

in the long-chain fatty acid transport proteins causes interference with this specific class. These patients are managed with low-fat diets supplemented with medium-chain triglycerides to bypass the transporter requirement.<sup>55</sup> Finally, the very-long-chain fatty acids are handled by a third set of transformations involving peroxisomal enzymes as discussed later in this chapter.

Genetic effects manifesting in that pathway produce another type of fatty acid oxidation difficulty.

### Elongation and Desaturation

Fatty acids can be modified by desaturation enzymes that introduce double bonds, and are lengthened by elongation reactions that add 2-carbon units to the

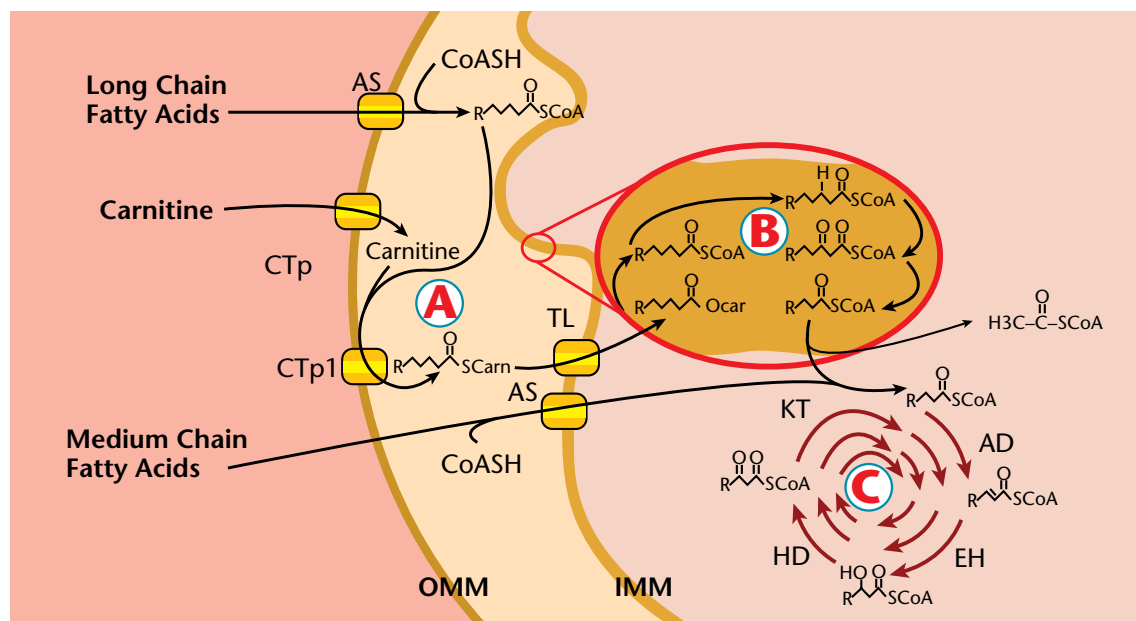


FIGURE 5.4 — Intracellular Fatty Acid Transport and Oxidation

Plasma carnitine gains entry to cells via a specific carnitine transport protein (CTp). The carnitine cycle (A) that operates in the *trans*-membrane space causes formation and breakage of fatty acyl carnitine. Acylcarnitine synthetase (AS) catalyzes the attachment of coenzyme A to the fatty acid. Then the translocase enzyme (TL) acts as a gate keeper for entry of LCFAs passing them to enzymes attached to the inner mitochondrial membrane. There, the inner membrane cycle (B) carries out two-carbon chain length reductions, producing acetyl-CoA with each chain-length reduction. When the chain length drops below 14, the fatty acyl-CoA product enters the beta oxidation cycle (C) carried out by acyl dehydrogenase (AD), enoyl hydratase (EH), hydroxyacyl dehydrogenase (HD) and ketoacyl thiolase (KT) enzymes. The riboflavin-dependent step is carried out by the FAD-requiring enzyme, AD. Medium chain fatty acids do not require the carnitine cycle since their chain length allows them to enter the  $\beta$ -oxidation cycle directly as acyl-CoA esters.

**Fatty acid Transport:** Activation of long-chain fatty acids and their transport into the transmembrane space is done via long-chain acyl-CoA synthetase (AS) located in the outer mitochondrial membrane (OMM).<sup>290</sup> Once inside the transmembrane space they cannot readily traverse the inner mitochondrial membrane and must be coupled to carnitine. The carnitine cycle (A) causes formation and breakage of fatty acyl carnitine. Carnitine acylcarnitine translocase (TL) shuttles the acylcarnitine through the inner mitochondrial membrane (IMM), where enzymes located on the matrix side of the membrane couple the acyl moiety to carnitine and regenerates acyl-CoA. Medium-chain fatty acids do not require such transport for mitochondrial import. They are attached to CoA and passed directly into the mitochondrial matrix via medium-chain acyl-CoA synthetases (AS).<sup>291</sup>

**Fatty acid Oxidation:** (B) Long-chain fatty acid oxidation takes place in the inner membrane-bound complex, and carries out two-carbon chain length reductions, producing acetyl-CoA with each chain-length reduction. When the chain length drops below 14, the acyl-CoAs are further oxidized by the specific enzymes in the mitochondrial matrix system. (C) Medium- and short-chain fatty acids are degraded in the matrix system.<sup>292-294</sup>  $\beta$ -Oxidation degrades fatty acids completely to acetyl-CoA, which is then oxidized by the citric acid cycle or, during starvation, condensed into ketone bodies.