ANATOMY OF A METABOLIC CRISIS: FAOD-style

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NORMAL PHYSIOLOGY

Anabolic –

- Eating well
- Calories eaten > body's needs

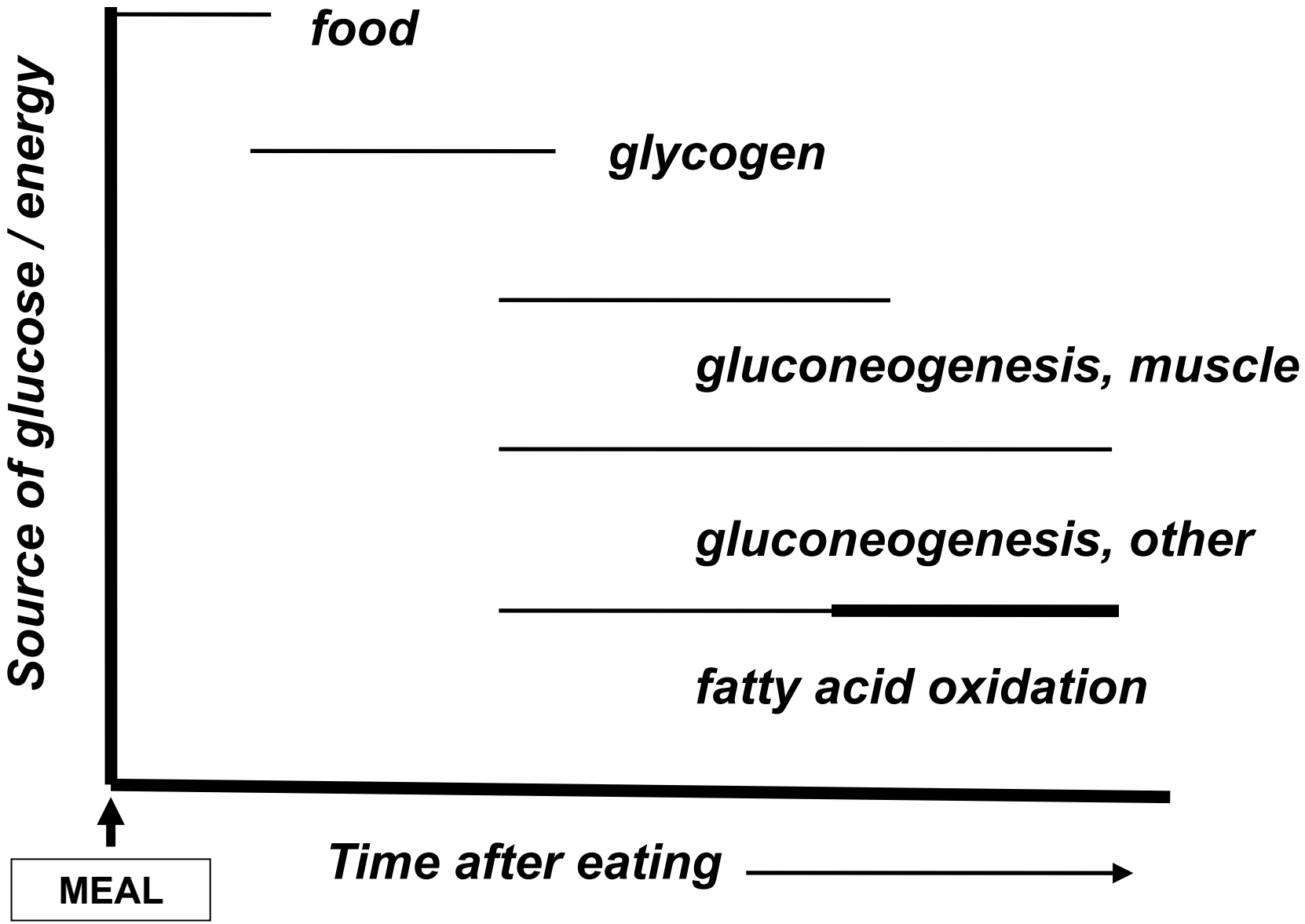
BRAIN	MUSCLE
uses	uses
GLUCOSE	GLUCOSE and FAT

NORMAL PHYSIOLOGY

Catabolic –

- Not eating well; fasting
- Body's needs > calories eaten

BRAIN	MUSCLE
uses	uses
GLUCOSE	GLUCOSE and FAT


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

NORMAL PHYSIOLOGY

Catabolic –

- Not eating well; fasting
- Body's needs > calories eaten

BRAIN	MUSCLE
uses	uses
~~GLUCOSE~~	GLUCOSE
FAT	and
(as ketones)	FAT

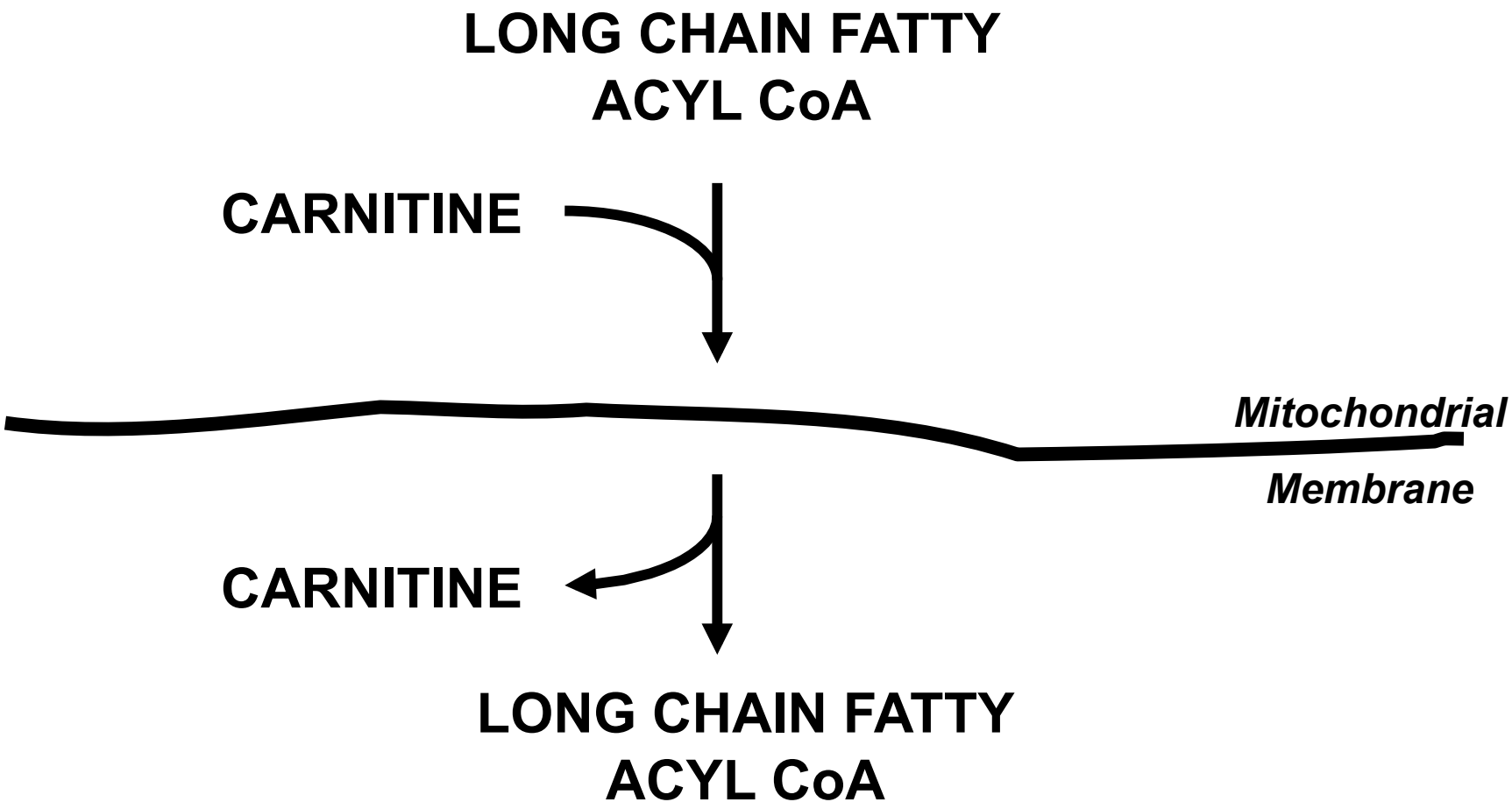
NORMAL PHYSIOLOGY

Exercise –

FAT DEPOSITS

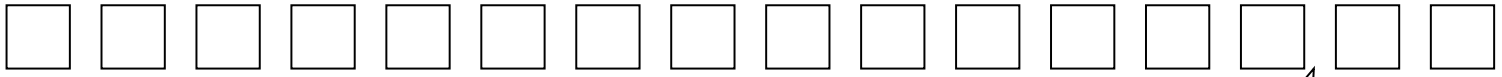
fatty acids

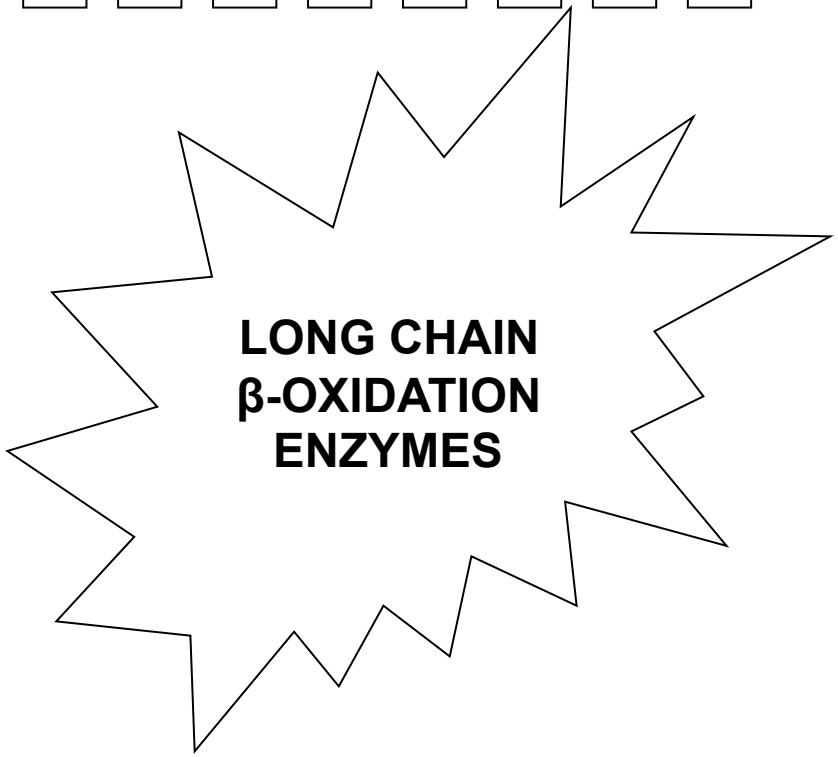
LIVER


LONG CHAIN FATTY
ACYL CoA
CARNITINE
Mitochondrial
Membrane
CARNITINE
LONG CHAIN FATTY
ACYL CoA

Mitochondrial Membrane

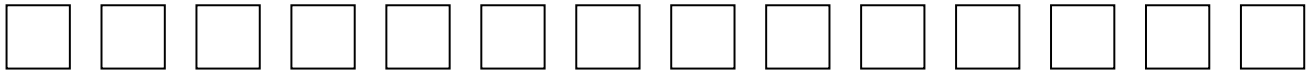
LONG CHAIN FATTY ACYL CoA

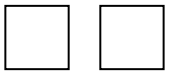




Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA



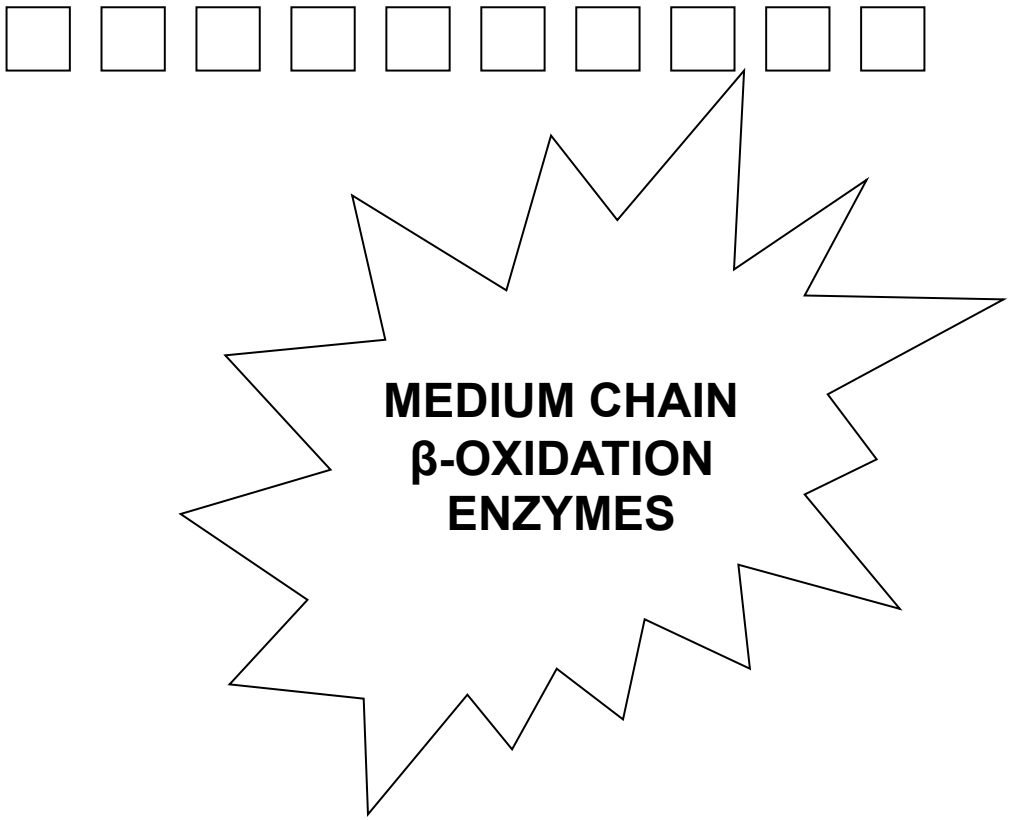


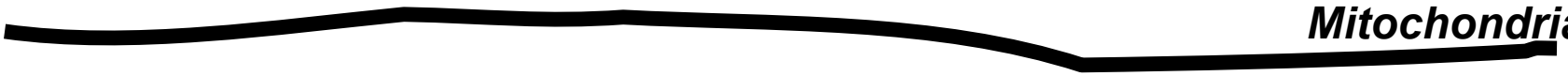
ACETYL CoA

KETONE BODY

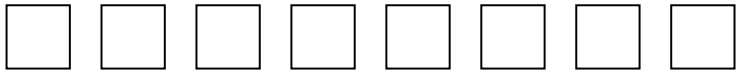
Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA

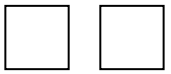




MEDIUM CHAIN FATTY ACYL CoA



ACETYL CoA

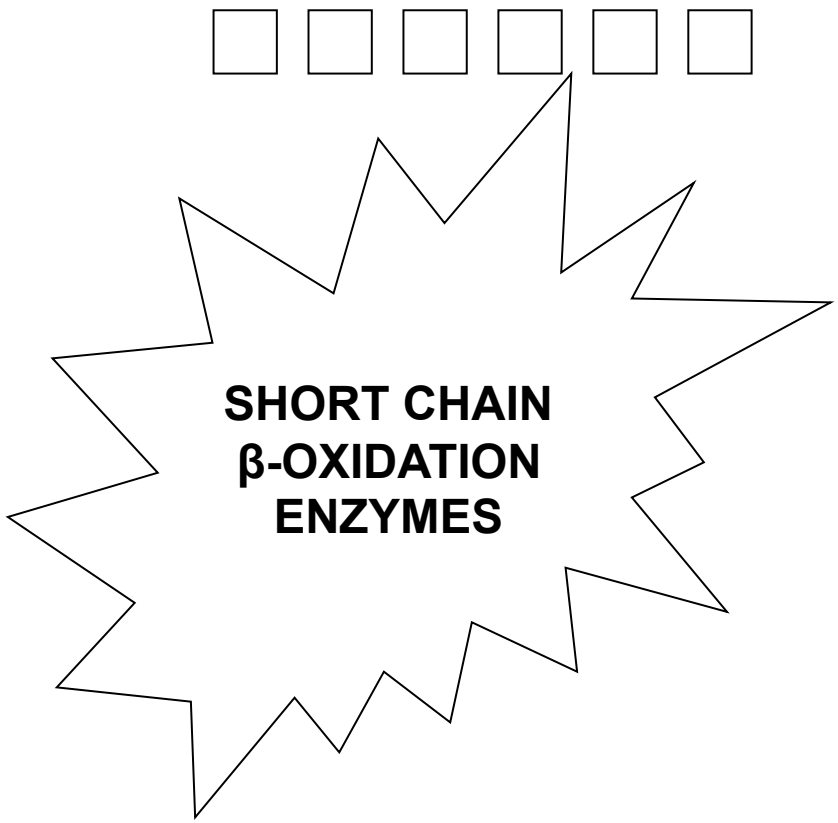


KETONE BODY

Mitochondrial

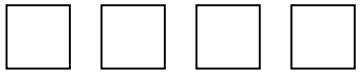
Membrane

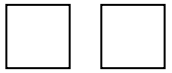
SHORT CHAIN FATTY ACYL CoA



Mitochondrial Membrane

SHORT CHAIN FATTY ACYL CoA

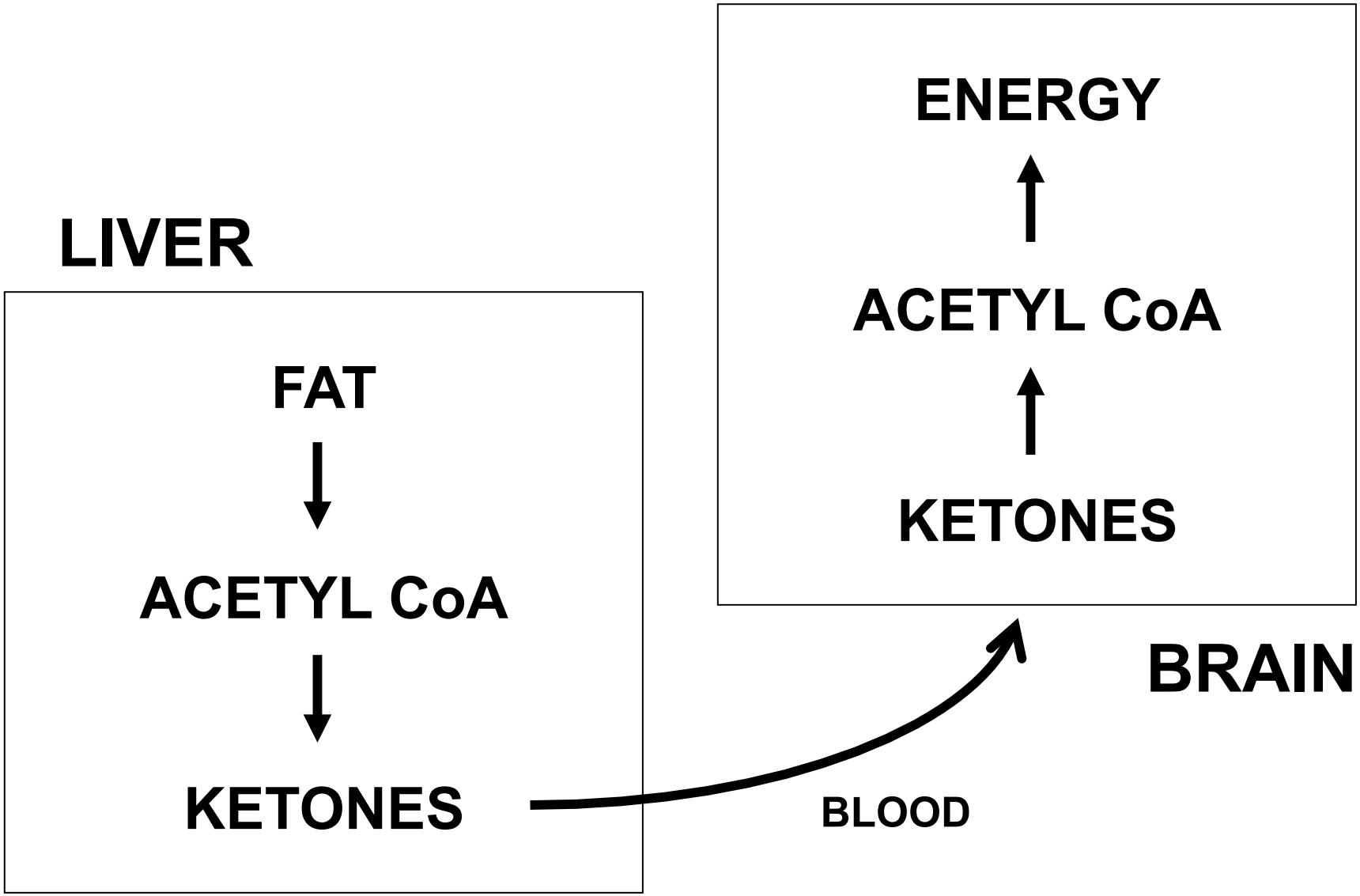




ACETYL CoA

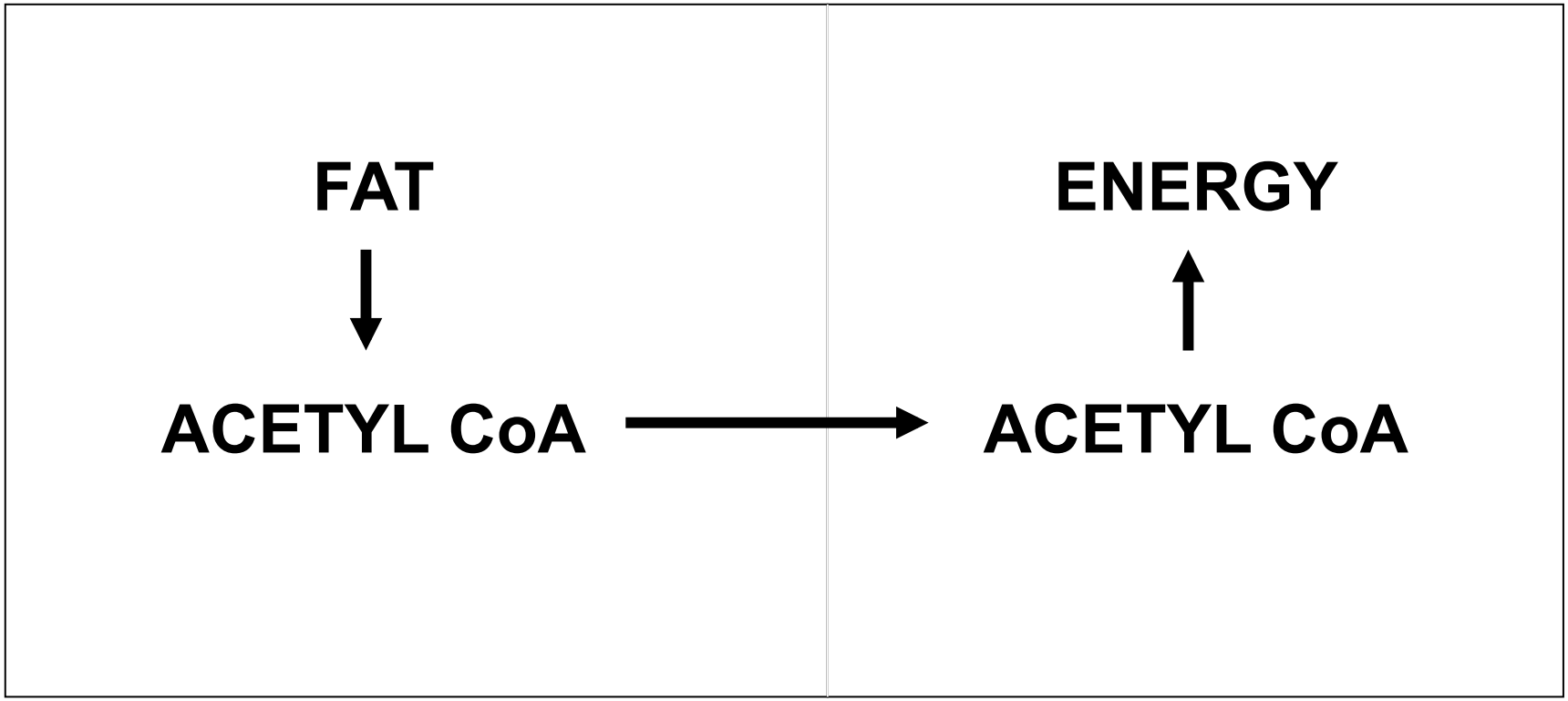
KETONE BODY

NORMAL PHYSIOLOGY



NORMAL PHYSIOLOGY

MUSCLE



MEET EC, with MCAD deficiency

- Patient EC started sleeping through the night at 4-5 months of age.
- At 13 months, she developed her first episode of lethargy. Parents had difficulty waking her up in the morning. In the ER, ?viral infection.
- She had eight episodes of early morning lethargy between 13 and 20 months of age.

EC, with MCAD deficiency

- The episodes usually occurred in the morning - if she missed her bed-time snack, or if she had an infection. She went limp and/or stared without responding. Her temperature could drop to 94-95°F. This would last for 4-6 hours. Then she “returned to normal”, recovering after drinking juice.

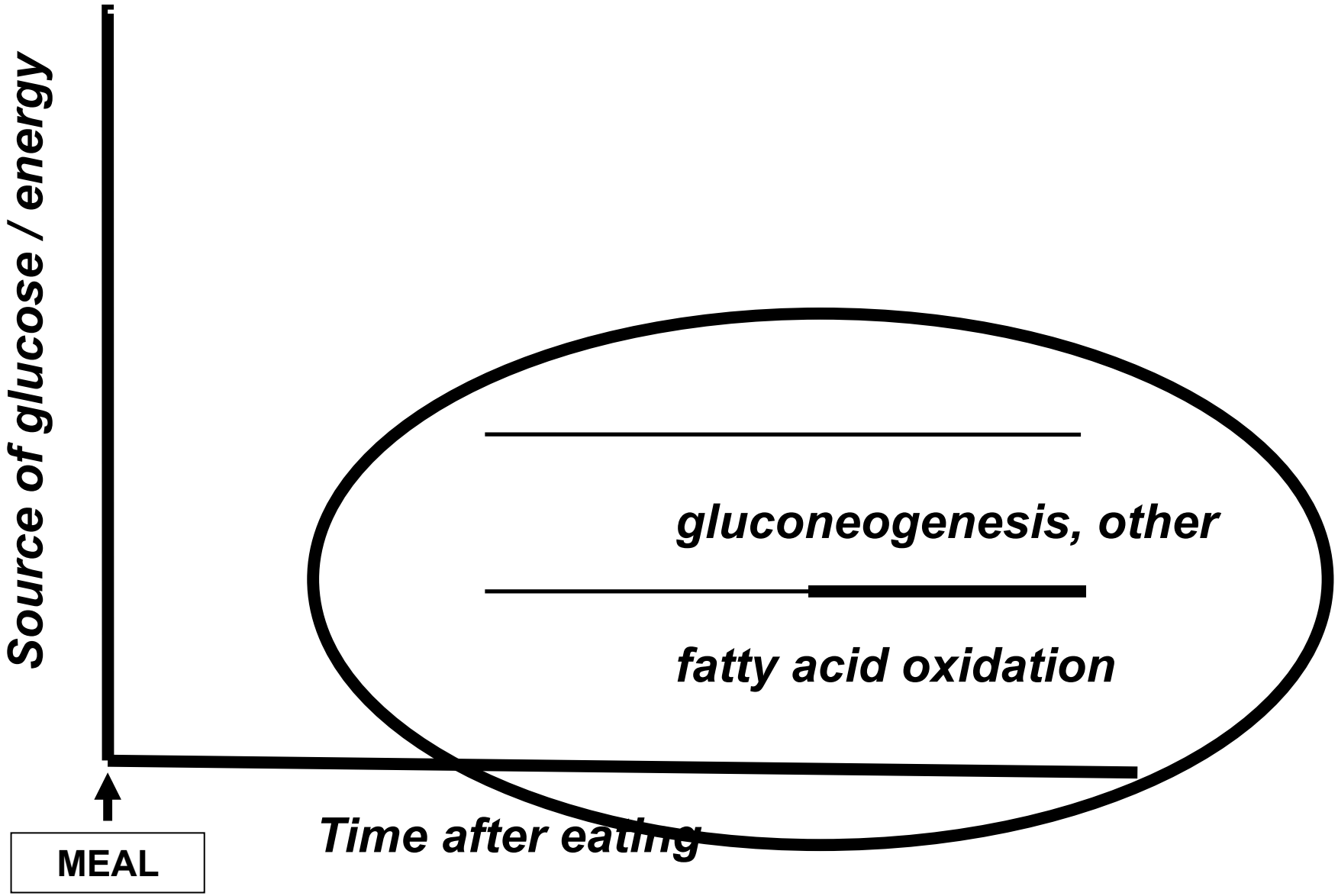
EC, with MCAD deficiency

- EC's development was appropriate.
- She was evaluated by Neurology for the possibility of seizures; an EEG was normal.

EC, with MCAD deficiency

- On one occasion, EC found lethargic, and brought to the ER:
- **Glucose = 36 mg/dL (LOW)**
- Insulin = 0.2 IU/mL (LOW)
- Cortisol = 21.9 μg/dL (HIGH)
- Free fatty acids = 2.66 mEq/dL (HIGH)
- **β-hydroxybutyrate = 0.3 mmol/L (LOW)**

KETONE BODY


Source of glucose / energy
gluconeogenesis, other
fatty acid oxidation
Time after eating
MEAL

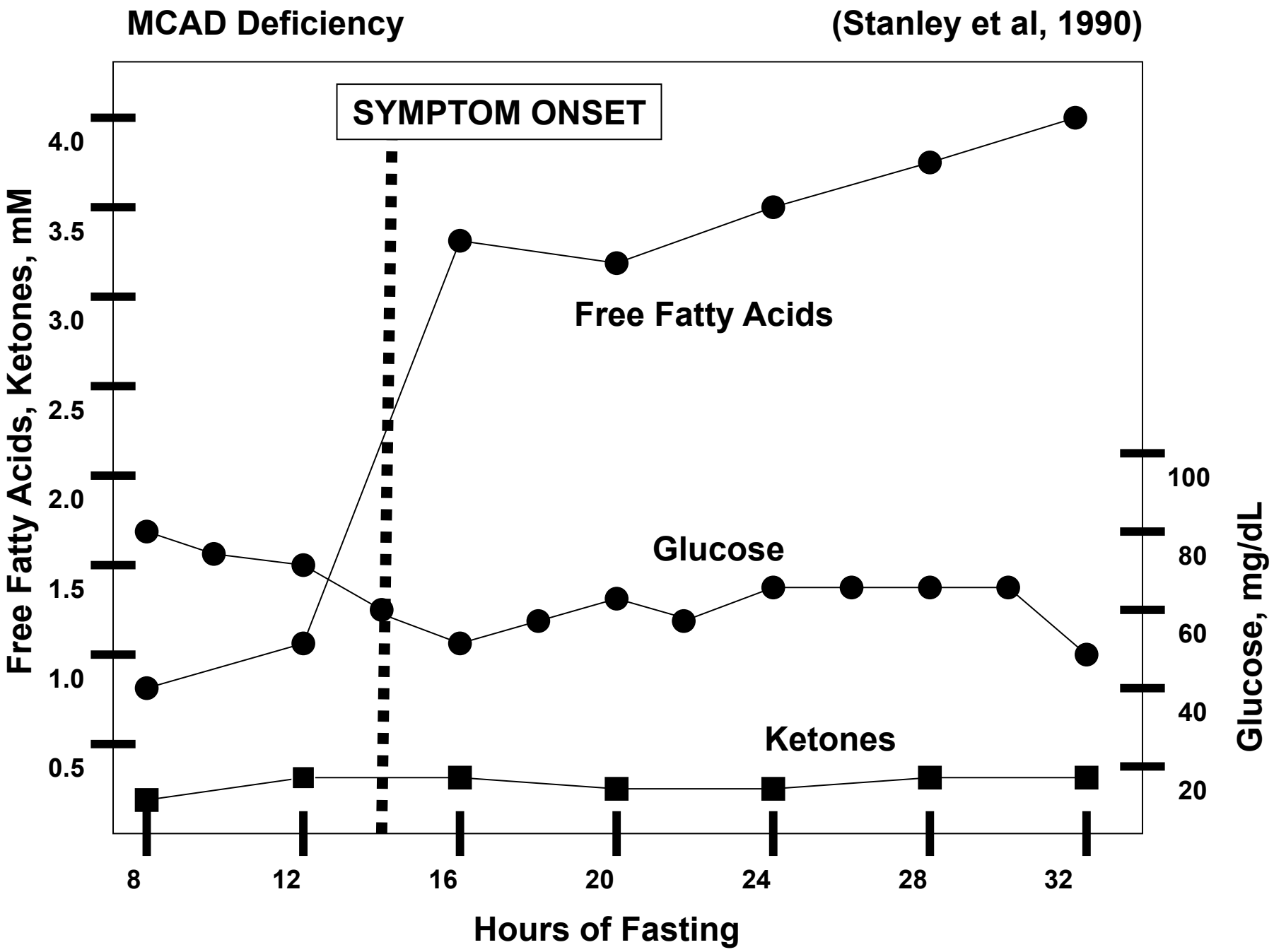
COMPONENTS OF EC's CRISIS

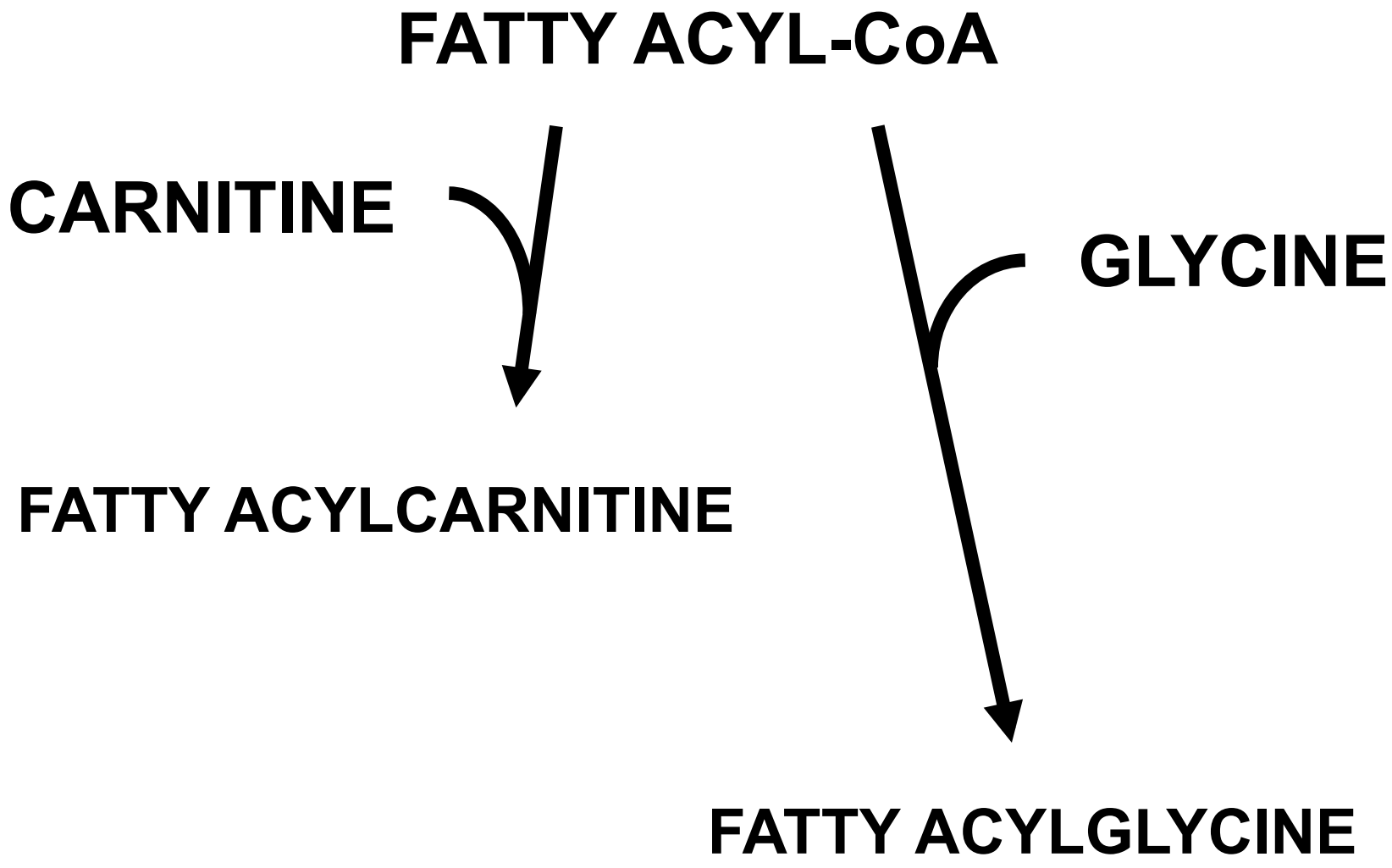
LOW ENERGY

COMPONENTS OF EC's CRISIS

BUT patients can be very sick

AND NOT BE HYPOGLYCEMIC


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


FATTY ACYL-CoA
CARNITINE
GLYCINE
FATTY ACYLCARNITINE
FATTY ACYLGLYCINE

ACYLCARNITINES in MCAD deficiency

- C6 - hexanoic acid → hexanoylcarnitine
- C8 – octanoic acid → octanoylcarnitine
- C10 – decanoic acid → decanoylcarnitine

ACYLCARNITINES in MCAD deficiency

- Long and medium chain fat can be toxic to brain cells → coma
- Fatty acids, acylcarnitines and the lack of CoA disrupt enzymes involved in glucose production, and energy production pathways
- Evidence of severe energy stress in the brain (oxidative damage)

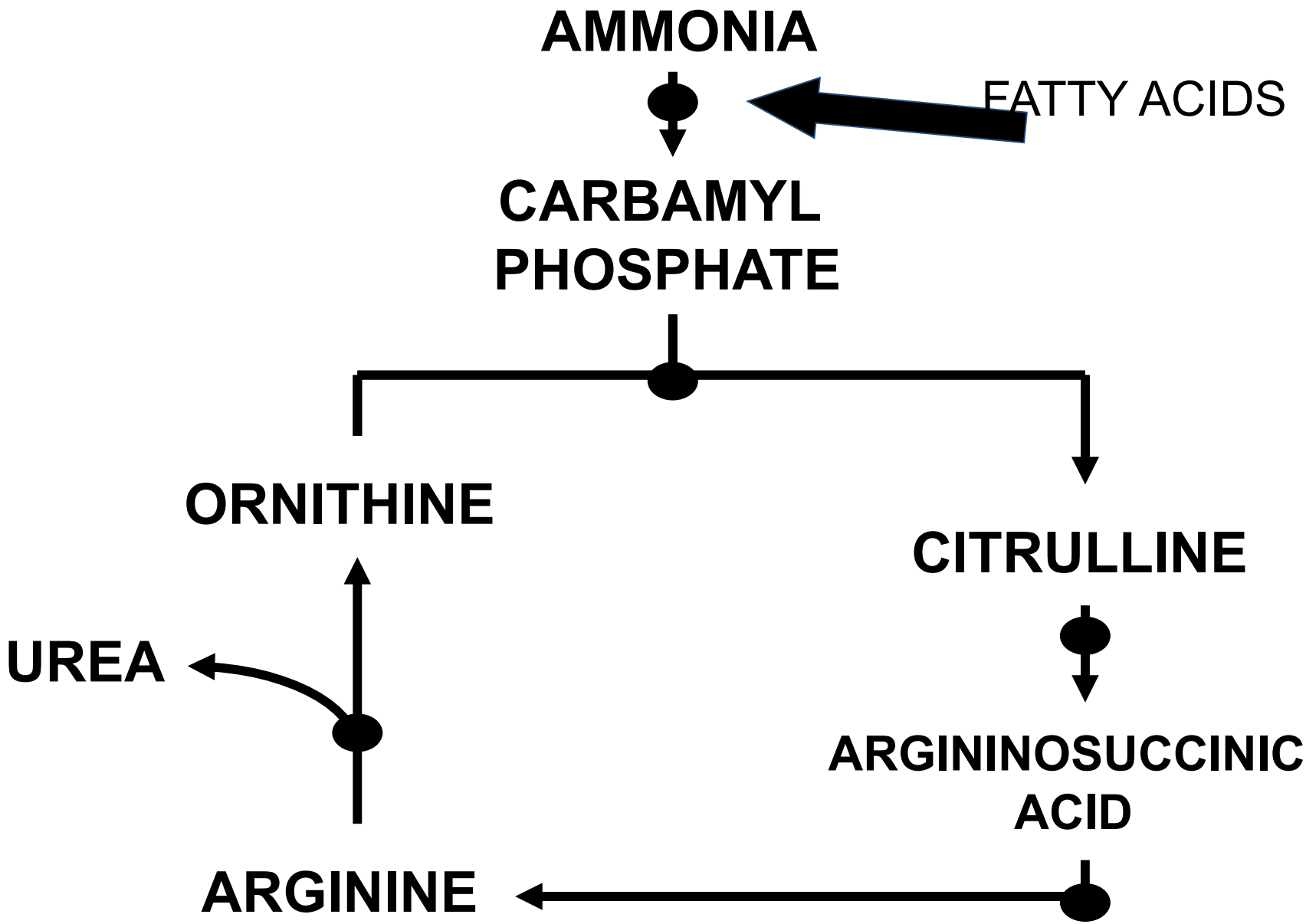
COMPONENTS OF EC's CRISIS

TOXICITY

ACYLCARNITINES in MCAD deficiency

- C6 - hexanoic acid → hexanoylcarnitine
- C8 – octanoic acid → octanoylcarnitine
- C10 – decanoic acid → decanoylcarnitine

➡ These can interfere with the metabolism of ammonia


AMMONIA
FATTY ACIDS
CARBAMYL PHOSPHATE
ORNITHINE
CITRULLINE
UREA
ARGININOSUCCINIC ACID
ARGININE

AMMONIA

- Toxic to the brain
- Accumulation causes brain swelling

COMPONENTS OF EC's CRISIS

TOXICITY

FAT DEPOSITS

fatty acids

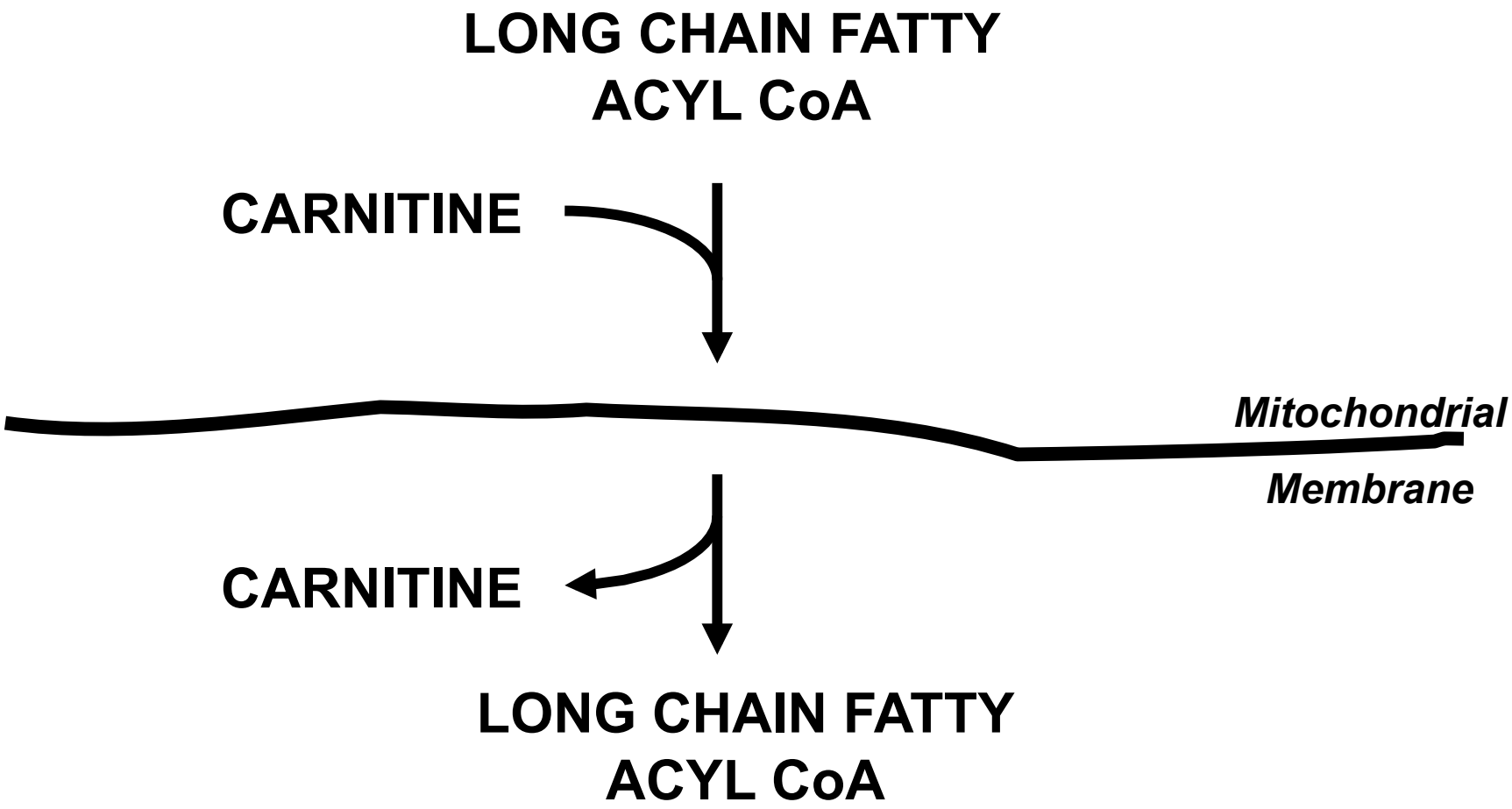
LIVER

ALSO – LIVER DISEASE

- Acylcarnitines interrupt the metabolism of fat
- Liver dysfunction – high liver enzymes
- Acute fatty liver

COMPONENTS OF EC's CRISIS

TOXICITY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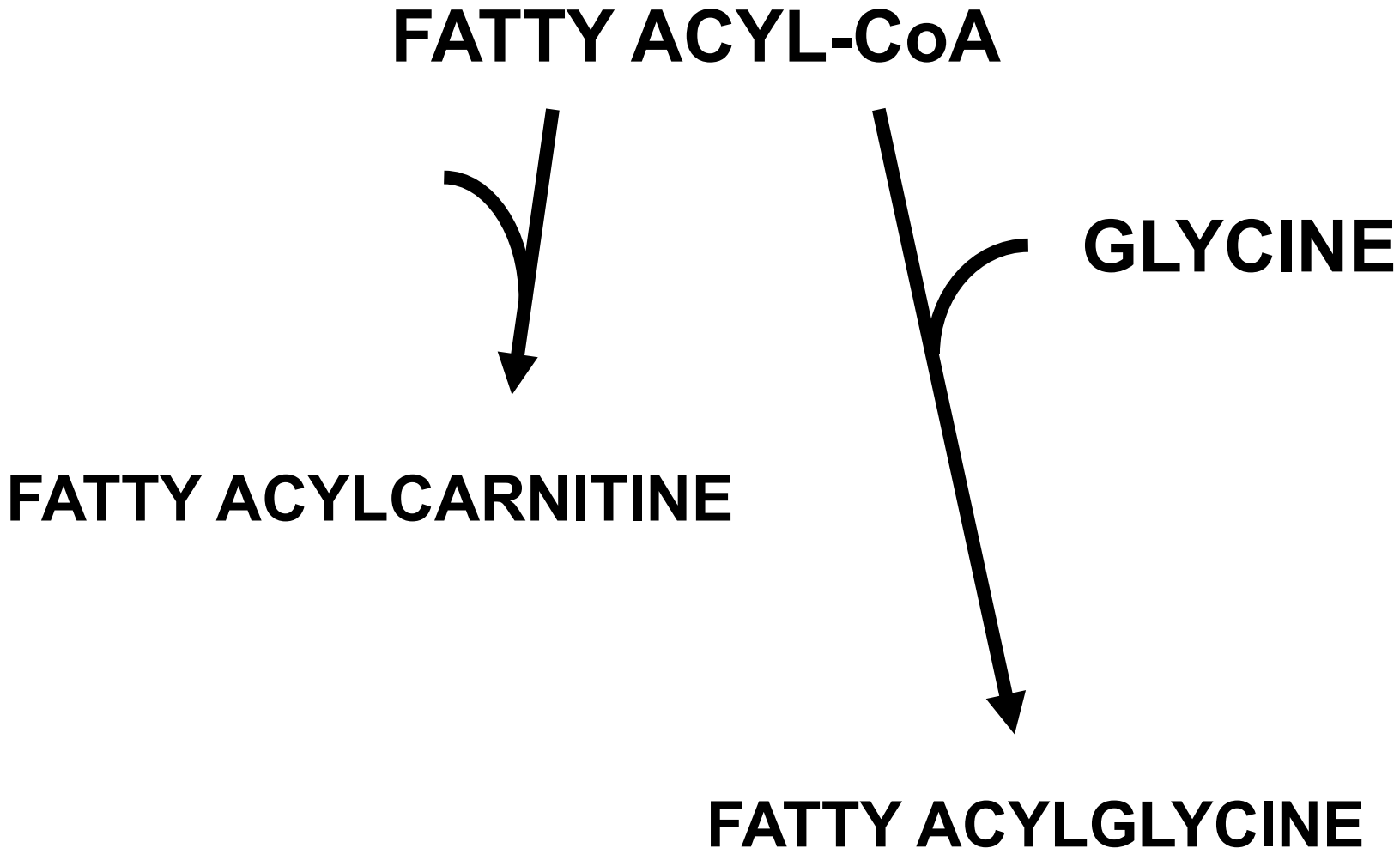

FATTY ACYL-CoA
GLYCINE
FATTY ACYLCARNITINE
FATTY ACYLGLYCINE

LOW CARNITINE

- Reduced ability to bind the toxic intermediate compounds and facilitate their excretion
- Reduced ability to liberate CoA for other important reactions
- Its degree of importance remains controversial

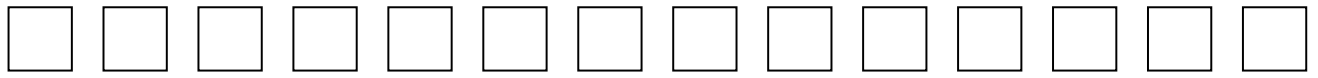
SHORT/MEDIUM CHAIN FATTY ACYL CoA

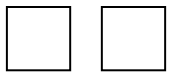
NEW KETONE BODIES

SHORT, MEDIUM CHAIN DEFECT → MANY KETONE BODIES

HAPPY MUSCLES

LONG CHAIN FATTY ACYL CoA





NEW KETONE BODY

LONG CHAIN OXIDATION DEFECT → FEW KETONE BODIES

ANGRY MUSCLES

MUSCLE DISEASE

- In long chain fatty acid oxidation defects
- Skeletal muscle –
  - muscle pain, weakness
  - muscle damage (rhabdomyolysis) → spilling into the urine (myoglobinuria)
  - severe myoglobinuria can cause acute kidney failure and heart rhythm problems
- Cardiac muscle –
  - Cardiomyopathy → heart failure

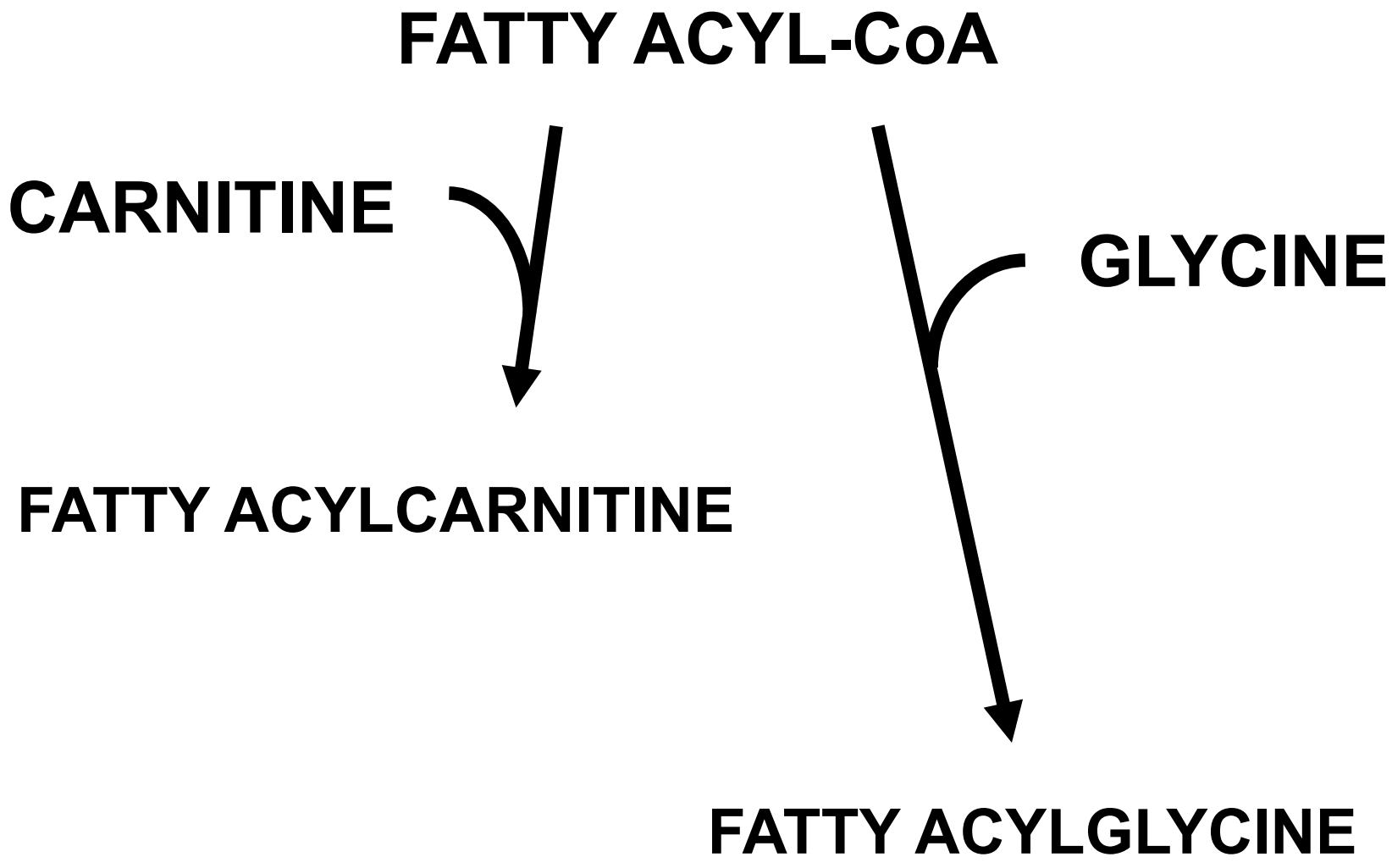
LONG CHAIN FAO CRISIS

LOW ENERGY

LONG CHAIN FAO CRISIS

TOXICITY

DIAGNOSIS


FATTY ACYL-CoA
CARNITINE
GLYCINE
FATTY ACYLCARNITINE
FATTY ACYLGLYCINE

NEWBORN SCREENING IN MASSACHUSETTS (2012)

AMINO ACID DISORDERS

PKU
[illegible]
OTC deficiency
Argininosuccinic aciduria
Arginase deficiency

Galactosemia

ORGANIC ACID DISORDERS

Maple syrup urine disease
Biotin[illegible]
Prop[illegible]
Meth[illegible]a (s)
Isova[illegible]
β-ketothiolase deficiency
Glutaric acidemia I

FATTY ACID OXIDATION DEFECTS

MCAD deficiency
[illegible]
[illegible]ef'y
[illegible]efect

OTHER DISORDERS:
Congenital hypothyroidism
Congenital adrenal hyperplasia
Congenital toxoplasmosis
Hemoglobinopathies
Cystic fibrosis

PRIMARY SCREEN

DIAGNOSIS CONFIRMATION

- DNA testing
- Enzyme or FAO function studies (usually from skin cells/fibroblasts)

MANAGEMENT

MANAGEMENT

PROVIDE ENERGY AS GLUCOSE

Why 10% Dextrose When Sick?

- “Catabolism” 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:
  $y=0.0014\ x^3 – 0.214\ x^2 + 10.411\ x – 9.084$
  y=glucose production rate (mg/min)
  x=body weight (kg)

Example: 10 kg child

- **$y=0.0014\ x^3 – 0.214\ x^2 + 10.411\ x – 9.084$**
  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 1.25x maintenance provides 87 mg/min (or 8.7 mg/kg/min)

PROVIDING GLUCOSE

- Provides energy:
  - to all organs
- Suppresses catabolism:
  - production of the toxic compounds
  - reduces production of ammonia
  - clears the fat accumulation in the liver and the liver dysfunction
  - helps limit muscle damage

MEDIUM CHAIN FAT IN LONG CHAIN FAO

- Bypasses the enzyme block and enables fat to be used as a source of energy

PROVIDE CARNITINE