Pharmacology & Therapeutics 120 (2008) 149–156

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: K. Suckling

Carnitine in metabolic disease: Potential for pharmacological intervention

Arduino Arduini [a,*], Mario Bonomini [b], Vincenzo Savica [c], Antonino Amato [d], Victor Zammit [e]

[a] R&D Department, Iperboreal Pharma Srl, Chieti, Italy
[b] Department of Nephrology and Dialysis, University Hospital of Chieti, Chieti, Italy
[c] Nephrology and Dialysis Unit, University of Messina, Messina, Italy
[d] Clinical Research Unit, Sigma Tau Pharmaceuticals Spa, Pomezia, Italy
[e] Clinical Sciences Research Institute, Warwick Medical School, CV7 4AL, UK

ARTICLE INFO

Keywords:
L-carnitine
Hemodialysis
Uremia
Peritoneal dialysis
Insulin resistance
Diabetes
Metabolism
Dyslipidemia

Abbreviations:
LC, L-carnitine
ESRD, end-stage renal disease
HD, hemodialysis
CPT-1, carnitine palmitoyltransferase 1
IR, insulin resistance
T2D, type 2 diabetes
PD, peritoneal dialysis
PDH, pyruvate dehydrogenase
CAT, carnitine acetyltransferase
TG, triglycerides
VLDL, very low density lipoprotein
HDL, high density lipoprotein

ABSTRACT

L-carnitine (LC) deficiency is commonly observed in chronic hemodialysis (HD) patients. As a result of this and other causes of secondary LC deficiencies, LC has been described as a "conditionally essential nutrient" or "conditional vitamin". Although a large number of clinical trials regarding the beneficial effects of LC administration in HD patients have been published, some controversy about its use in this indication persists. In this article, we will review the use of LC in dialysis patients, by focussing mainly on those experimental and clinical data supporting the notion that supra-physiological concentrations of LC in plasma and target organs may exert beneficial effects on several metabolic parameters that have derangements of a common origin (e.g. insulin resistance, type 2 diabetes, dyslipidemia) and which are frequently present in end-stage renal disease (ESRD) patients undergoing dialysis.

Contents

* Corresponding author. Tel.: +39 085 4460811; fax: +39 085 2309876.
E-mail address: a.arduini@iperboreal-pharma.com (A. Arduini).

0163-7258/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2008.08.008

1. Introduction

LC is a naturally occurring compound widely distributed in nature. Mammalian tissues contain relatively high amounts of LC, ranging between low μM to low mM, with the highest concentrations in heart and skeletal muscles (Bremer, 1983). Although LC may be obtained primarily from the diet, mammals are capable of endogenous synthesis of LC from lysine and methionine (Vaz & Wanders, 2002; Steiber et al., 2004). LC involvement in intermediary metabolism is essential to mammalian bioenergetic processes, where a major role for LC is in the formation of acylcarnitine esters of long-chain fatty acids, a step required for the transfer the acyl moieties destined for β-oxidation across the mitochondrial inner membrane with the retention of separate intra- and extra-mitochondrial pools of (non-permeant) acyl-CoA (Bremer, 1983; Ramsay & Arduini, 1993; Zammit, 1999). This reaction is catalysed by carnitine palmitoyltransferase 1 (CPT-1), but LC is also a substrate for other members of the carnitine acyltransferase family of enzymes, with various chain-length specificities and intracellular distributions [see (Zammit, 1999) for review]. The main kinetic attribute of the general reaction catalysed by such carnitine-dependent acyltransferases is the freely reversible transfer of the acyl mojety from CoA to LC (Ramsay & Naismith, 2003).Therefore, carnitine acyltransferases have the ability to modulate the acyl-CoA/CoA ratio in the various intracellular compartments, thus exerting a much wider role in metabolism. Since transporters for acylcarnitine esters across membranes exist, this acts as a mechanism through which the cell may easily dispose different acyl moieties between cellular organelles according to their metabolic requirements. In addition, as the reaction catalysed by such carnitine-dependent acyltransferases is very sensitive to the mass action of the various substrates, pharmacological strategies aimed at increasing the LC concentration may be used to attain favourable metabolic outcomes.

Treatment with LC is increasingly being practised in ESRD, since losses during dialysis and reduced renal synthesis have been suggested as causes of LC deficiency in HD patients (Ahmad, 2001). Dialysis patients are very often affected by several metabolic disorders such as insulin resistance (IR), type 2 diabetes (T2D), dyslipidemia, atherosclerosis, obesity and other elements of the metabolic syndrome (Prichard, 2003; Wahba & Mak, 2007). In this respect, it has become appreciated that the use of glucose, the most commonly used osmotic agent for peritoneal dialysis (PD) media, may exacerbate obesity, hyperglycemia, dyslipidemia and insulin resistance in ESRD patients undergoing PD (Gokal, 2002). Since macrovascular complications are frequent sequelae of such metabolic disorders, it is not surprising that cardiovascular disease is the leading cause of mortality in dialysis patients (Kazory & Boss, 2008). However, despite a relatively large number of published clinical trials describing the beneficial effects of LC administration in HD patients, some controversy and misunderstandings about its use in this indication persist (Hurot et al., 2002; Schreiber, 2005; Steinman, 2005).

Therefore, the main aim of the current review is mainly to focus on the discussion of those experimental and clinical data supporting the notion that supra-physiological concentrations of LC may beneficially affect metabolic disorders commonly observed in IR and T2D. We will also attempt to reconcile the various strands within the controversy about the outcome LC therapy of ESRD patients undergoing dialysis treatment.

2. Carnitine pharmacology: metabolic interventions

The pharmacological actions of LC may be essentially described as: 1) metabolic, such as those linked to the physiological role played by LC and its metabolic partners (i.e., carnitine-dependent acyltransferases) in lipid and glucose metabolism, and 2) biophysical, such as those stemming from the physico-chemical interactions between LC and plasma membrane lipid components (see for example Arduini et al., 1993). However, it is not possible to give a comprehensive review of the large literature on LC in the metabolic field. Therefore, this discussion places emphasis on those experimental and clinical studies pertinent to metabolic interventions that have relied on the achievement of relatively high concentrations of LC in target organs.

3. Metabolic effects of carnitine on cardiac, skeletal muscle and liver

3.1. Cardiac metabolism

The notion of modulating the energy metabolism of the heart in order to ameliorate the performance of the dysfunctional myocardium is well established (Stanley et al., 1997; Huss and Kelly, 2005; Stanley et al., 2005; Dyck et al., 2006). For example, increased rates of fatty acid oxidation associated with lower rates of glucose oxidation (and higher rates of glycolysis) are considered to play a pivotal role in myocardial ischemic injury (Stanley et al., 2005). Since the uncoupling between glycolysis and glucose oxidation increases the production of reducing equivalents in the ischemic heart, and as coronary flow is diminished concomitantly, protons accumulate resulting in an increase in intracellular acidosis. Due to the activity of specific ion exchange channels, increased production of protons can lead to greater influx of Na^+ and Ca^{++} (Stanley et al., 1997) which utilises ATP to re-establish ion homeostasis thus resulting in lower ATP availability to support contractile function. This is exacerbated by the adverse effect of lowered pH on the functional efficiency of the contractile proteins (Stanley et al., 1997). Several pharmacological agents (e.g., etomoxir, dichloroacetate, trimetazidine, ranolazine) capable of affecting cardiac energy substrate metabolism have been shown to exert a favourable therapeutic action in animal and human studies of acute ischemia–reperfusion and heart failure (Stanley et al., 1997; Huss et al., 2005). Despite their different mode of action, these agents share the ability to drive energy metabolism toward glucose oxidation via a direct or indirect activation of pyruvate dehydrogenase (PDH) possibly through inhibition of PDH kinase (Lopaschuk et al., 2002; Stanley et al., 2005).

A detailed study on the metabolic effect of supra-physiological concentrations of LC in the intact normal working rat heart was carried out by Broderick et al. (1992). This study showed that a two-fold increase of LC concentration in the myocardium, obtained by adding LC in the perfusion medium at a concentration of 10 mM, greatly stimulated flux through PDH and, hence, glucose consumption. The mode of action of LC in stimulating PDH may be summarized as follows. Due to the presence within the mitochondrial matrix of carnitine acetyltransferase (CAT), an enzyme that catalyses the reversible transfer of the acetyl moiety from CoA to LC, an increase in the intracellular concentration of LC drives the reaction catalysed by CAT toward acetyl-L-carnitine. This is suggested to lead to a decrease of the intramitochondrial concentration of acetyl-CoA, a potent activator of PDH kinase, thereby keeping PDH in a more active state (Fig. 1a). Interestingly, and apparently paradoxically, LC also decreased the fatty acid oxidation rate (Broderick et al., 1992). This latter counterintuitive pharmacological action of LC seems to result from the fact that the effect of the lowered mitochondrial matrix acetyl-CoA overcomes the mass-action effect of increased LC concentration on CPT 1 activity, resulting in an increased flux through the electron transport chain (and ATP formation) associated with the higher rate of pyruvate oxidation (Saddik et al., 1993). It is well established that an increase in the rate of glucose oxidation relative to that of fatty acid oxidation improves the efficiency of cardiac function (Broderick et al., 1992). However, it has to be appreciated that the concentration dependence of the balance between the mass-action effect of raised intracellular carnitine concentrations and the effects on the acetyl-CoA:acetyl-L-carnitine equilibrium may be biphasic, and that at the lower concentrations achievable *in vivo* the mass-action effect on CPT 1 activity due to more moderately raised intracellular carnitine may predominate (see Ramsay & Zammit, 2004, and below).