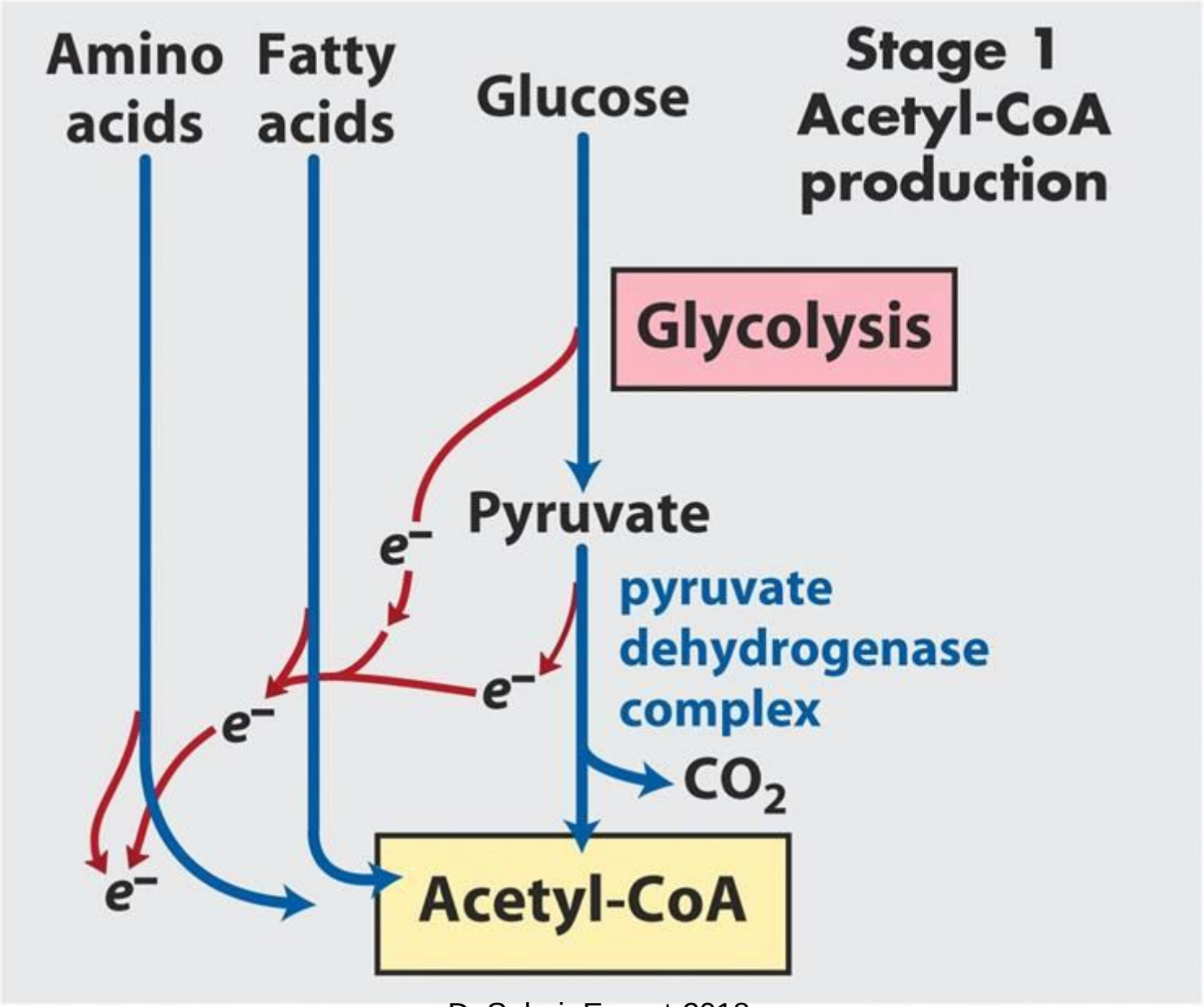
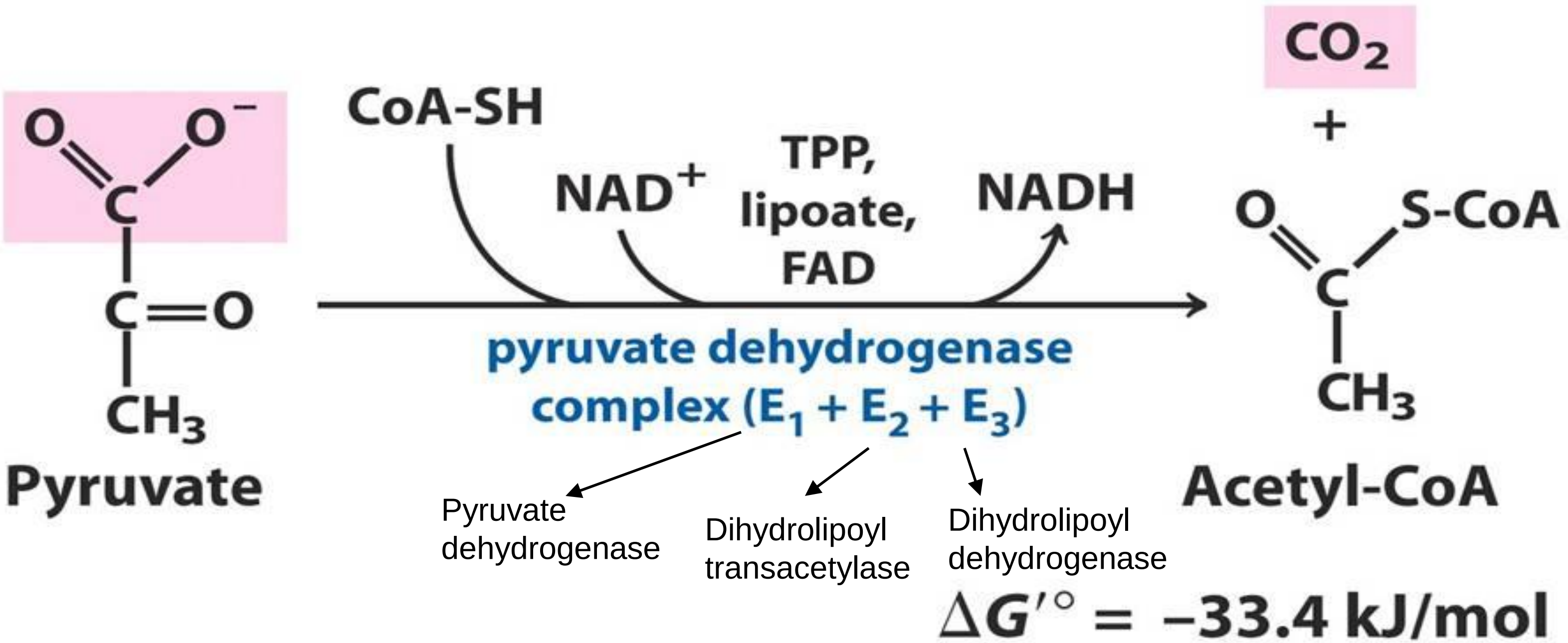
Pyruvate dehydrogenase complex


Amino acids
Fatty acids
Glucose
Stage 1
Acetyl-CoA production
Glycolysis
Pyruvate
e⁻
e⁻
e⁻
e⁻
pyruvate dehydrogenase complex
CO2
Acetyl-CoA

Pyruvate Dehydrogenase



- **irreversible;**
- **in mitochondria**.

Oxidative –decarboxylation of Pyruvate

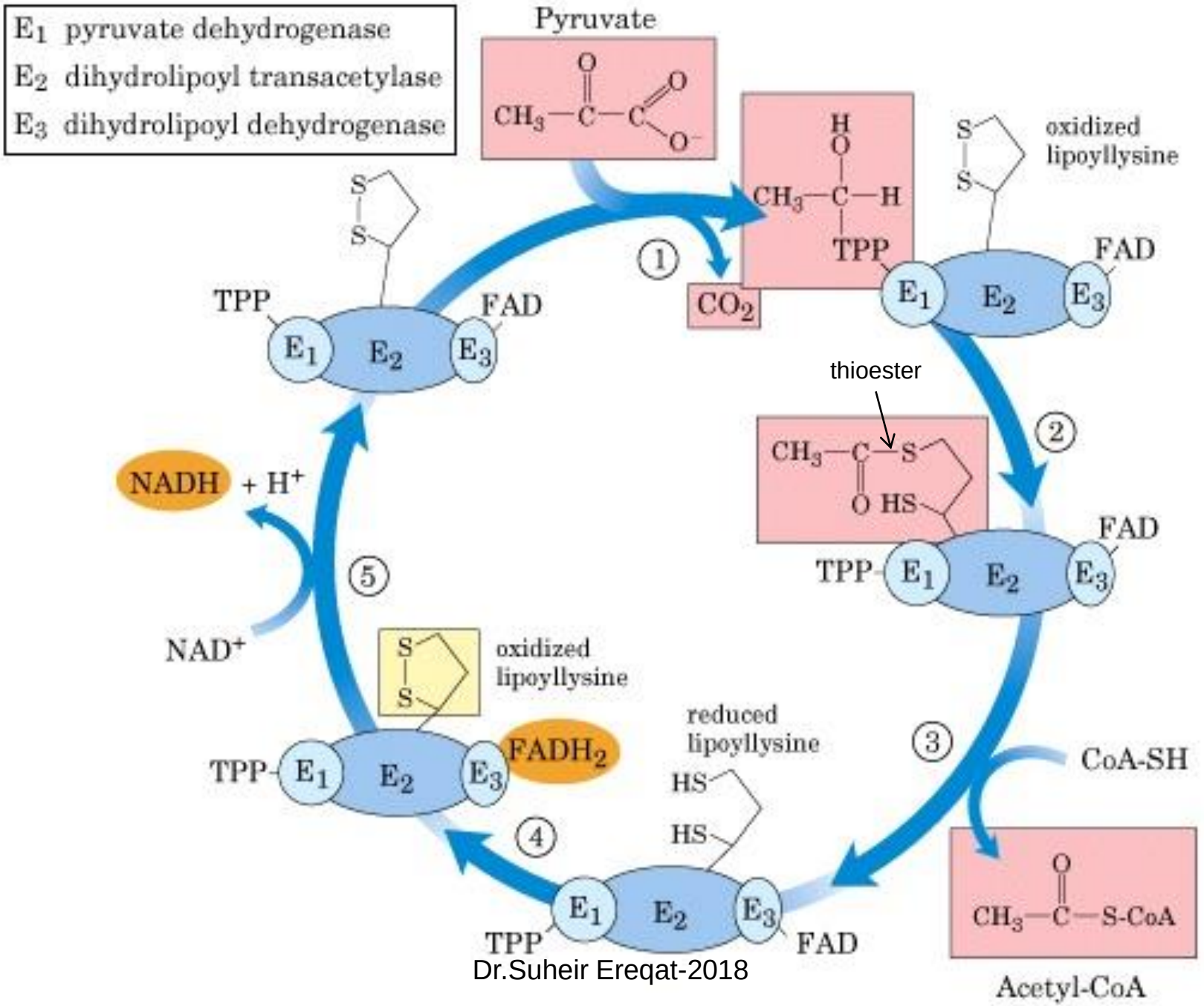
Pyruvate dehydrogenase complex:

3 Es

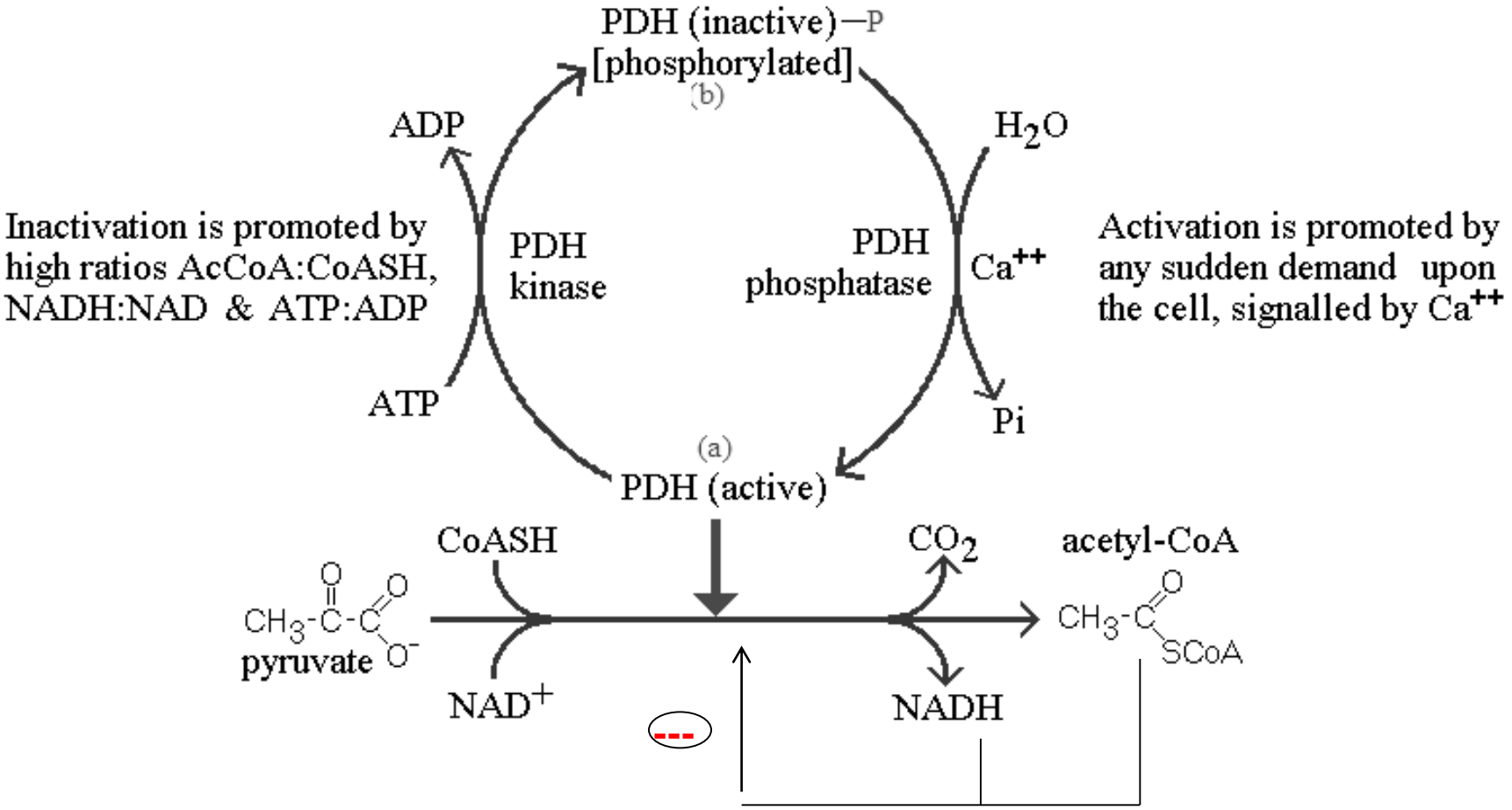
- **E_1 pyruvate dehydrogenase**
- **E_2 dihydrolipoyl transacetylase**
- **E_3 dihydrolipoyl dehydrogenase**

5 Coenzymes (Vitamins)

- **Thiamine pyrophosphate, TPP (VB_1)**
- **Lipoic Acid**
- **CoA (pantothenic acid)**
- **FAD (VB_2)**
- **NAD^+ (VB3)**


E1 pyruvate dehydrogenase
E2 dihydrolipoyl transacetylase
E3 dihydrolipoyl dehydrogenase
Pyruvate
oxidized lipoyllysine
thioester
reduced lipoyllysine
CoA-SH
Acetyl-CoA
NADH + H+
NAD+
FADH2
CO2
TPP
FAD
E1
E2
E3
1
2
3
4
5

Pyruvate dehydrogenase complex



Regulation of Pyruvate Dehydrogenase Complex:

Product inhibition (feedback inhibition) by **NADH** & **acetyl CoA**:

- **NADH** competes with NAD^+ for binding to $\mathbf{E_3}$.
- **Acetyl CoA** competes with CoASH for binding to $\mathbf{E_2}$.

During **starvation**:

- **Pyruvate Dehydrogenase Kinase increases** in amount in most tissues, including skeletal muscle, via increased gene transcription.
- Under the same conditions, the amount of **Pyruvate Dehydrogenase Phosphatase decreases**.

The resulting **inhibition** of **Pyruvate Dehydrogenase** prevents muscle and other tissues from catabolizing glucose & gluconeogenesis precursors.

- Metabolism shifts toward fat utilization.
- Muscle protein breakdown to supply gluconeogenesis precursors is increased.
- Available glucose is spared for use by the brain.

Pyruvate dehydrogenase deficiency

Pyruvate Dehydrogenase Deficiency (*PDH*) is a genetic disease that involves human metabolism. Some of the genetic causes are extremely rare in the order of 1 in millions. It affects a gene which codes for a critical enzyme complex. *PDH* deficiency is most commonly linked to the alpha unit of E1, which is X-linked, but autosomal recessive variants also exist.

PDH deficiency causes elevated serum lactate, pyruvate and alanine (lactic acidosis). Symptoms are varied, and include developmental and neurological defects which generally result in death .

Treatment

- Use of a ketogenic diet:

  The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet. The diet mimics aspects of starvation by forcing the body to burn fats rather than carbohydrates.

- Current research is being conducted on the viability of Dichloroacetic acid to treat the lactic acidosis commonly accompanied by this disorder.

- Salts of DCA have been studied as potential drugs because they stimulates the activity of the enzyme pyruvate dehydrogenase by inhibiting the enzyme pyruvate dehydrogenase kinase. Thus, it decreases lactate production by shifting the metabolism of pyruvate from glycolysis towards oxidation in the mitochondria.

Thiamin (Vitamin B1) deficiency causes Beriberi

Thiamine pyrophosphate (TPP) is an important cofactor of pyruvate dehydrogenase complex, or PDC a critical enzyme in glucose metabolism. Thiamine is neither synthesized nor stored in good amounts by most vertebrates.

It is required in the diets of most vertebrates. Thiamine deficiency ultimately causes a fatal disease called Beriberi characterized by neurological disturbances, paralysis, atrophy of limbs and cardiac failure. Note that brain exclusively uses aerobic glucose catabolism for energy and PDC is very critical for aerobic catabolism. Therefore thiamine deficiency causes severe neurological symptoms.

Prevalence

Beriberi is rare in developed countries because most foods are now vitamin-enriched. one can get enough thiamine by eating a normal, healthy diet. Today, beriberi occurs mostly in patients who abuse alcohol. Drinking heavily can lead to poor nutrition, and excess alcohol makes it harder for the body to absorb and store thiamine.