Catabolism of branched chain amino acids

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Branched chain AA are: Isoleucine, Leucine, Valine

* Essential AA

•Metabolized primarily by the peripheral tissues (muscles) and not In the liver like other amino acids.

*All three have similar route of catabolism

Amino acids that form succinyl CoA

Leucine-Ketogenic aa

- Metabolism of Leucine produce: Acetoacetate and AcetylCoA

) Valine and Isoleucine → Metabolism of Isoleucine Also give Acetyl CoA and hence Is both glucogenic and ketogeic

Valine and Isoleucine

↓

Propionyl CoA

↓ Requires vitamin B12 and Biotin

Succinyl CoA → TCA cycle

Branched chain amino acid degradation

- Degradation of Ile, Leu, and Val use common enzymes for the first three steps

1. **Transamination to the corresponding α-keto acid**
2. **Oxidative decarboxylation to the corresponding acyl-CoA**
3. **Dehydrogenation by FAD to form a double bond.**

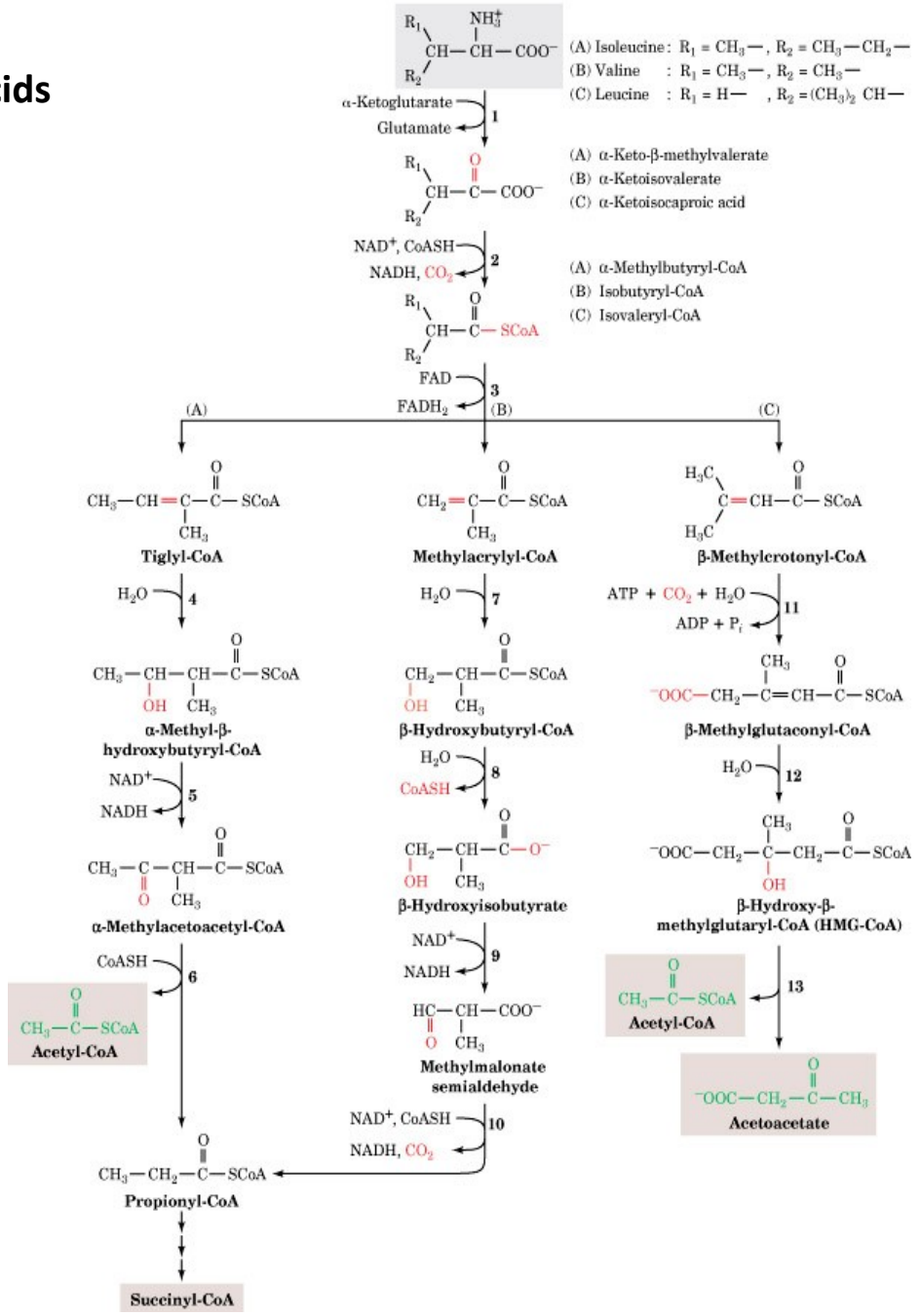
First three enzymes

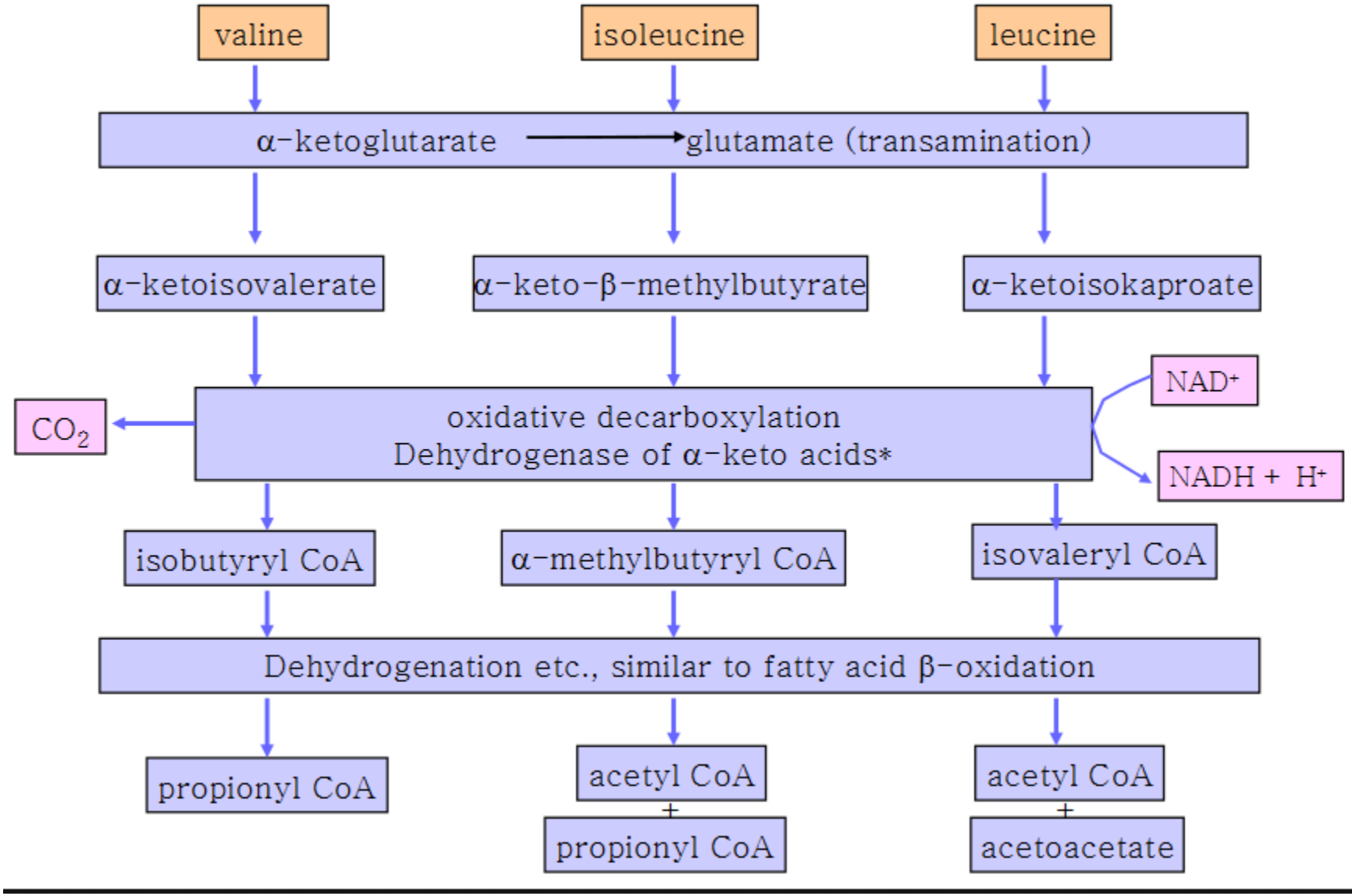
1. **Branched-chain amino acid aminotransferase**
2. **Branched-chain α–keto acid dehydrogenase (BCKDH)**
3. **Acyl-CoA dehydrogenase**

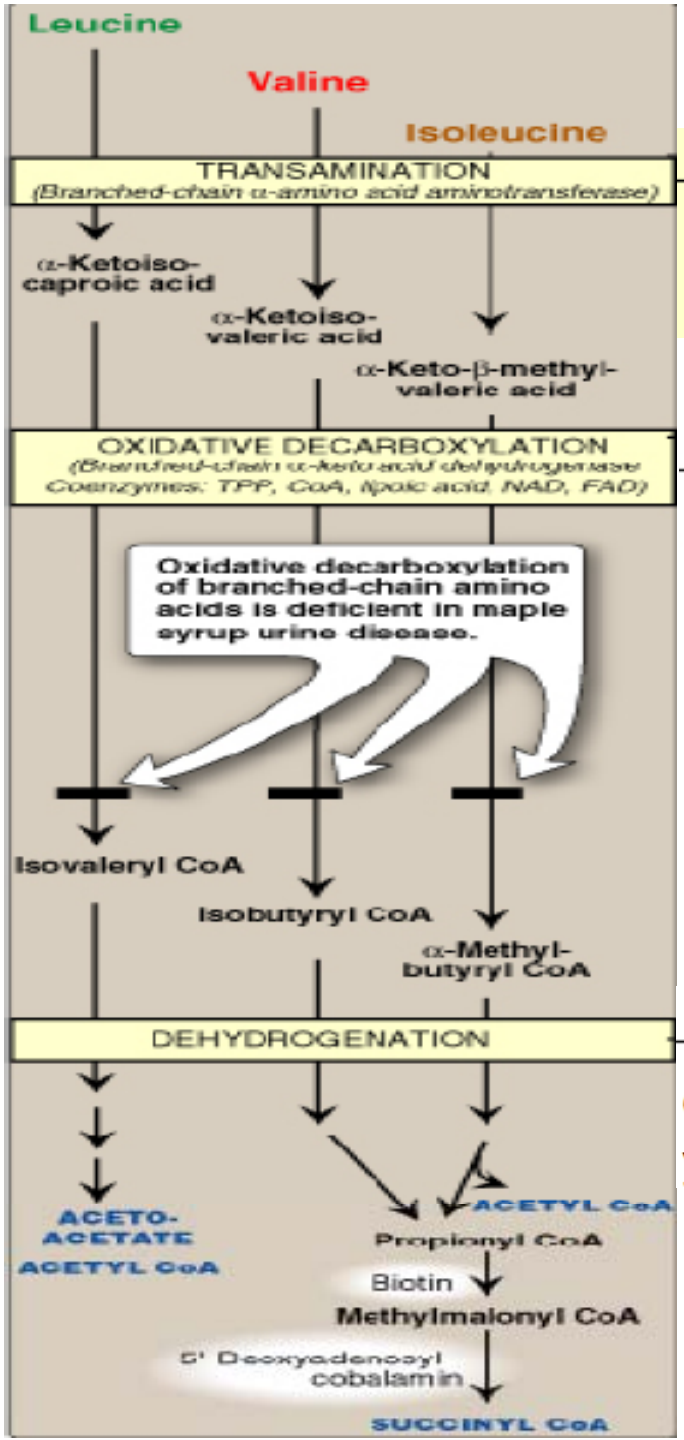
The degradation of the branched-chain amino acids
(A) isoleucine, (B) valine, (C) leucine.

First three enzymes:

1. Branched-chain amino acid aminotransferase
2. Branched-chain α–keto acid dehydrogenase (BCKDH)
3. Acyl-CoA dehydrogenase
4. Enoyl-CoA hydratase - double bond hydration
5. β-hydroxyacyl-CoA dehydrogenase- dehydrognation by NAD+
6. Acetyl-CoA acetyltransferase - thiolytic cleavage
7. Enoyl-CoA hydratase - double bond hydration
8. β-hydroxy-isobutyryl-CoA hydrolase -hydrolysis of CoA
9. β–hydroxyisobutyrate dehydrogenase - second dehydration
10. Methylmalonate semialdehyde dehydrogenase - oxidative carboxylation
11. β-methylcronyl-CoA carboxylase-carboxylation reaction (biotin)
12. β-methylglutaconyl-CoA hydratase-hydration reaction
13. HMG-CoA lyase




valine
isoleucine
leucine
α-ketoglutarate
glutamate (transamination)
α-ketoisovalerate
α-keto-β-methylbutyrate
α-ketoisokaproate
NAD+
CO2
oxidative decarboxylation
Dehydrogenase of α-keto acids*
NADH + H+
isobutyryl CoA
α-methylbutyryl CoA
isovaleryl CoA
Dehydrogenation etc., similar to fatty acid β-oxidation
propionyl CoA
acetyl CoA
+
propionyl CoA
acetyl CoA
+
acetoacetate



Transamination

Catalyzed by a single Vitamin B6-requiring enzyme, Branched-chain α-amino acid aminotransferase.

Oxidative decarboxylation

The removal of carboxyl group of the α-keto acids from these three AAs is catalyzed by the same branched-chain α-keto acid dehydrogenase complex.

This enzyme uses thiamine pyrophosphate, lipoic acid, FAD, NAD+, and CoA as cooenzymes).

Dehydrogenase

Oxidation of the products formed in the decarboxylation reaction yields α-β-unsaturated acyl CoA derivatives.

- The branched chain amino acids initially share in part a common pathway.
- **Branched Chain α-Keto Acid Dehydrogenase** (BCKDH) is a multi-subunit complex homologous to Pyruvate Dehydrogenase complex.
- Genetic deficiency of BCKDH is called **Maple Syrup Urine Disease** (MSUD).
- High concentrations of branched chain keto acids in urine give it a characteristic odor.

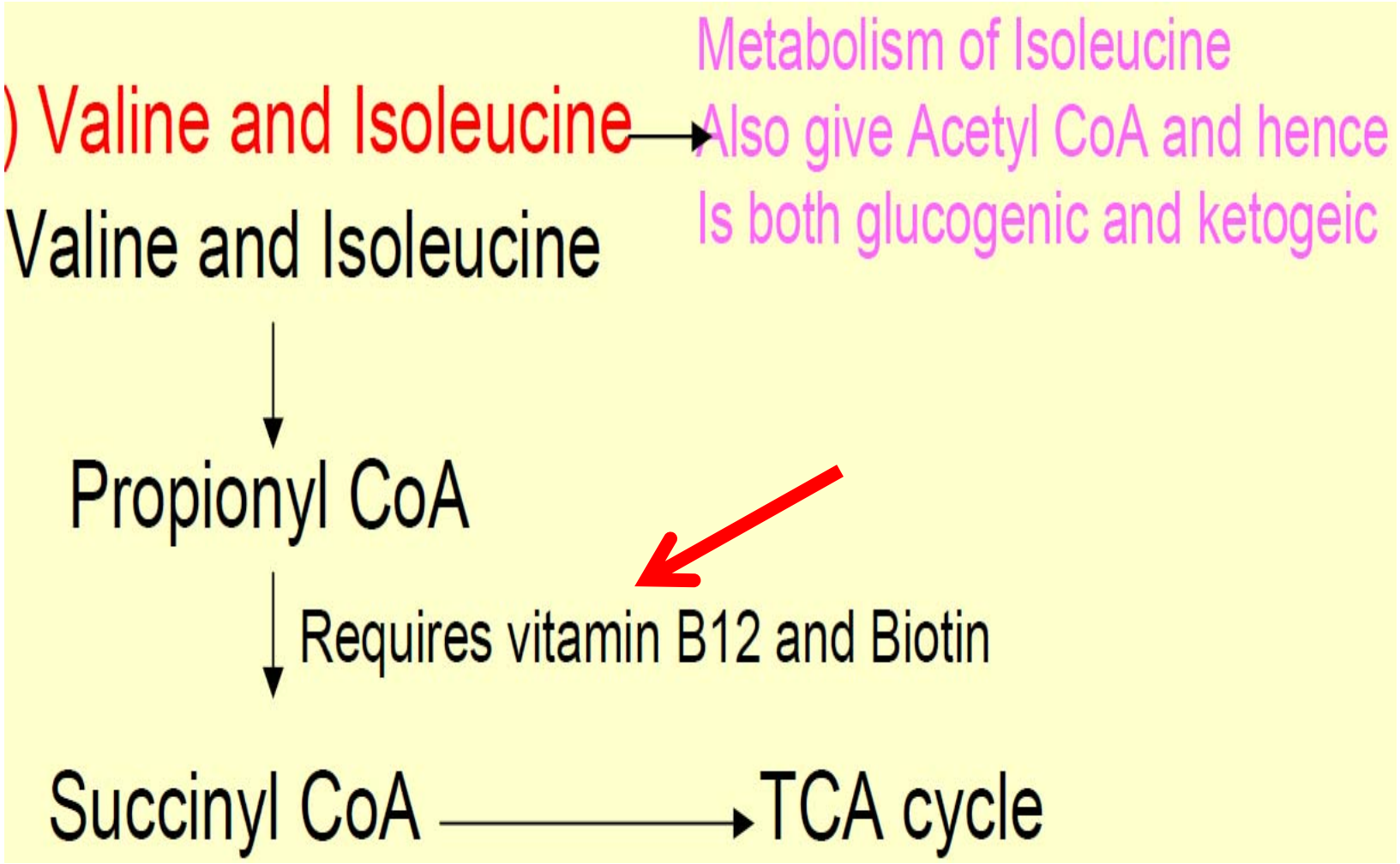
Branched-chain aminoaciduria

Disease also called Maple Syrup Urine Disease (MSUD) (because of the characteristic odor of the urine in affected individuals).

Deficiency in an enzyme, **branched-chain α-keto acid dehydrogenase** leads to an accumulation of three branched-chain amino acids and their corresponding branched-chain α-keto acids which are excreted in the urine.

There is only one dehydrogenase enzyme for all three amino acids.

Mental retardation in these cases is extensive.


Metabolism of Isoleucine
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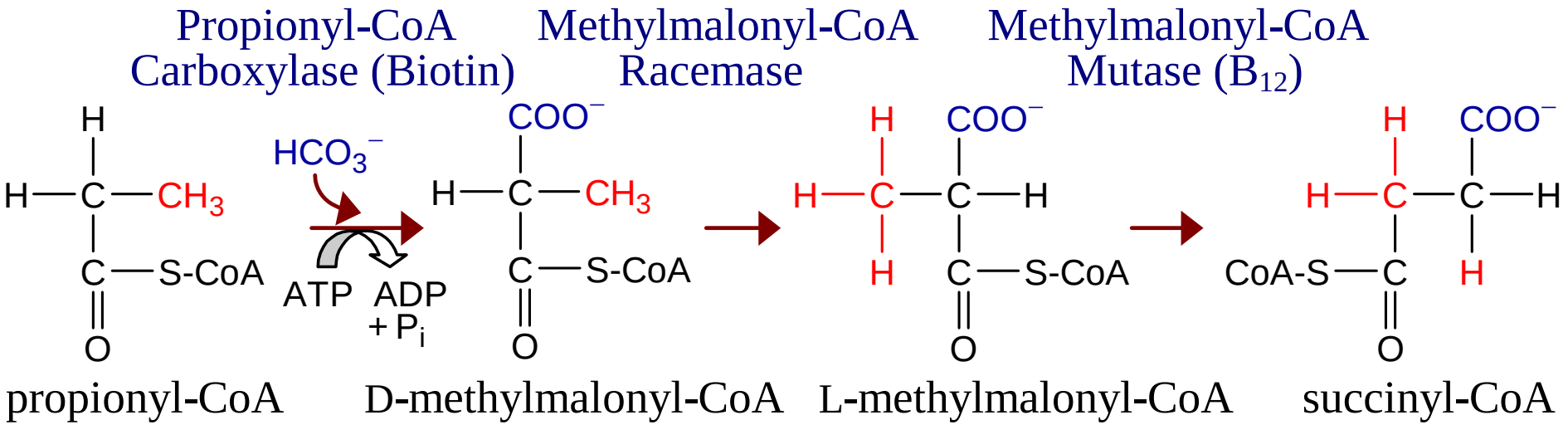
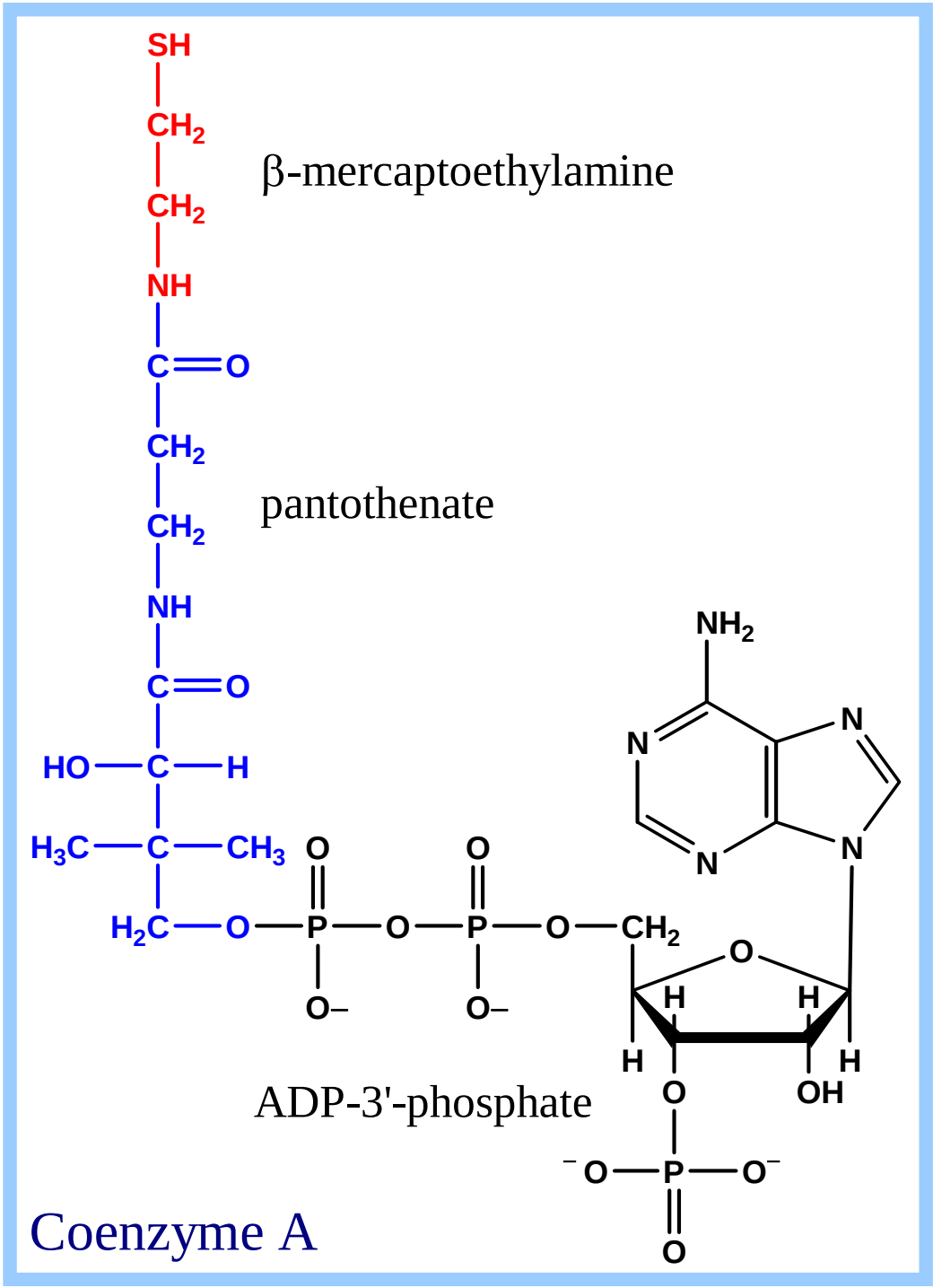
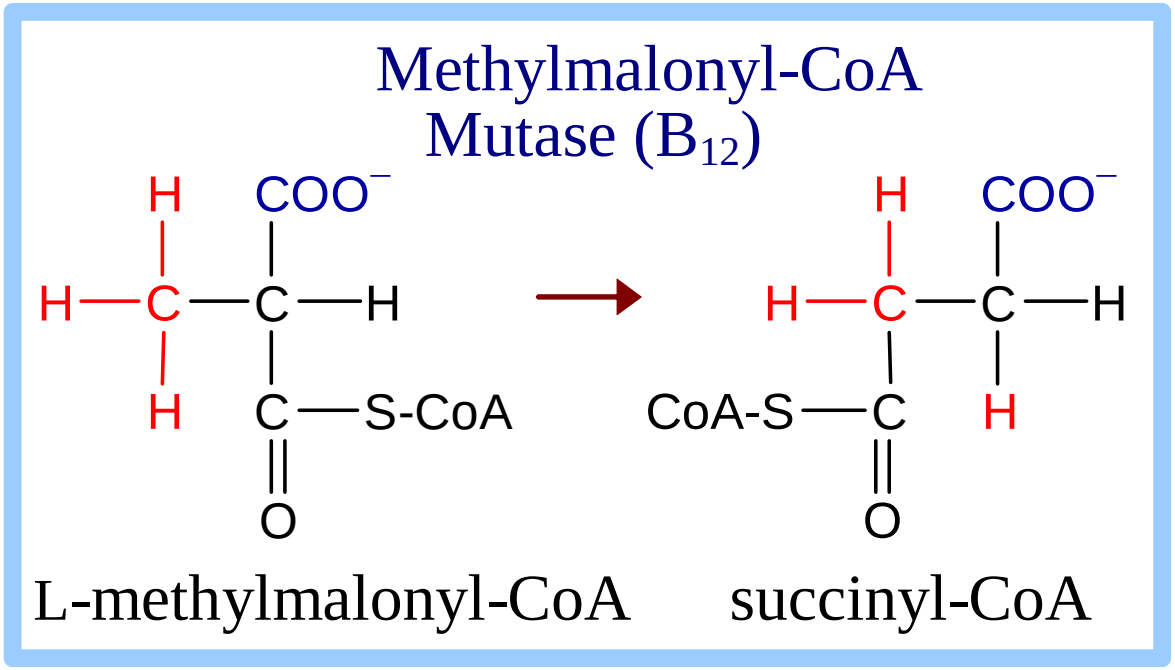


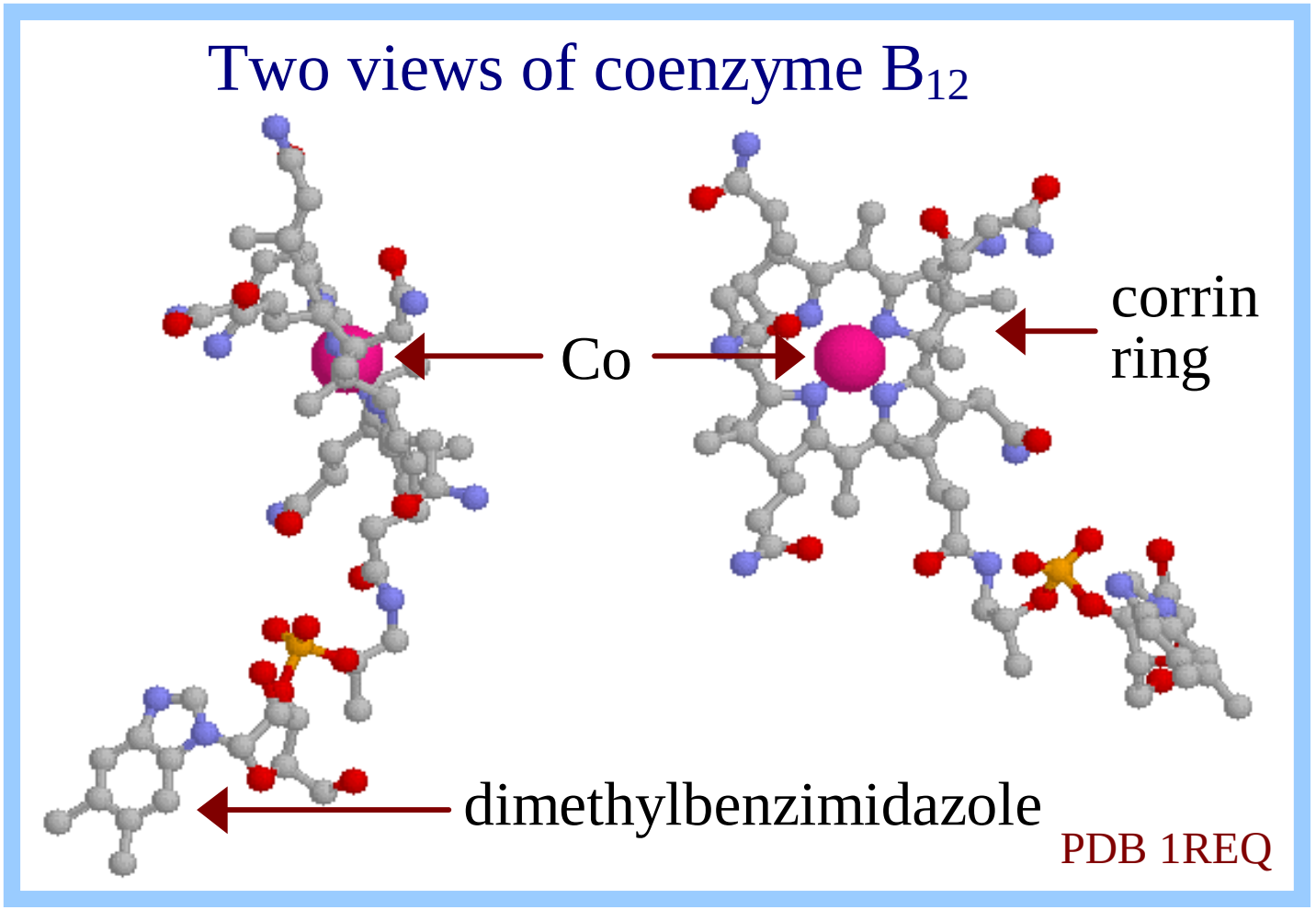
- **Propionyl-CoA** is carboxylated to methylmalonyl-CoA.
- A **racemase** yields the L-isomer essential to the subsequent reaction.
- **Methylmalonyl-CoA Mutase** catalyzes a molecular rearrangement: the branched C chain of methylmalonyl-CoA is converted to the linear C chain of succinyl-CoA.
- The **carboxyl** that is in ester linkage to the thiol of coenzyme A is **shifted** to an adjacent carbon atom, with **opposite shift of a hydrogen atom**.

Recall that **coenzyme A** is a large molecule.





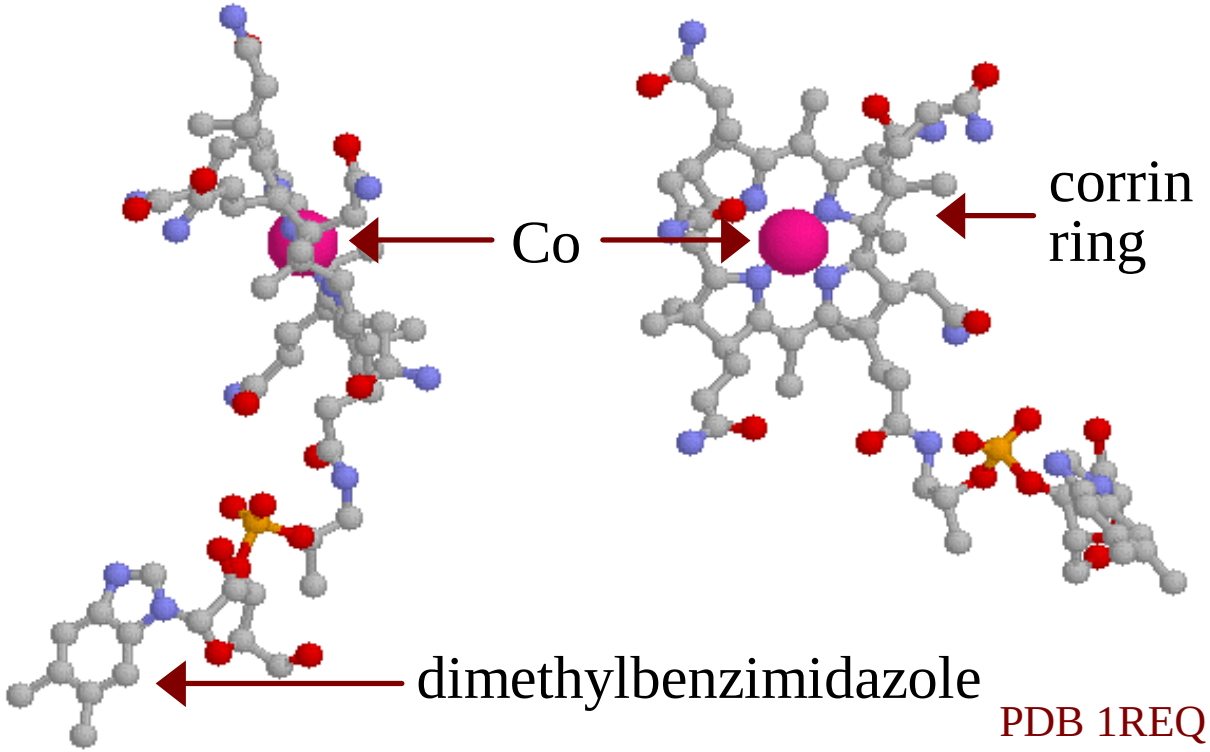
Coenzyme B_{12}, a derivative of **vitamin B_{12}** (**cobalamin**), is the prosthetic group of **Methylmalonyl-CoA Mutase**.



A crystal structure of the **enzyme-bound coenzyme B_{12}**.

Coenzyme B_{12} contains a heme-like **corrin ring** with a **cobalt** ion coordinated to **4** ring **N** atoms.

Within the active site, the Co atom of coenzyme B_{12} has **2 axial ligands**:



- methyl **C** atom of **5'-deoxyadenosine** (not shown).
- an enzyme **histidine N**

When B_{12} is free in solution, a ring **N** of the **dimethylbenzimidazole** serves as **axial ligand** to the cobalt.

When B_{12} is **enzyme-bound**, a **His** side-chain **N** substitutes for the dimethylbenzimidazole.

- **Methyl group transfers** are also carried out by **B_{12}** (cobalamin).

- **Methyl-B_{12}** (methylcobalamin), with a **methyl axial ligand** substituting for the deoxyadenosyl moiety of coenzyme B_{12}, is an intermediate of such transfers.

- E.g., **B_{12}** is a prosthetic group of the mammalian enzyme that catalyzes methylation of homocysteine to from **methionine**.

- **Vitamin B_{12} is synthesized only by bacteria.**

  Ruminants get B_{12} from bacteria in their digestive system.

  Humans obtain B_{12} from **meat** or **dairy products**.

- **Vitamin B_{12}** bound to the protein **gastric intrinsic factor** is absorbed by cells in the upper part of the human small intestine via **receptor-mediated endocytosis**.

  - B_{12} synthesized by bacteria in the large intestine is unavailable.
  - **Strict vegetarians** eventually become **deficient in B_{12}** unless they consume it in pill form.

- **Vitamin B_{12}** is transported in the **blood** bound to the protein **transcobalamin**, which is recognized by a receptor that mediates uptake into body cells.

Summary of catabolism of Branched Amino acids