

BIOTIN (BIOTINIDASE) DEFICIENCY

Marc E. Tischler, PhD;
University of Arizona

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- biotin in the body is recycled by its removal from carboxylase enzymes to which it is attached (Fig. 1)
- four carboxylase reactions in the body require biotin:
 - ✓ pyruvate carboxylase (Figure 2):
 - required for glucose production; inactivity lowers blood sugar (**hypoglycemia**)
 - lactic acid not used for making glucose accumulates (**lactic acidosis; lactic acidemia**)
 - ✓ acetyl-CoA carboxylase (Figure 3):
 - required for biosynthesis of fatty acids by liver and fat cells
 - lowers availability of stored fatty acids for exercise (**weak muscles; hypotonia**)
 - ✓ propionyl-CoA carboxylase (Figure 4):
 - required for breakdown of certain amino acids (i.e., isoleucine, valine, methionine, threonine) and fatty acids with an odd number of carbons
 - leads to formation of propionic acid and hydroxypropionic acid (**acidosis**)
 - leads to formation of methylcitrate that interferes with normal functioning of citric acid cycle, lowering cell energy production especially in the brain (**developmental delays**)
 - ✓ β -methylcrotonyl-CoA carboxylase (Figure 5):
 - required for breakdown of leucine
 - formation of methylcrotonic acid that leads to hydroxyvaleric acid, which reacts with carnitine; lowered carnitine diminishes oxidation of fatty acids for energy production
 - methylcrotonic acid combines with glycine which is excreted in the urine (**methylcrotonylglycinuria**)

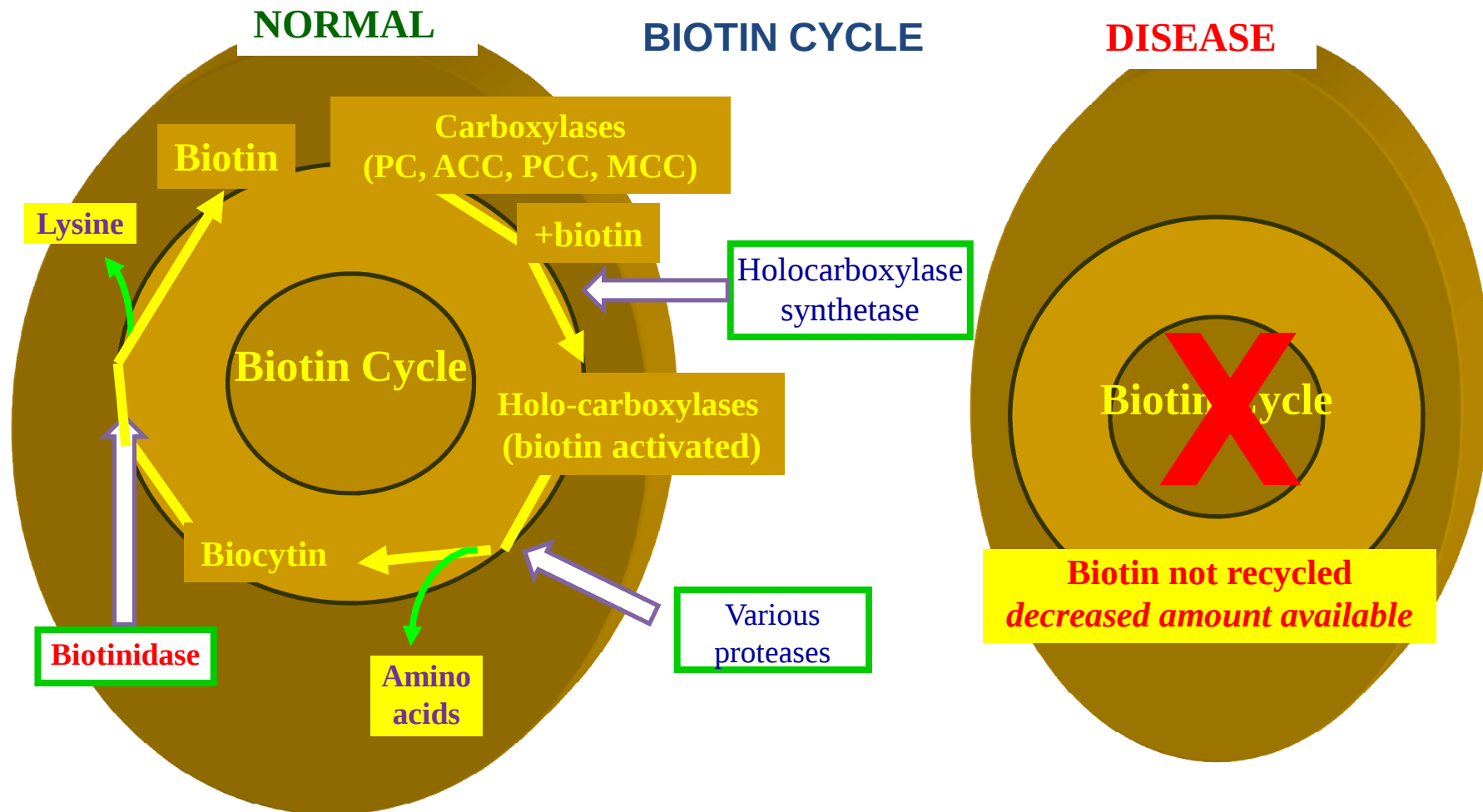


Figure 1. Though biotin is taken in from the diet, recycling via the biotin cycle is essential for maintaining adequate amounts. In the **biotin cycle** (left), the four carboxylase enzymes (pyruvate carboxylase, PC; acetyl-CoA carboxylase, ACC; propionyl-CoA carboxylase, PCC; methycrotonyl-CoA carboxylase, MCC) become active by acquiring biotin, which is attached to a lysine (amino acid) on each enzyme. Biotin is released by breaking down these enzyme via proteases. The action of proteases releases biotin still attached to its lysine, termed **biocytin**. Biocytin is cleaved by **biotinidase** to produce free biotin and lysine. In **biotin deficiency** due to **biotinidase** defect, the biotin cycle loses function (X). Hence biotin becomes relatively deficient and supplements must be provided.

EFFECT OF BIOTIN (BIOTINIDASE) DEFICIENCY ON PYRUVATE CARBOXYLASE IN LIVER CELLS

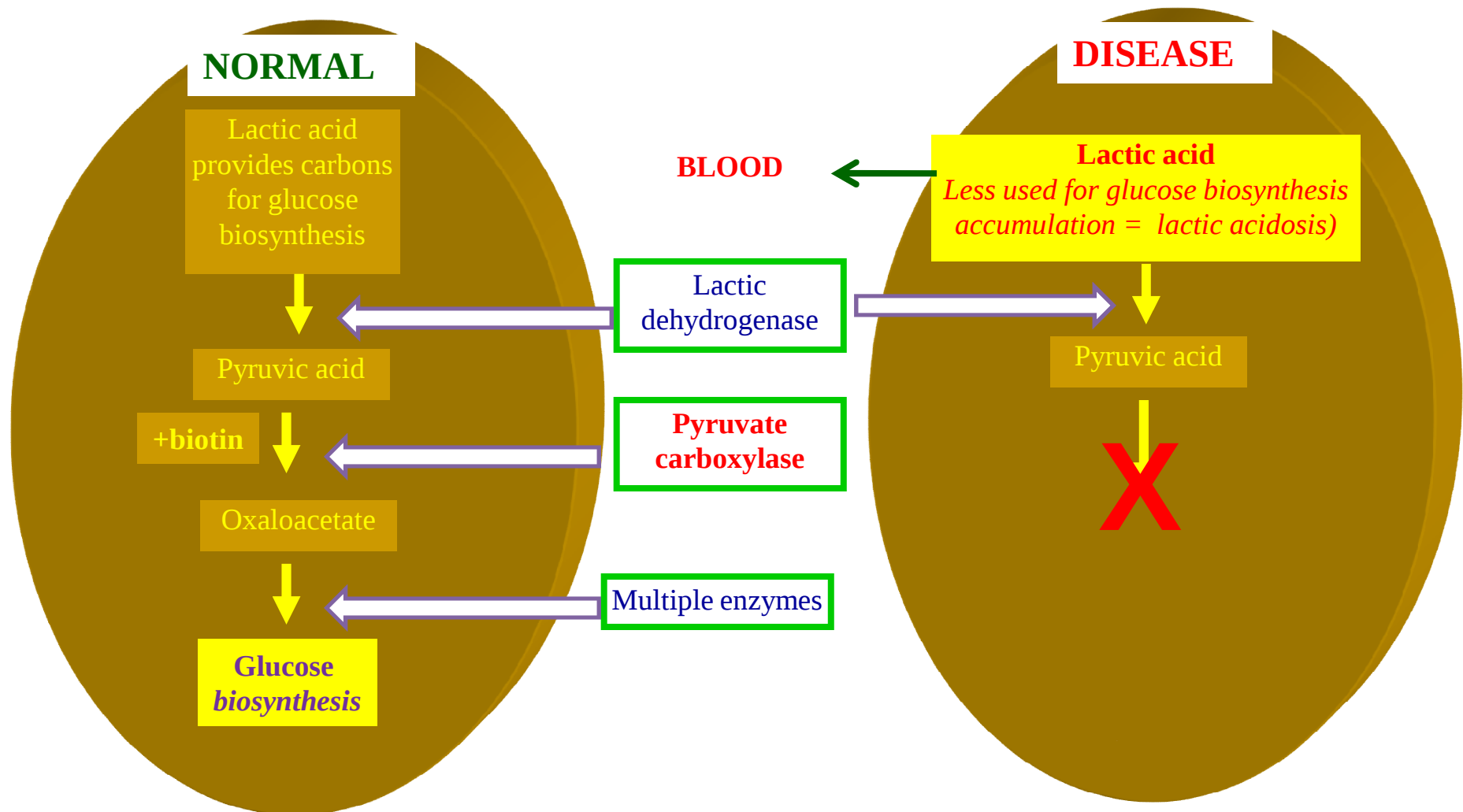


Figure 2. Normally in liver cells, lactic acid is metabolized to form glucose using **pyruvate carboxylase** (left). In **biotinidase deficiency**, the decreased amounts of biotin cause a lower activity of **pyruvate carboxylase** (X). Instead lactic acid accumulates in the blood (**lactic acidosis**). This adds to the acidosis problem caused by accumulation of other acids in this disease (see Figures 4-6) .

EFFECT OF BIOTIN (BIOTINIDASE) DEFICIENCY ON ACETYL-CoA CARBOXYLASE IN LIVER AND FAT CELLS

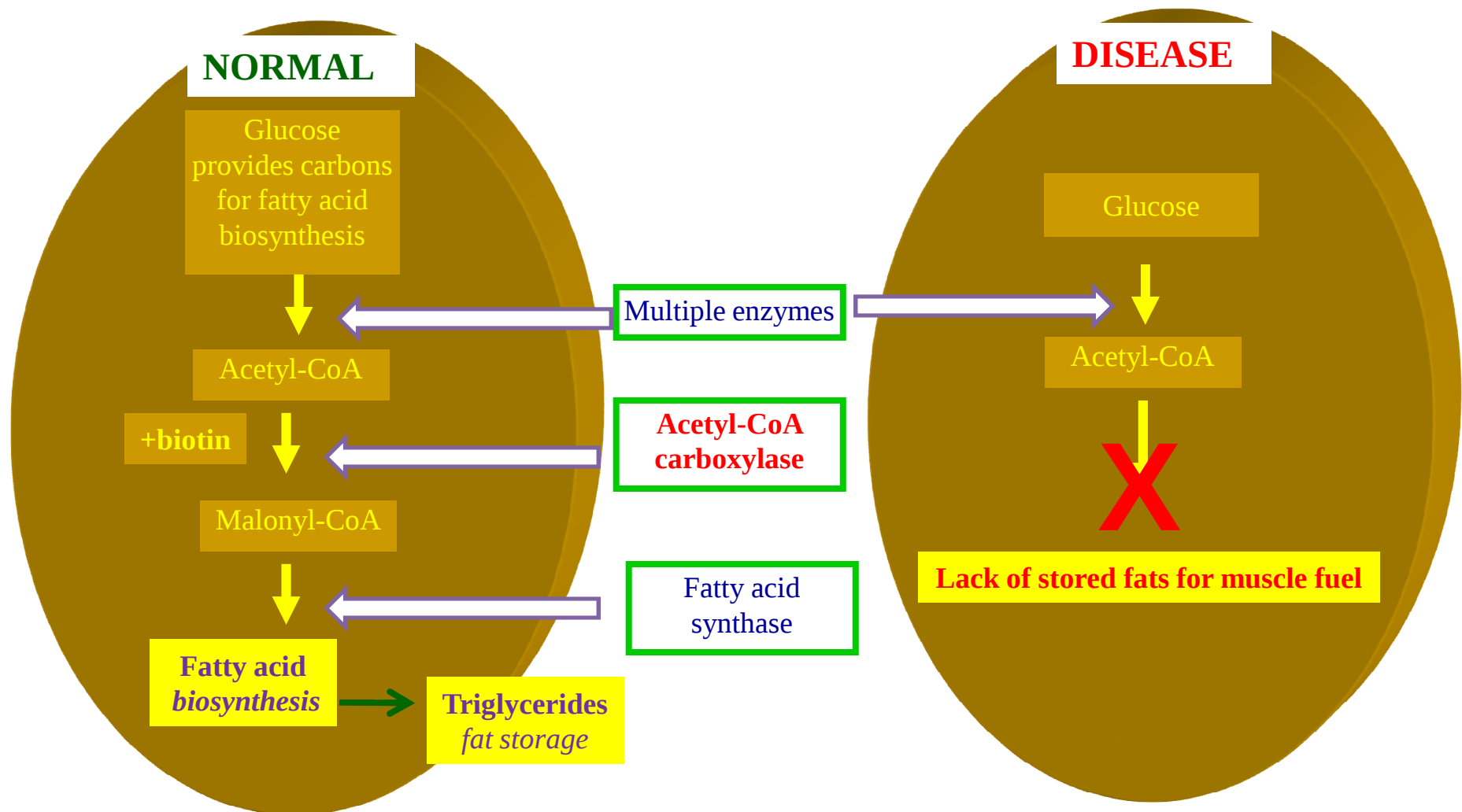


Figure 3. Normally in liver and fat cells, glucose is metabolized to form fatty acids using **acetyl-CoA carboxylase** (left). In **biotinidase deficiency**, the decreased amounts of biotin cause a lower activity of **acetyl-CoA carboxylase** (X). Instead glucose is diverted to other functions. However decreased formation of fatty acids reduces their storage and availability for exercise, hence the **weak muscles and hypotonia**.

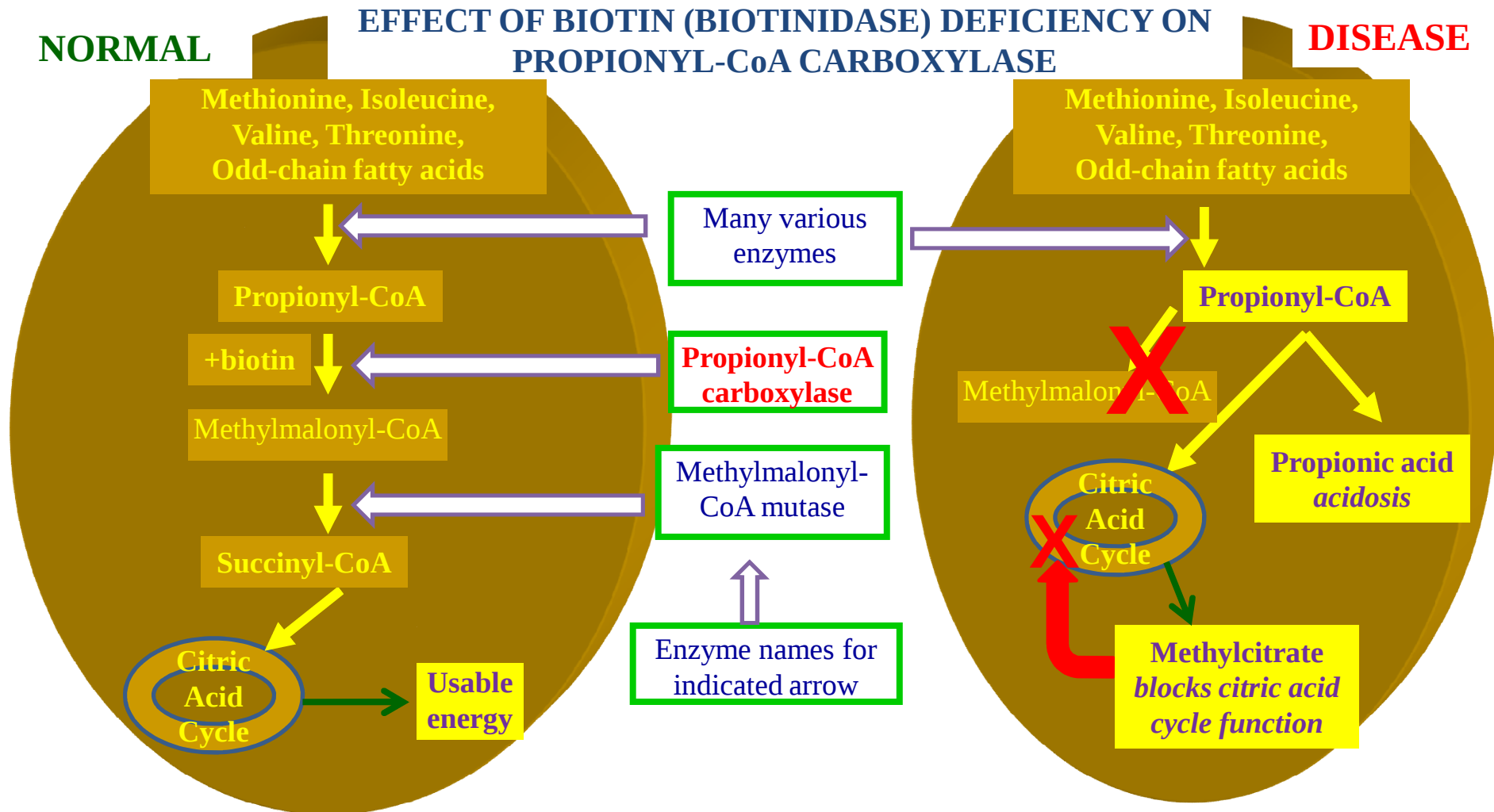


Figure 4. Metabolism of 4 amino acids and odd-chain fatty acids all depend on propionyl-CoA carboxylase. Propionyl-CoA is metabolized ultimately to succinyl-CoA that enters the citric acid cycle, which produces usable energy for the cell. In **biotinidase deficiency**, the decreased amounts of biotin cause a lower activity of **propionyl-CoA carboxylase** (X) so that propionyl-CoA accumulates. Propionyl-CoA is instead converted to **propionic acid** that causes **acidosis**, a life-threatening condition. Propionyl-CoA also is processed, by an enzyme in the citric acid cycle, to **methylcitrate**. Methylcitrate blocks normal functioning of the citric acid cycle to limit energy output, especially in brain cells that require large amounts of energy. Low activity of propionyl-CoA carboxylase can, in rare instances, be due to poor interaction with biotin so that providing more of this biotin may have some benefits in treatment.

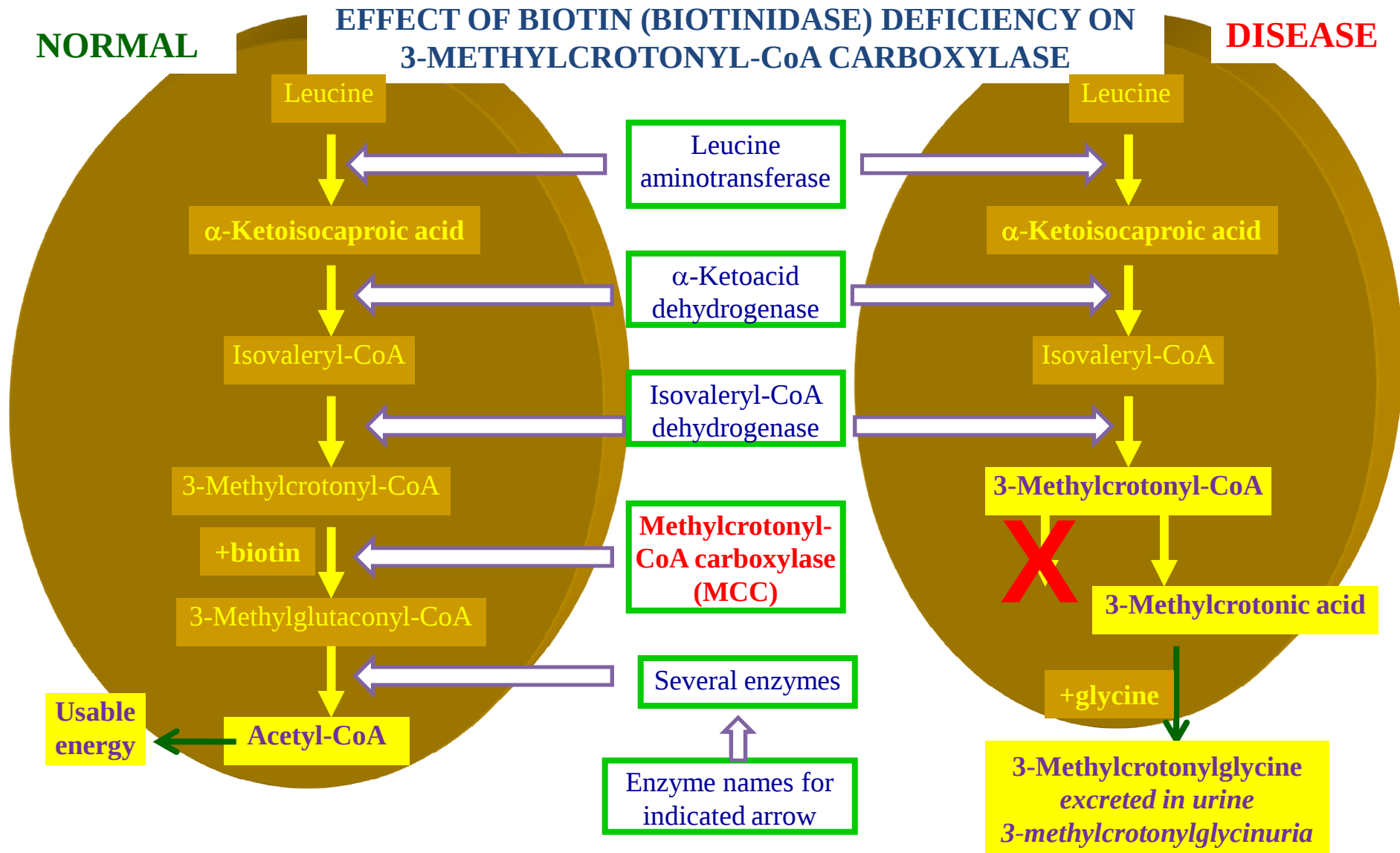


Figure 5. Leucine is metabolized in cells to acetyl-CoA that is then converted to usable energy. In **biotinidase deficiency**, the decreased amounts of biotin cause a lower activity of **methylcrotonyl-CoA carboxylase (MCC)** (X) so that 3-methylcrotonyl-CoA accumulates. 3-Methylcrotonyl-CoA is converted to 3-methylcrotonic acid. One fate of 3-methylcrotonic acid is combining with glycine to form 3-methylcrotonylglycine that is excreted in the urine (3-methylcrotonylglycinuria). Other consequences of the disease are depicted in Figs 6 and 7).

DIMINISHED FAT OXIDATION DUE TO LOWER MCC ACTIVITY WITH BIOTINIDASE DEFICIENCY

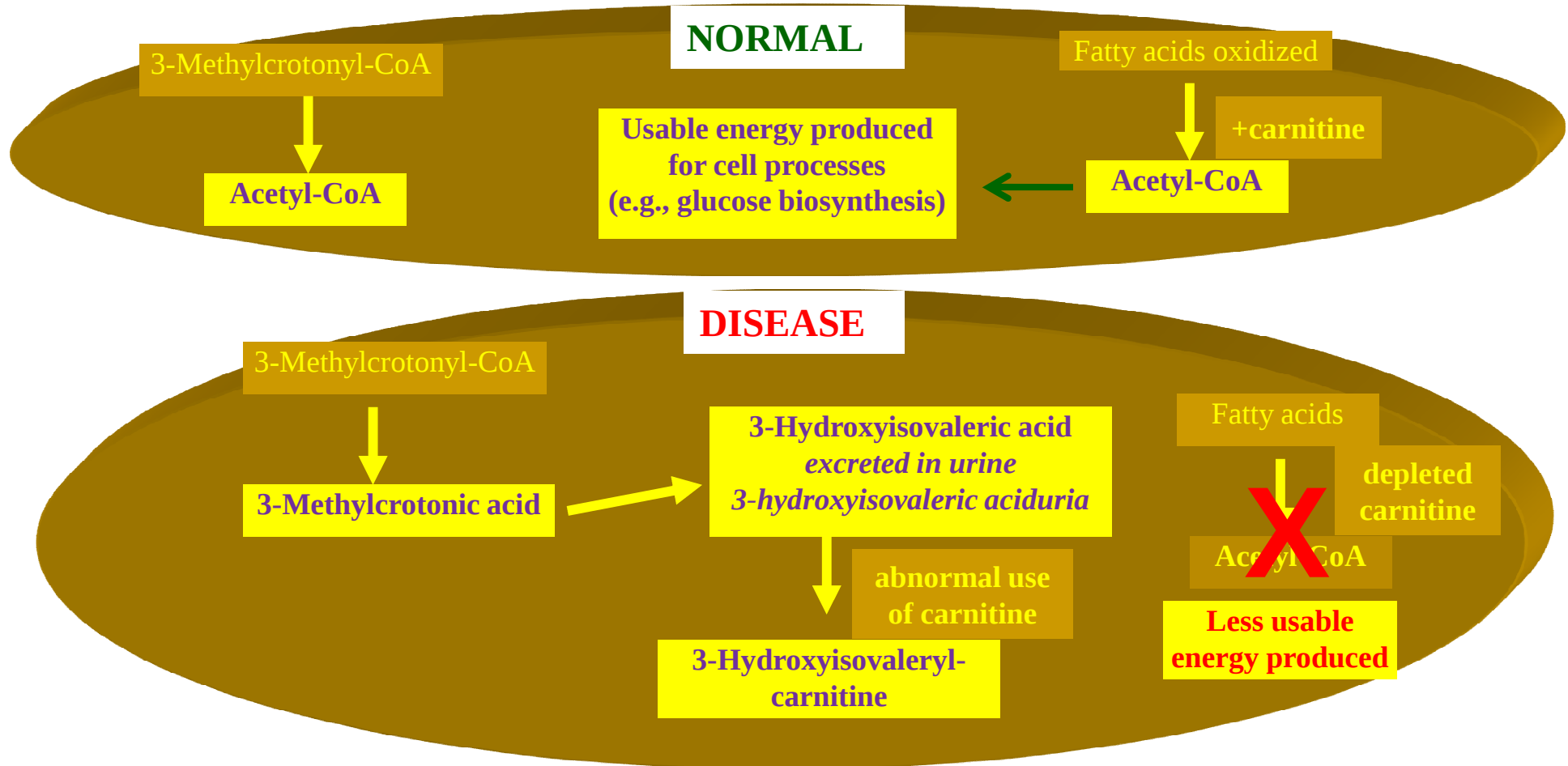


Figure 6. In **biotinidase deficiency** (lower), the lower activity of **MCC** leads to formation of 3-methylcrotonic acid, which is modified to 3-hydroxyisovaleric acid. These two acids cause **acidosis** and potential neurological damage. 3-Hydroxyisovaleric acid combines with carnitine to form 3-hydroxyisovaleryl-carnitine. This latter reaction lowers the amount of carnitine in patients. Carnitine is essential for fatty acid oxidation (upper) to produce energy that is required for cell processes, such as biosynthesis of glucose (blood sugar). The potential depletion of carnitine in untreated **biotinidase deficiency** can cause impairment of fatty acid oxidation (X) leading to less usable energy for cell processes.

HYPOGLYCEMIA AND LACTIC ACIDEMIA DUE TO LOWER MCC ACTIVITY WITH BIOTINIDASE DEFICIENCY IN LIVER CELLS

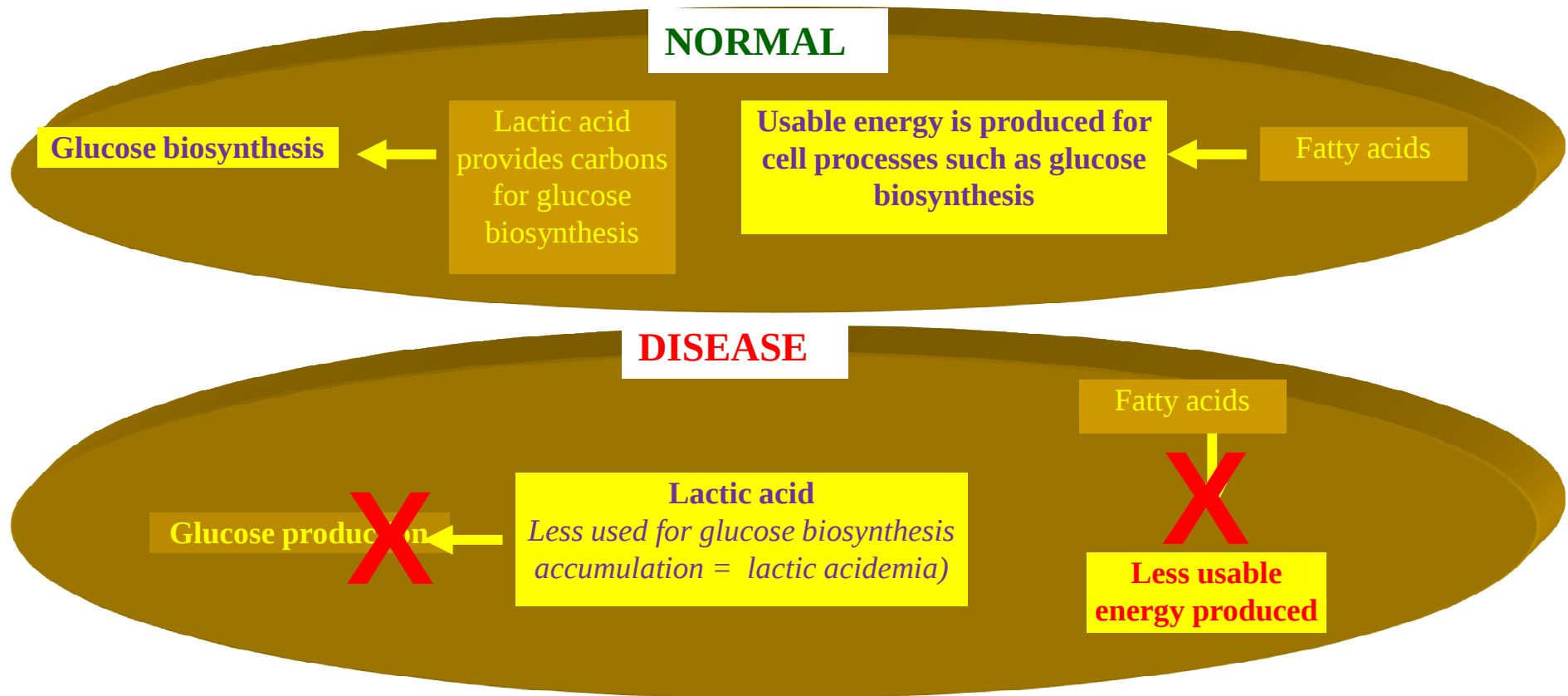


Figure 7. Normally the oxidation of fatty acids produces usable energy that can power the biosynthesis of glucose with the carbons coming from lactic acid (upper). As noted in Fig. 6, in **biotinidase deficiency** the oxidation of fatty acids potentially is lowered leading to less usable energy for cell processes such as glucose biosynthesis. Decreased production of glucose leads to a lower amount of blood glucose (**hypoglycemia**). Lactic acid normally provides carbons for glucose biosynthesis (upper). In **biotinidase deficiency** (lower) because there is less usable energy to power glucose biosynthesis, less lactic acid is used for producing glucose. Instead blood lactic acid can accumulate (**lactic acidemia**). This adds to the acidosis problem caused by 3-methylcrotonic acid and 3-hydroxyisovaleric acid (see Fig. 5).