Propionic acidemia

Introductory information

Written by: S. Kölker & P. Burgard

Reviewed & Revised for North America
by: S. van Calcar

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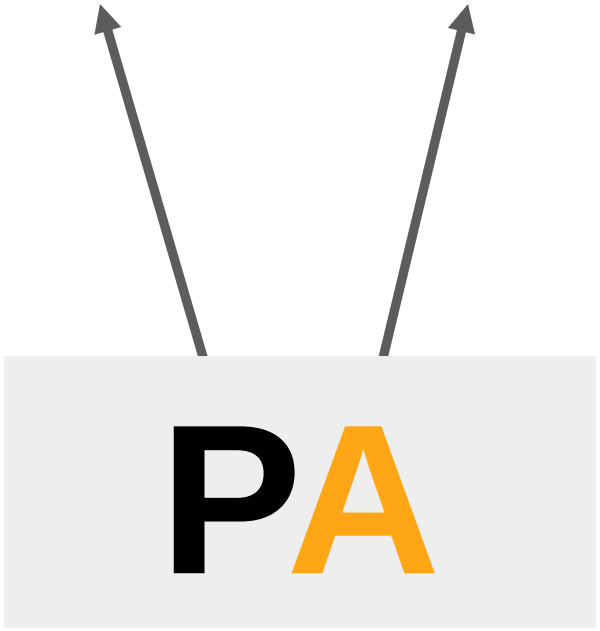
Propionic acidemia



Propionic acidemia

Propionic **acid** **in blood**

PA

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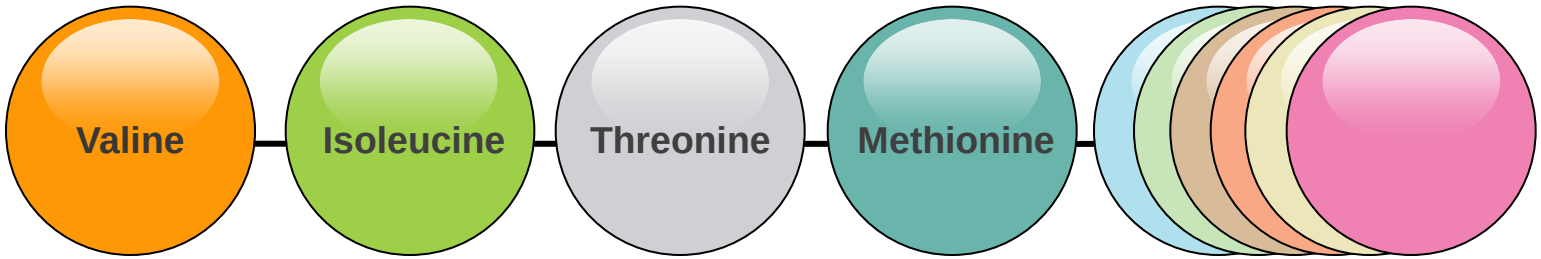
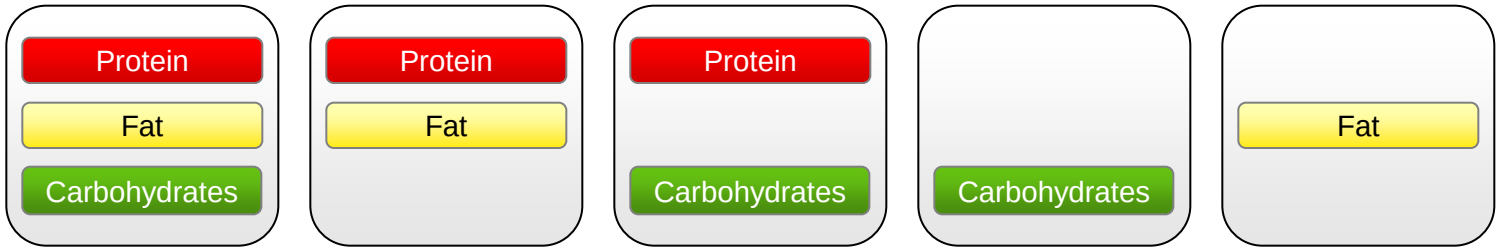
Food – Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids



Natural Food



eg. milk, yogurt, nuts,

eg. meat, poultry, fish, cheese, egg

eg. fruit, vegetables, potatoes, cereal, rice, pasta

eg. sugar, juice

eg. oil, margarine

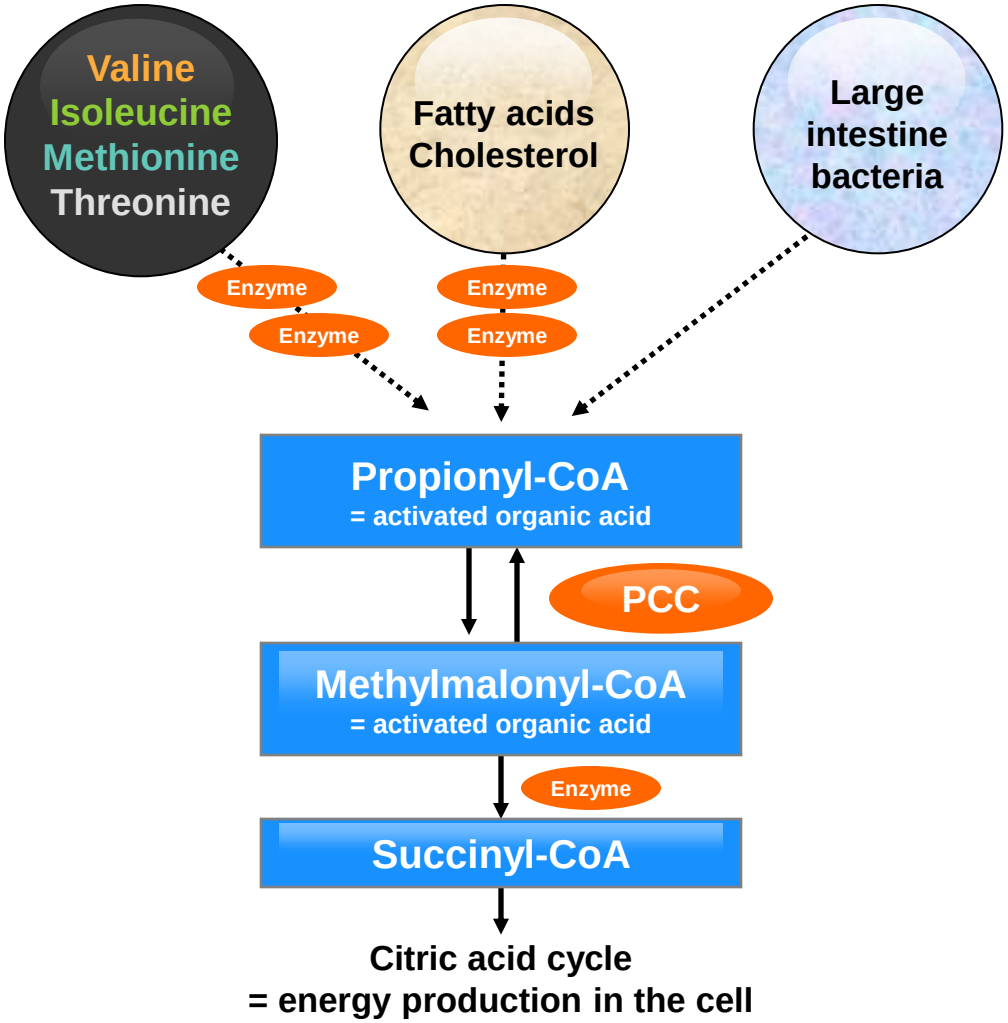
Enzymes

Enzymes are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all the substances in the body. This is called metabolism

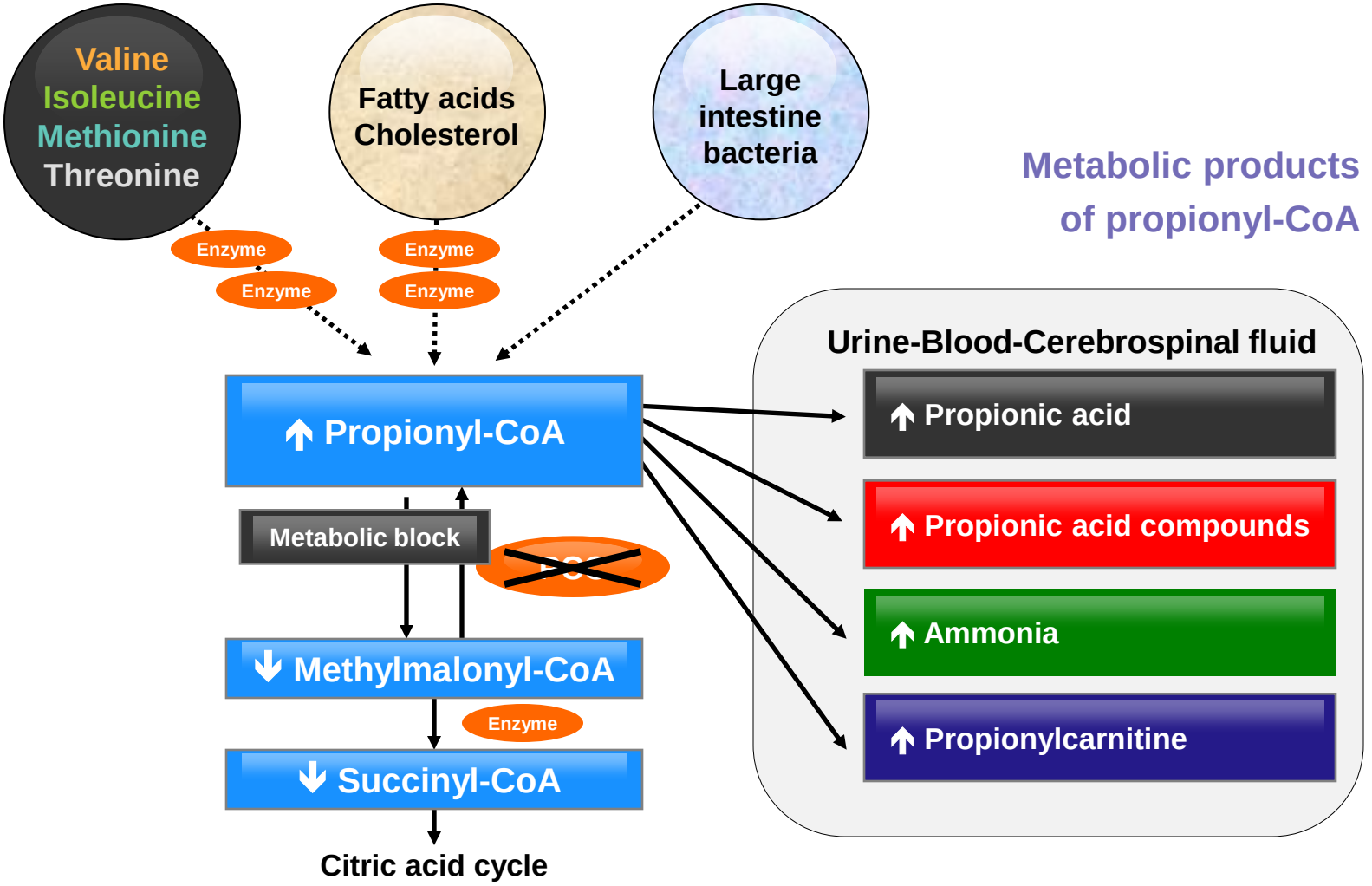
Propionyl-**C**oA **c**arboxylase (PCC) is an enzyme that is necessary for the metabolism of **the amino acids valine, isoleucine, threonine and methionine.**

In PA the activity of the PCC enzyme is decreased.

In a person without PA: PCC works

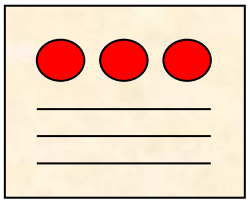


In a patient with PA: PCC is deficient



Metabolic products of propionyl-CoA

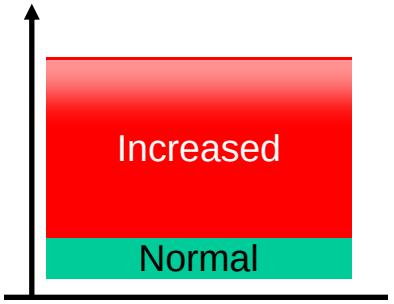
Diagnosis of PA

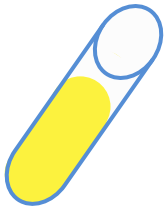


Dried blood spots

Newborn screening

Propionylcarnitine

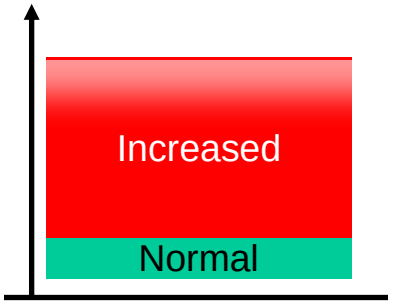




Urine sample

Confirmation of diagnosis

Propionic acid + propionic acid compounds



Pathogenesis

1. Toxic effects of organic acids

Accumulation of

- **Propionyl-CoA**
- **Propionic acid compounds**
- **Ammonia**

can result in damage to various organs

The brain is the most commonly affected organ

Less commonly affected are:

- Blood
- Pancreas
- Heart
- Eyes
- Kidneys

Pathogenesis

2. Problems resulting from carnitine deficiency

Propionylcarnitine

Reduces amount of carnitine in the body

The increased production of propionylcarnitine and its elimination in the urine reduces the amount of carnitine in the body

Carnitine is important to assure a sufficient supply of energy to many organs to maintain their function.

Low amounts of carnitine can reduce the production of energy.

Pathogenesis

3. Metabolic crises

Propionyl-CoA, propionic acid compounds and ammonia can be especially high during metabolic crises. The following situations can lead to a metabolic crisis in PA:

- **Febrile illnesses**
  e.g. diarrhea, fever, infectious disease, etc.
- **Vaccinations**
- **Surgeries**
- **Malnutrition**

In these situations catabolism develops

The term **"catabolism"** refers to the metabolic reactions leading to the breakdown of body tissues.

Propionyl-CoA, propionic acid compounds and ammonia are produced from body proteins, especially the breakdown of muscle!

What are the symptoms of a metabolic crisis?

- Unusual tiredness, unresponsiveness
- Loss of appetite, vomiting
- Quick and deep breathing
- Seizures
- Movement disorders (the child cannot sit or stand anymore, becomes “floppy”, develops abnormal movements)
- The child is very difficult to wake up or you cannot get him to wake up at all (coma)

It is critical that management be started immediately to prevent the patient’s condition from deteriorating. Metabolic crises can be fatal.

Catabolism in a newborn

In the first days of life, catabolism develops with the degradation of body tissues.

This can lead to a metabolic crisis with encephalopathy (brain involvement).

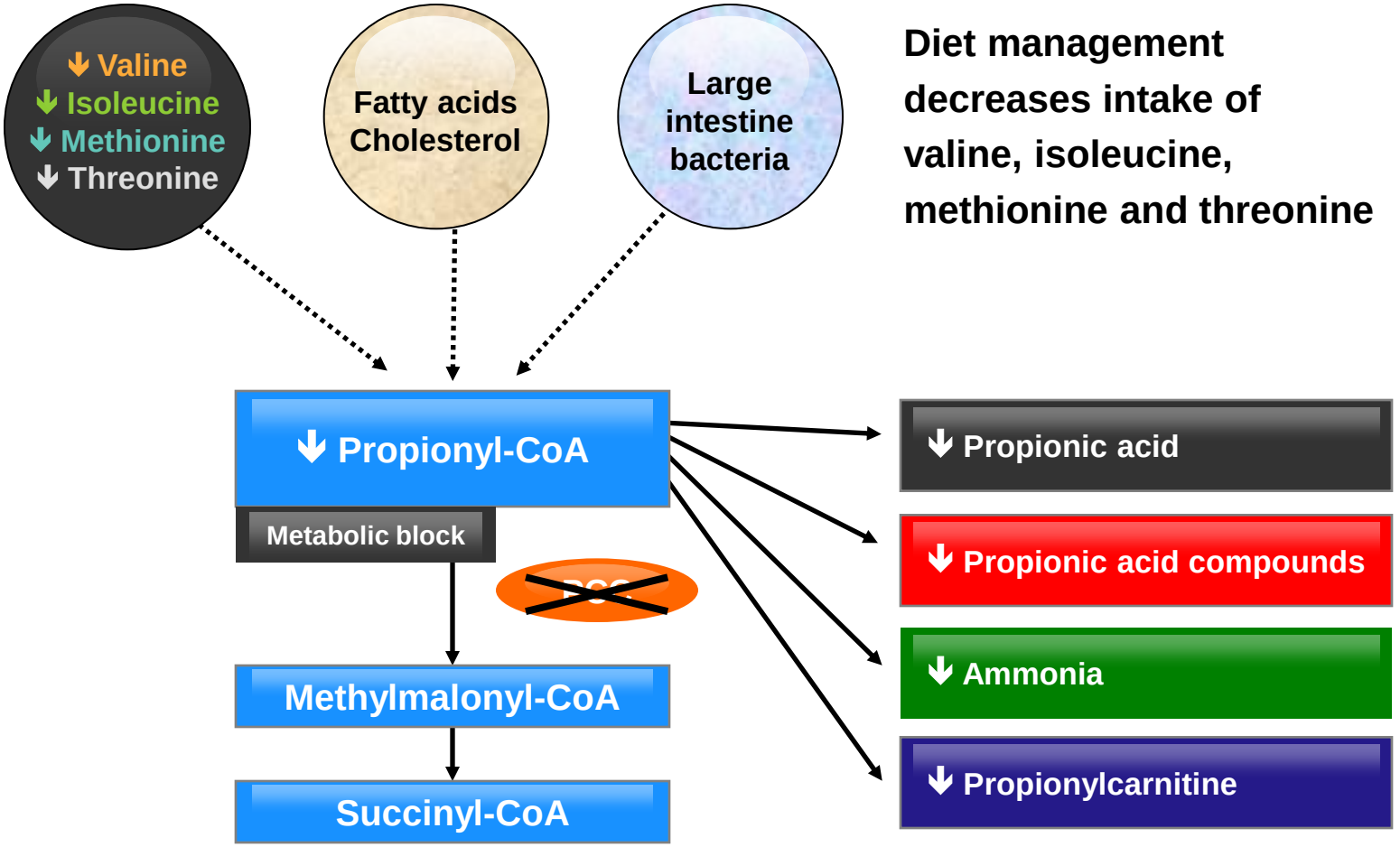
Symptoms:	poor sucking, vomiting, weak response to stimuli, muscle weakness, reduced movement, dehydration, deep breathing, neurological symptoms, coma
Laboratory tests:	⬆ ammonia, ketoacidosis, blood smear abnormalities
Management:	prompt detoxification

Developmental abnormalities

1. Some children may have delayed development, various neurological symptoms such as seizures and/or abnormal movements

2. Children may **lose developmental skills** following a **metabolic crisis.** The risk of developmental abnormalities increase with the severity and number of metabolic crises.

Principles of management

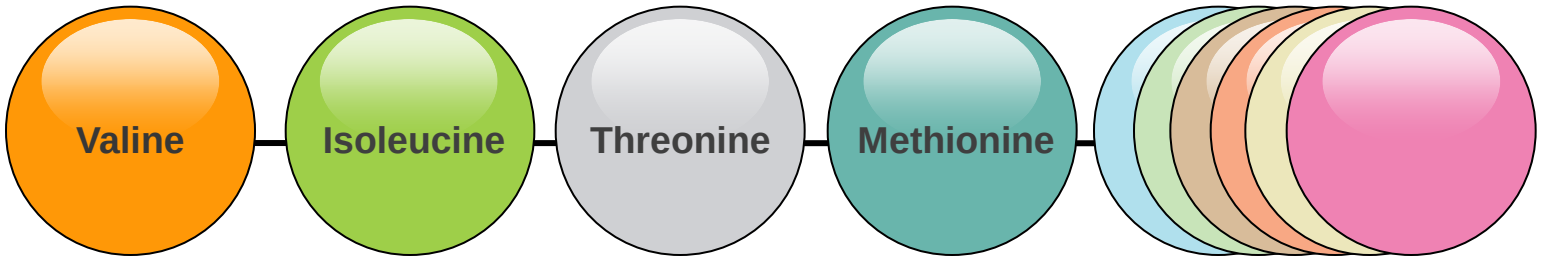


Diet management decreases intake of valine, isoleucine, methionine and threonine

Components of a normal diet

Protein | Fat | Carbohydrates

Protein consists of chains of amino acids

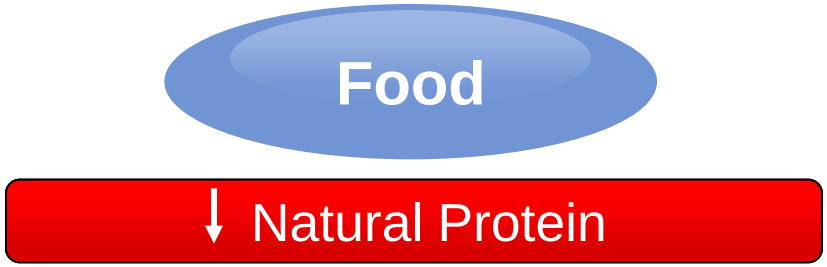


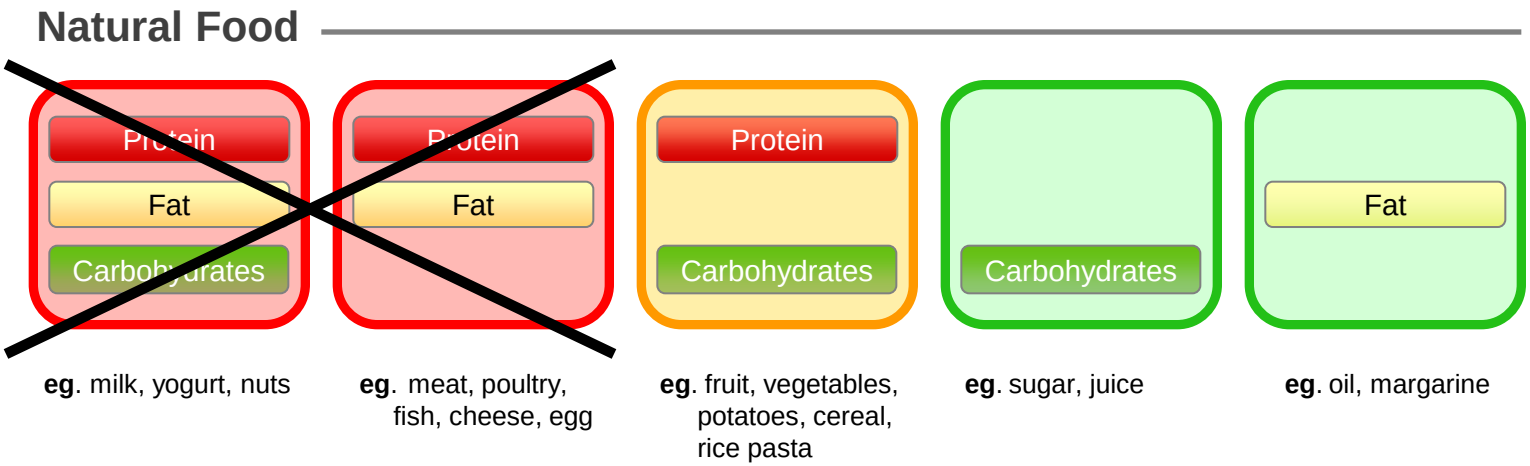
Natural Food

Protein, Fat, Carbohydrates	Protein, Fat	Protein, Carbohydrates	Carbohydrates	Fat
eg. milk, yogurt, nuts	**eg**. meat, poultry, fish, cheese, egg	**eg**. fruit, vegetables, potatoes, cereal, rice, pasta	**eg**. sugar, juice	**eg**. oil, margarine

Principles of management:

1. Low in natural protein food





Principles of management:

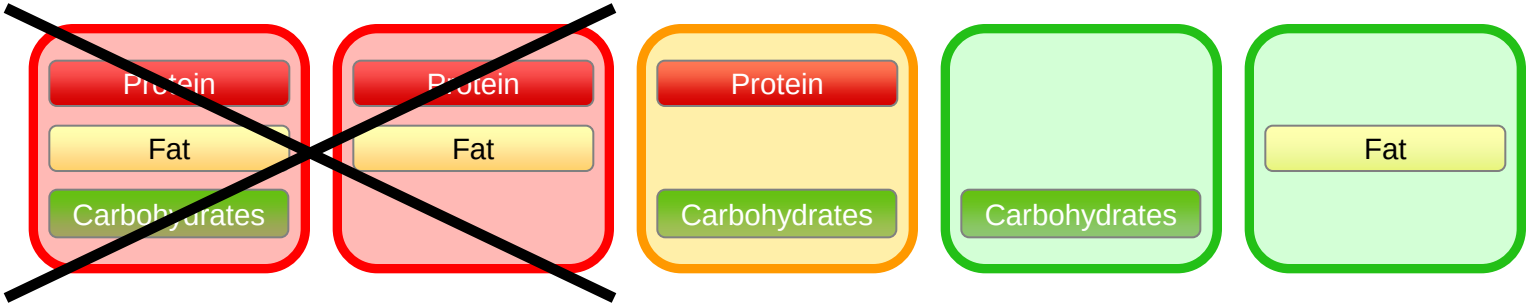
2. Low in natural protein food + a metabolic formula that does not contain valine, isoleucine, methionine or threonine

Food

↓ Natural Protein

+ a PA formula that contains all amino acids except valine, isoleucine, methionine and threonine

Natural Food



eg. milk, yogurt

eg. meat, poultry, fish, cheese, egg

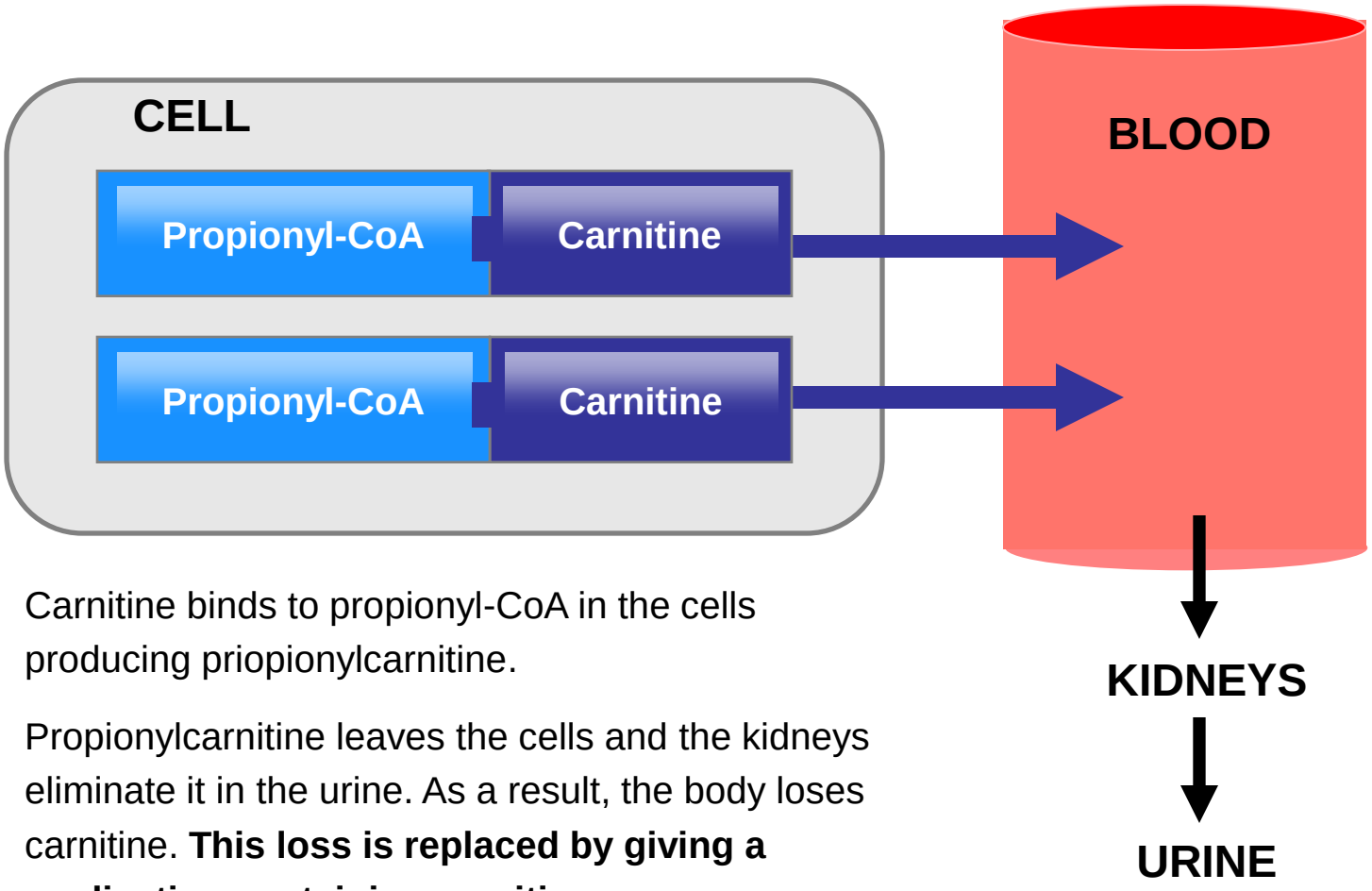
eg. fruit, vegetables, potatoes, cereals, pasta, rice

eg. sugar, juice

eg. oil, margarine

Principles of management:

3. Carnitine supplementation

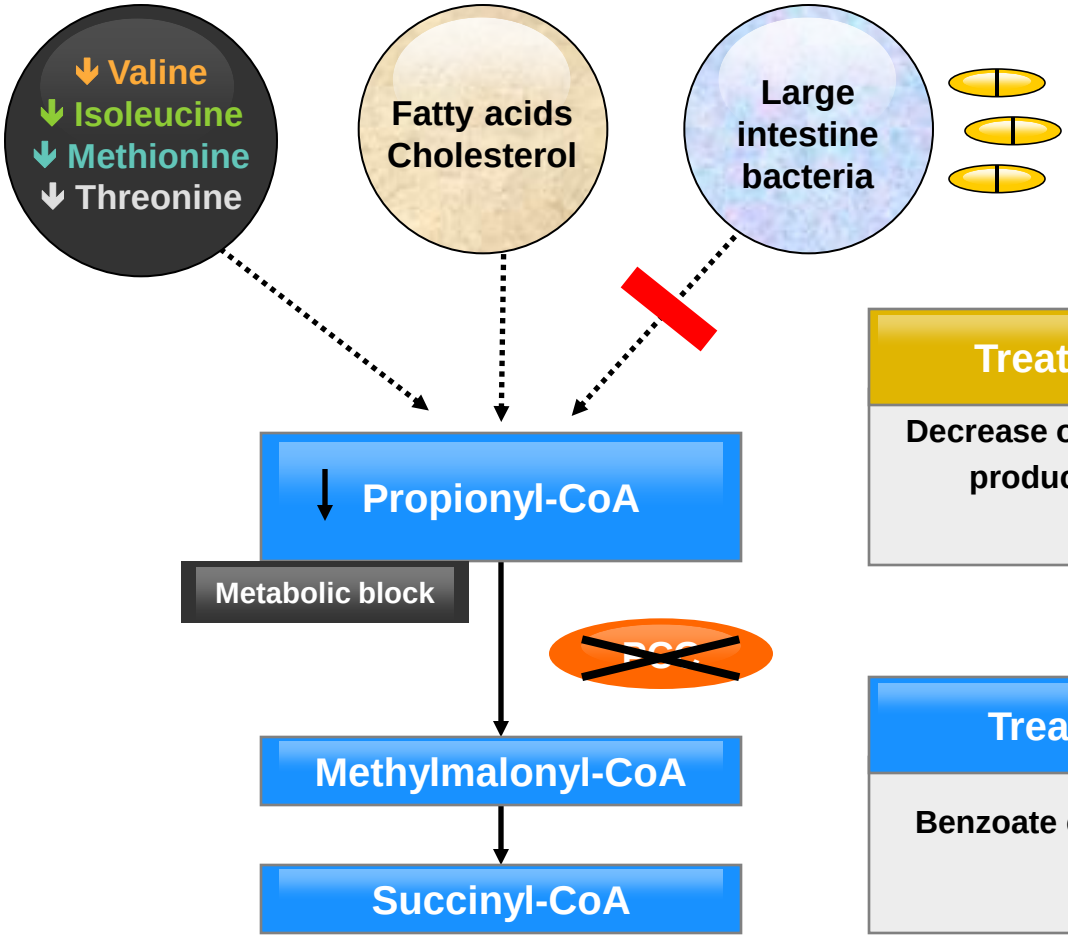


Carnitine binds to propionyl-CoA in the cells producing priopionylcarnitine.

Propionylcarnitine leaves the cells and the kidneys eliminate it in the urine. As a result, the body loses carnitine. **This loss is replaced by giving a medication containing carnitine.**

Principles of management:

4. Drugs



Treatment with antibiotics

Decrease of the amount of propionyl-CoA produced by bacteria in the large intestine

Treatment with benzoate

Benzoate can be prescribed to decrease the ammonia level

Four management components

1. Diet low in natural protein + metabolic formula with all amino acid except valine, isoleucine, methionine and threonine.
2. Carnitine supplementation.
3. Antibiotics to reduce bacteria in the large intestine.
4. **Emergency management:** Follow an **emergency plan** including prompt management during acute illness:
   a) Decrease of the amount of natural protein from food
   b) Frequent carbohydrate-rich meals
   c) Continue carnitine
   d) If the patient's condition deteriorates, contact the metabolic clinic immediately for further directions. An ER visit may be necessary.

Important: All patients with PA need an emergency protocol and plans for emergency management at the nearest children's hospital

Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

A **gene** is like a recipe in the cookbook.

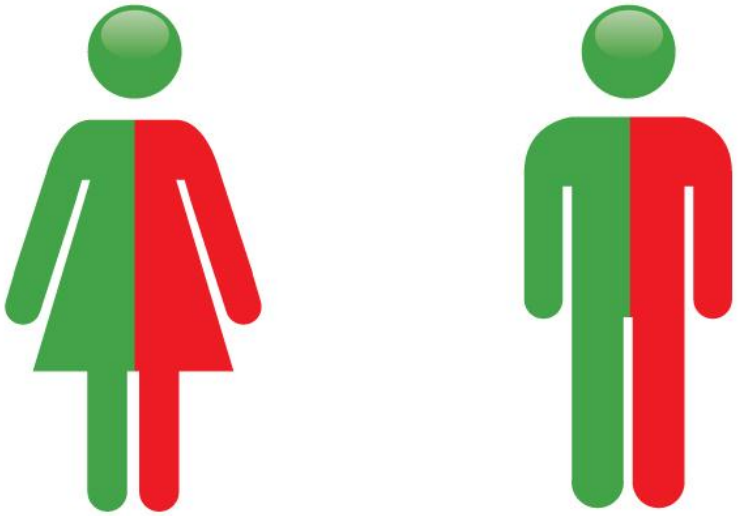
A **mutation** is like an error in the recipe or even a complete lack of a recipe.

The **enzyme** **p**ropionyl-**C**oA **c**arboxylase (PCC) is produced constantly in the body following a specific recipe (**gene**). If the gene contains abnormal **mutations,** the **enzyme** cannot be properly produced.

Inheritance of PA

Both parents are carriers in autosomal inheritance

Mother is a carrier of
PA



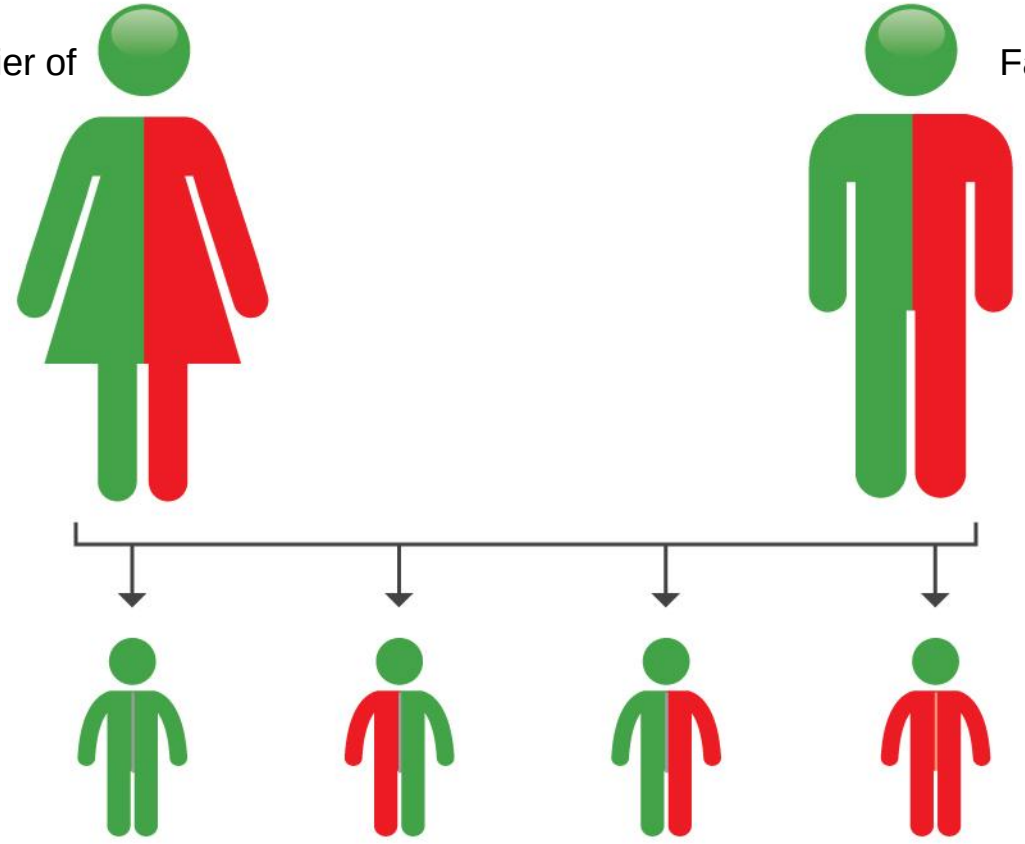
Father is a carrier of
PA

Inheritance of PA

There are 4 possible combinations for any child born to parents who are carriers

Mother is a carrier of **PA**

Father is a carrier of **PA**



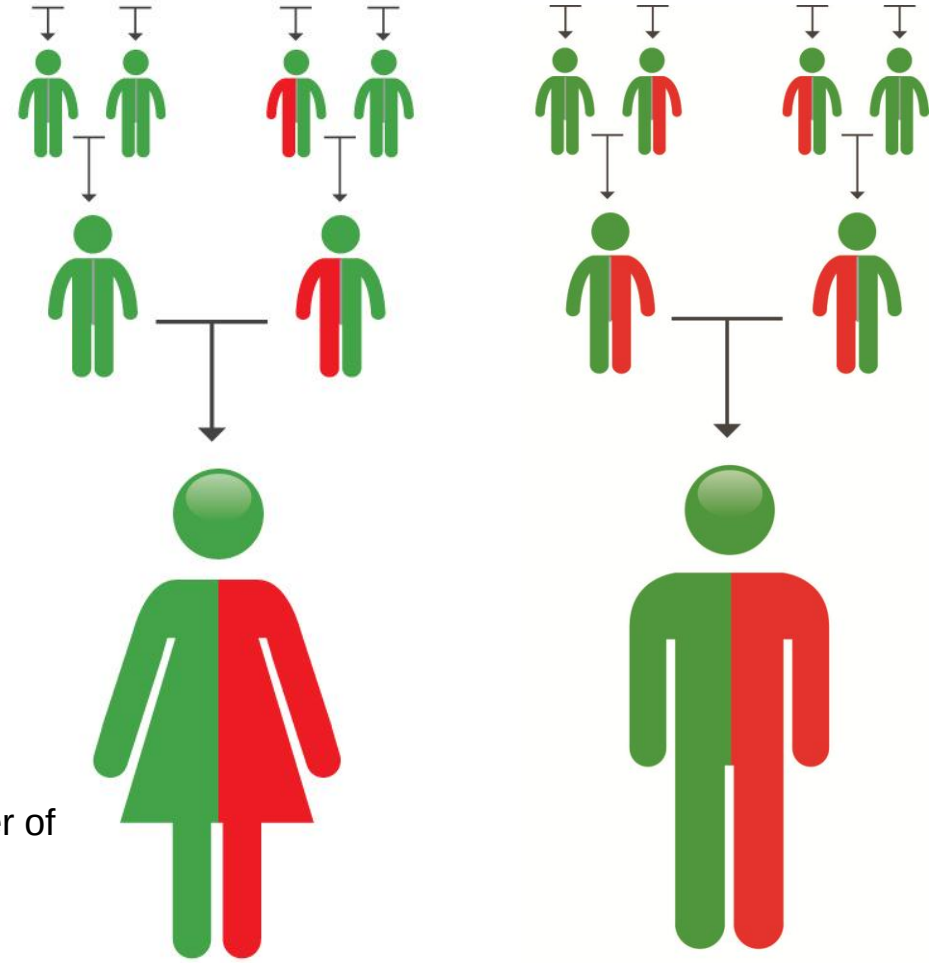
Child **will not be** a carrier of **PA**

Child **will be** a carrier of **PA**

Child **will have PA**

Inheritance of PA

How PA is inherited in families



Mother is a carrier of **PA**

Father is a carrier of **PA**

Summary

What is PA?	Abnormality of metabolism of four amino acids – threonine, valine, isoleucine and methionine
	⬆ Propionyl-CoA, ⬆ Propionic acid, ⬆ 3-Hydroxypropionic acid, ⬆ Ammonia

Optimal management

1. **Low in natural protein foods + a PA formula without threonine, valine, isoleucine and methionine**
2. **Early and effective treatment of metabolic crises**
3. **Pharmacologic treatment with the use of carnitine, antibiotics and benzoate**

Follow-up

- **Laboratory tests**
  Metabolic tests may include:
  Amino acids, acylcaritines, carnitine, ammonia, urine organic acids
  Routine tests
- **Physical development**
  height and weight,
  head circumference
- **Psychomotordevelopment**
  Neuropsychological tests,
  Intelligence(IQ), motor evaluations
- **Brain imaging**
  Ultrasound, MRI
- **Cardiology examination**

Management results vary and may include

- **Developmental delay of various degree**
- **Neurological abnormalities of various degree (movement disorders, spasticity, dystonia)**
- **Epilepsy**
- **Abnormalities in brain MRI**
- **Cardiomyopathy**