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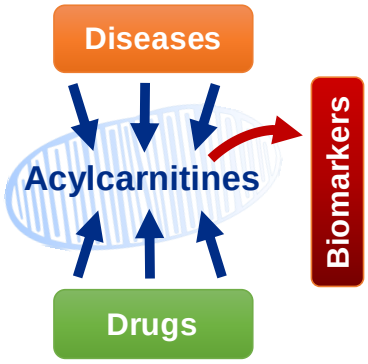

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Mitochondrial metabolites acylcarnitines: therapeutic potential and drug targets

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Abstract

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/decreased levels of plasma acylcarnitine concentrations and the mechanisms associated with these changes. Altered acylcarnitine metabolome is characteristic of certain inborn errors of fatty acid metabolism, as well as 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, as well as explains off-target effects of some clinically used drugs.

1. Introduction

Acylcarnitines are emerging as important fatty acid metabolites and biomarkers for the diagnosis of inherited diseases of fatty acid metabolism, insulin resistance, and heart failure (Dambrova M 2022). An increasing number of metabolomic studies analyzing plasma/serum samples from different diseases and conditions produce new evidence regarding the involvement of acylcarnitines in mitochondrial energy metabolism processes and the pathogenesis of related diseases. For example, measurements of acylcarnitine profiles were 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 and Tang 2018). The recently updated Human Metabolome Database now includes chemical structure information and biochemical pathway description for 1240 acylcarnitines (Wishart et al 2022). However, the physiological role of all detected acylcarnitines is not clear and more research data are needed to understand the regulatory pathways of different acylcarnitines in health and disease.

2. Sources of acylcarnitines

Acylcarnitines in the cell are produced by conjugating an acyl group with L-carnitine by the enzymes 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) is synthesizing acylcarnitines with acyl group chain lengths up to 8 carbons (Violante et al 2013). Carnitine O-octanoyltransferase (CrOT, EC:2.3.1.137) is responsible for the transesterification of medium-chain (C6-C12) and probably long-chain (>C12) acylcarnitines in peroxisomes to ensure acyl group transport 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 outer mitochondrial membrane that converts long-chain acyl-CoA to their corresponding long-chain acyl-carnitines and is the rate-limiting step in long-chain fatty acid oxidation in mitochondria (Finocchiaro et al 1990). CPT1 has two main isoforms specific to the liver and skeletal muscle, while in the 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 beta-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). It has been determined, that acylcarnitines of differing chain lengths are transported into the bloodstream from different organs or tissues. The highest content of acylcarnitines is found in the 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 long-chain 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.

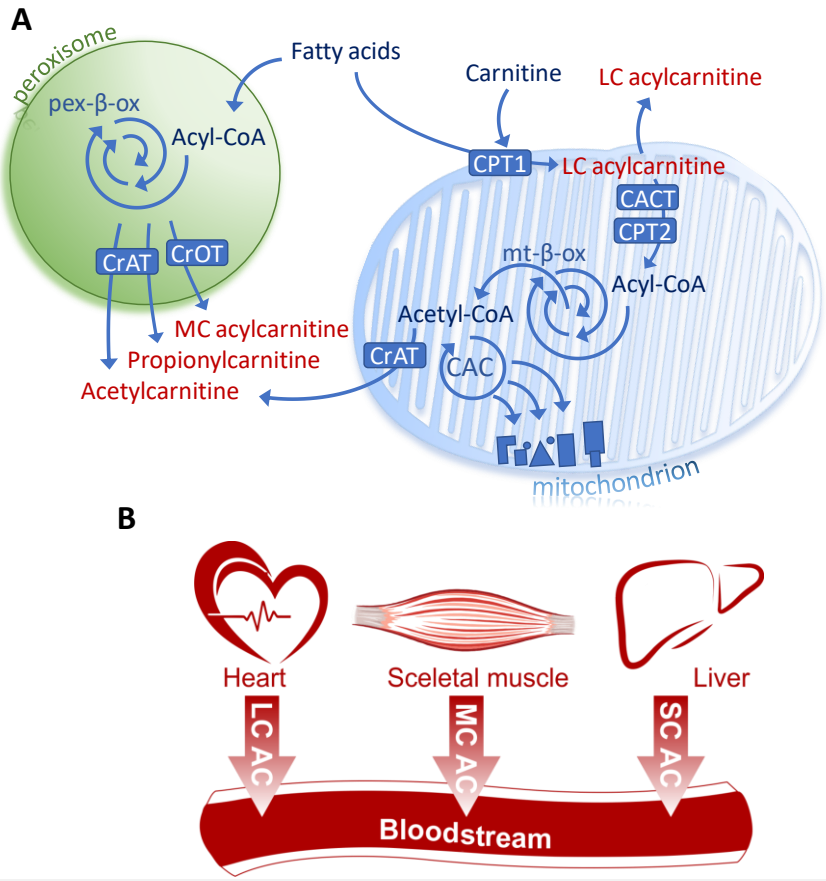

Figure 1. (a) Synthesis of acylcarnitines in mitochondria and peroxisomes. **(b)** The main contributors delivering acylcarnitines to the plasma pool are the heart (long-chain), skeletal muscles (medium-chain) and liver (short-chain). CPT1: carnitine palmitoyltransferase 1; CPT2: carnitine palmitoyltransferase 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; CAC: citric acid cycle; CACT: carnitine/acylcarnitine translocase.

In the skeletal muscles, the fatty acid metabolism pattern is similar to the heart but the content of long-chain acylcarnitines is significantly lower. This is likely linked to skeletal muscles mainly contributing to the plasma availability of medium-chain (C6 to C12) acylcarnitines, but not long-chain 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 efflux any acylcarnitines that are longer than C4 (Schooneman et al 2015, Xu et al 2016).

3. Acylcarnitines in diseases

Acylcarnitines are invaluable biomarkers used for screening a series of genetic disorders affecting fatty acid oxidation and amino acid metabolism (Costanzo et al 2017, Wanders et al 2020). Meanwhile, changes in acylcarnitine concentrations in the blood are also 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 have shown increased concentrations of short-chain (C2-C5),

medium-chain (C6-C12), long-chain (C13-C20) and hydroxyl-/dicarboxyl-chain acylcarnitines (Table 1). Moreover, increased levels of long-chain 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 individuals with obesity. Increased blood concentration of acylcarnitines has been observed not only in the case of cardiometabolic diseases but also in liver and central nervous system (e.g., chronic fatigue syndrome) disorders.

Conversely, several diseases are characterized by decreased levels of acylcarnitines in the blood. Decreased blood levels of short-chain 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, long-chain, very-long-chain (>C21), unsaturated-chain, branched-chain, and hydroxyl-/dicarboxyl-chain acylcarnitine concentrations in blood have been 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). Decreased blood concentrations of medium-chain acylcarnitines have been demonstrated 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).

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

Acylcarnitine (AC) type	Concentration in the 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 and 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)

4. Acylcarnitines and drugs

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

Acylcarnitines are typically being measured in studies with antihyperglycemic drugs, antihyperlipidemics, fatty acid analogs, carnitine supplements, but also hormone replacements, and antidepressants (Dambrova M 2022). The accumulation of long-chain 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 drug metformin, dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin, and glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide have been shown to impact energy metabolism homeostasis and induce changes in the acylcarnitine concentration profile (Table 2).

Table 2. Examples of acylcarnitine levels-affecting drugs

Drug	Target/mechanism	Condition	Ref
Metformin	antidiabetic drug, multi-target	Diet-induced obesity and type 2 diabetes, preclinical	(Tomasova et al 2019)
Vildagliptin	antidiabetic antihyperglycemic drug, inhibitor of DPP-4	Diet-induced obesity and type 2 diabetes, preclinical	(Tomasova et al 2019)
Liraglutide	antidiabetic drug, GLP-1 receptor agonist	Insulin resistance, clinical	(Hussein et al 2021)
Meldonium	cardiometabolic drug, OCTN2 inhibitor	Ischemic heart disease, 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	(Ryan et al 2017)
Rosuvastatin	blood cholesterol-lowering, cardiovascular disease prevention, HMG-CoA reductase inhibitor	Hyperlipidemia, clinical	(Lee et al 2018)
Sildenafil	erectile dysfunction, pulmonary arterial hypertension treatment, phosphodiesterase-5 inhibitor	Heart failure with preserved ejection fraction, clinical	(Wang et al 2017)
Propofol	intravenous anesthetic, GABA receptor agonist	Propofol-related infusion syndrome, clinical	(Vollmer et al 2018, McCann et al 2021)
Acetaminophen	nonsteroidal anti-inflammatory drug, analgesic and anti-fever, cyclooxygenase inhibitor	Acetaminophen toxicity, preclinical	(Bhattacharyya et al 2013)

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 long-chain acylcarnitine accumulation disturbs mitochondrial functionality and energy metabolism in ischemia-reperfusion (Liepinsh et al 2016, Kuka et al 2017). At elevated concentrations, long-chain 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 long-chain acylcarnitine levels rise in interest as potential mito-protective and anti-ischemic drugs (Dambrova et al 2021). For example, the cardiometabolic drug meldonium decreases long-chain 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). Some other examples of acylcarnitine profile-affecting cardiovascular drugs include statins and sildenafil (Table 2).

Pathologically altered levels of acylcarnitines have been noted also in some cases of drug-induced toxicity. The intravenous anesthetic propofol was found to increase levels of acylcarnitines in peripheral blood of a patient and inhibit the electron transport system in mitochondria (Table 2). Also, 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 cases.

In conclusion, several clinically approved drugs have been shown to reduce long-chain acylcarnitine concentrations *in vivo* and would be worth investigating whether these compounds could be repurposed for treatment of long-chain acylcarnitine accumulation-induced conditions, such as cardiac arrhythmia during ischemia, insulin resistance and in some cases of inherited fatty acid metabolism disorders. 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. Future perspectives

Acylcarnitines emerge from mitochondrial energy metabolism processes 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 biosamples, blood, and tissue, under physiological and pathological conditions, are needed for the comprehensive understanding of their validity as biomarkers and regulation of their plasma and tissue levels by dietary and pharmacological means to treat certain diseases.

Abbreviations:

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

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