Induction To Todays Topic

Can Any One Guess Todays Topic Of Teaching and Learning?

Biochemistry Of Starvation

Specific Learning Objectives

- What is Starvation?
- Which Conditions develop Starvation?
- What are Stages/Phases of Starvation?
- Which Hormones play imp role in starvation?
- Factors of Biochemical adaptation in Starvation
- How Organs adapt to Starvation?
- What are Consequences of Starvation?

What Is Starvation?

- Starvation is **complete stoppage of eating food** by a human body.

What Is Total Starvation?

- Total starvation is **complete stoppage of Food and Water**.

Conditions Developing Starvation

Conditions Developing Starvation

- **Food Scarcity**

(Natural Calamities , Draughts Floods and ,Famines)

- **Extreme Poverty**
- **Lost in Sea routes for long durations**
- **Clinical Conditions:** Major Surgeries, Severe Burns
- **Desire to loose rapid weight**
- **Political Issues**: Hunger Strikes

During Starvation Body is under Metabolic Stress

Features Of Starved Body

- **No entry of exogenous food nutrients**
- **Starved body is deprived of:**
  - **Calories** (Carbs and Lipids)
  - **Building blocks** (Proteins)
  - **Growth Factors**(Vitamins and Minerals)
  - **Protectors** (Antioxidants)

Biochemical Adaptations During Starvation

Important Factors Responsible For Adaptation In Starvation

- Content Of **Endogenous Stores**
- **Health** of Associated **Organs and System**
- Associated Metabolic Processes involved with:
  - **Hormones**
  - **Enzymes**
  - **Coenzymes**

- **During Starvation** a body is in an **emergency/critical condition**
  - Has to face Biochemical Challenge
  - Has to get adapted
  - Manage with endogenous metabolite reserve stores
  - Communicate and Cooperate through hormones
  - Overcome state by biochemical alterations
  - Try Survive as per condition

Survival Period During Starvation

- **Survival period** during Starvation depends upon **:**
- **Reserve TAG stores of Adiposecytes:**

  –**More content of TAG in Adiposecytes**

  –**More is duration of survival in Starvation and vice a versa.**

Length Of Survival In Starvation

- **Due to deprivation of only Food:**
  - **3 to 4 Weeks**
  - **Longer up to 65 days**
- **Deprivation of water alone then survival is only for few days**
  - **Less than a week**

Effects Of Starvation

OR

Human Body Adaptation In Starvation

Biochemical Alterations In Starvation

Different Modes

To Study Biochemical Adaptations

During Starvation Phases

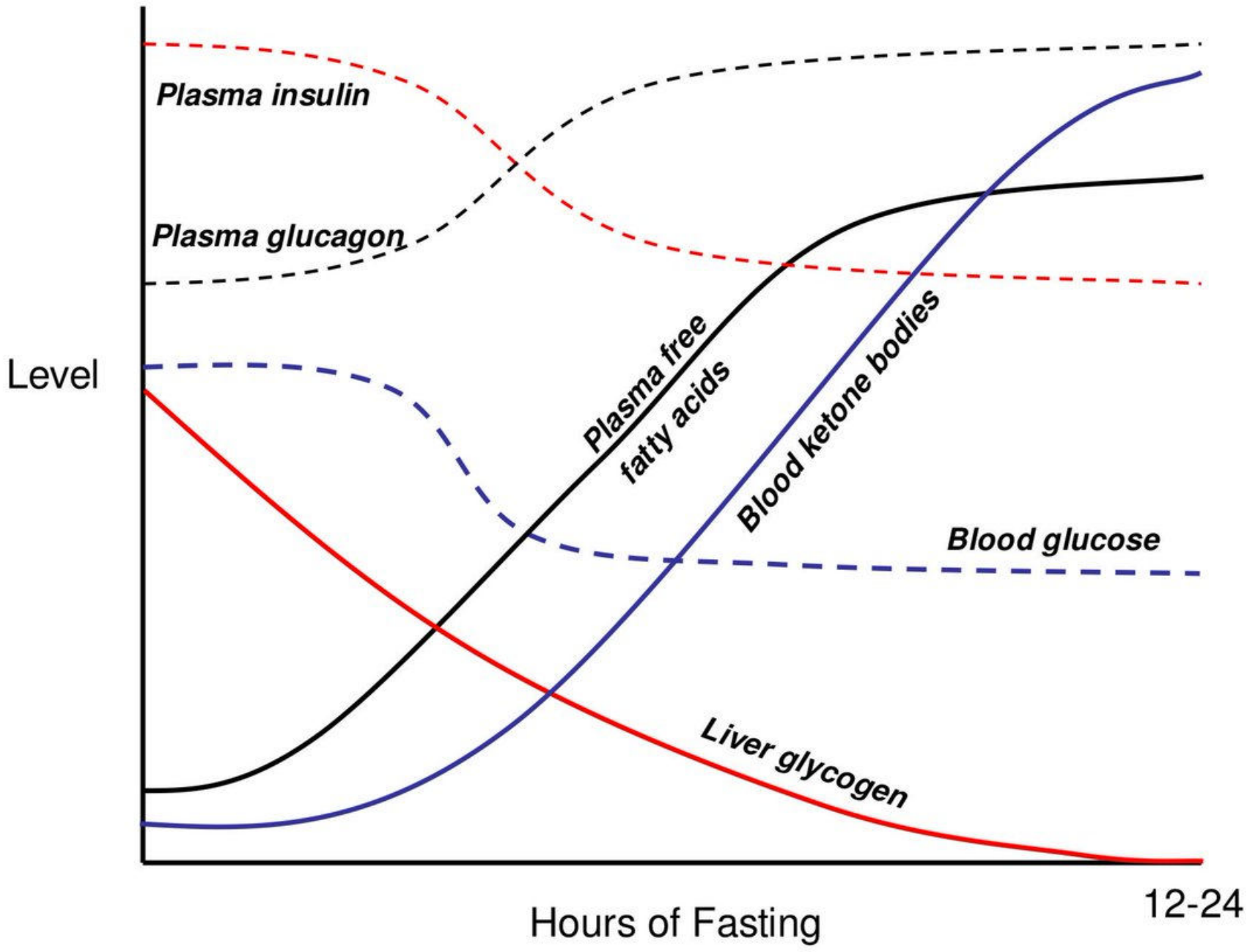
Study Of Biochemistry Of Starvation
With Respect To

- Stages
- Metabolism
- Organs

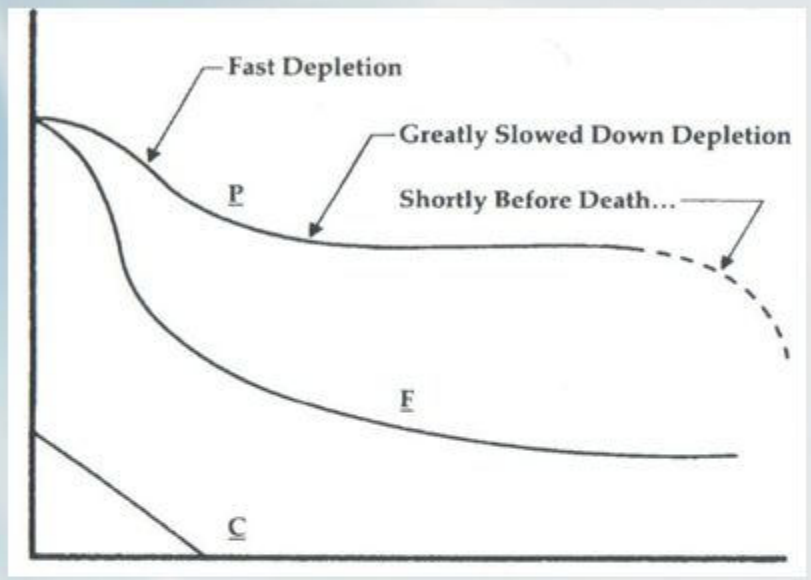
Alternative Adaptations
In Different
Metabolic Processes
During Starvation

Occurrence Of Four Stages During Starvation OR Metabolic Alterations During Starvation

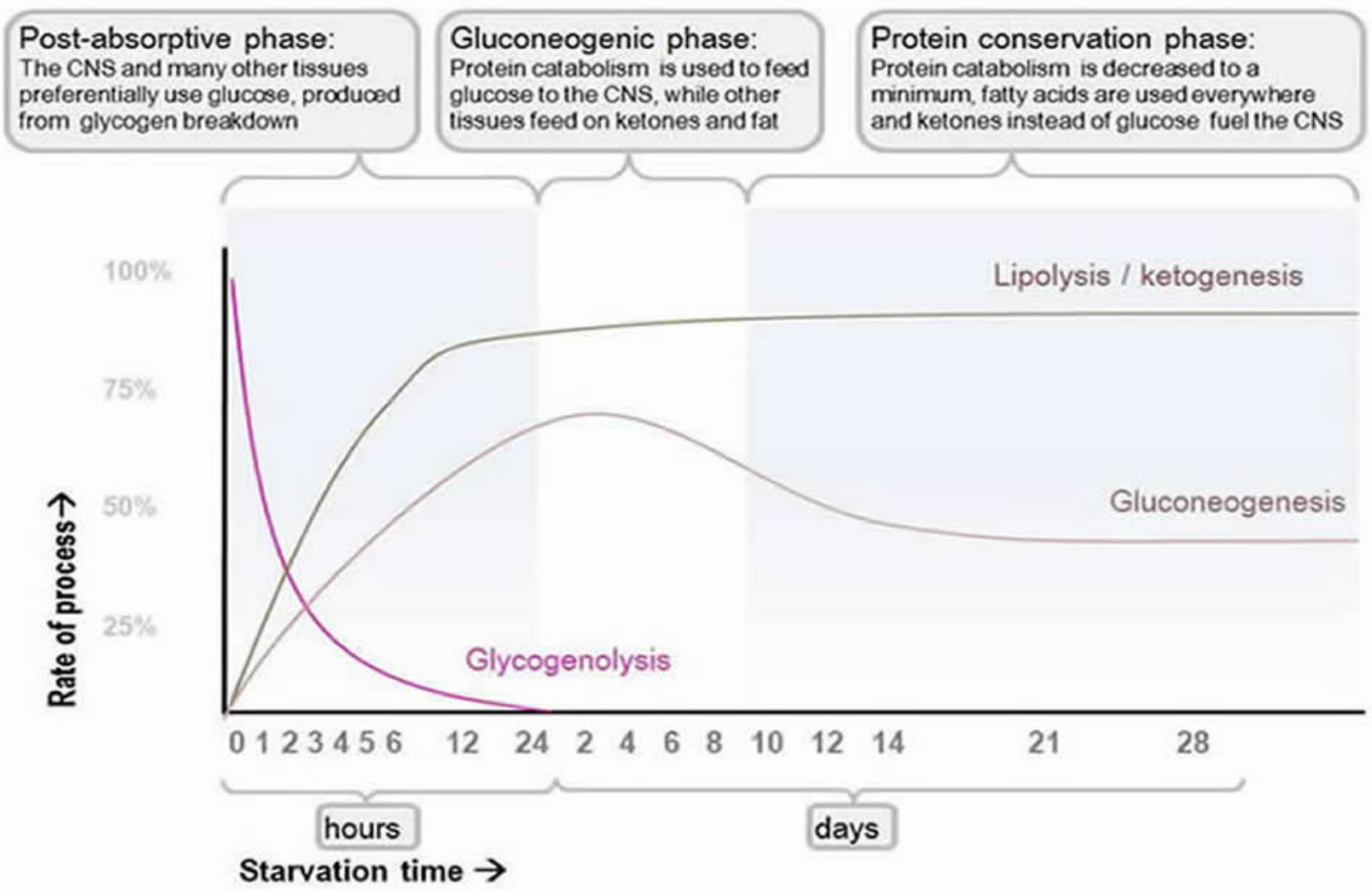
Starvation Stages	Metabolic Alterations
1	Increased Glycogenolysis
2	Proteolysis Glucose Alanine Cycle Increased Gluconeogenesis
3	Increased Lipolysis Fatty acid Beta Oxidation(Incomplete
4	Increased Ketogenesis Ketosis



Stages of Starvation (Fasting)



1. Carbohydrates go immediately.
2. Fats go next.
3. Protein-The medical research states that protein undergoes three phases of depletion during starvation.
   - Phase 1: There is a "fast depletion of protein at first"
   - Phase 2: then a "greatly slowed down depletion"
   - Phase 3: protein falls off "just shortly before death".



METABOLIC CHANGES IN STARVATION

- Early ,Intermediate, Advance stages of starvation
- Early stage (2 days)
  - Glycogenolysis and gluconeogenesis are imp source of blood glucose.
  - Energy from alternate source (β oxdn FA, KB).
- Intermediate stage (24 days)
  - glycogen stores mostly depleted not serve as source blood glucose.
  - FA ,KB supplied to heart, kidney ,muscles.
- Advanced stage (>24 days)
  - KB supplies to heart, kidney ,muscles is decreased , limited to brain only.
  - Heart, kidney ,muscles on FA as main source.
  - Gluconeogenesis will enhanced due to increased activity of enzymes pyruvate carboxylase, fructose 1,6 bisphosphates,

2. Early Fasting State

Glucagon:

-> signals starved state

-> mobilizes glycogen stores (break down)

-> inhibits glycogen synthesis

-> main target organ is liver

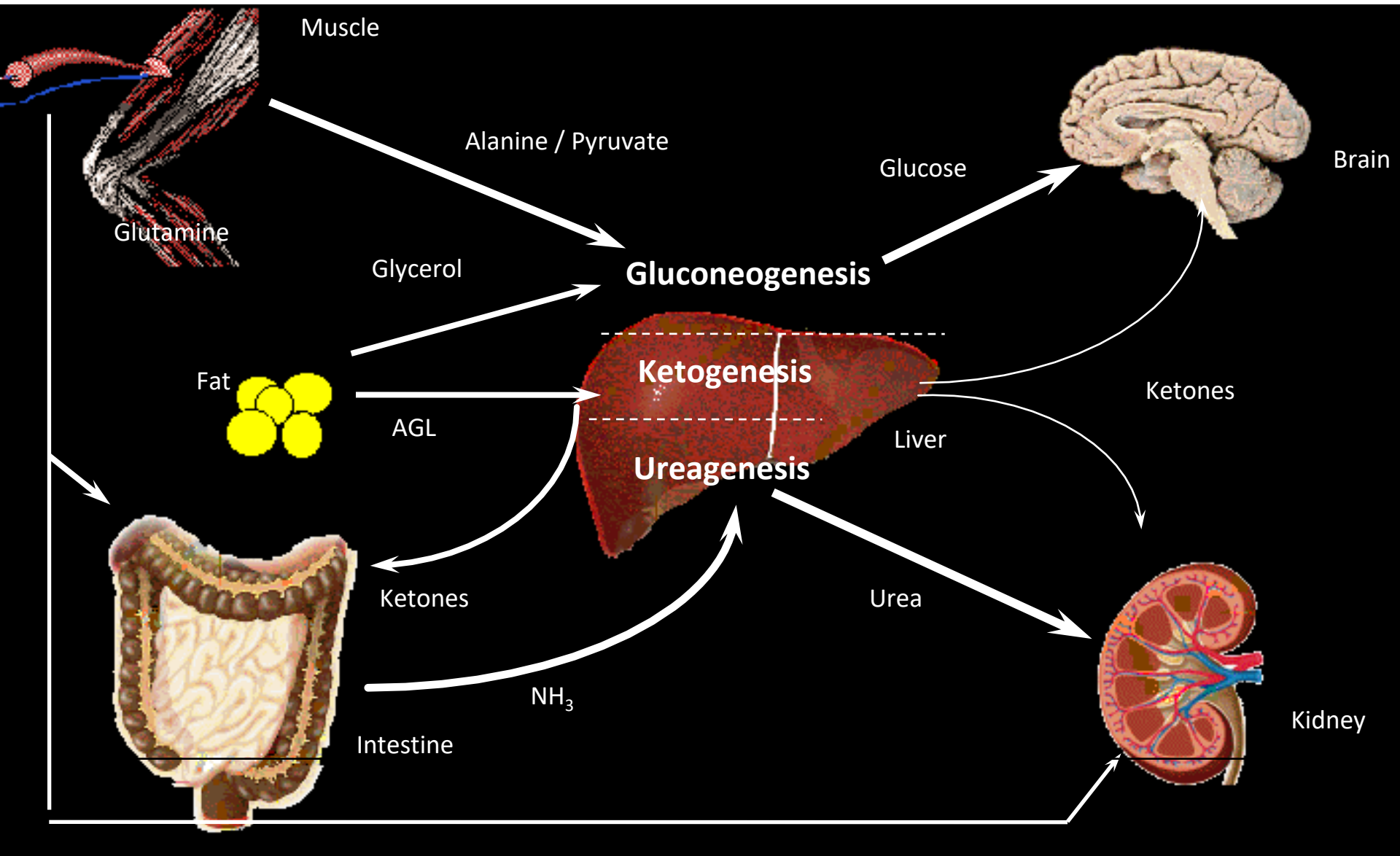
-> inhibits fatty acid synthesis

-> stimulates gluconeogenesis in liver

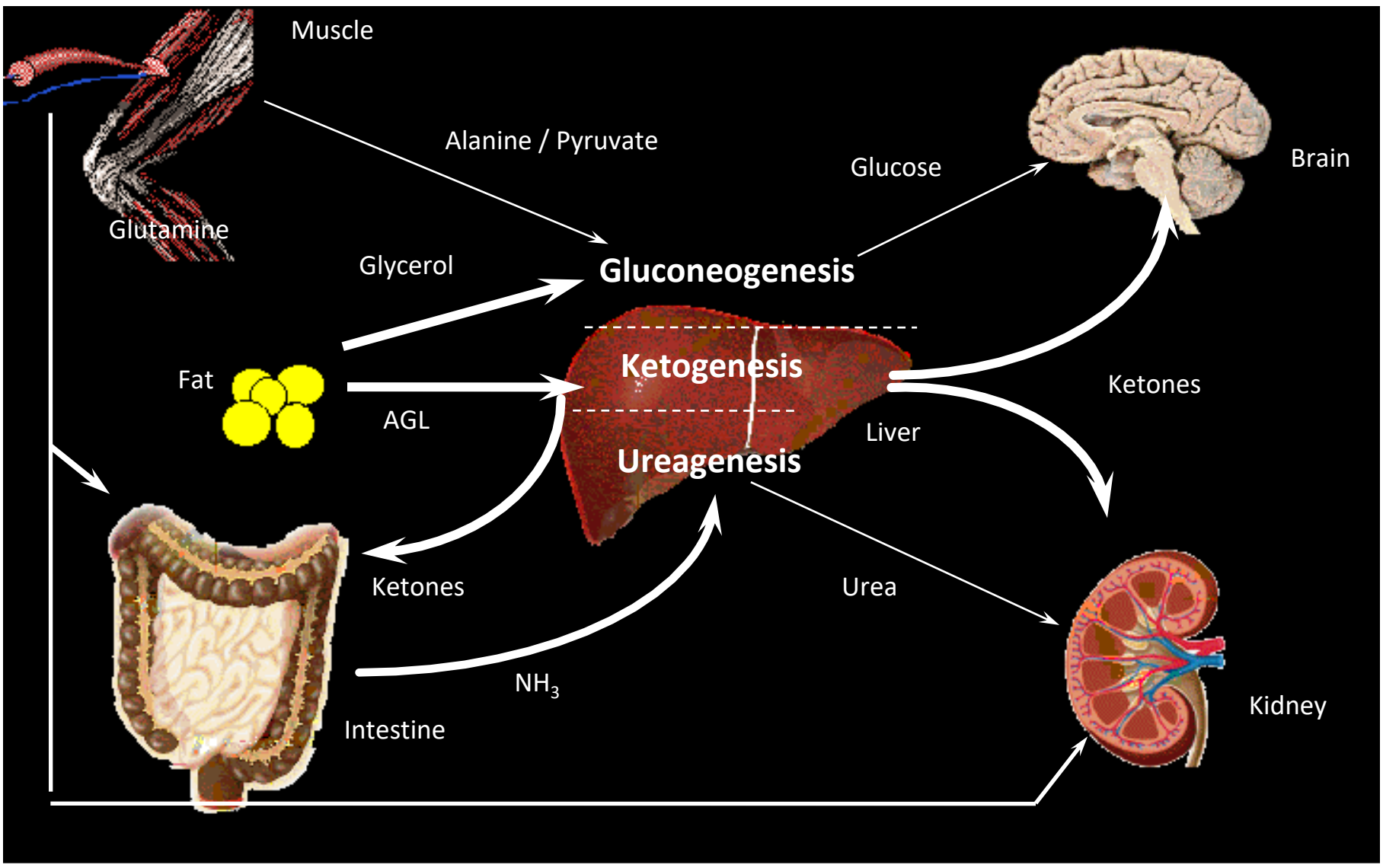
-> large amount of glucose in liver released to blood stream -> maintain blood-glucose level

Muscle + Liver use fatty acids as fuel when blood-glucose level drops

Fasting – Early Stage



Fasting – Late Stage



Role Of Hormones In Starvation

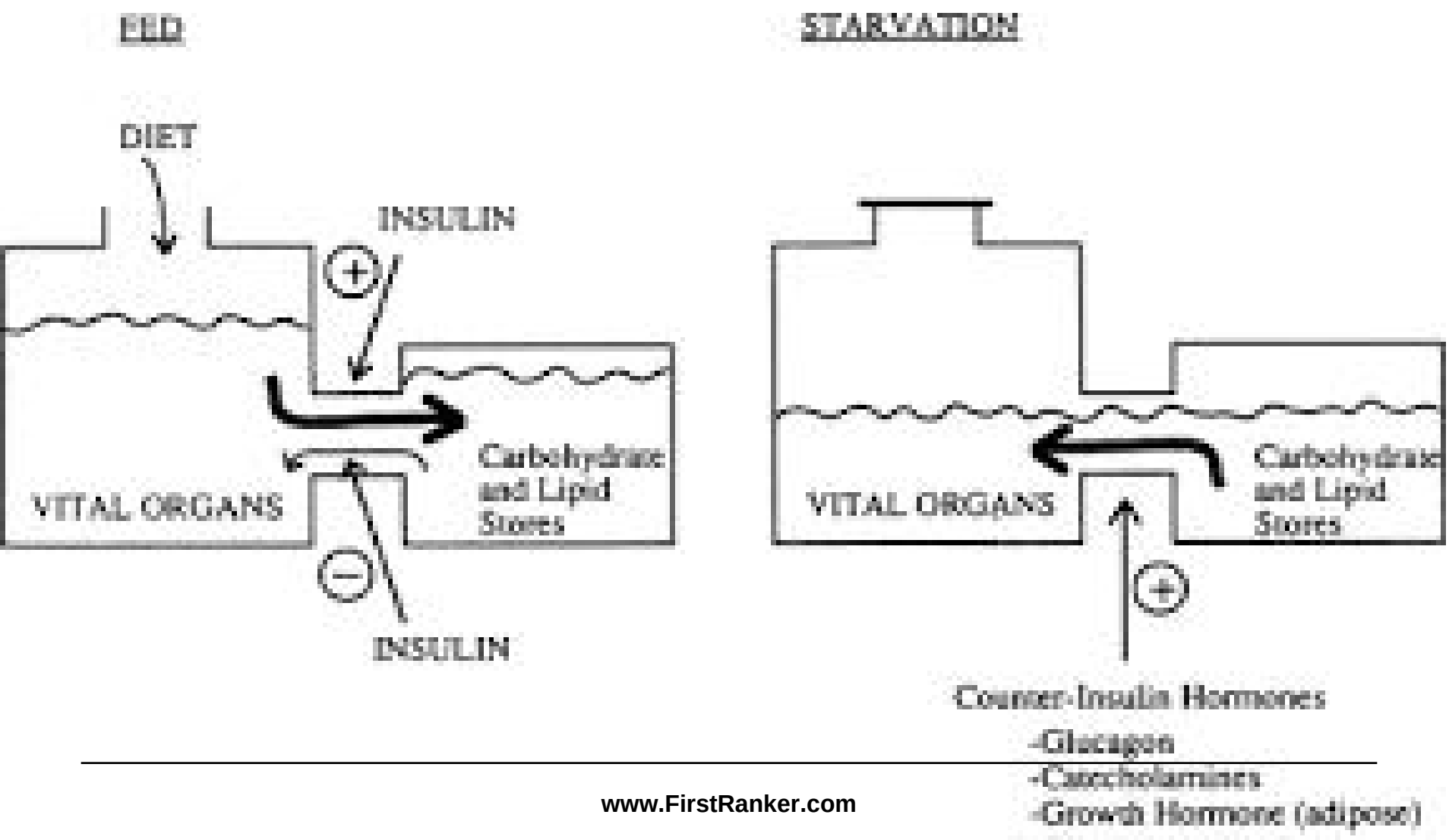
- When **food is in Short supply**
- Metabolic activity decreases to spare fuel.
- **Conservation of energy** is basic adaptive response to calorie reduction

- **Hormones influences an utilization of endogenous reserve stores and**
- **Supply fuels to body organs during starvation phase.**

Hormonal Alterations In Starvation

- **Insulin secretion decreased**
- **Glucagon and Epinephrine increased**

Metabolic Role Of Hormones



Hormonal Influences In Starvation

Hormone	Source	Change in Secretion
Norepinephrine	Sympathetic Nervous System	↓↓↓
Norepinephrine	Adrenal Gland	↑
Epinephrine	Adrenal Gland	↑
Thyroid Hormone T4	Thyroid Gland (changes to T3 peripherally)	↓↓↓

- **Norepinephrine and T3 participate to**

- **Decrease metabolic activity** when calorie intake decreases.

- Thus biochemical alterations during Starvation are **influenced by hormonal actions.**
- **Glucagon and Epinephrine** in starvation act upon target organs
- **Stimulate metabolic pathways** which **supply fuels**
- **Improve survival phase during Starvation.**

Metabolic Alterations In Starvation

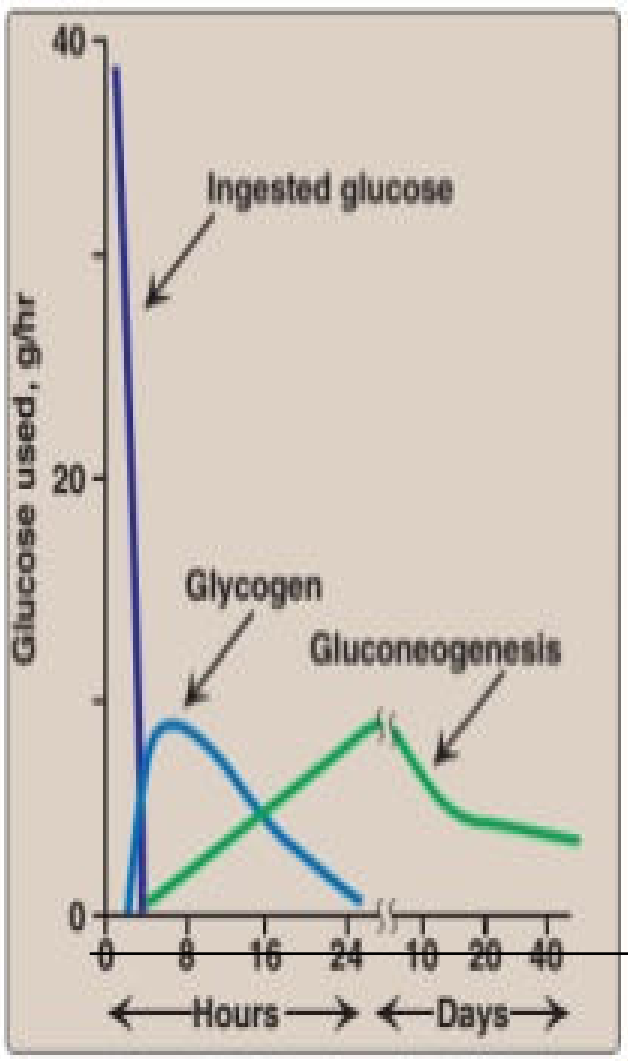
Biochemical Alterations Of Carbohydrate Metabolism During Starvation Phase

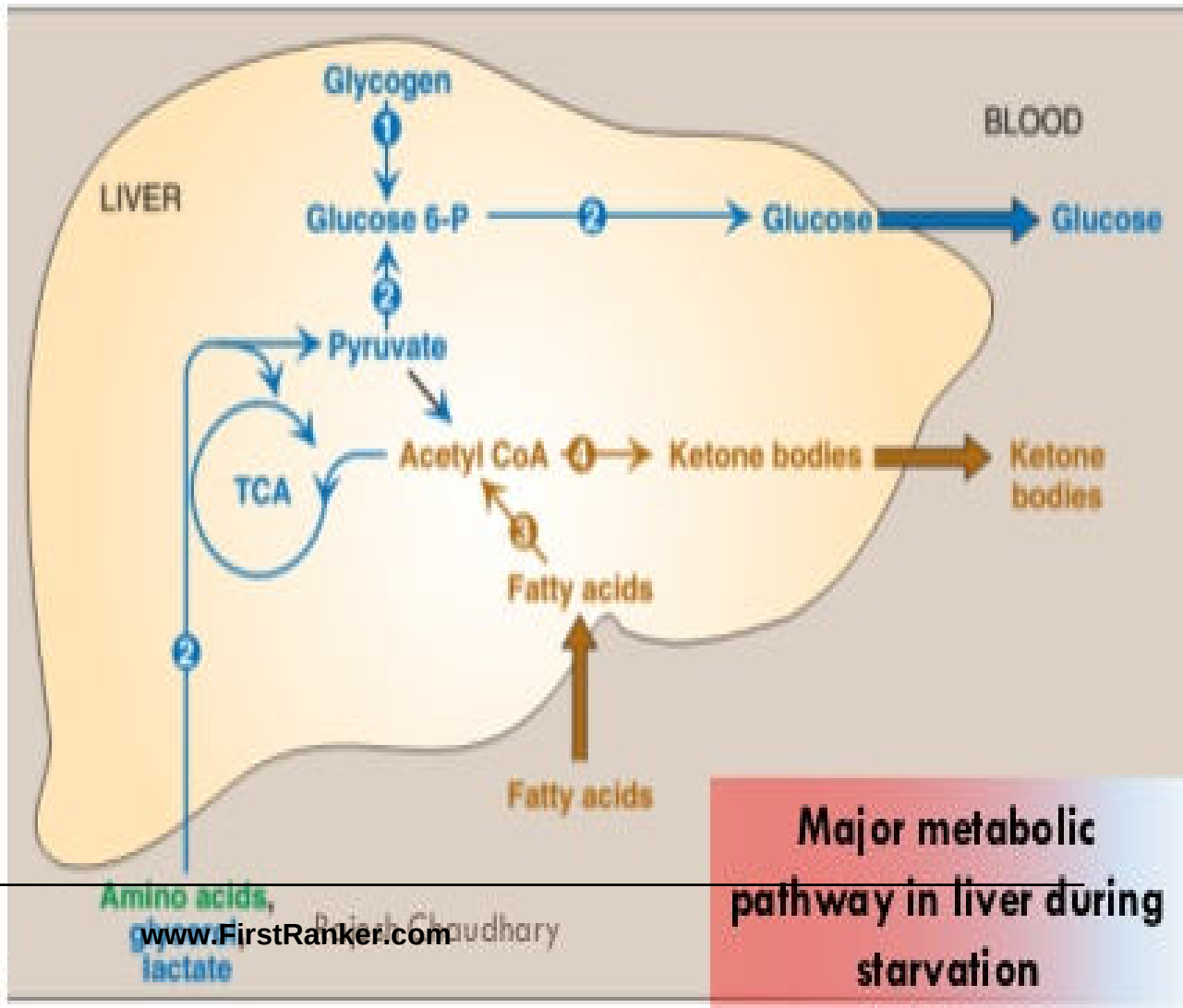
Carbohydrate Metabolism In Liver During Starvation Phase

- **Glycogenolysis Increased**
- Glycogenesis Decreased
- **Glucose Alanine Cycle increased**
- **Gluconeogenesis Increased**
- Glycolysis Decreased
- TCA operation Decreased
- HMP Shunt Decreased
- **Blood Glucose level Decreases** (later stages)
- **Cellular Glucose Deprivation** (In Muscle Cells)

- **PDH a Multi Enzyme Complex** is **inhibited during Starvation**

Liver in fasting (Carbohydrate metabolism)





Major metabolic pathway in liver during starvation

Alterations In Protein Metabolism During Starvation

Proteins Serve as Calorific During Starvation

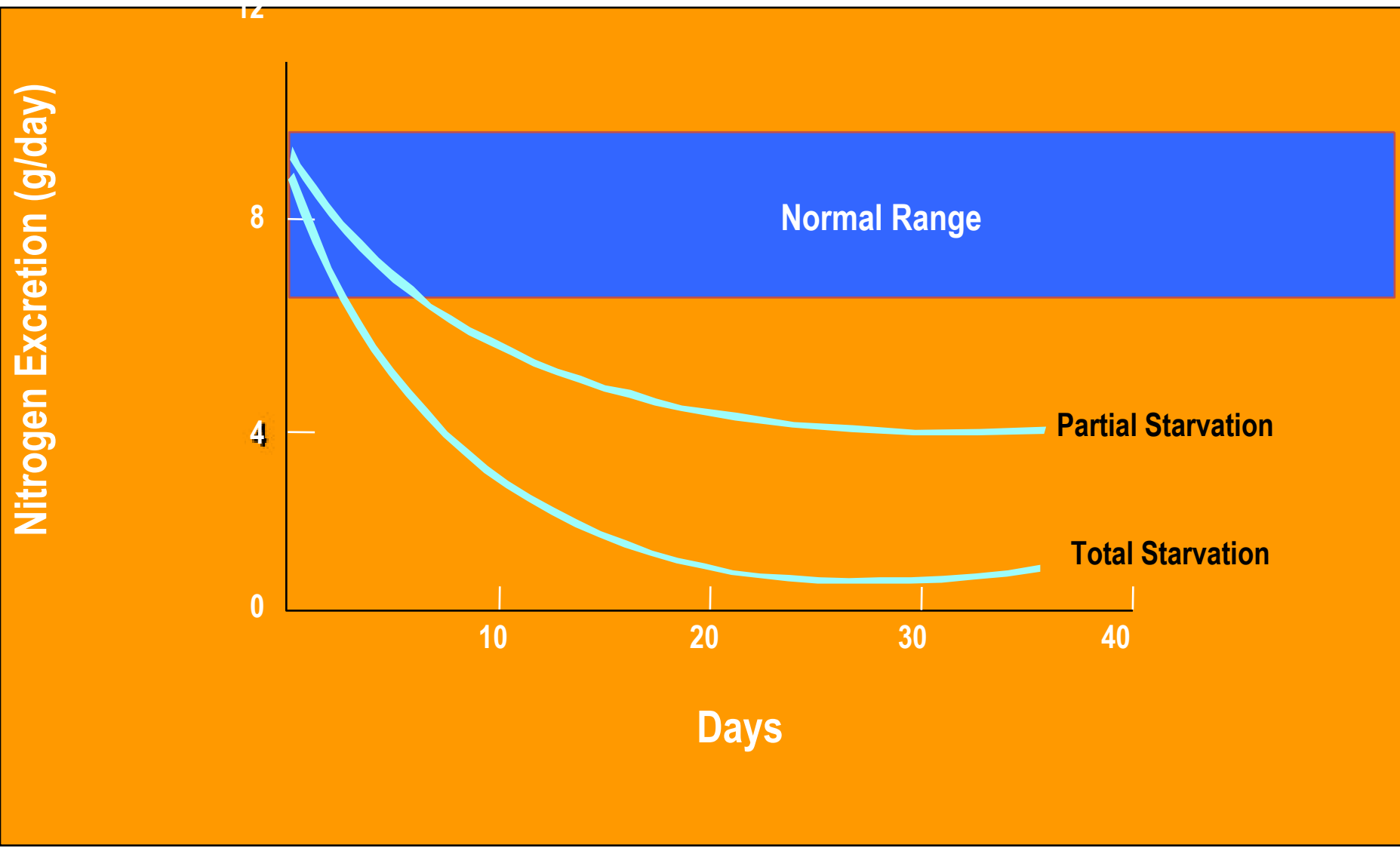
- Muscle Proteins are catabolized to provide carbon skeleton for **Liver Gluconeogenesis**
- Liver Gluconeogenesis increased via **Glucose Alanine cycle regulates blood Glucose levels**
- Glucose produced initially via Gluconeogenesis to **Brain and Erythrocytes**

Protein Metabolism During Starvation

- **As Glucose levels lowers in blood**
- **Catabolism** Of **Muscle Proteins increased**
- **Transdeamination** reaction of Amino acids is **increased**
- **To release Glucogenic amino acids**
- **Glucose Alanine Cycle elevates**

- Ammonia Detoxification and **Urea production increased initially** and **decreased as Starvation phase prolongs**.
- Body is in **negative Nitrogen Balance.**
- Concentration of **Functional Proteins Decreases**.

Nitrogen Excretion in Starvation



Glucose Nitrogen Ratio Increased In Starvation

⑦ GLUCOSE - NITROGEN RATIO (GN - Ratio)

OR

DEXTROSE - NITROGEN RATIO (DN - ratio)

GN ratio "is" - Ratio of Glucose (Dextrose) to Urea Nitrogen in Urine From Proteins.

$$\text{GN ratio} = \frac{\text{Glucose in gm}}{\text{Urea Nitrogen in Urine in gm}} = \frac{3.65 \text{ gm of Glucose}}{1 \text{ gm of Urea Nitrogen From Proteins}}$$

GN ratio = 3.65

Since Proteins contains 16 % Nitrogen

What is the amount of Glucose produced by 100 gm of Proteins?

$$3.65 = \frac{G}{16}$$

GN ratio indicates the rate of Muscle protein breakdown & Gluconeogenesis during Starvation phase.

∴ G = 58.4 % of Protein is Glucogenic.

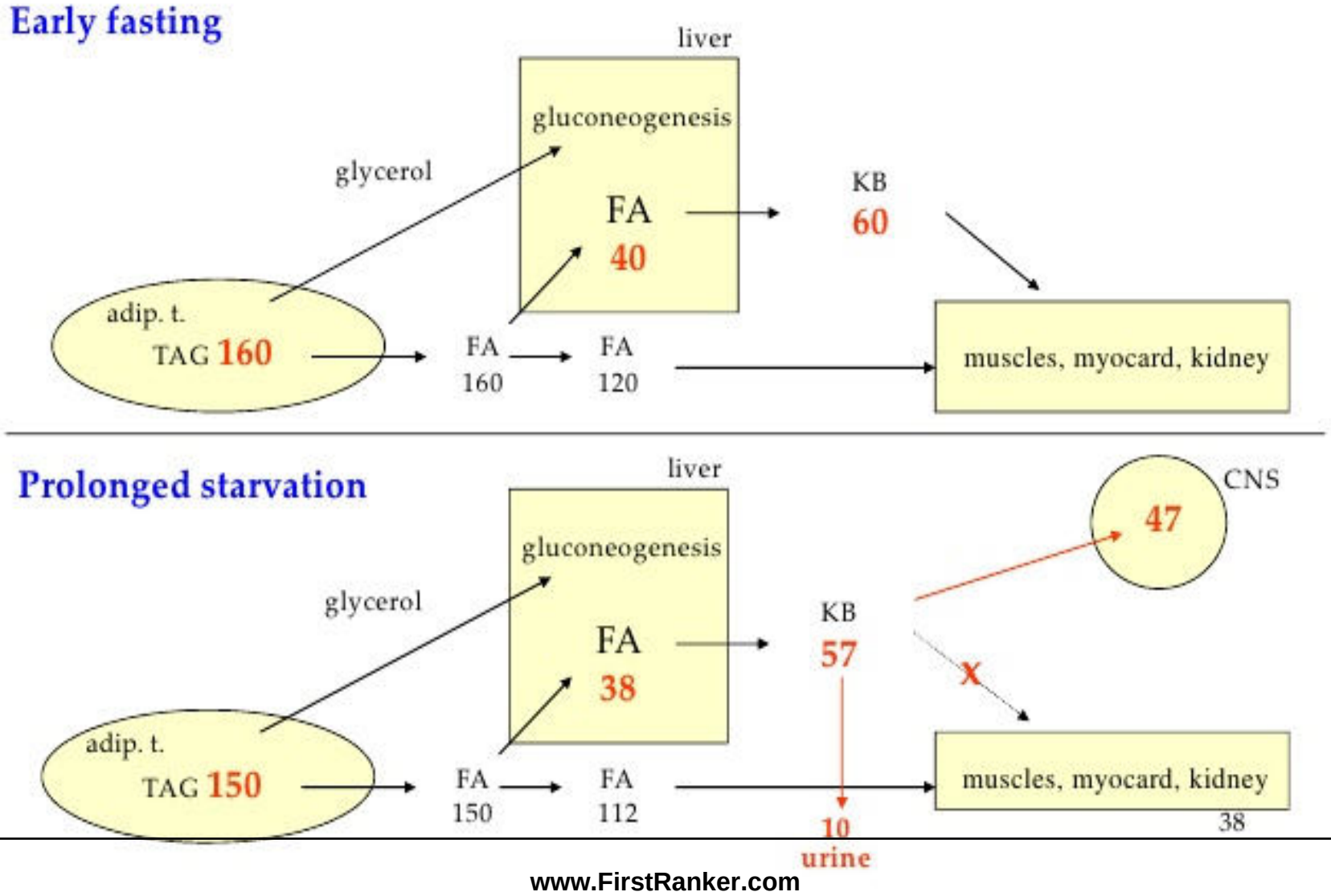
GN RATIO ↑ed in STARVATION
Diabetes Mellitus
CANCER
HYPERTHYROIDISM.

Biochemical Alterations of Lipid Metabolism In Starvation

Lipid Metabolism During Starvation

- **Lipolysis is Increased**
- **Mobilization of Free Fatty acids increased**
- **Beta oxidation of Fatty acids increased**
- **Incomplete Fatty acid Oxidation increased**
- **Ketogenesis Increased**
- **Ketolysis Decreased**
- **Ketosis Noted** (Ketoacidosis)-**Rotheras Test +ve**
- **Lipogenesis is Decreased**

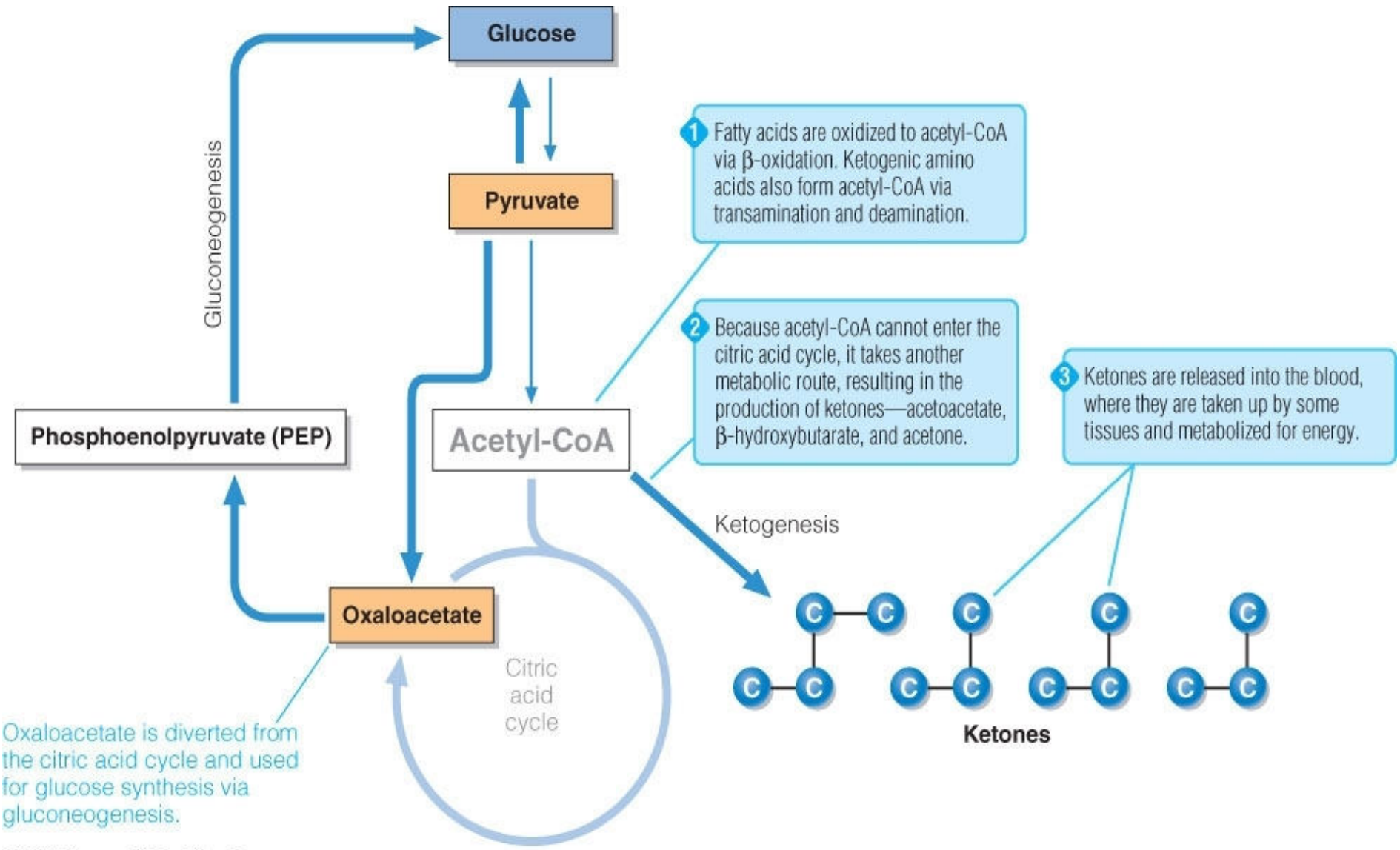
Metabolic turn-over of lipids in fasting (g/d)



- **Enzyme Acetyl Carboxylase** is **inhibited during Starvation**

Levels Of Ketone Bodies Increases As Starvation Phase Prolongs

Increased Ketogenesis In Starvation



What Happens? When Ketone body production Exceeds than the Ketone body Utilization?

– When Prolonged Starvation ?

- Cellular Glucose deprivations occurs
- Glycogen stores depletes within 24 hrs of fasting
- Fat burns under flame of Carbohydrates
- Fatty acid are incompletely oxidized
- Acetyl-CoA of fatty acid oxidation is metabolized to ketone bodies and mobilized out of Hepatocytes
- Ketogenesis increased Ketolysis decreased
- Leads to Ketosis-Ketonemia and Ketonuria

Prolonged Starvation Leads to

- **Ketosis (Ketonemia and Ketonuria)**
  - **High levels of Ketone Bodies in blood and urine**
- **Ketoacidosis**
  - **Severe Ketosis**
  - **Lowered blood pH**
  - **Nausea ,Acetone breath**
  - **Coma, Death**

–3 days starvation

[Ketone Bodies]=3mM

–3 weeks starvation

[Ketone Bodies]=7mM

Cure For Ketosis

- Ketosis Cured by **infusion of Glucose**.

III. Skeletal muscle in starvation

A- CHO metabolism

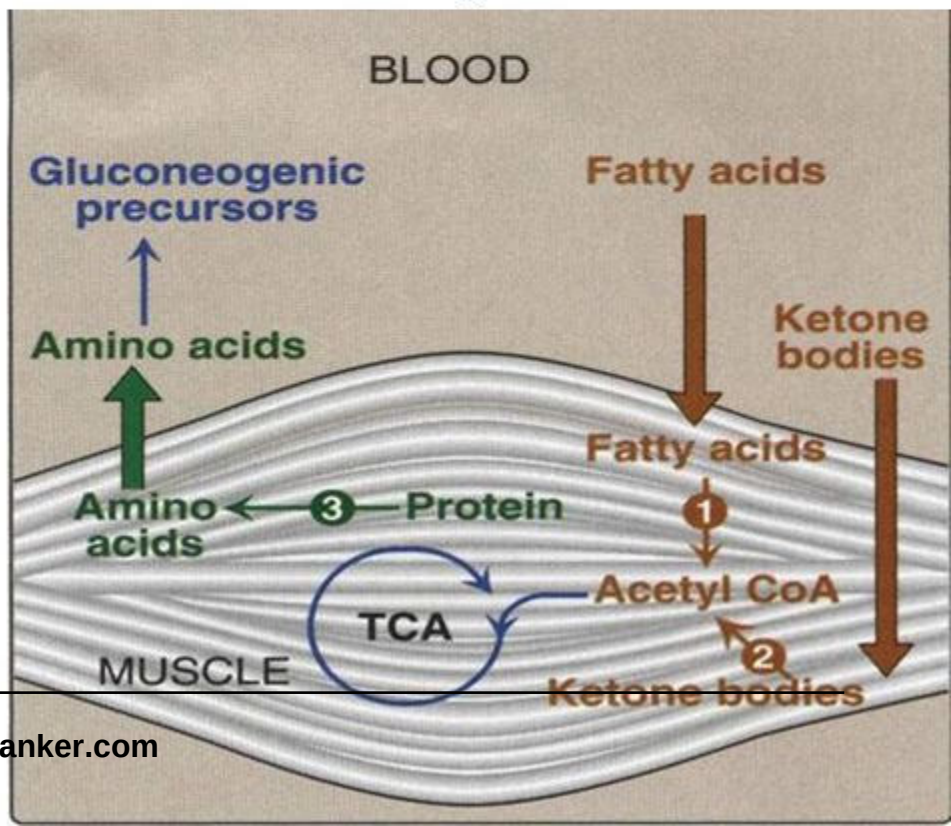
low insulin ➔ decrease uptake of glucose by skeletal muscle ➔ glucose metabolism is decreased.

B- Lipid metabolism

During the first two weeks of starvation muscle uses fatty acids from adipose tissue and ketone bodies as fuel. After three weeks muscle decrease utilization of ketone bodies and use only fatty acids ➔ increase circulating ketone bodies.

C- Protein metabolism

During the first few days of starvation rapid degradation of muscle protein providing a.a for gluconeogenesis.
After several weeks of starvation, the rate of muscle protein degradation decrease ➔ a decline in need for glucose as fuel for brain.



During Starvation Alterations Occur In Water and Electrolyte And Acid Base Balance

- **Reduction in Body Water**
- **Reduction of Potassium ions**
- **Acidic blood pH** due to increased Ketone bodies

- **On prolonged phase of Starvation there results**

- **Severe dehydration and Acid Base imbalance**

Starvation Alters BMR

- **BMR is first affected in starvation**

- **In starvation metabolism decreases**

- During starvation **BMR is Decreased**

Pathophysiology: Starvation State

- Goal: spare body protein
- Fat stores → main energy source
- The shift to fat breakdown releases large amounts of glycerol
  - Assure a continued supply of glucose as fuel for the brain
- Eventually ketosis occurs
  - Ketone bodies are delivered to skeletal muscle, heart, and brain
- Survival time
  - 3 months
- When the fat reserves are depleted the body uses essential protein
  - Loss of liver and muscle function and eventually death

Gropper, S. S., Smith, J. L., & Groff, J. L. (2009).

Biochemical Adaptations
By Organs
During Starvation Phase

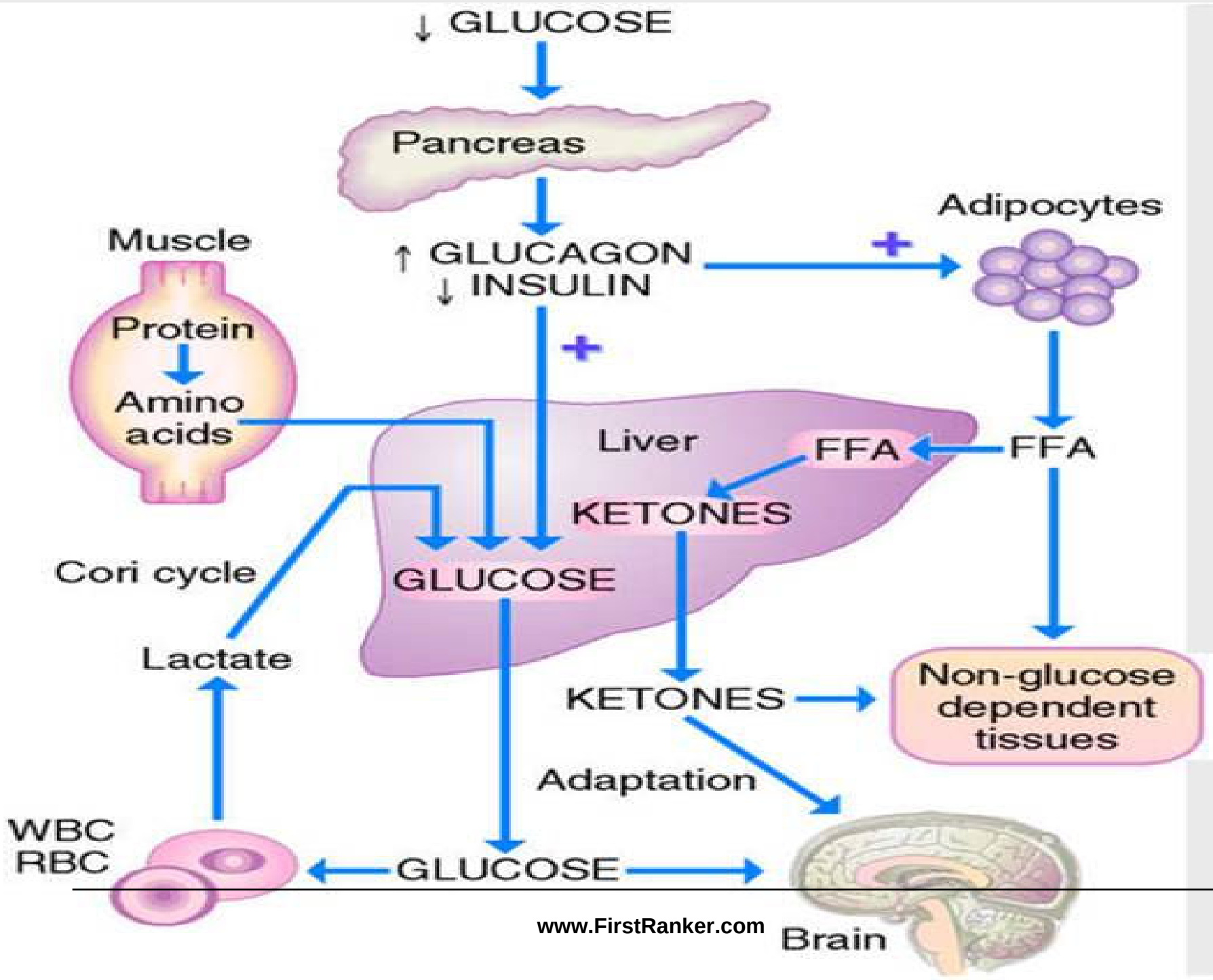
2) Which metabolic fuels can be utilized by each organ?

- **Carbohydrates** → glucose
- **Fats** → fatty acids & ketone bodies
- **Protein** → aminoacids

	RBCs	Brain	Liver	Muscle	Adipose
Order of preference	1. Glucose	1. Glucose 2. Ketone bodies	1. Glucose 2. Fatty acids	1. Glucose 2. Fatty acids & Ketone bodies	1. Glucose 2. Fatty acids

Glucose is first-choice fuel for ALL organs
Glucose is only fuel for RBCs → need constant supply

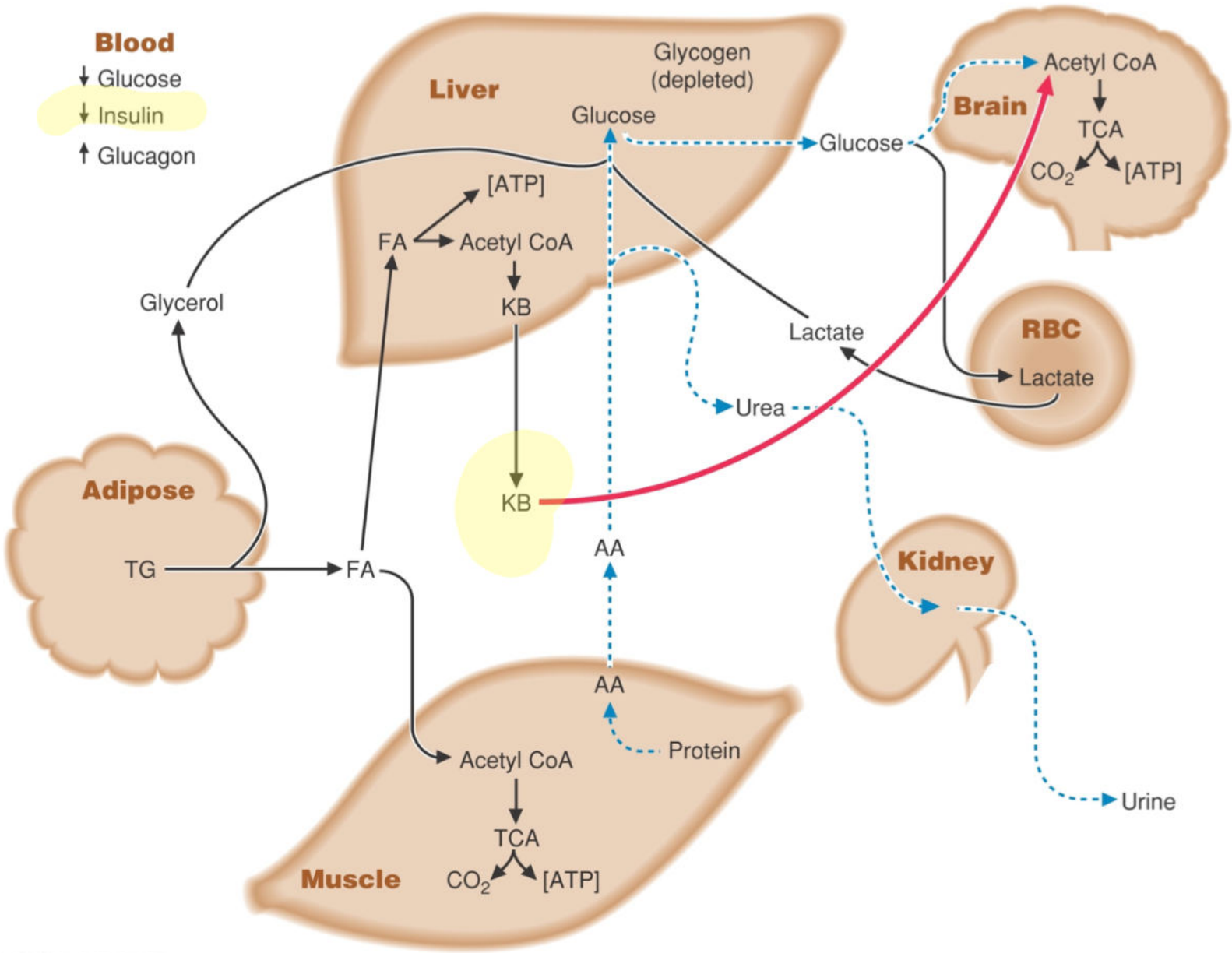
**Ketone bodies are generated from fatty acids and are an alternative form of fuel

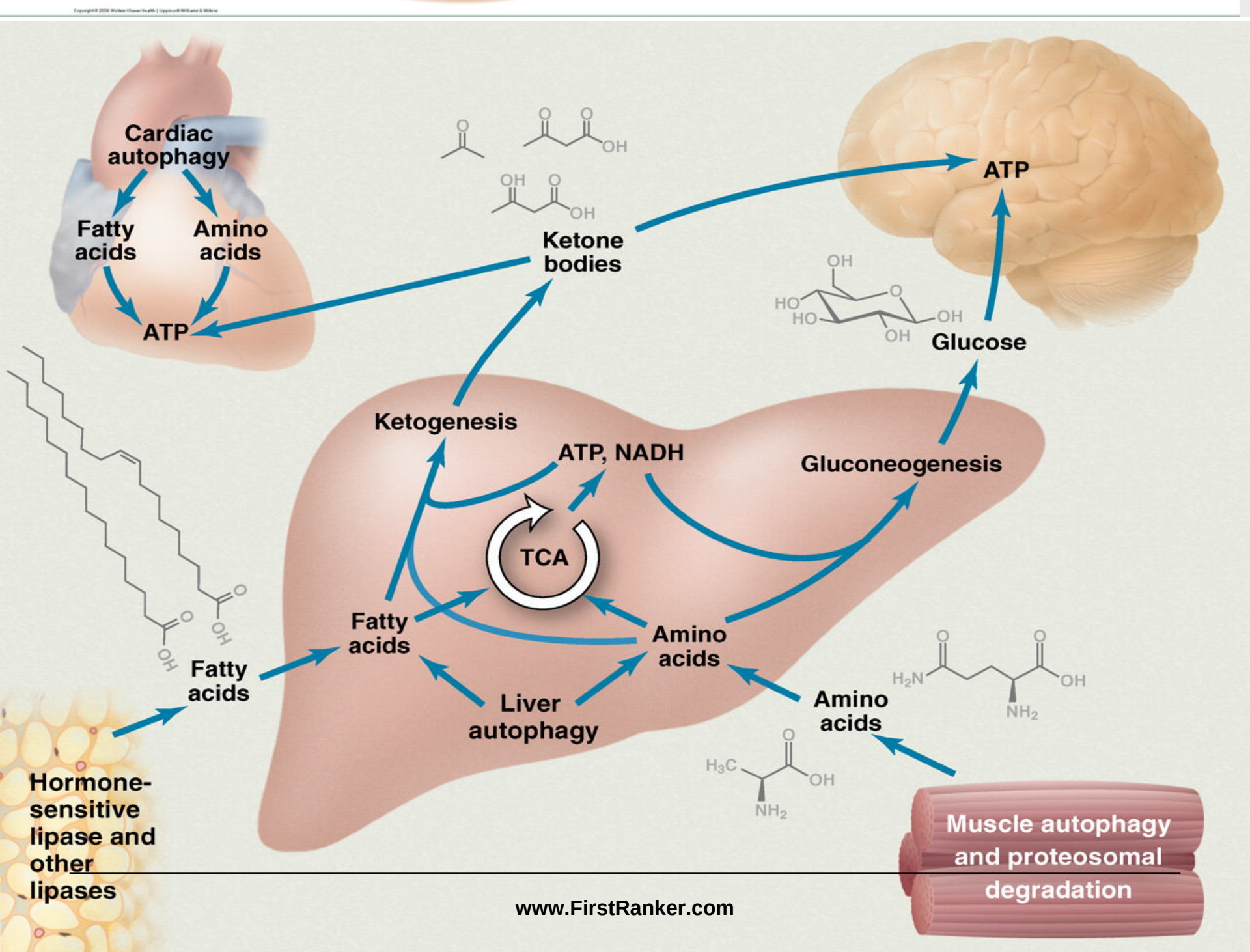


High Yield

The Starved State

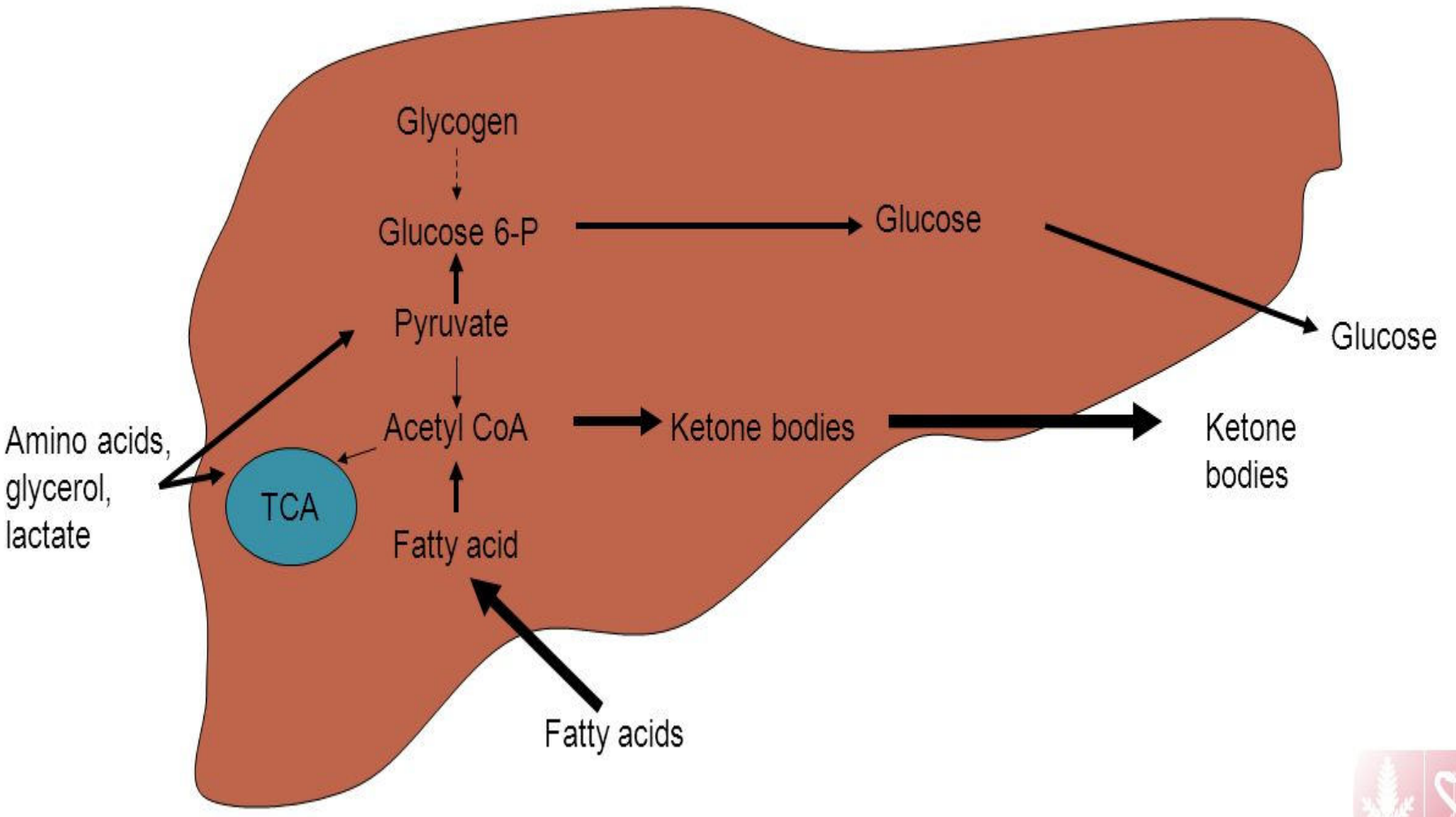
High Yield





Starvation: Liver

↓ Insulin, ↑Glucagon



Starvation (protective adaptation occurs)

- Overall energy needs decrease
- Metabolic rate decreases 20–25 kcal/kg/d
- Energy from fat storage >90% of kcal
- Energy from protein < 10% for gluconeogenesis
- Protein store protected

Energy Depot
Fat/Fatty Acid

Ketones

Liver
Glucose

Pyruvate

Lower metabolic rate
20–25 kcal/kg/d

For Obligate Users (Brain)

Energy Production

Protein Synthesis

Urea

Alanine

Amino Acids

Lean Mass

Minimal catabolism to meet glucose needs

Erosion Minimal

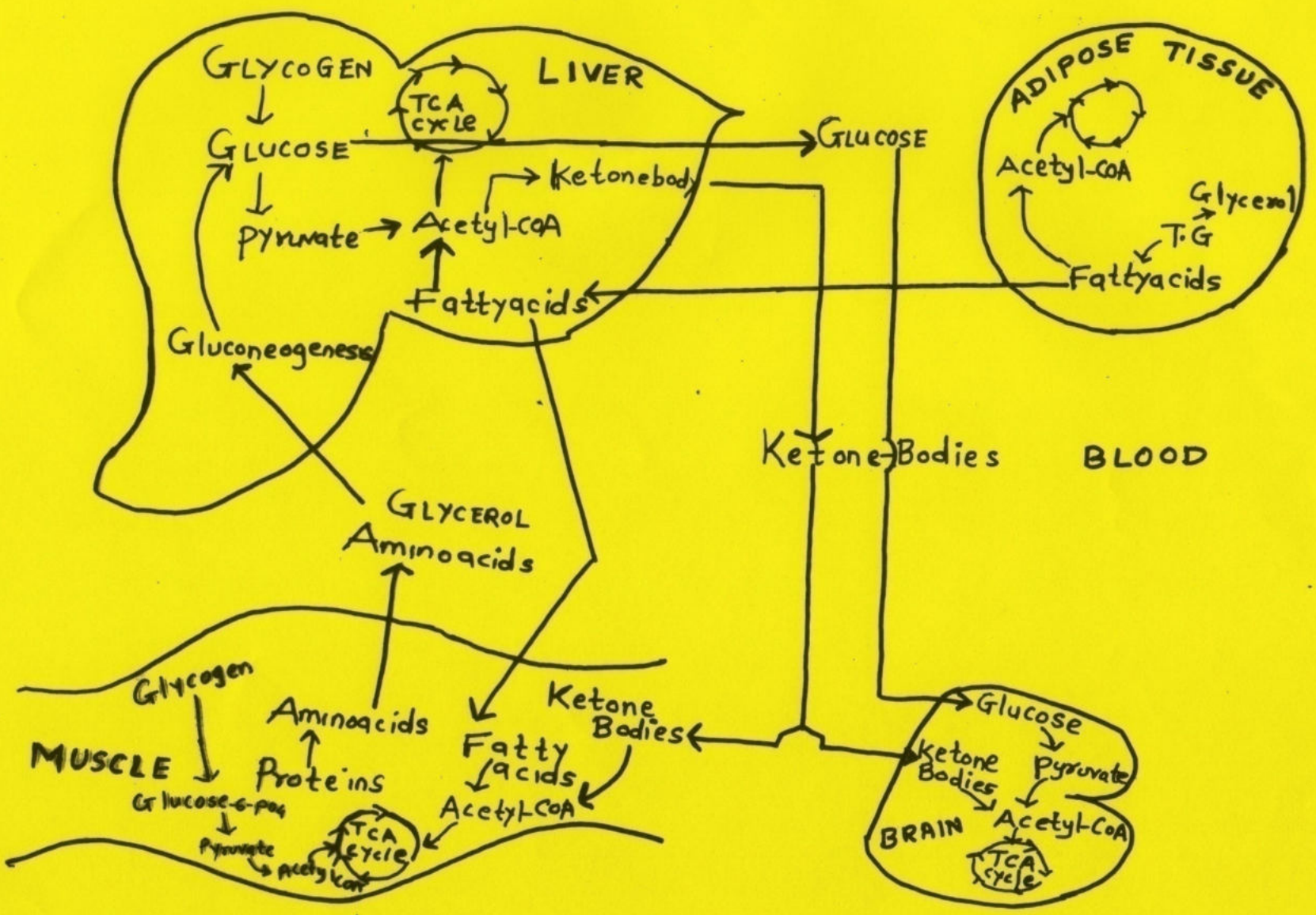
Intact skin

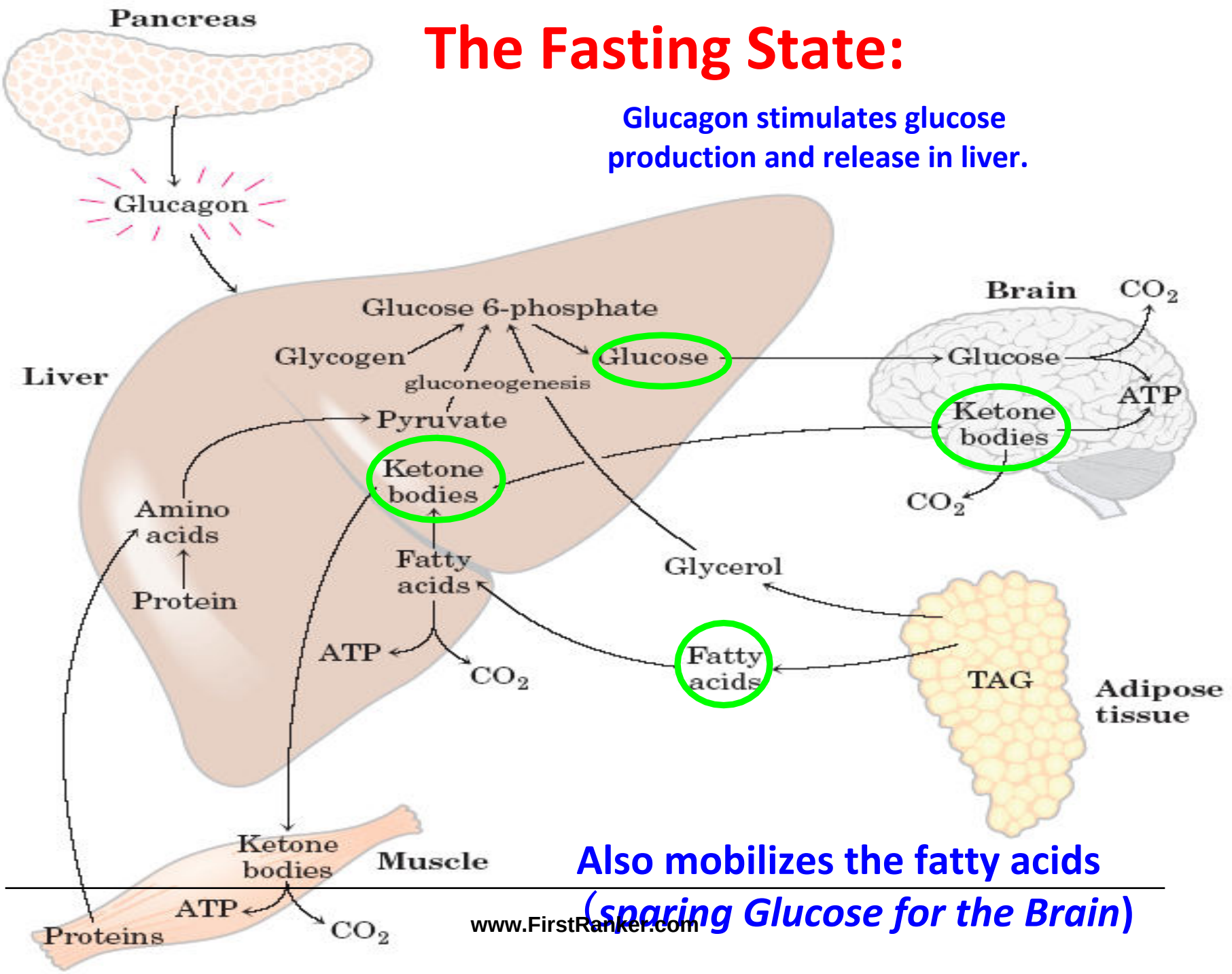
8888888888

Hormone adaptation preserve protein

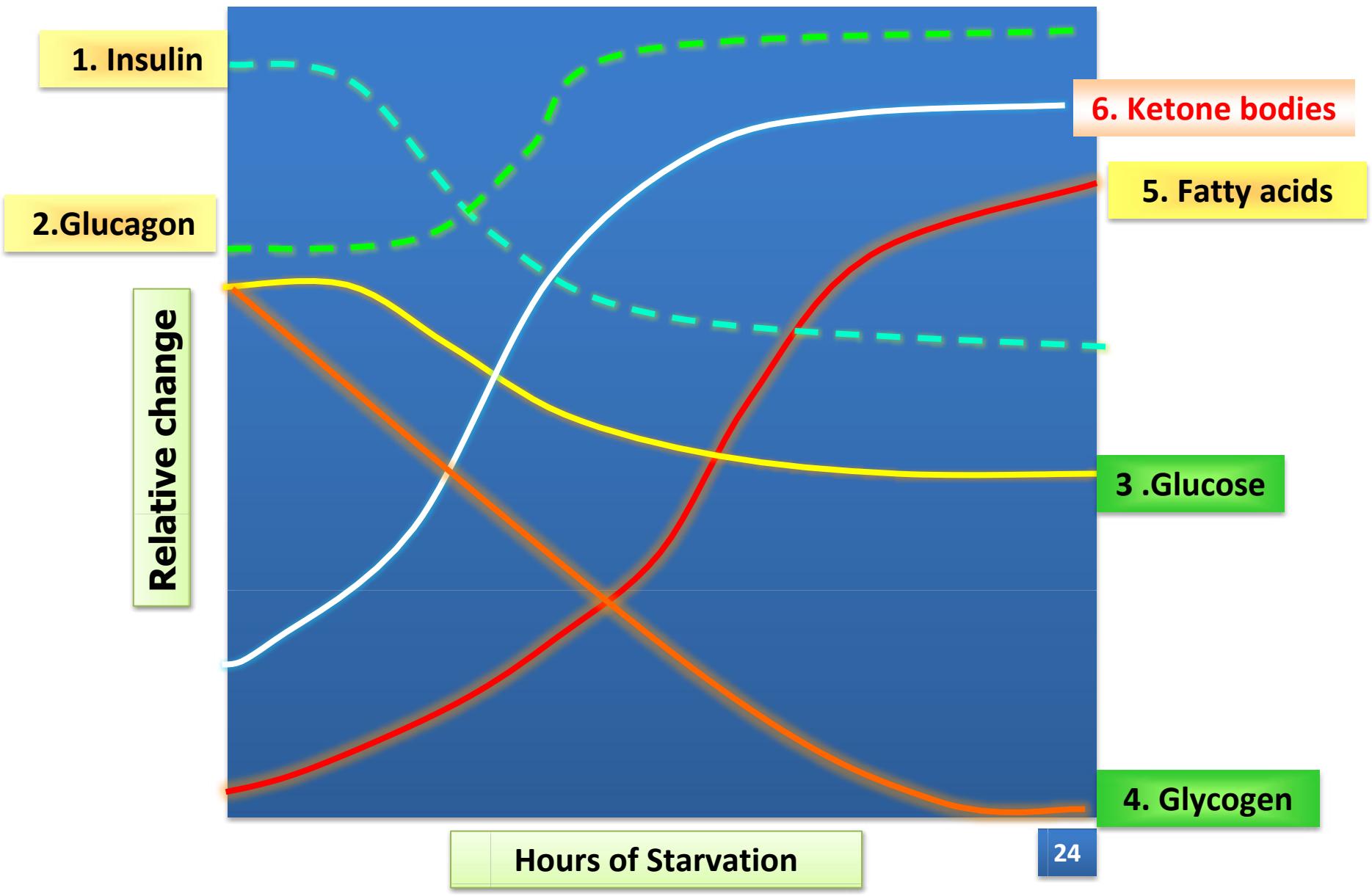
Protein synthesis

METABOLIC INTERRELATIONSHIP AMONG MAJOR TISSUES DURING STARVATION

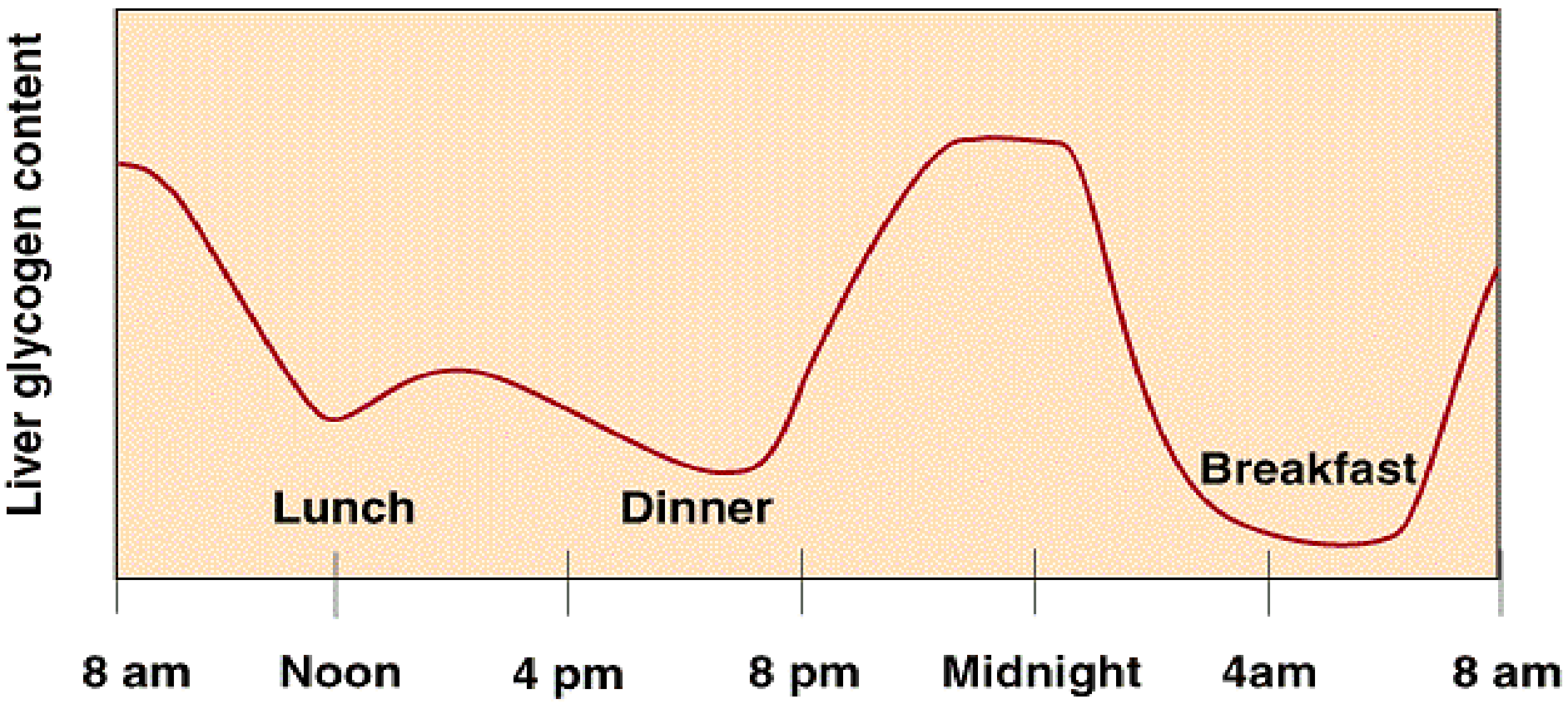




FUEL CHOICE DURING STARVATION

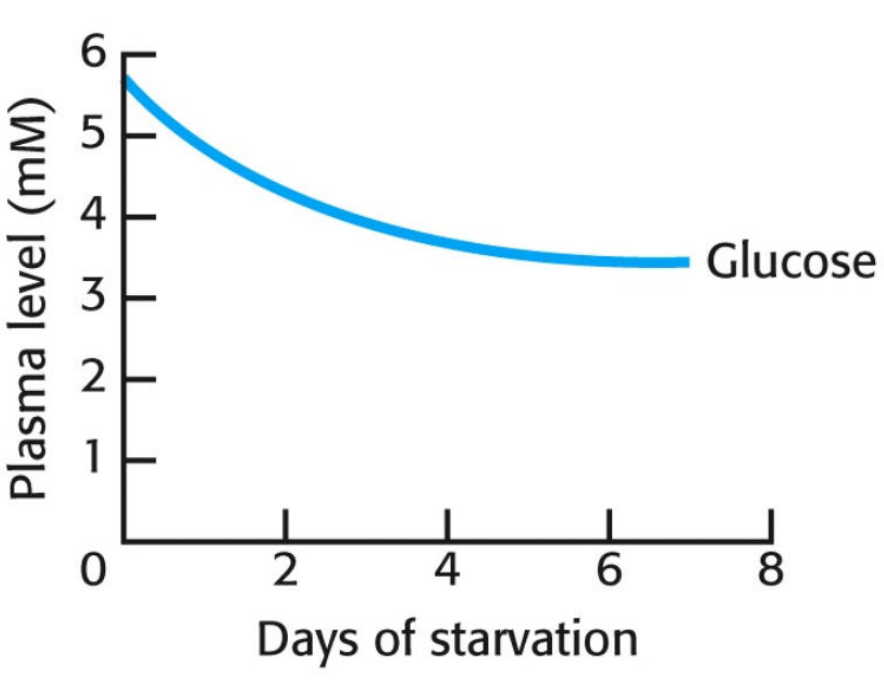


Changes Of Liver Glycogen Content

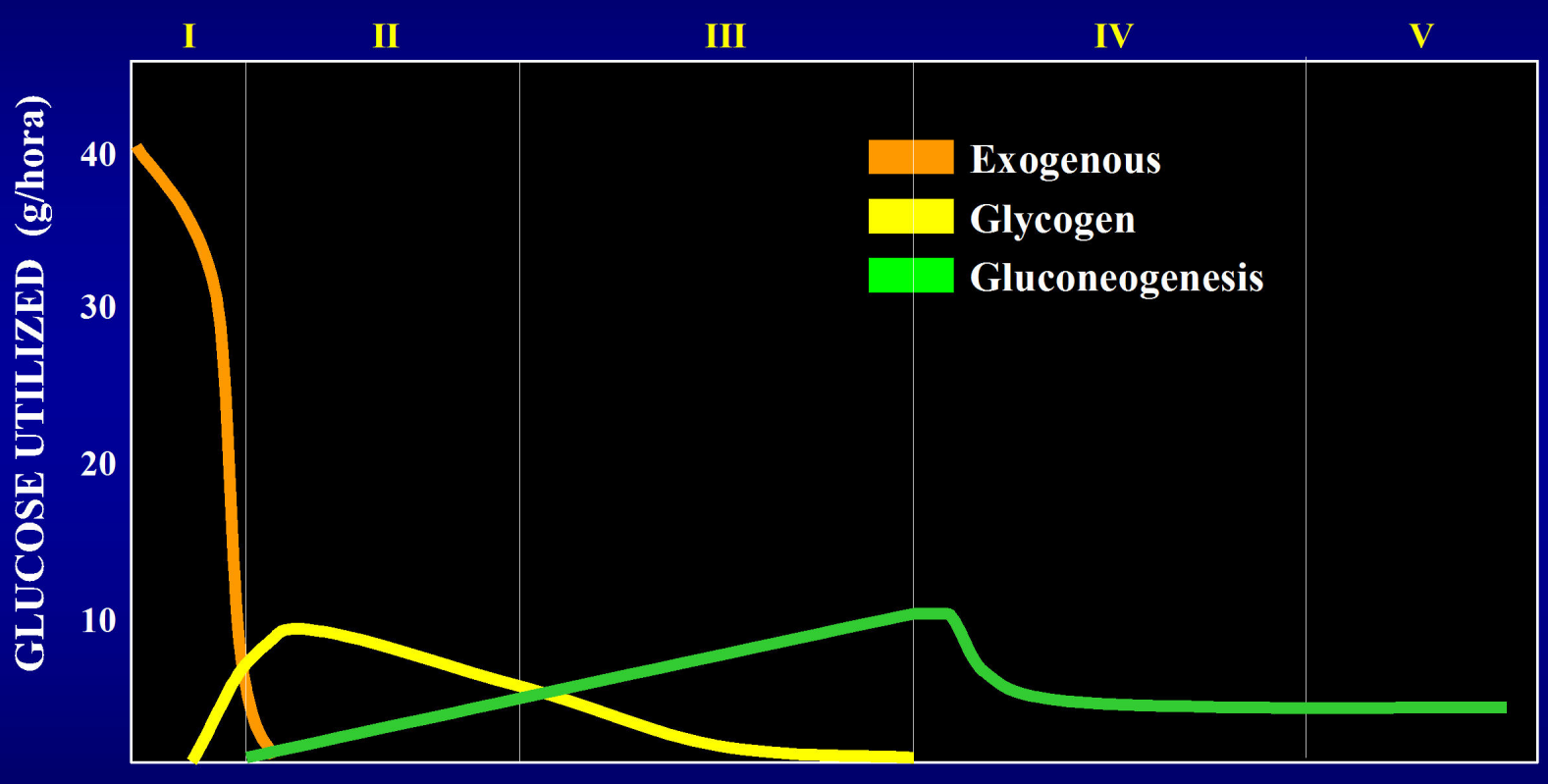


During Starvation

- Fuel changes from Glucose to Fatty acids to Ketone bodies

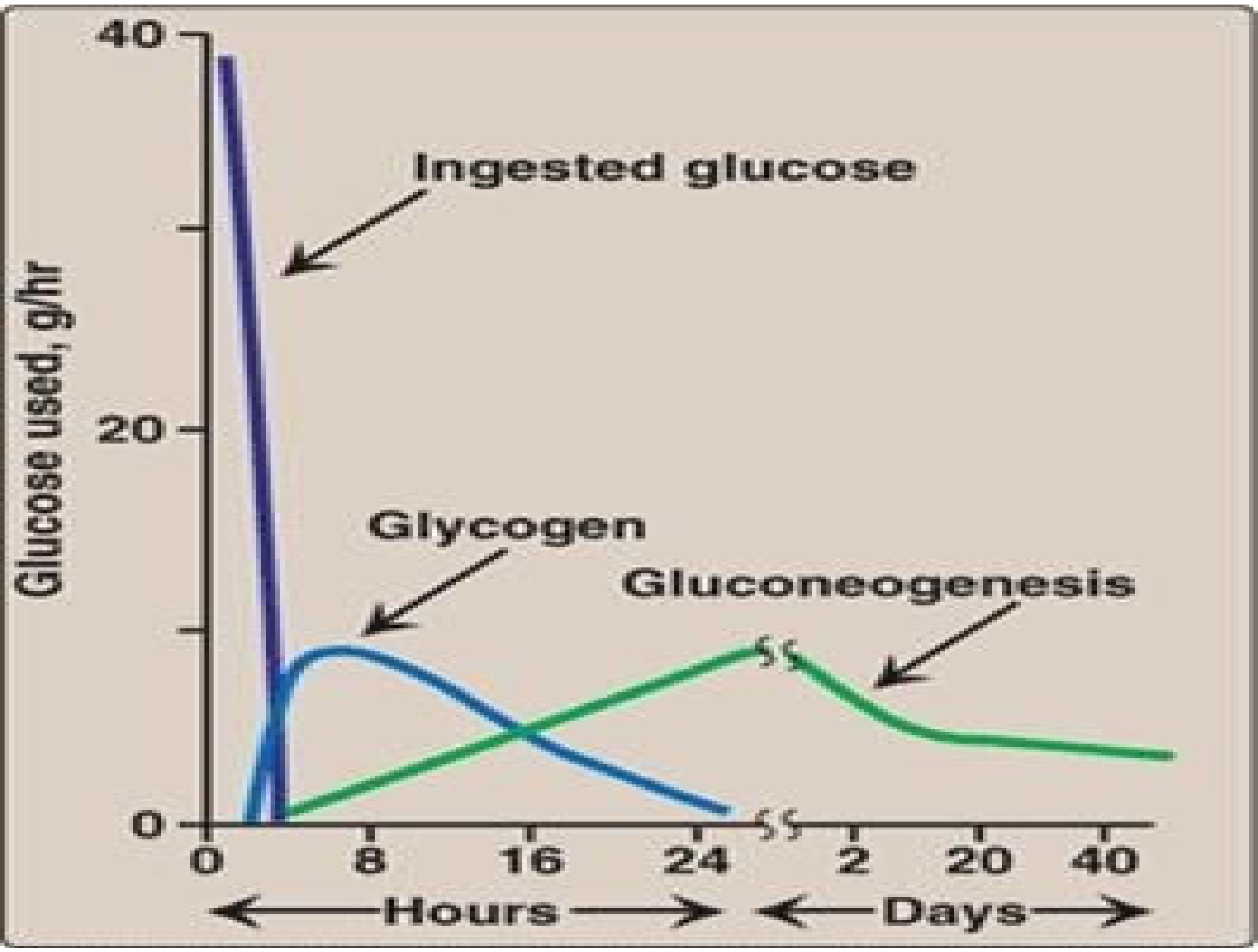


Metabolic Response To Fasting

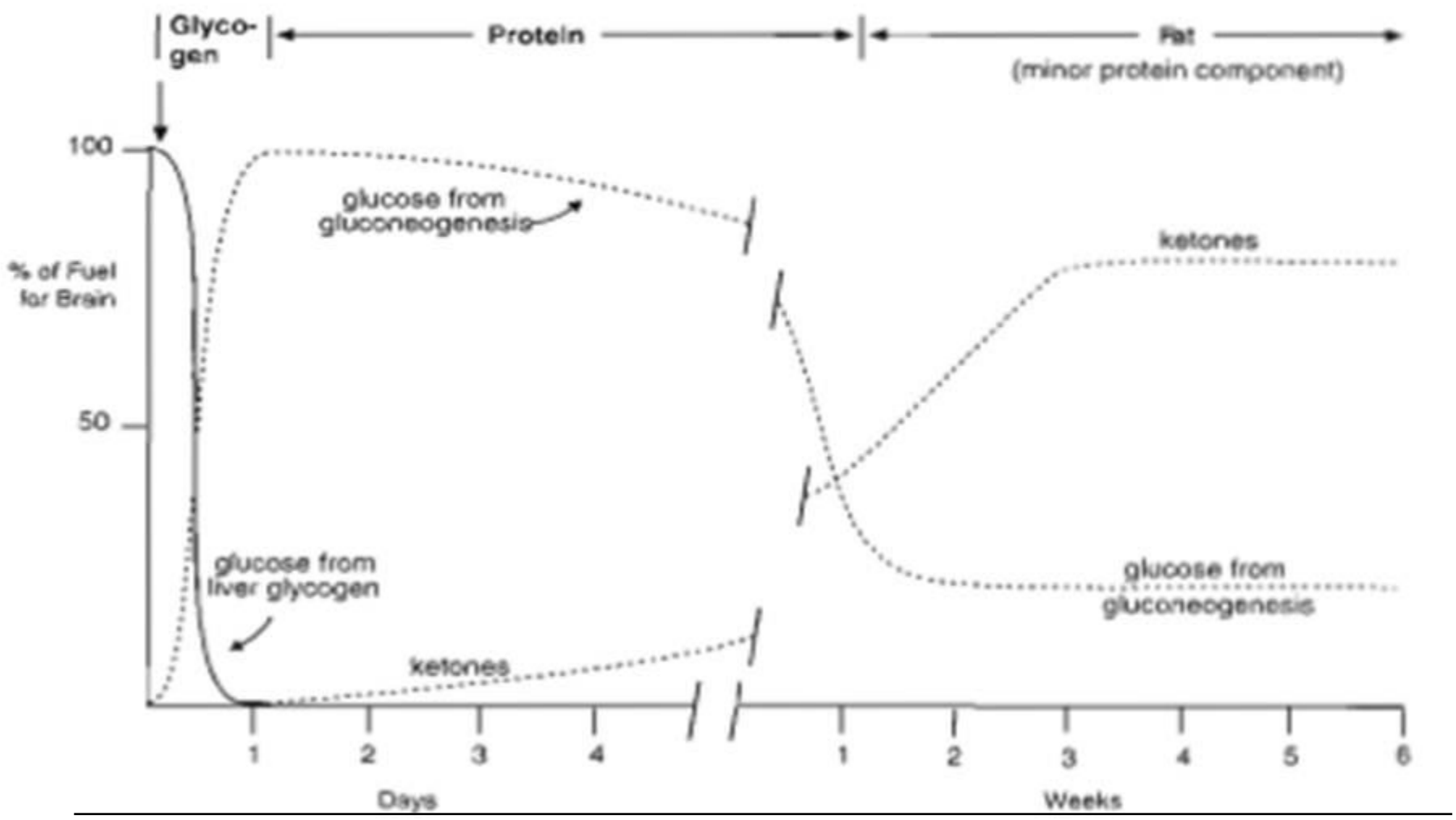


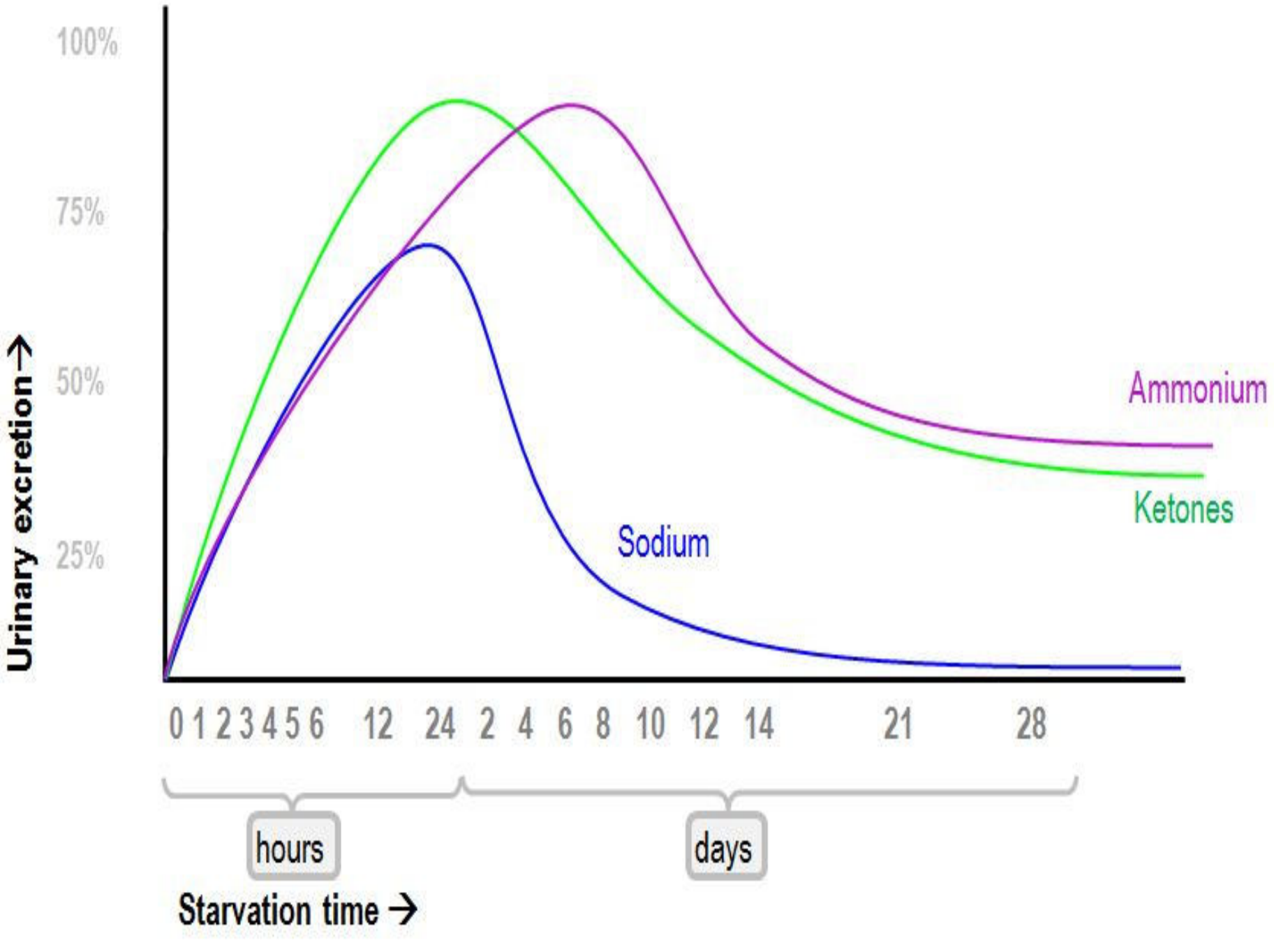
LEGEND	I	II	III	IV	V
FUEL FOR BRAIN	GLUCOSE	GLUCOSE	GLUCOSE	GLUCOSE, KETONES	GLUCOSE, KETONES

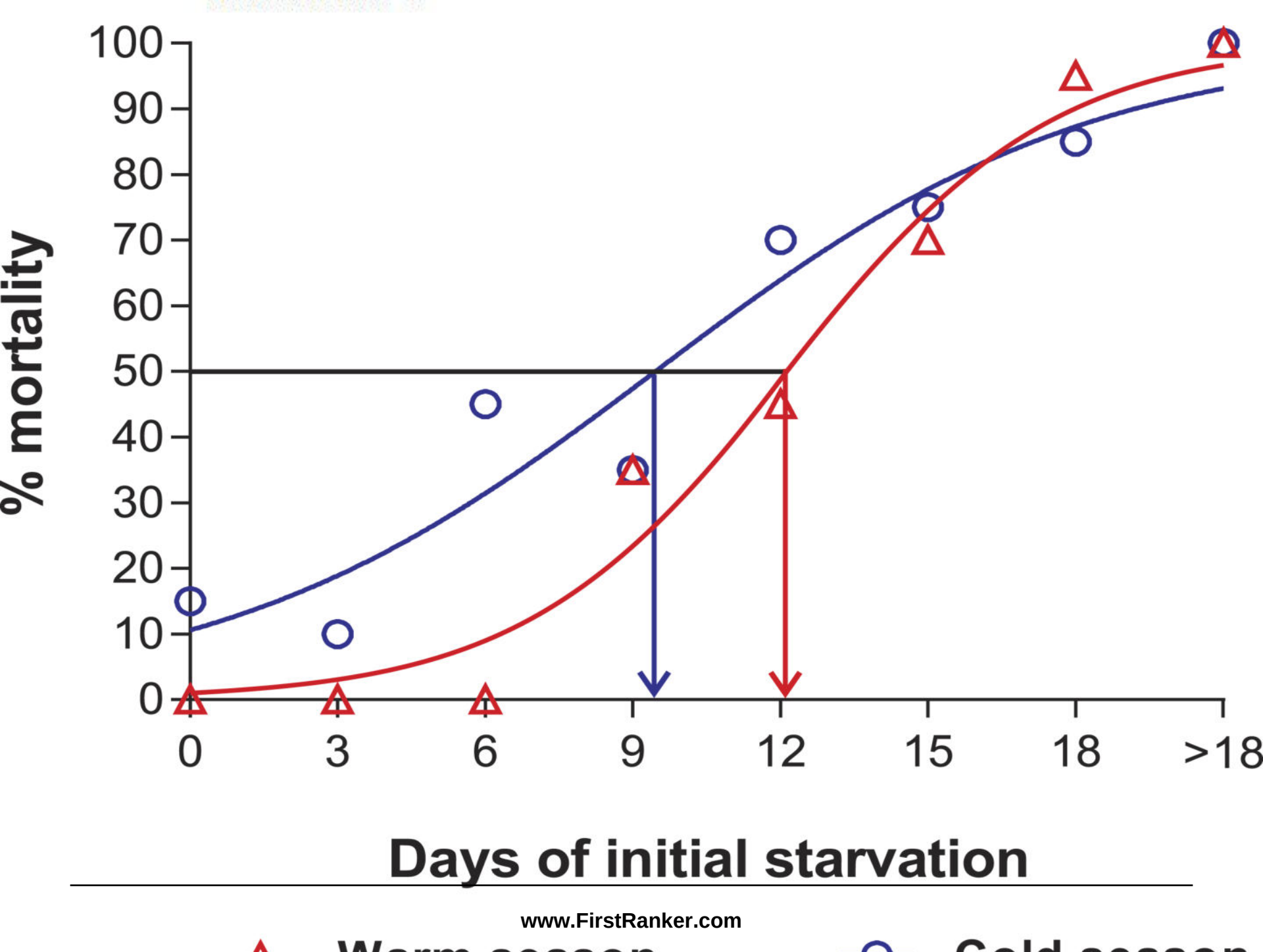
Ruderman NB. *Annu Rev Med* 1975;26:248



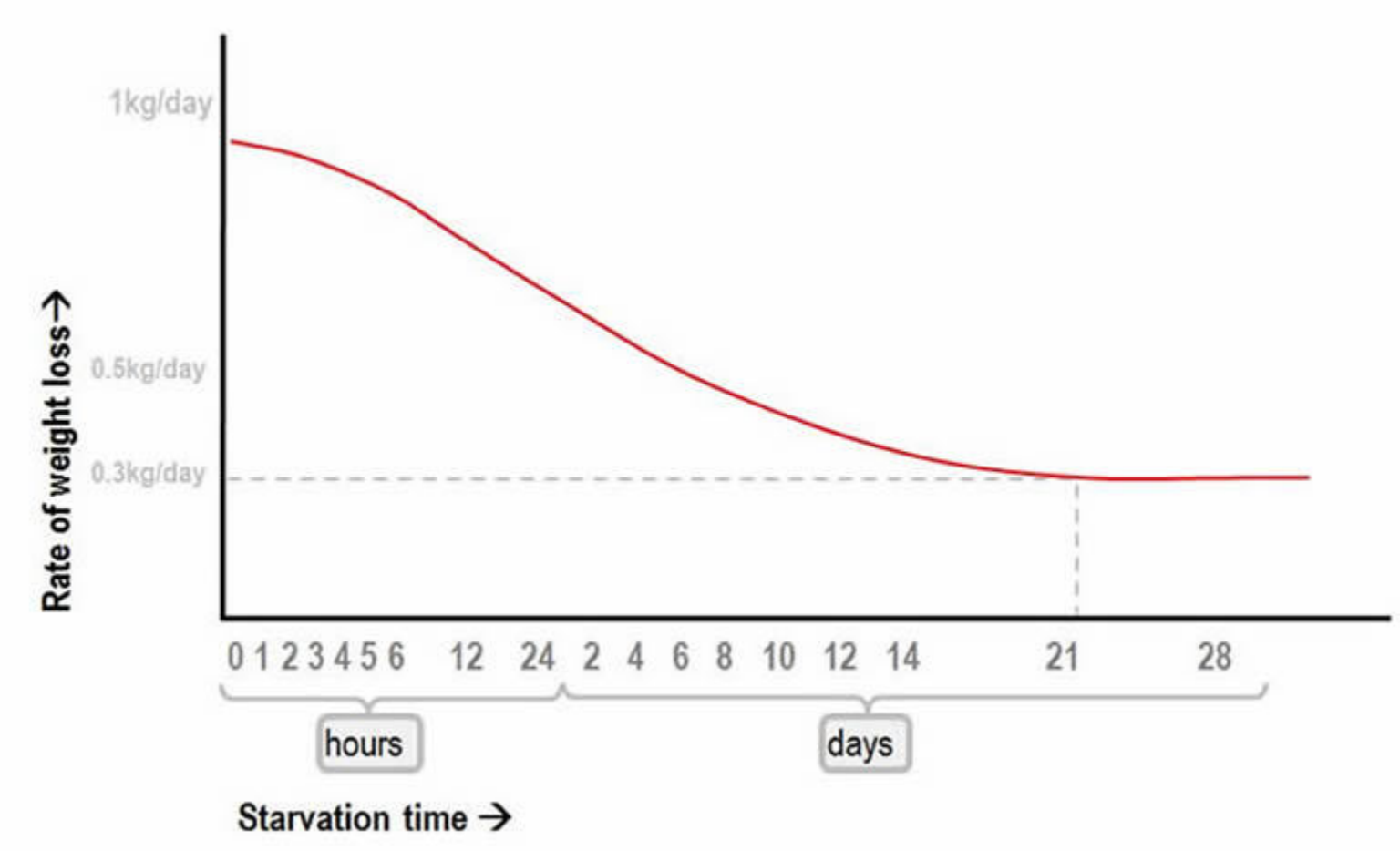
Energy source during fasting and starvation

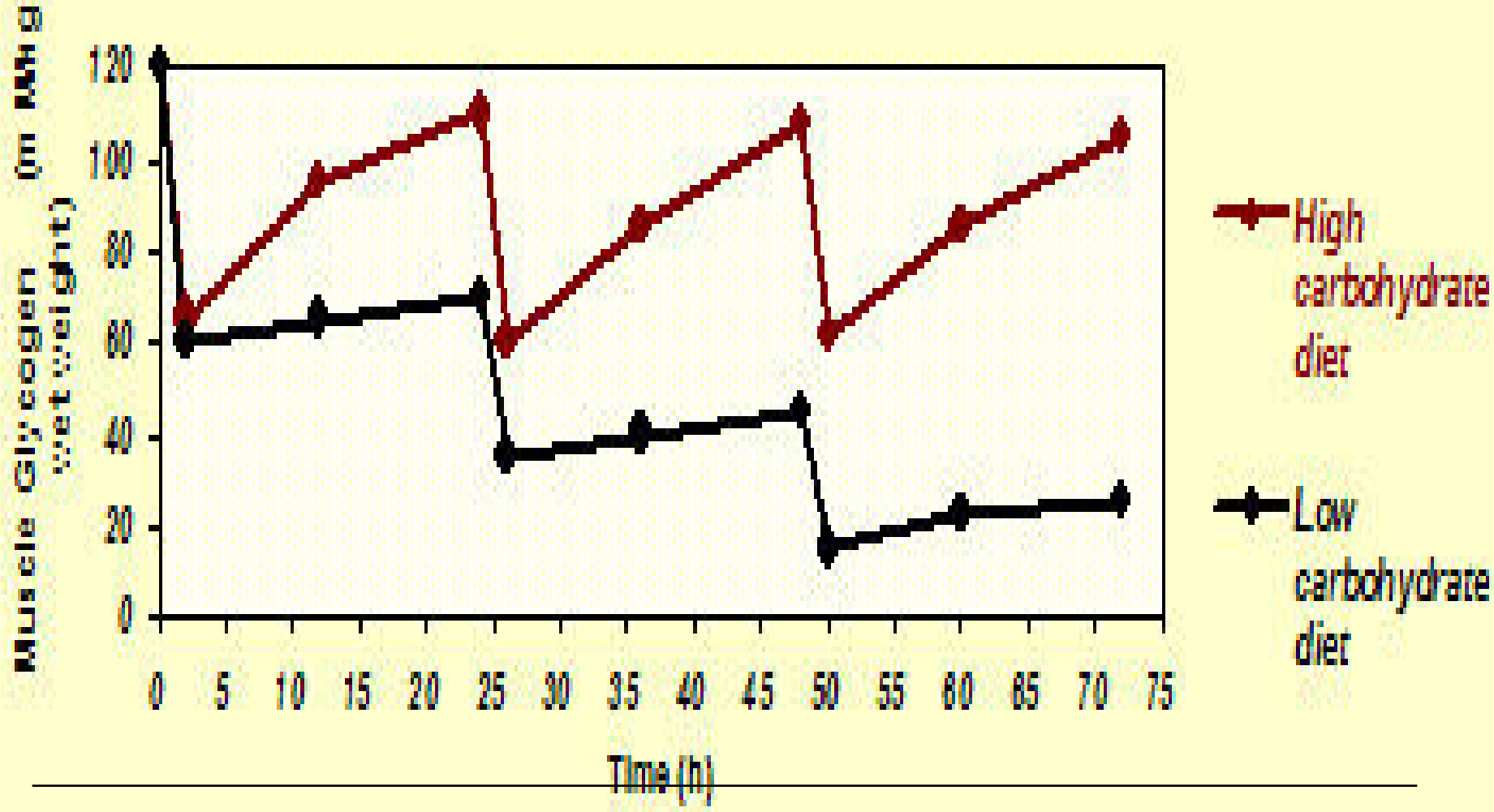


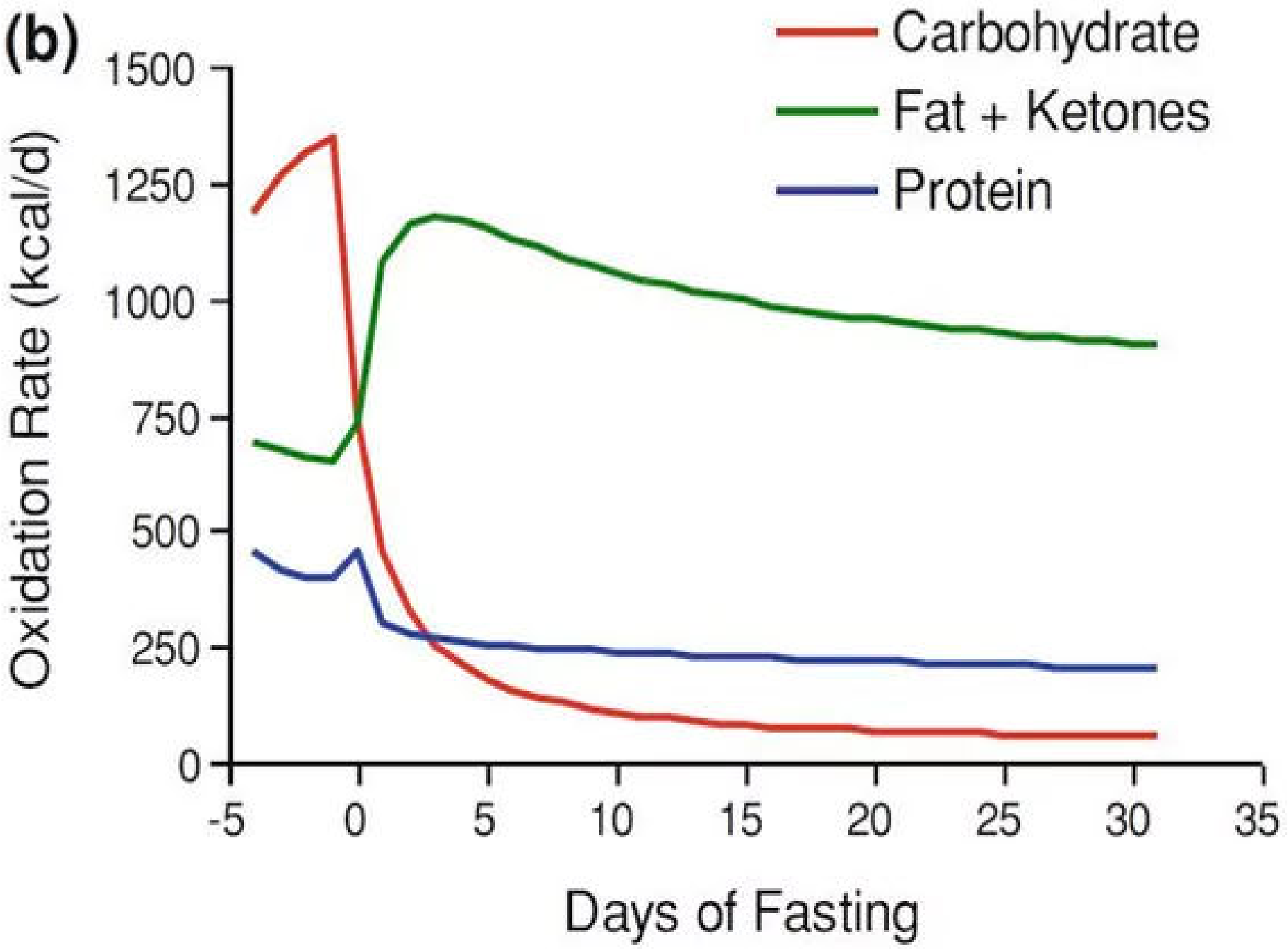




Warm season Cold season







Metabolic Response to Starvation is Characterized

- Switch from carbohydrate metabolism to fat metabolism,
- Context of a hypometabolic state, with minimized catabolism
- Initially, stores of carbohydrate precursors (eg. glycogen) are depleted via Glycogenolysis within 24 hrs.
- In first 24-48 hours there is increased gluconeogenesis from amino acids and glycerol.

- Subsequently, Ketogenesis takes over, and much of the body metabolic needs are met by ketone bodies and free fatty acids.

- This is the consequence of decreasing insulin levels, and relatively increased influence from catecholamines and cortisol.

- Over prolonged starvation, protein catabolism begins, resulting in degradation of structurally important proteins, and organ system dysfunction.

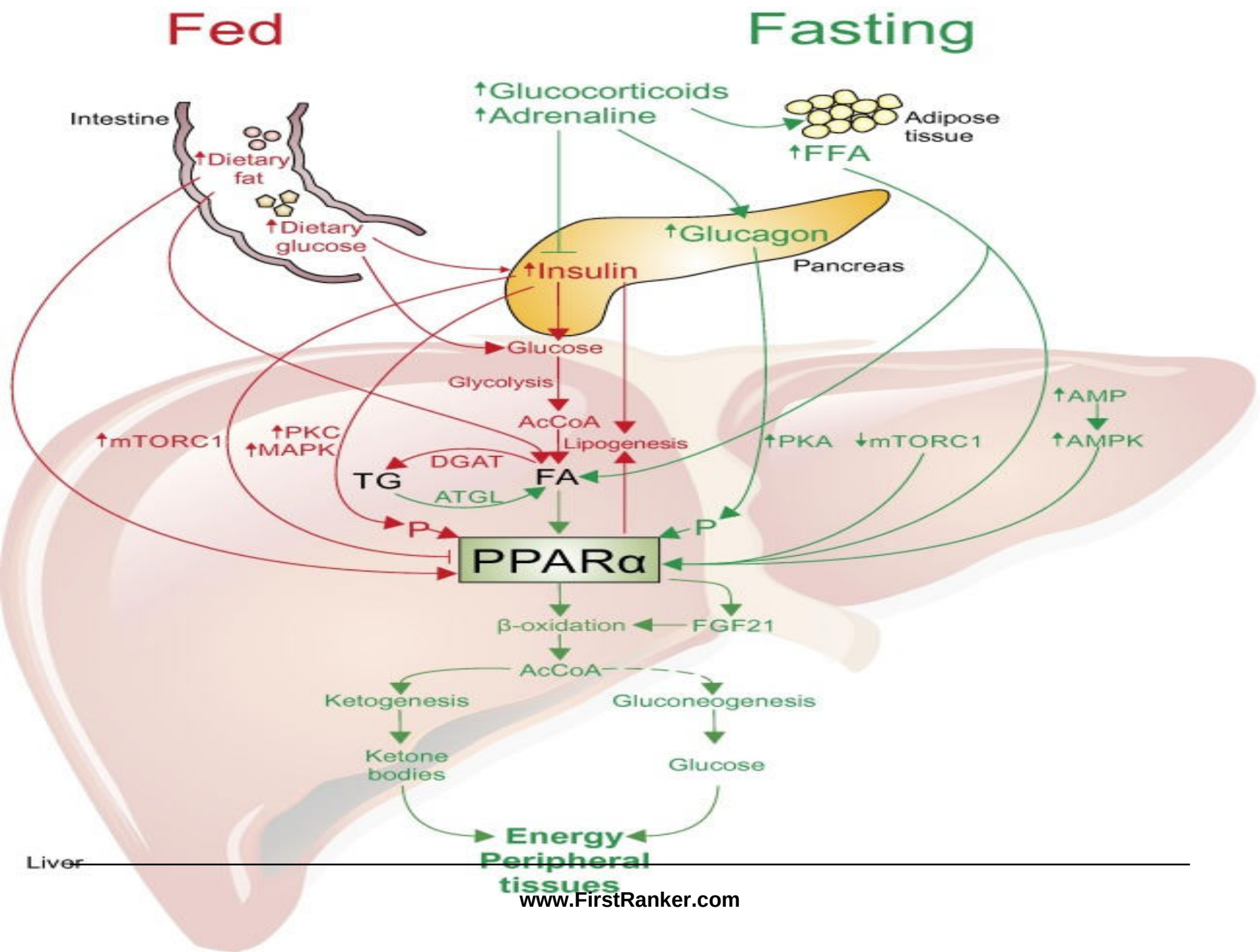
Metabolic Adaptations to Starvation

Metabolic adaptation to food shortages has been preserved over evolutionary time to ensure survival during famine. The human body adapts to these near starvation conditions **by altering the flux of metabolites between various tissues** in order to extend life.

The primary metabolic challenge is to **provide enough glucose for the brain** to maintain normal neuronal cell functions. Although fatty acids released from adipose tissue are plentiful in the blood, the brain cannot use **fatty acids for metabolic fuel** because they cannot cross the blood-brain barrier.

Red blood cells (erythrocytes) are also dependent on serum glucose as a sole source of energy to generate ATP. Mature erythrocytes **lack mitochondria** and are not able to utilize fatty acids for energy because fatty acid oxidation takes place in the mitochondrial matrix.

Differentiation In Well Fed And Fasting States Of Human Body



	WELL-FED STATE	FASTING STATE
Hormones	↑ Insulin	↑ Glucagon, Adrenaline, Cortisol
Response of the body	Hyperglycemia ↑ Glycogenesis ↑ Lipogenesis ↑ Protein synthesis	Hypoglycemia ↑ Lipolysis ↑ Ketogenesis ↑ Proteolysis

	WELL-FED STATE	FASTING STATE
Source of Glucose	from food	from stores (Glycogen) Gluconeogenesis
Fate of Glucose	Glycolysis formation of Glycogen and TAG stores	Glycolysis

	WELL-FED STATE	FASTING STATE
Source of Fatty acids	from food TAG	from storage TAG
Fate of Fatty acids	β-oxidation synthesis of TAG and Store as Depot Fat	↑ β-oxidation (Incomplete one) Ketogenesis

	WELL-FED STATE	FASTING STATE
Source of Amino acids	from food	From muscle Proteins
Fate of Amino acids	Protein synthesis	Glucogenic amino acids Produce Glucose via Gluconeogenesis

Preferred fuels By Human body In the Well-Fed and Fasting States

Organs	Well-Fed	Fasting
Liver	Glucose & Fatty acids	Fatty acids
Resting skeletal Muscle	Glucose & Fatty acids	Fatty acids & KB
Cardiac muscle	Fatty acids	FA,AA & KB
Adipose tissue	Glucose	Fatty acids
Brain	Glucose	Glucose ,Later KB
RBCs	Glucose	Glucose

Enzyme	Pathway	Starvation
glucokinase	glycolysis	↓
glucose 6-phosphate DH 6-phosphogluconate DH	pentose-P pathway	↓ ↓
acetyl-CoA carboxylase fatty acid synthase ATP citrate lyase malic enzyme	FA synthesis	↓ ↓ ↓ ↓
glucose 6-phosphatase fructose bisphosphatase	GNG	↑ ↑
carnitine acyltransferase	β-oxidation	↑
serine dehydratase various aminotransferases	AA catabolism	↑ ↑

BIOCHEMICAL PROFILE OF EARLY FASTING STATE

- Blood Glucose levels decreases
  - 65 mg/dl
- Active Glycogenolysis
  - Muscle and Liver
- Shift of metabolic fuel from Glucose to fatty acids
  - Fatty acid mobilization from adipose tissues
- Gluconeogenesis
  - Glucose Alanine cycle

BIOCHEMICAL PROFILE OF STARVED STATE

- GLUCOSE levels more decreased
  - 40 mg/dL
- PROTEIN CATABOLISM increased
  - Sequesters Nitrogen as urea
  - Excretes 20 to 30 grams daily
- Gluconeogenesis taking place using precursors as
  - Amino acids
  - Lactate
  - Glycerol
- KETONE BODIES increased
  - Acetyl CoA converted to ketone bodies via Ketogenesis

In Prolonged Starvation

- **After 3 days of Starvation ->** Liver forms large amounts of Ketone bodies

  (Due to shortage of Oxaloacetate)
- Ketone Bodies -> released into blood
- **Brain and Heart start to use ketone bodies as fuel during phase of Starvation.**

Starvation Of Several Weeks

- **After several weeks of starvation -> Ketone bodies become major fuel of Brain**
- **After depletion of TAG stores**
- **Proteins degradation accelerates**
- **Death due to loss of Heart, Liver, and Kidney function.**

Summary: Metabolism in the fasted state

1. Glycogen supplies become depleted after ~16-24 hours of fasting
2. Liver begins synthesizing glucose as glycogen becomes depleted
3. **The energy required for gluconeogenesis is provided by oxidation of fatty acids to acetyl CoA .**
4. A low insulin:glucagon ratio causes the release of fatty acids from adipose tissue by activation (phosphorylation) of **hormone sensitive lipase by** cAMP-dependent protein kinase A. Hormone sensitive lipase hydrolyses triglycerides in fat deposits to release free fatty acids.
5. The relatively insoluble fatty acids are transported to the liver bound to **serum albumin** in the blood.
6. The rate limiting step for oxidation of fatty acids is **transport** into the mitochondrial matrix. An intermediate of fatty acid synthesis (**malonyl CoA) inhibits** this inner membrane transport system (Carnitine Acyl Transferase- I = CAT-1 or **CPT-1**).
7. Beta oxidation of fatty acyl CoA produces **NADH** and **FADH2** for the electron transport chain, as well as **acetyl CoA** for 1) ketone body synthesis (liver) or 2) the citric acid cycle (muscle other tissues).

Consequences Of Starvation

- Severe Nutrient deficiency
- Affects vitality and Damages Importan
  Internal Organs /System
- Anaemia (Iron and Protein deficiency)
- Decreased BMR
- Fatigue, Weakness
- Low Immunity
- Increases Sleep

- Night blindness (Vitamin A deficiency)
- Scurvy (Vitamin C deficiency)
- Irregular Menses
- Constipation
- Bone Loss
- Dehydration

- **Water Electrolyte Imbalance**
- **High Blood Pressure**
- **Brain Defects**
- **Coma and Death (Life Ends)**

CONSEQUENCES OF STARVATION : (8)

STARVATION

↓

STOPPAGE OF FODD
NO SUPPLY OF EXOGENOUS SOURCES OF FUEL; BUILDING BLOCKS : GROWTH FACTOR

↓

★ METABOLIC STRESS DEVELOPED.
★ ENDOGENEOUS RESERVE STORES OF FUEL UTILIZED AND DEPLETED.
★ INITIALLY BODY CRAVES FOR FOOD LATER CRAVING FOR FOOD SUBSIDES AND DESIRE FOR FOOD VANISHES.
★ PHYSICAL & MENTAL WEAKNESS GRADUALLY ↑s
★ IF BODY IS IN GROWING PHASE – GROWTH AFFECTED
★ SLEEP INCREASES; PERSON BECOME SEMICONSCIOUS
★ MUSCLE WASTING; BODY WT STEADILY LOST.
★ RESPIRATION & HEART FUNCTION SLOWS DOWN
★ EXCRETION RATE ↓es – AMOUNT OF URINE & UREA CONTENT FALLS
★ ANAEMIA; OEDEMA; ACIDOSIS; DEHYDRATION
★ IMMUNITY SUPPRESSED; VITAL ORGANS AFFECTED
★ COMA & DEATH → LIFE ENDS

Questions

- Explain the different stages of starvation & biochemical alterations in the body during these stages.

OR

- **Biochemical alterations/adaptations during starvation**.

- Describe role of following organs during various stages of starvation
- Liver
- Brain
- Muscles
- Adipose tissues

THANK YOU

Biochemistry