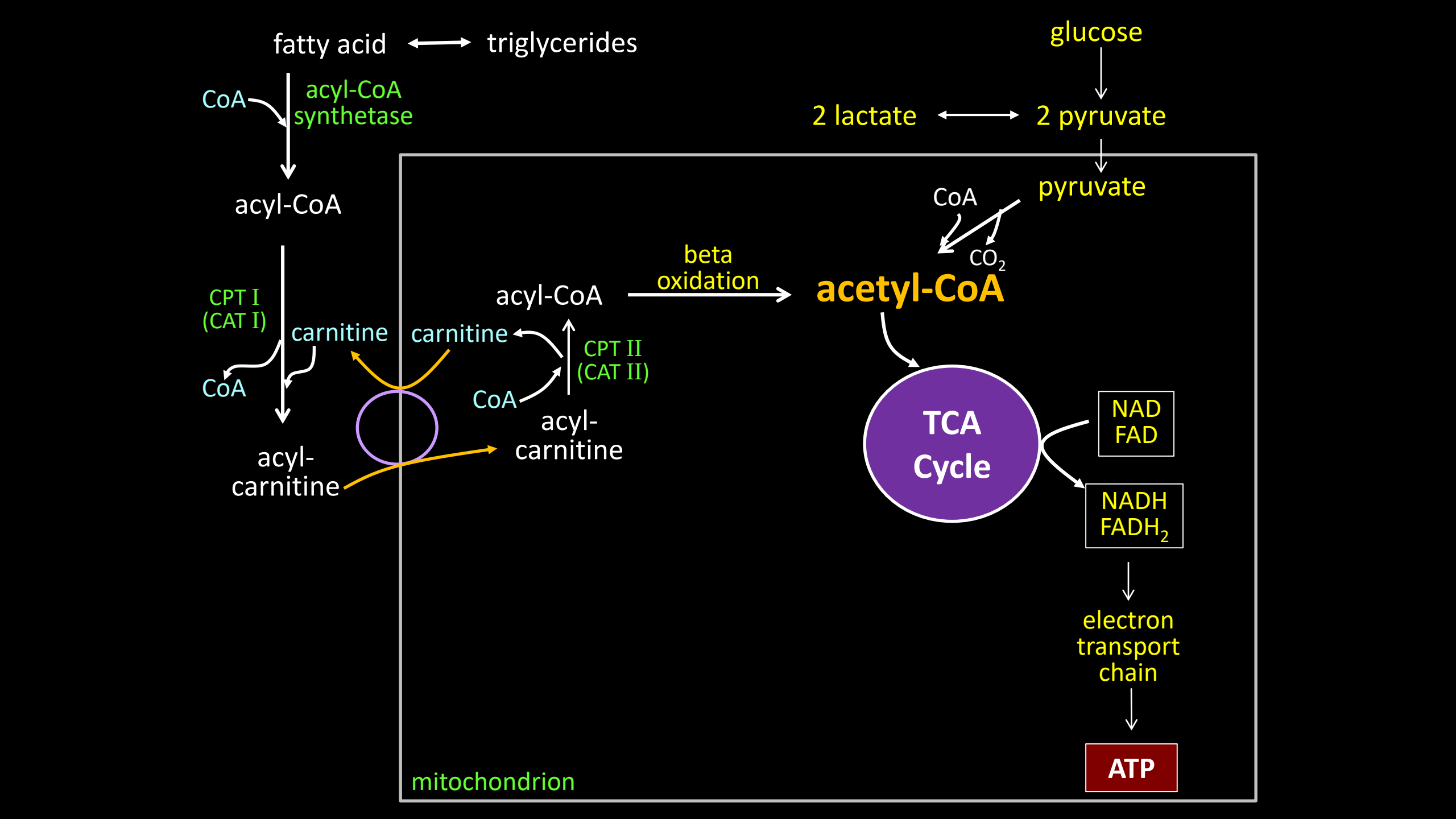
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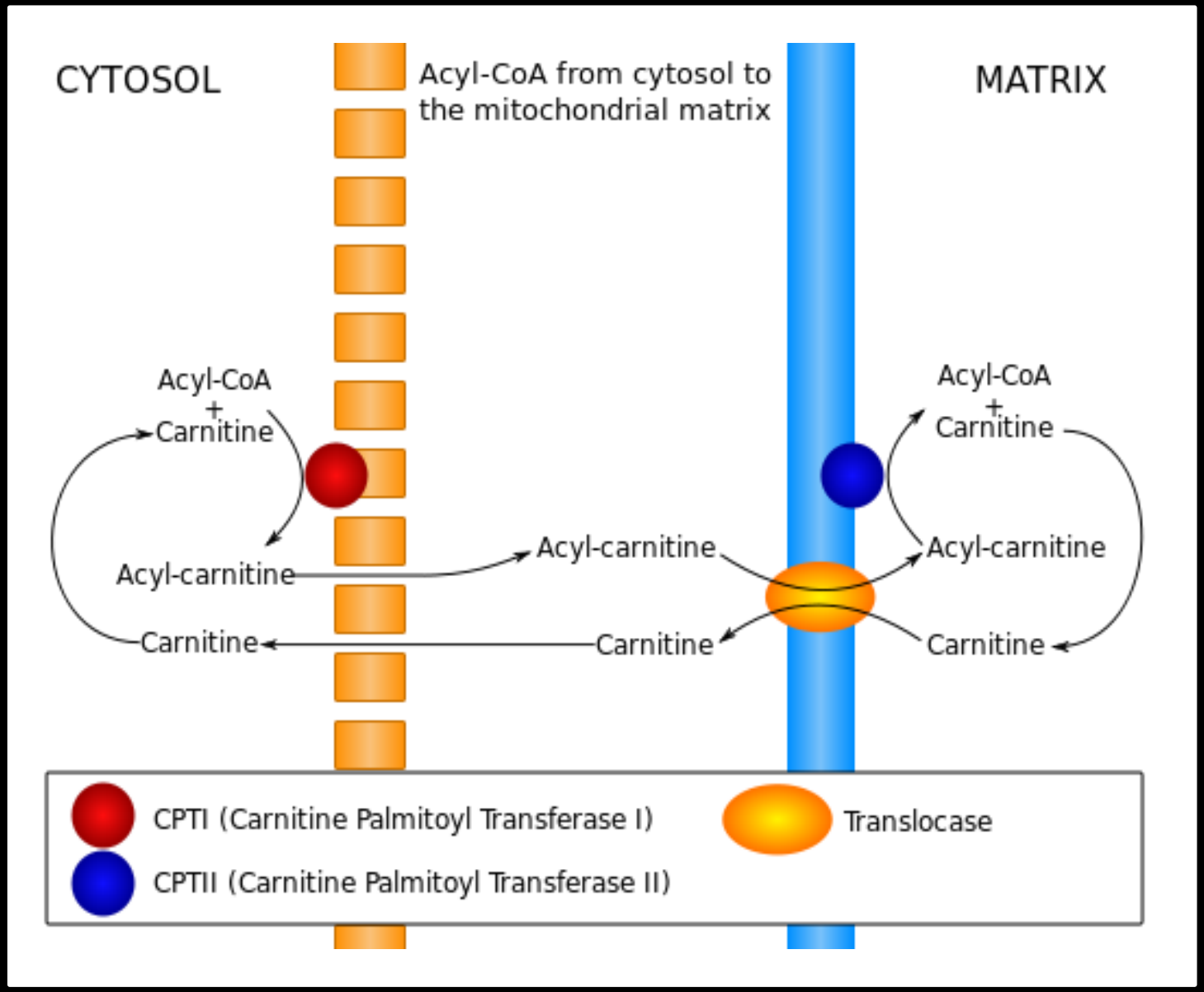
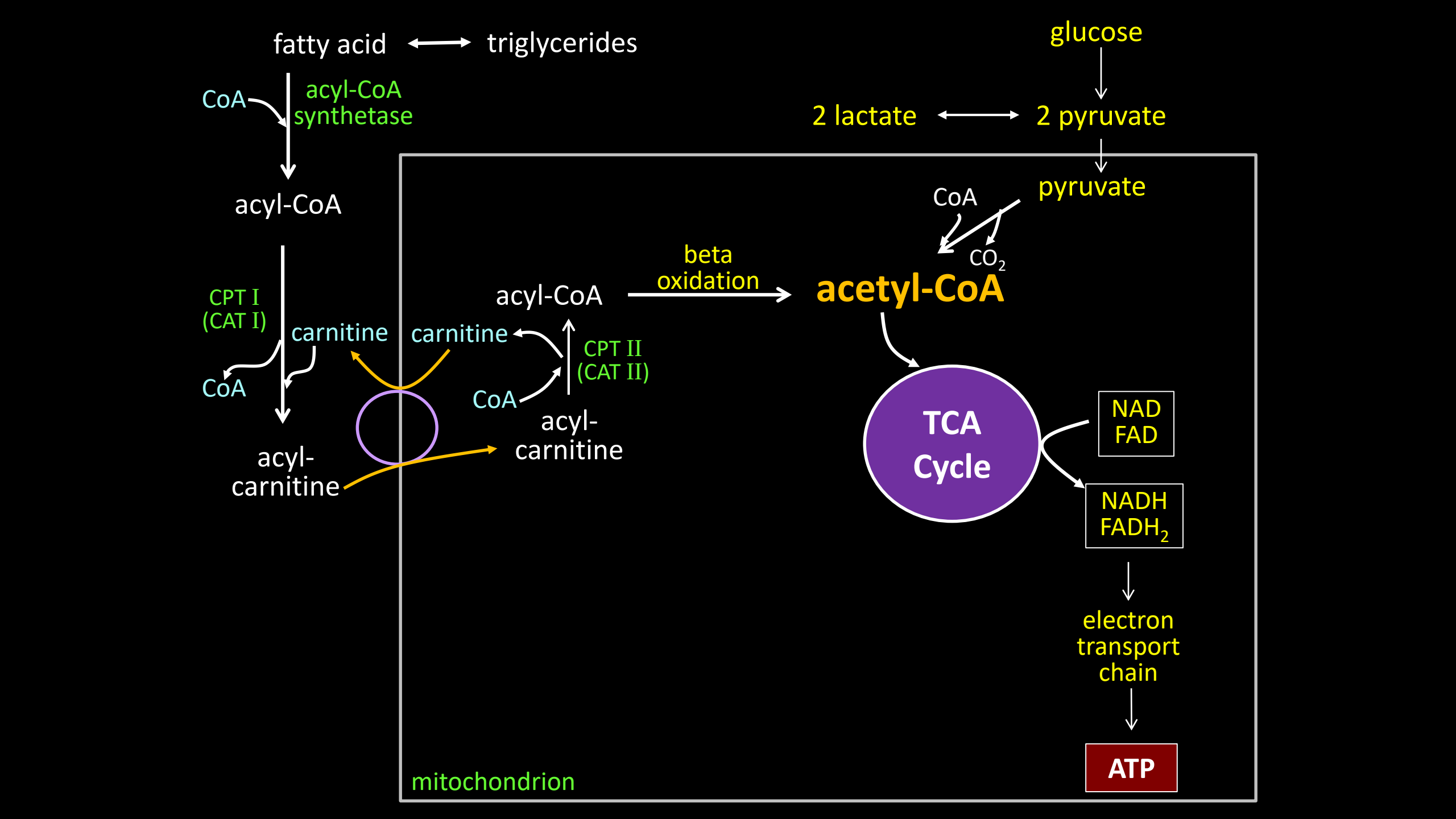


wikipedia.com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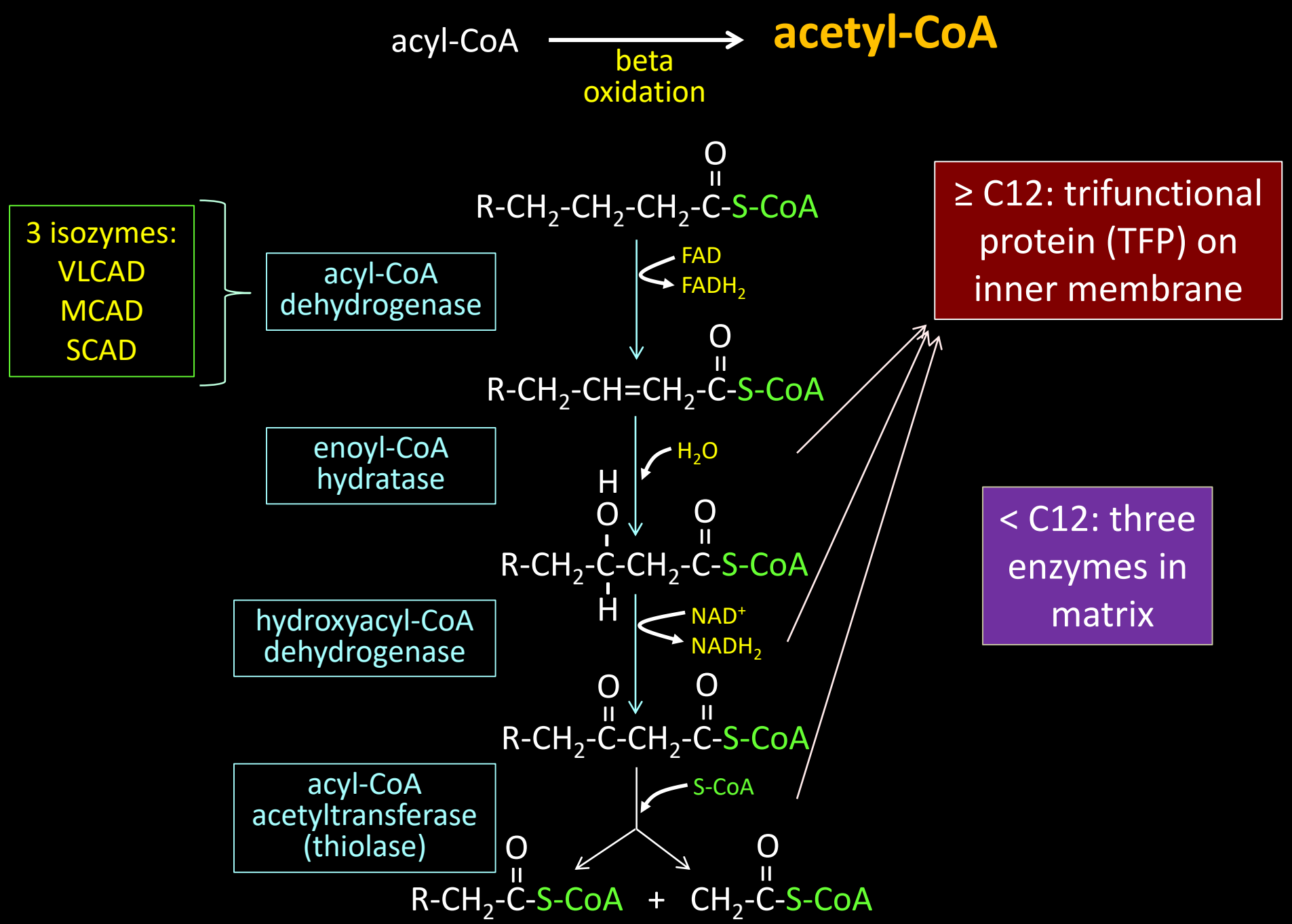
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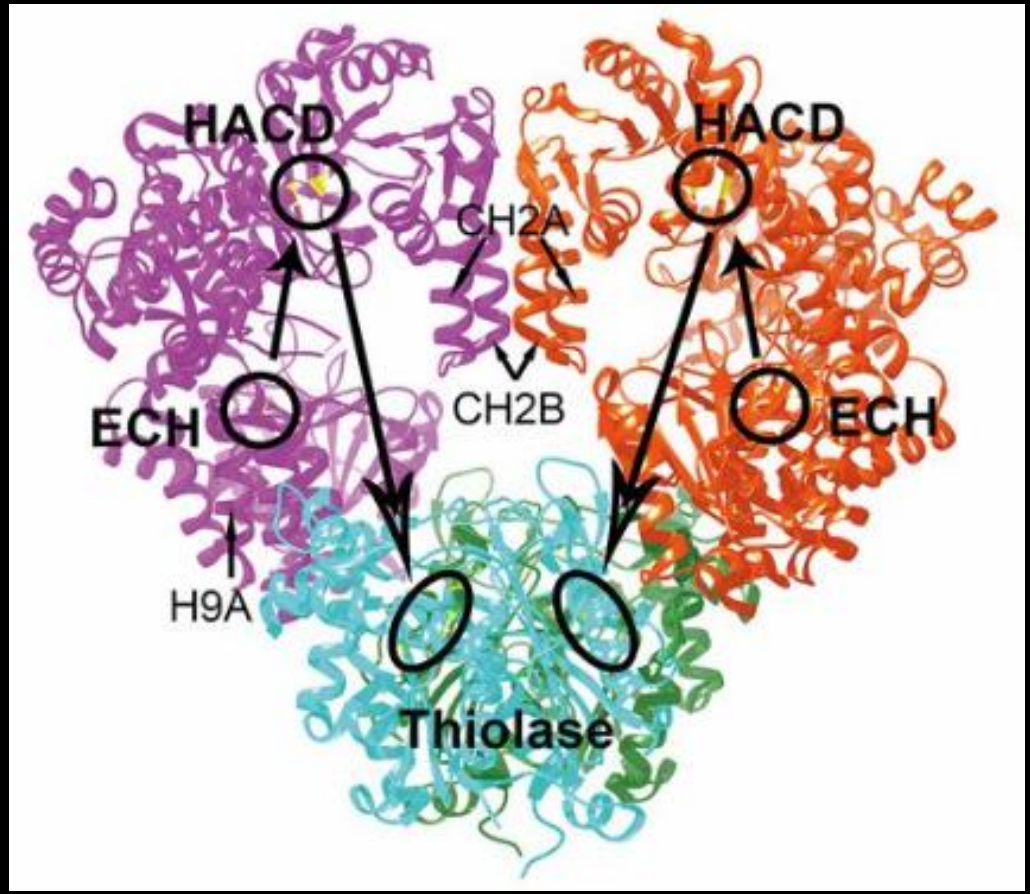
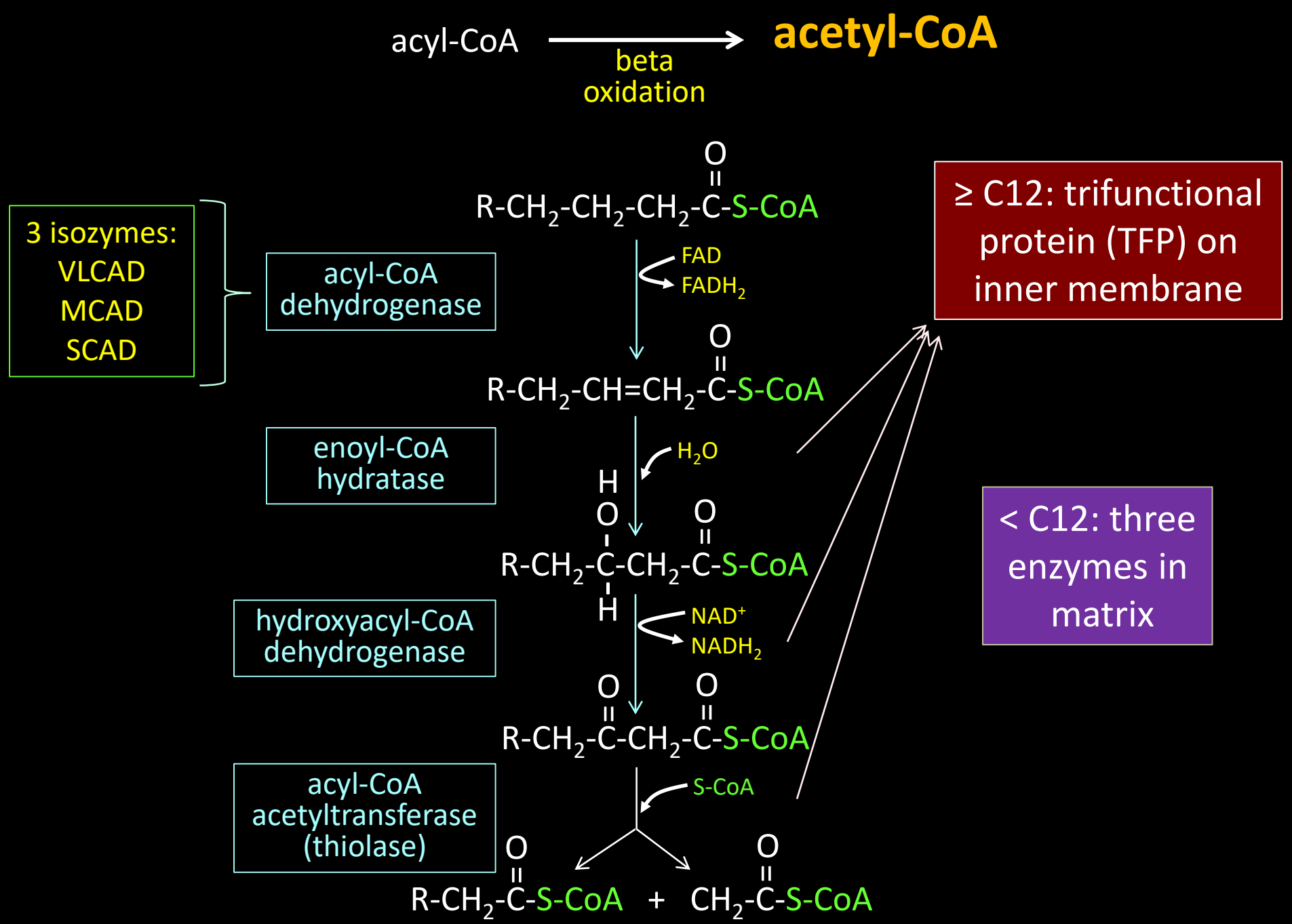
≥ C12: trifunctional protein (TFP) on inner membrane
< C12: three enzymes in matrix



human mitochondrial trifunctional protein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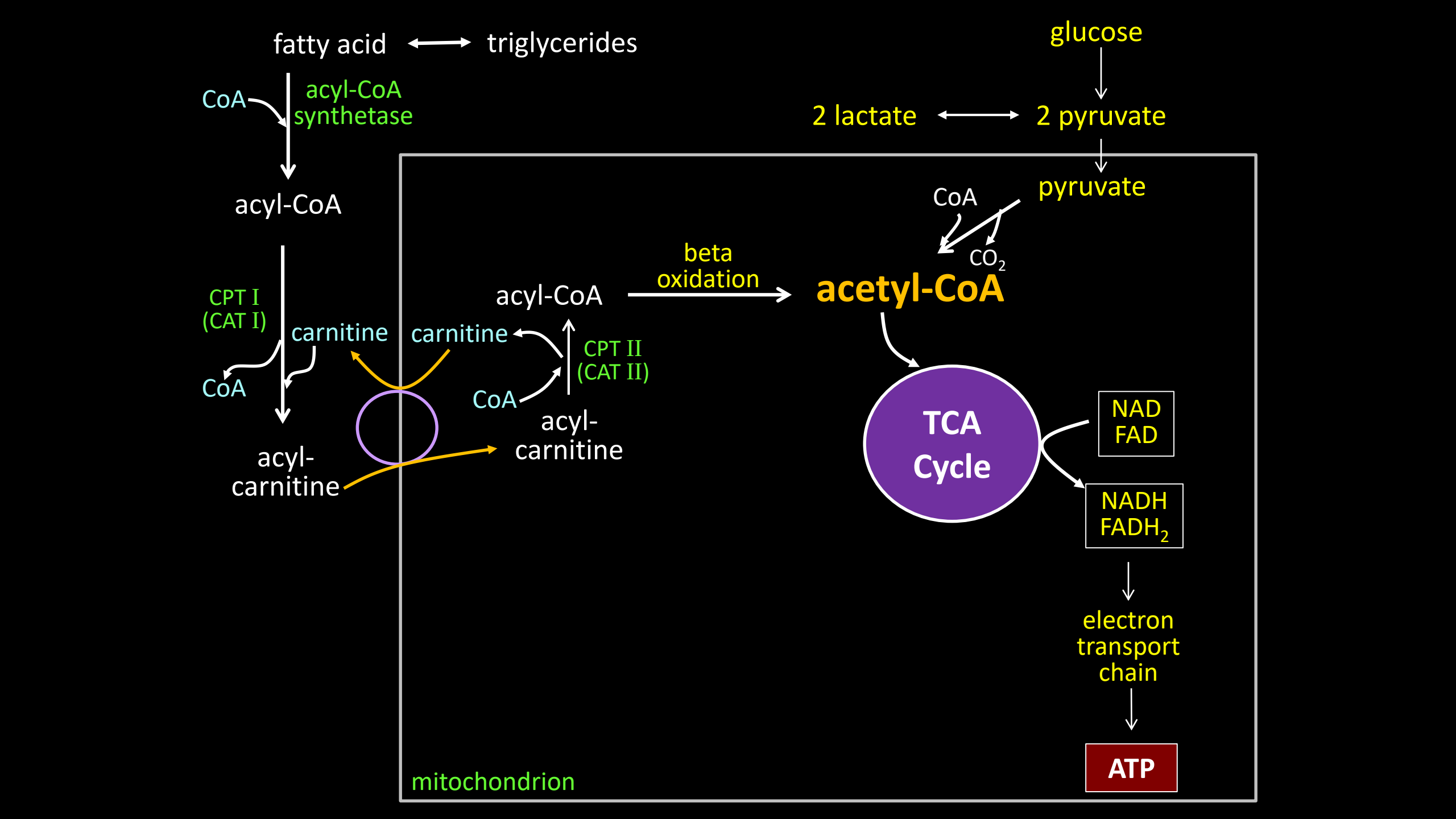
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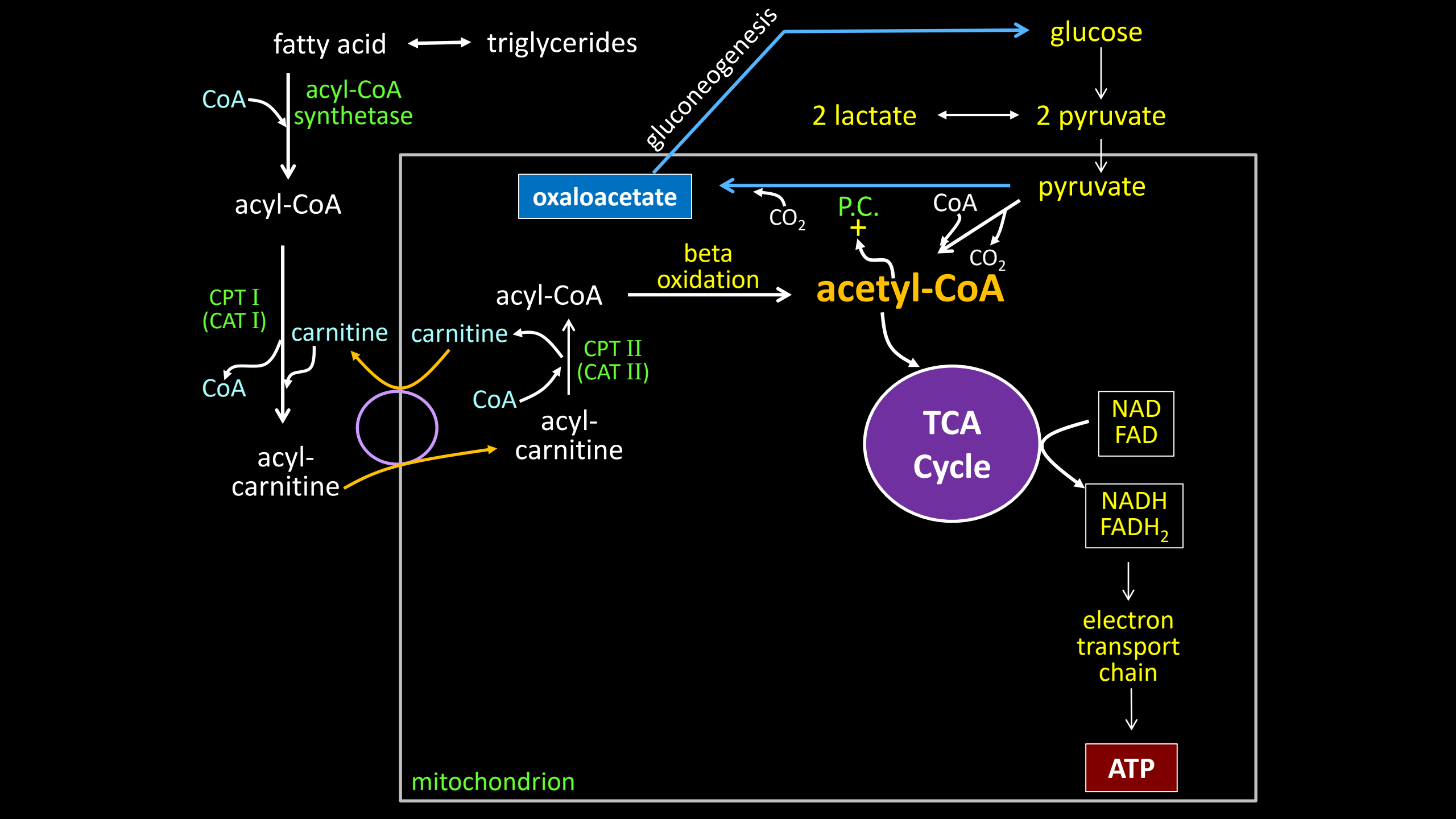
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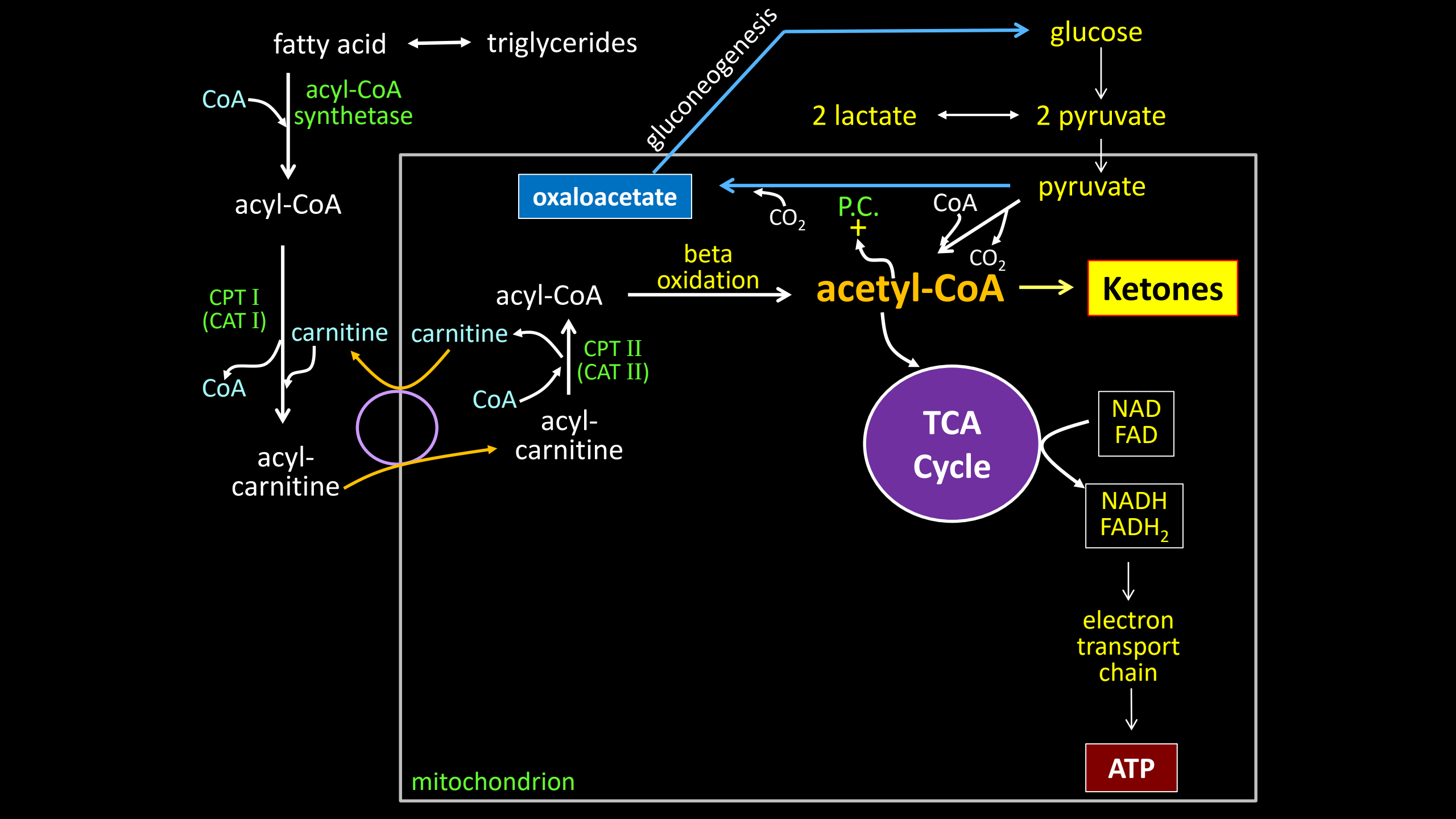
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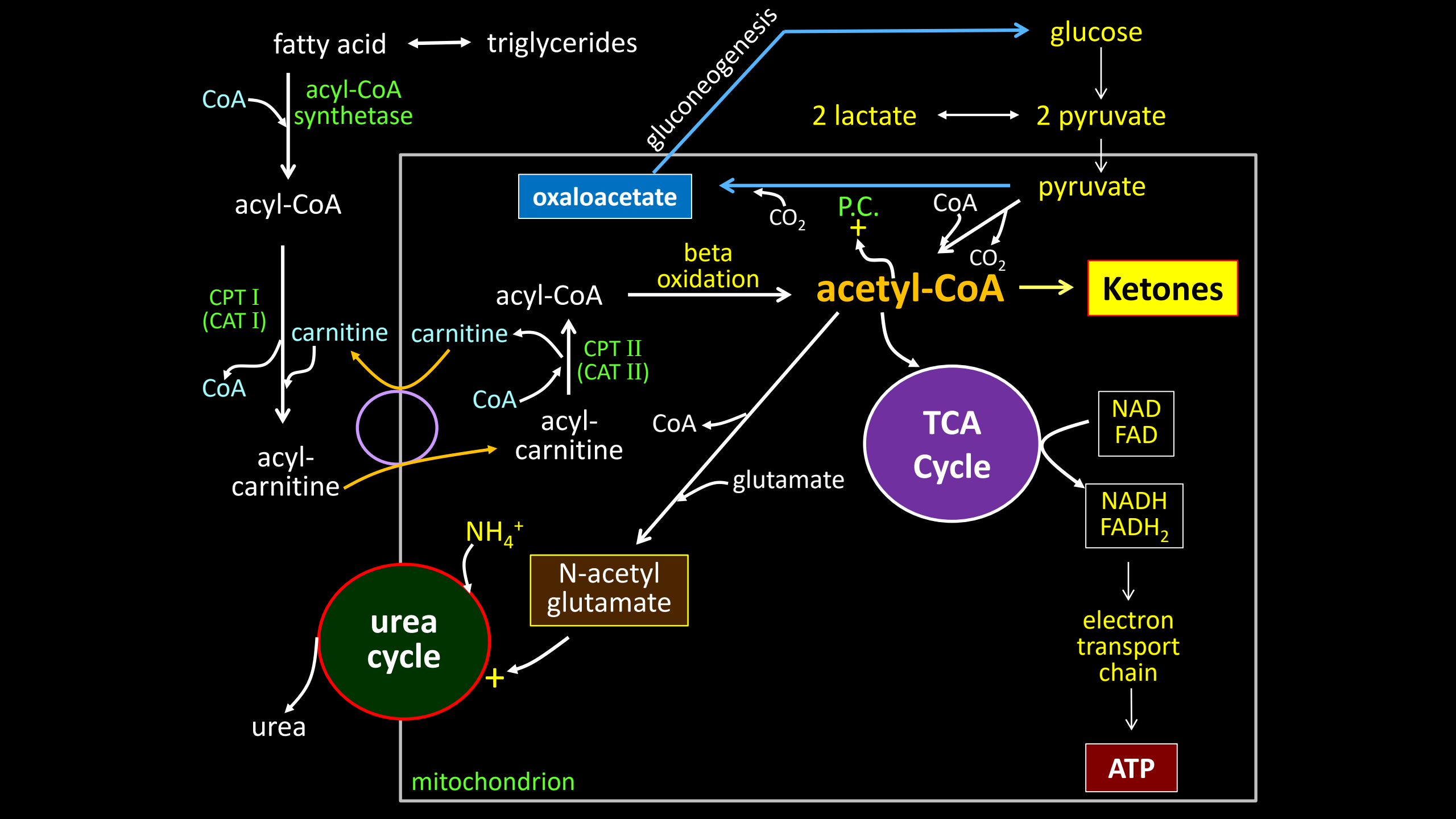
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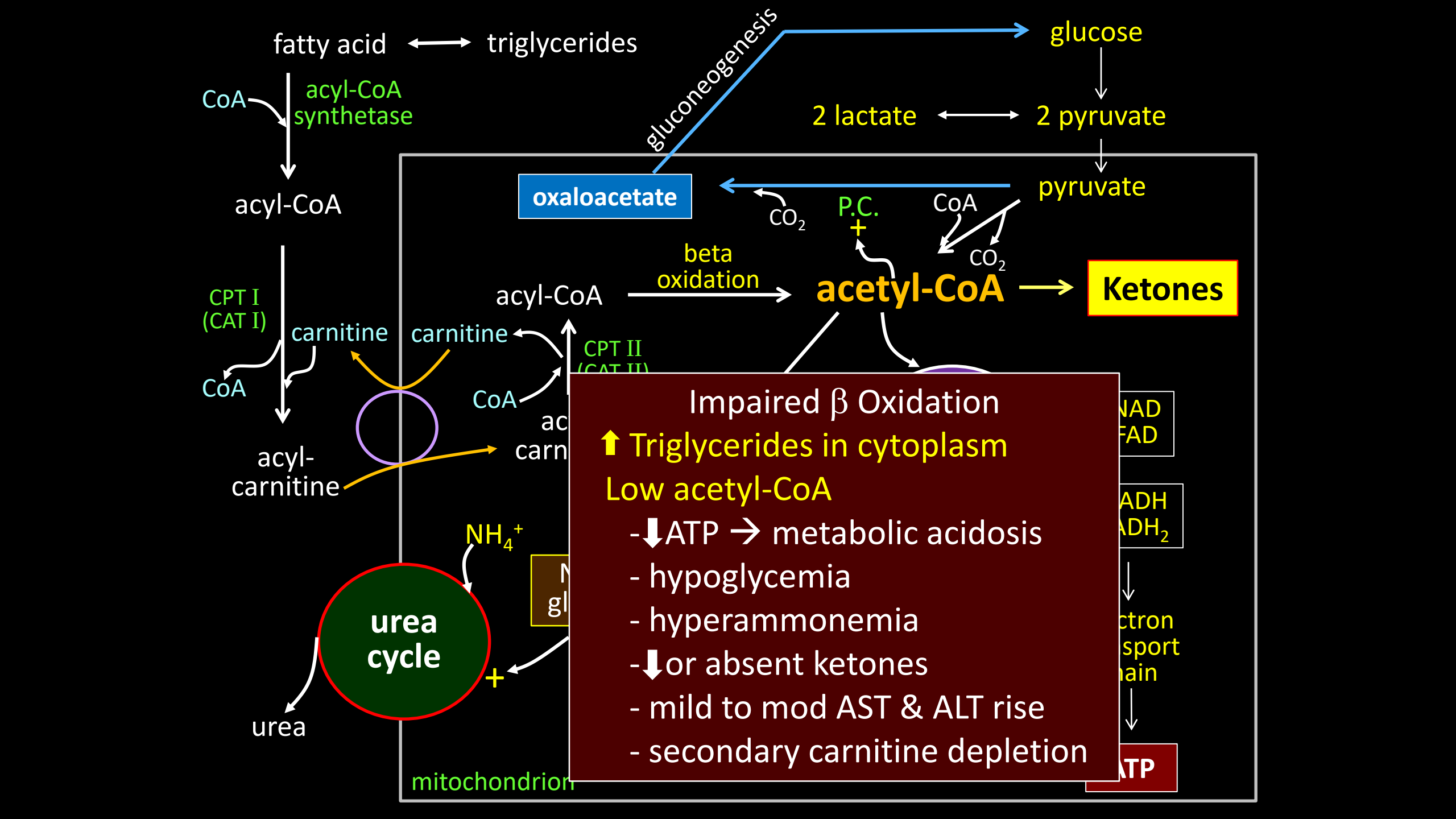
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CPT II
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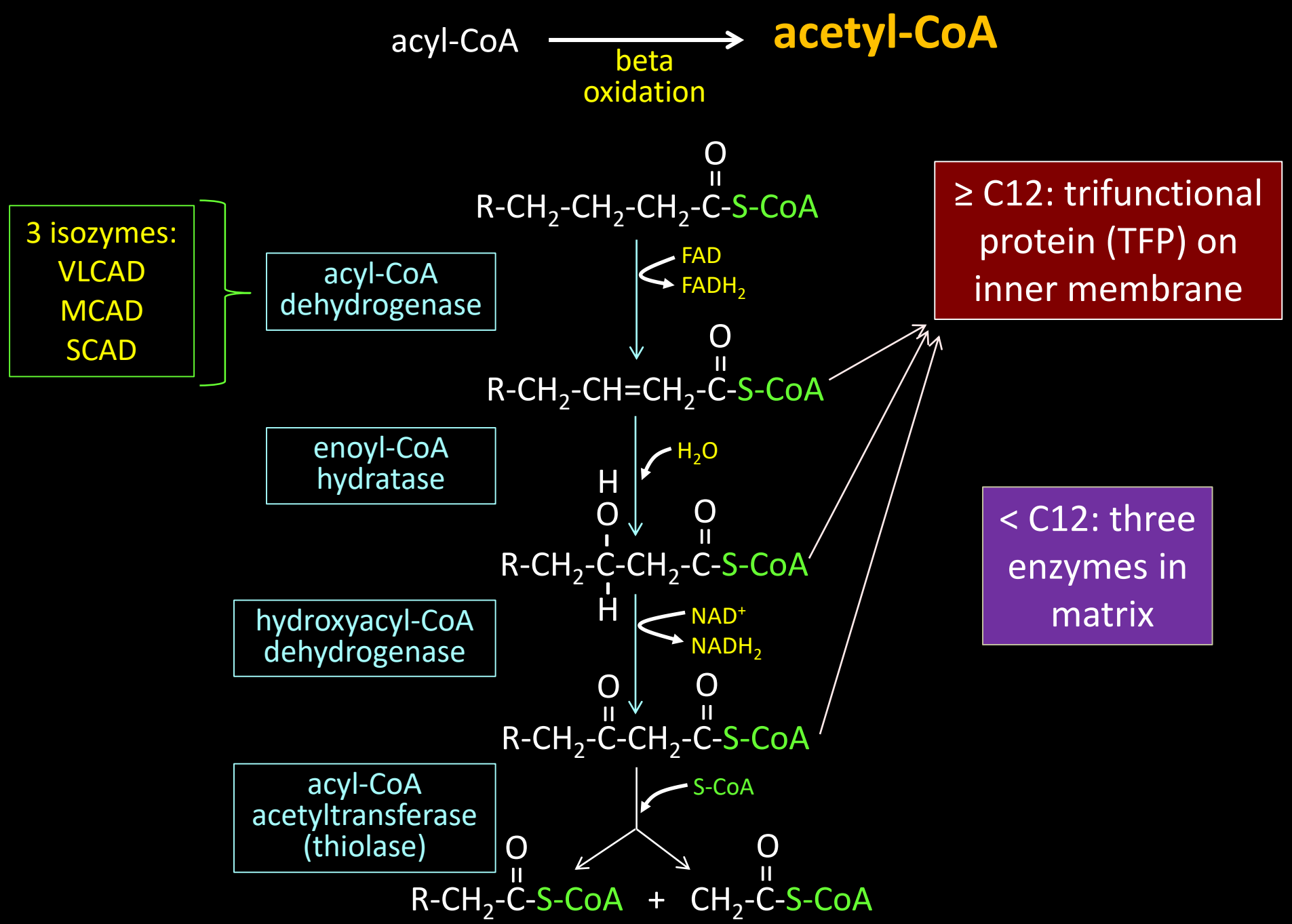
NH_4^+
urea cycle
+
urea
mitochondrion
Impaired β Oxidation
⬆ Triglycerides in cytoplasm
Low acetyl-CoA
-⬇ATP → metabolic acidosis
- hypoglycemia
- hyperammonemia
-⬇or absent ketones
- mild to mod AST & ALT rise
- secondary carnitine depletion

Microvesicular Steatosis from Impaired β Oxidation of Fatty Acids

Inborn errors of metabolism

MCAD deficiency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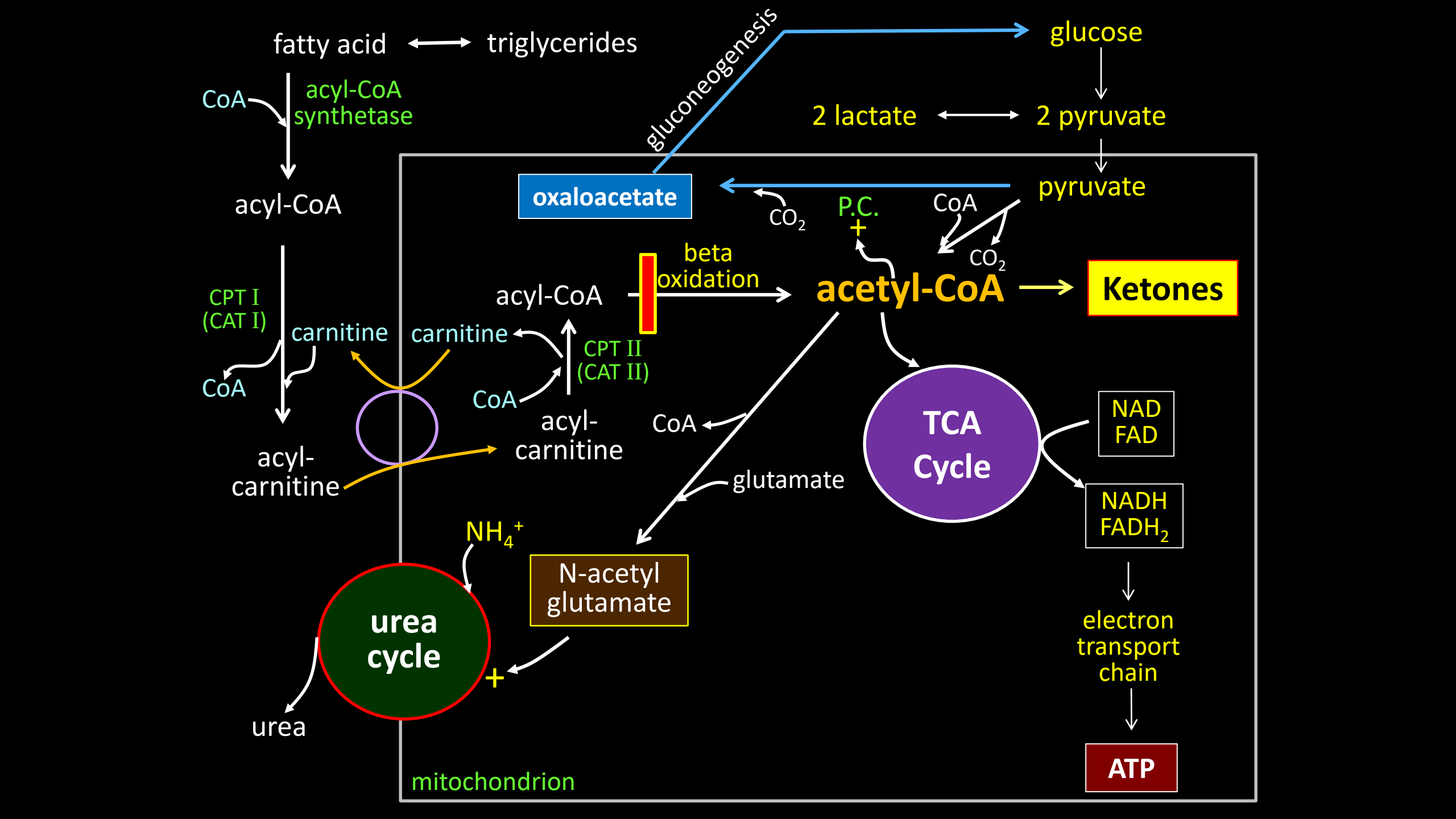
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CO_2
P.C.
+
CoA
CO_2
beta oxidation
acyl-CoA
acetyl-CoA
Ketones
CPT I (CAT I)
carnitine
CoA
acyl-carnitine
carnitine
CPT II (CAT II)
CoA
acyl-carnitine
CoA
TCA Cycle
NAD
FAD
glutamate
NH_4^+
N-acetyl glutamate
NADH
$FADH_2$
urea cycle
+
electron transport chain
urea
ATP
mitochondrion

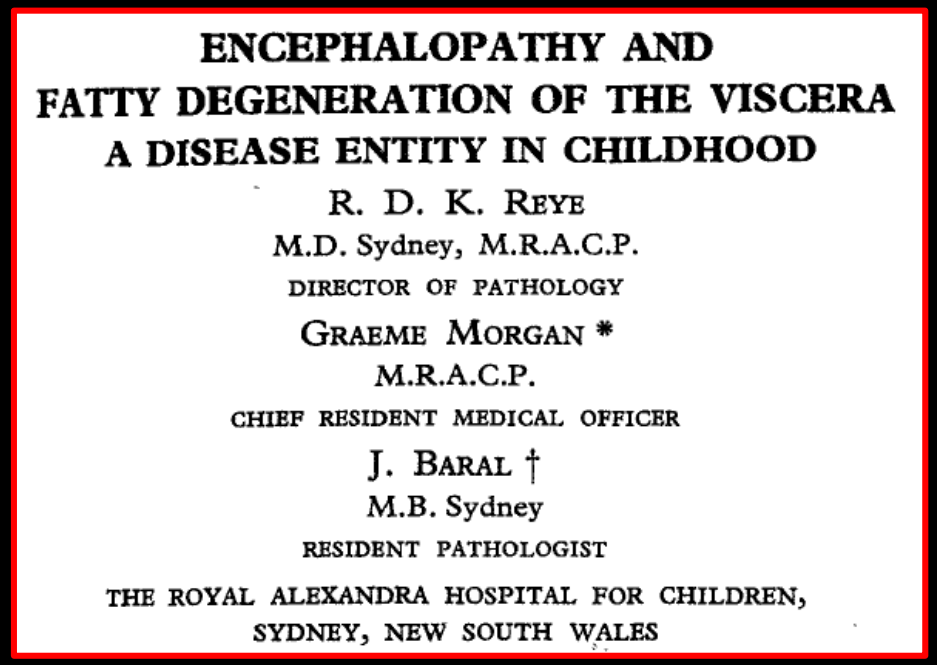
Microvesicular Steatosis from Impaired β Oxidation of Fatty Acids

Inborn errors of metabolism

MCAD deficiency

Reye's Syndrome

Vomiting
Lethargy, coma
Hypoglycemia
Hyperammonemia
AST, ALT < 600 IU/L



ENCEPHALOPATHY AND
FATTY DEGENERATION OF THE VISCERA
A DISEASE ENTITY IN CHILDHOOD

R. D. K. REYE
M.D. Sydney, M.R.A.C.P.
DIRECTOR OF PATHOLOGY
GRAEME MORGAN *
M.R.A.C.P.
CHIEF RESIDENT MEDICAL OFFICER
J. BARAL †
M.B. Sydney
RESIDENT PATHOLOGIST
THE ROYAL ALEXANDRA HOSPITAL FOR CHILDREN,
SYDNEY, NEW SOUTH WALES

The Lancet: 12 Oct 1963

Whatever happened to Reye's syndrome? Did it ever really exist?

Orlowski, James P. MD, FAAP, FCCP, FCCM
From the Pediatric Intensive Care Unit, University Community Hospital, Tampa, FL.
Critical Care Medicine August, 2009

Microvesicular Steatosis from Impaired β Oxidation of Fatty Acids

Inborn errors of metabolism

MCAD deficiency. "Reye's Syndrome".

Fatty liver of pregnancy

Mother heterozygous for LCHAD deficiency or other β oxidation enzyme deficiency. Infant homozygous. Not all cases explained by β oxidation defect.

Absence of the G1528C (E474Q) Mutation in the α-Subunit of the Mitochondrial Trifunctional Protein in Women with Acute Fatty Liver of Pregnancy

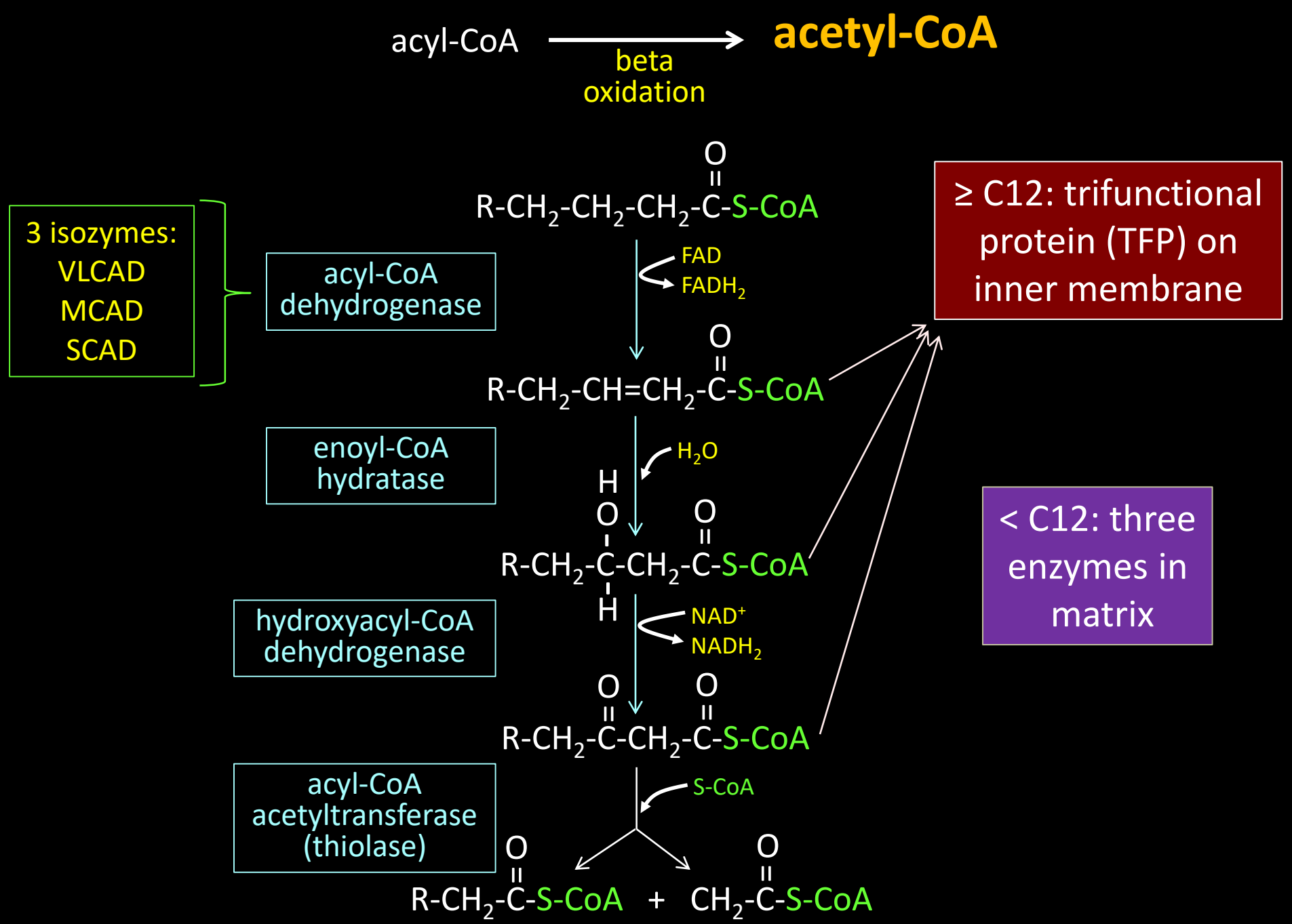
(*Pediatr Res* 51: 658–661, 2002)

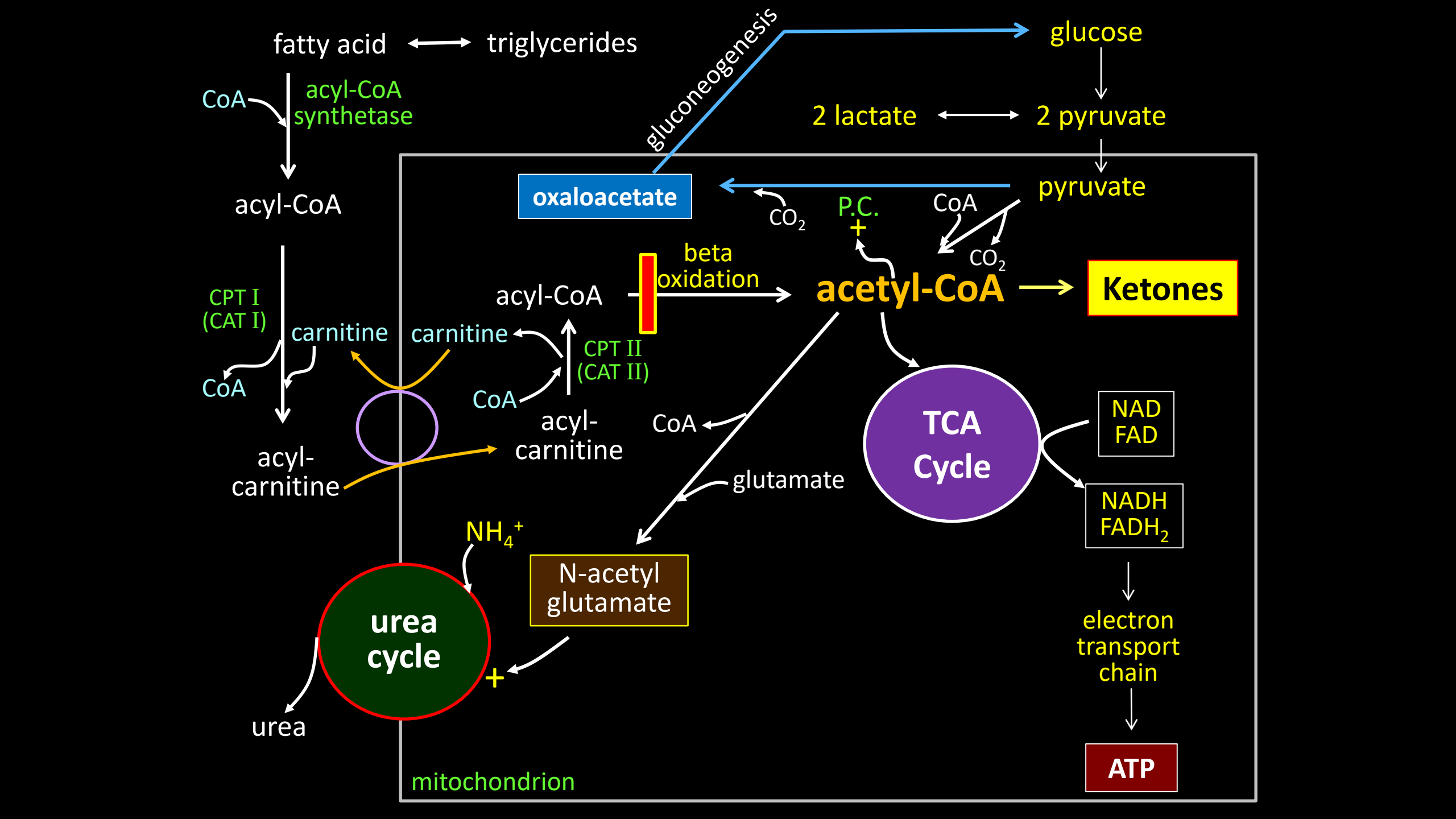
ANIRBAN MAITRA, RANA DOMIATI-SAAD, NICOLE YOST, GARY CUNNINGHAM, BEVERLY BARTON ROGERS, AND MICHAEL J. BENNETT

The molecular basis of pediatric long chain 3-hydroxyacyl-CoA dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy

Proc. Natl. Acad. Sci. USA 92 (1995)

HAROLD F. SIMS*†, JEFFREY C. BRACKETT‡, CYNTHIA K. POWELL*†, WILLIAM R. TREEM§, DANIEL E. HALE¶, MICHAEL J. BENNETT‖, BEVERLY GIBSON*†, SCOTT SHAPIRO*†, AND ARNOLD W. STRAUSS*†**


acyl-CoA
beta oxidation
acetyl-CoA
3 isozymes:
VLCAD
MCAD
SCAD
acyl-CoA dehydrogenase
FAD
FADH2
enoyl-CoA hydratase
H2O
hydroxyacyl-CoA dehydrogenase
NAD+
NADH2
acyl-CoA acetyltransferase (thiolase)
S-CoA
≥ C12: trifunctional protein (TFP) on inner membrane
< C12: three enzymes in matrix


fatty acid
triglycerides
CoA
acyl-CoA synthetase
acyl-CoA
gluconeogenesis
glucose
2 lactate
2 pyruvate
pyruvate
oxaloacetate
CO_2
P.C.
+
CoA
CO_2
beta oxidation
acyl-CoA
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Ketones
CPT I (CAT I)
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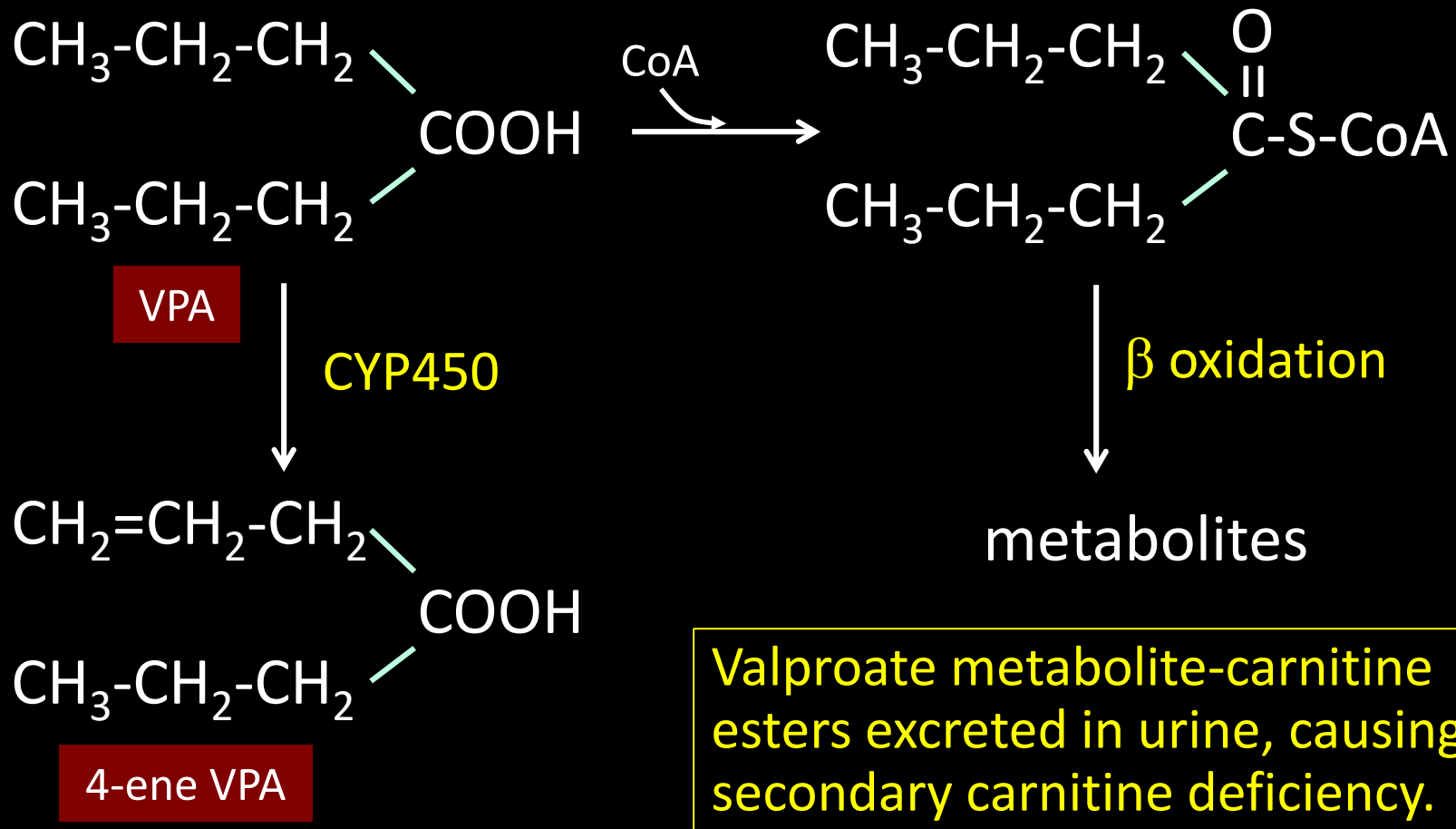
carnitine
CPT II (CAT II)
CoA
acyl-carnitine
CoA
TCA Cycle
NAD
FAD
glutamate
NH_4^+
N-acetyl glutamate
NADH
$FADH_2$
urea cycle
+
electron transport chain
urea
ATP
mitochondrion

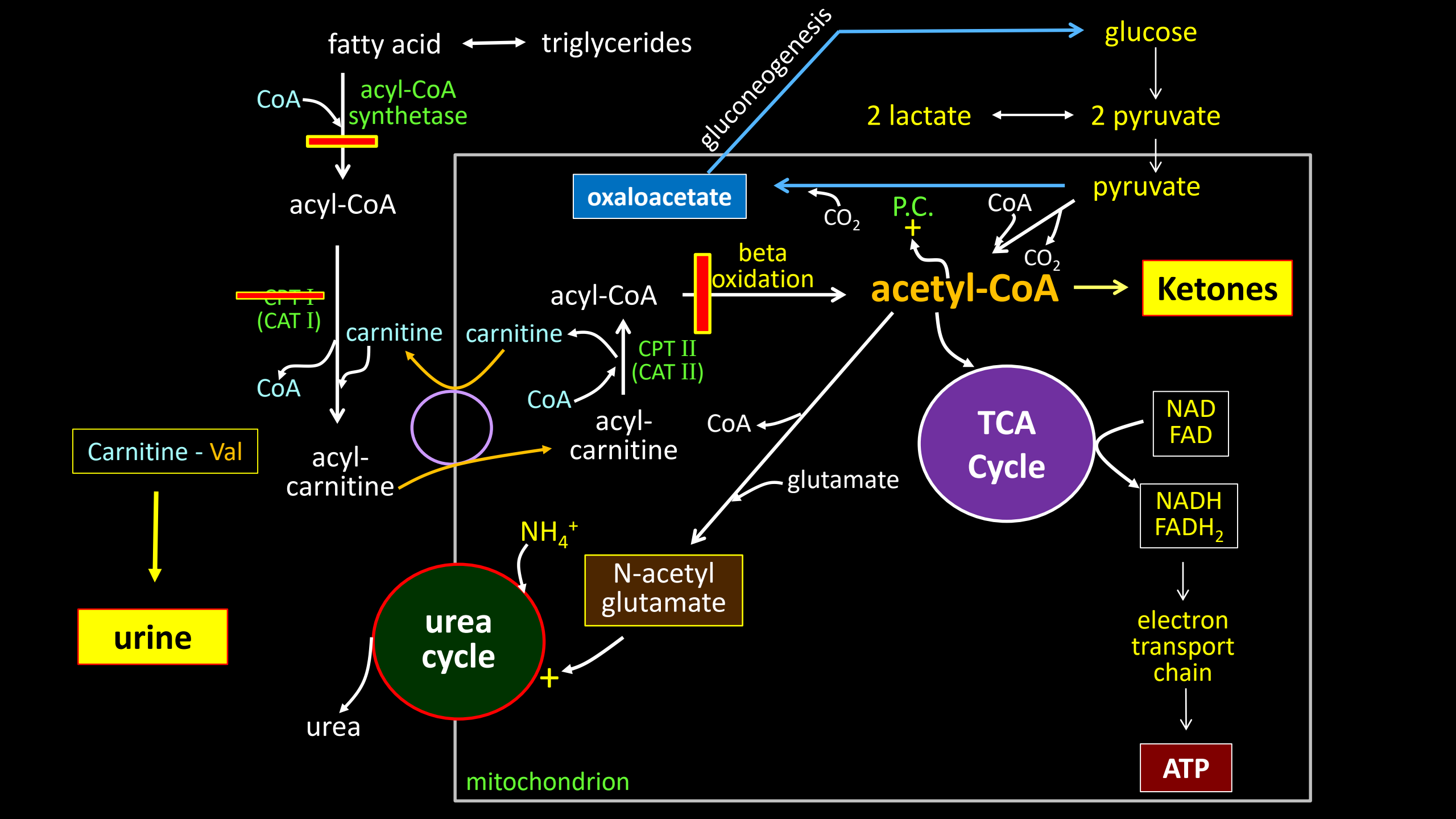
Microvesicular Steatosis from Impaired β Oxidation of Fatty Acids

Drugs and toxins that inhibit fatty acid oxidation

- Valproic acid – young children develop "Reye Syndrome"
- Tetracyclines



Valproate metabolite-carnitine esters excreted in urine, causing secondary carnitine deficiency.


fatty acid
triglycerides
CoA
acyl-CoA synthetase
acyl-CoA
gluconeogenesis
glucose
2 lactate
2 pyruvate
pyruvate
oxaloacetate
CO_2
P.C.
+
CoA
CO_2
beta oxidation
acyl-CoA
acetyl-CoA
Ketones
CPT I (CAT I)
carnitine
CoA
acyl-carnitine
carnitine
CPT II (CAT II)
CoA
acyl-carnitine
CoA
TCA Cycle
NAD
FAD
NADH
$FADH_2$
Carnitine - Val
glutamate
NH_4^+
N-acetyl glutamate
urea cycle
+
urine
urea
electron transport chain
ATP
mitochondrion

Tetracycline

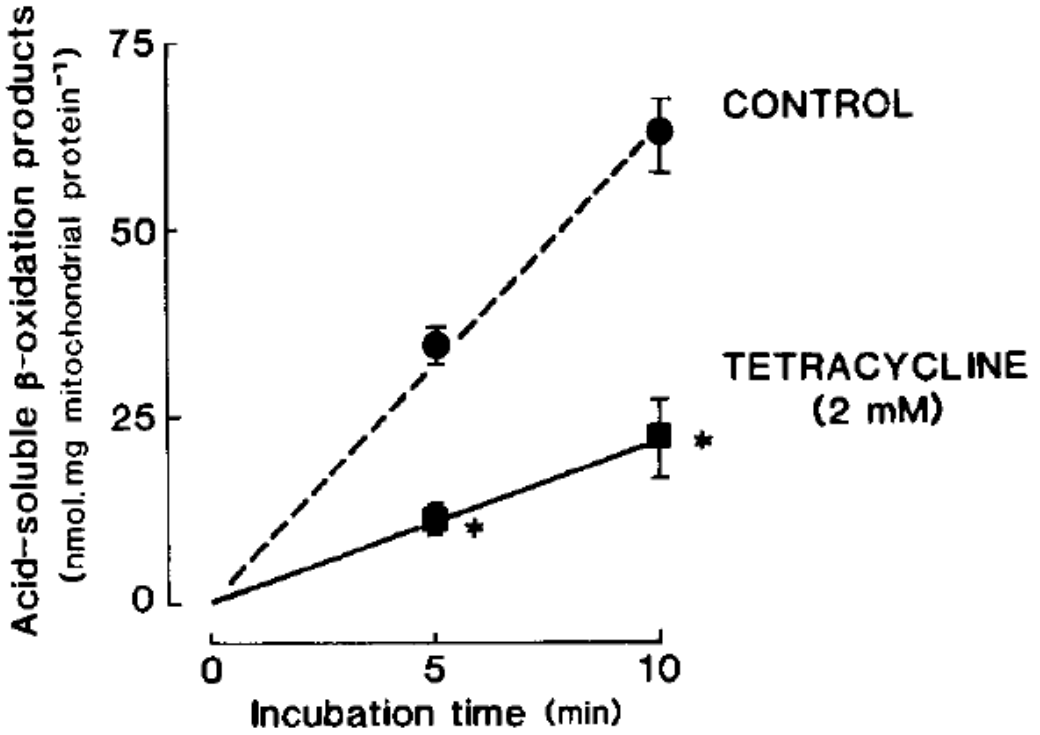


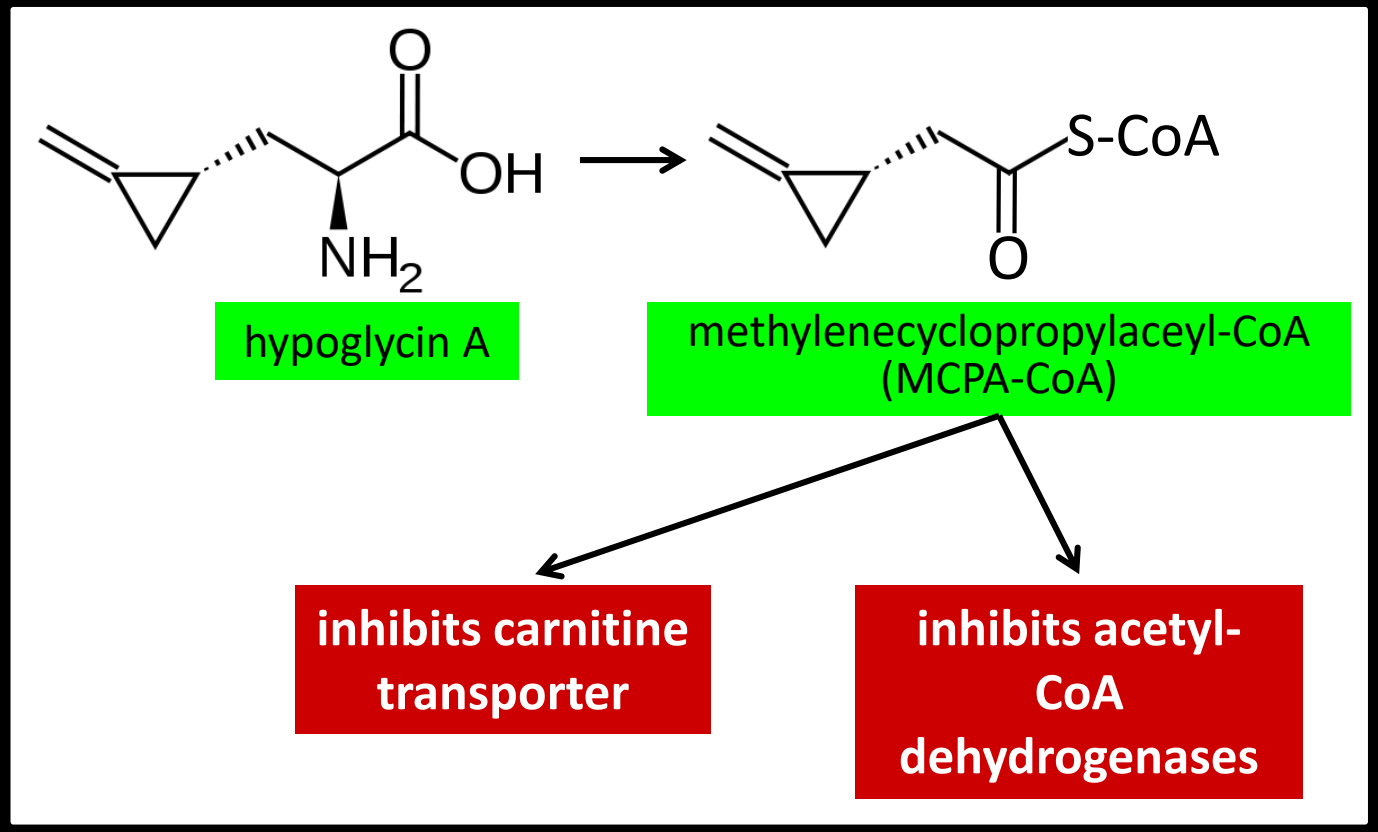
FIG. 1. Time course for the *in vitro* formation of [^{14}C]acid-soluble β-oxidation products from [U-^{14}C]palmitic acid by mouse liver mitochondria. Mitochondria were incubated at 30°C for 5 or 10 min with [U-^{14}C]palmitic acid (40 μM, 0.05 μCi per 2 ml), ATP, carnitine and coenzyme A, in the presence or absence of tetracycline (2 mM). Results are means ± S.E. for four experiments. The *asterisks* indicate significant differences from values in incubations made without tetracycline ($p < 0.01$).

....NSAIDs

Microvesicular Steatosis from Impaired β Oxidation of Fatty Acids

Drugs and toxins that inhibit fatty acid oxidation

- Tetracyclines
- Valproic acid
- Hypoglycin A from unripen Ackee fruit

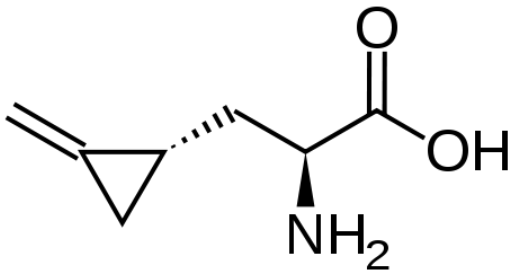


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 64 / No. 3
January 30, 2015

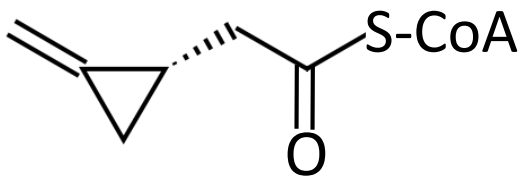
Outbreaks of Unexplained Neurologic Illness — Muzaffarpur, India, 2013–2014

FIGURE 1. Litchi fruit orchards have been a focus of the investigation into outbreaks of unexplained neurologic illness among children — Muzaffarpur, India, 2013–2014

Lychees (Litchi)



hypoglycin A



methylenecyclopropylaceyl-CoA
(MCPA-CoA)

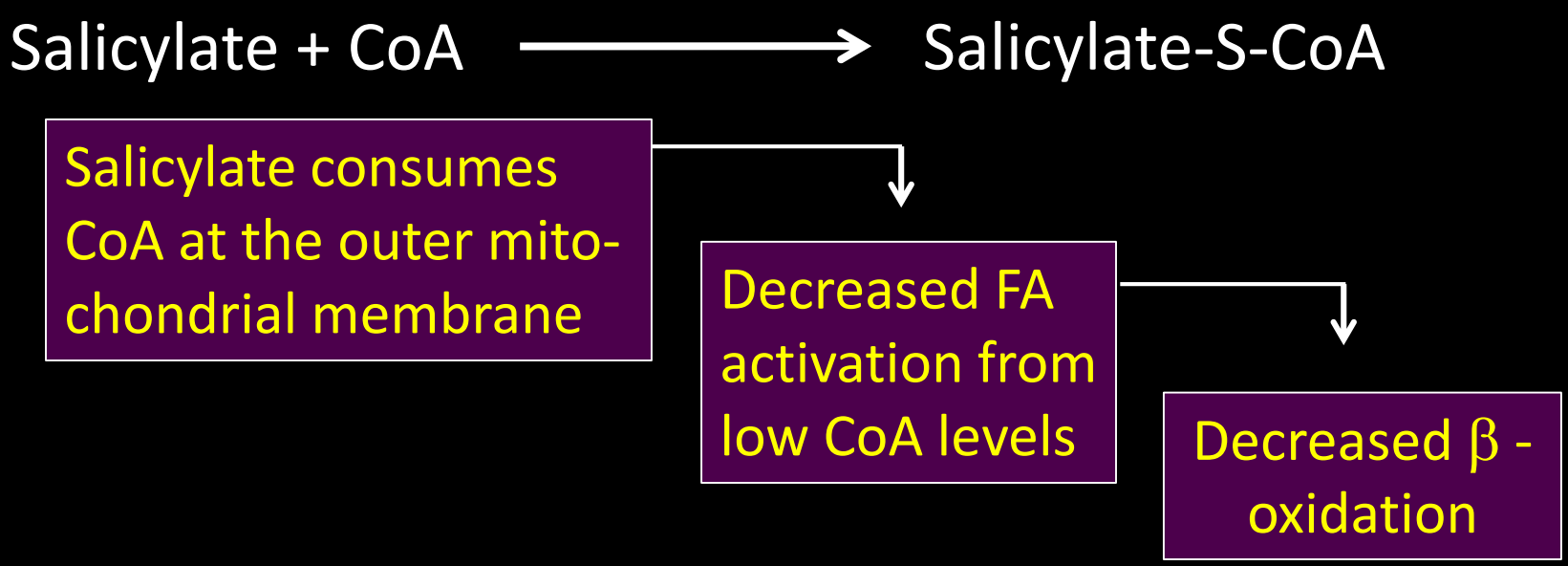
Lychee (Litchi) chinesis

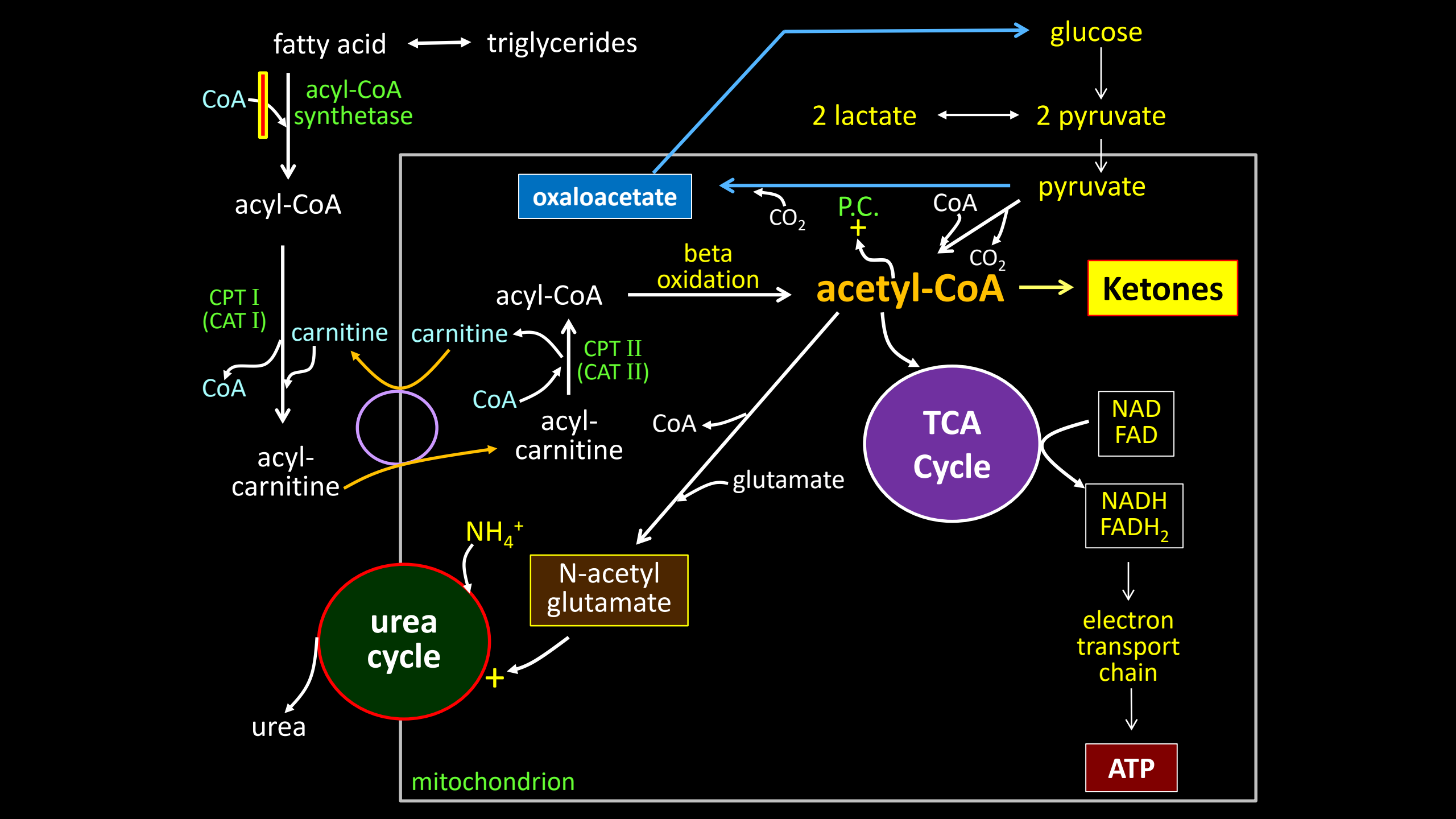
Microvesicular Steatosis from Impaired β Oxidation of Fatty Acids

Drugs and toxins that inhibit fatty acid oxidation

- Tetracyclines
- Valproic acid
- Hypoglycin A from ackee fruit
- Salicylate in fatal or near-fatal doses

80% of children dying from salicylate toxicity display microvesicular steatosis.




fatty acid
triglycerides
CoA
acyl-CoA synthetase
acyl-CoA
glucose
2 lactate
2 pyruvate
pyruvate
oxaloacetate
CO_2
P.C.
+
CoA
CO_2
beta oxidation
acyl-CoA
acetyl-CoA
Ketones
CPT I (CAT I)
carnitine
CoA
acyl-carnitine
carnitine
CPT II (CAT II)
CoA
acyl-carnitine
CoA
TCA Cycle
NAD
FAD
NADH
$FADH_2$
glutamate
NH_4^+
N-acetyl glutamate
urea cycle
+
urea
electron transport chain
ATP
mitochondrion

Objectives

- Microvesicular steatosis results from mitochondrial failure/dysfunction and sometimes appears with macrovesicular steatosis. Onset over a day to weeks.
- Two major mitochondrial pathogeneses:

Primary impaired β oxidation of fatty acids

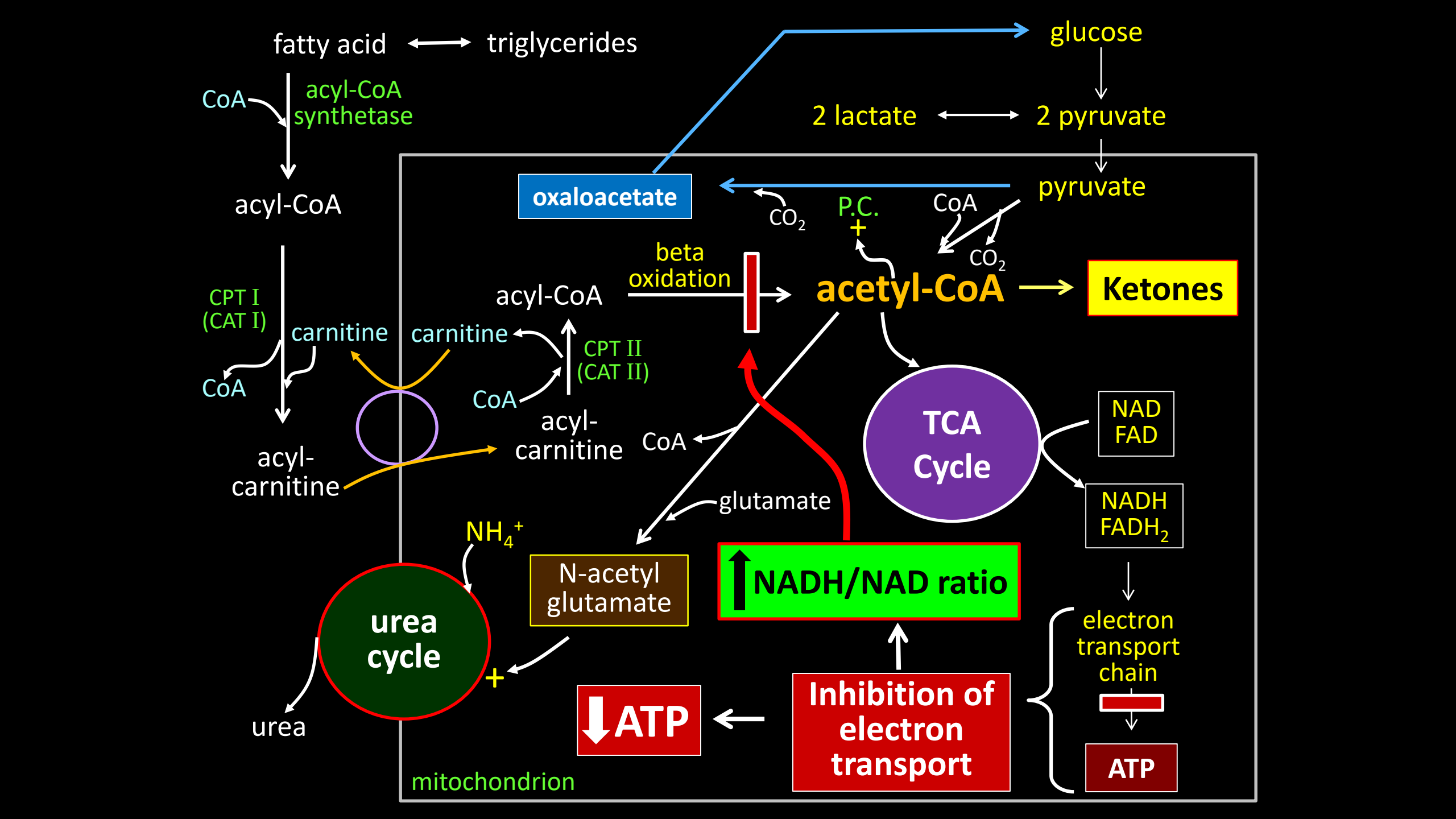
Primary impaired oxidative phosphorylation

- AST & ALT nl to ~ 600 IU/L
- hyperammonemia
- hypoglycemia
- low ketones
- metabolic acidosis

- ketones commonly low or absent
- hypoglycemia more common

- significant lactic acidosis more common
- higher AST & ALT with necrosis, when present

- Treatment: high CH_2O diet and IV carnitine during crisis

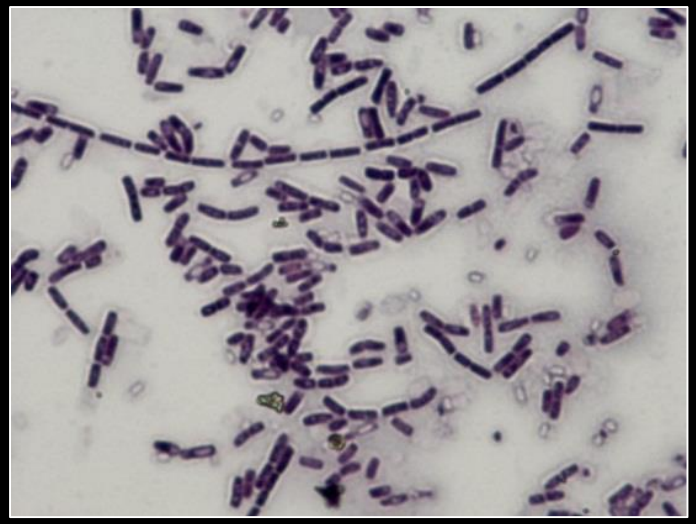

fatty acid
triglycerides
glucose
CoA
acyl-CoA synthetase
2 lactate
2 pyruvate
acyl-CoA
oxaloacetate
pyruvate
CO_2
P.C.
+
CoA
CO_2
beta oxidation
acyl-CoA
acetyl-CoA
Ketones
CPT I (CAT I)
carnitine
carnitine
CPT II (CAT II)
CoA
CoA
acyl-carnitine
acyl-carnitine
CoA
TCA Cycle
NAD
FAD
glutamate
NH_4^+
N-acetyl glutamate
NADH/NAD ratio
NADH
$FADH_2$
urea cycle
+
urea
ATP
Inhibition of electron transport
electron transport chain
ATP
mitochondrion

FULMINANT LIVER FAILURE IN ASSOCIATION WITH THE EMETIC TOXIN OF *BACILLUS CEREUS*

The New England Journal of Medicine 1997;336:1142-8.

HELLMUT MAHLER, PH.D., AURELIO PASI, M.D., JOHN M. KRAMER, B.SC., PETRA SCHULTE, GRAD.ENG., ANNE C. SCOGING, B.SC., WALTER BÄR, M.D., AND STEPHAN KRÄHENBÜHL, M.D., PHARM.D.

- 17-year-old boy and father ate spaghetti and pesto, 4 days old.
- Gastroenteritis within 30 minutes, less severe in son.
- Son's illness worsened with lethargy and jaundice over 2 days.
- Died in hospital despite supportive care on 3rd day.
- Afebrile, AST 2140; ALT 5270; total bilirubin 7; pH 7.27.



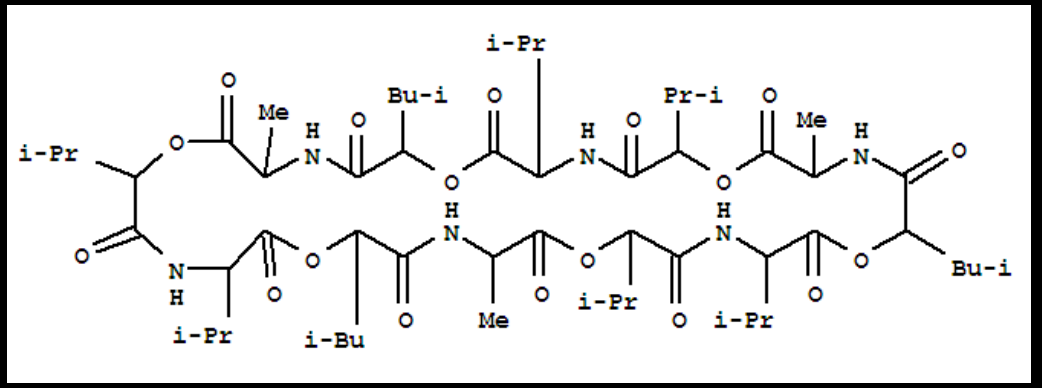
B. cereus

enterotoxin

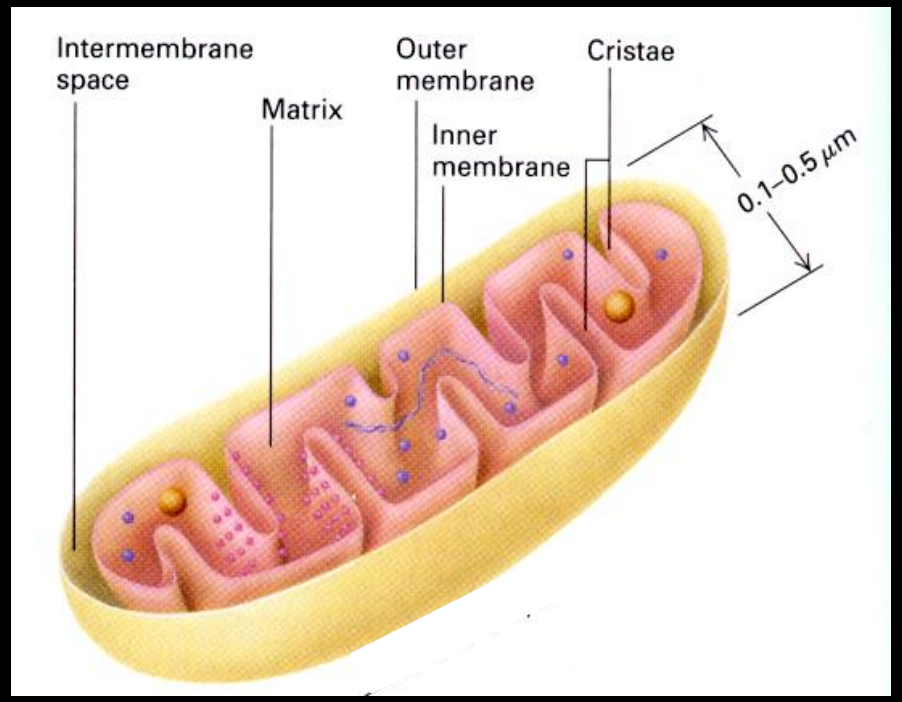
cereulide

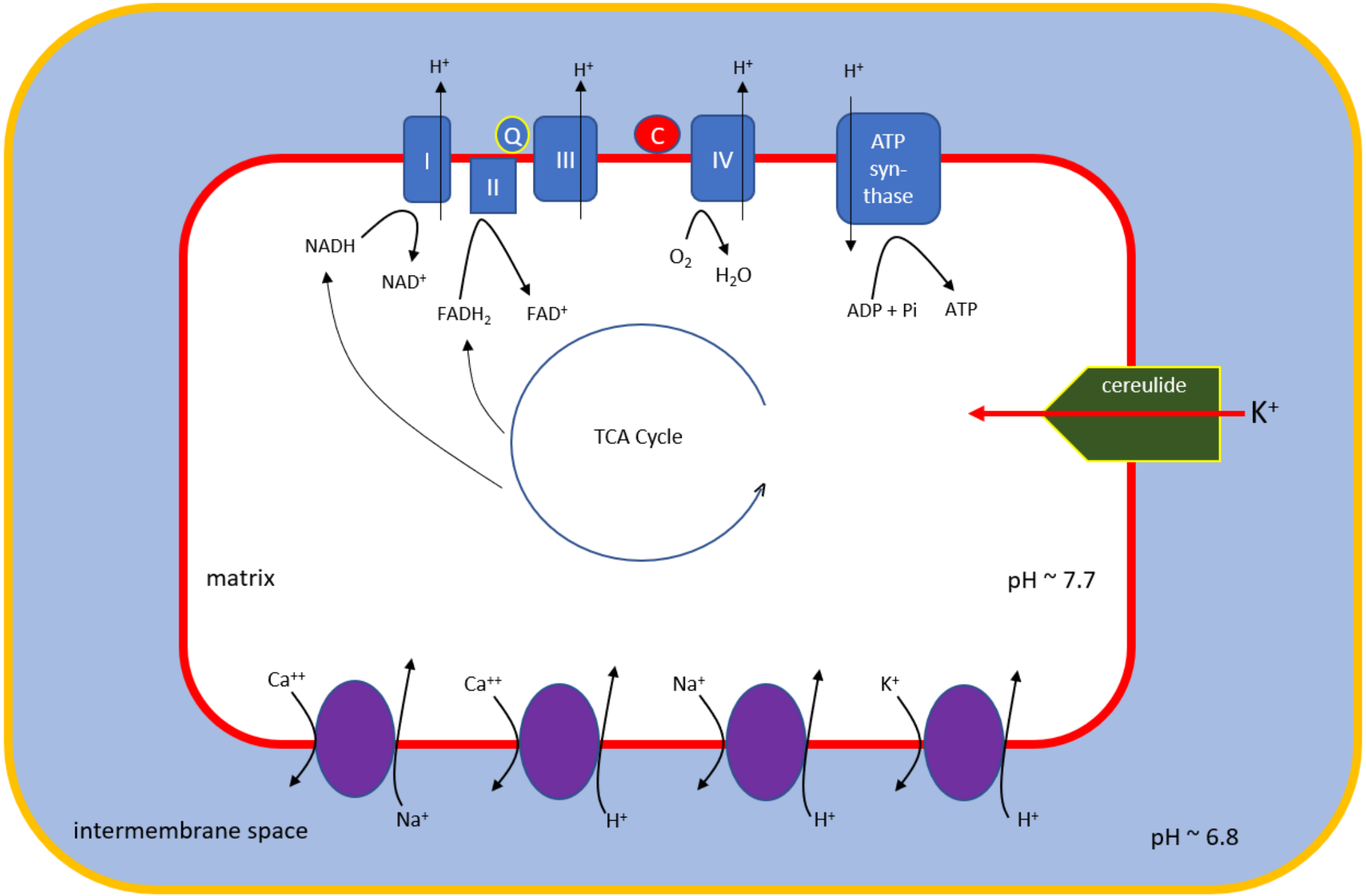
diarrhea

emesis



- Structurally similar to valino-mycin.
- Transports K^+ across inner mitochondrial membrane.
- Depolarizes mitochondrial membrane.
- Inhibits oxidative phosphory-lation through uncoupling.



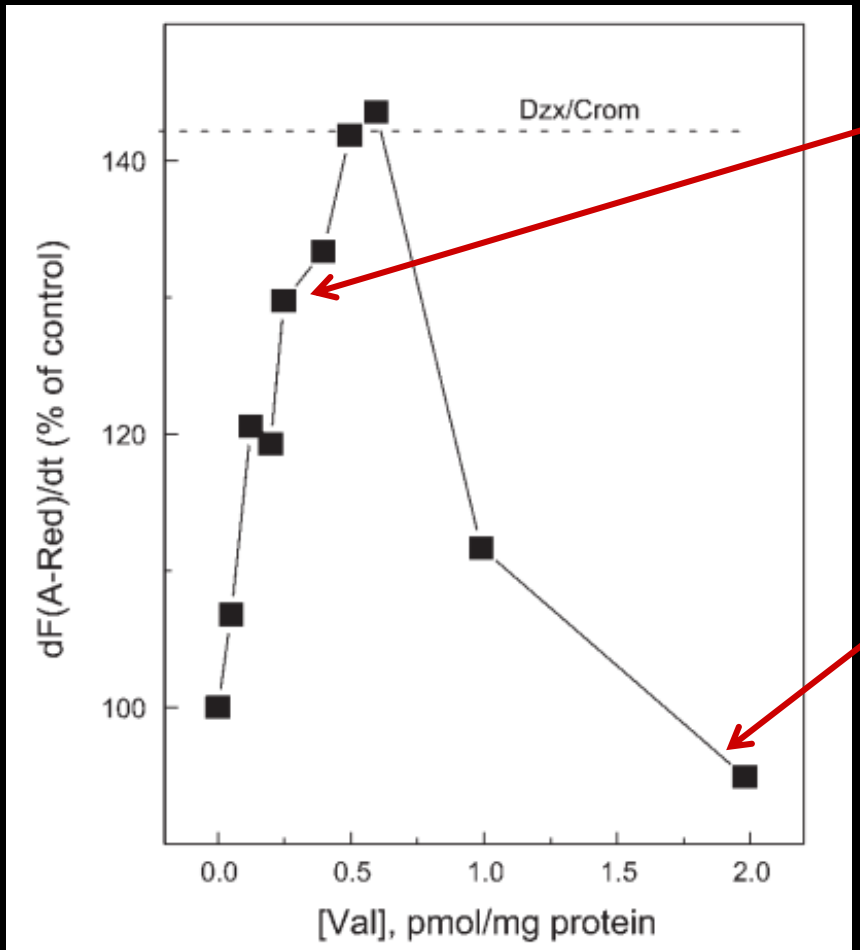

H+
H+
H+
H+
I
Q
II
III
C
IV
ATP syn-thase
NADH
NAD+
FADH2
FAD+
O2
H2O
ADP + Pi
ATP
TCA Cycle
cereulide
K+
matrix
pH ~ 7.7
Ca++
Ca++
Na+
K+
Na+
H+
H+
H+
intermembrane space
pH ~ 6.8

Am J Physiol Heart Circ Physiol 291: H2067–H2074, 2006.
First published June 23, 2006; doi:10.1152/ajpheart.00272.2006.

Opening mitoK$_{ATP}$ increases superoxide generation from complex I of the electron transport chain

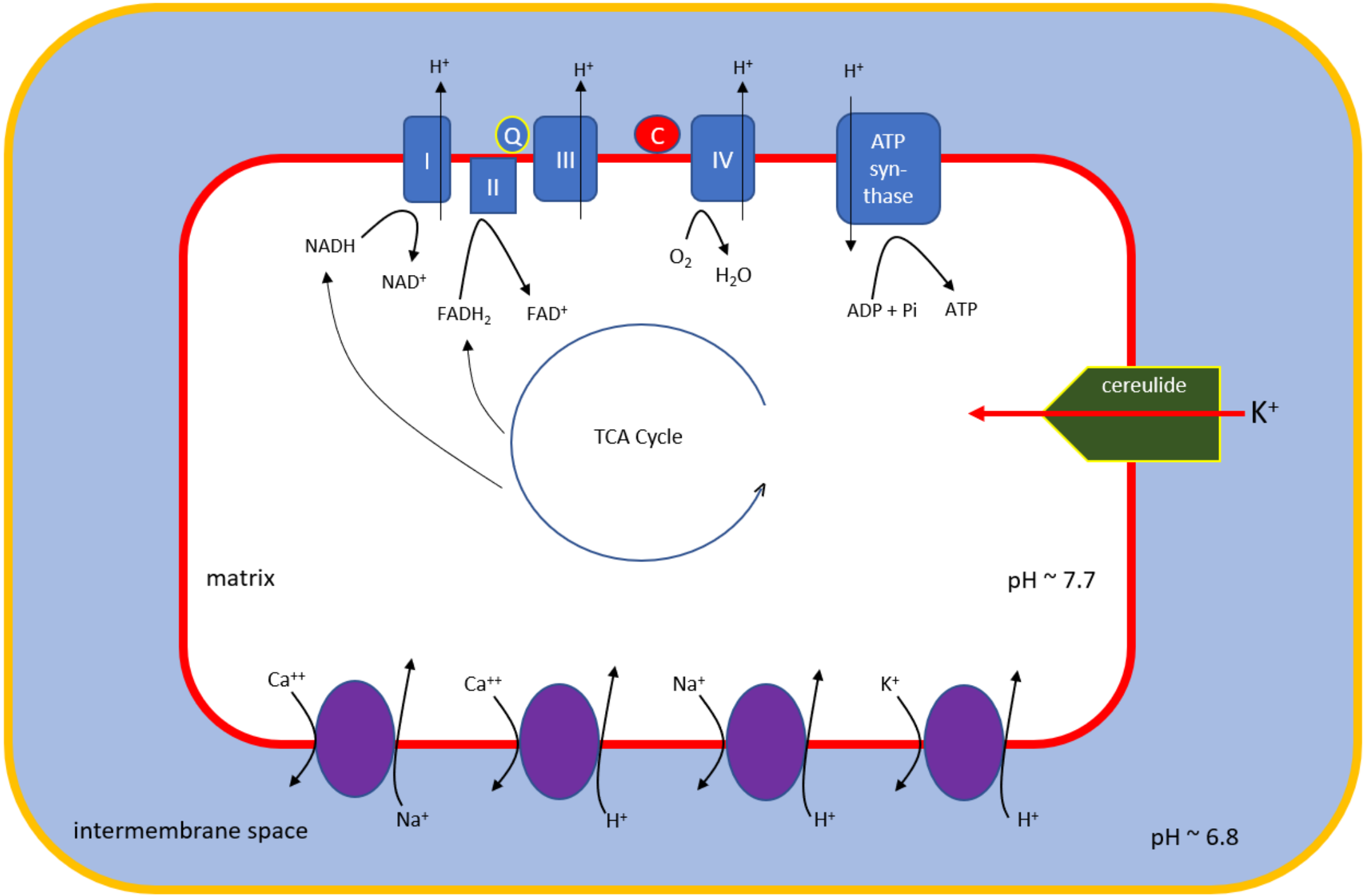
Anastasia Andrukhiv, Alexandre D. Costa, Ian C. West, and Keith D. Garlid
Department of Biology, Portland State University, Portland, Oregon

NADH/NAD



Low K+ influx from valinomycin, increased pH as K^+ replaces H^+ and blocks redox activity of ubiquinone, and increases NADH/NAD ratio (?) and ROS generation.

High K^+ influx from valinomycin, membrane depolarization leads to uncoupling and increased oxygen consumption and decreased ATP formation, with low NADH/NAD ratio.

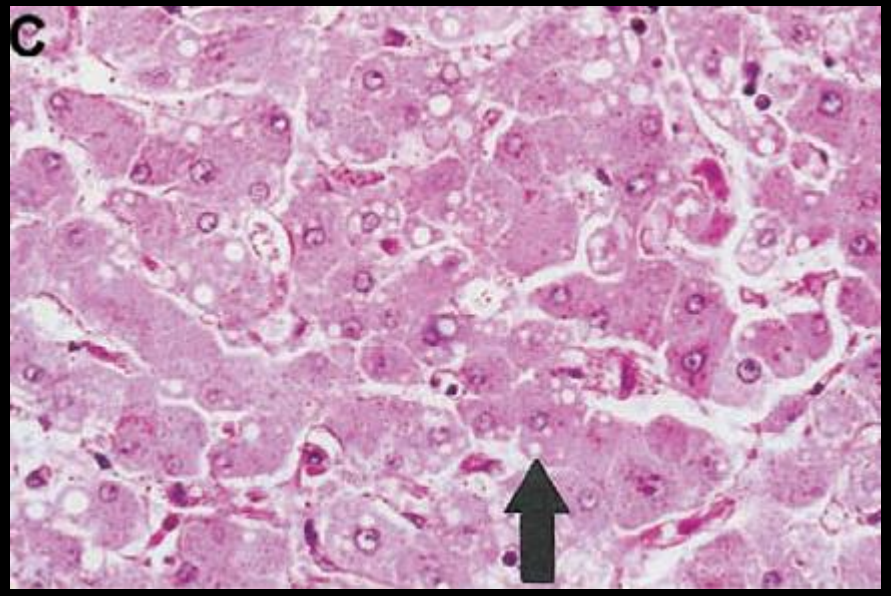

H+
H+
H+
H+
I
Q
II
III
C
IV
ATP syn-thase
NADH
NAD+
FADH2
FAD+
O2
H2O
ADP + Pi
ATP
TCA Cycle
cereulide
K+
matrix
pH ~ 7.7
Ca++
Ca++
Na+
K+
Na+
H+
H+
H+
intermembrane space
pH ~ 6.8

Symptomatic Lactic Acidosis in Hospitalized Antiretroviral-Treated Patients with Human Immunodeficiency Virus Infection: A Report of 12 Cases

CID 2001:33 (1 December)

Michael E. Coghlan,[1] Jean-Pierre Sommadossi,[2] Nirag C. Jhala,[3] Wickliffe J. Many,[1] Michael S. Saag,[1] and Victoria A. Johnson[1,4]

Departments of [1]Medicine, [2]Pharmacology and Toxicology, and [3]Anatomic Pathology, University of Alabama at Birmingham School of Medicine, and the [4]Birmingham Veterans Affairs Medical Center, Birmingham, Alabama

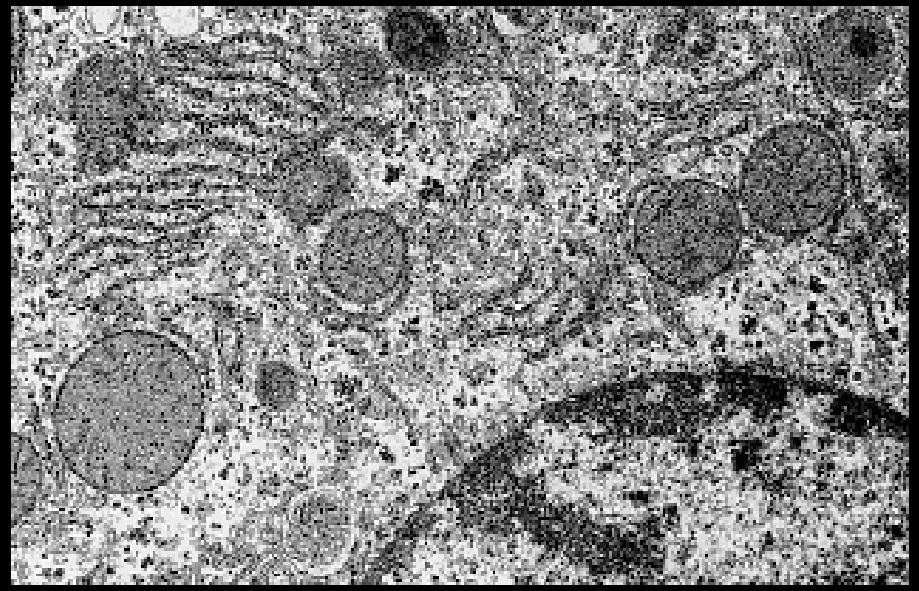


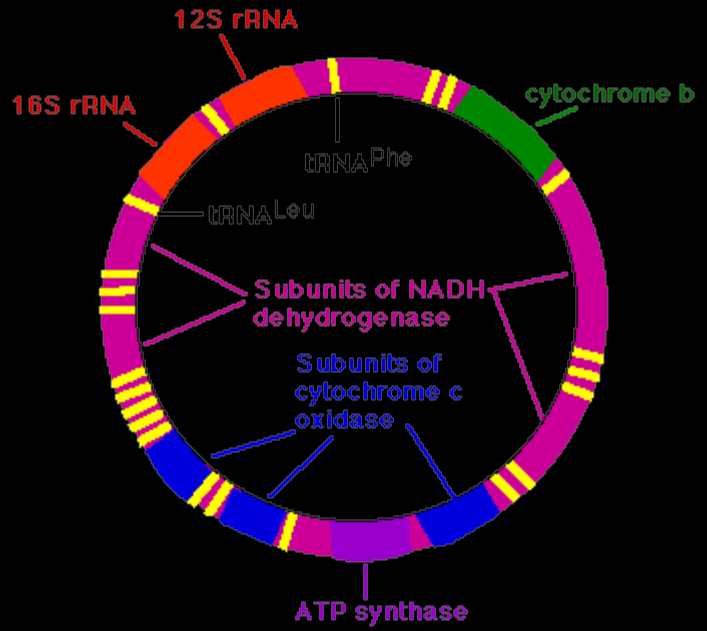
AST 41 to 1455, with all but one < 600.

PAS stain with arrow pointing at microvesicular steatosis.

Both macro- and microves-icular steatosis were report-ed in this series, usually in the same patients.

Mitochondria





- Most cells contain 500 to 2000 mitochondria.
- An average of 5 circular DNA molecules per organelle, with ~ 2,500 to 10,000 mDNA per cell.
- mDNA codes for:
  - 13 peptides for ETC
  - 22 tRNAs
  - 2 rRNAs

Mitochondria

- Every time cell replicates, thousands of mtDNA must replicate
- DNA polymerase-γ responsible for mtDNA replication
- Inhibition of DNA polymerase-γ impairs OP
  - decreased OP
  - metabolic acidosis
  - hepatic steatosis
  - pancreatitis
  - peripheral neuropathy
  - others

γ-DNA Polymerase Inhibition

Nucleoside Reverse Transcriptase Inhibitors

- didanosine (ddI)
- zalcitabine (ddC)
- abacavir (ABV)
- zidovudine (ZDV)
- adefovir (PMEA)
- lamivudine (3TC)
- stavudine (d4T)
- lodenosine (Fdda)
- emtricitabine (FTC)

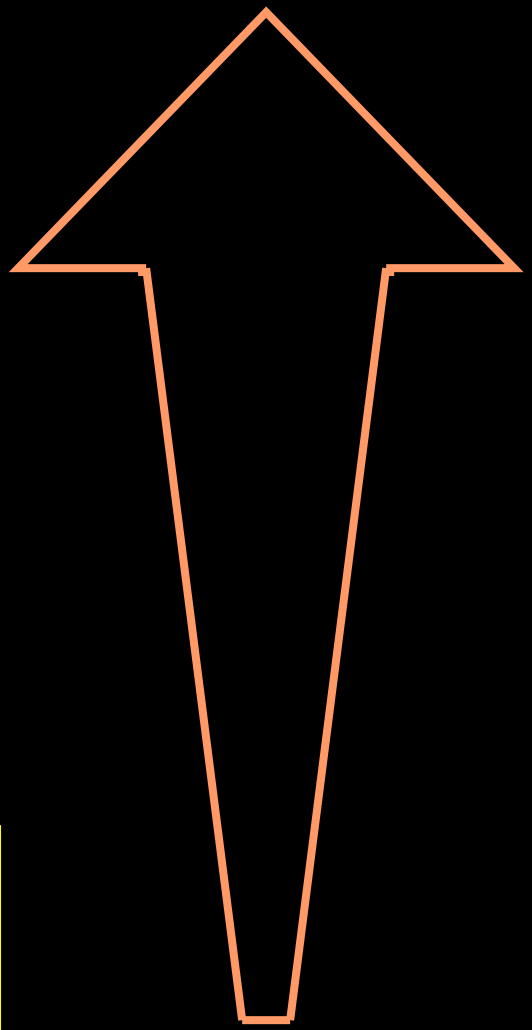
lactic acidosis
hepatic steatosis
?encephalopathy

Enzyme assays and cell cultures demonstrate hierarchy of γ-DNA polymerase inhibition

zalcitabine
didanosine
stavudine
lamivudine
zidovudine
abacavir

exact order controversial

most inhibition

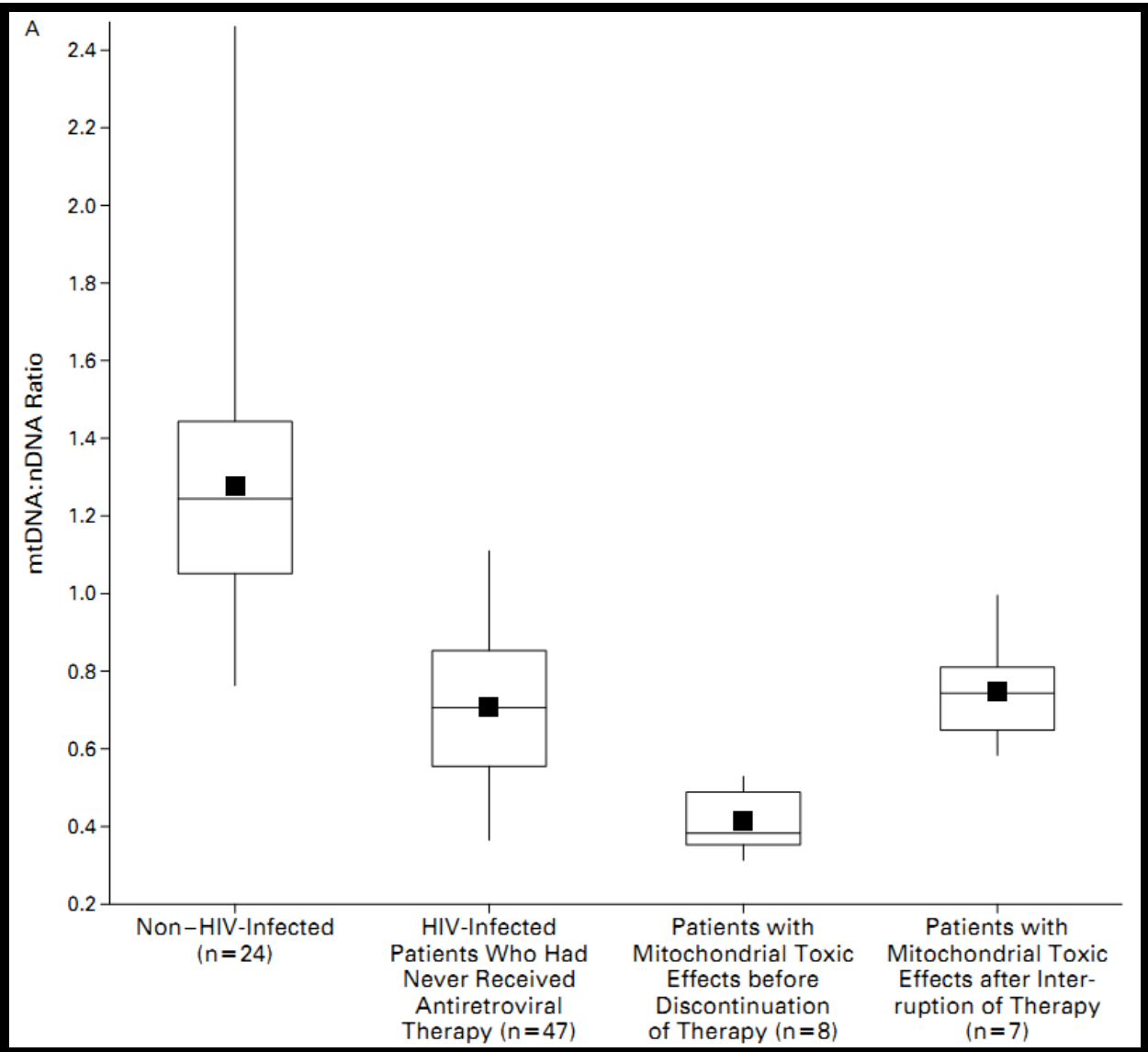


least inhibition

CHANGES IN MITOCHONDRIAL DNA AS A MARKER OF NUCLEOSIDE TOXICITY IN HIV-INFECTED PATIENTS

N Engl J Med, Vol. 346, No. 11 · March 14, 2002

HÉLÈNE C.F. CÔTÉ, PH.D., ZABRINA L. BRUMME, B.S., KEVIN J.P. CRAIB, M.MATH., CHRISTOPHER S. ALEXANDER, PH.D., BRIAN WYNHOVEN, B.S., LILLIAN TING, B.S., HUBERT WONG, PH.D., MARIANNE HARRIS, M.D., P. RICHARD HARRIGAN, PH.D., MICHAEL V. O'SHAUGHNESSY, PH.D., AND JULIO S.G. MONTANER, M.D.



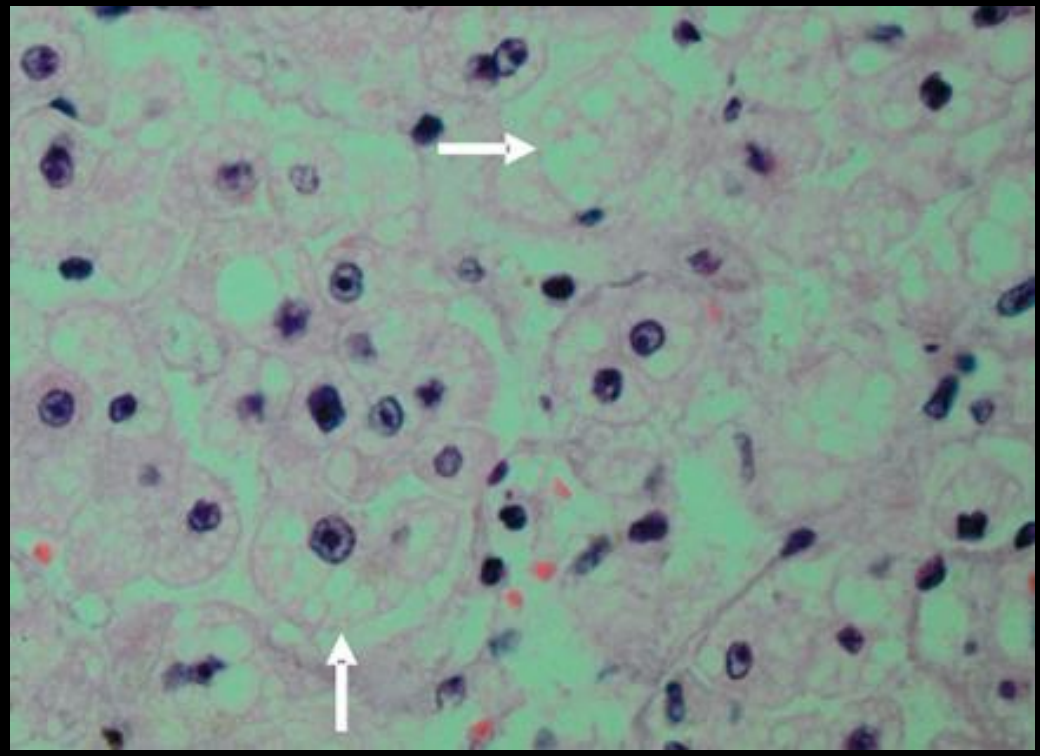
Severe Drug-induced Liver Injury Associated with Prolonged Use of Line

J. Med. Toxicol. (2010) 6:322–326

Liesbet De Bus · Pieter Depuydt · Louis Libbrecht · Linos Vandekerckhove · Joke Nollet · Dominique Benoit · Dirk Vogelaers · Hans Van Vlierberghe

Woman developed lactic acidosis and liver failure after IV linezolid X 50 days.

AST 9 – 755
ALT 10 – 547
Bilirubin up to 12.8 mg/dL



Linezolid-Induced Inhibition of Mitochondrial Protein Synthesis

Clinical Infectious Diseases 2006; 42:1111–7

An S. De Vriese,[1] Rudy Van Coster,[3] Joél Smet,[3] Sara Seneca,[4] Andrew Lovering,[6] Lindsey L. Van Haute,[4] Ludo J. Vanopdenbosch,[2] Jean-Jacques Martin,[5] Chantal Ceuterick-de Groote,[5] Stefaan Vandecasteele,[1] and Johan R. Boelaert[1]

63-year-old woman admitted with lactic acidosis, obtundation, blindness, myopathy, quadriparesis, renal failure and hepatic dysfunction after or linezolid X 120 days.

Liver biopsy: microvesicular steatosis with some macrovesicular findings.

Table. 1. Activity of respiratory chain complexes in tissue samples obtained from a patient with prolonged use of linezolid therapy.

Tissue sample	Activity ratio (*z* score), by complex			
	I[a]/CS	II[b]/CS	III[c]/CS	IV[d]/CS
PBMCs	0.5 (1.26)	0.64 (−0.23)	0.67 (0.25)	0.89 (1.05)
Liver	ND	1.02 (−0.52)	0.83 (0.64)	**0.51 (−5.02)**
Kidney	**0.27 (−4.08)**	0.78 (−0.73)	0.60 (−1.77)	**0.54 (−5.4)**
Muscle	**0.43 (−3.33)**	0.67 (−0.65)	0.77 (0.28)	**0.66 (−3.93)**

Objectives

- Microvesicular steatosis results from mitochondrial failure/dysfunction and sometimes appears with macrovesicular steatosis. Onset over a day to weeks.
- Two major mitochondrial pathogeneses:

Primary impaired β oxidation of fatty acids

Primary impaired oxidative phosphorylation

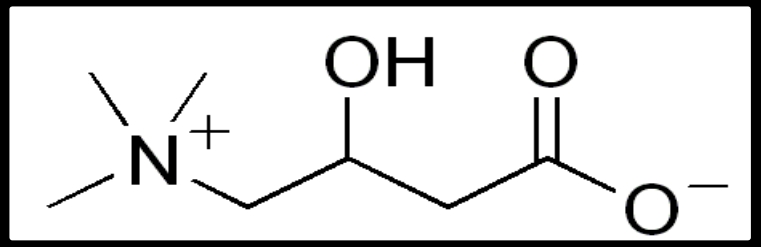
- AST & ALT nl to ~ 600 IU/L
- hyperammonemia
- hypoglycemia
- low ketones
- metabolic acidosis

- ketones commonly low or absent
- hypoglycemia more common

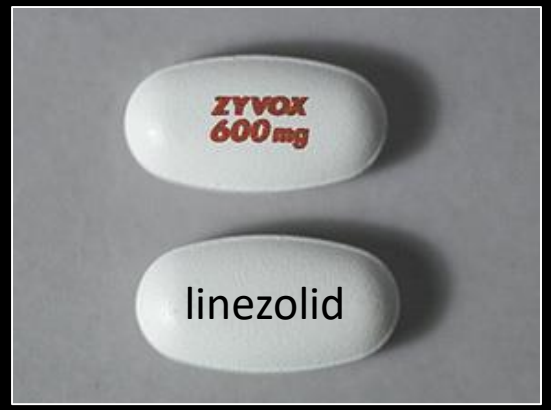
- significant lactic acidosis more common
- higher AST & ALT with necrosis, when present

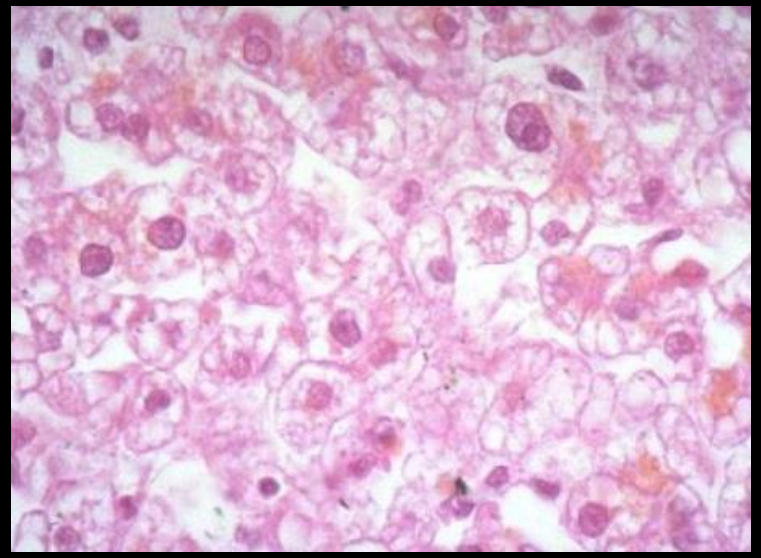
Summary

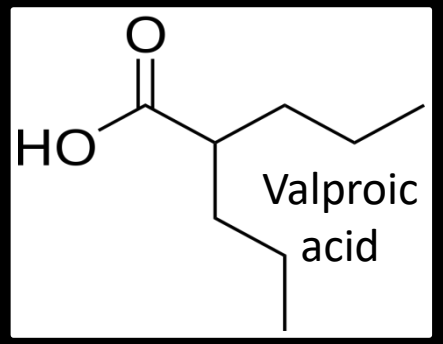
- Treatment
  - Stop offending agent
  - Attempt to support caloric requirement with carbohydrate to maintain intracellular acetyl-CoA levels and prevent need for FA oxidation.
  - Carnitine supplementation
  - Supportive care

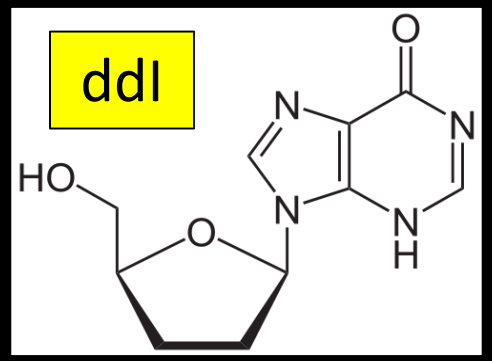


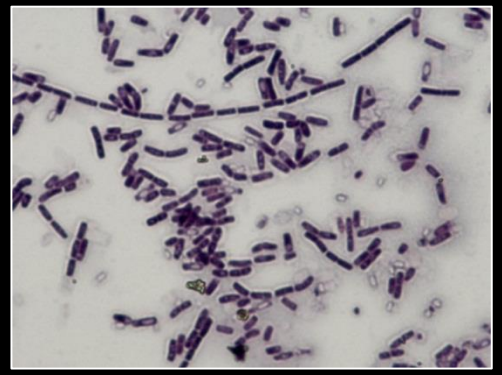
HMS Bounty











Garden Museum, Lambeth, London