

## **Acylcarnitines: Nomenclature, biomarkers, therapeutic potential, drug targets and clinical trials**

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### **Abbreviations:**

ACC, acetyl-CoA carboxylase; ACS, acyl-CoA synthetases; ACSL, long-chain acyl-CoA synthetase; ACSM, medium-chain acyl-CoA synthetase; ACSS, short-chain acyl-CoA synthetase; Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; CACT, carnitine/acylcarnitine translocase; CNS, central nervous system; CPT1, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; CrAT, carnitine acetyltransferase; CrOT, carnitine octanoyltransferase; FAODs, fatty acid oxidation disorders; FDA, Food and Drug Administration; GTT, glucose tolerance test; HMDB, Human Metabolome Database; LCAD, long-chain acyl-CoA dehydrogenase; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; MCD, malonyl-CoA decarboxylase; MDD, major depressive disorder; (Na<sup>+</sup>/K<sup>+</sup>)-ATPase, sodium-potassium exchanger; OCT1, organic cation transporter 1; OCTN2, organic cation novel type 2 transporter; OXPHOS, oxidative phosphorylation; PCOS, polycystic ovary syndrome, PGC1, peroxisome proliferator-activated receptor gamma coactivator 1; PI3K, phosphoinositide-3 kinase; PPAR- $\alpha$ , peroxisome proliferator-activated receptor  $\alpha$ ; ROS, reactive oxygen species; SERCA, sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase; SCD, sudden cardiac death; VLCAD, very-long-chain acyl-CoA dehydrogenase

# Abstract

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Acylcarnitines are fatty acid metabolites that play important roles in many cellular energy metabolism pathways. They have historically been used as important diagnostic markers for inborn errors of fatty acid oxidation and are being intensively studied as markers of energy metabolism, deficits in mitochondrial and peroxisomal  $\beta$ -oxidation activity, insulin resistance, and physical activity. Acylcarnitines are increasingly being identified as important indicators in metabolic studies of many diseases including metabolic disorders, cardiovascular diseases, diabetes, depression, neurological disorders and certain cancers. The Food and Drug Administration (FDA)-approved drug L-carnitine, along with short-chain acylcarnitines (acetylcarnitine and propionylcarnitine), is now widely used as a dietary supplement. In light of their growing importance, we have undertaken an extensive review of acylcarnitines and provided a detailed description of their identity, nomenclature, classification, biochemistry, pathophysiology, supplementary use, potential drug targets and clinical trials. Moreover, we also summarize these updates in the Human Metabolome Database (HMDB), which now includes information on the structures, chemical formulae, chemical/spectral properties, descriptions and pathways for 1240 acylcarnitines. This work lays a solid foundation for identifying, characterizing and understanding acylcarnitines in human biosamples. We also discuss the emerging opportunities for using acylcarnitines as biomarkers and as dietary interventions or supplements for many wide-ranging indications. The opportunity to identify new drug targets involved in controlling acylcarnitine levels is also discussed.

## **Significance statement**

This review provides a comprehensive overview of acylcarnitines including their nomenclature, structure and biochemistry, and their use as disease biomarkers and pharmaceutical agents. We present updated information contained in the HMDB website as well as substantial mapping of the known biochemical pathways associated with acylcarnitines, thereby providing a strong foundation for further clarification of their physiological roles.

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## I. Introduction

Acylcarnitines are esters arising from the conjugation of fatty acids (i.e., acyl-groups) with L-carnitine. They are widely used and produced in cellular energy metabolism pathways. The well-established biological function of acylcarnitines is to transport acyl groups from the cytosol into the mitochondrial matrix for  $\beta$ -oxidation, leading to the production of energy to sustain cell activity (Indiveri et al., 2011). The energy production by  $\beta$ -oxidation is significant, with  $7n-6$  ATP molecules being produced per acylcarnitine, where  $n$  is the number of acyl- carbons (Jain et al., 2021). Over the past three decades, many additional actions and roles of acylcarnitines have been discovered. For instance, it is now increasingly clear that long-chain acylcarnitines play a role in insulin resistance and the development of cardiovascular diseases (Adams et al., 2009; Aitken-Buck et al., 2020; Guasch-Ferre et al., 2016; McCoin et al., 2015a). The role of acylcarnitines as important diagnostic biomarkers is also growing. For example, plasma long-chain acylcarnitine measurements are widely used in newborn screening to identify inborn errors of fatty acid oxidation and to diagnose deficits in energy metabolism (Knottnerus et al., 2018; Ramos-Roman et al., 2012). Acylcarnitines are also becoming a very important group of biomolecules within the field of metabolomics, as an increasing number of diseases and nutritional states exhibit distinct acylcarnitine profiles. Interest in acylcarnitines has thus risen substantially. For example, in the past ten years, the number of publications on acylcarnitines has tripled, and the same trend can be seen in the number of acylcarnitine clinical studies that have been launched.

The first review in the area of acylcarnitines was published in 1975 with a primary focus on the role of acylcarnitines in fatty acid oxidation arising from ischemia (Hull et al., 1975). Since then, over 200 reviews have been written on or about acylcarnitines. In 2010, Santra and Hendriksz published a review on the use of different acylcarnitines as vehicles to diagnose inborn errors of metabolism (Santra and Hendriksz, 2010). In 2020, Wanders et al. extended this

work and addressed the involvement of acylcarnitines in inborn metabolic disorders and their utility for newborn screening (Wanders et al., 2020). Acylcarnitines also play important roles in other metabolic disorders, including diabetes and cancer. In 2013, Schooneman et al. reviewed the physiological functions of medium- and long-chain acylcarnitines, concluding that the concentrations of different acylcarnitines correlate with a number of different metabolic disease states (Schooneman et al., 2013). In 2015, McCoin et al. published a review on long-chain acylcarnitines and their functions as both transporters in oxidative catabolism and as modulators of a number of physiological and pathophysiological functions, such as cardiac electrophysiology, insulin signaling, cellular stress and inflammation (McCoin et al., 2015a). In 2019, Li et al. reviewed the role of acylcarnitines in hepatocellular carcinoma, a primary liver cancer, and discussed the metabolism of acylcarnitines in relation to different concentrations of short-, medium- and long-chain acylcarnitines (Li et al., 2019). It was concluded that acylcarnitines could be used as both diagnostic and prognostic biomarkers for hepatocellular carcinoma. In addition to the many roles that medium- and long-chain acylcarnitines play in human physiology and pathophysiology, the smallest acylcarnitine of all, acetylcarnitine, is emerging as a useful supplemental option to alleviate the development of neurological disorders (Maldonado et al., 2020; McCann et al., 2021).

While acylcarnitine research is expanding and reviews on their roles in metabolic disorders continue to grow, there has been relatively little effort to comprehensively address other important issues regarding acylcarnitines. These include their nomenclature, classification, biochemistry, pathology, and use as investigative pharmaceuticals. To address these issues we performed a systematic and comprehensive search covering all acylcarnitine-related information available through PubMed from 1975 until now. This literature survey was further complemented with information found in other databases such as PubChem, Clinicaltrials.gov, Drugbank.ca, AdisInsight and Molecularyou.com. This consolidated information on acylcarnitines is not only presented here but has also been deposited into the Human Metabolome Database or HMDB (Wishart et al., 2018). In particular, the latest release of the HMDB also includes many details (structures, nomenclature, pathways, MS spectra, etc.) that could not be fully presented in this manuscript (Wishart et al., 2022). Together, these two resources should serve as a comprehensive foundation for information about acylcarnitines and should allow for regular online updates as the field continues to grow.

## II. Acylcarnitine molecules

### A. Repertoire of acylcarnitines and major update of the HMDB database

The physiological role of acylcarnitines was first discovered nearly 60 years ago in studies involving rodents (Bremer, 1962; Fritz, 1959). Since then, acylcarnitines or enzymes synthesizing acylcarnitines have been found in plants (Bourdin et al., 2007; Nguyen et al., 2016), yeasts (Hiltunen et al., 2003), arthropods (Skottene et al., 2019) and all vertebrates (Lopes-Marques et al., 2015). In that time, approximately 80 different acylcarnitines have been rigorously studied and described in the literature or cataloged in databases (Wishart et al., 2018). However, it is known that the actual number of acylcarnitines is far greater than this, as carnitine moieties can be promiscuously added to almost any organic acid. Moreover, several metabolomic studies have provided evidence that many more acylcarnitines (hundreds to thousands) likely exist in the human body (Blazenovic et al., 2019; Wishart et al., 2018; Yan et al., 2020; Yu et al., 2018; Zuniga and Li, 2011). As of Jan. 2021, the HMDB contained only 146 acylcarnitines.

In the course of preparing this review, members of the HMDB curation staff extensively reviewed the extant literature for newly identified or tentatively identified acylcarnitines. Published reports have indicated that MS-based experimental evidence exists for more than 1000 acylcarnitines (Blazenovic et al., 2019; van der Hooft et al., 2015; Yan et al., 2020; Yu et al., 2018; Zuniga and Li, 2011). Based on the proposed (partial) structures and chemical formulae appearing in these papers, our HMDB team developed a computer program to generate possible linear acyl chains using experimental (formula and partial structure) constraints as well as knowledge regarding the structure of known fatty acids in the animal/plant kingdom. First, the program generated all combinations of linear, saturated, unsaturated, hydroxylated, keto- and branched-chain fatty acids ranging in size from C2 to C25. This process created more than 40,000 possible acyl chains. Then a further set of filtering steps was applied to generate more realistic and biologically feasible acyl chains that complied with the experimental observations reported in the literature (Blazenovic et al., 2019; van der Hooft et al., 2015; Yan et al., 2020; Yu et al., 2018; Zuniga and Li, 2011). These included the following rules: 1) no successive carbon-carbon double bonds; 2) no double bonds, hydroxyl groups or keto groups at the terminal carbon; 3) no hydroxyl groups at an unsaturated carbon; 4) if three carbon-carbon double bonds exist within a fatty acid, those three double bonds must adhere to two specific spacing patterns, namely, one single bond between two carbon-carbon double bonds or two single bonds between two carbon-carbon double bonds; and 5) if there are more than three carbon-carbon double

bonds in the fatty acid, those isomers must be limited to those experimentally identified in the literature or databases.

This process generated 2883 fatty acid isomers. These fatty acids were then compared against known fatty acids in the HMDB, and duplicates were removed. Curators and chemists on the HMDB team then manually checked the collection for long-chain unsaturated fatty acids with multiple double bonds and kept only those that were reported in the literature or online databases to further reduce the number of fatty acids to 1096. In generating this set of fatty acyl chains, the curation team did not consider the stereo configuration (cis or trans) of these 1096 fatty acid isomers. If these cis/trans isomers were included, the total would be 4381. Using this set of 1096 computationally generated acyl groups, the HMDB team then used in-house software to create the structures in various formats (Mol, SDF and SMILES) for 1096 acylcarnitines, all of which have now been deposited into the latest release of the HMDB. Another 36 “exotic” acylcarnitines consisting of nonlinear organic acids or dicarboxylic acids were also generated from free organic acids found in the HMDB, for which experimental evidence also supported their existence. Combined with the previously existing acylcarnitines, there are now a total of 1240 acylcarnitines in the HMDB (Figure 1).

## **B. Classification of acylcarnitines**

Currently, most acylcarnitines are classified according to the chemical structure of the variable acyl moiety in the acylcarnitine molecule. As a result, the classification of acylcarnitines is often similar to the classification of fatty acids (e.g., short-, medium-, long- and very-long-chain fatty acids) (Kimura et al., 2020; Ratnayake and Galli, 2009). However, it is important to note that there is also no unanimity about the classification of fatty acids, and classification methods can differ among different authors (Kimura et al., 2020; Ratnayake and Galli, 2009). Usually, the first parameter that is considered in categorizing an acylcarnitine is the length of the carbon chain. Based on the number of carbon atoms in the acyl-chain, we propose that acylcarnitines can be divided into four groups: short-chain (C2-C5), medium-chain (C6-C12), long-chain (C13-C20) and very-long-chain (>C21) acylcarnitines (Figure 2). Moreover, acylcarnitines can also be classified by the saturation degree of the fatty acid moiety: either an unsaturated or saturated fatty acid moiety. Saturated acylcarnitines can be further divided into monounsaturated and polyunsaturated acylcarnitines. Likewise, the cis- and trans-configurations of the fatty acid moiety can be taken into account. In addition, acylcarnitines can be classified according to the chemical structure of their acyl moiety. The majority of acylcarnitines have an aliphatic, straight-chain fatty acid moiety, but there are also acylcarnitines with branched-chain



fatty acid moieties and even cyclic organic acids. Finally, the fatty acid moiety of acylcarnitines can be substituted by several other chemical groups (e.g., hydroxyl- or carboxyl groups). It should be noted that inclusion of a given acylcarnitine within a certain group can overlap with an affiliation to another chemical group. For instance, there are short-chain, branched dicarboxylic acylcarnitines (e.g., 3-methylglutaryl-carnitine) or long-chain hydroxyl-unsaturated acylcarnitines (3-hydroxyoctadecenoyl-carnitine), as well as simple acylcarnitines (acetyl-, propionyl- or palmitoyl-carnitines), which comprise the largest part of the body's acylcarnitine pool (Figure 2).

More rarely, acylcarnitines can be classified according to the source of the acyl- moiety (Schooneman et al., 2013). Most acylcarnitines are synthesized during fatty acid metabolism (see Section 3); however, several acylcarnitines (mainly branched-chain varieties) can be synthesized from degradation products of amino acids (lysine, valine, leucine, and isoleucine). Likewise, certain carbohydrate metabolic byproducts can be a source of the acyl-moiety for some short-chain acylcarnitines (Topping and Clifton, 2001; Violante et al., 2013a). Other metabolic intermediates that may yield acylcarnitines are ketone bodies (Soeters et al., 2012). Acylcarnitines can also be divided into groups according to the organelles in which they are synthesized. The majority of acylcarnitines are synthesized by enzymes linked to the mitochondria, although some acylcarnitines can be products of peroxisomal metabolism (Hunt et al., 2012). Finally, acylcarnitines can be classified according to their appearance during certain physiological processes or specific pathological conditions. For instance, there are acylcarnitines (usually branched-chain acylcarnitines, long-chain dicarboxylcarnitines or hydroxyl-acylcarnitines) that mainly appear and accumulate through acquired or inborn metabolic diseases. On the other hand, some acylcarnitines can be found in significant concentrations in the plasma/urine and tissues of healthy individuals.

### **C. Short-chain acylcarnitines**

Short-chain acylcarnitines (C2-C5) have been suggested to be the most abundant group of acylcarnitines in the body, with plasma levels reaching nearly 80% or more of all acylcarnitines (Adams et al., 2009; Bene et al., 2005; Costa et al., 1997). We have provided detailed information on 50 short-chain acylcarnitines in the HMDB, which corresponds to approximately 4% of the total listed acylcarnitines. C2 carnitine or acetylcarnitine is the main acylcarnitine found in plasma (Adams et al., 2009; Costa et al., 1997; Reuter et al., 2008). In addition to its important role in energy production, acetylcarnitine provides acetyl groups for the synthesis of acetylcholine (Onofrij et al., 2013). Short-chain acylcarnitines (mainly acetylcarnitine and

propionylcarnitine) have been studied as supplements or experimental treatments for various diseases and pathologies. In many countries, acetylcarnitine is approved and indicated for treating several neurological disorders (<https://www.drugbank.ca/drugs/DB08842>) (see also section 5). Altered concentrations of different short-chain acylcarnitines have been demonstrated in a number of genetic diseases (Table 1); therefore, deviations from reference acylcarnitine levels have been used to diagnose inborn errors of metabolism. Moreover, abnormal levels of short-chain acylcarnitine have been identified in a number of chronic or acquired metabolic, oncologic and cardiovascular diseases (Table 1).

#### **D. Medium-chain acylcarnitines**

Medium-chain (C6-C12) acylcarnitines are much less abundant than short-chain acylcarnitines, but their number is substantially higher, with 476 now listed in the HMDB. They are typically derived from the corresponding medium-chain fatty acids by esterification with L-carnitine in a process that is described in more detail in a later section (see Section 3). The other source of medium-chain acylcarnitines is peroxisomal metabolism of long-, very-long- and branched-chain fatty acids (Violante et al., 2019; Violante et al., 2013b). After their synthesis, medium-chain acylcarnitines are usually transported into the mitochondria and metabolized to carbon dioxide and water (Schonfeld and Wojtczak, 2016). Medium-chain acylcarnitine levels in various body fluids (e.g., plasma, urine or serum) are invaluable markers for inherited diseases of fatty metabolism (Table 2). In addition, altered medium-chain acylcarnitine concentrations have been identified in other diseases, such as diabetes, cardiovascular disorders and cancer (Table 2).

#### **E. Long-chain acylcarnitines**

Long-chain acylcarnitines (C13-C20) are generated as the product of L-carnitine esterification with long-chain fatty acids that are obtained from the diet or generated *de novo* from lipogenesis (see Section 3). Among the different acylcarnitine classes, long-chain acylcarnitines have the highest number, with 533 members in the HMDB. Their main function is to ensure long-chain fatty acid transport into the mitochondria (Reuter and Evans, 2012). Tissue and plasma long-chain acylcarnitine levels are significantly higher in the fasted state than in the fed state (Makrecka-Kuka et al., 2017). Palmitoylcarnitine is the most abundant unsaturated long-chain acylcarnitine in plasma (Bene et al., 2005; Costa et al., 1997). Elevated long-chain acylcarnitine concentrations have been found in patients with inborn errors of long- or very-long-chain fatty acid metabolism, although there are also inborn disorders with decreased plasma levels of long-chain acylcarnitines (Table 3). Moreover, there is a growing body of evidence that the altered levels of circulating long-chain acylcarnitines are linked to various cardiovascular diseases

(Table 3). To a minor extent, altered long-chain acylcarnitine levels have been identified in patients with noncardiovascular diseases.

#### **F. Very-long-chain acylcarnitines**

Very-long-chain acylcarnitines are acylcarnitines containing an acyl- moiety with more than 20 carbon atoms, and 183 of them are now found in the HMDB. Very-long-chain fatty acids are synthesized in the cytoplasm by fatty acid synthase or are absorbed from food (Sassa and Kihara, 2014). These fatty acids are too long to become involved in mitochondrial  $\beta$ -oxidation. As a result, peroxisomes are the main organelles where very-long-chain fatty acids are metabolized and their acylcarnitines are synthesized (Duranti et al., 2008). Normally, in peroxisomes very-long-chain acyl- moieties are cleaved into shorter fragments that form short-chain or medium-chain acylcarnitines (see Section 3). These shorter acylcarnitines can then migrate into the mitochondria where they become involved in  $\beta$ -oxidation (Ferdinandusse et al., 2004). However, if there is an inborn error of metabolism involving some peroxisomal enzymes or altered biogenesis of peroxisome intermediates of catabolism of very-long-chain fatty acids, then very-long-chain acylcarnitines can accumulate (Table 4). It has been shown that in the case of X-linked adrenoleukodystrophy, there is a significantly elevated level of C26:0-carnitine in plasma as well as in bloodspots (van de Beek et al., 2016). Another study demonstrated that very-long-chain acylcarnitines (C22:0, C24:0 and C26:0) together with long-chain dicarboxylacylcarnitines are elevated in the plasma and urine of patients with peroxisomal enzyme defects (D-bifunctional protein deficiency) or peroxisomal biogenesis disorders (Zellweger spectrum disorders) (Duranti et al., 2008; Klouwer et al., 2017). In addition, elevated concentrations of very-long-chain acylcarnitines have been found in patients with type 2 diabetes. This may point to some diabetes-induced dysfunction of peroxisomes (Zhang et al., 2014). On the other hand, several studies have demonstrated that diabetes increases the level of peroxisomal very-long-chain fatty acid catabolism (Dhaunsi and Bitar, 2004).

#### **G. Unsaturated-chain acylcarnitines**

Unsaturated-chain acylcarnitines are a large class of acylcarnitines that include acylcarnitines with differing lengths of an unsaturated fatty acid moiety (Table 5). There are 716 of these acylcarnitines in the HMDB (while there are only 526 saturated fatty acid acylcarnitines in the HMDB). It has been shown that unsaturated-chain acylcarnitines can be synthesized by human cells from the corresponding fatty acid (Chegary et al., 2009). In addition, human cells contain enzymes that can convert saturated fatty acids into unsaturated fatty acids (Igal and Sinner, 2021). Thus, unsaturated fatty acids for the esterification with L-carnitine can be synthesized

endogenously and consumed via the diet. Altered unsaturated-chain fatty acid levels have been documented in inborn metabolic disorders as well as in a number of acquired diseases (Table 5).

#### H. Branched-chain acylcarnitines

The main source of short- to medium-length branched-chain acylcarnitines is from the catabolism of branched-chain amino acids (e.g., valine, leucine, and isoleucine). However, dietary and microbial sources can also lead to branched-chain acylcarnitines. We cataloged 347 branched-chain and 895 aliphatic straight-chain acylcarnitines in the HMDB. Among those derived from branched-chain amino acids, the corresponding amino acids are first deaminated to alpha-keto acids and then decarboxylated to form acyl-CoA derivatives, which can be further transformed into the corresponding acylcarnitines (Neinast et al., 2019). Branched-chain amino acids are converted to branched-chain fatty acids mainly by mitochondrial enzymes (Brosnan and Brosnan, 2006; Crown et al., 2015), and the synthesis of branched-chain acylcarnitines is catalyzed by carnitine acetyltransferase (CrAT, EC:2.3.1.7) (Violante et al., 2013a) or peroxisomal carnitine octanoyltransferase (CrOT, EC:2.3.1.137), which accepts longer branched-chain fatty acids as substrates (Ferdinandusse et al., 1999).

The accumulation of branched-acylcarnitines (i.e., isovalerylcarnitine, or 2-methylbutyrylcarnitine) in the blood has been observed in a number of inborn errors of branched-chain amino acid catabolism (Table 6), such as short-/branched-chain acyl-CoA dehydrogenase (EC:1.3.99) deficiency (Porta et al., 2019) and isovaleryl-CoA dehydrogenase (EC:1.3.8.4) deficiency (also known as isovaleric acidemia) (Roe et al., 1984). Another inborn error of metabolism, known as isobutyryl-CoA dehydrogenase (EC:1.3.99.) deficiency, elevates the level of isobutyryl-carnitine concentrations in plasma (Pedersen et al., 2006).

Phytanic acid and pristanic acid are the main sources of long-chain branched-acylcarnitines. These acids can be obtained through the consumption of dairy products, ruminant animal fats, and certain fish (Hellgren, 2010). The metabolism of phytanic and pristanic acid occurs mainly in the liver and kidney tissue peroxisomes where peroxisomal  $\alpha$ -oxidation of phytanoyl-CoA yields pristanoyl-CoA that can be further  $\beta$ -oxidized (Wierzbicki, 2007). It is hypothesized that the synthesis of these long-chain acylcarnitines is catalyzed by peroxisomal CrOT (Herzog et al., 2017), as phytanic and pristanic acids are poor substrates for carnitine palmitoyltransferase 1 (CPT1, EC:2.3.1.21) (Singh and Poulos, 1995).

It has been suggested that phytanoyl- and pristanoyl-carnitines could serve as markers for the diagnosis of inborn peroxisomal disorders. However, a recent study demonstrated that although the plasma concentration of both acylcarnitines can be elevated, they both lack

sensitivity and specificity for the conclusive diagnosis of peroxisomal disorders, including Refsum disease and alpha-methylacyl-CoA racemase (EC:5.1.99.4) deficiency (Herzog et al., 2017). Interestingly, decreased circulating branched acylcarnitine levels have been observed in some gastrointestinal disorders and in traumatic brain injury (Table 6).

### I. Hydroxyl-/dicarboxyl-acylcarnitines

Hydroxyl-/dicarboxyl-acylcarnitines are a large class of acylcarnitines that, due to their diversity, can be divided into several groups according to their acyl chain length. We compiled data for 380 hydroxyl-acylcarnitines and 218 dicarboxyl-acylcarnitines in the HMDB. The acylcarnitine with the shortest acyl chain of this group is malonylcarnitine. This compound accumulates in patients suffering from malonic aciduria due to the absence of functional malonyl-CoA decarboxylase (MCD, EC:4.1.1.9). This leads to a subsequent elevation of malonyl-CoA, which can be converted to its carnitine derivative (Liu et al., 2016). Short-chain hydroxyl acylcarnitines (e.g., 3-hydroxybutyrylcarnitine) can be formed directly from 3-hydroxybutyrate (a ketone body) or 3-hydroxybutyryl-CoA (Soeters et al., 2012). 3-Hydroxybutyrylcarnitine has been associated with fasting and ketosis, but also with insulin resistance and type 2 diabetes (Soeters et al., 2012). Other short-chain (C3-C5) dicarboxyl-acylcarnitines are catabolic products of amino acid metabolism (Chen et al., 2020; Tuncel et al., 2018) or the Krebs cycle (Rizzo et al., 2014). Some short-chain dicarboxyl-acylcarnitines can be synthesized from long-chain dicarboxylic acids by peroxisomes (Ferdinandusse et al., 2004). In addition, a certain portion of medium-chain dicarboxyl-acylcarnitines can be synthesized by peroxisomes by cleaving longer-chain dicarboxyl-acylcarnitines (Ferdinandusse et al., 2004). Other medium-chain dicarboxyl-acylcarnitines can be synthesized from hydroxyl-/dicarboxyl-fatty acids, which are formed from hydroxyl-/dicarboxyl-acyl-CoA due to incomplete  $\beta$ -oxidation along with subsequent omega-oxidation (Ribel-Madsen et al., 2016).

It has been shown that long-chain dicarboxyl-acylcarnitines are elevated in the urine in patients with inborn peroxisomal disorders (Table 7). The fatty acid moiety for the synthesis of long-chain dicarboxyl-acylcarnitines can be obtained from fatty acid omega-oxidation (Wanders et al., 2011). However, it is not clear which enzymes and organelles synthesize long-chain dicarboxyl-acylcarnitines. A recent study using primary rat cardiomyocytes and an *in vivo* mouse model showed that both mitochondria and peroxisomes contribute to dicarboxylic acid metabolism. In the same study, oxidation of dicarboxylic acids in mouse liver homogenate was inhibited by the CPT-1 inhibitor etomoxir, underlining the importance of mitochondrial metabolism in this process.(Bharathi et al., 2020) Another study demonstrated that longer

dicarboxyl-acylcarnitines were excreted in the urine of patients with peroxisomal biogenesis disorders due to dysfunctional peroxisomes (Duranti et al., 2008). Therefore, it can be hypothesized that peroxisomal dysfunction leads to the accumulation of dicarboxyl-fatty acids, which are converted to long-chain dicarboxyl-acylcarnitines in the mitochondria and excreted via urine. Increased dicarboxyl-acylcarnitine concentrations in blood and urine have also been noted in a number of acquired diseases (Table 7).

### **III. Biosynthesis and regulation**

#### **A. Enzymology of acylcarnitine biosynthesis**

Acylcarnitines in the body are generally produced by conjugating a specific fatty acid with L-carnitine through the help of the carnitine acyltransferase system. Under normal conditions, carnitine homeostasis is maintained by three mechanisms: 1) biosynthesis, 2) uptake from dietary sources and 3) reuptake from the glomerular filtrate in kidney proximal tubules via organic cation novel type 2 transporter (OCTN2)-mediated transport. The regulation of carnitine homeostasis has been extensively reviewed previously, and readers are referred to the papers by (Longo et al., 2016; Rebouche, 2004; Strijbis et al., 2010) for an in-depth understanding.

Carnitine is required as a substrate for the function of carnitine acyltransferases to generate acylcarnitines. As a result, decreasing carnitine availability is often used to treat disorders related to acylcarnitine accumulation in the body. For fatty acids to be incorporated into acylcarnitines by carnitine acyltransferases, fatty acids first need to be activated to their respective acyl-CoA esters with the help of acyl-CoA synthetases (ACS). The function, regulation and composition of the ACS family have been extensively reviewed elsewhere (Grevengoed et al., 2014). The ACS family includes multiple short-chain (ACSS), medium-chain (ACSM) and long-chain (ACSL) members. It should be noted that the specific loss of long-chain ACS (acyl-CoA synthetase long-chain family member 1 (ACSL1, EC:6.2.1.3)) activity in mouse liver tissues results in a decrease in long-chain acylcarnitines and an increase in medium-chain acylcarnitine content due to the upregulation of peroxisomal fatty acid oxidation (Li et al., 2009). Overexpression of ACSL1 and ACSL4 (acyl-CoA synthetase long-chain family member 4, EC:6.2.1.3) has been shown to increase acylcarnitine levels in human colorectal cancer cells (Sanchez-Martinez et al., 2017) and in primary cultured Schwann cells isolated from rat sciatic nerve tissues (Hinder et al., 2014).

Carnitine acyltransferases each support the transfer of acyl-groups with different chain lengths to carnitine to form short-, medium- and long-chain acylcarnitines (Figures 3 and 4).

Moreover, acyltransferases ensure the reversible shuttling of acyl groups between free CoA and carnitine. Thus, CrAT (EC:2.3.1.7) is mostly responsible for the synthesis of both short- (up to C5) and branched-chain acylcarnitines. However, the human enzyme can also effectively synthesize acylcarnitines with carbon chain lengths up to C8 and, to a slightly lesser extent, up to C10 (Violante et al., 2013a). Human CrOT (EC:2.3.1.137) is mostly responsible for the synthesis of medium-chain (C6-C12) and branched-chain acylcarnitines in peroxisomes (Ferdinandusse et al., 1999). CPT1 (EC:2.3.1.21, which has three tissue-specific isoforms; see Section 3.1.3) is involved in the synthesis of long-chain acylcarnitines (more than C12) on the mitochondrial outer membrane. Human liver CPT1 can also synthesize acylcarnitines from acyl-CoAs with a carbon length starting from C6 (Finocchiaro et al., 1990), while equivalent rat liver and avian muscle enzymes have been shown to produce acylcarnitines from very-long-chain unsaturated acyl-CoAs (Gavino et al., 2003; Price et al., 2011). Mitochondrial carnitine/acylcarnitine translocase (CACT, SLC25A20) shuttles long-chain acylcarnitines inside the mitochondrial matrix, where carnitine palmitoyltransferase 2 (CPT2, EC:2.3.1.21) converts these acylcarnitines back to their respective long-chain acyl-CoA (Rufer et al., 2009).

### 1. Carnitine acetyltransferase

Mammalian carnitine acetyltransferase, or CrAT, is found in the mitochondrial matrix, the peroxisomal matrix, the endoplasmic reticulum and the nucleus (Markwell et al., 1973; Ramsay et al., 2001). Recently, its activity has also been reported in the cytosol of mouse cardiomyocytes (Altamimi et al., 2018). In the mitochondria CrAT regulates the acetyl-CoA/free CoA ratio to prevent depletion of free CoA. For example, during intensive physical exercise when overproduction of acetyl-CoA occurs in muscle tissue, this process ensures replenishment of free CoA to facilitate pyruvate metabolism, but when the physical load ends, transacetylation of acetylcarnitine provides acetyl-CoA for the Krebs cycle (Stephens et al., 2007). The main function of CrAT in peroxisomes is to aid in the export of products of peroxisomal  $\beta$ -oxidation (Westin et al., 2008). In the murine cardiomyocyte cytosol, the reverse activity of CrAT might be related to providing acetyl-CoA for the biosynthesis of malonyl-CoA to inhibit fatty acid oxidation (Altamimi et al., 2018). It is also known that CrAT, by decreasing the availability of acetyl-CoA in the presence of carnitine overload (or when overexpressed), can alleviate inactivation of pyruvate dehydrogenase and increase glucose utilization in primary human skeletal myocytes (Noland et al., 2009). This can facilitate insulin secretion in  $\beta$  cells (Berdous et al., 2020). During ischemia, the lack of oxygen limits mitochondrial  $\beta$ -oxidation and respiration in isolated rat hearts, leading to the accumulation of both short-/long-chain



acylcarnitines and acyl-CoA intermediates along with the corresponding decrease in free CoA (Whitmer et al., 1978). While limited reserves of cytosolic CoA are likely converted to acyl-CoAs under acute stress conditions, preserving CrAT activity is crucial to ensure repletion of free CoA inside the mitochondria to support energy metabolism as long as possible.

## 2. Carnitine octanoyltransferase

Carnitine octanoyltransferase, or CrOT, is found only in peroxisomes, and similar to CrAT, this enzyme aids the export of products of peroxisomal  $\beta$ -oxidation (Westin et al., 2008). The highest activity of CrOT is toward C4-C12 containing acylcarnitines as indicated by studies using rat and mouse liver enzymes (Figure 4), while the activity rapidly decreases for chains with more than 14 carbons (Farrell et al., 1984; Miyazawa et al., 1983). It is interesting to note that while CrOT can use C10-CoA and 4,8-dimethylnonanoyl-CoA (a C11-CoA product of peroxisomal oxidation of pristanic acid) to produce the respective acylcarnitines, the human enzyme is inactive against 2,6-dimethylheptanoyl-CoA (C9-CoA), which is produced when C11-CoA is further  $\beta$ -oxidized (Ferdinandusse et al., 1999). Peroxisomes, via the help of CrOT, can partially contribute to medium-chain acylcarnitine production from the metabolism of medium- and long-chain fatty acids. Peroxisomes can also contribute to the myocardial oxidation of these fatty acids under normoxic conditions in isolated perfused rat hearts (Bian et al., 2005), particularly when mitochondrial fatty acid oxidation is impaired or overloaded as shown in a study using human skin fibroblasts (Violante et al., 2013b). Studies in isolated rat hearts indicate that peroxisomal fatty acid oxidation can provide more than 50% of the acetyl-groups that are used to produce malonyl-CoA (Reszko et al., 2004). Moreover, the study of intact isolated rat hearts indicates that acetyl-CoA molecules formed from fatty acids that undergo the first steps of oxidation only in peroxisomes are used for malonyl-CoA biosynthesis but are not transferred to the mitochondria in detectable amounts (Bian et al., 2005). Similar to CPT1, CrOT contains a malonyl-CoA-sensitive domain and can be inhibited by malonyl-CoA at physiological concentrations (A'Bhaird and Ramsay, 1992; Morillas et al., 2002). More than 30 years ago, it was suggested that the inhibition of rat liver peroxisomal long- and medium-chain acyltransferase (i.e., CrOT) by malonyl-CoA could be important for the regulation of mitochondrial fatty acid oxidation (Derrick and Ramsay, 1989). This is likely true for peroxisomal fatty acid oxidation itself, as the overexpression of the CrOT gene in human hepatic cancer cell lines results in an increase in CrOT activity and subsequent upregulation of enzymes that encode peroxisomal fatty acid oxidation. Conversely, siRNA-induced knockdown of CrOT has been shown to result in decreased mRNA levels of key proteins of fatty acid metabolism in



peroxisomes (Le Borgne et al., 2011). Overexpression of CrOT leads to a decrease in medium- and very-long-chain fatty acid levels, while long-chain fatty acid levels are not affected. Furthermore, hepatic cancer cells with CrOT knockdown demonstrate an increase in medium-chain fatty acid levels (Le Borgne et al., 2011). Moreover, CrOT overexpression can result in an increase in the mRNA levels of key proteins involved in peroxisomal fatty acid metabolism but not mitochondrial CPT1 and acyl-CoA thioesterase. Notably, the redirection of myocardial fatty acid oxidation from the mitochondria to peroxisomes decreases ischemic damage in isolated rat hearts and improves recovery during reperfusion (Liepinsh et al., 2013).

### 3. Carnitine palmitoyltransferases

Carnitine palmitoyltransferase 1, or CPT1, is the only carnitine acyltransferase with three isoforms present (CPT1A, liver isoform; CPT1B, muscle isoform; and CPT1C, brain isoform). Each of these isoforms is specific for different tissue types. The heart is one of the tissues where both CPT1A and CPT1B are present. Although liver and muscle isoforms share a high degree of sequence homology, they differ significantly in their physiological response to and regulation by malonyl-CoA and carnitine. A seminal paper by McGarry and colleagues describes, in great detail, the differences between the liver and muscle isoforms of CPT1 from rats, dogs and humans (McGarry et al., 1983). The  $K_m$  of carnitine for CPT1 ranges from 32 and 39  $\mu\text{M}$  in rat and human liver tissues to 500-600  $\mu\text{M}$  in human, rat and dog skeletal muscles, and 197 and 695  $\mu\text{M}$  in rat and dog cardiac tissues, respectively. The muscle isoform has a low affinity for carnitine, and the opposite is true for the liver isoform (Distler et al., 2009; McGarry et al., 1983). The  $\text{IC}_{50}$  for malonyl-CoA of CPT1 in human and rat liver tissue is in the low micromolar range (1.6-2.7  $\mu\text{M}$ ), while it is in the medium to low nanomolar range in rat and dog cardiac tissues (25-100 nM) and rat, dog and human skeletal muscle (17-34 nM) (McGarry et al., 1983). This high affinity toward the physiological inhibitor, malonyl-CoA, means that muscle and cardiac tissues are more sensitive to malonyl-CoA than liver tissues (Bird and Saggerson, 1984). During fasting, when the malonyl-CoA tissue content decreases by factors of 4.4-, 3.3- and 3-fold in liver, cardiac and muscle tissues, respectively (McGarry et al., 1983), the activity of CPT1 increases only in the liver and not in cardiac tissues (Bonfont et al., 2004; Paulson et al., 1984). On the other hand, a diet rich in carbohydrates activates insulin signaling. As a result, adenosine monophosphate-activated protein kinase (AMPK) is inhibited, and the production of malonyl-CoA by acetyl-CoA carboxylase (ACC, EC:6.4.1.2) is increased, leading to the inhibition of liver CPT1 activity, which facilitates liponeogenesis. Unlike heart and muscle tissues that predominantly express the ACC2 isoform, liver tissue expresses both ACC1 and

ACC2, with the latter being responsible for malonyl-CoA synthesis (Munday, 2002). In a fasted state the activity of ACC is inhibited via phosphorylation by AMPK. When the inhibitory activity of malonyl-CoA is averted, hepatic fatty acid  $\beta$ -oxidation is increased and triacylglycerol accumulation is prevented (Akkaoui et al., 2009). Within cardiac tissues, when the sensitivity of CPT1B toward malonyl-CoA is reduced, cardiac fatty acid utilization is increased (van Weeghel et al., 2018). Together, the interplay between malonyl-CoA and CPT1 is crucial for regulating long-chain fatty acid oxidation rates in liver, heart and muscle tissues. Missense mutations may result in a deficiency of CPT1A that leads to partial or even complete loss of enzymatic activity (Gobin et al., 2003). This deficiency is characterized by life-threatening hypoketotic hypoglycemia and fasting intolerance (Bennett et al., 2004; Stoler et al., 2004).

The brain isoform of rat CPT1C has a 2-fold lower  $K_m$  than CPT1A for carnitine and a 5-fold higher  $K_m$  for palmitoyl-CoA, but its catalytic activity is up to 320-fold lower (Sierra et al., 2008). While the exact role of CPT1C in brain tissue remains to be elucidated, recent studies have demonstrated that CPT1C and the availability of malonyl-CoA are required for proper axon growth by regulating anterograde transport of late endosomes and lysosomes (Palomo-Guerrero et al., 2019). Moreover, CPT1C is involved in the regulation of ceramide metabolism. Thus, the overexpression of this enzyme results in increased ceramide levels. Furthermore, it has been shown that a deficit of CPT1C diminishes ceramide levels and results in altered dendritic spine morphology and impaired spatial learning in mice (Carrasco et al., 2012). Overall, CPT1 enzymes are key regulators of long-chain acylcarnitine availability and thus have served as the primary target for altering long-chain acylcarnitine levels. Strategies to treat these CPT1-related conditions include increasing malonyl-CoA levels via inhibition of MCD (Fillmore and Lopaschuk, 2014) using CPT1 inhibitors, which have been proven effective in treating ischemic heart disease in an *in vivo* pig model (Cheng et al., 2006). Direct inhibition of CPT1 with pharmacological agents such as etomoxir (etomoxiryl-CoA) (Lopaschuk et al., 1988) or decreasing the availability of substrate (carnitine) by using OCTN2 inhibitors such as meldonium or methyl-GBB (Liepinsh et al., 2015) have also been explored as cardioprotective strategies in rat (*in vivo*) and isolated heart ischemia–reperfusion injury models.

CPT2 is another isoform of carnitine palmitoyltransferase that is located on the matrix side of the inner mitochondrial membrane and is tasked with converting long-chain acylcarnitines back to the respective long-chain acyl-CoAs. CPT2 is not sensitive to malonyl-CoA and catalyzes the transfer of the acyl group of long-chain fatty acid-carnitine conjugates onto CoA. Data obtained from rat liver mitochondria suggest that CPT2 aids in the export of

long-chain acyl-CoA esters from the mitochondria (Ventura et al., 1998) and can synthesize C8–C20 acylcarnitines (Figure 4). On the other hand, human CPT2 has virtually no activity in handling shorter acyl-CoAs or very-long-chain acyl-CoAs, or acyl-CoAs derived from branched-chain amino acid metabolism (Violante et al., 2010). While this activity could potentially remove toxic long-chain acyl-CoA esters from the mitochondrial matrix, it could also lead to the accumulation of long-chain acylcarnitines in the mitochondrial intermembrane space.

#### 4. Acylcarnitine transporters

The transporter CACT catalyzes the equimolar exchange of long-chain acylcarnitines for carnitine to ensure long-chain acylcarnitine transfer across the inner mitochondrial membrane (Murthy and Pande, 1984) via a ping-pong mechanism with one binding site alternately exposed to each side of the membrane. Moreover, carnitine uniport is also possible (Palmieri, 1994). Another transporter, human OCTN2 or SLC22A5, is involved not only in the transport of carnitine but also in the transport of acetylcarnitine (Wu et al., 1999). In rodents, OCTN2 also ensures the transport of acetylcarnitine across the blood–brain barrier (Kido et al., 2001). More recently, in a study using a mouse acylcarnitine transporter, it was shown that organic cation transporter 1 (OCT1, SLC22A1) is involved in the hepatic efflux of short-chain (C2–C6) acylcarnitines (Figure 4) and participates in the regulation of plasma short-chain acylcarnitine levels (Kim et al., 2017). It remains to be determined which transport proteins (Table 8), if any, are involved in the efflux/transport of medium- and long-chain acylcarnitines.

#### B. Acylcarnitine production sites – Organelles

Based on the locations of carnitine acyltransferases and their contribution to the overall pool of acylcarnitines, two distinct sites of acylcarnitine production can be identified from an organelle perspective: the mitochondria and peroxisomes. As highlighted in Section 3.1.1, due to the presence of CrAT, both organelles can generate acetylcarnitine from acetyl-CoA. Acetyl-CoA itself is a product of multiple catabolic reactions and is predominantly generated in the mitochondrial matrix by glycolysis,  $\beta$ -oxidation and the catabolism of branched-chain amino acids (Pietrocola et al., 2015). While CrAT in peroxisomes aids the export of acetyl- moieties via acetylcarnitine (Westin et al., 2008), the reverse activity of CrAT in the cytosol ensures that acetyl-moieties are used for the biosynthesis of malonyl-CoA (Altamimi et al., 2018). Studies using rodent peroxisomes and rodent mitochondria indicate that on average, peroxisomal contributions to the oxidation of C16–C24 saturated and unsaturated fatty acids are 15–31%, 14–46% and 18–38% in rat liver, cardiac and muscle tissues, respectively (Reubsæet et al., 1989). Comparable findings have been reported for pig liver, kidney and cardiac tissues (Yu et al.,

1997). In other words, acetylcarnitine of peroxisomal origin contributes to the overall pool of acetylcarnitine to a lesser extent than acetylcarnitine derived from mitochondria. Peroxisomal metabolism of pristanic acid and odd-chain fatty acids serves as a source for propionyl-CoA, which is subsequently converted to propionyl-carnitine by CrAT to exit peroxisomes (Jakobs and Wanders, 1995). Peroxisomal metabolism of long- and very-long-chain fatty acids usually results in the production of C12-C14 chain length acyl-CoAs (Reszko et al., 2004), while metabolism of octanoate usually involves shortening by 2 acetyl- moieties (Kasumov et al., 2005). As a result, peroxisomes can also contribute to the production of butyrcarnitine and C12-C14-acylcarnitine pools. Since peroxisomes do not have CPT1 and CrOT has a strong preference for acyl-CoAs with chain lengths of up to C14 (Farrell et al., 1984; Miyazawa et al., 1983), it is unlikely that peroxisomes could produce meaningful amounts of any acylcarnitines with acyl-moieties longer than C14. When peroxisomes oxidize medium-chain fatty acids such as lauric acid (C12), C12-, C10-, C8- and C6-acylcarnitines are formed and exported (Violante et al., 2019). This, in turn, means that mitochondria serve as the main source for acylcarnitines with carbon chain lengths of C16 and above. Mitochondria do not have CrOT, meaning that their acylcarnitine production is limited to acyl- moieties with chain lengths preferred by CrAT and CPT1/2 (Figure 4). Nevertheless, human CrAT can convert acyl-CoAs with chain lengths up to C10 to the respective acylcarnitines (Violante et al., 2013a), while CPT1 can produce acylcarnitines from saturated fatty acids with chain lengths starting from C6 to C18 (Finocchiaro et al., 1990; Schaefer et al., 1997). CPT1 can also produce acylcarnitines from unsaturated fatty acids (Price et al., 2011), including very-long-chain polyunsaturated fatty acids (Gavino et al., 2003). As a result, mitochondria take part in the production of acylcarnitines with virtually every chain length.

### **C. Enzymes, transporters and energy metabolism pathways affecting acylcarnitine levels**

The modulation of fatty acid metabolism typically changes the content of acylcarnitines as well as their metabolism in mitochondria (Figure 5). Physiologically, energy metabolism is regulated during the fed-fasted cycle via activation of AMPK or insulin signaling pathways. AMPK stimulates fatty acid metabolism, while insulin-mediated signaling inhibits fatty acid metabolism by affecting CPT1-dependent acylcarnitine synthesis. CPT1 activity in insulin-sensitive tissues is regulated via changes in the malonyl-CoA level (McGarry et al., 1977). Accordingly, a low malonyl-CoA content leads to increased CPT1 activity and an increased acylcarnitine synthesis rate. Malonyl-CoA is generated by ACC and degraded by MCD. The activity of ACC is

inhibited by the AMPK-mediated phosphorylation of enzymes, while inactivation of AMPK turns ACC into the dephosphorylated state and increases enzyme activity (Dyck and Lopaschuk, 2006). The activation of insulin signaling prevents ACC phosphorylation and thus stimulates malonyl-CoA synthesis followed by CPT1 inhibition (Witters and Kemp, 1992). Malonyl-CoA-mediated decarboxylation is catalyzed by MCD, which converts malonyl-CoA into acetyl-CoA. Improvement in insulin sensitivity by insulin mimetics such as glucagon-like peptide 1 could accelerate insulin action and support the insulin-induced reduction in fatty acid metabolism. In contrast, negative regulation of the phosphoinositide-3 kinase/protein kinase B (PI3K/Akt) pathway by activation of various phosphatases, such as protein tyrosine phosphatase 1B, protein phosphatase 2 A, and phosphatase and tensin homolog, could potentially increase the acylcarnitine content and fatty acid metabolism rate (Liao and Hung, 2010).

Long-chain acylcarnitine synthesis is dependent on CPT1 expression and the availability of substrates. For instance, muscle-specific CPT1 KO mice (Wicks et al., 2015) have lower medium- and long-chain acylcarnitine contents in their muscle tissue. Likewise, pharmacological inhibition of CPT1 by the drug oxfenicine results in a lower long-chain acylcarnitine content in heart tissues (Karwi et al., 2020; Kennedy et al., 2000). Additionally, the availability of carnitine significantly influences the acylcarnitine synthesis rate and content of acylcarnitines in plasma and tissues (Liepinsh et al., 2015; Rahbeeni et al., 2002). Stimulation of fatty acid metabolism in mitochondria has been considered as strategy to reduce long-chain acylcarnitine levels. Thus, when decreased CPT1-dependent acylcarnitine production is accompanied by preserved or stimulated mitochondrial  $\beta$ -oxidation, the mitochondria are further protected against lipid overload-induced accumulation of long-chain acylcarnitines (Liepinsh et al., 2015; Makrecka-Kuka et al., 2020a). Similarly, the regulation of mitochondrial fatty acid oxidation is mediated by sirtuins (a well-conserved family of signaling proteins involved in metabolic regulation), which change the acetylation/deacetylation balance of mitochondrial proteins (Matsushima and Sadoshima, 2015). Thus, long-chain acyl-CoA dehydrogenase (LCAD), an important enzyme in mitochondrial  $\beta$ -oxidation, is hyperacetylated in the absence of sirtuin 3 and results in an increased content of long-chain acylcarnitines (Hirschey et al., 2010). In the sirtuin 5 KO mouse model, impaired  $\beta$ -oxidation and increased contents of medium- and long-chain acylcarnitines in the liver and muscles were also observed (Rardin et al., 2013). Overall, inhibiting their synthesis and the stimulation of mitochondrial fatty acid  $\beta$ -oxidation are important mechanisms for the prevention of acylcarnitine accumulation.

#### D. Acylcarnitine production sites – Tissues

Plasma concentrations of acylcarnitines are frequently used as markers to diagnose inborn fatty acid oxidation defects and other diseases leading to incomplete fatty acid metabolism (Rinaldo et al., 2008; Wanders et al., 2020). Acylcarnitines of differing chain lengths may appear in the plasma as a result of efflux from different organs or tissues. The heart, skeletal muscle and liver all contain various acylcarnitine species. Therefore, these tissues could be proposed as the main contributors to the plasma acylcarnitine pool. Increased plasma concentrations of medium- and long-chain acylcarnitines are observed in the fasted state due to increased lipolysis and fatty acid oxidation rates when compared to the fed state (Liepinsh et al., 2014; Makrecka et al., 2014). Similar differences in the acylcarnitine content between different nutritional states are detected in metabolically flexible tissues such as the heart and muscles, but not in the liver (Makrecka-Kuka et al., 2017; Schooneman et al., 2014). Moreover, the content of long- and medium-chain acylcarnitines in rodent plasma is comparable with that in heart tissue, indicating that the heart is a major contributor to plasma acylcarnitine concentration changes, particularly for medium- and long-chain acylcarnitines (Makrecka-Kuka et al., 2017). This allows one to use plasma long-chain acylcarnitine concentrations as indicators of cardiac acylcarnitine content and mitochondrial functionality. Although skeletal muscles have an energy metabolism pattern similar to that of the heart, multiple studies in rodents (Makrecka-Kuka et al., 2017), pigs (Schooneman et al., 2015) and humans (Xu et al., 2016) have shown that there is no significant contribution (efflux) of long-chain acylcarnitines from skeletal muscle to the plasma. Indeed, in studies involving fasted mice, it was found that the muscle tissue content of long-chain acylcarnitines increased during exercise, but the plasma concentration did not change (Makrecka-Kuka et al., 2017). Even though the liver is the main source of circulating acetyl- and propionyl-carnitine (Schooneman et al., 2015; Xu et al., 2016), it does not contribute to the long-chain acylcarnitine blood pool, even when liver CPT2 is absent and the liver tissue content of acylcarnitines is increased (Lee et al., 2016). Skeletal muscles in humans have been shown to contribute to the plasma availability of C8 to C12 (C12:1) acylcarnitines, particularly during exercise, in contrast to during the resting state (Xu et al., 2016). This is the case despite the fact that the cardiac content of medium-chain acylcarnitines is significantly higher than that of the muscles and the fact that the heart significantly more contributes to the plasma availability of medium-chain acylcarnitines at a resting state (Makrecka-Kuka et al., 2017). However, during the exercise, both the heart and skeletal muscles appear to contribute to the plasma medium-chain acylcarnitine pool (Xu et al., 2016; Zhang et al., 2017a). Overall, it can be concluded that the heart is the main contributor to the long-chain acylcarnitine pool in plasma and that skeletal

muscles and the heart contribute to the medium-chain acylcarnitine pool, while the liver is the main contributor to the short-chain acylcarnitine pool in plasma.

## IV. Diseases and pathways

### A. Biomarkers of pathological conditions and diseases

#### 1. Acylcarnitines for the diagnosis of inherited rare diseases and conditions

Inherited fatty acid oxidation disorders (FAODs) may be diagnosed if any part of the mitochondrial  $\beta$ -oxidation pathway affecting plasma membrane functions, mitochondrial fatty acid transport or the short-, medium- or long-chain fatty acid  $\beta$ -oxidation pathways has been adversely affected. The FAODs related to the transport of long-chain acylcarnitines across the mitochondrial inner membrane (CACT deficiency) and conversion of acylcarnitines back to the respective acyl-CoAs (CPT2 deficiency) have been previously described (Houten et al., 2016; Marsden et al., 2021; Vishwanath, 2016). Defects in enzymes involved in mitochondrial  $\beta$ -oxidation such as very-long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein deficiency are often characterized by elevated long- and very-long-chain acylcarnitine levels. These conditions have been extensively reviewed before, and readers are referred to the papers of (Houten et al., 2016; Marsden et al., 2021; Vishwanath, 2016) for an in-depth understanding.

CACT-mediated transport is an essential step in the long-chain fatty acid  $\beta$ -oxidation pathway. Carnitine-acylcarnitine translocase deficiency is a rare autosomal recessive disease characterized by mutations in the CACT gene (SLC25A20). This condition may result in hypoketotic hypoglycemia, elevated creatine kinase and transaminases, dicarboxylic aciduria, very low free carnitine and marked elevation of long-chain acylcarnitines (Rubio-Gozalbo et al., 2004). This can lead to cardiac complications (cardiac arrhythmia, cardiomyopathy, and heart block), muscle weakness and seizures (Vitoria et al., 2015). Another condition called CPT2 deficiency is the most common of the rare disorders related to the metabolism of long-chain fatty acid oxidation. Particularly rare are lethal neonatal and severe infantile forms of CPT2 deficiency. On the other hand, the more common and milder version of this disease is the muscle form of CPT2 deficiency (Joshi and Zierz, 2020). It should be noted that severe carnitine deficiency and increased long-chain acylcarnitine levels are characteristic of this disorder. Long- and medium-



chain acylcarnitine levels are used for the diagnosis of not only CACT disorders but also CPT2 and several  $\beta$ -oxidation enzyme deficiencies (Figure 6).

## **2. Long-chain acylcarnitine measurements for the diagnosis of insulin resistance**

While acylcarnitines have long been used to diagnose inherited metabolic disorders, they are also being studied for the diagnosis of acquired metabolic disorders such as diabetes and insulin resistance. Currently, glucose and glycated hemoglobin A1c are the main diagnostic markers of type 2 diabetes used in clinical practice (American Diabetes, 2017; Inzucchi et al., 2015). Recently, assessments of triglycerides and total cholesterol have been included as markers of diabetes progression and therapeutic efficacy (American Diabetes, 2017). Other circulating lipid metabolites have not yet been accepted into clinical practice as markers of insulin resistance. Given the role of insulin in the suppression of lipid metabolism, it would be reasonable to evaluate insulin sensitivity by measuring the levels of fatty acid metabolism intermediates. In this regard, long-chain acylcarnitines appear to be promising biomarkers.

Energy metabolism is significantly changed during fed-and-fasted cycles, as it depends on the availability of energy substrates in the circulation. The utilization of fatty acids dominates in a fasted state while in response to increased availability of glucose, insulin-sensitive tissues switch to carbohydrate metabolism in a fed state. Long-chain acylcarnitines are produced from long-chain fatty acids in skeletal muscles and the heart. However, only the heart is thought to be the main contributor to the plasma long-chain acylcarnitine pool (Koves et al., 2008; Makrecka-Kuka et al., 2017). Activation of insulin signaling decreases CPT1 activity and thus reduces the long-chain acylcarnitine content in muscle and cardiac tissues (Mihalik et al., 2010). The inability to reduce fatty acid metabolism in a fed state is a metabolic inflexibility caused by insulin resistance (Goodpaster and Sparks, 2017; Smith et al., 2018). The plasma concentrations of long-chain acylcarnitines reflect the changes in acylcarnitine tissue contents in the fed and fasted states and thus can serve as a valuable marker of tissue-specific insulin sensitivity (Makarova et al., 2019). Importantly, insulin levels in a fasted state are substantially lower than those in a fed state. Therefore, the measurement of plasma acylcarnitine concentrations in the fasted state does not help with the characterization of insulin sensitivity. Accordingly, high concentrations of long-chain acylcarnitines in the postprandial or fed state are markers of insulin resistance. This is a result of insulin's inability to inhibit CPT1-dependent fatty acid metabolism in the heart (Ngu et al., 2008; Ramos-Roman et al., 2012). In patients with type 2 diabetes, insulin resistance usually presents in the heart and skeletal muscle concurrently. Thus, long-



chain acylcarnitine measurements might be useful for the diagnosis of insulin resistance in skeletal muscles (Luong et al., 2021; Paternostro et al., 1996).

In the clinical setting, the postprandial state is not well defined. Therefore, the oral glucose tolerance test (GTT) or a controlled high carbohydrate-containing meal is better suited for diagnosing diabetes, prediabetes or insulin sensitivity. The GTT is widely accepted as a diagnostic method, and measurements of acylcarnitines before and after glucose administration are feasible in clinical situations (Jagannathan et al., 2020). GTT measurements characterize either mitochondrial energy status in the fasted state or in the insulin-mediated transition from a fasted to a postprandial state. The concept that insulin-resistant subjects are not able to adequately decrease long-chain acylcarnitine plasma concentrations during an insulin clamp or a standard meal has been validated in several clinical studies (Bouchouirab et al., 2018; Mihalik et al., 2010). Thus, measurements of plasma long-chain acylcarnitine levels during GTT and insulin clamp tests are suitable for evaluating insulin sensitivity in both muscle tissues and the heart.

### **3. Incomplete long-chain acylcarnitine metabolism – A marker of heart failure and a predictor of major cardiovascular events**

Oxidative phosphorylation (OXPHOS) in the mitochondria is the central energy production pathway of the heart. As a result, mitochondrial dysfunction has been considered to be an important reason for contractile failure in the heart. Long-chain fatty acids are the main energy substrates for oxidative metabolism in the heart, and fatty acid metabolism is primarily affected when there is reduced mitochondrial OXPHOS capacity. Insufficient fatty acid metabolism in the mitochondria results in a decreased ATP generation rate and persistent energy deficiency. AMPK can sense an increased AMP/ATP ratio and stimulate CPT1 activity. Since acylcarnitine accumulation does not induce any feedback inhibition of CPT1, acylcarnitine levels can increase significantly over time as the pathology progresses. During the progression of heart failure, cardiac metabolism switches to other available energy substrates, but these derangements do not affect acylcarnitine production. Heart tissues are suggested to be the main contributors to the plasma long-chain acylcarnitine pool (Makrecka-Kuka et al., 2017); therefore, long-chain acylcarnitine measurements in plasma are particularly suitable for the diagnosis of cardiac diseases related to mitochondrial dysfunction.

During fasting, plasma concentrations of medium- and long-chain acylcarnitines are continuously increasing in tissues and plasma as a result of stimulated intracellular fatty acid metabolism, which is proportional to the duration of the fast (Elizondo et al., 2020; Hung et al.,

2020). This is a result of the low concentrations of insulin in the circulation, the limited availability of glucose as a metabolic substrate, and the stimulation of intracellular fatty acid metabolism. Increased fatty acid availability and facilitated CPT1 activity are appropriate metabolic condition for the evaluation of mitochondrial capacity to metabolize fatty acids. In situations where  $\beta$ -oxidation and OXPHOS capacity are not capable of utilizing high amounts of synthesized acylcarnitines, elevated levels of medium- and long-chain acylcarnitines will appear in the plasma (Adams et al., 2009; Elizondo et al., 2020). Overall, a fasted state (or being on a ketogenic diet) is the most appropriate condition for the diagnosis of mitochondrial dysfunction in the heart.

Several studies have measured increased levels of circulating long-chain acylcarnitines in chronic heart failure patients (Ahmad et al., 2016; Hunter et al., 2016; Ruiz et al., 2017; Ueland et al., 2013). In all studies with heart failure patients, elevated circulating levels of long-chain acylcarnitines were independently associated with adverse clinical outcomes. In the clinical trial HF-ACTION, higher plasma concentrations of long-chain acylcarnitines were independently associated with lower peak  $\text{Vo}_2$  as well as both the primary and secondary clinical endpoints of the parent trial (Ahmad et al., 2016). In particular, plasma levels of C16, C18:1, and C18:2 acylcarnitines were significantly higher in patients with end-stage heart failure. In patients who underwent left ventricular assist device placement, plasma levels of long-chain acylcarnitines were decreased. Increased long-chain acylcarnitine concentrations reflect dysfunctional fatty acid metabolism in mitochondria and probably in peroxisomes (Houten et al., 2016). This suggests an important mechanism contributing to global lipid perturbations in humans with heart failure. Overall, long-chain acylcarnitines appear to be promising biomarkers for diagnosis or therapeutic interventions in HF patients.

Multiple metabolomic profiling studies have been performed to identify biomarkers that predict major cardiovascular events (Rizza et al., 2014; Shah et al., 2012). A metabolomic profiling study identified medium- and long-chain acylcarnitines as biomarkers that could predict major cardiovascular events in elderly people (Shah et al., 2012). In another study, aging, mitochondrial dysfunction and increased levels of long-chain acylcarnitines (evaluated by metabolomic profiling) were associated with major cardiovascular events, independent of standard predictors (Shah et al., 2012). Therefore, higher levels of plasma long-chain acylcarnitines can be a predictor for an increased risk of major cardiovascular events.

## B. Long-chain acylcarnitine accumulation-induced disorders

### 1. Enzymes, ion channels and (signaling) pathways affected by acylcarnitines

Certain pathological states are linked to inappropriate regulation of long-chain acylcarnitine synthesis or incomplete metabolism (McCoin et al., 2015a). This leads to an accumulation of long-chain acylcarnitines that may interact with several cytosolic and mitochondrial enzymes, ion channels and signaling pathways (Figure 7). The long-chain acylcarnitine palmitoylcarnitine has been shown to decrease OXPHOS-dependent mitochondrial respiration with complex I/II and complex II substrates in a dose-dependent manner. It has also been shown to induce mitochondrial membrane hyperpolarization and the subsequent production of reactive oxygen species (Liepinsh et al., 2016). Palmitoylcarnitine can also induce mitochondrial damage leading to apoptotic cell death via activation of the caspase pathway (McCoin et al., 2015b; Mutomba et al., 2000). At physiologically relevant concentrations palmitoylcarnitine was able to significantly decrease mitochondrial pyruvate and lactate oxidation (Makrecka et al., 2014) and to impact cellular energy metabolism pathways through dephosphorylation of the insulin receptor and protein kinase B (Akt) (Vilks et al., 2021).

The sodium-potassium exchanger ( $(\text{Na}^+/\text{K}^+)\text{-ATPase}$ , EC 7.2.2.13, multiple isoforms) is inhibited by long-chain acylcarnitines (Adams et al., 1979; Lamers et al., 1984; Meszaros and Pappano, 1990). Moreover, the activity of the sarco/endoplasmic reticulum  $\text{Ca}^{2+}\text{-ATPase}$  (SERCA, EC 7.2.2.10, multiple isoforms) is increased in the presence of long-chain acylcarnitine concentrations below 20  $\mu\text{M}$  and decreased when long-chain acylcarnitine concentrations are above 20  $\mu\text{M}$ . This means that long-chain acylcarnitines facilitate  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum (Adams et al., 1979; Dumonteil et al., 1994; McCoin et al., 2015b; Yamada et al., 2000). In addition, it has been shown that extracellular long-chain acylcarnitines interact with the extracellular site of the voltage-gated potassium channel hERG ( $\text{Kv}11.1$ ,  $\text{KCNH2}$ ) to increase the  $I_{\text{hERG}}$  amplitude (Ferro et al., 2012). While it is clear that long-chain acylcarnitines affect cardiac excitation-contraction coupling (Aitken-Buck et al., 2020), it remains to be determined whether they have a relevant pathological meaning (e.g., leading to a pro-arrhythmic action). These effects are further discussed in the following Sections as risk factors for cardiometabolic diseases.

## 2. Detrimental effects of acylcarnitines in ischemic heart disease and heart failure

The high energy demand and limited glucose availability in the heart ensure that fatty acid metabolism is the predominant energy production mechanism for this organ (Stanley et al., 2005). In the postprandial and fasted states, 60-95% of the heart's ATP is produced from fatty acid oxidation, respectively (Liepinsh et al., 2014). The content of acylcarnitines fully depends on their production and utilization rates. Therefore, if stimulated fatty acid flux and accelerated synthesis of acylcarnitines are not fully coupled with oxidation, then acylcarnitines will accumulate in cardiac mitochondria and other intracellular compartments. Acylcarnitine accumulation to relatively high levels can be considered a normal physiological response to fasting or starving. For example, during the fasted state, the acylcarnitine content in the heart can be elevated by 5-fold compared to the fed state (Makrecka et al., 2014). The content of acylcarnitines increases even further in the case of prolonged fasting or starvation (Soeters et al., 2009). In a healthy heart, an increase in long-chain acylcarnitines does not lead to mitochondrial or cardiac damage; however, in the fasted state, cardiac oxygen utilization efficiency is significantly reduced (Liepinsh et al., 2014; Makrecka-Kuka et al., 2020b). In patients, fasting- and starvation-induced accumulation of long-chain acylcarnitines might lead to more pronounced cardiac damage in cases of ischemia (Liepinsh et al., 2014). Likewise, in patients with insulin resistance, the increased risk of heart disease (Peters et al., 2015) might be linked to higher levels of long-chain acylcarnitines in the heart.

During ischemia, the low oxygen availability in the heart limits mitochondrial  $\beta$ -oxidation (Fillmore et al., 2014), and incompletely metabolized fatty acids, along with their CoAs and carnitine esters start to accumulate. Energetic deficiencies in the ischemic heart stimulate a number of energy production pathways, including long-chain fatty acid uptake and the corresponding long-chain acylcarnitine synthesis in mitochondria by CPT1. Accordingly, high CPT1 (A and B isoforms) activity in cardiac tissues results in an increased long-chain acylcarnitine production rate (Liepinsh et al., 2016). At the same time, within the ischemic mitochondrial matrix, the long-chain acylcarnitine utilization rate is substantially reduced because of limited CPT2 activity and subsequent  $\beta$ -oxidation. For their proper functioning, CPT2 and  $\beta$ -oxidation enzymes need a sufficient amount of free CoA as a cofactor; however, during ischemia, the acyl-CoA/CoA ratio is significantly increased, leading to a deficiency of free CoA (Whitmer et al., 1978). Additionally, oxygen deficiency induces the accumulation of NADH and FADH<sub>2</sub>, which inhibits  $\beta$ -oxidation enzymes (Jaswal et al., 2011; Neely and

Feuvray, 1981). Altogether, long-chain acylcarnitines accumulate in ischemic mitochondria because of stimulated synthesis and a limited utilization rate.

Multiple studies have noted the accumulation of fatty acid metabolites in the infarcted heart (Corr et al., 1984; Ford et al., 1996; Idell-Wenger et al., 1978; Whitmer et al., 1978). Moreover, there is direct evidence that long-chain acylcarnitine accumulation reaches levels in cardiac mitochondria that induced detrimental effects in an isolated rat heart infarction study (Liepinsh et al., 2016). The mechanisms of mitochondrial dysfunction induced by long-chain acylcarnitines have been described in several studies (Korge et al., 2003; Siliprandi et al., 1992; Tominaga et al., 2008). The main detrimental effects of long-chain acylcarnitine in mitochondria are related to the inhibition of OXPHOS, further resulting in inhibited ATP synthase activity and increased reactive oxygen species (ROS) production (Dambrova et al., 2021; Tominaga et al., 2008). This is supported by the finding that the highest measured levels of long-chain acylcarnitines are bound to the mitochondrial membranes and in the intermembrane space (Liepinsh et al., 2016). In addition to the direct effects on mitochondrial OXPHOS, long-chain acylcarnitines inhibit pyruvate and lactate metabolism in cardiac mitochondria (Makrecka et al., 2014). Overall, long-chain acylcarnitine accumulation is very harmful to mitochondrial functioning and is likely a factor that contributes to the energetic crisis in the myocardium during ischemia–reperfusion.

The amphiphilic nature of long-chain acylcarnitines and their nonspecific interaction with membranes have been widely studied (McCoin et al., 2015a). However, the presumptive nonspecific actions ascribed to long-chain acylcarnitines are somewhat doubtful because fatty acid-binding proteins are present in various intracellular and extracellular compartments and protect cardiomyocytes and mitochondria against the amphiphilic effects of long-chain acylcarnitines (Liepinsh et al., 2016). However, for *in vitro* studies, the role of fatty acid-binding proteins as factors limiting long-chain acylcarnitine toxicity effects has to be taken into account. Fatty acid-binding proteins scavenge fatty acids and metabolic intermediates to reduce their free fraction and deliver intermediates only for specific reactions in the appropriate target proteins, thus preventing nonspecific toxic reactions (Glatz and vanderVusse, 1996; Neess et al., 2015). In the circulation, the free fraction of long-chain acylcarnitines is very low because they are tightly bound to serum albumin. In the cell cytosol, the high abundance of fatty acid-binding proteins could be responsible for the handling of fatty acids and long-chain acylcarnitines (Liepinsh et al., 2016). In myoglobin-rich tissues, long-chain (C12-C18) acylcarnitines can also bind to oxymyoglobin and participate in the regulation of long-chain acylcarnitine pools (Chintapalli et al., 2018; Chintapalli et al., 2016). Currently, the protective effects of binding proteins have not

been studied in detail and such assumptions are based on indirect evidence. Depending on whether an individual is in the fed or fasted state, long-chain acylcarnitine concentrations in the heart vary between 10-50  $\mu\text{M}$ . The effects of long-chain acylcarnitines on ion channels, insulin signaling enzymes, pyruvate metabolism and OXPHOS in mitochondria are typically found to occur between 5-20  $\mu\text{M}$  if tested in the absence of cytosol or serum albumin. The addition of cytosolic fractions significantly limits the detrimental action of long-chain acylcarnitines on mitochondrial functionality (Liepinsh et al., 2016); which suggests the presence of protective proteins in the cytosol. Importantly, if fatty acids and long-chain acylcarnitines compete for the same binding protein, an increased level of fatty acids during starving and ischemia results in an increased free fraction of long-chain acylcarnitines. Since deoxy-myoglobin has limited acylcarnitine binding compared to oxymyoglobin, it has also been hypothesized that this could contribute to the higher free acylcarnitines during hypoxia (Chintapalli et al., 2018; Chintapalli et al., 2016). Therefore, conditions with increased fatty acid flux and hypoxia can be harmful because of the higher possibility of nonspecific actions of long-chain acylcarnitines.

### **3. Pro-arrhythmic effects of acylcarnitines**

Most sudden cardiac deaths (SCDs) are caused by arrhythmias, in particular ventricular fibrillation. The majority of cases of SCD occur in patients who do not have traditional risk factors for arrhythmia (Srinivasan and Schilling, 2018). During cardiac ischemia and reperfusion, the concentration of long-chain acylcarnitines is markedly elevated and therefore associated with life-threatening arrhythmias (Aitken-Buck et al., 2020). Long-chain acylcarnitines can interfere with excitation-contraction coupling, cause arrhythmias, and reduce the conductivity between cardiac cells (reviewed in (Aitken-Buck et al., 2020; McCoin et al., 2015a)). It has been demonstrated that attenuation of increasing long-chain acylcarnitine levels during hypoxia through CPT1 inhibition is able to protect against hypoxia-mediated alterations in cardiomyocyte action potentials (Knabb et al., 1986). Several mechanisms of long-chain acylcarnitine interference have been proposed, including direct channel interaction (Yamada et al., 1994), nonselective permeabilization of the sarcolemma (Liu et al., 1991), reduction in gap junction permeability, and interference with calcium release from the sarcoplasmic reticulum (Liu et al., 1991). Furthermore, an extracellular increase in long-chain acylcarnitine levels has been shown to induce arrhythmias at the single-cell level (Wu and Corr, 1992). It must be noted that all of these observed effects of long-chain acylcarnitines strongly depend on the employed concentrations. It is therefore not well defined which of the long-chain acylcarnitine effects

achieved at certain concentrations *in vitro* and *ex vivo* can be attributed to effects during ischemia *in vivo*.

Despite the strong indications that long-chain acylcarnitines interfere with cellular electrophysiology and excitation-contraction coupling and even though long-chain acylcarnitines promote arrhythmias in animal models, the targeting of long-chain acylcarnitine concentrations as an antiarrhythmic treatment strategy has not been tested in the clinic. Taking into account that there are clinically approved compounds that can be used for reducing long-chain acylcarnitine concentrations in humans, it would be reasonable to explore whether these compounds could find a new use in a patient group at high risk of cardiac arrhythmia during ischemia.

#### **4. Acylcarnitine accumulation-induced complications in inherited rare diseases and conditions**

Several inborn errors of metabolism involve fatty acid metabolism defects and the accumulation of acylcarnitines (McCoin et al., 2015a). Altered energy metabolism and marked accumulation of long-chain acylcarnitines in the blood and many tissues have been observed in a number of rare inborn disorders, such as CACT, CPT2, VLCAD, LCHAD, and mitochondrial trifunctional protein deficiency. The enzymes associated with these deficiencies are involved in the transport and metabolism of long-chain acylcarnitines and facilitate mitochondrial fatty acid  $\beta$ -oxidation. Long-chain acylcarnitine accumulation is not present in all FAOD; it is present only when there is an enzyme deficiency in the fatty acid mitochondrial metabolism pathway downstream of CPT1 (A and B isoforms).

The clinical phenotypes seen in FAODs are heterogeneous and of different severity, even when the same fatty acid oxidation gene is deficient (Baruteau et al., 2013; Joshi et al., 2014). Considerable effort has been devoted to identifying discriminating biochemical factors determining the more severe phenotypes and to identifying pathological mechanisms leading to disease complications. Energy deficiency in the heart and muscles is considered the main reason for acute and long-term complications of fatty acid oxidation deficiencies. Often acute onset of the metabolic crisis and clinical symptoms appear when patients are in a fasted state or during exercise (Joshi et al., 2014). Thus, certain adaptation mechanisms can compensate for a single gene deficiency and exhibit a normal metabolic phenotype despite fatty acid metabolism having an essential role in energy production in the heart and skeletal muscle. To large extent, compensation for deficiencies in fatty acid mitochondrial metabolism is possible because of the switch to carbohydrate oxidation, which replaces fatty acids as energetic substrates. Additionally, during carbohydrate intake, activation of insulin signaling limits long-chain

acylcarnitine synthesis (Elizondo et al., 2020). Instead, during prolonged fasting and exercise, the limited availability of glucose cannot match the energy demand and fully compensate for fatty acid metabolism deficiency (Houten et al., 2016). During fasting and exercise, a marked increase in the content of long-chain acylcarnitines is a physiological response, and cells and mitochondria can usually tolerate elevated levels of acylcarnitines (Xu et al., 2016). In patients with inherited deficiencies in mitochondrial fatty acid metabolism, increased production is not coupled with acylcarnitine metabolism, and long-chain acylcarnitines accumulate, often substantially exceeding tolerable baseline levels (Chace et al., 2001; McHugh et al., 2011). Since the high content of long-chain acylcarnitines induces harmful effects on the mitochondria and energy metabolism pathways, long-chain acylcarnitines are involved in the induction of an energetic crisis (McCoin et al., 2015a).

More than 50% of patients with these conditions exhibit cardiac complications, including cardiomyopathy, arrhythmias, and SCD (Bonnet et al., 1999). The same cardiovascular events are linked to excessive accumulation of acylcarnitines in experimental and clinical studies in subjects without an inherited deficiency. In patients with deficiencies of primary carnitine carriers, CPT1, and medium-chain acyl-CoA dehydrogenase, long-chain acylcarnitines do not accumulate and arrhythmias are not observed (Bonnet et al., 1999). In the postmortem blood specimen samples from deceased patients with mitochondrial fatty acid oxidation deficiencies, the level of long-chain acylcarnitines was up to 100 times greater than the levels observed in noninherited cardiac disorders (Chace et al., 2001; McHugh et al., 2011). In comparison, during myocardial infarction, mitochondrial long-chain acylcarnitine levels are increased 2–4-fold (Liepinsh et al., 2016). Patients with heart failure were found to have 2-fold higher concentrations of circulating long-chain acylcarnitine than control subjects (Ruiz et al., 2017). This evidence confirms that the long-chain acylcarnitine accumulation has a distinct role in the pathological mechanism of cardiovascular complications.

The main treatment currently available for FAODs is a dietary intervention to limit long-chain fatty acids and increase consumption of carbohydrates to ensure adequate energy production (Spiekerkoetter et al., 2009). This treatment strategy could also affect long-chain acylcarnitine production because of reduced long-chain fatty acid flux and activated insulin signaling. Additionally, these dietary interventions might be based on diet supplementation with medium-chain fatty acid triglycerides, which are known to improve cardiac parameters but do not reduce rhabdomyolytic crises in fatty acid oxidation-deficient patients (Gillingham et al., 2017; Vockley et al., 2021). Fatty acids with an uneven number of carbons might be beneficial because they replenish the Krebs cycle.



A less studied compensatory mechanism is the redistribution of fatty acid metabolism from mitochondria to peroxisomes. Long- and very-long-chain fatty acids can be metabolized in peroxisomes, and in case of limited mitochondrial metabolism, peroxisomal proliferation and fatty acid oxidation are stimulated via activation of the peroxisome proliferator-activated receptor gamma coactivator 1/peroxisome proliferator-activated receptor  $\alpha$  (PGC1/PPAR- $\alpha$ ) pathway (Liepinsh et al., 2013; Wicks et al., 2015). Peroxisomes shorten (very) long-chain fatty acids with chain lengths down to C6, thereby generating acetyl-CoA and acetylcarnitine, which increases acetyl-group availability for metabolism in the Krebs cycle. At the same time, this process reduces the mitochondrial load of long-chain acylcarnitines. Additionally, in patients with at least some residual fatty acid oxidation enzyme activity, stimulation of fatty acid metabolism by PPAR- $\alpha$  agonists might be beneficial. Indeed, bezafibrate treatment in CPT2-deficient patients reduced the average C16+C18:1 level from 38.39 to 7.73  $\mu$ M with a concomitant decrease in creatine kinase levels (Yamada et al., 2018). However, PPAR- $\alpha$  agonists are not effective in all patients because stimulation of fatty acid flux via CPT1 might induce additional acylcarnitine accumulation, especially in patients with a lack of residual mitochondrial enzyme activity (Yamada et al., 2018).

Despite early diagnosis and dietary therapy, a significant number of patients with FAODs still develop symptoms, which underlines the need for additional individualized treatment strategies. Targeted long-chain acylcarnitine-lowering strategies are currently not used for the treatment of mitochondrial FAODs. Promising results have been obtained in a recent *in vitro* study using the drug etomoxir. The reduced long-chain acylcarnitine production by etomoxir rescues the pro-arrhythmia defects in human induced pluripotent stem cells derived from fibroblasts of patients with VLCAD deficiency (Knottnerus et al., 2020). In patients with blocked mitochondrial fatty acid oxidation, the reduction in long-chain acylcarnitine synthesis appears to ensure certain benefit. Novel diagnostic methods using detailed functional studies in fibroblasts would help in the design of individualized treatments for patients with mitochondrial fatty acid oxidation deficiencies.

## 5. Prodiabetic effects of acylcarnitines

Insulin resistance, which is the main feature of type 2 diabetes, involves inappropriate glucose and fatty acid metabolism. Disturbances in glucose metabolism can be induced by a high fatty acid load in the diet which results in the accumulation of lipid metabolites. Among the fatty acid intermediates involved in the development of insulin resistance are long-chain acylcarnitines. However, this is not widely acknowledged (McCain et al., 2015a; Schooneman et al., 2013).

Generally, the increased levels of long-chain acylcarnitines have been viewed as a marker of incomplete mitochondrial metabolism of fatty acids that activate proinflammatory pathways implicated in insulin resistance (Adams et al., 2009). However, because long-chain acylcarnitine-induced effects on insulin signaling were previously demonstrated (Aguer et al., 2015; Blackburn et al., 2020; Liepinsh et al., 2017; Vilks et al., 2021), an increased intracellular content of long-chain acylcarnitines results in feedback inhibition of insulin action (Figure 7). Thus, insulin- and AMPK-mediated regulation of CPT1 activity has significant physiological impacts, and long-chain acylcarnitines are beginning to emerge as important metabolites involved in the regulation of energy metabolism. Long-chain acylcarnitines are also very active intermediates and effectively inhibit pyruvate and lactate oxidation in mitochondria. This compromises glucose metabolism in models of isolated rat cardiac mitochondria (Makrecka et al., 2014), cells in culture (Aguer et al., 2015), and *ex vivo* isolated rat hearts (Makrecka et al., 2014). It has been hypothesized that in the fasted state, long-chain acylcarnitines inhibit glucose uptake and metabolism to reduce the risk of hypoglycemia and generate energy from existing lipid stores (Liepinsh et al., 2017). Thus, long-chain acylcarnitines are important players in metabolism with important roles in the development of insulin resistance.

In several studies, it has been confirmed that long-chain acylcarnitines are not only markers for incomplete fatty acid oxidation but are also actively involved in the regulation of carbohydrate and lipid metabolism (Aguer et al., 2015; Blackburn et al., 2020; Liepinsh et al., 2017; Makrecka et al., 2014). The acute and chronic administration of palmitoylcarnitine *in vivo* inhibits the activation of insulin signaling and insulin-dependent glucose uptake in murine muscles (Liepinsh et al., 2017). Increased levels of long-chain acylcarnitines in muscle-specific CPT2 KO mice (SK<sup>-/-</sup>) were shown to significantly reduce Akt Ser473 phosphorylation in liver and adipose tissue while in muscles from high fat diet (HFD)-fed mice, a marked decrease in Akt Ser473 phosphorylation in Sk<sup>-/-</sup> mice compared to wild-type mice (Sk<sup>+/+</sup>) was observed (Pereyra et al., 2020). Recently, it was discovered that long-chain acylcarnitines induce dephosphorylation of the insulin receptor through increased activity of protein tyrosine phosphatase 1B (Vilks et al., 2021). The same study reported that palmitoylcarnitine decreases Akt phosphorylation independent of the insulin receptor phosphorylation level. Thus, the mechanism behind long-chain acylcarnitine action in muscles appears to involve the dephosphorylation of the insulin receptor and Akt. Importantly, increased levels of insulin *in vitro* and *in vivo* can suppress the long-chain acylcarnitine effects on Akt phosphorylation (Liepinsh et al., 2017). This explains how, in the transition from a fasted to a fed state, increased levels of insulin overcome the effects of long-chain acylcarnitine and enable insulin signaling,

which enhances glucose metabolism, and inhibits fatty acid metabolism (Consitt et al., 2016; Soeters et al., 2009). In addition, to support the transition from fatty acid metabolism to glucose metabolism and to overcome transient insulin insensitivity in the muscles and heart, long-chain acylcarnitines appear to stimulate insulin release (Liepinsh et al., 2017; Soni et al., 2014) via suppression of Akt signaling in insulin-releasing cells (Vilks et al., 2021).

In healthy subjects, the increased concentration of insulin effectively inhibits long-chain acylcarnitine production via the increased tissue content of malonyl-CoA (Koves et al., 2008; Ussher et al., 2009). If insulin fails to inhibit long-chain acylcarnitine production in the fed state, it results in disturbances in glucose uptake and oxidation. In the early stage of insulin resistance, elevated levels of insulin can compensate for insulin resistance and thereby overcome the long-chain acylcarnitine-induced effects. In the later stages of insulin resistance, the inability of insulin to inhibit long-chain acylcarnitine production is accompanied by an increased concentration of long-chain acylcarnitines, which further stimulates the progression of glucose intolerance. Thus, the increased tissue content of long-chain acylcarnitines accelerates the progression of insulin resistance.

## 6. Acylcarnitine effects on inflammation

Inflammation is one of the key pathologies for many diseases and disorders, including insulin resistance, cardiomyopathy, organ rejection and central nervous system (CNS)-related disorders. It has been previously demonstrated that when present in sufficiently high concentrations, palmitoylcarnitine ( $\geq 10$ - $25$  n  $\mu$ M) promotes inflammation and oxidative stress in C2C12 myotubes and murine monocytes (Adams et al., 2009; Aguer et al., 2015; McCoin et al., 2015b). More recently, it was shown that the loss of CPT2 and subsequent endogenous accumulation of long-chain acylcarnitines does not affect palmitate-induced inflammation in C2C12 myotubes (Blackburn et al., 2020), suggesting that skeletal muscle cell inflammation cannot be attributed to the accumulation of long-chain acylcarnitine alone. However, the inhibition of CPT2 *in vivo* by aminocarnitine exacerbates inflammation in cardiac tissues in classic models of lipopolysaccharide-induced endotoxemia in mice (Makrecka-Kuka et al., 2020a). This suggests that further upregulation of inflammation in the case of endotoxemia and/or sepsis could be related to the accumulation of long-chain acylcarnitines.

In murine monocyte/macrophage cell lines acylcarnitines activate proinflammatory signaling pathways in an acyl-chain length (C10-C18)-dependent and a concentration-dependent (5-25  $\mu$ M) manner (Adams et al., 2009; Rutkowsky et al., 2014). In addition, it has been suggested that the long-chain acylcarnitine-induced proinflammatory response is mediated not

through the Toll-like receptor but downstream of the MyD88 component (Rutkowsky et al., 2014). In FAOD patients with increased levels of long-chain acylcarnitines several changes in inflammatory proteins were observed. These included modestly increased plasma concentrations of IFN- $\gamma$  and IL-8 and a decreased concentration of IL-10, an inflammation-dampening cytokine (McCoin et al., 2019). These findings suggest that long-chain acylcarnitines could take part in the activation of inflammatory signaling. It has also been shown that an excess of long-chain acylcarnitines, in combination with insufficient  $\beta$ -oxidation, promotes Th17 inflammation in patients with type 2 diabetes (Nicholas et al., 2019). Overall, these data suggest that the accumulation of long-chain acylcarnitines induces inflammation, thus potentiating the progression of diseases such as diabetes. Likewise, a drug-induced reduction in acylcarnitine availability has been shown to decrease the accumulation of macrophages and monocytes in atherosclerotic lesions. This also decreases the level of circulating inflammatory cytokines in an experimental model of atherosclerosis (Vilskersts et al., 2015). Moreover, enforced expression of CPT1A and increased fatty acid oxidation in murine macrophage cell lines have been shown to result in attenuated proinflammatory processes (Malandrino et al., 2015). This is likely related to the reduced accumulation of acylcarnitines in cells. Taken together, these findings suggest that the enzymes and proteins involved in long-chain acylcarnitine transport and production could serve as potential drug targets to attenuate inflammatory processes in chronic disorders.

Taking into account the growing significance of immunometabolism, it is intriguing to consider the role of acylcarnitines in the immune cell response. It should be noted that to date, studies on immune cells are mainly focused on the investigation of fatty acid oxidation *per se* but not on the possible role of fatty acid metabolites, such as acylcarnitines, in immune cell functioning. Historically, it has been suggested that fatty acid oxidation is necessary for macrophage anti-inflammatory (M2) phenotype regulation (Vats et al., 2006). Follow-up studies in primary rodent cells and human T cells and cultured human cells using etomoxir, an irreversible CPT1A inhibitor, demonstrated interesting off-target effects (Divakaruni et al., 2018; Raud et al., 2018) and brought into question whether fatty acid oxidation is essential for human macrophage M2 polarization (Namgaladze and Brune, 2014). Moreover, later studies have shown that CPT2 deletion in bone marrow-derived macrophages derived from mice does not affect polarization toward an M2 (anti-inflammatory) phenotype (Nomura et al., 2016). Overall, the current thinking in the immunometabolism field suggests that the anti-inflammatory macrophage response is more robustly supported by mitochondrial OXPHOS than by fatty acid oxidation. Interestingly, none of the abovementioned studies measured acylcarnitine profiles. High concentrations of etomoxir are known to induce the accumulation of long-chain

acylcarnitines in the rat myocardium (Lopaschuk et al., 1988), which could further inhibit mitochondrial OXPHOS (Liepinsh et al., 2016). Thus, it could be hypothesized that etomoxir-induced mitochondrial dysfunction in macrophages could be secondary to the accumulation of long-chain acylcarnitines and that the accumulation of fatty acid metabolites could attenuate macrophage polarization to the M2 phenotype. However, this idea needs to be tested.

Interestingly, higher concentrations of circulating long- and medium-chain acylcarnitines have been found in sepsis nonsurvivors (Langley et al., 2013; Puskarich et al., 2018). This suggests the possible role of acylcarnitines in immune cell proinflammatory activation. However, data on the roles of fatty acid oxidation and long-chain acylcarnitines in the proinflammatory response are lacking. Given that the accumulation of long-chain acylcarnitines inhibits pyruvate metabolism and phosphorylation of Akt in rodent mitochondria and murine myoblasts (Liepinsh et al., 2017; Makrecka et al., 2014), it might be suggested that the availability of acylcarnitines could determine the energy metabolism pattern in immune cells and thus direct immune cell activation toward a proinflammatory phenotype.

## **7. Possible effects of acylcarnitines in neurodegenerative and neuropsychiatric disorders**

Fatty acid oxidation is not the primary energy production pathway in the brain (Schonfeld and Reiser, 2013). However, the role of fatty acid oxidation and acylcarnitines, especially long- and medium-chain acylcarnitines, in the progression of CNS-related disorders is increasingly being studied. A growing number of studies have observed unique acylcarnitine signatures in patients with neurodegenerative and neuropsychiatric disorders. In clinical studies, higher levels of circulating long- and medium-chain acylcarnitines have been found in patients with Alzheimer's disease (van der Velpen et al., 2019). Moreover, higher levels of long-chain acylcarnitines are associated with disease progression (Chatterjee et al., 2020) and with cognitive impairment (Toledo et al., 2017). However, in larger cohorts, it has been shown that the higher serum levels of medium- and long-chain acylcarnitines actually predicted a lower risk of Alzheimer's disease incidence (Huo et al., 2020). Furthermore, clinical trials of patients with Parkinson's disease have consistently shown that circulating levels of long-chain acylcarnitines are decreased (Chang et al., 2018; Molsberry et al., 2020; Saiki et al., 2017). In both schizophrenia and psychosis patients, the levels of C3-carnitine and palmitoylcarnitine in the circulation were decreased (Cao et al., 2019; Kriisa et al., 2017). The levels of individual long-chain acylcarnitines in those patients do not follow the same pattern. Thus, for patients with schizophrenia the levels of the majority of long- and medium-chain acylcarnitines are decreased

(Cao et al., 2019), while for patients with psychosis an increase in long-chain acylcarnitines was found (Kriisa et al., 2017). Overall, the metabolomic analysis of acylcarnitines in patients with CNS-related disorders has consistently identified alterations in circulating acylcarnitines. However, it is not clear whether acylcarnitine levels in the circulation could correspond to acylcarnitine levels in brain tissues or if an altered acylcarnitine profile in the plasma indicates possible cross-talk in neurodegenerative and neuropsychiatric disorders.

Interestingly, although fatty acid oxidation is not the main energy source for neuronal tissues, key enzymes involved in acylcarnitine synthesis, specifically CPT1, ACC and MCD, are highly expressed in the hypothalamus (Jernberg et al., 2017; Lopez et al., 2006; Santos et al., 2013; Sorensen et al., 2002). This result suggests a possible involvement of acylcarnitine availability in the hypothalamic regulation of energy homeostasis. Previous studies have shown that the inhibition or genetic ablation of the acylcarnitine synthesizing enzyme CPT1 induces a reduction in food intake (Obici et al., 2003; Wolfgang et al., 2008; Wolfgang et al., 2006). This finding implies that acylcarnitines could be involved in the regulation of nutrient sensing. Overall, these data suggest that acylcarnitine availability or content in the brain could alter energy metabolism in peripheral tissues (e.g., muscle and liver) by regulating hypothalamic nutrient sensing. Thus, it is more likely that changes in the circulating acylcarnitine profile are not directly driven by changes in the acylcarnitine profile in neuronal tissues; rather, these changes represent energy metabolism alterations in peripheral tissues.

In brain tissues, the acylcarnitine synthesis and turnover rate is extremely low compared to other tissues (Schonfeld and Reiser, 2013). Thus, disturbances in acylcarnitine metabolism might induce changes in the neuronal acylcarnitine content/profile and subsequent alterations in signaling pathways only over the long term. In general, the pathogenesis of many CNS-related disorders involves mitochondrial dysfunction and inflammation (Golpich et al., 2017; Lucas et al., 2006; Skaper et al., 2018). It has been shown that the accumulation of long-chain acylcarnitines in mitochondria induces disturbances in OXPHOS, stimulates ROS production in the heart (Liepinsh et al., 2016; Tominaga et al., 2008), and potentially promotes inflammation (Makrecka-Kuka et al., 2020a; Rutkowsky et al., 2014). Similarly, in the brain, the long-term accumulation of long-chain acylcarnitines could promote or enhance mitochondrial dysfunction along with inflammation-related disturbances.

## V. Drugs, supplements and clinical trials

### A. The effects of supplementation with acetylcarnitine and propionylcarnitine

A number of recent patient studies have presented interesting and compelling relationships between acetylcarnitine deficiency and several mental illnesses, including depression, schizophrenia, attention deficit hyperactivity disorder and autism spectrum disorder (Cao et al., 2019; Frye et al., 2013; Nasca et al., 2018; Van Oudheusden and Scholte, 2002). Most of these articles argue for the possibility of diagnosing and even treating mental disorders with acylcarnitine measurements or supplements. Short-chain acylcarnitines, that is, acetylcarnitine and propionylcarnitine, are the most abundant group of acylcarnitines in the body and the most commonly used supplements (Tables 9 and 10). Altered levels of different short-chain acylcarnitines have been demonstrated in a number of genetic diseases and in many different mental illnesses (Table 1) (Nasca et al., 2018). Beyond its important role in general metabolism, acetylcarnitine provides acetyl-groups for the synthesis of acetylcholine (Onofrj et al., 2013). Acetylcarnitine supplementation has been suggested to enhance cholinergic neurotransmission (Jones et al., 2010; Nalecz et al., 2004) and has been shown to increase the norepinephrine and serotonin contents in murine brains (Smeland et al., 2012). These results suggest that acetylcarnitine supplements could affect a number of different types of mental illness both directly, by compensating for carnitine deficiency, and indirectly, by enhancing cholinergic neurotransmission. A list of clinical studies reported a positive effect of acetylcarnitine on the outcome of neuropsychiatric conditions and metabolic diseases, as shown in Table 9. Such nutritional supplementation is considered treatment option for several conditions, including schizophrenia (Bruno et al., 2016), autism spectrum disorder (Ziats et al., 2015), attention deficit hyperactivity disorder (Abbasi et al., 2011; Van Oudheusden and Scholte, 2002) and alcohol use disorder (Martinotti et al., 2011) (see the more comprehensive list in Figure 8). However, the most studied condition associated with acetylcarnitine supplementation is major depressive disorder (MDD) which has been assessed in multiple clinical trials (see Section 5).

It is well established that many current antidepressant treatment strategies do not provide an adequate treatment response in a substantial number of patients (Bauer et al., 2013; Trivedi et al., 2006). This is manifested by a treatment response that is only achieved after many weeks and by side effects of the medications that can cause low compliance, prompting alternative treatments for MDD. A recent meta-analysis investigated the effect of acetylcarnitine on depressive symptoms across twelve randomized controlled trials (Veronese et al., 2018). This

report shows a significant decrease in depressive symptoms in the acetylcarnitine supplementation as a monotherapy intervention, compared with placebo or with no intervention. Moreover, the incidence of adverse effects under acetylcarnitine treatment was found to be similar to placebo and much lower (79%) than under standard antidepressants, while the effectiveness of acetylcarnitine monotherapy was found to be comparable to standard antidepressants (Veronese et al., 2018). In contrast, a randomized controlled trial by Brennan and colleagues (2013) studying a combination of acetylcarnitine and alpha-lipoic acid in 40 depressed bipolar affective disorder patients did not show a significant antidepressant effect (Brennan et al., 2013). Accordingly, the Canadian Network for Mood and Anxiety Treatments, which has produced clinical guidelines for the management of adults with MDD (2016), recommends acetylcarnitine monotherapy as third-line therapy for mild to moderate MDD (Ravindran et al., 2016), but not in the depression phase of bipolar affective disorders (Yatham et al., 2018). In Brennan's study, brain levels of high-energy phosphate were evaluated with <sup>31</sup>P-MRS in a subgroup of participants. Corresponding to the negative finding in terms of clinical effects, <sup>31</sup>P-MRS failed to detect a significant change from baseline at weeks 1 and 12 of acetylcarnitine and alpha-lipoic acid treatment (Brennan et al., 2013). In contrast, a preliminary study reported that the antidepressant effect of acetylcarnitine in two geriatric MDD patients was associated with the normalization of high-energy phosphate levels in prefrontal regions (Pettegrew et al., 2002). Acetylcarnitine was also found to be effective in dysthymia both in the general adult population and in elderly patients (Bella et al., 1990; Bersani et al., 2013; Zanardi and Smeraldi, 2006).

Acetylcarnitine was shown to be effective not only in treating MDD but also in reducing the severity of depressive symptoms accompanying other diseases (Table 9). A randomized controlled trial comparing the antidepressant agent duloxetine to acetylcarnitine in fibromyalgic patients reported that acetylcarnitine improved depressive symptoms and pain (Leombruni et al., 2015). A meta-analysis investigated the effectiveness of acetylcarnitine treatment in reducing depressive symptoms in Alzheimer's disease when used as an adjunct to Alzheimer's disease medication (Meister et al., 2016). By analyzing 34 studies and 4769 patients with persistent depressive symptoms, lower rates of adverse events and increased adherence to drug therapy in the group that received adjunct acetylcarnitine were reported (Meister et al., 2016).

In summary, acetylcarnitine supplementation seems to decrease depressive symptoms compared with placebo or no intervention in MDD patients. Moreover, acetylcarnitine shows a better tolerance rate and seems to be a better candidate as a rapid-acting antidepressant.



However, findings on the effectiveness of acetylcarnitine supplementation in other psychiatric disorders are not consistent across studies.

Long-term supplementation with carnitine has been suggested to positively affect physical performance (Karlic and Lohninger, 2004). Theoretically, supplementation should increase the muscle carnitine content and subsequently improve fatty acid oxidation and exercise function in humans (Gnoni et al., 2020). As might be expected, carnitine supplementation also induces certain effects on the concentrations of serum acylcarnitines. Metabolomic studies have shown that carnitine supplementation increased a broad range of acylcarnitine concentrations in patients with septic shock (Puskarich et al., 2018). Carnitine supplementation has also increased postexercise acetylcarnitine concentrations and reduced long-chain acylcarnitine species in patients with impaired glucose tolerance (Bruls et al., 2019). It has been reported that decreased long-chain acylcarnitine levels have been found after carnitine supplementation (Bohles et al., 1987). However, the role of carnitine in the generation of the proatherogenic metabolite trimethylamine N-oxide and the associated longitudinal effects on the cardiovascular system still need to be critically assessed (Sawicka et al., 2020). Overall, considering that the global market of carnitine supplements is very large (estimated to be nearly 170 million USD in 2018 with a yearly growth of 5% (<https://www.grandviewresearch.com/industry-analysis/l-carnitine-market>)), the effect of carnitine supplementation on acylcarnitine metabolism warrants more consideration.

In addition to the positive effects of carnitine and acetylcarnitine, a number of studies also report positive outcomes of propionylcarnitine supplementation (Table 10). For example, propionylcarnitine has been used together with acetylcarnitine as a supplement for the treatment of sexual dysfunction and depressed moods in older males (Cavallini et al., 2004). Other studies have reported positive effects in treating several different vascular diseases, intermittent claudication, colitis and ischemia (Table 10). Propionylcarnitine is believed to interact with CACT and to increase fatty acid transport across the mitochondrial membrane (Heggermont et al., 2016). It also stimulates energy production in ischemic muscles by increasing Krebs cycle flux (Wiseman and Brogden, 1998).

## **B. Carnitine deficiency and related disorders**

Carnitine (levocarnitine) supplementation has long been used to treat carnitine deficiencies arising from inborn errors associated with its uptake and transport. Carnitine has also been used to reduce body weight and prevent the development of certain cardiometabolic diseases, especially cardiomyopathy and diabetes (Figure 8). Long-term supplementation with carnitine

has been shown to positively affect physical performance, but its role in the generation of proatherogenic metabolite TMAO and associated longitudinal effects on the cardiovascular system still need to be critically assessed (Sawicka et al., 2020). As expected, carnitine supplementation induces certain effects on serum acylcarnitines. Metabolomic studies have shown that carnitine supplementation increased a broad range of acylcarnitine concentrations in patients with septic shock (Puskarich et al., 2018). Carnitine supplementation has also increased postexercise acetylcarnitine concentrations and reduced long-chain acylcarnitine species in patients with impaired glucose tolerance (Bruls et al., 2019). Decreased long-chain acylcarnitine levels have even been found after carnitine supplementation (Bohles et al., 1987). Overall, given the amount of money spent on carnitine supplements, the effect of carnitine supplementation on acylcarnitine metabolism warrants more consideration.

### C. Clinical trials

To assess the state of acylcarnitines currently registered in clinical studies, ClinicalTrials.gov was searched using the keywords ‘acylcarnitine’ and ‘levocarnitine’ without any date constraints. ClinicalTrials.gov is the official U.S. database of privately and publicly funded clinical studies that holds information on nearly 370,000 trials (<https://clinicaltrials.gov/>). Additionally, the scientific literature published in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) was searched using the keyword ‘acylcarnitine’ with the clinical trials filter. The results from these methods were manually curated and classified.

In total, 190 clinical studies were identified. These included 126 interventional studies that used levocarnitine as a primary pharmacological intervention, and 72 other clinical trials that used acylcarnitine levels as biomarkers or outcome measurements (previously discussed). The 64 trials using acylcarnitine biomarkers can be divided into six different types of studies: pharmacological interventions (58%), nutritional diet interventions (20%), behavioral interventions (12%), nutritional supplementation studies (6%), observational studies (2%), and procedural studies (2%) (Figure 8A). These studies investigated acylcarnitine levels as biomarkers for different conditions (20 studies), and as study outcome measurements (40 studies). While the use of acylcarnitines as biomarkers or outcome measures in drug and nutritional diet studies has been discussed previously, it is interesting to note that ~5% of the clinical trials investigated acylcarnitines in behavioral interventions for these purposes. The eight behavioral studies evaluated acylcarnitine levels in exercise, lifestyle, and weight loss interventions as biomarkers for fatty acid oxidation or future markers for weight loss or to assess acylcarnitine levels as outcome measures.

The use of direct carnitine supplementation with FDA-approved levocarnitine is being investigated in 126 interventional studies. Levocarnitine was first approved in 1985 and is indicated for persons with certain types of carnitine-related metabolic disorders. It is the only treatment with a direct connection to carnitine-acylcarnitine homeostasis. These interventional studies assessed the use of carnitine for treating conditions such as carnitine deficiencies in patients undergoing hemodialysis, peripheral vascular diseases, complications from prematurity, glucose intolerance, hepatic disease, and a number of different neurological disorders including neuromuscular, neuropsychiatric and neuropathy (Figure 8D). The dominant categories of conditions treated with carnitine were cardiovascular disease (11 studies), infections including viral infections and sepsis (14 studies), neuromuscular disorders (11 studies) and renal disease (14 studies) (Figure 8D). Furthermore, as discussed in Section 4, lower levels of acetylcarnitine, which is a metabolite of carnitine, are linked with depression disorders (Nasca et al., 2018), and acetylcarnitine has been recommended as an interventional treatment (Table 9). While we did not identify any current clinical studies registered in ClinicalTrials.gov that investigate acetylcarnitine as an interventional therapy, two studies were identified that are assessing acetylcarnitine levels as a biomarker in mood disorders – one is investigating the mechanism of action of ketamine (NCT00088699) and another study is predicting depression recovery after antidepressant use (NCT00590863).

Two clinical trials are using levocarnitine to develop a standard of care in cases of phosphide poisoning (NCT03953248 and NCT04509258). This specific use of the drug is unique in comparison to other trials focusing on specific diseases or conditions. The two phosphide poisoning trials are in phase I and phase IV, respectively, but neither of the two trials have yet published any results. The impetus for the use of levocarnitine for treating phosphide toxicity comes from a rat study that was published in 2015 that demonstrated how phosphide toxicity triggers oxidative stress and further mitochondrial dysfunction. This toxicity could potentially be limited by the use of levocarnitine (Baghaei et al., 2016). Another distinctive condition being studied in clinical trials is polycystic ovary syndrome (PCOS). A 2015 study evaluated PCOS and found that it is associated with modified mitochondrial OXPHOS and often insulin resistance, which affects acylcarnitine metabolism (Cree-Green et al., 2019). Therefore, treatment with levocarnitine supplementation may attenuate symptoms of this disease. Six clinical trials have begun since 2016, representing 15% of all levocarnitine trials in this period.

In addition to the FDA-approved L-carnitine formulation levocarnitine and acetylcarnitine, 22 FDA-approved drugs and one investigational drug are in trials where acylcarnitines are being assessed as biomarkers for different conditions (12 studies) or as

primary or secondary study outcome measures (19 studies; 2 studies are not specified, and 1 study uses acylcarnitine levels for inclusion/exclusion criteria). Acylcarnitines are already in use as biomarkers for insulin resistance and cardiovascular events (Albert and Tang, 2018; Davies et al., 2014). Furthermore, they are being investigated as potential diagnostic markers for the progression of depression, liver disease, propionic and methylmalonic acidemias, diabetes, and energy storage diseases. In addition, studies with acylcarnitines as outcome measures are also being explored for patients with myopathies, inborn errors of metabolism, cardiovascular disease, heart failure and heart defects, sepsis, and Klinefelter syndrome. Interestingly, a new study has been initiated that involves assessing the change in C14:1 long-chain acylcarnitines as a primary outcome measure following testosterone cypionate treatment in male infants born with the most common chromosomal abnormality, XXY, also known as Klinefelter syndrome.

Diabetes, insulin resistance, and obesity are the most common conditions in studies where acylcarnitines are being used as biomarkers for outcome measures. In particular, they are being assessed in studies with antihyperglycemic drugs as well as nutritional diet and behavioral interventional trials (NCT00047437 and NCT01373814). Some of the most common classes of pharmacological therapies, including carnitine supplements and medium-chain fatty acid triglycerides (for example, triheptanoin, a triglyceride used to treat long-chain fatty acid oxidation disorders, (Shirley, 2020)), coincide with several of the most prevalent disorders, including deficiency disorders and energy storage diseases (Figure 8C).

The use of acylcarnitines as interventional treatments and as both diagnostic biomarkers and primary and secondary outcome measurements is clearly expanding. Indeed, acylcarnitines are being assessed in a variety of study types and conditions – beyond simple carnitine deficiency and metabolic disorders – to help diagnose different stages of disease (NCT02426775, NCT02856555, and NCT00088699). This robust utilization of acylcarnitines signifies an increasing understanding of their beneficial uses and a growing interest in them for drug discovery.

## **VI. Future perspectives**

This review provides a comprehensive overview of the identity, nomenclature, classification, biochemistry, pathophysiology, supplementary use, pharmacological use, potential pharmaceutical agents and clinical trials for acylcarnitines. Our substantial update of the HMDB with regard to detailed data on acylcarnitines provides a strong foundation for further clarification of the physiological roles of acylcarnitines. However, it is also clear that the identity

and physiological role of many recently identified acylcarnitines are obscure and that the majority of acylcarnitines recently added to the HMDB are not linked to any specific physiological function, illustrating the complex task ahead. This review also clarifies several issues regarding the nomenclature of acylcarnitines. For example, we formalized the definition of the acyl-chain lengths among acylcarnitines corresponding to short-chain, medium-chain, long-chain and very-long-chain acylcarnitines. The presently used classification is derived from the respective fatty acid classes (Kimura et al., 2020; Ratnayake and Galli, 2009), but its relation to acylcarnitine-specific target proteins and transporters remains obscure (Figures 3 and 4). It is likely that further development of other classification categories will be needed as many of the long-chain and branched-chain acylcarnitines seem to be present in much higher numbers than previously anticipated (Figure 1). We aim to do this in collaboration with the HMDB as well as other open sources that are lacking more detailed information on a variety of acylcarnitines.

As part of this review, we have also provided substantial mapping of the known biochemical pathways associated with acylcarnitines, providing a framework for basic physiological functions (Figures 5 and 7). The concepts illustrated in these pathways have been extended to all acylcarnitine pathways in the HMDB. However, it is clear that much more work is needed to clarify the many pathological processes associated with acylcarnitine deficiencies and how individual genotypic differences affect how these pathways actually work. Understanding acylcarnitine metabolic and signaling pathways provides a better rationale for selecting targets for therapeutic interventions. It is also helpful to explain how many current drugs, such as metformin, various statins, liraglutide and triheptanoin, and various supplements interfere with acylcarnitine metabolism.

The importance of acylcarnitines as biomarkers is clearly growing (McCann et al., 2021; Wanders et al., 2020) and the list of different diseases linked with altered levels of different acylcarnitines (see Tables 1-7) is increasing. Significant progress in the breadth and depth of acylcarnitine measurements by metabolomic studies has illustrated how different acylcarnitines are affected in different disease states. However, more information is needed to determine what “normal” levels are (i.e., changes in acylcarnitines in the fed/fasted cycle and the impact of nutrition/diets) to better define their validity as biomarkers and ascertain possible drug targets. Nevertheless, based on the wealth of data already at hand, it is reasonable to conclude that acylcarnitines play a role in many diseases.

This observation is also supported by the many clinical trials that make use of acylcarnitines as biomarkers in both pharmacological and dietary intervention studies (see Figure 8). Interestingly, there are a number of behavioral intervention studies that use

acylcarnitines as biomarkers. The role of acylcarnitines as biomarkers for inborn errors of fatty acid oxidation is clear, but there is increasing interest in using acylcarnitines as biomarkers for acquired metabolic and cardiovascular diseases. This is demonstrated by the fact that long-chain acylcarnitine measurements have been shown to be particularly useful for the diagnosis of insulin resistance. Likewise, the byproducts of incomplete long-chain acylcarnitine metabolism appear to offer interesting biomarkers for heart failure and represent potential predictors of major cardiovascular events (Albert and Tang, 2018; Ruiz-Canela et al., 2017).

Another important area that is emerging is the use of acylcarnitines as biomarkers for low-grade inflammation. Inflammation is increasingly considered to be an underlying cause not only of metabolic disorders, cardiovascular diseases and many cancers but also of several CNS disorders including depression and autism spectrum disorder (Kepka et al., 2021; Traina, 2016). The need for new biomarkers for psychiatric disorders is great and this could be a field that will attract significant attention in the future. Overall, there is a clear need for more systematic and standardized approaches to measure and analyze acylcarnitines. This strategy will enable a more comprehensive and sophisticated analysis of acylcarnitine data. Indeed, the use of advanced analytical methods such as artificial intelligence and machine learning, with their superior pattern recognition abilities, should lead to even more robust biomarker discoveries concerning acylcarnitines.

The use of L-carnitine (levocarnitine) as both a drug and a supplement is rapidly growing. The vast dietary supplement industry associated with short-chain acylcarnitines (acetylcarnitine and propionyl-carnitine) has been driven by numerous reports that acetylcarnitine deficiency might lead to different conditions including neurological and psychiatric diseases (Pennisi et al., 2020; Virmani and Binienda, 2004). Unfortunately, detailed biological investigations assessing the widespread use or benefits of such supplementation are lacking. This may be because these supplements are both cheap (not patent protected) and not considered drugs. As such, they do not require complex clinical trials nor are there studies motivated by the high earning potential that often drives such trials. Nevertheless, there are many clinical trials that have been initiated with L-carnitine as a primary pharmacological agent in interventional studies. Hopefully, these trials will garner more attention, while the consequences related to overall acylcarnitine metabolism may need more attention.

Key proteins within the biochemical pathways associated with acylcarnitine transport, synthesis and utilization are gaining interest as potential drug targets. Table 8 lists several of the proteins that are involved in acylcarnitine biosynthesis and transport. OCTN2, MCD and CPT1 are now widely considered potential drug targets for cardiometabolic diseases (Figure 5). There

are, however, arguments that the development of drugs targeting acylcarnitine transport or metabolism could lead to potential side effects because acylcarnitines play such key roles in physiological energy metabolism pathways and reflect general mitochondrial and peroxisomal metabolism reactions. A better understanding of the transport of unmetabolized acylcarnitines into the circulation is clearly warranted as this would lead to a better understanding their role in pathology and their potential for drug development. In general, the role of circulating acylcarnitines needs further attention at both the physiological and molecular levels. More studies are also needed to understand the molecular mechanisms regarding acylcarnitine actions in different organ systems before we will be able to fully interpret the cascade of metabolomic studies linking acylcarnitines to specific disorders. Nevertheless, it is already clear that controlling the levels of long-chain acylcarnitines will be an important goal for the treatment of inherited diseases of fatty acid oxidation, diabetes/insulin resistance, and cardiovascular diseases (McCann et al., 2021; Pallares-Mendez et al., 2016; Wanders et al., 2020).

In summary, controlling the levels of acylcarnitines either through drugs that target their synthesis and transport or through dietary interventions and supplements (such as acetylcarnitine and propionylcarnitine) appear to have wide-ranging and significant effects on human health.

### **Authorship Contributions**

*Participated in research design:* Dambrova, Makrecka-Kuka, Kuka, Vilskersts, Wishart, Liepinsh, and Schiöth

*Performed data analysis:* Dambrova, Makrecka-Kuka, Kuka, Vilskersts, Liepinsh, Nordberg, Attwood, Smesny, Sen, Guo, Oler, Tian, and Zheng

*Wrote or contributed to the writing of the manuscript:* Dambrova, Makrecka-Kuka, Kuka, Vilskersts, Smesny, Attwood, Wishart, Liepinsh, and Schiöth.

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## **Footnotes**

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## Tables

**Table 1 Short-chain acylcarnitines and diseases with altered short-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

Acylcarnitine, (Fatty acid moiety)	Sample	↑/↓	Disease with altered acylcarnitine concentration
Acetylcarnitine, (C2:0)	Blood	↑	Very-long-chain acyl-CoA dehydrogenase deficiency (Costa et al., 1997); Colorectal cancer (Ni et al., 2014); Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (Clayton et al., 2001); Paclitaxel induced neuropathy (Sun et al., 2018); Type 2 diabetes (Abu Bakar and Sarmidi, 2017; Adams et al., 2009; Ciborowski et al., 2015; Mai et al., 2013); Chronic heart failure (Ueland et al., 2013); Ornithine transcarbamylase (Ohtani et al., 1988); Pre-diabetes (Mai et al., 2013; Wang-Sattler et al., 2012); Type 1 diabetes (Adal et al., 2006); Methylmalonic acidemia (Minkler and Hoppel, 1993); Myeloma (Steiner et al., 2018); Diastolic heart failure (Zordoky et al., 2015)
		↓	3-Methyl-crotonyl-glycinuria (Thomsen et al., 2015); Antiviral drug induced neuropathy (Famularo et al., 1997; James, 1997); Alzheimer disease (Cristofano et al., 2016); Major depressive disorder (Nasca et al., 2018); Carnitine palmitoyltransferase 2 deficiency (Hori et al., 2010); Familial Mediterranean fever (Kiykim et al., 2016); Chronic fatigue syndrome (Kuratsune et al., 1998); Methylmalonic acidemia (Vernez et al., 2004); Hepatocellular carcinoma (Lu et al., 2016; Takaya et al., 2019); Coronary artery disease (Shah et al., 2010)
	Urine	↑	Colorectal cancer (Ni et al., 2014); Uterine fibroids (Wang et al., 2020); Heart failure (Matsui et al., 1994); Diabetes (Dellow et al., 1999); Hepatocellular carcinoma (Ladep et al., 2014)
		↓	Carnitine palmitoyltransferase 2 deficiency (Hori et al., 2010)
Propionylcarnitine, (C3:0)	Blood	↑	Methylmalonic academia/methylmalonyl-CoA mutase (Ghoraba et al., 2015; Han et al., 2015; Kang et al., 2020; Keyfi et al., 2019); Propionic academia/mitochondrial propionyl-CoA carboxylase deficiency (Curnock et al., 2020; Monostori et al., 2017); Obesity and type 2 diabetes (Libert et al., 2018); Cobalamin C deficiency (Rahmandar et al., 2014); Chronic heart failure (Ueland et al., 2013); Diastolic heart failure (Zordoky et al., 2015); Systolic heart failure (Zordoky et al., 2015)
		↓	Familial Mediterranean fever (Kiykim et al., 2016); Type 2 diabetes (Adams et al., 2009)
	Urine	↓	Obesity (Cho et al., 2017a)
Butyrylcarnitine, (C4:0)	Blood	↑	Short-chain acyl-CoA dehydrogenase (An et al., 2016; Battisti et al., 2007; Dawson et al., 1995; Forni et al., 2010; Gallant et al., 2012; Lampret et al., 2015; Tonin et al., 2016; van Maldegem et al., 2006; van Maldegem et al., 2010; Young et al., 2003); Glutaric aciduria 2 (Forni et al., 2010; Prasad and Hussain, 2015); Heart failure (Cheng et al., 2015); Ethylmalonic encephalopathy (Drousiotou et al., 2011; Zafeiriou et al., 2007); Non-alcoholic fatty liver disease (Kalhan et al., 2011); Obesity (Butte et al., 2015);

			Systolic heart failure (Zordoky et al., 2015)
		↓	Celiac disease (Bene et al., 2005); Acute cerebral infarction (Zhang et al., 2017b)
	Urine	↑	Short-chain acyl-CoA dehydrogenase deficiency (Bhala et al., 1995); Obesity (Cho et al., 2017a)
Valerylcarnitine, (C5:0)	Blood	↑	Exudative age-related macular degeneration (Chao de la Barca et al., 2020); Type 2 diabetes (Mihalik et al., 2010; Sun et al., 2020); Obesity (Mihalik et al., 2010); Acute cerebral infarction (Zhang et al., 2017b); Diastolic heart failure (Zordoky et al., 2015); Systolic heart failure (Zordoky et al., 2015)
		↓	Pregnancy ((Bahado-Singh et al., 2014)- in serum of pregnant women with fetus with congenital heart defect)

**Table 2 Medium-chain acylcarnitines and diseases with altered medium-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

Acylcarnitine, (Fatty acid moiety)	Sample	↑/↓	Disease with altered acylcarnitine concentration
Caproylcarnitine, (C6:0)	Blood	↑	Psoriasis (Chen et al., 2021); Cardiovascular diseases (Kukharensko et al., 2020); Norman-Roberts syndrome (Caksen et al., 2004); Type 2 diabetes (Adams et al., 2009; Batchuluun et al., 2018; Mihalik et al., 2010); Carnitine palmitoyltransferase 2 deficiency (Fontaine et al., 1998); Familial Mediterranean fever (Kiykim et al., 2016); Multiple acyl-CoA dehydrogenase deficiency (Saral et al., 2018); Cardiovascular diseases in type 2 diabetes (Zhao et al., 2020); Gestational diabetes (Batchuluun et al., 2018)
		↓	Celiac disease (Bene et al., 2005)
	Urine	↑	Medium-chain acyl-CoA dehydrogenase deficiency (Bennett et al., 1990; Schmidt-Sommerfeld et al., 1992)
Octanoylcarnitine, (8:0)	Blood	↑	Glutaric aciduria 2 (Prasad and Hussain, 2015); Ulcerative colitis (Kolho et al., 2017); Crohn's disease (Kolho et al., 2017); Medium-chain acyl-CoA dehydrogenase deficiency (Costa et al., 1997; Khalid et al., 2010; Rhead, 2006); Multiple acyl-CoA dehydrogenase deficiency (Saral et al., 2018); Exfoliation syndrome (Leruez et al., 2018); Gestational diabetes (Batchuluun et al., 2018); Type 2 diabetes (Adams et al., 2009; Batchuluun et al., 2018; Mihalik et al., 2010); Cardiovascular diseases in type 2 diabetes (Zhao et al., 2020); Cardioembolic stroke, its recurrence (Seo et al., 2018); Diastolic heart failure (Zordoky et al., 2015)
		↓	Celiac disease (Bene et al., 2005); Very-long-chain acyl-CoA dehydrogenase deficiency (Costa et al., 1997); Breast cancer (Park et al., 2019); Hepatocellular carcinoma and liver cirrhosis (Kim et al., 2019); Familial Mediterranean fever (Kiykim et al., 2016); Human immunodeficiency virus (Waagsbo et al., 2016); Pregnancy ((Bahado-Singh et al., 2014)- in serum of pregnant women with fetus with congenital heart defect); Coronary artery disease (Shah et al., 2010)
	Urine	↑	Medium-chain acyl-CoA dehydrogenase deficiency (Duran et al., 1984; Duran et al., 1985; Schmidt-Sommerfeld et al., 1992; Tserng et al., 1990); Obesity (Cho et al., 2017a); Multiple acyl-CoA dehydrogenase deficiency (Sugiyama et al., 1990; Vallee et al., 1994); Uterine fibroids (Wang et al., 2020)
Nonanoylcarnitine, (9:0)	Blood	↓	Psoriasis (Chen et al., 2021; Ottas et al., 2017); Pregnancy ((Bahado-Singh et al., 2014)- in serum of pregnant women with fetus with congenital heart defect)
	Urine	↓	Obesity (Cho et al., 2017a)
Decanoylcarnitine, (C10:0)	Blood	↑	Glutaric aciduria 2 (Prasad and Hussain, 2015); Ulcerative colitis (Kolho et al., 2017); Crohn's disease (Kolho et al., 2017); Obesity (Mihalik et al., 2010); Medium-chain acyl-CoA dehydrogenase deficiency disorders (Woo et al., 2011); Overweight (Kim et al., 2015); Multiple acyl-CoA dehydrogenase deficiency (Saral et al., 2018; Schmidt-Sommerfeld et al., 1993); Type 2 diabetes (Adams et al., 2009); Age-related increase in alanine aminotransferase (Jung et al., 2014); Prostate cancer (Zoni et al., 2019); Yin-deficiency-heat syndrome (Yi et al., 2020); Cardiovascular



			diseases in type 2 diabetes (Zhao et al., 2020); Cardioembolic stroke, its recurrence (Seo et al., 2018); Diastolic heart failure (Zordoky et al., 2015)
		↓	Celiac disease (Bene et al., 2005); Colorectal cancer (Tan et al., 2013); Esophageal squamous cell carcinoma (Xu et al., 2013); Inflammatory bowel disease (Danese et al., 2011); Phenylketonuria (Weigel et al., 2008); Intracerebral hemorrhage (Zhang et al., 2017b); Pregnancy ((Bahado-Singh et al., 2014)- in serum of pregnant women with fetus with congenital heart defect)
	Urine	↑	Overweight (Wang et al., 2011); Renal cell carcinoma (Niziol et al., 2018)
Lauroylcarnitine, (C12:0)	Blood	↑	Very-long-chain acyl-CoA dehydrogenase deficiency (Costa et al., 1997); Yin deficiency (Yi et al., 2020); Multiple acyl-CoA dehydrogenase deficiency (Saral et al., 2018); Cardiovascular diseases in type 2 diabetes (Zhao et al., 2020); Diastolic heart failure (Zordoky et al., 2015)
		↓	Celiac disease (Bene et al., 2005); Psoriasis (Ottas et al., 2017); Intracerebral hemorrhage (Zhang et al., 2017b); Pregnancy ((Bahado-Singh et al., 2014)- in serum of pregnant women with fetus with congenital heart defect)
	Urine	↑	Renal cell carcinoma (Niziol et al., 2018)

**Table 3 Long-chain acylcarnitines and diseases with altered long-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

Acylcarnitine, (Fatty acid moiety)	Sample	↑/↓	Disease with altered acylcarnitine concentration
Myristoylcarnitine, (14:0)	Blood	↑	Very-long-chain acyl-CoA dehydrogenase deficiency (Costa et al., 1997; Peng et al., 2013); Carnitine/acylcarnitine translocase deficiency (Wasant et al., 2002); Carnitine palmitoyl transferase 2 deficiency (Minkler et al., 2005); Glutaric acidemia type 2 (Peng et al., 2013); Sleep deprivation (Yoon et al., 2019); Type 2 diabetes (Adams et al., 2009); Cardiovascular diseases in type 2 diabetes (Zhao et al., 2020); Cardiovascular mortality in chronic kidney disease (Kalim et al., 2013)
		↓	Celiac disease (Bene et al., 2005); Chronic fatigue syndrome (Reuter and Evans, 2011)
	Urine	↑	Uterine fibroids (Wang et al., 2020)
Palmitoylcarnitine, (C16:0)	Blood	↑	Very-long-chain acyl-CoA dehydrogenase deficiency (Costa et al., 1997); Sleep deprivation (Yoon et al., 2019); Carnitine palmitoyl transferase 2 deficiency (Minkler et al., 2005); Carnitine/acylcarnitine translocase deficiency (Wasant et al., 2002); Type 2 diabetes (Mihalik et al., 2010; Qiu et al., 2016; Zhang et al., 2014); Non-alcoholic fatty liver disease (Chen et al., 2016); Obesity (Mihalik et al., 2010); Pulmonary arterial hypertension (Brittain et al., 2016); Chronic heart failure (Ueland et al., 2013); Cardiovascular mortality in chronic kidney disease (Kalim et al., 2013); Diastolic heart failure (Hunter et al., 2016; Zordoky et al., 2015); Systolic heart failure (Hunter et al., 2016); Increased all-cause mortality and hospitalization in heart failure patients (Ahmad et al., 2016)
		↓	Intracerebral hemorrhage (Zhang et al., 2017b); Carnitine palmitoyltransferase 1A deficiency (Fingerhut et al., 2001); Psoriasis (Chen et al., 2021)
	Feces	↑	Cirrhosis (Huang et al., 2013)
Stearoylcarnitine, (C18:0)	Blood	↑	Carnitine/acylcarnitine translocase deficiency (Wasant et al., 2002); Chronic fatigue syndrome (Reuter and Evans, 2011); Pulmonary Arterial Hypertension (Brittain et al., 2016); Carnitine palmitoyltransferase 2 deficiency (Minkler et al., 2005); Cardiovascular mortality in chronic kidney disease (Kalim et al., 2013); Diastolic heart failure (Hunter et al., 2016); Systolic heart failure (Hunter et al., 2016)
		↓	Intracerebral hemorrhage (Zhang et al., 2017b); Carnitine palmitoyltransferase 1A deficiency (Fingerhut et al., 2001)

**Table 4 Very-long-chain acylcarnitines and diseases with altered very-long-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

<b>Acylcarnitine, (Fatty acid moiety)</b>	<b>Sample</b>	<b>↑/↓</b>	<b>Disease with altered acylcarnitine concentration</b>
Behenoylcarnitine, (C22:0)	Blood	↓	Acute cerebral infarction (Zhang et al., 2017b)
	Urine	↑	Zellweger syndrome (Duranti et al., 2008); Infantile Refsum disease (Duranti et al., 2008); D-bifunctional protein deficiency (Duranti et al., 2008)
Lignoceroylcarnitine, (C24:0)	Blood	↑	Type 2 diabetes (Zhang et al., 2014)
		↓	Cardiovascular diseases in type 2 diabetes (Zhao et al., 2020)
Cerotoylcarnitine, (C26:0)	Urine	↑	Zellweger syndrome (Duranti et al., 2008); Infantile Refsum disease (Duranti et al., 2008); Type 2 diabetes (Zhang et al., 2014)
	Blood	↑	Zellweger syndrome (Klouwer et al., 2017), X-linked adrenoleukodystrophy (van de Beek et al., 2016), Cardiovascular mortality in chronic kidney disease (Kalim et al., 2013)
	Urine	↑	Zellweger syndrome (Duranti et al., 2008); Infantile Refsum disease (Duranti et al., 2008)

**Table 5 Unsaturated-chain acylcarnitines and diseases with altered unsaturated-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

Acylcarnitine, (Fatty acid moiety)	Sample	↑/↓	Disease with altered acylcarnitine concentration
Butenylcarnitine, (C4:1)	Blood	↑	Maternal obesity/prepregnant obesity of mothers (Schlueter et al., 2020)
Hexenylcarnitine, (C6:1)	Blood	↑	Obesity in adolescence (Cho et al., 2017a)
		↓	Adolescent idiopathic scoliosis (Sun et al., 2016b)
Decenylcarnitine, (C10:1)	Blood	↑	Overweight (Kang et al., 2018)
		↓	Schizophrenia (Cao et al., 2020); Familial Mediterranean fever (Kiykim et al., 2016)
Decadienylcarnitine, (C10:2)	Blood	↑	2,4-Dienoyl-CoA reductase deficiency (Kimura et al., 2004; Miinalainen et al., 2009; Roe et al., 1990)
		↓	Familial Mediterranean fever (Kiykim et al., 2016); Schizophrenia (Cao et al., 2020)
Dodecenylcarnitine, (C12:1)	Blood	↑	Mitochondrial dysfunction in diabetes patients (Abu Bakar and Sarmidi, 2017); Childhood obesity (Wahl et al., 2012)
		↓	Placental abruption (Gelaye et al., 2016) - increase in dodecanoylcarnitine/dodecenoylcarnitine ratio (C12 / C12:1)
Tetradecenylcarnitine, (C14:1)	Blood	↑	Very-long-chain acyl-CoA dehydrogenase deficiency (Hisahara et al., 2015; Laforet et al., 2009; Lepori et al., 2018; Shigematsu et al., 2003; Tajima et al., 2008; Wood et al., 2001); Trifunctional protein (mitochondrial long-chain ketoacyl-CoA thiolase) deficiency (Das et al., 2006); Mitochondrial dysfunction in diabetes patients (Abu Bakar and Sarmidi, 2017); Nonalcoholic fatty liver disease (Chen et al., 2016); Insulin resistance, type 2 diabetes (Mai et al., 2013)
Tetradecadienylcarnitine, (C14:2)	Blood	↑	Insulin resistance, type 2 diabetes (Mai et al., 2013) Alzheimer disease (Huo et al., 2020)
Hexadecenylcarnitine, (C16:1)	Blood	↑	Childhood obesity (Wahl et al., 2012)
		↓	Familial Mediterranean fever (Kiykim et al., 2016)
Octadecenylcarnitine, (C18:1)	Blood	↑	Carnitine palmitoyltransferase 2 deficiency (Brucknerova et al., 2008; Gempel et al., 2002; Gempel et al., 2001; Illsinger et al., 2008; Minkler et al., 2005; Tajima et al., 2017); Cardiovascular mortality in incident dialysis patients (Kalim et al., 2013); Schizophrenia (Cao et al., 2020); Succinic semialdehyde dehydrogenase deficiency (Kirby et al., 2020); Neonatal macrosomia (Wright and Baker, 2020); Liver cirrhosis (Miyaaki et al., 2020); Carnitine/acylcarnitine translocase deficiency (Iacobazzi et al., 2004); Ischemia/reperfusion (Rizza et al., 2014; Shah et al., 2012); Increased all-cause mortality and hospitalization in heart failure patients (Ahmad et al., 2016)
Octadecadienylcarnitine, (C18:2)	Blood	↑	Parkinson disease (Chang et al., 2018); Chronic heart failure (Ahmad et al., 2016; Hunter et al., 2016); Carnitine/acylcarnitine translocase deficiency (Iacobazzi et al., 2004); Ischemia/reperfusion (Rizza et al., 2014; Shah et al., 2012); Increased all-cause mortality and hospitalization in heart failure patients (Ahmad et al., 2016)

**Table 6 Branched-chain acylcarnitines and diseases with altered branched-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

Acylcarnitine, (Fatty acid moiety)	Sample	↑/↓	Disease with altered acylcarnitine concentration
Isobutyrylcarnitine, (C4:0 M)	Blood	↑	Isobutyryl-CoA dehydrogenase deficiency (Forni et al., 2010); Glutaric aciduria type 2 (Forni et al., 2010); Ethylmalonic encephalopathy (Forni et al., 2010); Gestational diabetes (Roy et al., 2018)
		↓	Traumatic brain injury (Jeter et al., 2013)
	Urine	↑	Glutaric aciduria type 2 (Sugiyama et al., 1990); Multiple acyl-CoA dehydrogenase deficiency (Kidouchi et al., 1988); Acute coronary syndrome (Wang et al., 2018)
Isovalerylcarnitine, (C5:0 I)	Blood	↑	Isovaleric acidemia (Couce et al., 2017; Forni et al., 2010; Lin et al., 2020; Shigematsu et al., 2007); Glutaric aciduria type 2 (Forni et al., 2010); 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Ma et al., 2011; Vaclavik et al., 2020); Cardiovascular diseases (Kukharensko et al., 2020); Acute kidney injury (Wan et al., 2019)
		↓	Daytime sleepiness (Pak et al., 2018); Inflammatory bowel disease (Danese et al., 2011); Ulcerative colitis (Bene et al., 2006); Traumatic brain injury (Jeter et al., 2013)
	Urine	↑	Glutaric aciduria type 2 (Shimizu et al., 1991); Multiple acyl-CoA dehydrogenation deficiency (Kidouchi et al., 1988)
2-Methylbutyryl carnitine, (C5:0 M)	Blood	↑	Short/branched-chain acyl-CoA dehydrogenase deficiency/2-methylbutyryl-CoA dehydrogenase deficiency (Forni et al., 2010; Madsen et al., 2006); Glutaric aciduria type 2 (Forni et al., 2010); Gout (Huang et al., 2020); Non-alcoholic steatohepatitis (Kalhan et al., 2011)
		↓	Pediatric obesity (Farook et al., 2015); Traumatic brain injury (Jeter et al., 2013)
Methylcrotonylcarnitine, (C5:1 I)	Blood	↑	3-methylcrotonyl-CoA carboxylase deficiency (van Hove et al., 1995); 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Vaclavik et al., 2020)
Tiglylcarnitine, (C5:1 M)	Blood	↑	Beta ketothiolase deficiency/acetyl-CoA acetyltransferase 1 gene mutation (Fukao et al., 2003; Millington et al., 1987; Wen et al., 2016); Short-chain enoyl-CoA hydratase deficiency (Pajares et al., 2020)
		↓	Familial Mediterranean fever (Kiykim et al., 2016); Lewis lung carcinoma (Wu et al., 2018); Metabolic syndrome, type 2 diabetes, cardiovascular diseases (Yu et al., 2014)
Pristanoyl-carnitine	Blood	↑	Alpha-methylacyl-CoA racemase deficiency (Herzog et al., 2017)
Phytanoyl-carnitine	Blood	↑	Refsum disease (Herzog et al., 2017); Rhizomelic chondrodysplasia punctata (Herzog et al., 2017)

**Table 7 Hydroxyl-/dicarboxyl-chain acylcarnitines and diseases with altered hydroxyl-/dicarboxyl-chain acylcarnitine levels in blood (serum, plasma, dried blood spots) or urine**

Acylcarnitine, (Fatty acid moiety)	Sample	↑/↓	Disease with altered acylcarnitine concentration
3-Hydroxy-propionylcarnitine, (C3-OH)	Urine	↓	Obesity (Cho et al., 2017a); Systolic heart failure (Zordoky et al., 2015)
Malonylcarnitine, (C3-DC)	Blood	↑	Malonyl-CoA decarboxylase deficiency (Ficicioglu et al., 2005; Santer et al., 2003); Propofol infusion syndrome (Wolf et al., 2001); Short-chain enoyl-CoA hydratase mutation (Pajares et al., 2020); Type 2 diabetes (Mai et al., 2013); Methylmalonic acidemia (Maeda et al., 2007)
		↓	Familial Mediterranean fever (Kiykim et al., 2016); Cleft lip (Hozyasz et al., 2010); Obesity (Libert et al., 2018); Acute cerebral infarction (Zhang et al., 2017b)
	Urine	↑	Malonyl-CoA decarboxylase deficiency (Yano et al., 1997); Methylmalonic acidemia (Maeda et al., 2007)
Methylmalonylcarnitine, (C3:0 DC M)	Blood	↑	Methylmalonyl-CoA epimerase deficiency/Methylmalonic acidemia (Maeda et al., 2007; Waters et al., 2016); Familial Mediterranean fever (Kiykim et al., 2016); Cobalamin C deficiency (Rahmandar et al., 2014)
		↓	Melanoma (Bayci et al., 2018); Intracerebral hemorrhage (Zhang et al., 2017b)
	Urine	↑	Methylmalonyl-CoA epimerase deficiency/Methylmalonic acidemia (Maeda et al., 2007; Waters et al., 2016)
3-Hydroxybutyrylcarnitine, (C4-OH)	Blood	↑	Short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (Clayton et al., 2001; Hussain et al., 2005); Prediabetes (Zhong et al., 2017); Type 2 diabetes (Zhong et al., 2017); Metallosis (Stepien et al., 2018); Mitochondrial acetoacetyl-CoA thiolase deficiency (Catanzano et al., 2010); Heart failure (Cheng et al., 2015)
		↓	Psoriasis (Chen et al., 2021)
	Urine	↑	Renal cell carcinoma (Niziol et al., 2018)
Succinylcarnitine, (C4-DC)	Blood	↑	Succinyl-CoA ligase deficiency (Jaberi et al., 2013; Van Hove et al., 2010)
Glutarylacarnitine, (C5-DC)	Blood	↑	Multiple acyl-CoA dehydrogenase deficiency (Saral et al., 2018); Glutaric acidemia type 1 (Couce Pico et al., 2008; Lee et al., 2013; Mohamed et al., 2015; Numata-Uematsu et al., 2017); Renal insufficiency (Hennermann et al., 2009)
		↓	Familial Mediterranean fever (Kiykim et al., 2016)
	Urine	↑	Multiple acyl-CoA dehydrogenase deficiency (Sakuma et al., 1991); Glutaric acidemia type 1 (Couce Pico et al., 2008; Kim et al., 2014; Korman et al., 2007)
Methylglutarylacarnitine, (C5-M-DC)	Blood	↑	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Roe et al., 1986; Santarelli et al., 2013; Vaclavik et al., 2020); Acute kidney injury (Wan et al., 2019); Pulmonary arterial hypertension (Mey et al., 2020)
		↓	Traumatic brain injury (Jeter et al., 2013); Metabolic syndrome (Gong et al., 2020)
	Urine	↑	3-Methylglutaconic aciduria (Jooste et al., 1994); Acute coronary syndrome (Wang et al., 2018)

3-Hydroxyvalerylcarnitine, (C5-OH)	Blood	↑	3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency (Grunert et al., 2017); Holocarboxylase synthetase deficiency (Donti et al., 2016)
		↓	Psoriasis (Chen et al., 2021)
3-Hydroxy-isovalerylcarnitine, (C5-OH-I)	Blood	↑	3-Methylcrotonyl-CoA carboxylase deficiency (van Hove et al., 1995); 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Bischof et al., 2004; Dos Santos Mello et al., 2015; Santarelli et al., 2013; Vaclavik et al., 2020); 3-Methylglutaconic aciduria type 1 (Tavasoli et al., 2017); Leigh syndrome (Balasubramaniam et al., 2017); Holocarboxylase synthetase deficiency (Yokoi et al., 2009)
		↓	Traumatic brain injury (Jeter et al., 2013)
	Urine	↑	3-Methylcrotonyl-CoA carboxylase deficiency (van Hove et al., 1995); Multiple carboxylase deficiency (Maeda et al., 2008; Nakanishi and Shimizu, 1993); Biotin deficiency (Stratton et al., 2011)
2-Methyl-3-hydroxy-butyrylcarnitine, (C5-OH-M)	Blood	↑	Mitochondrial acetoacetyl-CoA thiolase deficiency (Catanzano et al., 2010); Mitochondrial 2-methylacetoacetyl-CoA thiolase deficiency (Ngu et al., 2008)
3-Methylglutaconylcarnitine, (C5:1-M-DC)	Blood	↑	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Vaclavik et al., 2020)
	Urine	↑	3-Methylglutaconic aciduria (Jooste et al., 1994)
3-hydroxy-3-methylglutaryl-carnitine, (C5:1-M-OH-DC)	Blood	↑	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Vaclavik et al., 2020)
3-Hydroxy-hexanoylcarnitine, (C6-OH)	Urine	↑	Metabolic syndrome (Esperanza et al., 2020)
Adipylcarnitine, (C6-DC)	Blood	↑	Pulmonary arterial hypertension (Mey et al., 2020)
	Urine	↑	Glutaric aciduria type 1 (Matsumoto et al., 1990); 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (Grunert et al., 2017)
Dehydroadipylcarnitine, (C6:1-DC)	Urine	↓	Glutaric aciduria type 1 (Matsumoto et al., 1990)
Pimelylcarnitine, (C7-DC)	Blood	↑	Diastolic heart failure (Zordoky et al., 2015)
		↓	Psoriasis (Ottas et al., 2017)
Suberylcarnitine, (C8-DC)	Blood	↑	Pulmonary arterial hypertension (Mey et al., 2020); Type 2 diabetes (Adams et al., 2009)
Dodecanedioylcarnitine, (C12-DC)	Blood	↑	Chronic fatigue syndrome (Reuter and Evans, 2011)
	Urine	↑	Carnitine palmitoyltransferase 2 deficiency (Fontaine et al., 1998)
3-Hydroxy-tetradecanoylcarnitine, (C14-OH)	Blood	↑	Cardiovascular diseases in type 2 diabetes (Zhao et al., 2020)
Tetradecanedioylcarnitine, (C14-DC)	Urine	↑	Zellweger syndrome (Duranti et al., 2008); Infantile Refsum disease (Duranti et al., 2008); D-bifunctional protein deficiency (Duranti et al., 2008)
3-Hydroxy-tetradecenoylcarnitine,	Blood	↓	Psoriasis (Chen et al., 2021); Coronary artery disease (Shah et al., 2010)

(C14:1-OH)	Urine	↑	Obstructive sleep apnea (Cho et al., 2017b); Mitochondrial trifunctional protein deficiency (Park et al., 2009)
3-Hydroxy-hexadecanoylcarnitine, (C16-OH)	Blood	↑	Type 2 diabetes (Hameed et al., 2020; Mai et al., 2013; Zhang et al., 2014); Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency (Karall et al., 2015); Mitochondrial trifunctional protein deficiency (Park et al., 2009)
		↓	Psoriasis (Chen et al., 2021)
3-Hydroxy-hexadecenoylcarnitine, (C16:1-OH)	Blood	↑	Diastolic heart failure (Hunter et al., 2016); Systolic heart failure (Hunter et al., 2016)
		↓	Intracerebral hemorrhage (Zhang et al., 2017b); Psoriasis (Chen et al., 2021); Coronary artery disease (Shah et al., 2010)
Hexadecanedioylcarnitine, (C16-DC)	Blood	↑	Peroxisomal biogenesis disorders (Rizzo et al., 2003)
	Urine	↑	Zellweger syndrome (Duranti et al., 2008); Infantile Refsum disease (Duranti et al., 2008); D-bifunctional protein deficiency (Duranti et al., 2008)
3-Hydroxysteroylcarnitine, (C18-OH)	Blood	↑	Coronary artery disease (Shah et al., 2010)
3-Hydroxyoleylcarnitine, (C18:1-OH)	Blood	↑	Chronic fatigue syndrome (Reuter and Evans, 2011); Mitochondrial trifunctional protein deficiency (Park et al., 2009); Psoriasis (Chen et al., 2021)
Octadecanedioylcarnitine, (C18-DC)	Blood	↑	Peroxisomal biogenesis disorders (Rizzo et al., 2003)
	Urine	↑	Zellweger syndrome (Duranti et al., 2008); Infantile Refsum disease (Duranti et al., 2008); D-bifunctional protein deficiency (Duranti et al., 2008)



**Table 8 Proteins directly involved in acylcarnitine biosynthesis and transport or directly affected by acylcarnitines.**

<b>Protein and identifier (UniProt ID for human protein)</b>	<b>Involvement</b>	<b>Localization</b>	<b>References</b>
Carnitine acetyltransferase (CrAT) EC 2.3.1.7 (UniProtKB - P43155)	Catalyzes the reversible transfer of acyl groups (up to C4) from carnitine to CoA and regulates the acyl-CoA/CoA ratio and availability of free CoA during intensified fatty acid metabolism.	Mitochondrial matrix, peroxisomal matrix, endoplasmic reticulum, nucleus and cardiomyocyte cytosol	(Hsiao et al., 2004; Stephens et al., 2007; Wu et al., 2003)
Carnitine octanoyltransferase (CrOT) EC 2.3.1.137 (UniProtKB - Q9UKG9)	Catalyzes reversible transfer of acyl groups (C6-12, can go up to C16) from CoA to carnitine. Metabolism of branched chain fatty acids.	Peroxisomal matrix	(Ferdinandusse et al., 1999; Jogl et al., 2005)
Carnitine palmitoyltransferase 1 (CPT1) EC 2.3.1.21	Catalyzes reversible transfer of the acyl group of long-chain fatty acid-CoA conjugates onto carnitine. Broad specificity to acyl group, over the range C8 to C18, optimal substrate palmitoyl-CoA. Forward reaction inhibited by palmitoylcarnitine and malonyl-CoA.	Outer mitochondrial membrane	(McGarry and Brown, 1997)
CPT1A – liver isoform, UniProtKB - P50416	Expressed in most tissues. Low $K_m$ value for carnitine, sensitive to malonyl-CoA.	Outer mitochondrial membrane	
CPT1B – muscle isoform, UniProtKB - Q92523	Highest expression in heart and skeletal muscle, no expression in liver and kidney. High $K_m$ value for carnitine, sensitive to malonyl-CoA.	Outer mitochondrial membrane	
CPT1C – brain isoform, UniProtKB - Q8TCG5	Highest expression in brain and testis. Catalytic activity negligible, but can bind malonyl-CoA. Regulates energy homeostasis and involved in ceramide biosynthesis and regulation.	Conflicting reports on localization in mitochondria or endoplasmic reticulum	(Price et al., 2002; Sierra et al., 2008; Wolfgang et al., 2006)
Carnitine palmitoyltransferase 2 (CPT2) EC 2.3.1.21 (UniProtKB - P23786)	Catalyzes the transfer of the acyl group of long-chain fatty acid- carnitine conjugates onto CoA. Loss of CPT2 disables the acylcarnitine-mediated mitochondrial oxidation of long-chain fatty acids.	Inner mitochondrial membrane	(Pereyra et al., 2017)
Carnitine/acylcarnitine translocase (CACT) (UniProtKB - O43772)	Transport of acylcarnitines and carnitine across the mitochondrial inner membrane to and from mitochondrial matrix. Support of mitochondrial fatty acid-oxidation pathway.	Inner mitochondrial membrane	(Console et al., 2014)
Organic cation transporter 1 (OCT1) SLC22A1 (UniProtKB - O15245)	Involved in hepatic acylcarnitine efflux. Associated with serum acylcarnitine levels.	Cell membrane	(Kim et al., 2017)
Organic cation novel type 2 transporter (OCTN2) SLC22A5 (UniProtKB - O76082)	Involved in transport of acetylcarnitine.	Cell membrane	(Kido et al., 2001; Kobayashi et al., 2007)

**Table 9 Effects of acetylcarnitine supplementation**

<b>Disease/condition</b>	<b>Positive outcome of supplementation</b>	<b>Negative/neutral effect</b>
<b>Peripheral nervous system diseases</b>	(Bianchi et al., 2005; Campone et al., 2013; Cruccu et al., 2017; De Grandis et al., 1995; Flatters et al., 2006; Ghirardi et al., 2005a; Ghirardi et al., 2005b; Grandis, 1998; Hart et al., 2004; Herzmann et al., 2005; Li et al., 2016; Maestri et al., 2005; Memeo and Loiero, 2008; Onofrij et al., 1995; Osio et al., 2006; Scarpini et al., 1997; Sun et al., 2016a; Traina et al., 2009; Valcour et al., 2009; Xiao and Bennett, 2008; Youle and Osio, 2007)	(Callander et al., 2014; Curran et al., 2019; Hershman et al., 2013; Hershman et al., 2018)
<b>Alzheimer disease</b>	(Battistin et al., 1989; Bella et al., 1990; Bersani et al., 2013; Bianchetti et al., 2003; Bonavita, 1986; Brooks et al., 1998; Chan et al., 2008; Chan et al., 2010; Gavrilova et al., 2011; Jeong et al., 2017; Parnetti et al., 1993; Passeri et al., 1990; Pettegrew et al., 1995; Rai et al., 1990; Remington et al., 2015a; Remington et al., 2016; Remington et al., 2009; Remington et al., 2015b; Spagnoli et al., 1991; Thal et al., 1996)	(Campi et al., 1990; Thal et al., 2000)
<b>Cognitive dysfunction</b>	(Amen et al., 2011; Chan et al., 2010; Herrmann et al., 1990; Lino et al., 1992; Remington et al., 2015a; Remington et al., 2015b)	
<b>Dementia</b>	(Battistin et al., 1989; Gambi et al., 1989; Goety et al., 1990; Passeri et al., 1988; Remington et al., 2016; Salvioli and Neri, 1994; Sinforiani et al., 1990; Yang et al., 2018)	(Pueschel, 2006)
<b>Multiple sclerosis</b>	(Famularo et al., 1999; Maestri et al., 2005; Tomassini et al., 2004)	
<b>Neurodegenerative diseases</b>	(Calabrese et al., 2003)	
<b>Pain</b>	(Biagiotti and Cavallini, 2001; Cruccu et al., 2017; De Grandis and Minardi, 2002; Herzmann et al., 2005; Janiri et al., 2009; Leombruni et al., 2015; Malaguarnera et al., 2011b; Memeo and Loiero, 2008; Onofrij et al., 1995; Osio et al., 2006; Park et al., 2016; Rossini et al., 2007; Scarpini et al., 1997; Sima et al., 2005; Valcour et al., 2009; Xiao and Bennett, 2008; Youle and Osio, 2007)	
<b>Depressive disorder</b>	(Bella et al., 1990; Bersani et al., 2013; Cavallini et al., 2004; Cipolli and Chiari, 1990; Garzya et al., 1990; Guarnaschelli et al., 1988; Leombruni et al., 2015; Malaguarnera et al., 2011a; Pettegrew et al., 2002; Rossini et al., 2007; Salvioli and Neri, 1994; Suzuki et al., 2019; Tempesta et al., 1987; Zanardi and Smeraldi, 2006)	(Brennan et al., 2013; Tomassini et al., 2004)
<b>Fatigue, dystrophy</b>	(Benedini et al., 2009; Hoffman et al., 2010; Malaguarnera et al., 2014; Malaguarnera et al., 2008; Malaguarnera et al., 2011b; Malaguarnera et al., 2011c; Pereira et al., 2018; Rossini et al., 2007; Sun et al., 2016a; Vermeulen and Scholte, 2004)	(Ledinek et al., 2013; Marti-Carvajal et al., 2019)
<b>Ischemia</b>	(Adembri et al., 1994; Corbucci et al., 1992; Gasparetto et al., 1991; Postiglione et al., 1990; Postiglione et al., 1991)	
<b>Nerve degeneration</b>	(Hart et al., 2002)	
<b>Diabetic neuropathies</b>	(De Grandis and Minardi, 2002; Sima et al., 2005)	

<b>Neuralgia</b>	(Callander et al., 2014; Cruccu et al., 2017; Curran et al., 2016; Memeo and Loiero, 2008; Valcour et al., 2009; Xiao et al., 2012)	(Hershman et al., 2013; Hershman et al., 2018)
<b>Hyperammonemia</b>	(Malaguarnera et al., 2011c; Siciliano et al., 2006; Suzuki et al., 2017)	
<b>Type 2 diabetes</b>	(Fernandez et al., 2013; Giancaterini et al., 2000; Li et al., 2016; Ruggenti et al., 2009; Turpeinen et al., 2000)	(Condorelli et al., 2019; Parvanova et al., 2018; Rolim et al., 2019)

**Table 10 Effects of propionylcarnitine supplementation**

	<b>Positive outcome of supplementation</b>	<b>Negative/neutral effect</b>
<b>Depressive disorder</b>	(Cavallini et al., 2004)	
<b>Erectile dysfunction</b>	(Cavallini et al., 2005; Gentile et al., 2009; Gentile et al., 2004; Gianfrilli et al., 2012; Morano et al., 2007)	
<b>Penile induration</b>	(Cavallini et al., 2002)	(Safarinejad et al., 2007)
<b>Ulcerative colitis,</b>	(Gasbarrini et al., 2003; Mikhailova et al., 2011; Scioli et al., 2014)	
<b>Peripheral arterial disease</b>	(Bolognesi et al., 1995; Capecchi et al., 1997; Cittanti et al., 1997; De Marchi et al., 2012; Di Marzo et al., 1999; Loffredo et al., 2013; Loffredo et al., 2006; Santo et al., 2006; Scanlon, 1985; Signorelli et al., 2006a; Signorelli et al., 2006b; Taylor et al., 1996)	
<b>Intermittent claudication</b>	(Barker et al., 2001; Brevetti et al., 1999; Brevetti et al., 1995; Brevetti et al., 1997; Dal Lago et al., 1999; De Marchi et al., 2012; Di Marzo et al., 1999; Hiatt et al., 2001; Luo et al., 2013; Strano, 2002; Taylor et al., 1996)	(Hiatt et al., 2011)
<b>Ischemia</b>	(Chiddo et al., 1991; Greco et al., 1992; Lagioia et al., 1992)	
<b>Heart failure</b>	(Anand et al., 1998; Mancini et al., 1992)	(Failure, 1999) no effect on exercise duration
<b>Diabetes mellitus</b>	(Greco et al., 1992); diabetic angiopathy,	
<b>Peripheral vascular diseases</b>	(Allegra et al., 2008; Greco et al., 1992; Pola et al., 1992; Riccioni et al., 2008)	
<b>Reperfusion injury</b>	(Lango et al., 2005)	

## Figure legends

**Figure 1 Acyl-chain categories and respective numbers of acylcarnitines in each category.** The size of each mitochondrion depicts the relative abundance of short-, medium-, long- and very-long-chain acylcarnitines.

**Figure 2 Representative structures of various acylcarnitine classes.**

**Figure 3 Generalized model of acylcarnitine synthesis, transport and metabolism in peroxisomes (A) and mitochondria (B).** Acylcarnitines are generated in the mitochondria and peroxisomes of various tissues. BC – branched-chain, MC – medium-chain, LC – long-chain, VLC – very-long-chain, PEX – peroxisomes, MITO – mitochondria, pex- $\alpha/\beta$ -ox – peroxisomal fatty acid  $\alpha$ - or  $\beta$ -oxidation, mt- $\beta$ -ox – mitochondrial fatty acid  $\beta$ -oxidation, TCA cycle – tricarboxylic acid cycle, CrAT – carnitine acetyltransferase, CrOT – carnitine octanoyltransferase, CPT1/2 – carnitine palmitoyltransferase 1 or 2, OCTN2 – organic cation novel type 2 transporter, CACT – carnitine/acylcarnitine translocase, MCD – malonyl-CoA decarboxylase, ACC – acetyl-CoA carboxylase, FATP 1 – long-chain fatty acid transport protein 1.

**Figure 4 Enzyme and transporter preferences for acylcarnitines of various chain lengths (C2-C23).** Shading represents the enzyme/transporter preference for specific acylcarnitine lengths. Based on the literature data, a darker area indicates a higher preference for a specific acylcarnitine, while a lighter area indicates a lower preference for a specific acylcarnitine or limited data availability. CrAT – carnitine acetyltransferase, CrOT – carnitine octanoyltransferase, CPT 1/2 – carnitine palmitoyltransferase 1 or 2, OCT1 – organic cation transporter 1, OCTN2 – organic cation novel type 2 transporter.

**Figure 5 Enzymes, transporters and signaling pathways as potential targets to decrease the acylcarnitine content.** LC – long chain, FA – fatty acids, mt- $\beta$ -ox – mitochondrial fatty acid  $\beta$  oxidation, TCA cycle – tricarboxylic acid cycle, CPT1/2 – carnitine palmitoyltransferase 1 or 2, OCTN2 – organic cation novel type 2 transporter, CACT – carnitine/acylcarnitine translocase, MCD – malonyl-CoA decarboxylase, ACC – acetyl-CoA carboxylase, FATP 1 – long-chain fatty acid transport protein 1, IRS – insulin receptor substrate, PI3K – phosphoinositide 3-kinase, Akt – protein kinase B.  $\uparrow$  – increase. T – shaped arrows indicate inhibition. The interrupted arrow indicates indirect activation by the PI3K/Akt signaling pathway.

**Figure 6 Enzymes and transporters related to the development of FAOD and the accumulation of acylcarnitines.** Red arrows indicate reverse flux of acyl moieties and efflux of acylcarnitines. The main enzymes and transporters related to FAOD are marked in blue. ACAD9 – acyl-CoA dehydrogenase family member 9; ECH – enoyl-CoA hydratase; ETFQO – electron transfer flavoprotein-ubiquinone oxidoreductase; LCHAD, MCHAD, and SCHAD – long-, medium-, and short-chain 3-hydroxyacyl-CoA dehydrogenase; LCKAT and MCKAT – long- and medium -chain 3-hydroxy-acyl-CoA dehydrogenase; VLCAD – very-long-chain acyl-CoA dehydrogenase.

**Figure 7 Enzymes, ion channels and (signaling) pathways affected by long-chain acylcarnitines in myocytes.** LC – long chain, FA – fatty acids, mt- $\beta$ -ox – mitochondrial fatty acid  $\beta$  oxidation, TCA cycle – tricarboxylic acid cycle, CPT1/2 – carnitine palmitoyltransferase 1 or 2, OCTN2 – organic cation novel type 2 transporter, CACT – carnitine/acylcarnitine translocase, MCD – malonyl-CoA decarboxylase, ACC – acetyl-CoA carboxylase, FATP 1 –

long-chain fatty acid transport protein 1, IRS – insulin receptor substrate, PDC – pyruvate decarboxylase complex, PI3K – phosphoinositide 3-kinase, Akt – protein kinase B. ↑ – increase.

**Figure 8 Clinical trials involving acylcarnitines and L-carnitine.** We identified 64 trials using keyword searches with the term *acylcarnitine* in ClinicalTrials.gov and PubMed with the clinical trials filter. In addition, 8 studies assessing L-carnitine (levocarnitine) were identified, but these studies are investigated separately in Figure 8d. The data were subsequently manually curated and classified into different categories, such as the type of clinical study, condition/diagnosis and drug classes. **A)** Type of clinical study as defined in Clinical.Trials.gov with the number of clinical trials identified in each category. Study types included observational, procedural, nutritional supplementation (nutritional suppl.), behavioral interventions, nutritional diet interventions, and drug studies. Percent and number of clinical trials in parentheses. **B)** Condition/diagnosis of the participants. The data show several deficiencies (grouped as Deficiency), such as carnitine deficiency, vitamin B6 deficiency, malnutrition and infant nutrition disorders. Energy storage diseases include glucose transporter type 1 deficiency syndrome, glucose intolerance and glycogen storage disease type V. Fatty acid oxidation disorders (FAODs) include long-chain fatty acid transport deficiency, carnitine palmitoyl transferase type 1A (CPT1A) deficiency, and trifunctional protein deficiency. The category “Other” represents polycystic ovary syndrome (PCOS), inborn errors of metabolism, sepsis, complications from premature birth and Klinefelter syndrome. Type 2 diabetes (T2DM), insulin resistance (IR) and obesity are an often-combined study group in clinical trials and are thereby counted together as one category. Acidemias represent both propionic acidemia and methylmalonic acidemia. **C)** Drug classes. The “Other” group includes drugs that act as analgesics, growth hormone receptor antagonists, hepatoprotectants, amino acid analogs, and antihypertensives. **D)** Additionally, we identified 126 trials using keyword searches with the term *levocarnitine* in ClinicalTrials.gov. Conditions treated with levocarnitine with the number of studies in each category. Fertility-related disorders include polycystic ovary syndrome (PCOS) and male infertility. Type 2 diabetes (T2DM), glucose intolerance (GI), insulin resistance (IR) and obesity are an often-combined study group in clinical trials and are thereby counted together as one category. Cardiovascular disease (CVD) includes heart failure, vascular disease, atherosclerosis, heart septal defects, arterial disease and coronary artery disease. Neuromuscular disorders include spinal muscular atrophy, sarcopenia, postpoliomyelitis syndrome and muscle soreness. Infections are represented by sepsis and viral infections. In addition to these dominant conditions in the figure there are a minor number of studies in the areas of neurodegenerative disorders (3 studies), including progressive supranuclear palsy, Alzheimer’s disease and multiple sclerosis. Neuropsychiatric disorders (3 studies) include attention deficit hyperactivity disorder, bipolar disorder and autism. Other studies were related to prematurity (3 studies), thyroid-related disease (3 studies), fatigue (3 studies), ulcerative colitis (3 studies), toxicity (2 studies), central nerve injury (1 study), carnitine-related deficiency (1 study), Sjogren’s syndrome (1 study), sleep apnea (1 study), thalassemia (1 study), chronic pancreatitis (1 study), migraine (1 study), and dyslipidemia (1 study).