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Mitochondrial metabolites acylcarnitines: therapeutic potential and drug targets

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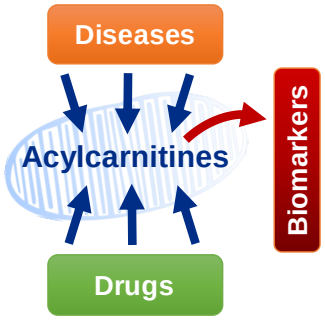
Summary

Acylcarnitines are esters of L-carnitine that emerge from the fatty acid metabolism pathways in mitochondria and peroxisomes.



Metabolomic profiling assays that investigate disease and nutrition states often include measurements of different acylcarnitines. This has resulted in increased interest regarding the consequences of increased or decreased plasma acylcarnitine concentrations and the mechanisms associated with these changes. An altered acylcarnitine metabolome is characteristic of specific inborn errors of fatty acid metabolism, and cardiovascular, metabolic, and neurological diseases in addition to some forms of cancer. Long-chain acylcarnitines accumulate under conditions of insufficient mitochondrial functionality reaching tissue levels that can affect enzyme and ion channel activities, and impact energy metabolism pathways and cellular homeostasis.

A better understanding of biochemical and molecular mechanisms behind the changes in acylcarnitine levels and their physiological and pathological roles forms the basis for future therapeutic target selection and preclinical drug discovery. This may explain off-target effects of some clinically used drugs and point to new indications for repurposing.

1. Introduction

Acylcarnitines are important fatty acid metabolites and biomarkers for the diagnosis of inherited diseases of fatty acid metabolism, insulin resistance, and heart failure (Dambrova et al 2022). A considerable number of metabolomic studies analyzing plasma/serum samples from different diseases and conditions have produced evidence regarding the involvement of acylcarnitines in mitochondrial energy metabolism and the pathogenesis of related diseases. For example, acylcarnitine profiling was suggested for better prediction of high-risk patients for progressive atherosclerosis-mediated diseases (Blair et al 2016). Alterations in acylcarnitines concentrations have been identified in different cancers (McCann et al 2021), insulin resistance, and cardiovascular events (Davies et al 2014; Albert, Tang 2018). The recently updated Human Metabolome Database now includes chemical structure information and biochemical pathway descriptions for 1240 acylcarnitines (Wishart et al 2022). However, the physiological role of all detected acylcarnitines is still not clear and more research is needed to understand the regulatory pathways of different acylcarnitines in health and disease.

2. Sources of acylcarnitines

Acylcarnitines are produced in the cell by conjugating an acyl group with L-carnitine by carnitine acyltransferases (Figure 1). Each acyltransferase transfers acyl-groups with different chain lengths to form respective short- (SC), medium- (MC) and long-chain (LC) acylcarnitines. Carnitine acetyltransferase (CrAT, EC:2.3.1.7) synthesizes acylcarnitines with acyl group chain lengths of up to 8 carbons (Violante et al 2013). Carnitine O-octanoyltransferase (CrOT, EC:2.3.1.137) is responsible for the transesterification of MC (C6-C12) and probably LC (>C12) acylcarnitines in peroxisomes to ensure the transport of acyl groups out of the peroxisome to the cytosol and mitochondria (Ferdinandusse et al 1999). Carnitine palmitoyltransferase 1 (CPT1, EC:2.3.1.21) is an enzyme in the mitochondrial outer membrane that converts LC acyl-CoA to their corresponding LC acylcarnitines and is the rate-limiting step in LC fatty acid oxidation in mitochondria (Finocchiaro et al 1990). CPT1 has two main isoforms specific to the liver and skeletal muscle, while in heart mitochondria both CPT1 isoforms are present. For further metabolism, acylcarnitines are transported into the mitochondrial matrix by carnitine/acylcarnitine translocase (CACT, SLC25A20), where carnitine palmitoyltransferase 2 (CPT2, EC:2.3.1.21) converts acylcarnitines to acyl-CoA for further β-oxidation (Rufer et al 2009).

Plasma concentrations of specific acylcarnitines are used for the diagnosis of inborn fatty acid oxidation defects and acquired diseases caused by incomplete fatty acid metabolism (Rinaldo et al 2008; Wanders et al 2020). Acylcarnitines of differing chain lengths are transported into the bloodstream from different organs or tissues. The highest content of acylcarnitines is found in heart, skeletal muscle, and liver, all of which contain short-, medium-, and long-chain acylcarnitine species. However, the heart is the main contributor to the plasma medium- and long-chain acylcarnitine pool (Makrecka-Kuka et al 2017). Therefore, plasma LC acylcarnitine concentrations are valuable markers of cardiac acylcarnitine content and can be successfully used for the diagnosis of mitochondrial fatty acid metabolism disorders in the heart.

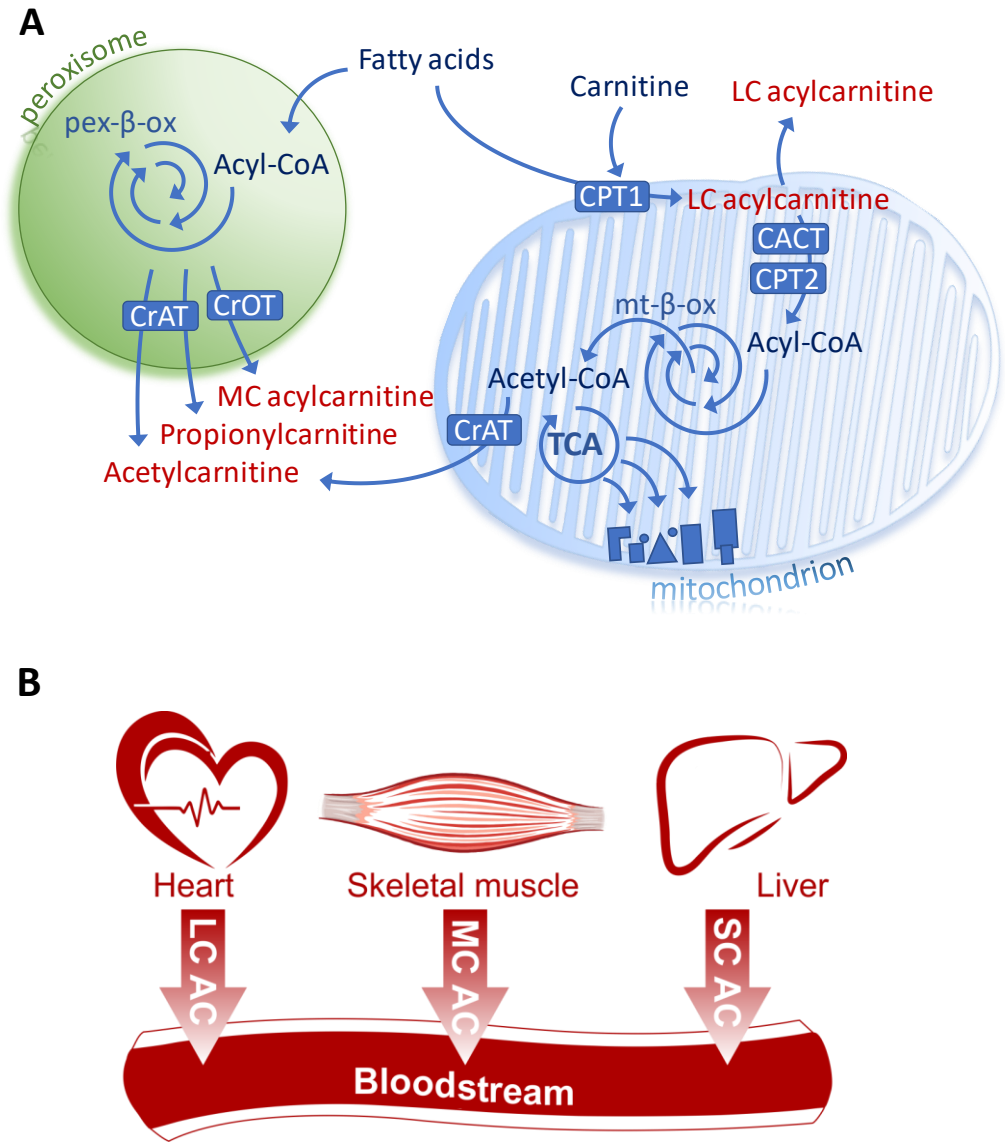


Figure 1. Sources of acylcarnitines (A) Synthesis of acylcarnitines in mitochondria and peroxisomes. **(B)** The main contributors delivering acylcarnitines to the plasma pool are the heart (long-chain), skeletal muscles (medium-chain) and liver (short-chain). CPT1: carnitine palmitoyltransferase 1; CPT2: carnitine palmitoyltransferase 2; pex-β-ox: peroxisomal β-oxidation; mt-β-ox: mitochondrial β-oxidation; LC AC: long-chain acylcarnitine; MC AC: medium-chain acylcarnitine; SC AC: short-chain acylcarnitine; CrAT: carnitine acetyltransferase; CrOT: carnitine O-octanoyltransferase; TCA: tricarboxylic acid cycle; CACT: carnitine/acylcarnitine translocase.

In skeletal muscle, the fatty acid metabolism pattern is similar to the heart but the content of LC acylcarnitines is significantly lower. This is likely linked to skeletal muscle mainly contributing to the plasma availability of MC (C6-C12) acylcarnitines, but not LC acylcarnitines (Schooneman et al 2015; Xu et al 2016; Makrecka-Kuka et al 2017). Importantly, the liver is the main source of circulating acetyl- and propionyl-carnitines, while it does not release any acylcarnitines that are longer than four carbons (C4) (Schooneman et al 2015; Xu et al 2016).

3. Acylcarnitines in diseases

Acylcarnitines are valuable biomarkers used for screening a series of genetic disorders that affect fatty acid oxidation and amino acid metabolism (Costanzo et al 2017; Wanders et al 2020). In addition, changes in acylcarnitine concentrations in the blood are linked to many acquired diseases (Table 1). Type 2 diabetes and heart failure are two diseases in which the blood concentrations of practically all types of acylcarnitines are elevated. Numerous studies show increased concentrations of SC (C2-C5), MC (C6-C12), LC (C13-C20) and hydroxyl-/dicarboxyl-chain acylcarnitines (Table 1). Moreover, increased levels of LC and hydroxyl-/dicarboxyl-chain acylcarnitines have been demonstrated in pulmonary arterial hypertension patients. Elevated blood concentrations of unsaturated-chain acylcarnitines with different fatty acid moiety lengths have been observed in patients with liver diseases and obesity. Increased blood concentration of acylcarnitines has been observed not only in the case of cardiometabolic diseases but also in the liver and central nervous system (e.g., chronic fatigue syndrome) disorders.

Table 1. Acquired diseases with altered acylcarnitine (AC) levels in the blood

Acylcarnitine type	Concentration in blood	Disease
Short-chain AC	increased	Heart failure (Cheng et al 2015; Zordoky et al 2015), type 2 diabetes (Mihalik et al 2010; Sun et al 2020)
	decreased	CNS diseases (Kuratsune et al 1998; Cristofano et al 2016; Nasca et al 2018)
Medium-chain AC	increased	Type 2 diabetes (Mihalik et al 2010; Batchuluun et al 2018), diastolic heart failure (Zordoky et al 2015)
	decreased	Celiac disease (Bene et al 2005), tumors (Tan et al 2013; Xu et al 2013; Kim et al 2019; Park et al 2019)
Long-chain AC	increased	Type 2 diabetes (Mihalik et al 2010; Zhang et al 2014), heart failure (Zordoky et al 2015; Hunter et al 2016), pulmonary arterial hypertension (Brittain et al 2016)
	decreased	Intracerebral hemorrhage (Zhang et al 2017)
Very-long-chain AC	increased	Type 2 diabetes (Zhang et al 2014)
	decreased	Acute cerebral infarction (Zhang et al 2017)
Unsaturated-chain AC	increased	Obesity and overweight (Wahl et al 2012; Schlueter et al 2020), liver diseases (Chen et al 2016; Miyaaki et al 2020)
	decreased	Schizophrenia (Cao et al 2020)
Branched-chain AC	increased	---
	decreased	Traumatic brain injury (Jeter et al 2013)
Hydroxyl-/dicarboxyl-chain AC	increased	Type 2 diabetes (Adams et al 2009; Hameed et al 2020), heart failure (Cheng et al 2015; Hunter et al 2016), pulmonary arterial hypertension (Mey et al 2020), chronic fatigue syndrome (Reuter, Evans 2011)
	decreased	Traumatic brain injury (Jeter et al 2013), intracerebral hemorrhage (Zhang et al 2017), psoriasis (Ottas et al 2017; Chen et al 2021)

Conversely, several diseases are characterized by decreased levels of acylcarnitines in the blood. Decreased blood levels of SC acylcarnitines have been observed in several central nervous system diseases: Alzheimer's disease (Cristofano et al 2016), major depressive disorder (Nasca et al 2018) and chronic fatigue syndrome

(Kuratsune et al 1998). In addition, LC, very-long-chain (>C21), unsaturated-chain, branched-chain, and hydroxyl-/dicarboxyl-chain acylcarnitine concentrations in blood are decreased in case of injury to the neurons of the central nervous system (e.g., traumatic brain injury or intracerebral hemorrhage) and schizophrenia (Table 1). Blood concentrations of MC acylcarnitines are decreased in celiac patients and patients with breast cancer (Park et al 2019), hepatocellular carcinoma (Kim et al 2019), colorectal cancer (Tan et al 2013) and esophageal squamous cell carcinoma (Xu et al 2013).

4. Acylcarnitines and drugs

Acylcarnitines are considered mitochondrial biomarkers for precision medicine for both inherited and acquired metabolic diseases, and drug-induced mitochondrial dysfunction (McCann et al 2021). More than 20 FDA-approved drugs are in trials (https://clinicaltrials.gov/) in which acylcarnitines are assessed as biomarkers or as a study outcome measure (Dambrova et al 2022). Acylcarnitine profile assessment is commonly used as an outcome measure in clinical trials of diabetes, insulin resistance, and obesity.

Acylcarnitines are typically measured in studies not only with antihyperglycemic drugs, antihyperlipidemics, fatty acid analogs, carnitine supplements but also hormone replacements, and antidepressants (Dambrova et al 2022). Accumulation of LC acylcarnitines inhibits pyruvate metabolism and phosphorylation of protein kinase B, also known as Akt, thus impacting the molecular mechanisms of insulin signaling and leading to insulin resistance and hyperinsulinemia (Makrecka et al 2014; Liepinsh et al 2017). Several clinically known drugs for the treatment of insulin resistance, diabetes, and obesity in addition to their identified molecular target activities affect also acylcarnitine levels. Thus, the well-known diabetes drugs insulin, metformin, dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin, and glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide impact energy metabolism homeostasis and induce changes in the acylcarnitine concentration profile (Table 2).

Long-chain acylcarnitine assessment is of particular interest because their increased concentrations are detected in concurrence with dysfunctional fatty acid metabolism, particularly in mitochondria (Houten et al 2016). In addition, detrimental LC acylcarnitine accumulation disturbs mitochondrial function and energy metabolism in ischemia-reperfusion (Liepinsh et al 2016; Kuka et al 2017). At elevated concentrations, LC acylcarnitines inhibit oxidative phosphorylation in mitochondria, induce membrane hyperpolarization, and stimulate reactive oxygen species production (Dambrova et al 2021). Therefore, it is not surprising that compounds that affect LC acylcarnitine levels rise in interest as potential mitochondria-protective and anti-ischemic drugs (Dambrova et al 2021). For example, the cardiometabolic drug meldonium decreases LC acylcarnitine levels and possesses anti-infarction and antiarrhythmic activity in preclinical models and is used clinically to treat heart failure (Rupp et al 2002; Liepinsh et al 2013). Other examples of acylcarnitine profile-affecting cardiovascular drugs include statins and sildenafil (Table 2).

Table 2. Examples of drugs affecting acylcarnitine levels

Drug	Target/mechanism	Condition	Effect on plasma acylcarnitines, sample origin	References
Insulin	antidiabetic drug, insulin receptor agonist	diet-induced obesity and type 2 diabetes	↓C2; ↓C3; ↓C4; ↓C5; ↓C6; ↓C8; ↓C10:1; ↓C14:1; ↓C16; ↓C18; ↓C18:1, clinical	(Mihalik et al 2010)
Metformin	antidiabetic drug, multi-target	diet-induced obesity and type 2 diabetes	↑C4; ↑C18:1, preclinical	(Tomasova et al 2019)
Vildagliptin	antidiabetic antihyperglycemic drug, inhibitor of DPP-4	diet-induced obesity and type 2 diabetes, preclinical	↑C2; ↑C4, preclinical	(Tomasova et al 2019)
Liraglutide	antidiabetic drug, GLP-1 receptor agonist	insulin resistance	↑C2; ↓C5; ↓C6; ↓C8; ↓C12; ↓C14; ↓C16, clinical	(Hussein et al 2021)
Meldonium	cardiometabolic drug, OCTN2 inhibitor	ischemic heart disease	↓C16, preclinical	(Liepinsh et al 2013; Dambrova et al 2016)
Atorvastatin	blood cholesterol-lowering, cardiovascular disease prevention, HMG-CoA reductase inhibitor	atherosclerosis, diet-induced obesity preclinical	↓C3; ↓C4; ↓C3-DC; ↓C14:1-OH; ↓C18, preclinical	(Ryan et al 2017)
Rosuvastatin	blood cholesterol-lowering, cardiovascular disease prevention, HMG-CoA reductase inhibitor	hyperlipidemia	↓C18:2, clinical	(Lee et al 2018)
Sildenafil	erectile dysfunction, pulmonary arterial hypertension treatment, phosphodiesterase-5 inhibitor	heart failure with preserved ejection fraction	↑C5-DC; ↑C10:1-OH/C8:1-DC; ↑C6-DC; ↑C16, clinical	(Wang et al 2017)
Propofol	intravenous anesthetic, GABA receptor agonist	propofol-related infusion syndrome	↑C3-DC, ↑C4, ↑C5, clinical	(Wolf et al 2001; Vollmer et al 2018)
Acetaminophen	nonsteroidal anti-inflammatory drug, analgesic and anti-fever, cyclooxygenase inhibitor	acetaminophen toxicity, preclinical	↑C16, ↑C18:1 (Delta9-cis), ↑C14, preclinical	(Chen et al 2009; Bhattacharyya et al 2013)

C2 acetylcarnitine, C3 propionylcarnitine, C4 butyrylcarnitine, C5 valerylcarnitine, C6 caproylcarnitine, C8 octanoylcarnitine, C10:1 decenoylcarnitine, C14:1 tetradecenoylcarnitine, C16 palmitoylcarnitine, C18 stearoylcarnitine, C18:1 (Delta9-cis)oleoylcarnitine, C12 lauroylcarnitine, C14 myristoylcarnitine, C3-DC malonylcarnitine, C14:1-OH hydroxy-tetradecenoylcarnitine, C18:2 linoleoylcarnitine, C5-DC glutarylcarnitine, C10:1-OH/C8:1-DC 3-hydroxy-decanoylcarnitine or suberoylcarnitine, C6-DC adipylcarnitine.

Pathologically altered levels of acylcarnitines have been noted in some cases of drug-induced toxicity. The intravenous anesthetic propofol increased acylcarnitine levels in the peripheral blood of a patient and inhibited the electron transfer system of mitochondria (Table 2). High doses of acetaminophen (paracetamol) induced acute

increase in acylcarnitine levels in a preclinical study. Acylcarnitine profile measurements could be a method of choice to investigate mechanisms of suspected drug-induced mitochondrial dysfunction.

In conclusion, some clinically approved cardiovascular and diabetes drugs (Table 2) reduce LC acylcarnitine concentrations *in vivo* and it would be worth investigating whether these compounds could be repurposed for the treatment of conditions induced by accumulation of LC acylcarnitine, such as cardiac arrhythmia during ischemia, insulin resistance, and in some cases of inherited fatty acid metabolism disorders. Currently, insulin and GLP-1 agonists are the most promising repurposing candidates for the treatment of diseases primarily or secondarily related to mitochondrial energy metabolism deficiency. It is expected that more metabolomics data will become available in the future, as metabolomics analysis of plasma samples collected during clinical trials become more affordable and popular, driving further the artificial intelligence and machine learning-supported drug repurposing and drug discovery.

5. Conclusions

Acylcarnitines emerge from mitochondrial energy metabolism and, if accumulated or deficient, play a pivotal role in the regulation of cellular energy homeostasis. More data on altered concentrations of acylcarnitines in human samples under physiological and pathological conditions are needed for a comprehensive understanding of their validity as biomarkers and the regulation of their plasma and tissue levels by dietary and pharmacological means to treat specific diseases.

Abbreviations:

AC	acylcarnitine	GABA	gamma-aminobutyric acid
CAC	citric acid cycle	GLP-1	glucagon-like peptide-1
CACT	carnitine/acylcarnitine translocase	LC	long-chain
CPT1	carnitine palmitoyltransferase 1	MC	medium-chain
CPT2	carnitine palmitoyltransferase 2	mt-β-ox	mitochondrial β-oxidation
CrAT	carnitine acetyltransferase	OCTN2	organic cation/carnitine transporter
CrOT	carnitine O-octanoyltransferase	pex-β-ox	peroxisomal β-oxidation
DPP-4	dipeptidyl peptidase-4	SC	short-chain

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