THE PHYSIOLOGY OF FASTING AND FATTY ACID OXIDATION DEFECTS

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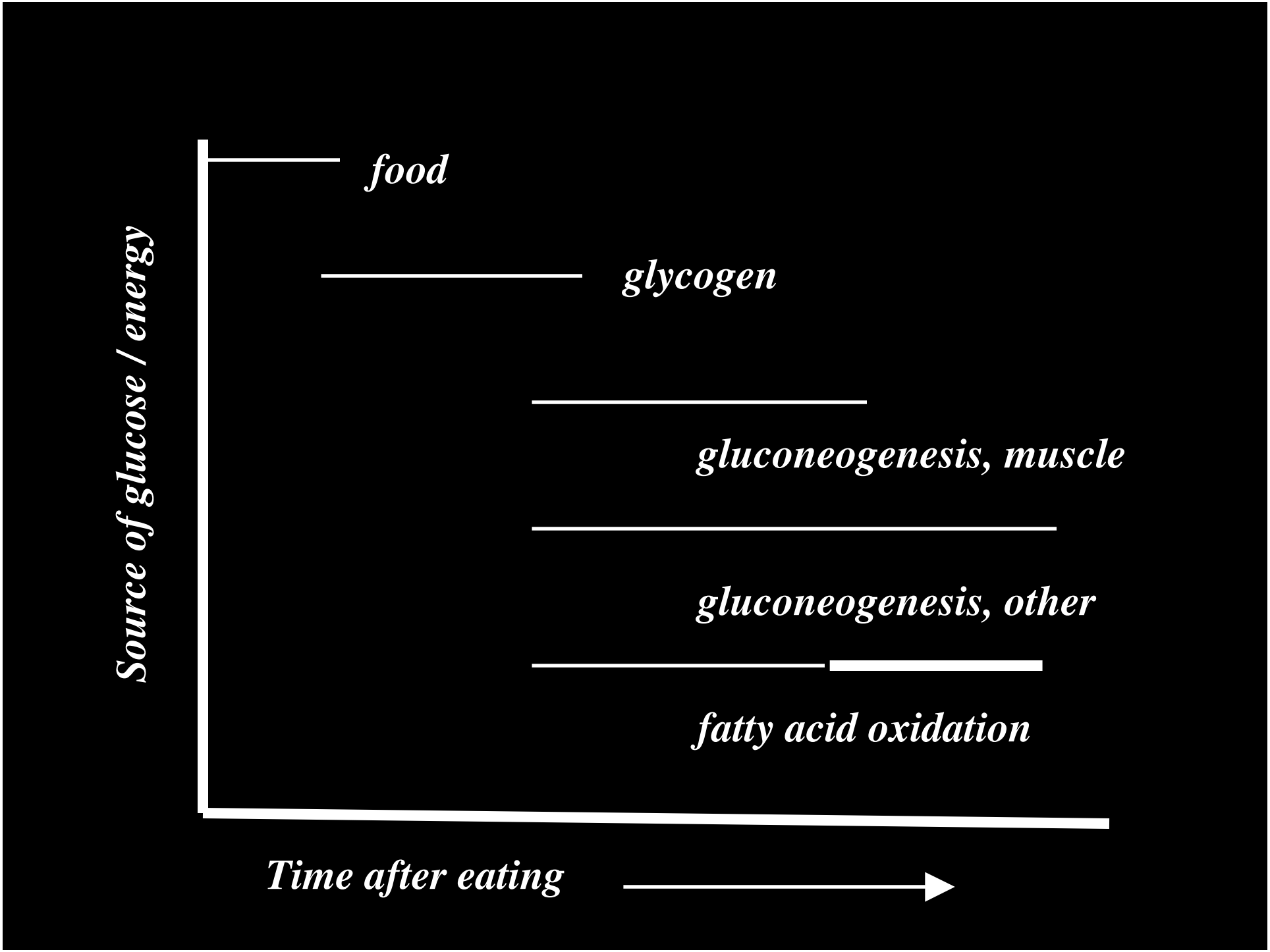
Boston, MA


food
glycogen
gluconeogenesis, muscle
gluconeogenesis, other
fatty acid oxidation
Source of glucose / energy
Time after eating

FED STATE

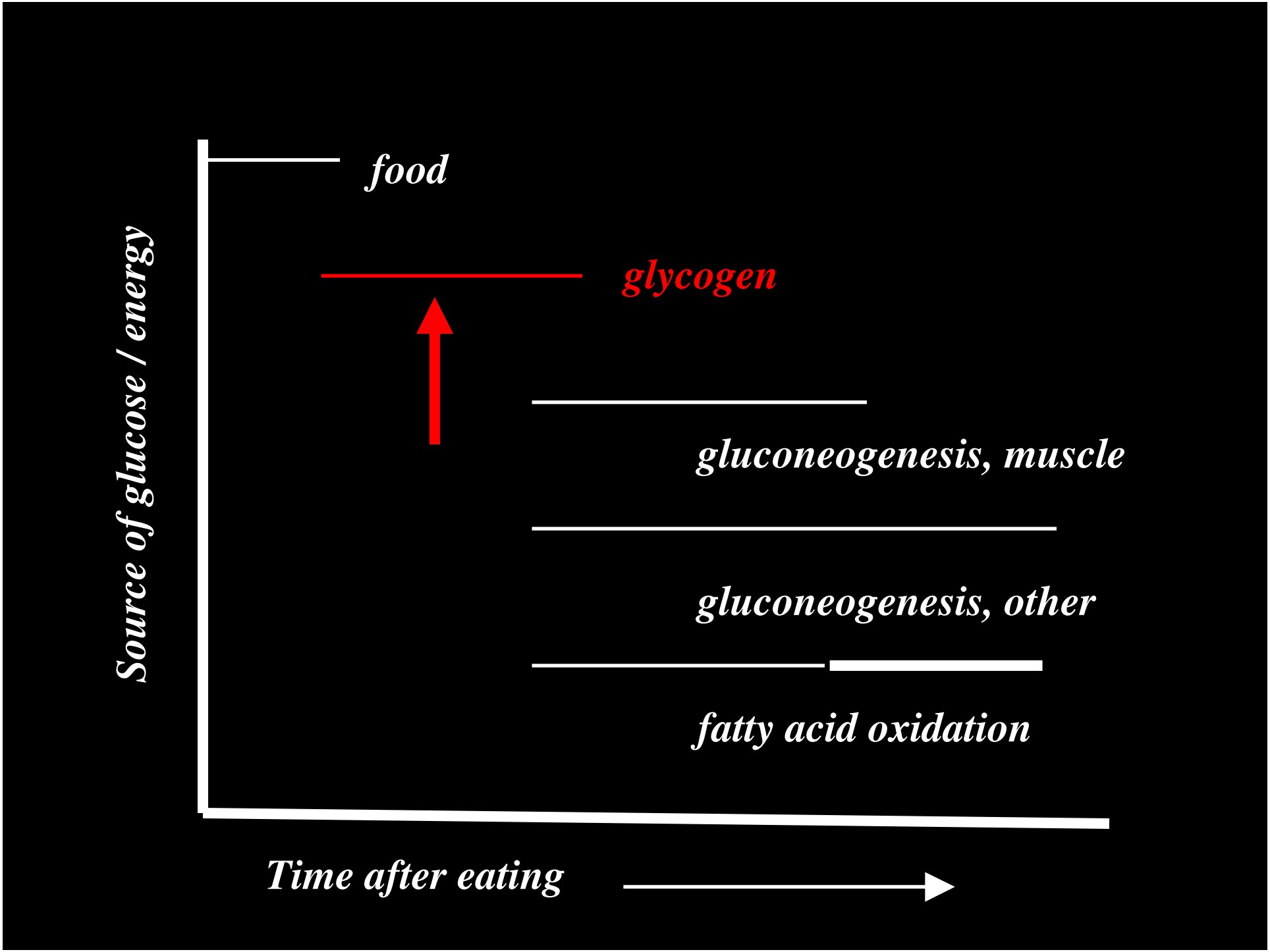
- The body uses glucose and nutrients from the last meal.
- The body/brain relies on glucose as the prime source of energy.
- The body synthesizes fat.

FED STATE to FASTING STATE:
Step One

- When eaten food is no longer a source of glucose or energy, stored glycogen in the liver gets broken down to form glucose.
- As the body's stores of glycogen are used up, the body starts to make "new" sugar from various sources including lactate and amino acids (from muscle).
- The body/brain continues to rely on sugar as the prime source of energy.
- The body synthesizes fat.

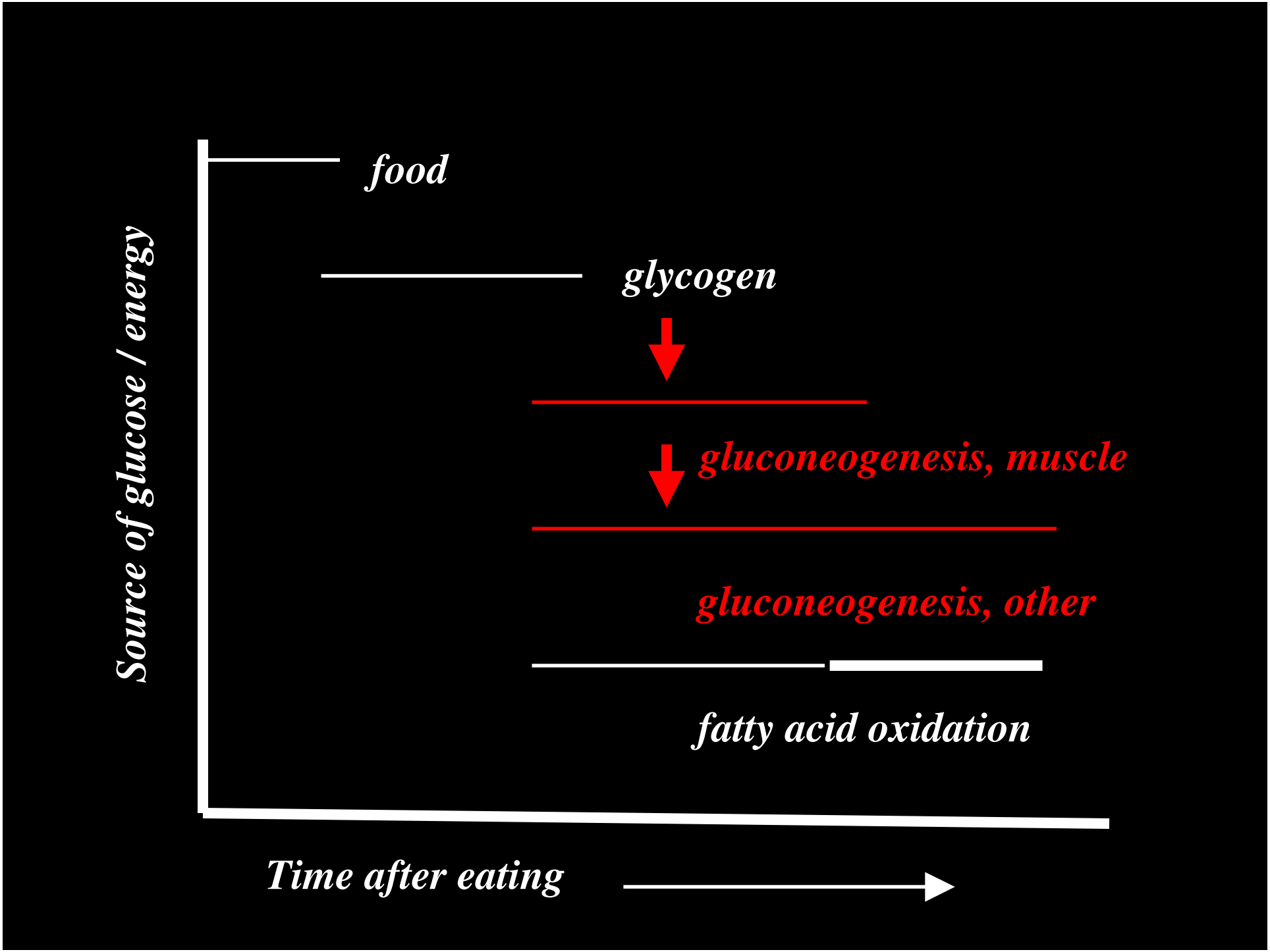
FED STATE to FASTING STATE:
Step Two

- Some glucose is still formed by the body (gluconeogenesis), but not from amino acids (muscle).
- Fat is oxidized to form ketones.
- During prolonged fasting, the body relies on fat conversion to ketones as the prime source of energy.


food
glycogen
gluconeogenesis, muscle
gluconeogenesis, other
fatty acid oxidation
Source of glucose / energy
Time after eating

Glycogen Storage Disease

- Stored sugar or glycogen cannot be accessed.
- Infants cannot go for longer than 3-4 hours without feeding.
- After 3-4 hours, hypoglycemia occurs.
- Glycogen cannot be broken down but just accumulates in the liver, causing liver enlargement.


food
glycogen
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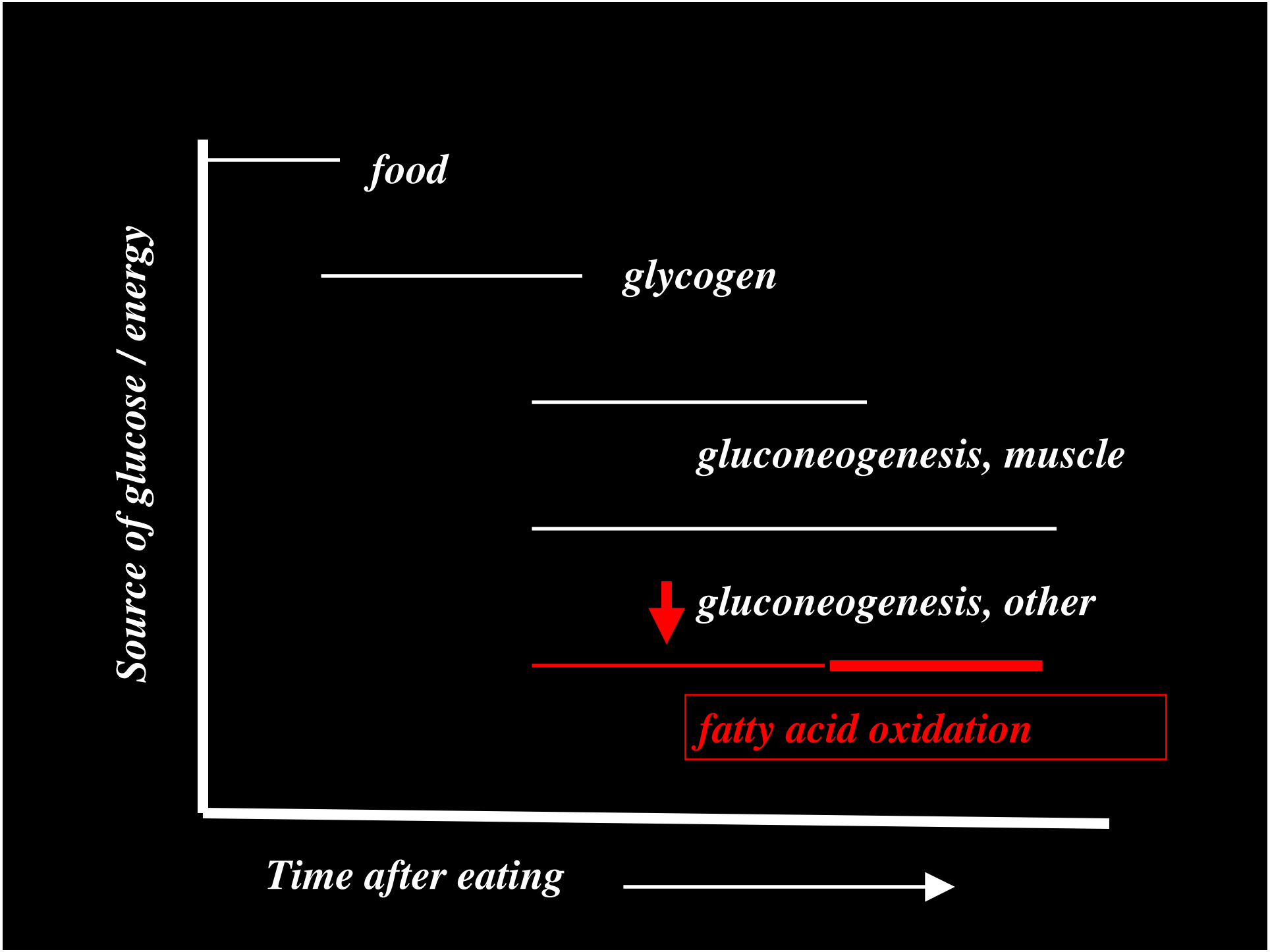
fatty acid oxidation
Source of glucose / energy
Time after eating

Disorders of Gluconeogenesis

- Glucose cannot be synthesized from certain substrates.
- Patients with severe disease are very affected neurologically – low muscle tone or spastic, seizures, developmentally delayed, failure to thrive.
- Lactic acid is usually elevated chronically.
- Symptoms, lactic acid become worse with fasting; hypoglycemia may occur at that time.


food
glycogen
gluconeogenesis, muscle
gluconeogenesis, other
fatty acid oxidation
Source of glucose / energy
Time after eating

Fatty Acid Oxidation Disorders

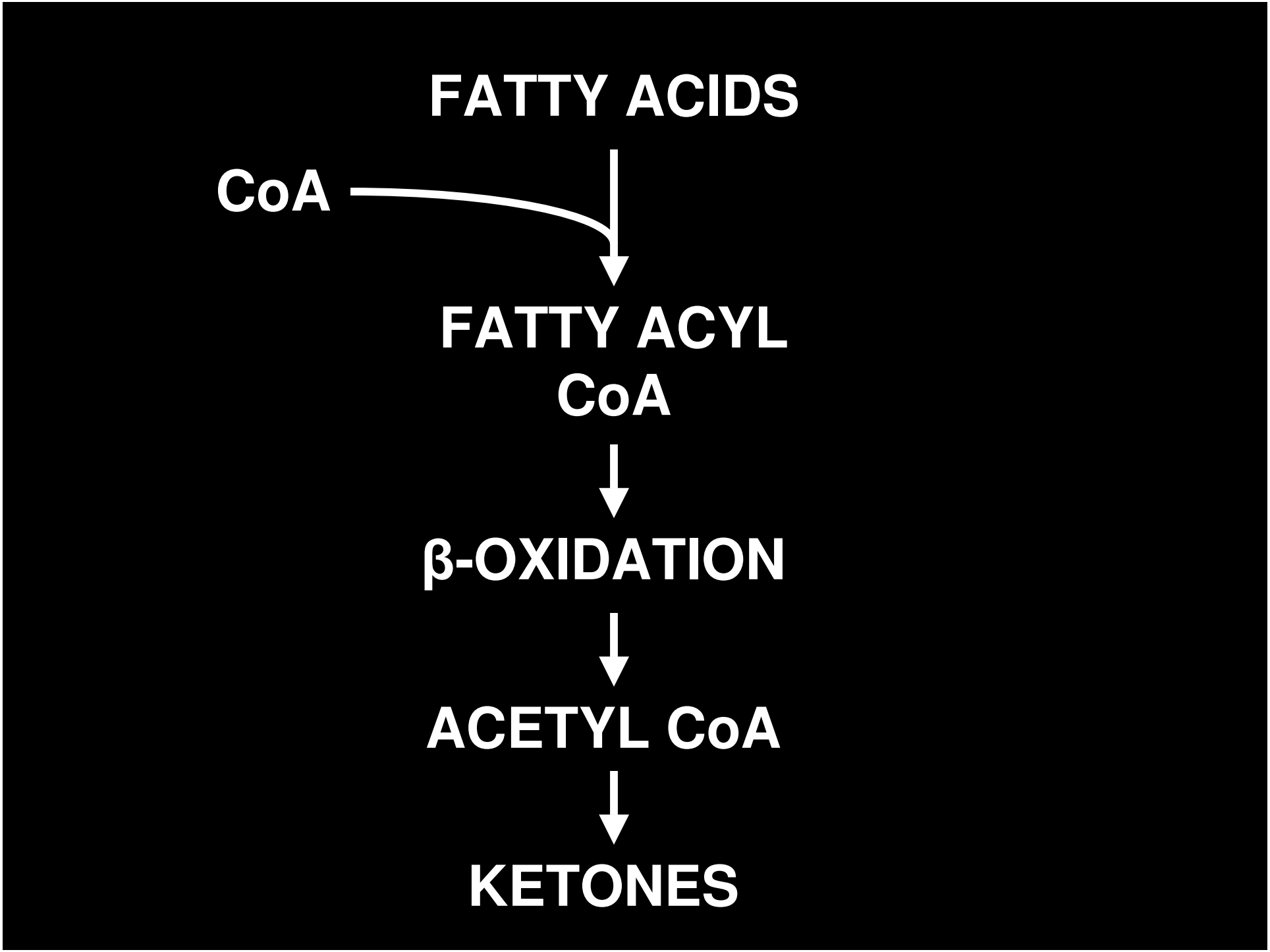
- When eating well, and while otherwise healthy, patients may show no symptoms.
- When food intake is inadequate and/or the patient is sick and food intake cannot keep up with demand, symptoms may occur.

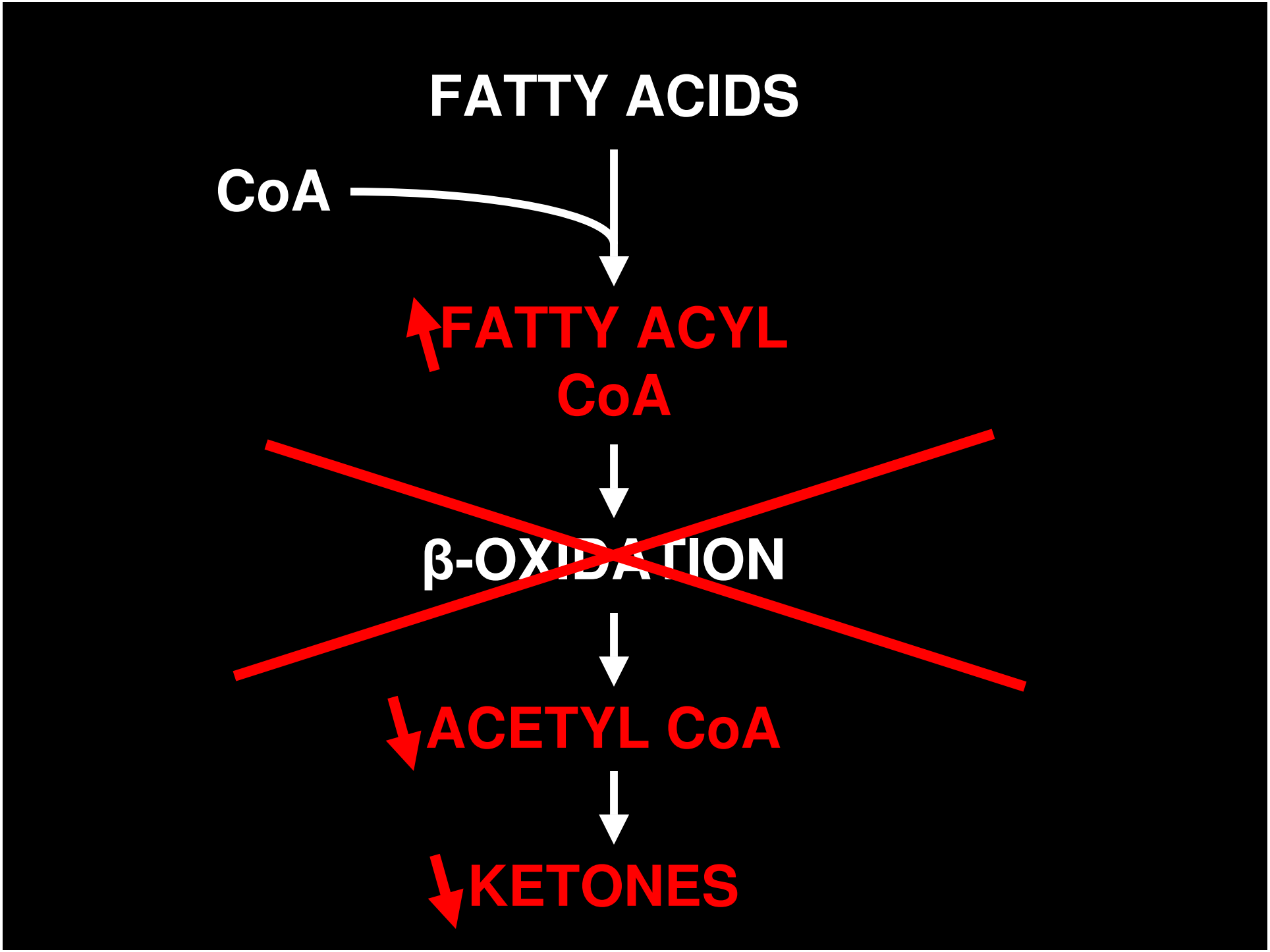
Fatty Acid Oxidation Disorders

- Nausea and vomiting
- Encephalopathy – lethargy, coma, seizures
- Liver enlargement, dysfunction
- Muscle and heart muscle dysfunction
- +/- Hypoglycemia

Encephalopathy: *Causes*

- Fatty acid oxidation disorders are disorders of energy metabolism in which the brain "runs out of energy":
  - glucose stores are exhausted.
  - ketone production is diminished.
- The accumulating metabolites are toxic to the brain, causing brain swelling and coma.


FATTY ACIDS
CoA
FATTY ACYL CoA
β-OXIDATION
ACETYL CoA
KETONES


FATTY ACIDS
CoA
FATTY ACYL CoA
β-OXIDATION
ACETYL CoA
KETONES

Encephalopathy: *Causes*

- The low concentrations of CoA and the accumulation of fatty acyl CoA molecules interfere with normal energy production in the Krebs cycle.
- Inadequate amounts of acetyl CoA impair gluconeogenesis or production of glucose in the body.

CLINICAL APPLICATIONS

CLINICAL APPLICATIONS

- ***Fasting avoidance is the cornerstone of therapy***

Fasting Avoidance

- If you rely on glucose and avoid relying on fat, symptoms are minimized.
- Exception: in long chain fatty acid oxidation defects, heart muscle and skeletal muscle depend on both glucose *and* fat.

CLINICAL APPLICATIONS

- Fasting avoidance is the cornerstone of therapy
- ***Is fat restriction necessary? Fat synthesis is not impaired (under healthy conditions).***

TR's Story

- TR was born following a normal pregnancy, labor and delivery. Developed hypoglycemia (12 mg/dL) on day 2 with associated lethargy and mottling.
- At four months, she became sweaty with feedings and often choked.
- At five months, she became irritable and less responsive and had staring spells.
- Examination revealed a gallop and murmur.
- Testing revealed cardiomyopathy & heart failure.

TR's Story (*continued…)*

- Metabolic testing revealed a diagnosis of VLCAD (very long chain acyl CoA dehydrogenase) deficiency. Enzyme testing confirmed the diagnosis.
- TR's diet: 30-35% of calories from fat -
  - 90% of fat from medium chain triglycerides
  - 10% of fat from long chain fat
- Carnitine given to maintain normal levels.
- Night-time feeds ended at 30 months; given corn starch instead with MCT during the day.

TR's Story (*continued...)*

- Heart size normalized over 24 months.
- Ventricular hypertrophy resolved by four years.
- Intercurrent illnesses associated with elevated liver enzymes and CPK; resolve with intravenous fluids.

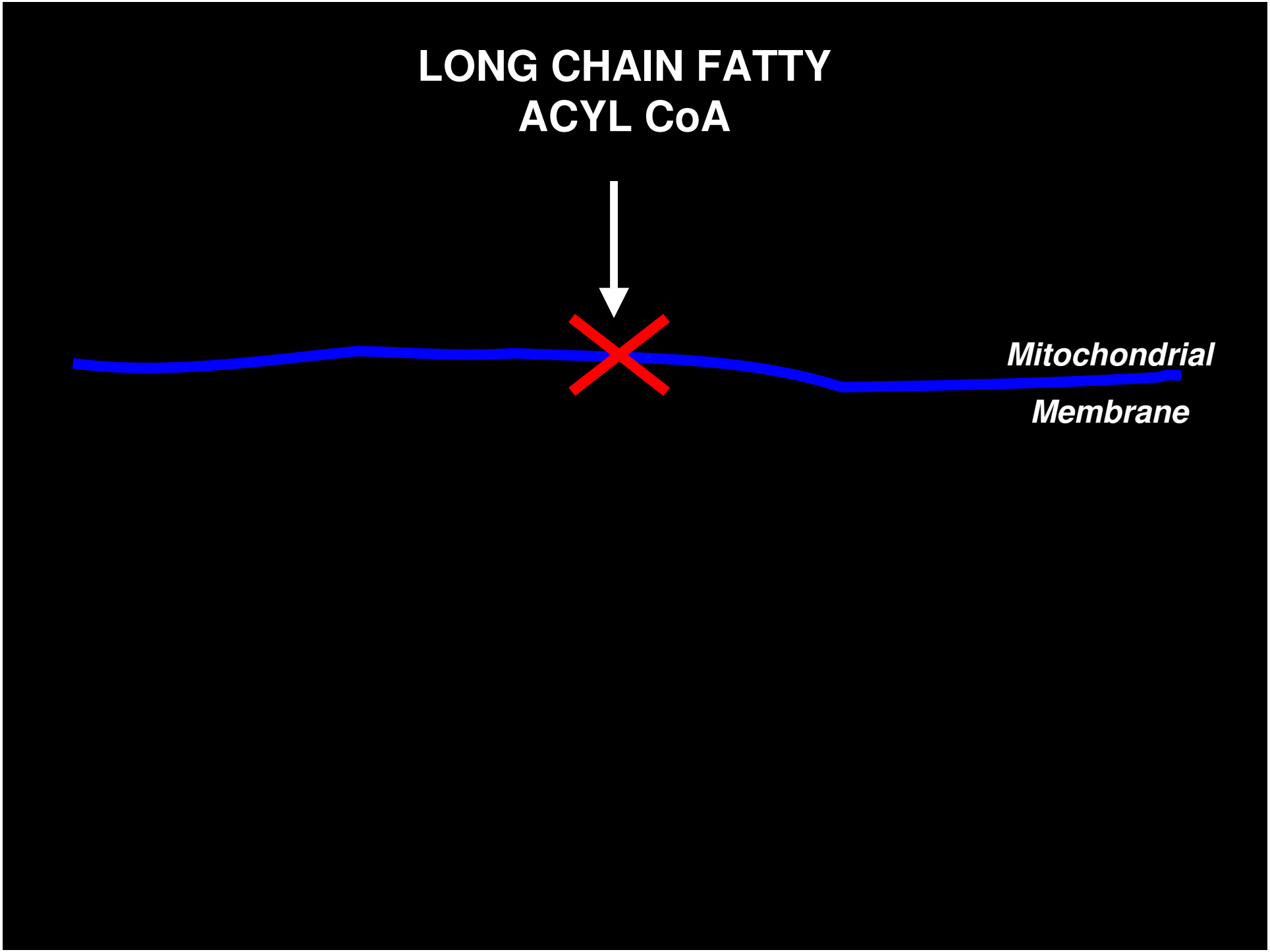
Fat Restriction

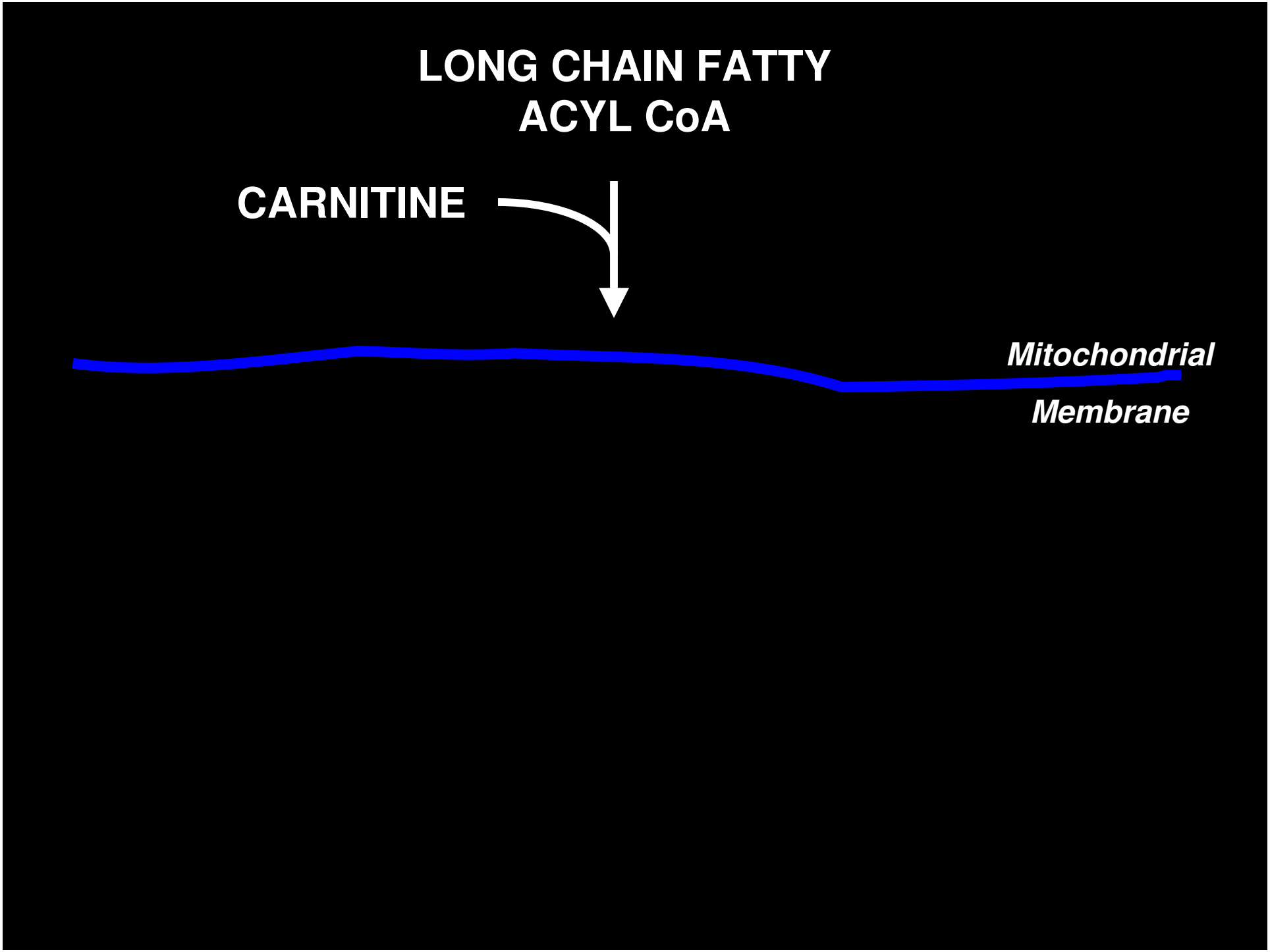
- When sick, energy demands rise and food intake diminishes; the body will use dietary fat to make ketones.
- The diet during times of illness should be high in carbohydrate and low in fat.
- Fat restriction may not be so important when the patient is otherwise healthy.

CLINICAL APPLICATIONS

- Fasting avoidance is the cornerstone of therapy
- Is fat restriction necessary?
- ***Medium chain fat supplementation (for long chain fatty acid oxidation disorders).***

DIETARY FAT AND BODY FAT STORES ARE LONG CHAIN IN LENGTH


LONG CHAIN FATTY
ACYL CoA
Mitochondrial
Membrane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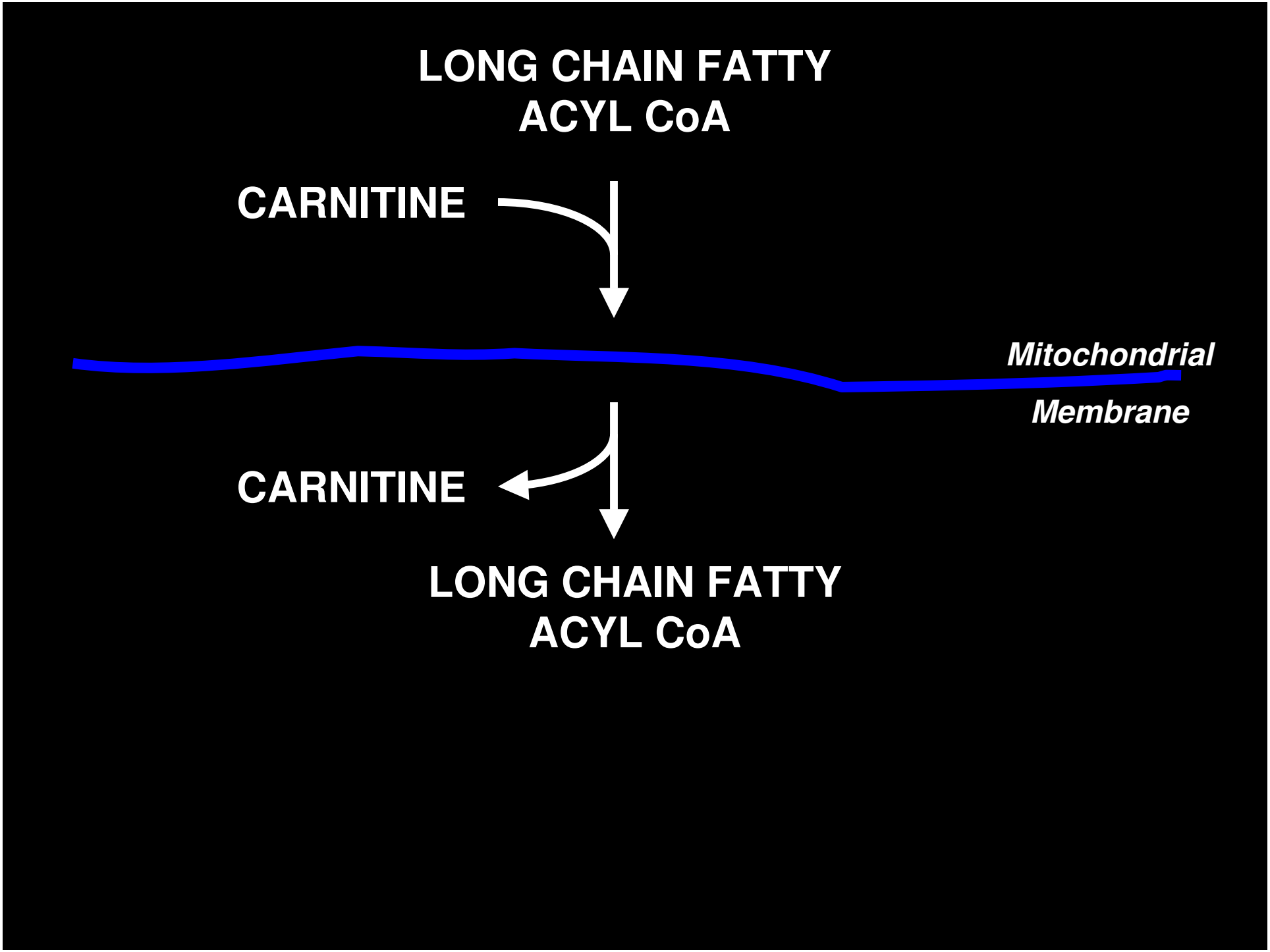
ACYL CoA
CARNITINE
Mitochondrial
Membrane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ACYL CoA
CARNITINE
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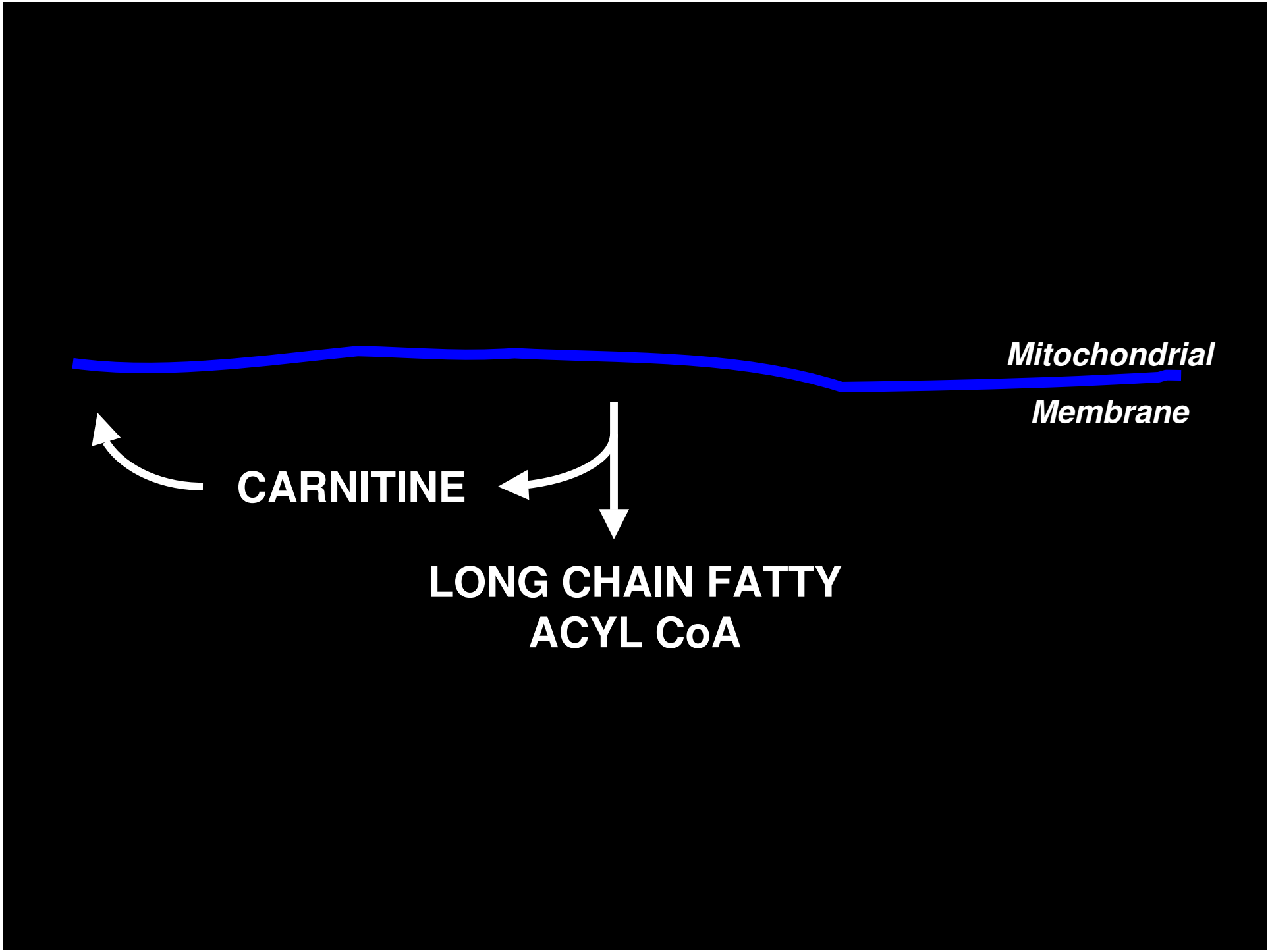
Membrane
CARNITINE
LONG CHAIN FATTY
ACYL CoA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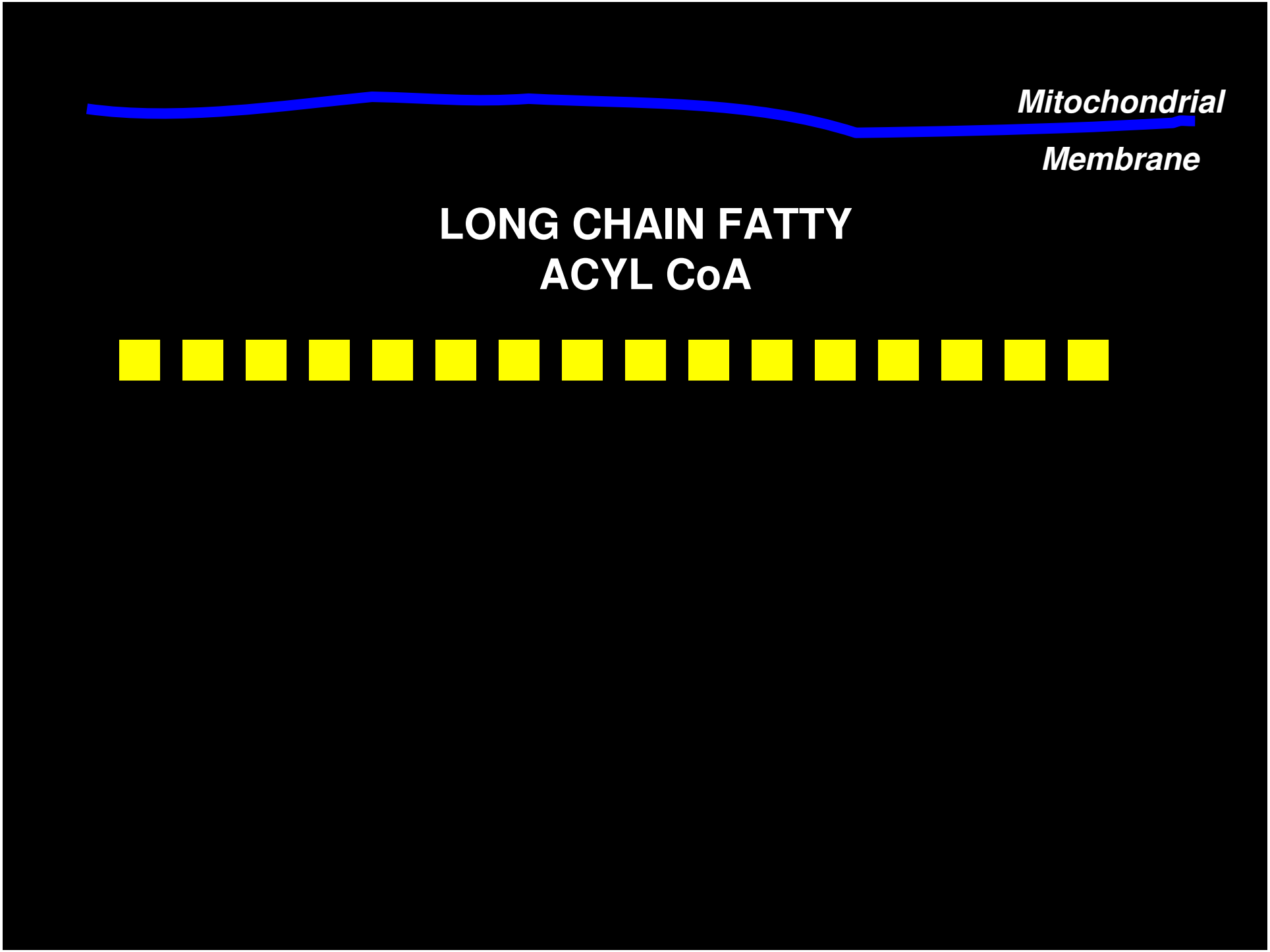
CARNITINE
LONG CHAIN FATTY
ACYL CoA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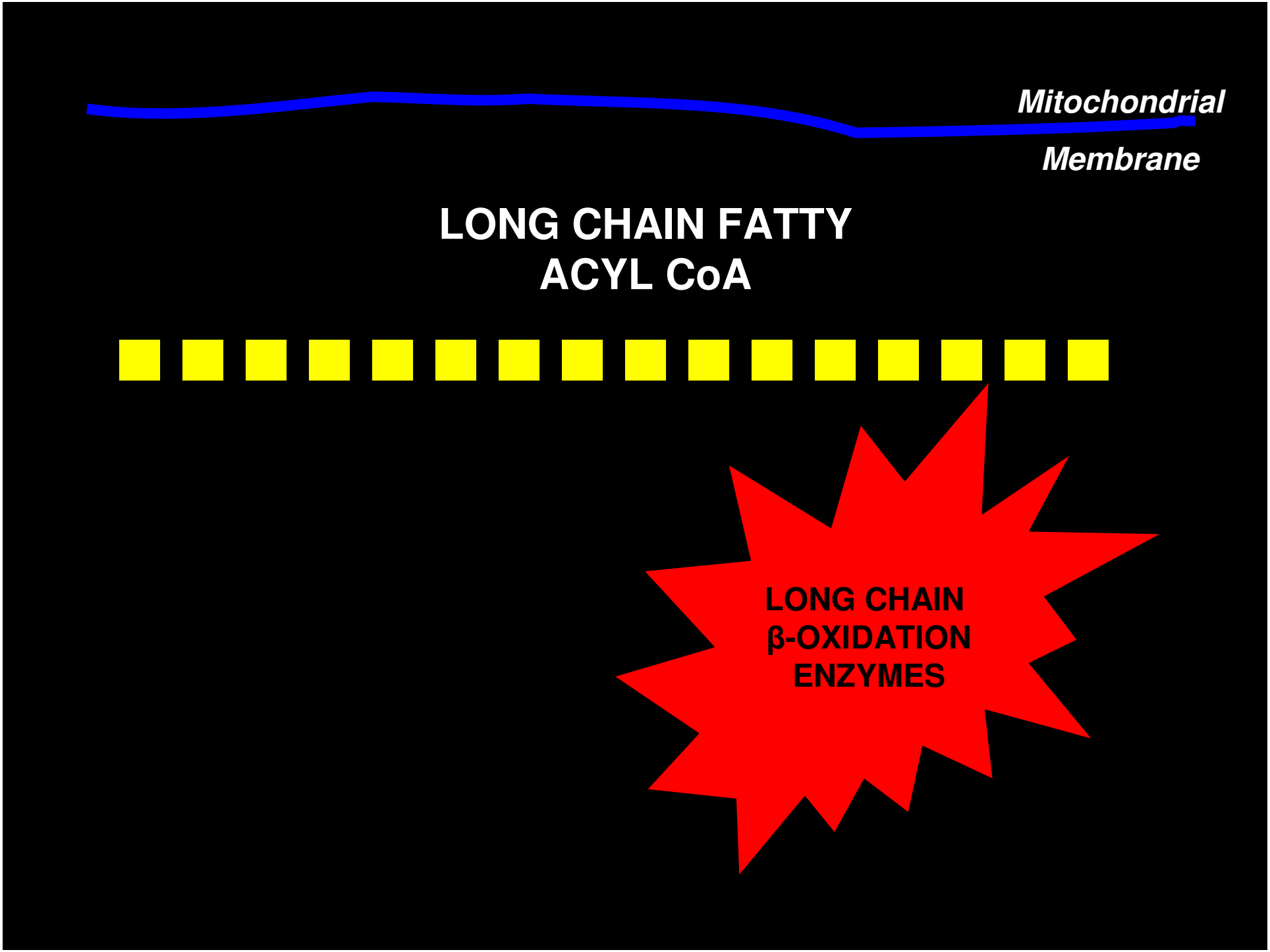
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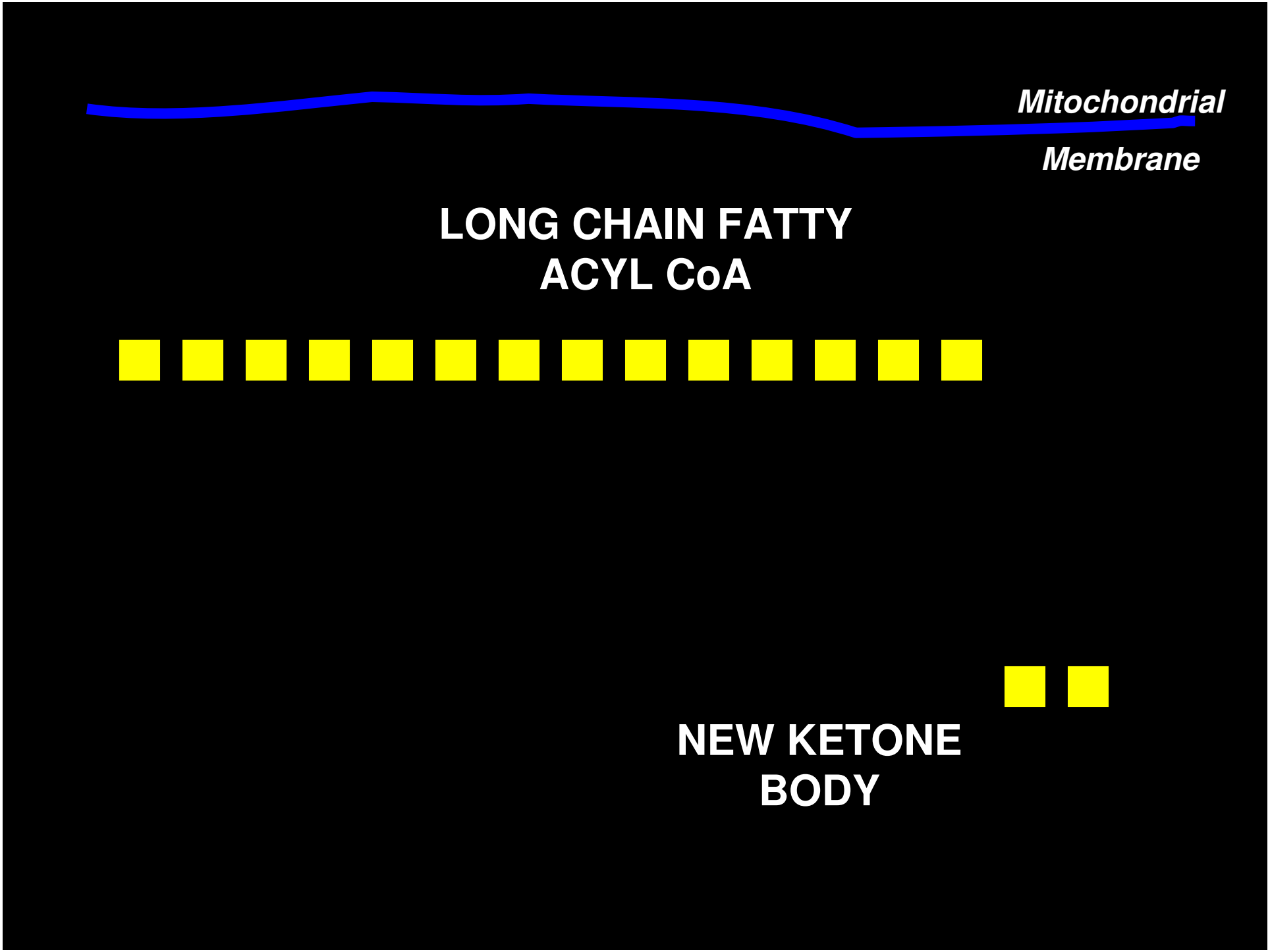
ACYL CoA
LONG CHAIN
β-OXIDATION
ENZYMES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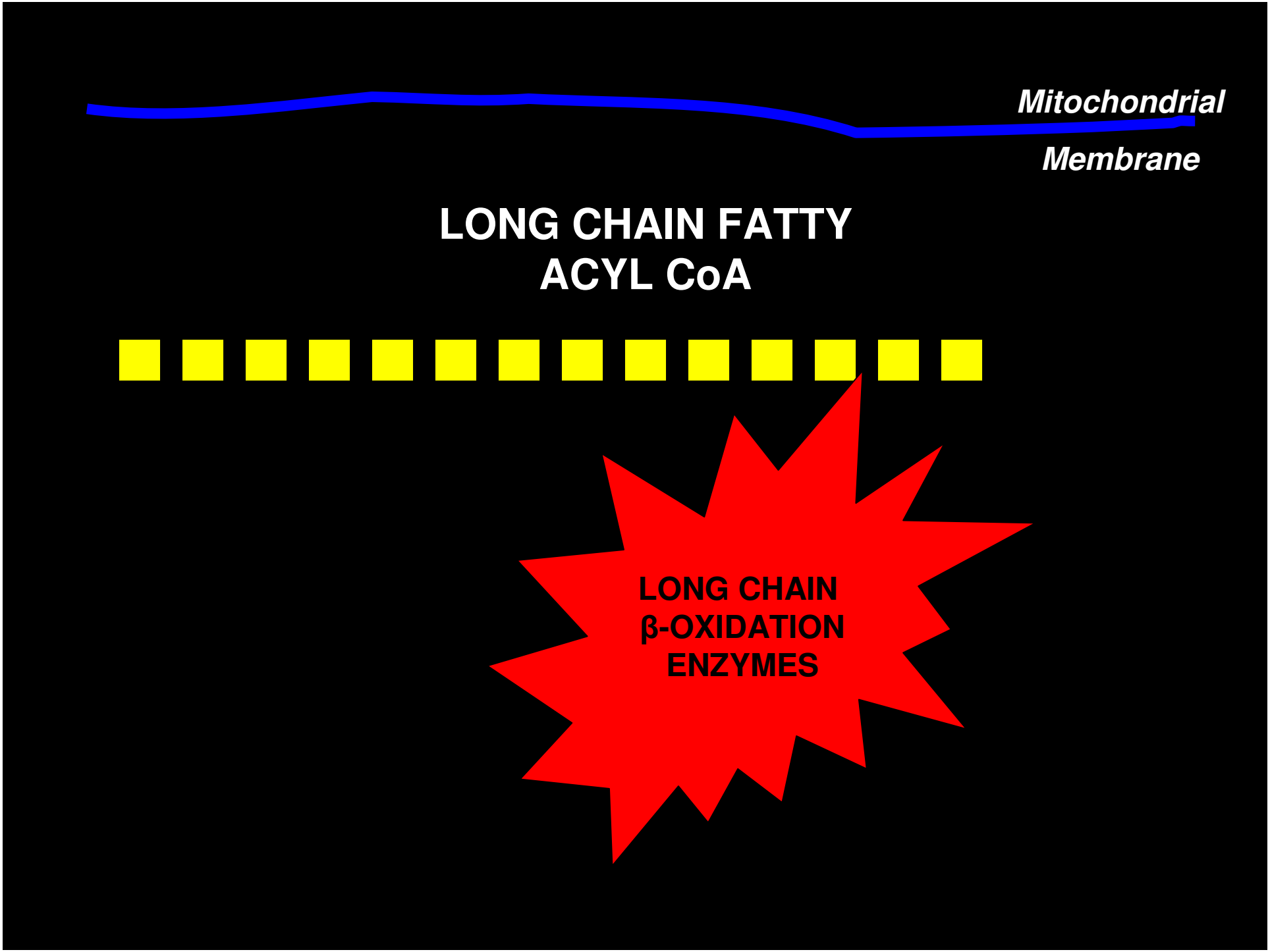
Membrane
LONG CHAIN FATTY
ACYL CoA
NEW KETONE
BODY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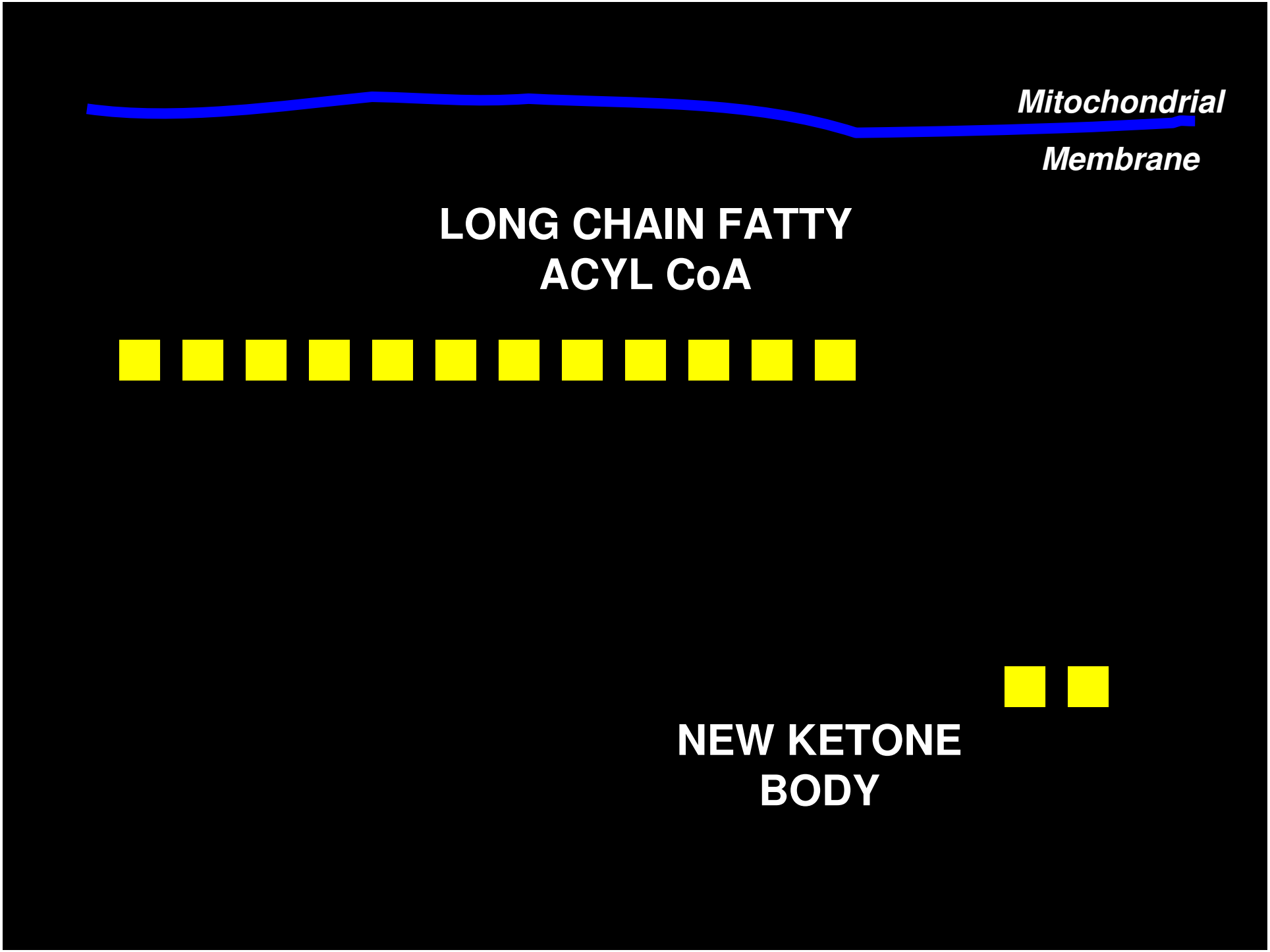
ENZYMES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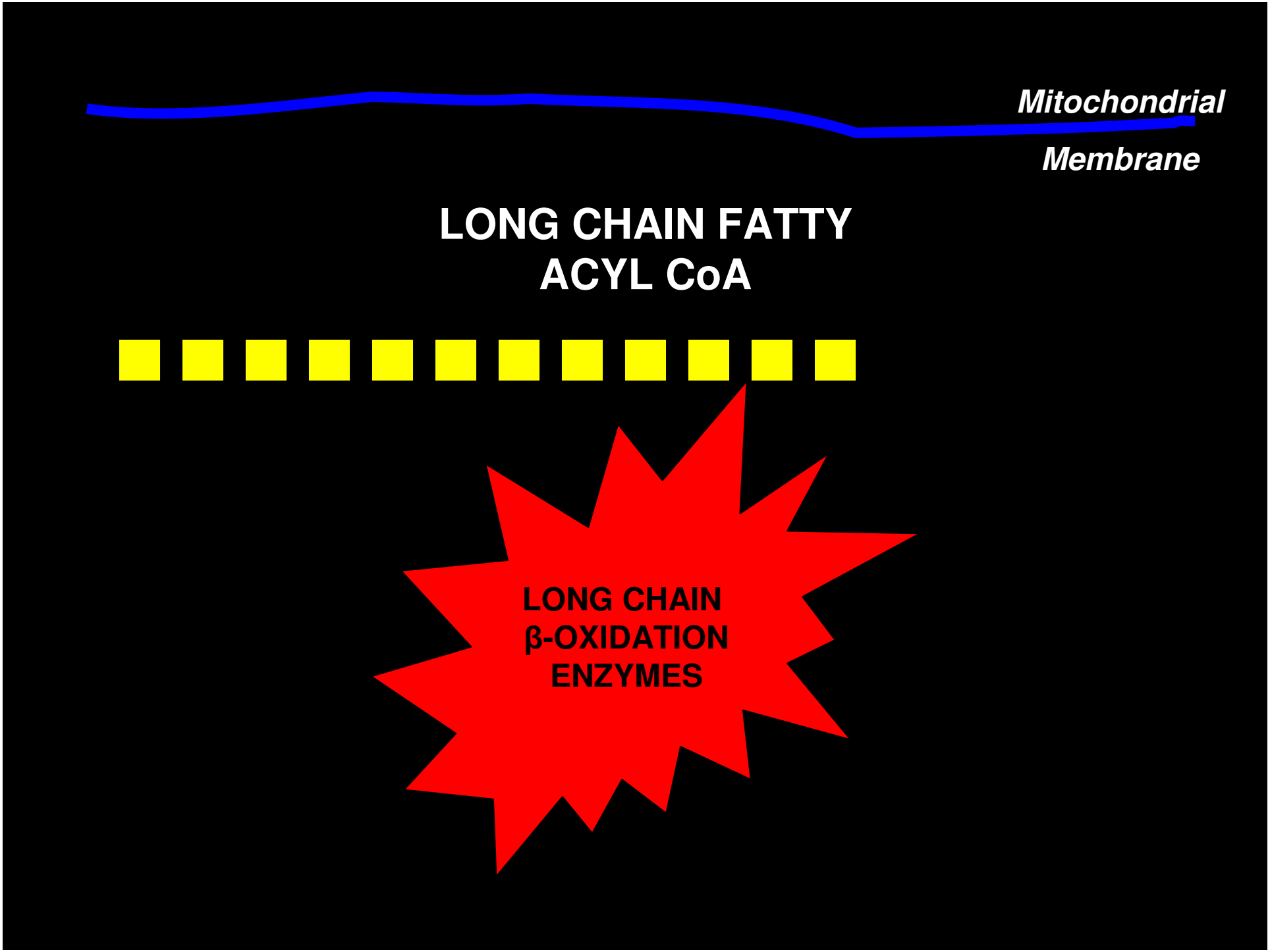
BODY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Membrane
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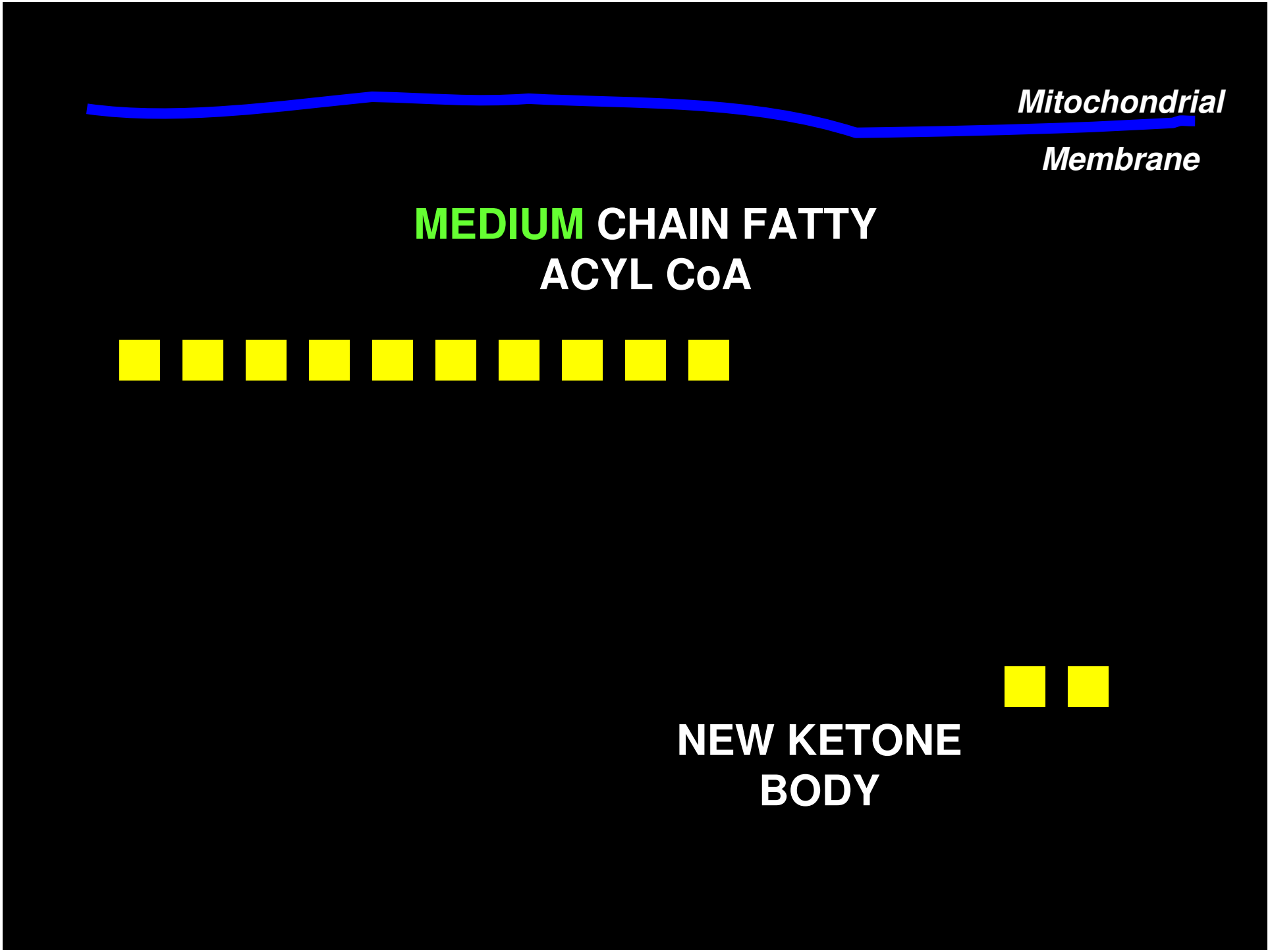
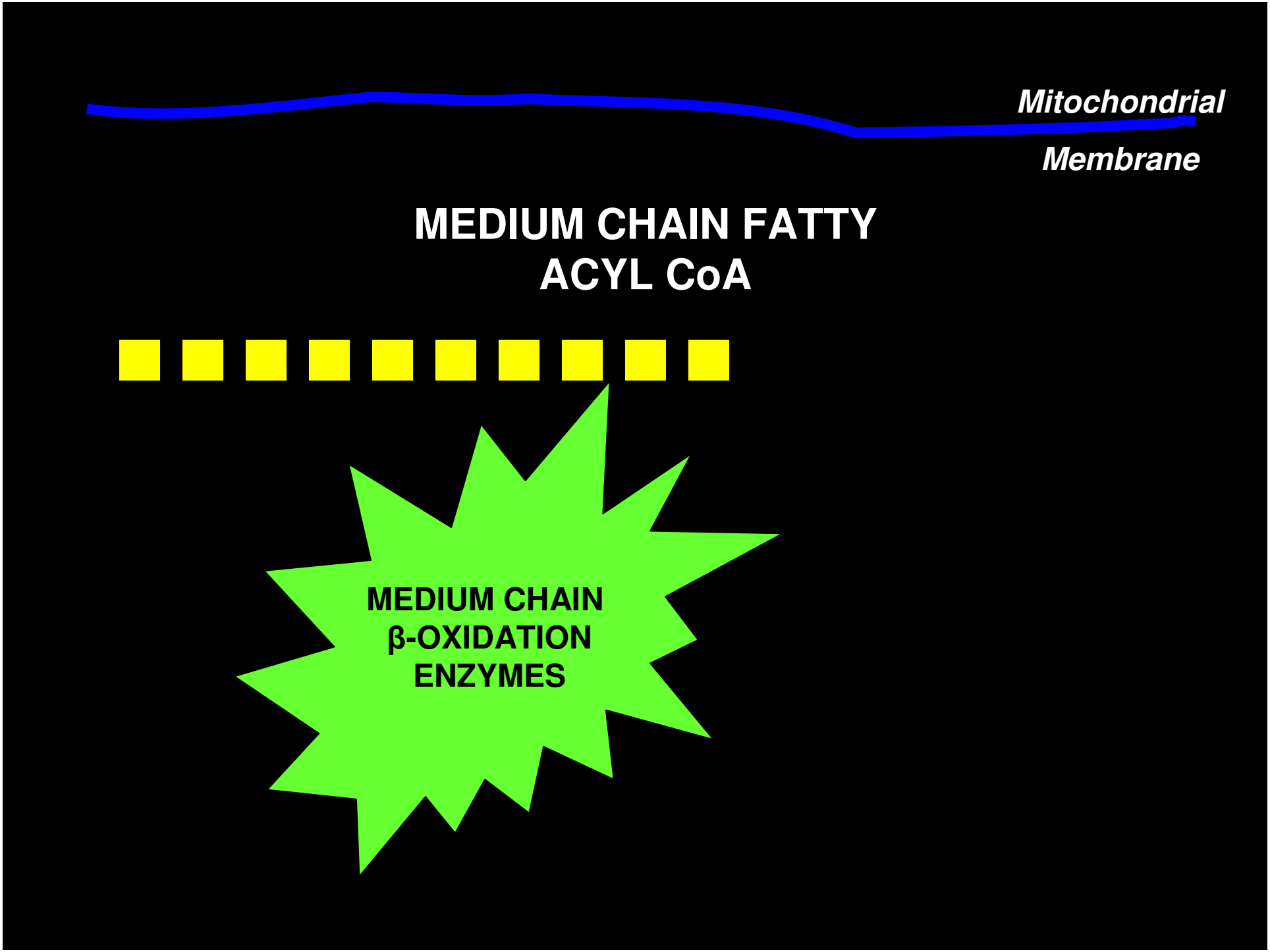
ACYL CoA
LONG CHAIN
β-OXIDATION
ENZYMES


Mitochondrial
Membrane
MEDIUM CHAIN FATTY
ACYL CoA
NEW KETONE
BODY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Membrane
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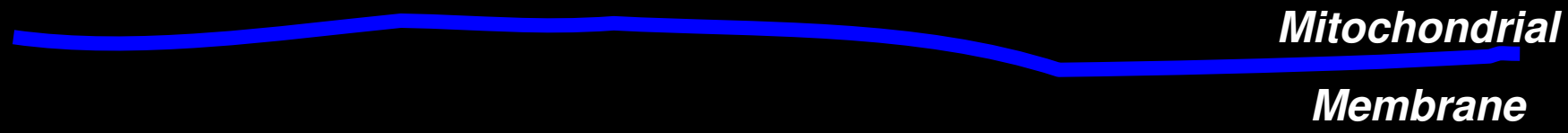
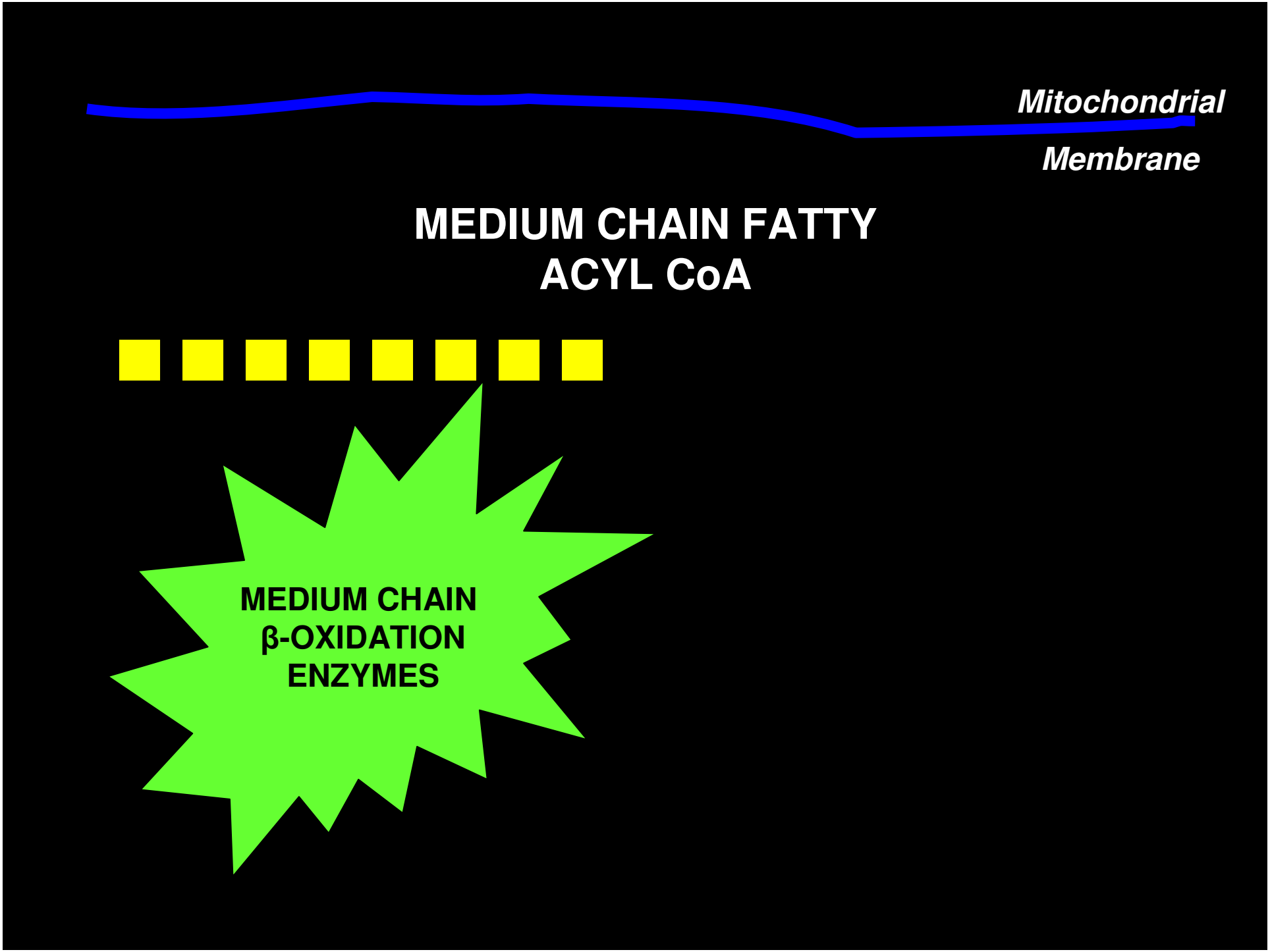
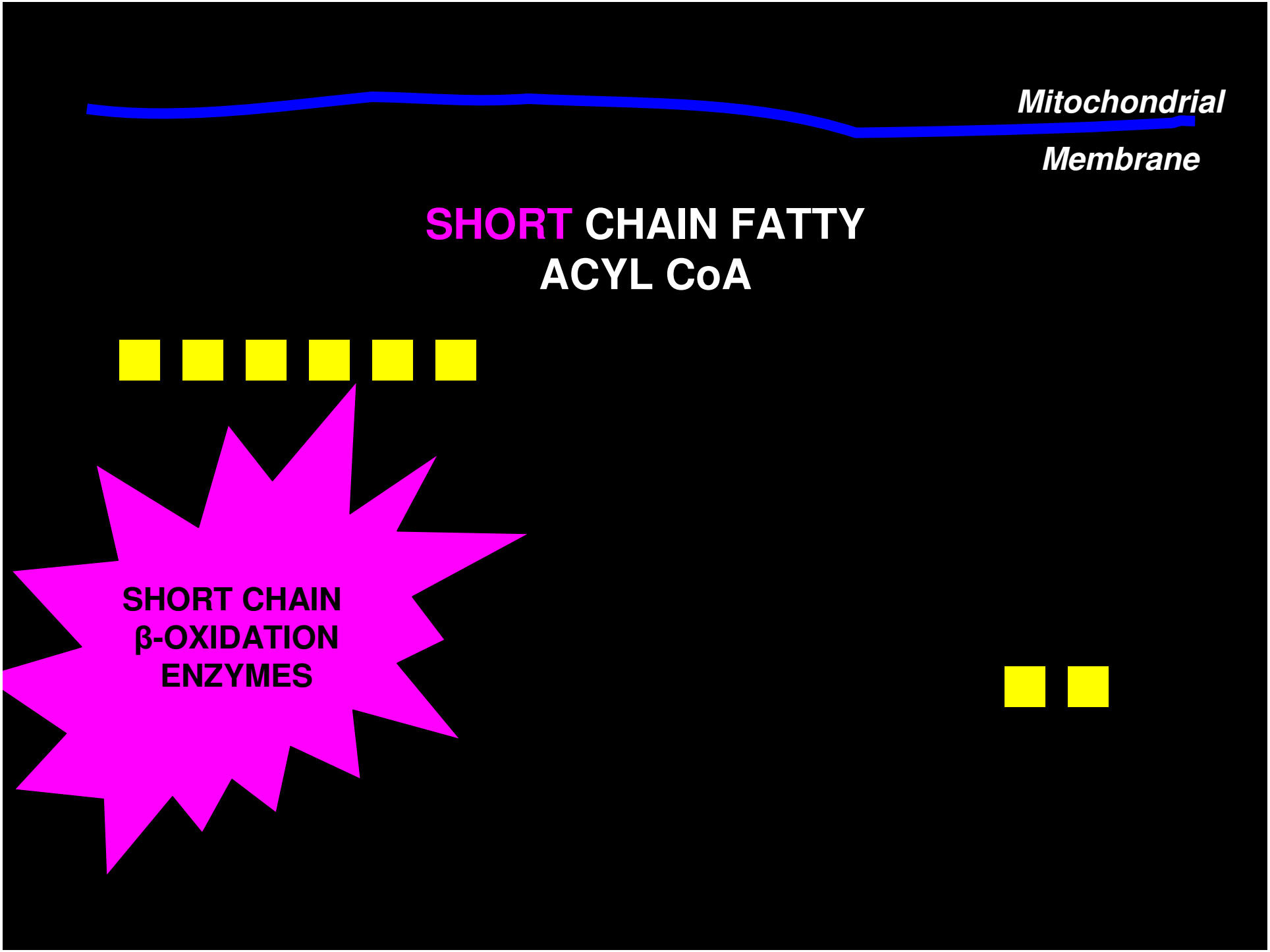
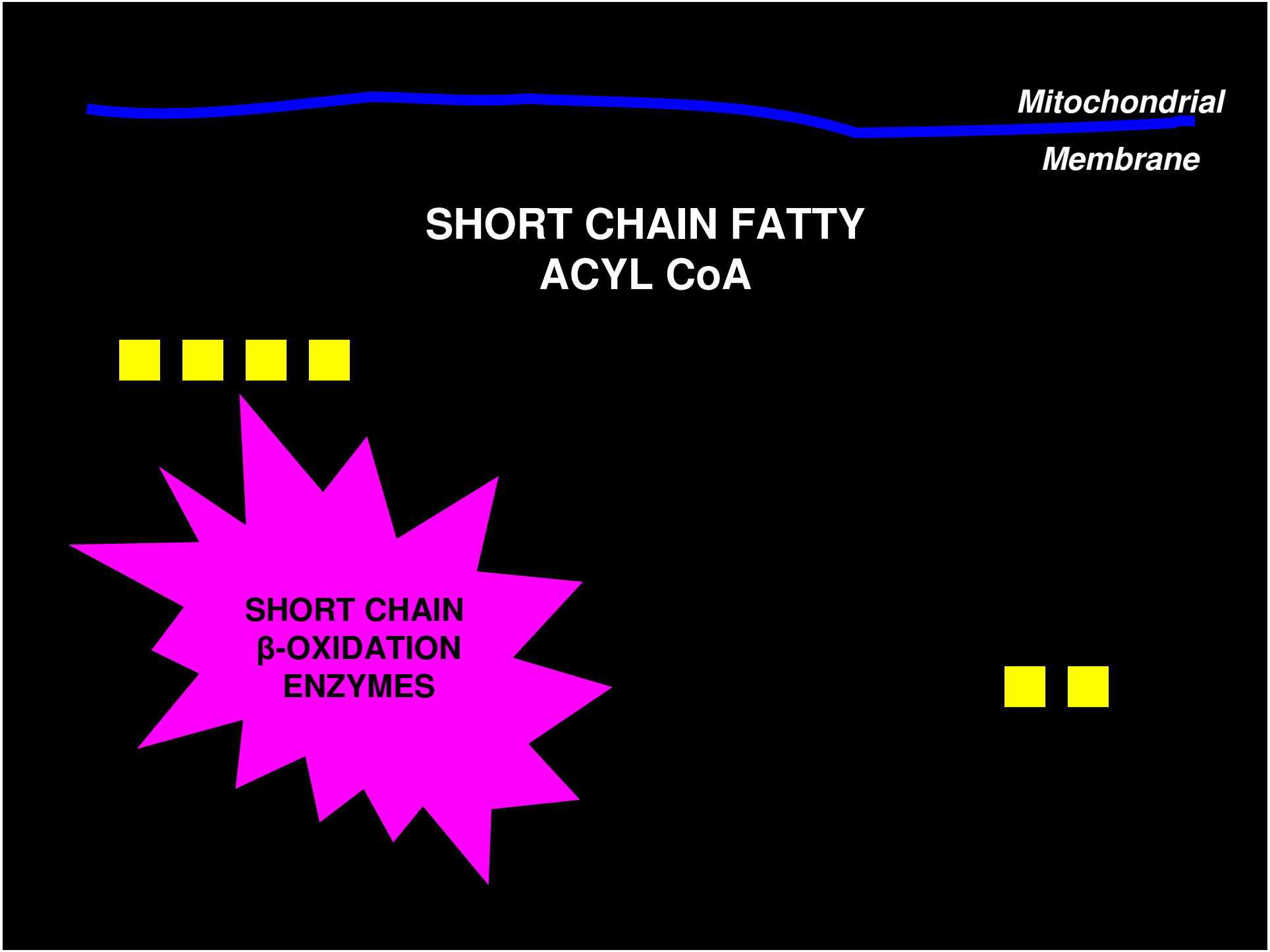
ACYL CoA
MEDIUM CHAIN
β-OXIDATION
ENZYMES



MEDIUM CHAIN FATTY ACYL CoA


Mitochondrial
Membrane
MEDIUM CHAIN FATTY
ACYL CoA
MEDIUM CHAIN
β-OXIDATION
ENZYMES


Mitochondrial
Membrane
SHORT CHAIN FATTY
ACYL CoA
SHORT CHAIN
β-OXIDATION
ENZYMES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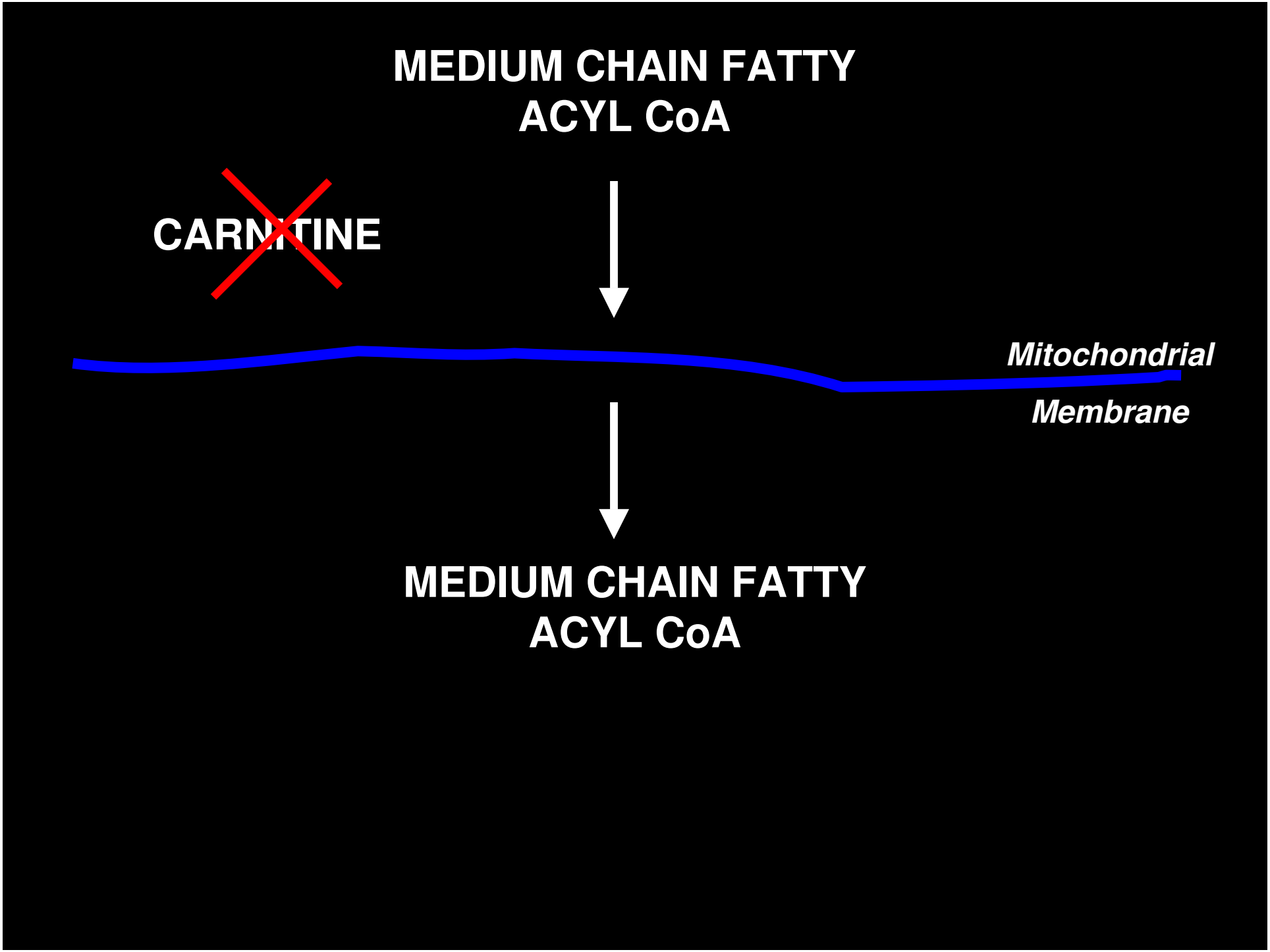
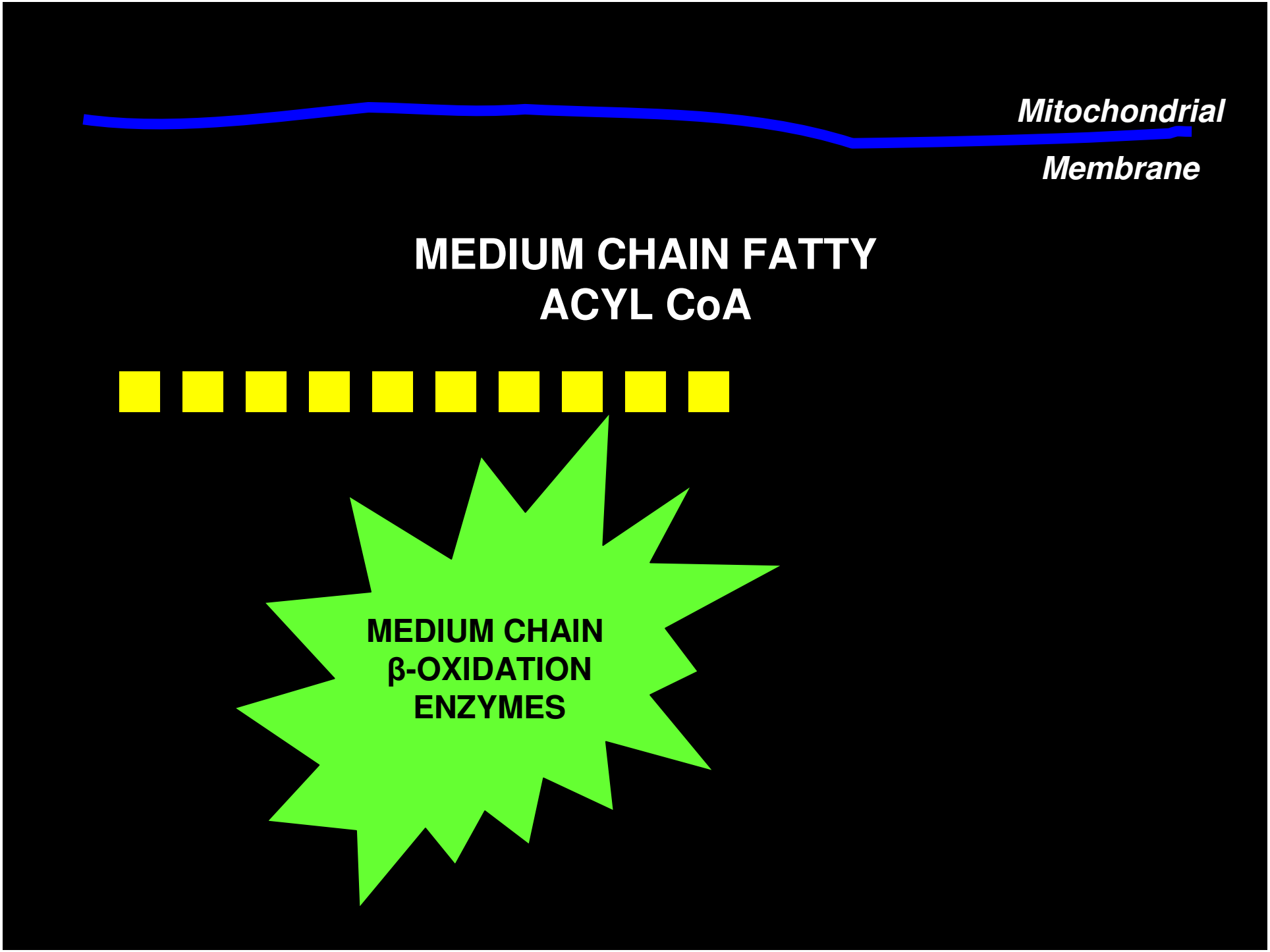
Membrane
SHORT CHAIN FATTY
ACYL CoA
SHORT CHAIN
β-OXIDATION
ENZYMES

SHORT CHAIN FATTY ACYL CoA


MEDIUM CHAIN FATTY
ACYL CoA
CARNITINE
Mitochondrial
Membrane
MEDIUM CHAIN FATTY
ACYL CoA


Mitochondrial
Membrane
MEDIUM CHAIN FATTY
ACYL CoA
MEDIUM CHAIN
β-OXIDATION
ENZYMES

Medium Chain Triglycerides

- MCT does not require carnitine, often deficient in any sick person, to be transported into the liver.
- MCT does not require oxidation by those enzymes that break down long chain fat; it *bypasses* them, and is broken down to form ketones using other, working enzymes.
- Important for long chain fatty acid defects

TR's Story (*continued...)*

- TR continued to avoid prolonged fasting and watched her fat intake but stopped taking daily MCT supplement.
- Complained of muscle cramping after exercising, increased muscle fatigue, jaw cramping in the morning.
- CPK levels ran 4000-5000 (normal<300).
- Once MCT supplementation restarted, symptoms diminished significantly, and CPK levels normalized.

CLINICAL APPLICATIONS

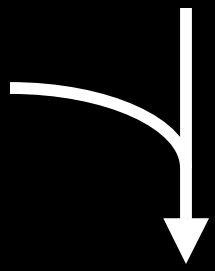
- Fasting avoidance is the cornerstone of therapy
- Is fat restriction necessary?
- Medium chain fat supplementation (in long chain fatty acid oxidation disorders).
- ***The role of carnitine.***

The Role of Carnitine

- Carnitine binds to the fatty acid oxidation intermediate molecules and facilitates their excretion for the body.
- Its benefit during periods of health are unclear; often levels are normal at these times. Deficiencies should be corrected.
- The benefit is more obvious when the patient is sick and producing large amounts of fatty acid intermediates.

Potentially Toxic
LONG CHAIN
FATTY ACYL CoA

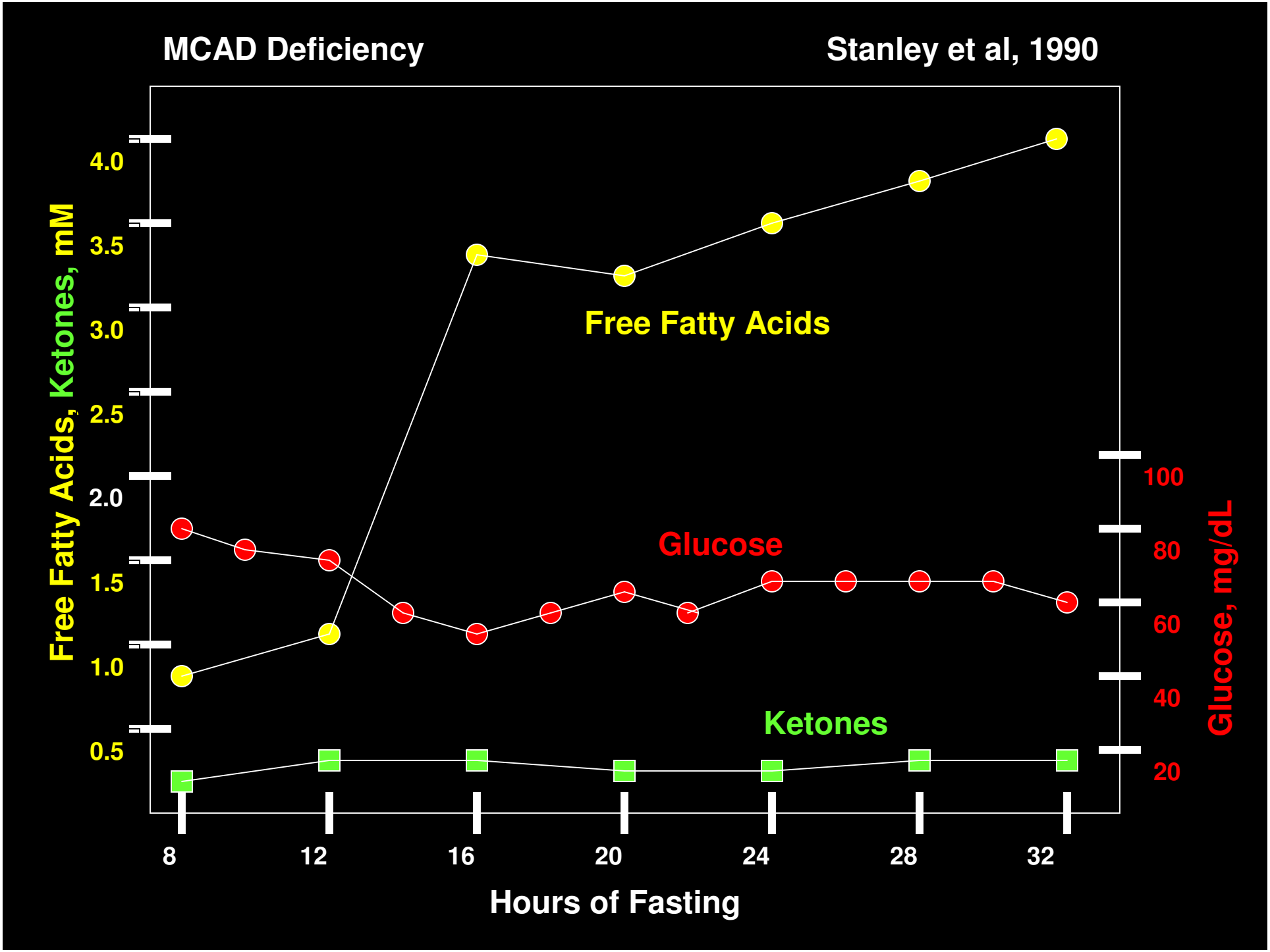
CARNITINE



LONG CHAIN
FATTY
ACYLCARNITINE

CLINICAL APPLICATIONS

- Fasting avoidance is the cornerstone of therapy
- Is fat restriction necessary?
- Medium chain fat supplementation (in long chain fatty acid oxidation disorders).
- The role of carnitine.
- ***Glucose monitoring.***


MCAD Deficiency
Stanley et al, 1990
Free Fatty Acids, Ketones, mM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Free Fatty Acids
Glucose
Ketones
100
80
60
40
20
Glucose, mg/dL
8
12
16
20
24
28
32
Hours of Fasting

Glucose Monitoring

- **Problem: Lethargy and coma can occur in the absence of a low blood sugar.**
- **Glucometer readings (if not hypoglycemic) may offer a false sense of security.**
- **The patient should be evaluated and treated if symptoms of concern are present *whether or not hypoglycemia is present.***

CLINICAL APPLICATIONS

- Fasting avoidance is the cornerstone of therapy
- Is fat restriction necessary?
- Medium chain fat supplementation (in long chain fatty acid oxidation disorders).
- The role of carnitine.
- Glucose monitoring.
- ***When sick, give 10% dextrose at >1.25 maintenance rate.***

Why 10% Dextrose When Sick?

- "Catabolism", including glycogen breakdown, and eventually gluconeogenesis and fatty acid oxidation, occurs when the amount of dietary or IV glucose falls below the basal glucose production rate in liver.
- Bier et al, 1977, determined this rate:
  $y=0.0014\ x3 - 0.214\ x2 + 10.411\ x - 9.084$
  y=glucose production rate (mg/min)
  x=body weight (kg)

Example: 10 kg child

- y=0.0014 x3 – 0.214 x2 + 10.411 x – 9.084
  y=glucose production rate (mg/min)
  x=body weight (kg)
- Basal glucose production rate = 75.03 mg/min of glucose (or 7.5 mg/kg/min)
- 10% dextrose at maintenance provides 70 mg/min (or 7.0 mg/kg/min)
- 10% dextrose at 1.25 maintenance provides 87 mg/min (or 8.7 mg/kg/min)

PREVENTION
is the ***best*** approach

Newborn screening….

- **Allows pre-symptomatic monitoring.**
- **Allows early intervention when symptoms arise.**
- **Allows prevention of complications that occur during metabolic crises.**

NEWBORN SCREENING

- **PRO:**
  - ***Allows prevention of serious morbidity and mortality***
- **CON:**
  - ***In some identified patients, it is difficult to prove whether or not they have clinically-significant disease.***

Approach to Confirming a Diagnosis

- Blood and urine testing (especially when sick)
- Skin fibroblast fatty acid oxidation testing
- Skin fibroblast enzyme testing
- ?Liver enzyme testing
- DNA testing

Approach to Confirming a Diagnosis

- Monitored fasting study, to evaluate the patient's physiologic response to fasting

Approach to Confirming a Diagnosis

- **Monitored fasting study –**
  - **Admit when healthy.**
  - **Fast for a prolonged period of time.**
  - **Monitor the physiologic response to fasting (e.g., fatty acids, ketones).**
  - **Monitor glucose.**
  - **When glucose drops or patient's mental status changes – draw final tests, then administer glucose and allow to eat.**
  - **Allows a "bottom-line" conclusion.**

DG's Story

- Well until 7 months of age; developed viral illness.
- Became lethargic, seen by pediatrician who diagnosed hypoglycemia with inappropriately low ketones in the urine.
- Urine sent for organic acid analysis: showed inappropriately low ketones and pattern suggestive of medium chain ketoacyl CoA thiolase deficiency.

DG's Story (*continued…)*

- Repeat blood and urine tests not informative.
- Skin biopsy did not show an abnormality in oxidation.
- The parents consented to a fasting study to evaluate DG's physiologic response to fasting; she was 26 months old.
- At 17 hours of fasting, glucose dropped <50 mg/dL. "Critical specimens" obtained.

DG's Story (*continued…)*

- DG showed a normal free fatty acid and ketone response.
- Other testing (acylcarnitines, acylglycines) all normal.

< sigh >

THERE'S SO MUCH MORE TO LEARN.

Thanks for listening.

Now go eat something.