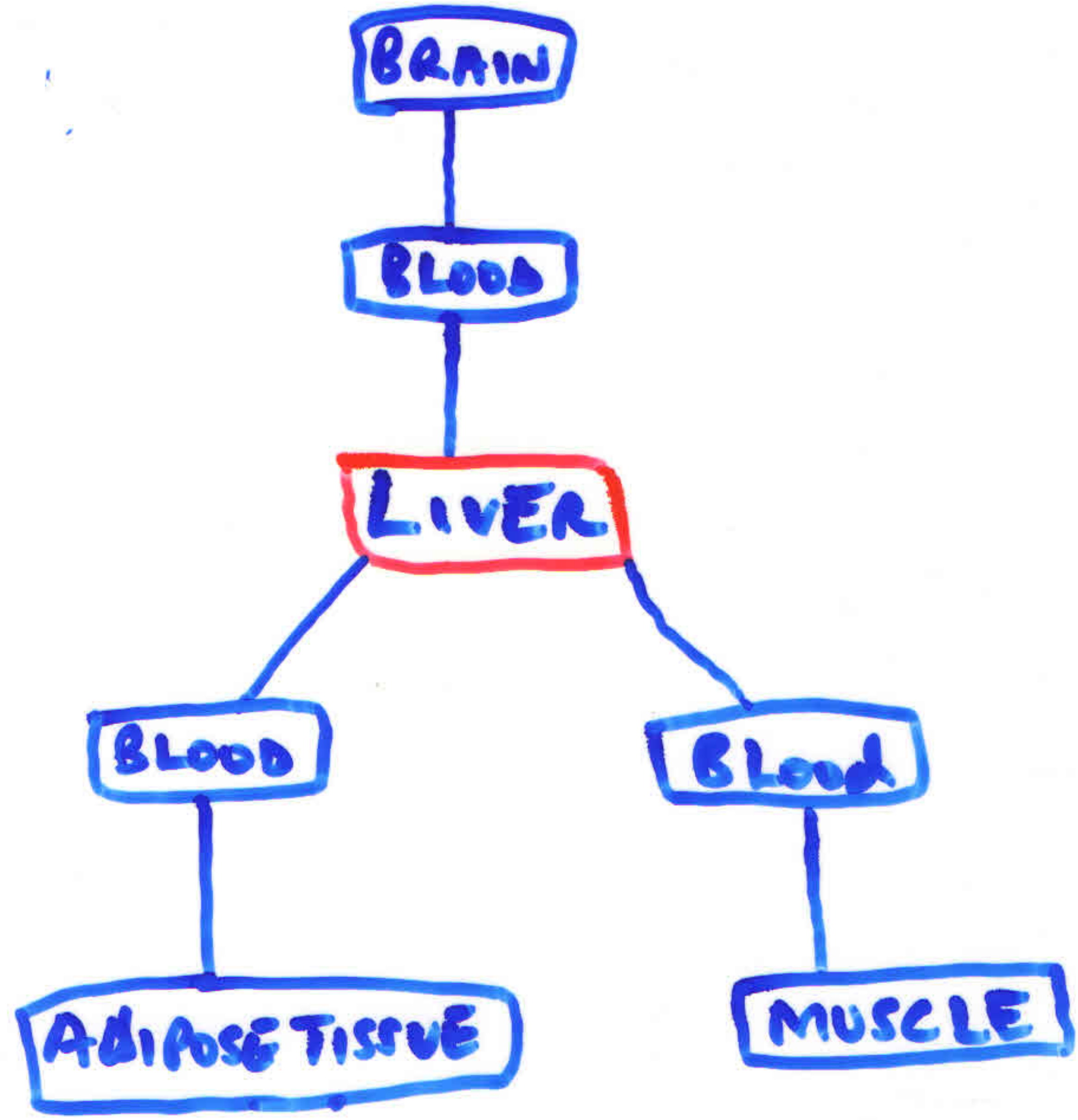
- INTEGRATION OF METABOLISM
- COMPARATIVE TISSUE METABOLISM
- THE ROLE OF HORMONES



5 Tissues

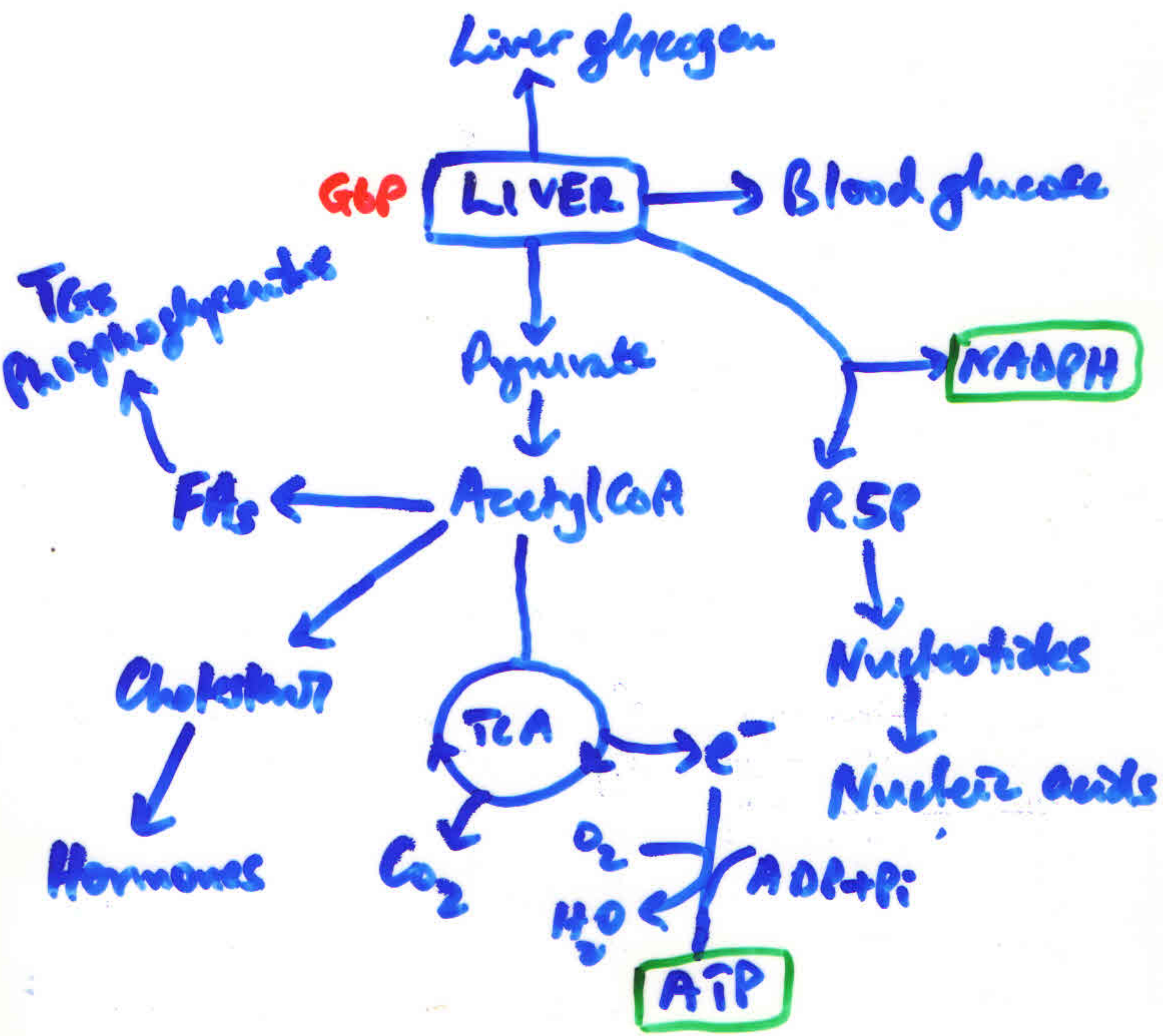
- Liver
- Muscle
- Adipose tissue
- Blood = RBCs
- Brain

} Division of labor "Specialized metabolism"

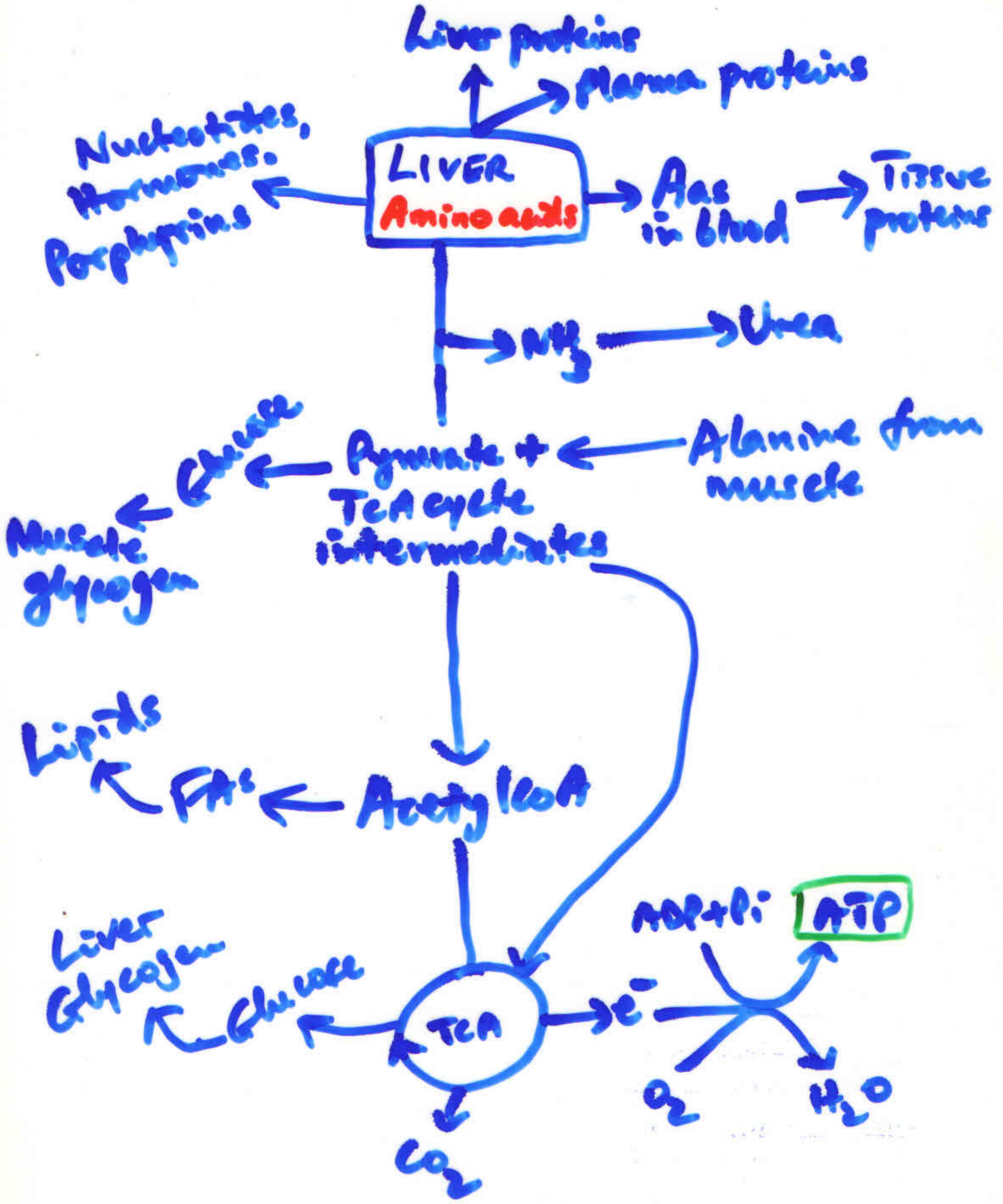
THE LIVER

- The central tissue
- It is a processor and distributor of fuel (CHOs, amino acids, TGs) and nutrients in form of precursors to other tissues.

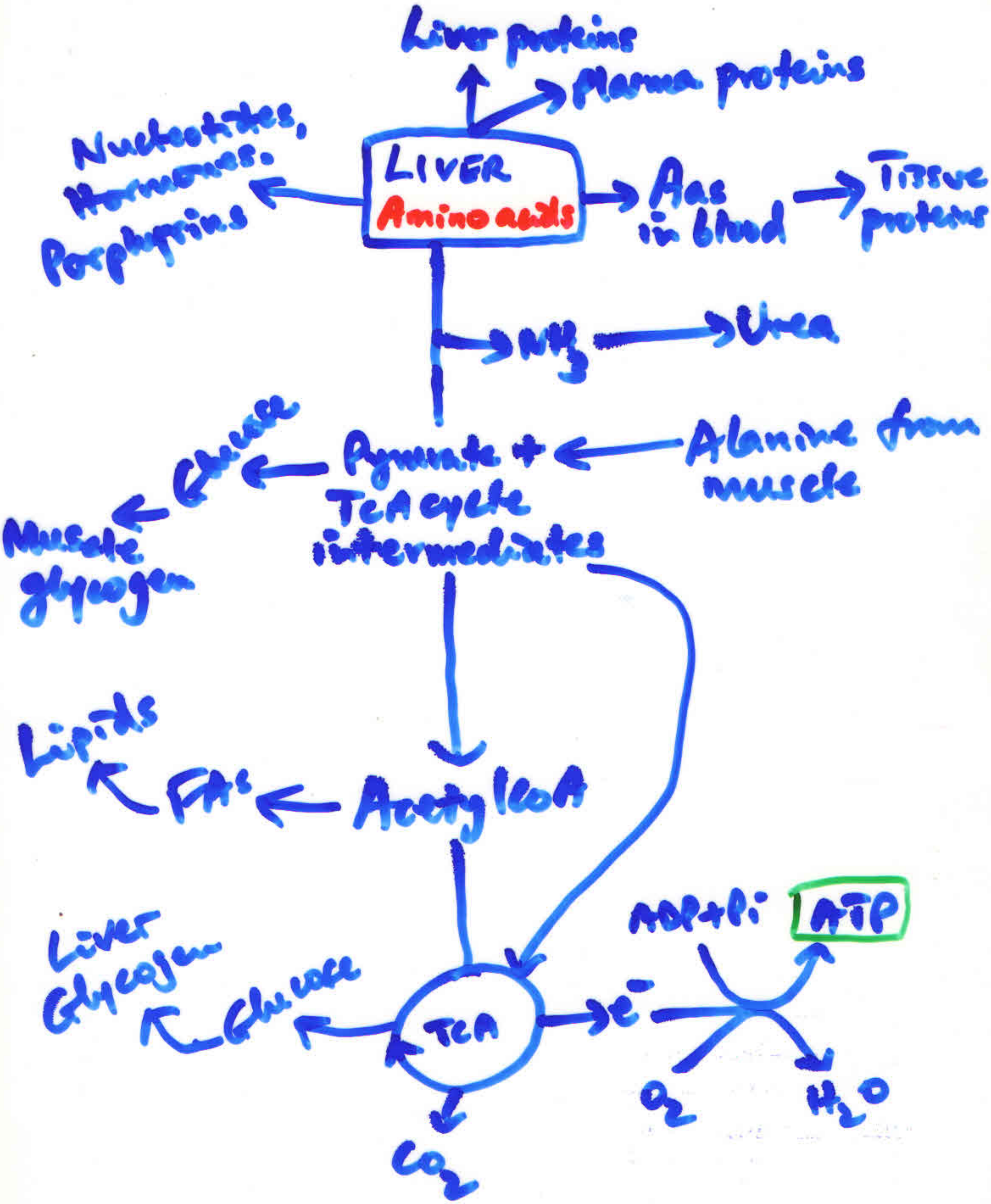
a) Sugars



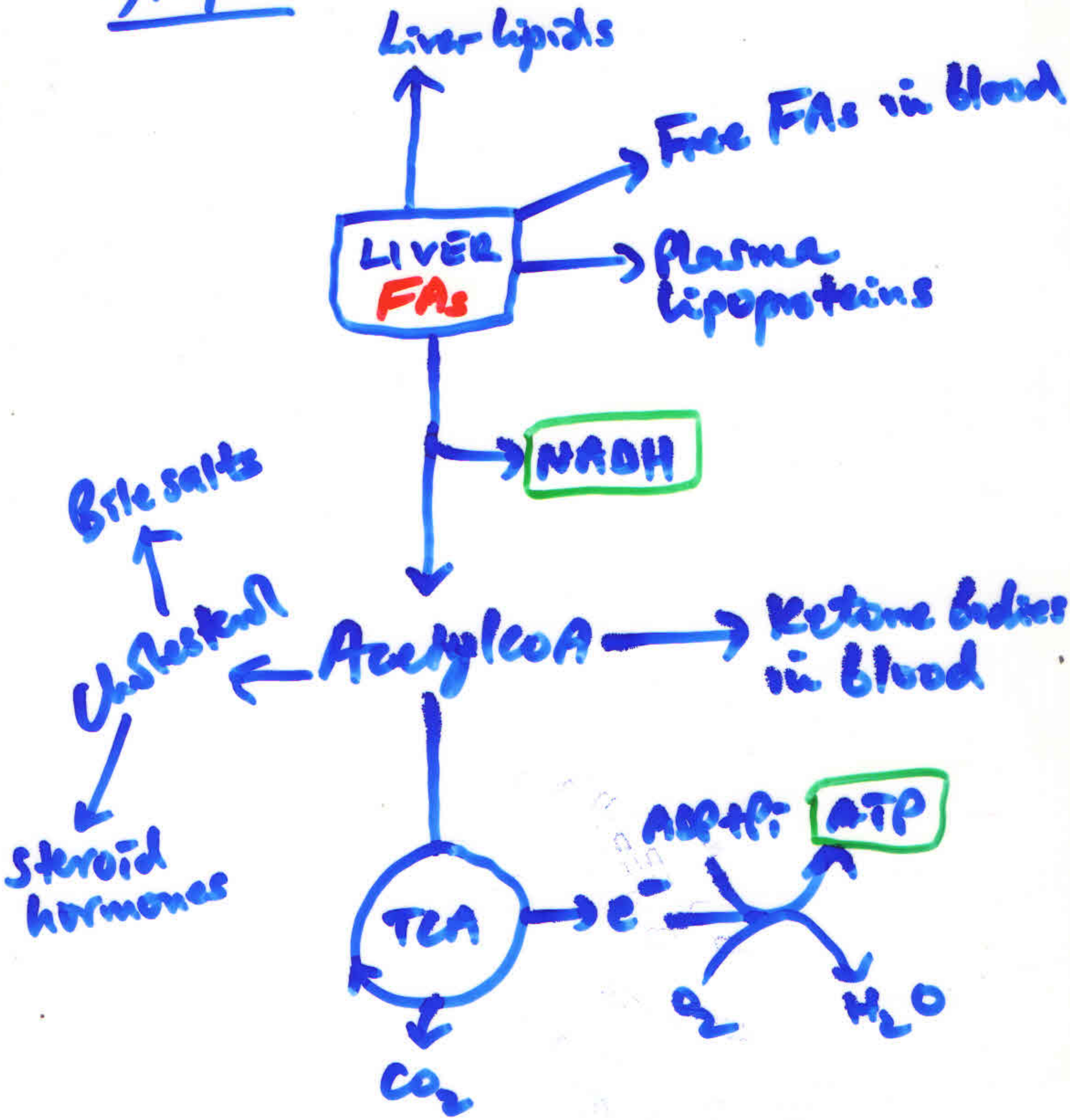
b) Amino acids



b) Amino acids



c) Lipids



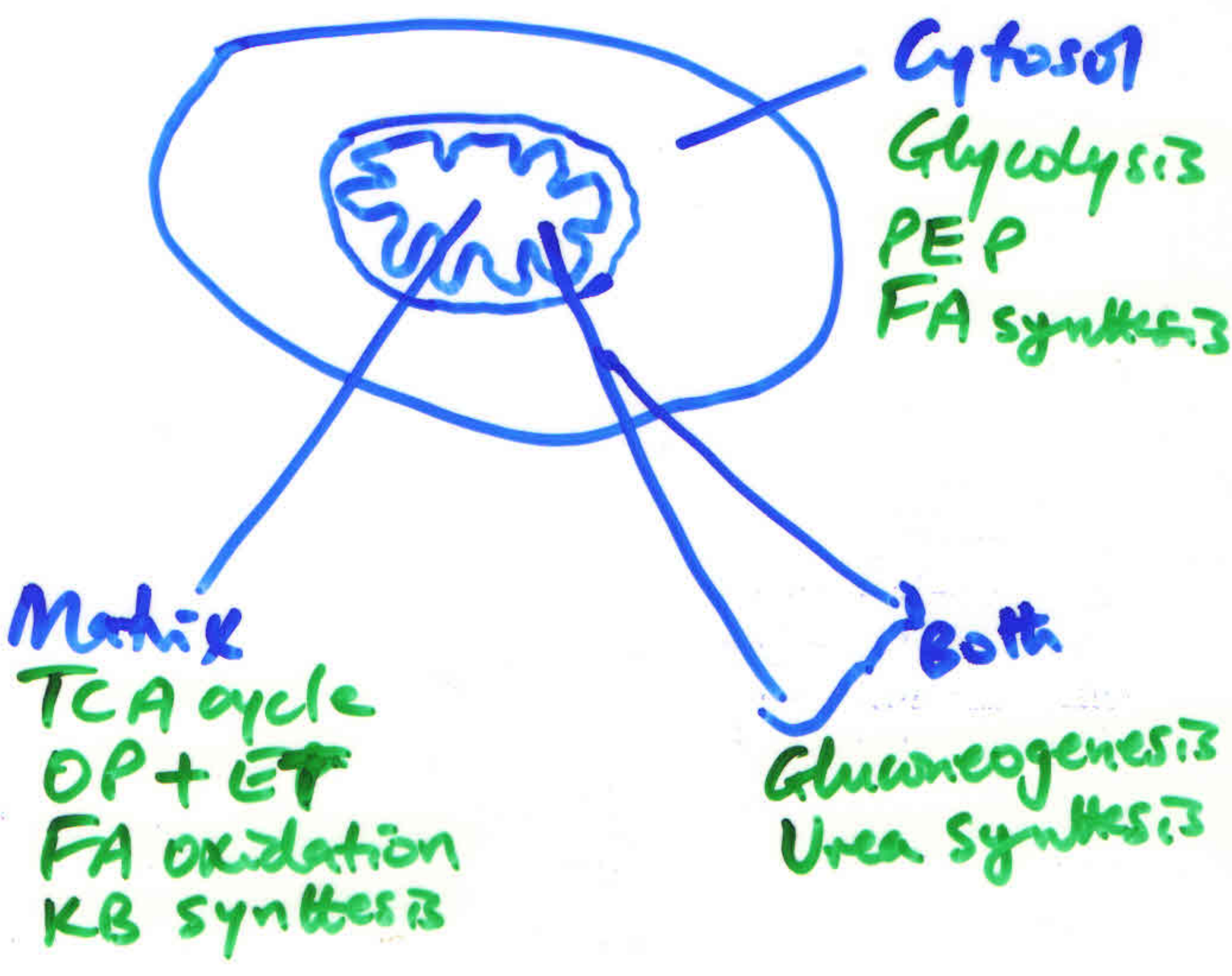
Q. What are the major metabolic pathways? In the liver!

1. Glycolysis
2. Gluconeogenesis
3. Glycogen metabolism

4) FA metabolism
5) TCA cycle
6) Oxidative phosphorylation + electron transport (OP + ET).
7) Amino acid metabolism

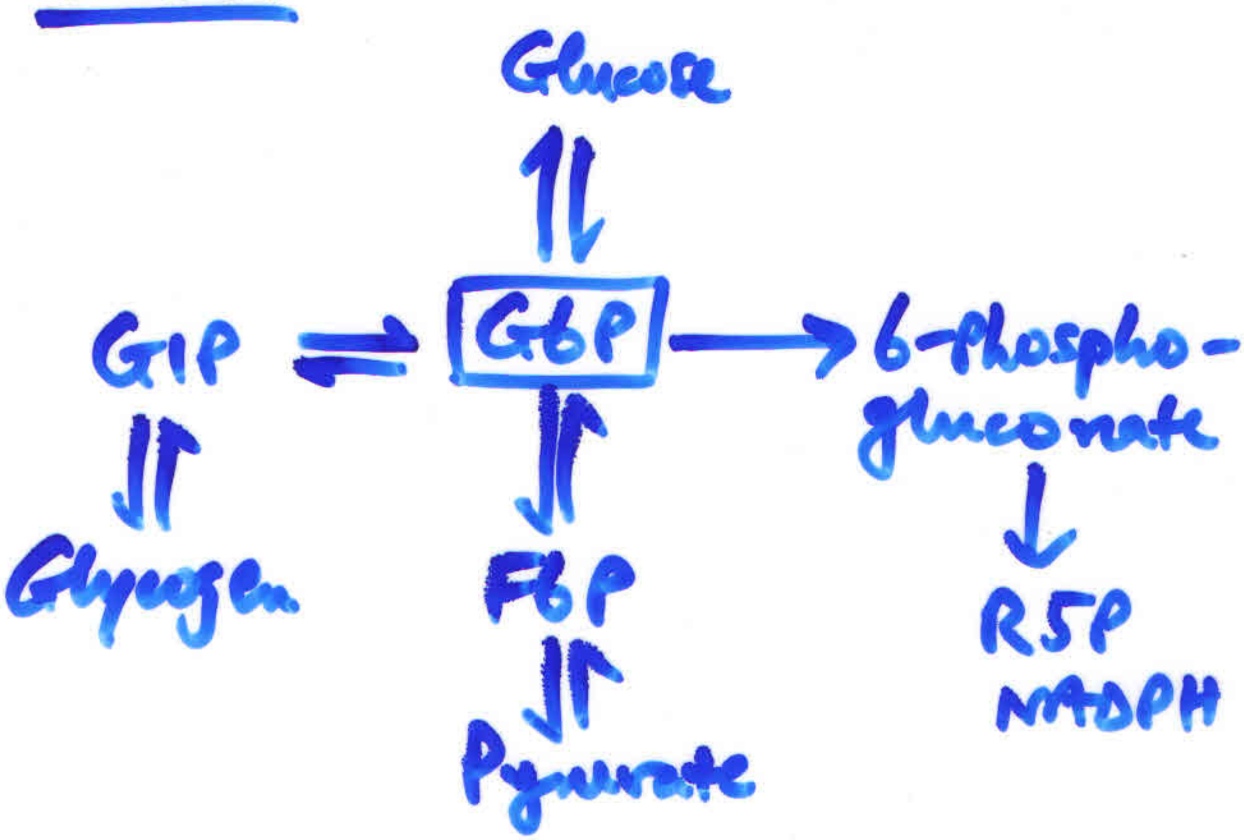
__NB__ Only the liver can carry out __all__ of the above pathways.

Hepatocyte

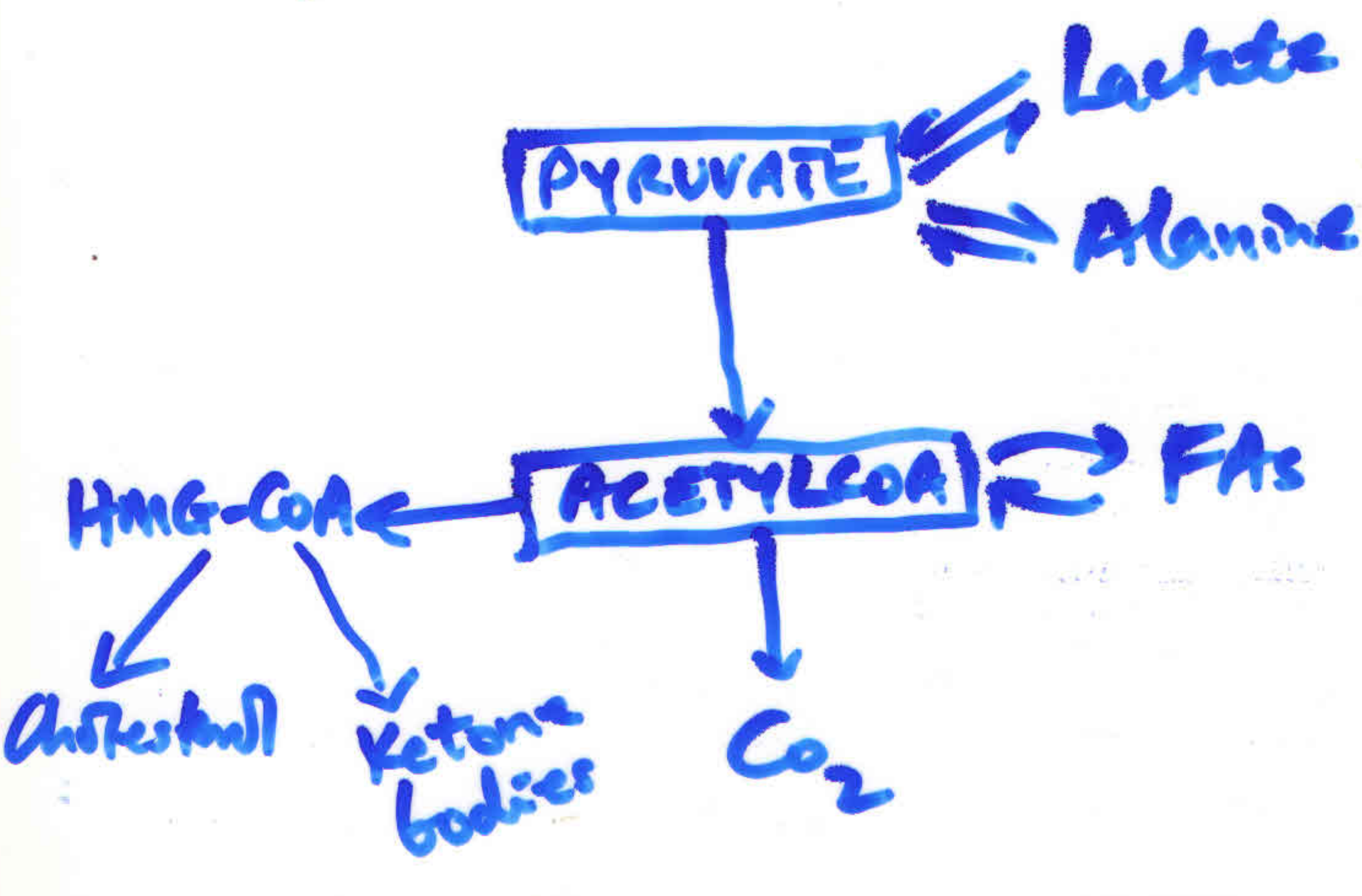


KEY junction points

1. G6P



2. Pyruvate and AcetylCoA



THE MUSCLE

- It utilizes glucose, fatty acids and ketone bodies for fuel to produce ATP for mechanical work.
- It does not utilize proteins directly! i.e. it uses proteins or "modified" proteins from other sources = liver.
- Utilize 50-90% of O_2 taken by humans.
- Resting muscle – uses FAs + KBs
- Moderately active – uses glucose, FAs and KBs
- Active muscle = Glucose (short time)
  = Glucose + FAs (long time)
- Glucose comes from stored glycogen

* Glycolysis > OP

↑ Lactic acid

↓ pH → ↓ muscle efficiency

Muscle glycogen = used only for glycolysis

* Role of Creatine kinase (CK).

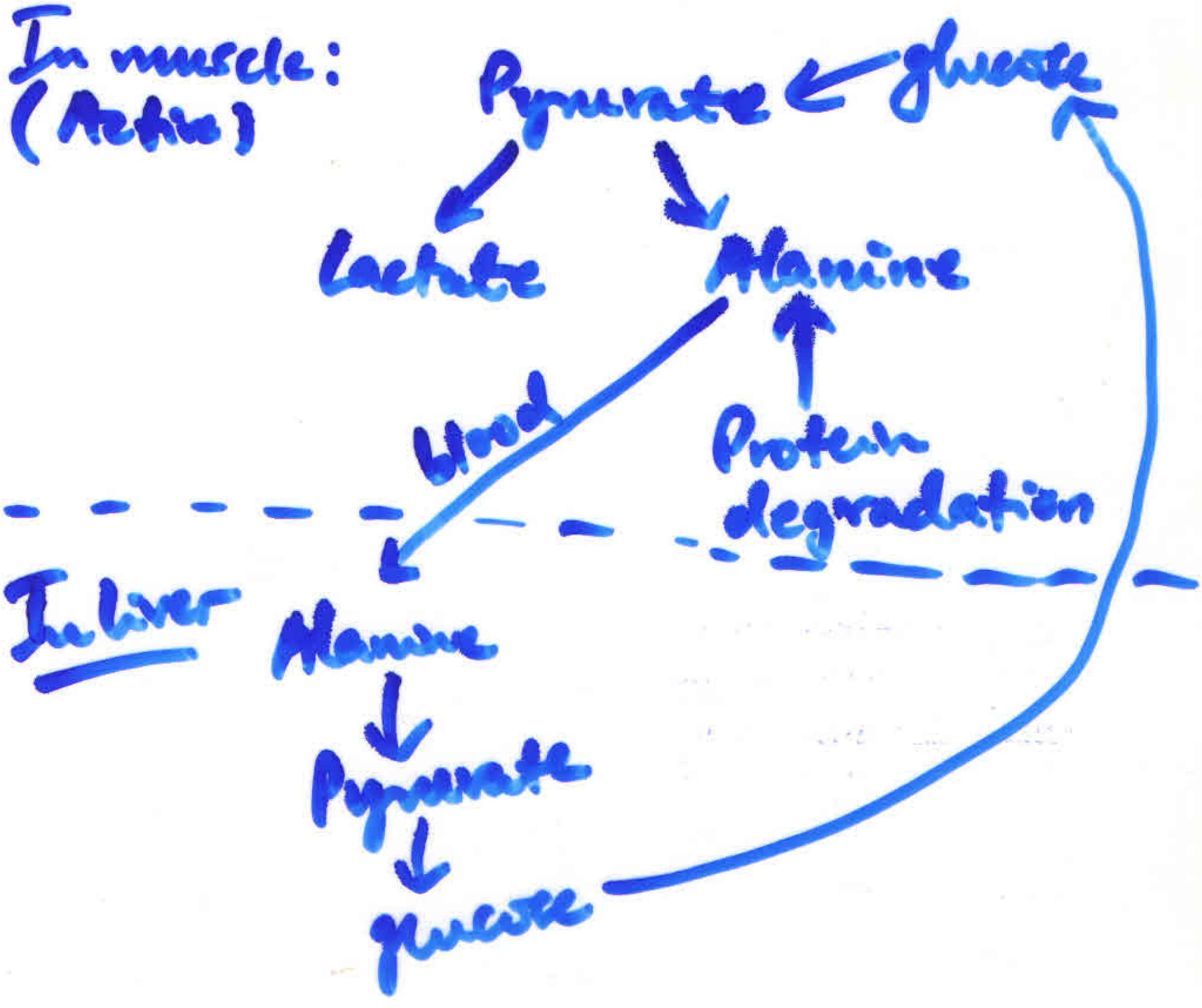
① The Cori cycle = metabolic cooperation between muscle and liver i.e. glycolysis Vs gluconeogenesis

Glycolysis = produce ATP

Gluconeogenesis = utilize ATP

* All available ATP in muscle is devoted to muscle contraction.

② The Glucose-Alanine cycle



Heart muscle: Aerobic
- FAs are its fuel of choice
- KBs
- Lactate

THE ADIPOSE TISSUE

- Metabolically active ↑ Glycolysis
- A storage organ - TGs
- TG synthesis = Esterification
- TG breakdown = Lipolysis

THE BRAIN

- Normally uses only glucose as fuel 120g/day.
- The energy is used to maintain the electrostatic potentials for nerve impulses i.e. maintain the Na^+, K^+ potentials.
- Synthesizes neurotransmitters.
- Prolonged CHO lack ⇒ it utilises KBs.
- * FA cannot be used by the brain – because they cannot traverse the brain blood barrier.
- Brain uses at least 20% of O_2 consumed at rest.

THE BLOOD

- Carries O_2, metabolites, hormones, proteins, cells, inorganic components, waste products and water.
- Human has 5-6 Litres of blood

* Glucose levels 60-90 mg/ml of blood (4.5mM)

60-90 Normal range

40-60 <
- Neurological signs
- Hunger
- ↑ Glucagon, epinephrine, cortisol, sweating, trembling etc.

20-40 — Lethargy, convulsions and coma

< 20 — Permanent head damage, Death.

∴ < 40 = Hypoglycemia.

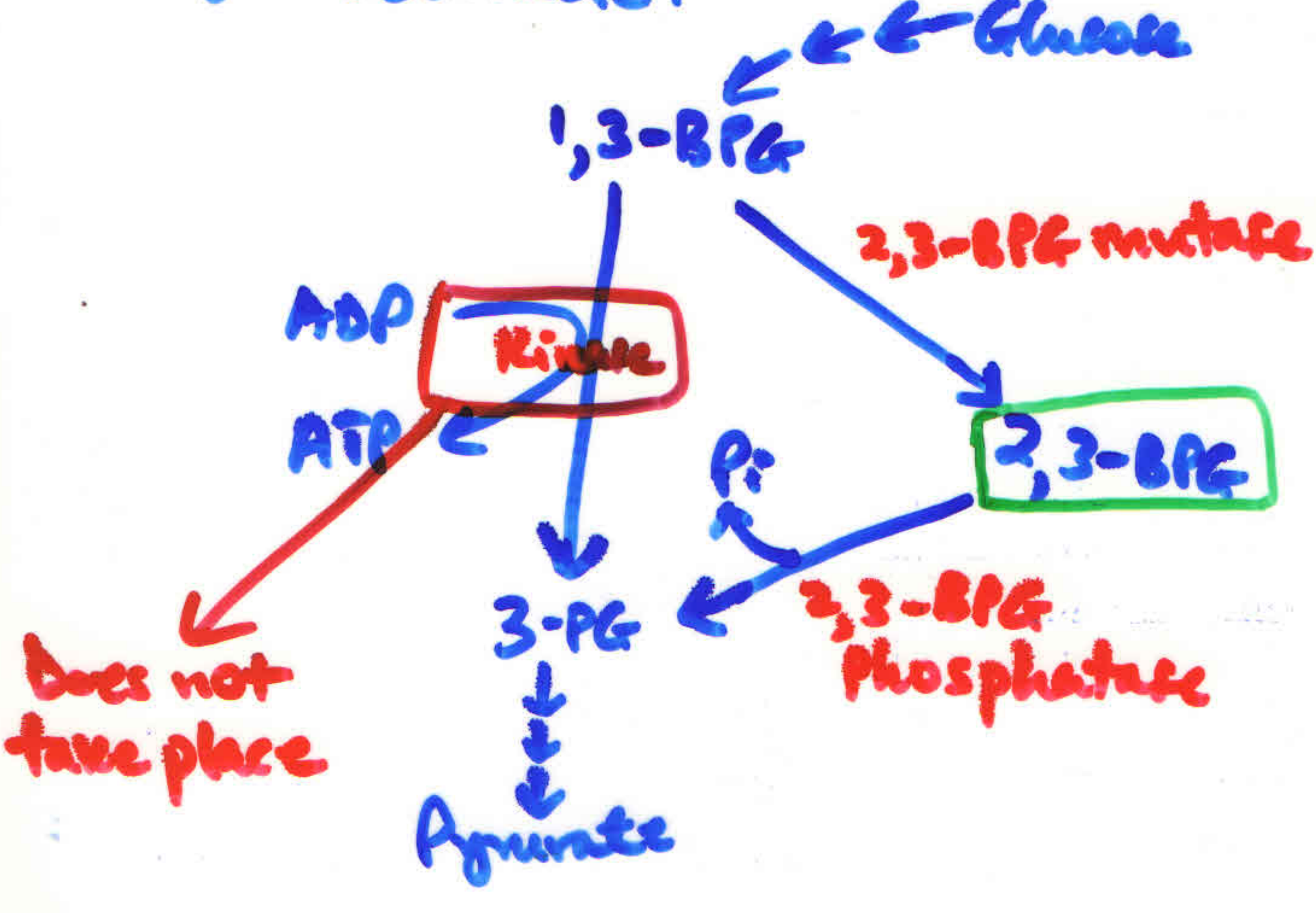
* Blood glucoce levels is very important to brain.
Homones Insulin, glucagon and epinephrine are the major players/regulators.

* Recent studies: The brain itself, through its hypothalamus is involved in maintaining blood glucose levels — and not insulin and glucagon does.
⟹ partnership between the pancreas and the hypothalamus.

Erythrocytes (RBCs)

- found in blood.
- Carry O_2 and CO_2.
- Utilises exclusively glucose
- Has no mitochondria - so their energy depends on glycolysis.
- Under less O_2 tension, RBCs modify their glycolytic pathway - making it shorter and energy loss per glucose oxidized to pyruvate.

* Role of glycolysis in adaptation to high altitude.



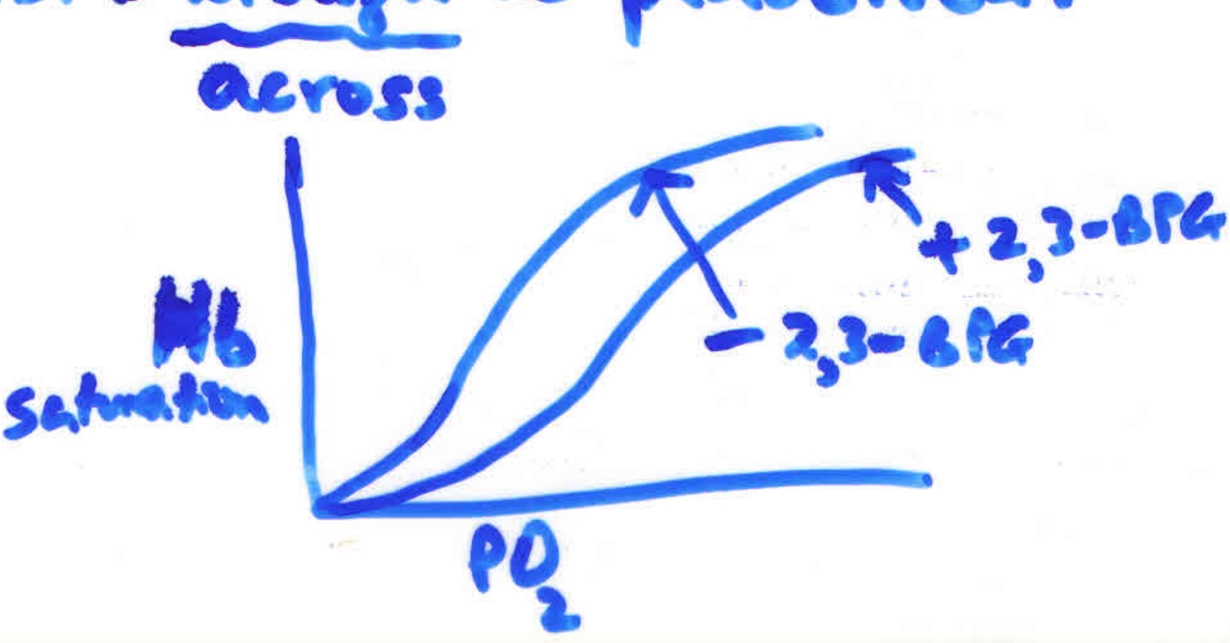
Significance;

- 2,3-BPG is a negative allosteric effector of the O_2 affinity of Hb.
- It decreases the O_2 affinity of deoxyHb, promoting the release of O_2 in peripheral tissue when O_2 tension and saturation is decreased in the lung.

  NB Acclimitazation

  ↑ [2,3-BPG] during adaptation to high altitude.

- HbF is less sensitive to the effects of 2,3-BPG - allowing O_2 transfer from the mother HbA to fetal HbF ~~through~~ across the placenta.



Hormonal regulation

- Metabolism is hormonally regulated.
- The major hormones are insulin, glucagon and epinephrine.

· Insulin signals high glucose in blood.
· Glucagon signals low blood glucose.
· Epinephrine signals impending activity.

* The action of the 3 hormones largely depend on the feeding state.

1. Insulin

Fed state: ↑ Insulin ↓ Glucagon

Metabolic effect	Target enzyme
- ↑ Glucose uptake (Muscle / Liver)	↑ Glucose transporter ↑ Glucokinase
- ↑ Glycogenesis (liver / muscle)	↑ Glycogen synthase
- ↓ Glycogenolysis (liver / muscle)	↓ Glycogen phosphorylase
- ↑ Glycolysis	↑ PFK-1
- ↑ FA synthesis (Liver)	↑ AcetylCoA carboxylase
- ↑ TG synthesis (Adipose tissue)	↑ Lipoprotein lipase

Manifestations of Insulin deficiency;

1. Diabetes mellitus
   - Type I (IDDM) – begins early in life and quickly becomes severe. Requires insulin therapy.
   - Type II (NIDDM) – slow to develop, milder and often goes unnoticed.

Thirst, polyuria, polydipsia = due to glucosuria

2. ↑ KBs synthesis — ↑ Ketosis – ↑ Acidosis

↑ Ketonemia ↑ Ketonuria

↑ Ketoacidosis

↑ Lipolysis
↑ β-oxidation

2. Glucagon

Several hours after dietary CHO intake; Level of blood glucose falls – due to consumption by tissues, including BRAIN.

Metabolic effect	Target enzyme
- ↑ Glycogenolysis (liver)	↑ Glycogen phosphorylase
- ↓ Glycogenesis (liver)	↓ Glycogen synthase
- ↓ Glycolysis (liver)	↓ PFK-1
- ↑ Gluconeogenesis (liver)	↑ F1,6 BPase
	↓ Pyruvate kinase
- ↑ FA mobilization (adipose tissue)	↑ TG lipase

Amino acids, Glycerol, OAA } → Glucose

* Glucagon targets the liver mainly
Effect on glucose; i.e. Production & Release.

- Glycogen → glucose.
- Less glucose stored as glycogen.
- Less glucose used as fuel in liver.
- Non-CHOs converted to glucose.
- Less glucose used as fuel by liver and muscle.

* SLOW acting

3. Epinephrine

↑ Heart rate
↑ BP
↑ Dilation of respiratory passages

} To increase delivery of O_2 to tissues

Epinephrine acts primarily on muscle, liver and adipose tissue.

Metabolic effect

↑ Glycogenolysis (liver/muscle)
↓ Glycogenesis (liver/muscle)
↑ Gluconeogenesis (liver)

} Increased production of glucose for fuel.

↑ Glycolysis (muscle) – Increased ATP production.

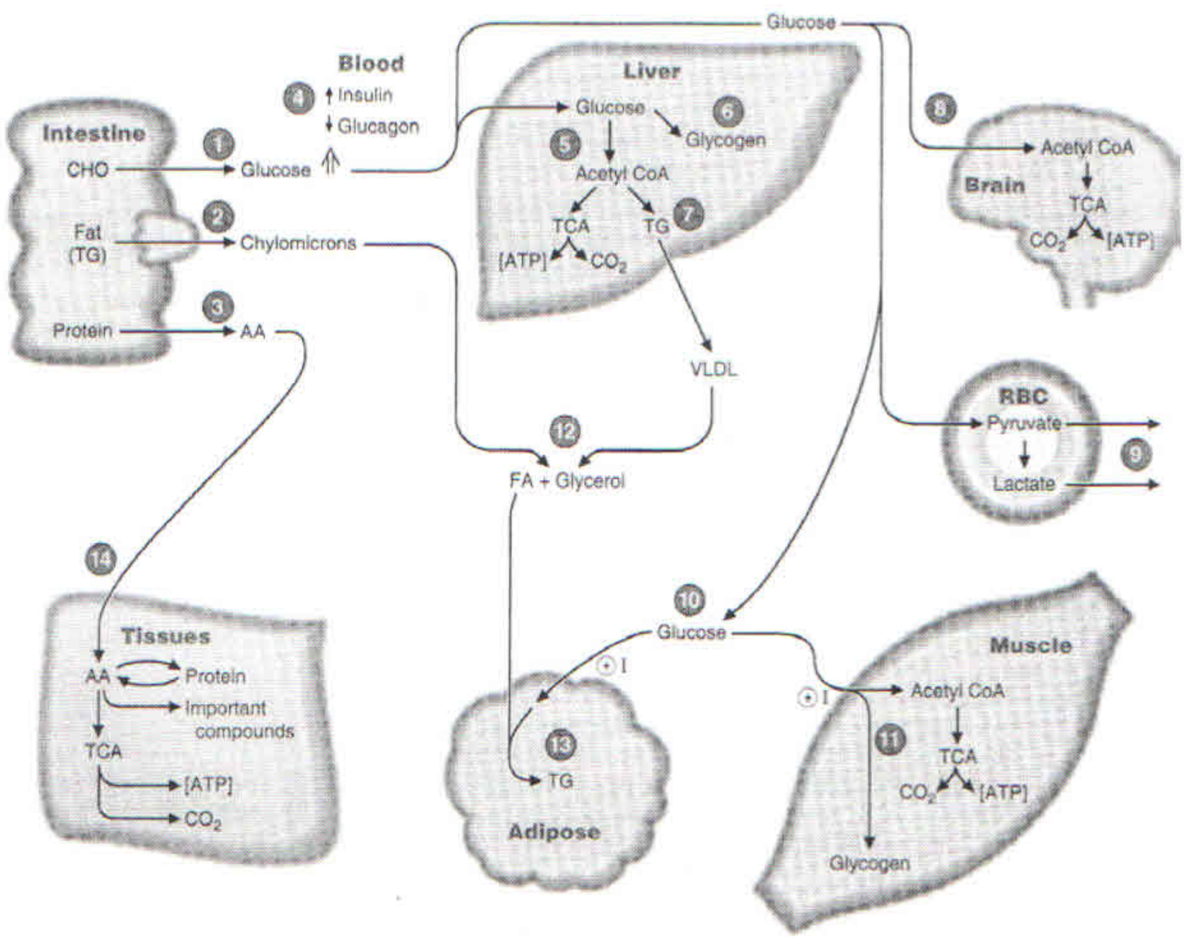
↑ FA mobilization (adipose tissue) – Increased availability of fatty acids as fuel.

↑ Glucagon
↓ Insulin

} Reinforce metabolic effects of epinephrine.

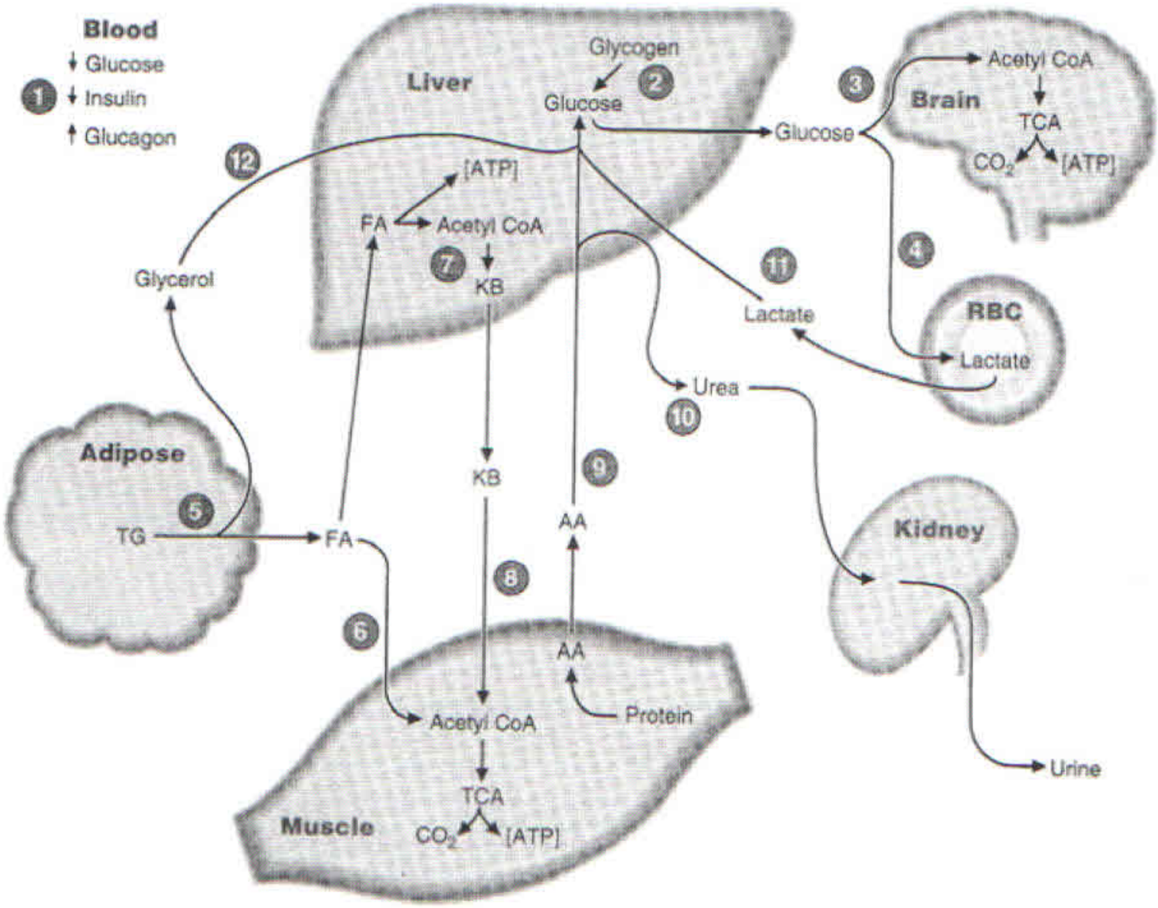
Metabolic States

1.) Fed State = CHO Plenty



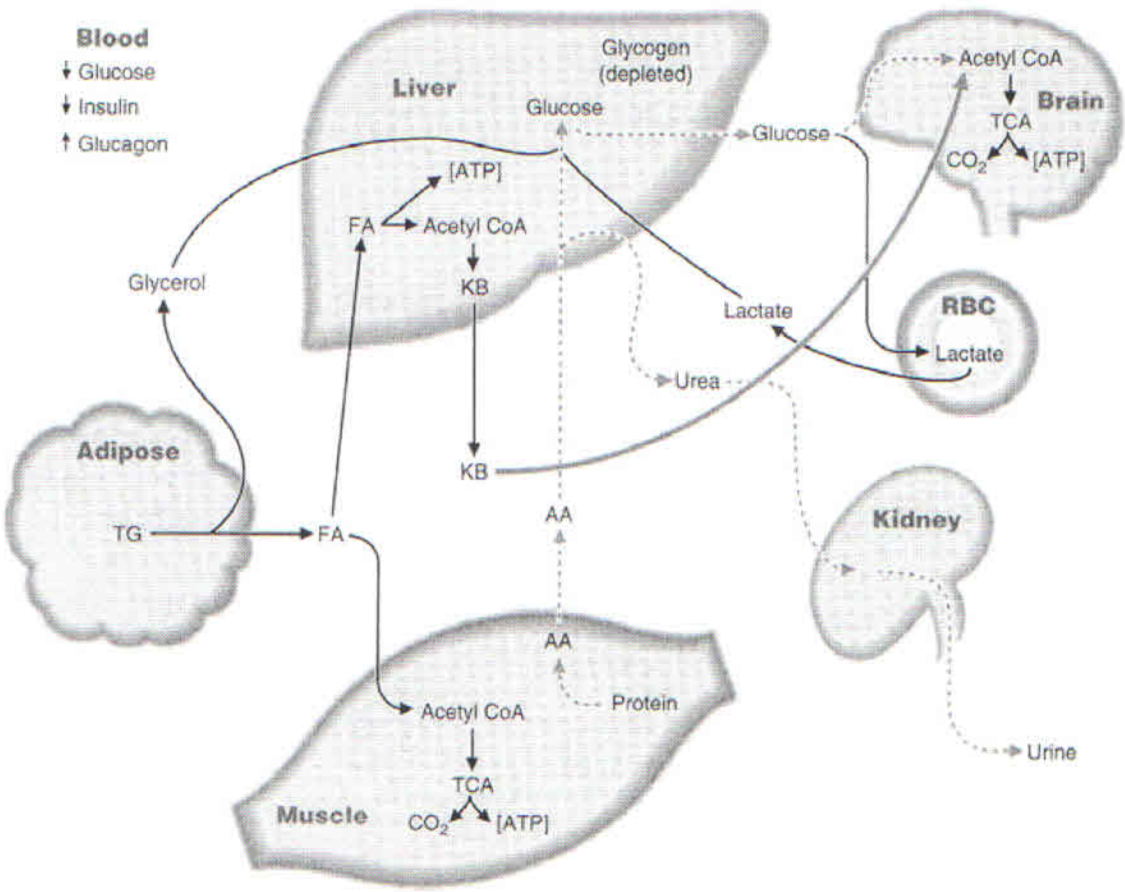
Metabolic States

2.) Fasted State = CHO Lack



Metabolic States

3.) Starved State



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