

Rate Limiting Enzymes In Biochemistry

A **rate-limiting enzyme** controls the speed of a metabolic pathway by catalyzing the slowest, most regulated step. Understanding these enzymes is crucial for grasping metabolic control and pharmacologic targets.

1. Glycolysis

- **Rate-limiting enzyme: Phosphofructokinase-1 (PFK-1)**
- **Function:** Converts fructose-6-phosphate to fructose-1,6-bisphosphate.
- **Regulation:** Activated by AMP, inhibited by ATP and citrate.
- **Clinical relevance:** Target for energy modulation in hypoxia and cancer metabolism (Warburg effect).

2. Gluconeogenesis

- **Rate-limiting enzyme: Fructose-1,6-bisphosphatase**
- **Correction: NOT PEP carboxykinase** (though important, it's not the rate-limiting step).
- **Function:** Converts fructose-1,6-bisphosphate to fructose-6-phosphate.
- **Regulation:** Inhibited by AMP and fructose-2,6-bisphosphate.

3. Glycogenesis (Glycogen Synthesis)

- **Rate-limiting enzyme: Glycogen Synthase**
- **Function:** Catalyzes the addition of glucose units to the growing glycogen chain.
- **Regulation:** Activated by insulin, inhibited by glucagon and epinephrine via phosphorylation.

4. Glycogenolysis (Glycogen Breakdown)

- **Rate-limiting enzyme: Glycogen Phosphorylase**
- **Function:** Cleaves glucose residues from glycogen.
- **Regulation:** Activated by glucagon (liver), epinephrine (muscle), and AMP; inhibited by insulin and ATP.

5. Citric Acid Cycle (Krebs Cycle)

- **Rate-limiting enzyme: Isocitrate Dehydrogenase**
- **Function:** Converts isocitrate to α -ketoglutarate, producing NADH.
- **Regulation:** Activated by ADP, inhibited by ATP and NADH.

6. Ketone Body Synthesis

- **Rate-limiting enzyme: HMG-CoA Synthase (mitochondrial)**
- **Function:** Converts acetyl-CoA into HMG-CoA, a precursor for ketogenesis.

- **Clinical relevance:** Upregulated in prolonged fasting and uncontrolled diabetes.

7. Cholesterol Synthesis

- **Rate-limiting enzyme: HMG-CoA Reductase**
- **Function:** Converts HMG-CoA to mevalonate.
- **Regulation:** Inhibited by statins and cholesterol; regulated by SREBP transcription factors.

8. Heme (Porphyrin) Synthesis

- **Rate-limiting enzyme: δ -Aminolevulinic Acid Synthase (ALA Synthase)**
- **Function:** Catalyzes condensation of glycine and succinyl-CoA to form ALA.
- **Regulation:** Inhibited by heme (end-product feedback).
- **Clinical relevance:** Defects can cause porphyrias.

9. Fatty Acid Synthesis

- **Rate-limiting enzyme: Acetyl-CoA Carboxylase (ACC)**
- **Function:** Converts acetyl-CoA to malonyl-CoA.
- **Regulation:** Activated by insulin and citrate; inhibited by glucagon and palmitoyl-CoA.

10. Purine Degradation (Uric Acid Synthesis)

- **Rate-limiting enzyme: Xanthine Oxidase**
- **Function:** Converts hypoxanthine \rightarrow xanthine \rightarrow uric acid.
- **Clinical relevance:** Target of **allopurinol** in gout treatment.