7

Metabolic Modulators to Treat Cardiac Arrhythmias Induced by Ischemia and Reperfusion

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1. Introduction

Cardiac arrhythmias are one of the important problems in coronary ischemia/reperfusion (I/R) therapy and constitute a major risk for sudden cardiac death after coronary artery occlusion (Pourkhalili et al., 2009). Arrhythmias occur in up to 25% of patients treated with digitalis, 50% of anesthetized patients, and over 80% of patients with acute myocardial infarction (AMI) (Hume & Grant, 2007). Although reperfusion is the only way to restore blood flow of coronary arteries and prevent the myocardium from suffering from necrosis, it will lead to the occurrence of life-threatening arrhythmias which containing premature ventricular beats (PVBs), ventricular tachycardia (VT) and ventricular fibrillation (VF) (Wei & Yang, 2006). There are few safe and effective antiarrhythmic drugs for use in patients with ischemic heart diseases (IHD). Class I antiarrhythmic agents such as quinidine, flecainide, propafenone, and procainamide have the potential to cause proarrhythmia and hemodynamic collapse in the setting of IHD and should be used with caution. The use of beta-adrenergic receptor blockers and calcium channel blockers such as diltiazem and verapamil may be limited by side effects such as heart rate slowing and blood pressure drop (Dhalla et al., 2009). Therapeutic strategies currently used for primary prevention of VF, VT, or cardiac arrest remain controversial as few trials have shown a survival benefit. In addition, sudden cardiac death caused by I/R-induced arrhythmias is a warning to the development of new antiarrhythmic agents (Pourkhalili et al., 2009). Pharmacological protection of the heart from I/R-induced damage has been investigated by academic and industrial scientists for a considerable period of time. A central aim of research directed towards the science and pharmacology of I/R injury is the discovery of drugs that can be used in human to prevent ischemic cardiac injury and its sequelae (Black, 2000).

This chapter reviews and describes the pharmacology of some important "metabolic agents" that suppress arrhythmias by metabolism modulating in cardiac cells.

2. Energy metabolism in the aerobic heart

The high energy demand of the heart is met by utilizing a variety of carbon substrates, including free fatty acids (FFAs), carbohydrates, amino acids and ketone bodies. FFAs and

carbohydrates are the major substrates from which heart derives most of its energy (Sambandam & Lopaschuk, 2003; Calvani et al., 2000). Under normal aerobic conditions, 50–70% of the total energy is obtained from fatty acids, while the majority of the rest is obtained from carbohydrates (mainly glucose and lactate) (Sambandam & Lopaschuk, 2003). The carbon substrates are all converted to acetyl coenzyme A (acetyl-CoA) and enter the citric acid (Krebs) cycle whereby they produce the high-energy phosphate molecule adenosine triphosphate (ATP) which powers both contractile and noncontractile functions (McBride & White, 2003). The citric acid cycle also generates the electron accepting molecule nicotinamide adenine dinucleotide (NADH), which produces additional ATP molecules by interacting with the electron transport chain inside the mitochondria. These 3 macronutrients possess different metabolic pathways to generate acetyl-CoA molecules. Glycogen is converted to glucose, which is then converted to pyruvate in the cytoplasm. Pyruvate enters the mitochondria and is converted to acetyl-CoA by pyruvate dehydrogenase (PDH). Conversely, fatty acids are converted to fatty acyl-CoA and then undergo several metabolic steps before being converted to acetyl-CoA by the β-oxidation pathway. The principal difference between the 2 pathways of energy production is the amount of oxygen required to produce a given amount of ATP. With fatty acid oxidation, 32 grams of oxygen will yield 5.5 ATP molecules while glucose oxidation produces 6.3 molecules of ATP (McBride & White, 2003). The rate of fatty acid oxidation is mainly regulated by the concentration of free fatty acids in the plasma, the activity of carnitine palmitoyl transferase-I (CPT-I), and the activity of a series of enzymes that catalyze the multiple steps of fatty acid β-oxidation. Fatty acid oxidation strongly inhibits glucose and lactate oxidation at the level of PDH (Sabbah & Stanley, 2002).

3. Myocardial ischemia and reperfusion injury

Myocardial ischemia is one of the major causes of death in nowadays cardiac diseases (Wei & Yang, 2006). Among the heart diseases, I/R-induced arrhythmias contribute to episodes of sudden death (Gandhi et al., 2009). Reperfusion of myocardium subjected to a transient ischemia rapidly induces ventricular arrhythmias including PVBs, VT and VF in both animals and human (Lu et al., 1999).

3.1 Myocardial function and energy production during ischemia

Myocardial ischemia is a condition that exists when there is a reduced coronary blood flow, and results in a decrease in the supply of oxygen and nutrients to the heart (Suleiman et al., 2001). Due to restricted oxygen supply to the myocardium during ischemic period, both fatty acid and carbohydrate oxidation decreases and ATP production is impaired. Glycolysis, a minor source of ATP in the aerobic heart, becomes a more significant source of energy during ischemia. In the severely ischemic myocardium, production of H^+ from hydrolysis of glycolytically derived ATP is the major contributor to acidosis (Sambandam & Lopaschuk, 2003; Suleiman et al., 2001; Calvani et al., 2000). In particular, lactic acid accumulates, leading to an increase in intracellular Na^+ and Ca^{2+} (Suleiman et al., 2001). The accumulation of fatty acids and their intermediates during myocardial ischemia as well as metabolic and ionic changes provoke a reduction of myocardial function and also have been shown to be deleterious to the recovery of myocardial function of the reperfused heart (Ford, 2002).

3.2 Myocardial function and energy production during reperfusion

Functional recovery upon reperfusion is largely dependent upon the duration of the ischemic period; the longer the period, the more likely the heart is to undergo irreversible damage. Consequences of reperfusion injury include cardiac arrhythmias, myocardial stunning and loss of intracellular proteins (Suleiman et al., 2001). Numerous mechanisms for the increase in tissue injury after reperfusion have been proposed including oxidative stress (Gandhi et al., 2009), the generation of oxygen-derived free radicals (Wei & Yang, 2006), calcium overload (Wei & Yang, 2006; Lu et al., 1999), and dysfunction of myocardial energy metabolism (Wei & Yang, 2006).

4. Metabolic pharmacology

As mentioned previously, the myocardium preferentially uses fatty acids for an energy source because the chemical bonds of fatty acid molecules have higher energy content and are capable of producing more ATP molecules per molecule of fatty acid consumed. Since the inhibition of β-oxidation could permit the heart to produce ATP at lower oxygen tensions, it is plausible that an inhibitor of β-oxidation could prevent damage to the myocardium when subjected to ischemia (McBride & White, 2003). The principal goal of the metabolic modulator approach is to decrease the rate of fatty acid oxidation by the heart and increase the oxidation of pyruvate derived from glucose, glycogen, and lactate (McCormack et al., 1998). Switching the source of acetyl CoA from fatty acids toward pyruvate results in: greater ATP yield and amelioration of the buildup of potentially harmful fatty acid metabolites, and should also act to decrease lactate and hydrogen ion production under low flow conditions and during postischemic reperfusion (McCormack et al., 1998).

5. Pharmacology of some important metabolism modifiers

5.1 L-carnitine (L-Car)

5.1.1 Structure

Carnitine, a name derived from the Latin *caro* or *carnis* (flesh), was discovered in muscle extracts in 1905. Soon after, the chemical formula $C_7H_{15}NO_3$ was accepted, and in 1927, its structure, a trimethylbetaine of γ-amino-β-hydroxybutyric acid, was identified and published (Fig 1). In 1962, the configuration of the physiological enantiomer was determined, and in 1997 confirmed as L(-) or R-(-)-3-hydroxy-4-N,N,N-trimethylaminobutyrate (Sweetman, 2002; Kerner and Hoppel, 1998; Rebouche and Seim, 1998).

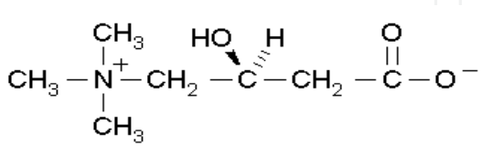

Fig. 1. Chemical structure of carnitine.

5.1.2 Pharmacokinetics

Oral doses of L-Car are absorbed slowly and incompletely from the small intestine via a stereoselective active transport system located in the intestinal mucosa of the duodenum

and ileum (Sweetman, 2002). L-Car transport does not appear to occur below the ileum in the large intestine. The transport system can concentrate L-Car, resulting in a 10 to 100 fold gradient between the extracellular and intracellular compartments. Additionally, a passive diffusion of L-Car has also been demonstrated in the intestine. Peak plasma levels of free and total carnitine occurs 3-5 hours after oral administration. The normal total plasma carnitine concentrations for healthy men and women are 59 μmol/L and 51 μmol/L, respectively (Bach et al., 1983). It does not appear to bind to plasma proteins (Rebouche, 2004; Sweetman, 2002). The plasma half-life of L-Car has been estimated to range from 2-15 h in humans. Although carnitine is largely eliminated via renal excretion, it is highly conserved by the kidney. L-Car is freely filtered at the renal glomerulus and greater than 90 percent of the filtered load is reabsorbed in the proximal kidney tubules and returned to the circulation when plasma carnitine levels are normal or low. L-Car given orally may undergo degradation in the gastrointestinal tract, leading to the formation of metabolites such as trimethylamine-*N*-oxide and γ-butyrobetaine (Sweetman, 2002).

5.1.3 Pharmacodynamics

L-Car facilitates oxidation of long-chain fatty acids (LCFAs) and is involved in trapping acyl residues from peroxisomes and mitochondria. It participates in metabolism of branched chain amino acids (Lango et al., 2001). Supplementation of the myocardium with L-Car results in an increased tissue carnitine content which restores carnitine losses and lessens the severity of ischemic injury. It also improves the recovery of heart functions during reperfusion. The beneficial effects of L-Car on heart function recovery from ischemia cannot be justified by this drug stimulating fatty acid oxidation only. Fatty acids, high in plasma during reperfusion, may provide 90 % of ATP production in the absence of L-Car treatment, whereas in its presence a marked increase in glucose oxidation is observed, without changes in total ATP production. Thus, these results suggest that the drug tends to restore the balance between fatty acid and glucose oxidation. L-Car is thought to increase glucose oxidation by relieving PDH inhibition caused by the elevated intramitochondrial acetyl-CoA/CoA ratio. This effect also results in an increased synthesis of malonyl-CoA, the physiological inhibitor of CPT-1, the first committed enzyme in overall fatty acid oxidation. Increased glucose oxidation is beneficial for cardiac cells because of a lower conversion of pyruvate into lactate, a metabolic step contributing to acidification of the intracellular compartment. Finally, L-Car have been proposed to mitigate the noxious effects of oxygen free radicals in the reperfused hearts and to render cardiac cells more resistant to I/R damage by stabilizing cellular membranes (Lango et al., 2001, Calvani et al., 2000).

5.1.4 Uses of L-Car in cardiovascular health and diseases

A decreased carnitine concentration in the heart was observed in patients who died of myocardial infarction (MI). In patients with AMI, a four fold increase was observed in free carnitine elimination and almost a two-fold increase in the elimination of short chain carnitine esters by kidney (Lango et al., 2001). There is some evidence that L-Car supplementation may exert a cardioprotective role. Benefit in patients with cardiomyopathies,reduction of infarct size and prevention of arrhythmias in patients with MI,increased exercise tolerance in patients with angina,and protection from the cardiotoxicity of the anthracycline antineoplastics have all been described in patients given

L-Car supplementation (Lango et al., 2001). Arsenian et al. demonstrated a decrease in mortality and incidence of circulatory failure in a group of patients with AMI, who were administered 3 g of L-Car along with solution of glucose, insulin, potassium and magnesium (Arsenian et al., 1996). L-Car supplementation in patients with congestive heart failure (CHF) for 12 weeks significantly improved the exercise tolerance of patients with effort angina. Studies involving about 2500 patients with coronary artery disease (CAD) treated with L-Car for a year also showed a reduced incidence of angina, a decreased need of cardiac drugs and a greater effort tolerance (Naguib, 2005). Placebo-controlled studies performed in patients with stable chronic effort angina suggest that L-Car given acutely (40 mg/kg, iv) or chronically (1–3 g daily for a month) improves exercise capacity and the electrocardiographic manifestations of ischemia (Ferrari et al., 2004). L-Car does not have hemodynamic effects in healthy volunteers or patients with CAD. However, an improvement of individual maximal aerobic power is demonstrated in healthy subjects and athletes after chronic treatment with L-Car (4 g daily over a period of 2 weeks) (Ferrari et al., 2004). In a randomized, double-blind, placebo controlled, multicenter study called the Levocarnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial was performed to evaluate the effects of L-Car administration on long-term left ventricular dilatation in patients with AMI. Placebo or levocarnitine (9 g iv daily for the first 5 days and then 6 g orally daily) was administered for 12 months. The primary end points of the trial were left ventricular volumes and ejection fraction, at 12 months after the emergent event, assessed by two-dimensional echocardiography. Treatment with the active compound resulted in a significant reduction of left ventricular dilatation. The percentages of both end-diastolic and end-systolic volumes were reduced significantly in the L-Car-treated group. No modification of left ventricular ejection fraction was observed. The incidences of death, congestive heart failure, and/or ischemic events were less in the L-Car-treated groups (Ferrari et al., 2004). Administration of L-Car, combined with other treatments, also proved effective in the treatment of childhood cardiomyopathy (Szewczyk and Wojtczac, 2002). Oral L-Car (3–4 g daily) normalizes plasma total cholesterol or triglyceride levels (or both) and increases high-density lipoprotein (HDL)–cholesterol in patients with type II and type IV hyperlipoproteinemia over a 2-month period (Ferrari et al., 2004). Oral L-Car (4 g daily for 21 days) improves the maximal walking distance of patients with intermittent claudication caused by peripheral arterial disease (Ferrari et al., 2004). Decreased level of free and total carnitine in diabetes, with a simultaneous increase in concentrations of long-chained acyl-CoA and long-chain carnitine esters has been shown. Some correlation has been also demonstrated between the left ventricular contraction index and long-chain acyl-carnitine concentration in the myocardium during reperfusion in patients after mitral valve replacement. These data suggest, in line with the results of experimental studies that carnitine and its derivatives protect human ischemic heart against oxidative stress not only by modifying carnitine acyl-transferase activity and metabolic effect, but by other mechanisms as well (Lango et al., 2001).

5.1.5 Experimental and clinical findings on beneficial effects of L-Car against cardiac arrhythmias

A prolonged L-Car therapy in patients with angina pectoris was associated with a considerable decrease in the frequency of ventricular arrhythmias (Lango et al., 2001).

Rizzon et al. noticed a statistically significant decrease of the frequency of ventricular arrhythmia in a group of patients with AMI who were administered 100 mg of L-Car/kg. Although the studied groups of patients were small, L-Car administration to patients with ischemic heart disease appears to be a promising therapy of ischemia-induced arrhythmia as potentially addressed to restoring of membrane rest-potential (Rizzon et al., 1989). Cardiac electrophysiology after L-Car administration (30 mg/kg over 3 min) did not show any changes either in the conductivity time or in refraction period. The cycle duration in the sinus node was shortened by 5%, while the arterial blood pressure remained unchanged (Lango et al., 2001). Results of some experimental studies showed protective effects of L-Car against I/R- induced injuries and cardiac arrhythmias. In a study, we tested the effects of 0.5, 2.5 and 5 mM/L of L-Car on cardiac arrhythmias in the ischemic reperfused isolated rat heart in Langendorff setup. At the ischemic phase, number, duration and incidence of VT were decreased by doses of 2.5 and 5 mM/L L-Car ($p<0.05$). In addition, L-Car by doses of 2.5 and 5 mM/L reduced the number of VT ($p<0.05$) at the reperfusion phase. The total number of ventricular ectopic beats (VEBs: Single+Salvos+VT) also were reduced in treated groups by 0.5-5 mM/L of L-Car versus the control group ($p<0.05$). However, duration of reversible VF (Rev VF) was decreased only by 5 mM/L L-Car (Najafi et al., 2005). In another study, the effects of pre-ischemic administration of 0.5, 2.5 and 5 mM/L of L-Car were investigated in isolated rat hearts. Interestingly, the results showed that short time pre-ischemic administration of L-Car (10 min before induction of 30 min regional ischemia) had concentration dependent arrhythmogenic effects on both ischemia and reperfusion-induced arrhythmias (Najafi et al., 2008). The authors hypothesized that pre-ischemic using of L-Car for an inadequate time can be harmful for the heart because of incomplete metabolism of fatty acids and more accumulation of their intermediates (Najafi et al., 2008). They concluded that L-Car produced a protective effect against reperfusion arrhythmias only when it is perfused for the whole period of the experiment. This protective action was reversed by concomitant using of etomoxir (palmitoylcarnitinetransferase-1 inhibitor), suggesting that the efficacy of L-Car is due to its mitochondrial action, but is probably not solely attribute to an increase in fatty acid oxidation (Najafi et al., 2008). Cui et al. investigated the effects of L-Car on the incidence of reperfusion-induced VF during 30 min global ischemia followed by 120 min reperfusion. Their results showed that different concentrations of L-Car failed to reduce the incidence of VF (Cui et al., 2003). Suzuki et al. reported intravenous pre-treatment of the ischemic dog heart by L-Car (100 mg/kg) reduced the grade of ventricular arrhythmias. They suggested that the administration of L-Car might be beneficial to prevent serious arrhythmias in ischemic heart disease, presumably by restoring the impaired free fatty acid oxidation (Suzuki et al., 1981). Recently, we reported that pre-ischemic administration of L-Car could precondition the heart as evidenced by its ability to lower the infarct size markedly ($p<0.001$) and improved postischemic ventricular functional recovery. L-Car reduced left ventricular end diastolic pressure (LVEDP) elevation at the reperfusion phase. Heart rate (HR) and coronary flow rate (CFR) did not show significant changes in treated groups as compared to the control. Among the three different concentrations, L-Car (2.5 mM) was found to be optimal for preconditioning purpose (Najafi et al., 2010a). It was also found in this study that pre-ischemic administration of L-Car in ischemic/reperfused hearts preconditions the hearts by reduction of left ventricular lactate content (Najafi et al., 2010a).

5.1.6 Uses of L-Car in other human diseases

As well as cardiovascular health and diseases, L-Car is administered to treat many other human diseases such as primary carnitine deficiency syndromes or secondary carnitine deficiency/insufficiency states (Ferrari et al., 2004). Primary carnitine deficiency results from inborn defects in specific proteins or carnitine transferases. Therapy with carnitine in primary deficiency states is considered to have a rational basis. Secondary causes of carnitine deficiency include inherited metabolic defects in fatty acid β-oxidation, mitochondrial myopathy, prematurity, carnitine deficiency in the diet, dialysis therapy, etc. The value of carnitine for these conditions is controversial (Sweetman, 2002; Szewczyk et al. 2002; Kerner & Hoppel, 1998).

5.1.6.1 Infant nutrition

Preterm infants require carnitine for life-sustaining metabolic processes. When infants were supplemented with 2.2 mg of L-Car/100 ml in the bovine milk formula, their plasma carnitine and acylcarnitine levels were similar to those observed in the breast-fed group (Naguib, 2005).

5.1.6.2 Immune system and AIDS

The effect of long-term L-Car supplementation on CD4 and CD8 absolute counts, rate, and apoptosis was studied in HIV-infected subjects, who were treated with daily infusions of L-Car (6 g) for 4 months. CD4 and CD8 are specific types of lymphocytes; their absolute counts are decreased in patients with AIDS, resulting in compromised immune function. At the end of the study, L-Car was found to substantially increase the rate and absolute counts of CD4 and, to a lesser degree, of CD8 lymphocytes (Ilias et al., 2004; De Simone & Tzantzoglou, 1993). In this case, the antioxidant activity of L-Car may be responsible for the observed changes in apoptosis because increases in free radical oxidative stress can accelerate this process (Moretti et al., 1998).

5.1.6.3 Brain health

L-Car has been considered of potential use in senile dementia of Alzheimer's because of its ability to enhance energy production and to restore aged cell membranes (Naguib, 2005). In brain tissue, the carnitine shuttle mediates translocation of the acetyl moiety from mitochondria into the cytosol and thus probably contributes to the synthesis of acetylcholine (Szewczyk & Wojtczac, 2002). Positive clinical effects of L-Car administration were also observed in brain ischemia (Lango et al., 2001) and hypoglycemia induced by insulin overdose (Hino K. et al. 2005). In addition, L-Car protects motor neuron cells from ischemic spinal cord injury (Akgun et al., 2004).

5.1.6.4 Physical performance

In addition to enhancing β-oxidation of LCFAs in skeletal muscle, L-Car may also benefit exercise performance by decreasing muscle glycogen depletion, shifting energy sources to the highly efficient aerobic glucose metabolic pathways, replacing decreased L-Car that has shifted to acylcarnitine during exercise, lowering content of toxic acyl groups and increasing of muscle blood flow secondary to vasodilation (Lango et al., 2001; Brass, 2000). Beneficial effect of L-Car in healthy subjects in an attempt to improve athletic performance is

controversial (Sweetman, 2002). However, it is used as legal dope in sports (Szewczyk & Wojtczac, 2002).

5.1.6.5 Other uses

L-Car treatment significantly improved symptoms in chronic fatigue syndrome (CFS) patients without side effects (Naguib, 2005). There is some suggestion that L-Car supplementation may be benefit in alleviating chemotherapy-induced fatigue (Sweetman, 2002). L-Car supplementation has been approved by the FDA not only for the treatment but also for the prevention of carnitine depletion in dialysis patients. Regular L-Car supplementation in hemodialysis patients can improve their lipid metabolism, protein nutrition, antioxidant status and anemia requiring large doses of erythropoietin. It also may reduce the incidence of intradialytic muscle cramps, hypotension, asthenia, muscle weakness and cardiomyopathy (Bellinghieri et al., 2003). Chronic hemodialysis produces cardiac damage caused by anemia, hypertension and overhydration. L-Car in a long-term supplementation has been shown to be beneficial to the function of erythrocytes in hemodialysed patients. Additionally, supplementing improves measures of vitality and overall self-perceptions of general health and quality of life in hemodialysed patients and the typical dialysis-associated muscle symptoms (Lango et al., 2001; Kazmi et al., 2005). Sodium valproate is a commonly used as an antiepileptic agent that has been reported to inhibit the biosynthesis of carnitine (Farkas et al., 1996) and reduce carnitine plasma concentrations via its ability to bind L-Car. Researchers have suggested that the incidence of idiosyncratic fatal hepatotoxicity caused by sodium valproate results from impaired β-oxidation of fatty acids in the liver. Valproate has also been shown to impair the tissue uptake of carnitine. Ataxia, hyperammonemia, lethargy, nausea and stupor characterize both carnitine deficiency and sodium valproate hepatic toxicity. In 1996, the pediatric neurology advisory committee recommended supplemental L-Car for younger patients who are taking sodium valproate, carbamazepine, phenytoin or phenobarbital. In addition, L-Car (i.v.) is considered as a treatment of choice to prevent potentially fatal liver dysfunction associated with valproate overdose (LoVecchio et al., 2005; Lango et al., 2001). L-Car alleviates the cardiotoxic effect of adriamycin. Adriamycin is highly toxic to nonmalignant tissues due to the generation of reactive oxygen species (ROS) (Szewczyk & Wojtczac, 2002). In diabetes, L-Car supplementation causes a decrease in triglyceride synthesis, a drop in the cellular free fatty acids (FFAs) uptake, and the removal from organism of excessive long-chain carnitine esters, as well as increase in glycolysis, oxidation of pyruvate, and improvement in neuronal transmission (Mingrone, 2004; Lango et al., 2001). Moreover, protective effects of L-Car against I/R-induced apoptosis were shown by immunohistochemical detection method in rat cardiomyocytes (Najafi et al., 2007).

5.1.7 Adverse effects of L-Car

Gastrointestinal disturbances such as nausea, vomiting, diarrhea, abdominal cramps (Sweetman, 2002), heart-burn, dyspepsia, seizures, blurred vision and headache (Lango et al., 2001) have been reported following the administration of L-Car. Unpleasant body odor that is similar to that of rotten fish has also been noticed in some patients (fish odour syndrome), possibly due to the formation of the metabolite trimethylamine (Lango et al., 2001). There are no reports to date of serious side effects caused by L-Car (Sweetman, 2002; Lango et al., 2001). Patients with severe renal impairment should not be given high orally

doses of L-Car for long periods, because of the accumulation of the metabolites trimethylamine and trimethylamine-N-oxide. Diabetic patients administered carnitine while receiving insulin or hypoglycemic drugs should be monitored for hypoglycemia (Sweetman, 2002).

5.2 Acetyl-L-carnitine (ALC)

ALC belongs neither to the vitamin nor the amino acid category. It is chemically similar to carnitine, but is more efficient. While it is synthesized by the liver from lysine and methionine, adequate amounts of vitamins C, B_3, and B_6, plus iron, lysine, and methionine are needed in the diet for this to occur (David, 2000). It is also synthesized in the human brain and kidney by the enzyme ALC transferase (Furlong, 1996). Its main body stores are skeletal and cardiac muscles. It is found along with free plasma carnitine and other acyl-esters of varying chain length (Goa & Brogden, 1987).

5.2.1 Structure of ALC

ALC is an ester of the trimethylated amino acid, L-carnitine (David, 2000) with following structure (molecular formula: C9H17NO4•HCl) (Budavari, 2001)

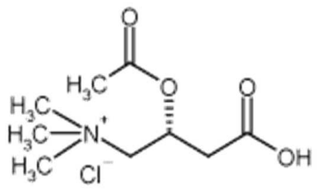

Fig. 2. Chemical structure of ALC. HCl.

5.2.2 Pharmacokinetics of ALC

ALC is administered orally or intravenously and is then absorbed in the jejunum by simple diffusion (Marcus & Coulston, 1996; Parnetti et al., 1992). Bioavailability of ALC is thought to be higher than L-Car. The results of in vitro experiments suggest that ALC is partially hydrolyzed upon intestinal absorption (Gross et al., 1986). Both IV and oral administration result in a corresponding increase in cerebrospinal fluid (CSF) concentrations of ALC, indicating it readily crosses the blood-brain barrier. ALC undergoes little metabolism and is subsequently excreted in the urine via renal tubular reabsorption (Marcus & Coulston, 1996; Parnetti et al., 1992). Though ALC is an ester of the L-Car, nutritional carnitine deficiencies have not been identified in healthy people without metabolic disorders, suggesting that most people can synthesize enough L-Car (Rebouche et al., 2006). Even strict vegetarians show no signs of carnitine deficiency, despite the fact that most dietary carnitine is derived from animal sources (Lombard et al., 1989).

5.2.3 Mechanism of action of ALC

ALC is an ester of carnitine and plays a fundamental role in normal mitochondrial function, being a transport molecule for free fatty acids and an important acetyl group donor in high energy metabolism and free fatty acid β-oxidation (Malaguarnera et al., 2008; Bremer, 1990;

Colucci & Gandour, 1988). Results of some studies show that ALC stabilizes the inner mitochondrial membrane and reverses the decline in activity of a number of mitochondrial translocases and of cytochrome c oxidase thus maintaining energy levels of the cells and stabilizing mitochondrial translocase activity (Qureshi et al., 1998; Paradies et al., 1994). ALC is known to have antioxidant effects by increasing intracellular coenzyme Q10 levels, which accounts for the increase in glutathione reductase activity and high levels of reduced glutathione. The augmentation in antioxidant defense system by ALC finally leads to quenching of free radicals and reduction in reactive oxygen species and lipid peroxidation (Barhwala et al., 2007). ALC could inhibit oxidant-induced DNA single-strand breaks in human peripheral blood lymphocytes (Liu et al., 2004).

5.2.4 Uses of ALC in cardiovascular health and diseases

Like L-Car, ALC enhances fatty acid transport for ATP production in the mitochondria of both skeletal and heart muscles, thereby affording protection from free radical damage (Furlong, 1996; Di Giacomo et al., 1993). Additionally, it may improve cardiolipin levels in the aged heart, a substance which maintains crucial membrane factors in cardiac mitochondria and thus ensures efficient phosphate transport for energy. In a rat mitochondrial model, it was shown that ALC administered to aged animals returned cardiolipin levels to that of young ones (Paradies et al., 1999; Furlong, 1996). Cerebral and peripheral circulation are apparently affected differently by administration of ALC. Ten patients with recent cerebral vascular accidents were given ALC intravenously which resulted in acute enhancement of cerebral blood flow to areas of ischemia via sensitive tomography assessments. In evaluation of patients with peripheral arterial occlusive disease, two studies show that the effect of carnitine esters on improved walking distance was due to metabolic vs. hemodynamic changes and that Propionyl L-carnitine (PLC) was clearly superior to L-Car in this effect. These studies demonstrate the ability of carnitine esters to positively influence tissue energetics which may prove beneficial in a chronic administration model (Paradies et al., 1999; Furlong, 1996).

5.2.5 Findings on beneficial effects of ALC against cardiac arrhythmias

In an experimental study, we focused on the pharmacological effects of ALC on I/R-induced cardiac arrhythmias and infarct size in isolated rat heart when it was used during 30 min regional ischemia followed by 30 min reperfusion. The results of this study showed that ALC produces antiarrhythmic effects against regional I/R-induced arrhythmias such as VEBs, VT and VF. Perfusion of ALC produced significant reduction in the number of VEBs, number and duration of ischemic VT, and duration and incidence of reversible VF by 0.375, 0.75 and 1.5 mM ($p<0.05$ for all) and total VF in ischemia time with mentioned concentrations ($p<0.05$). At the reperfusion phase, number of VT and VEBs were decreased by all concentrations of ALC, but they weren't statistically significant. In addition, VT duration and incidence of total VF were significantly lowered by 0.375, 1.5 and 3 mM of ALC ($p<0.05$). Our findings also demonstrated that ALC caused marked and potent protective activity against I/R injuries as reduction of infarct size in this model of study (Najafi et al., 2010b). In another study, Cui et al. investigated the effects of ALC on incidence of reperfusion-induced VF and infarct size after 30 min global ischemia in isolated rat heart.

Their results showed that perfusion of 0.5 and 5 mM of ALC for 10 min before the induction of global ischemia (not regional ischemia) failed to reduce the incidence of VF. Their results also demonstrated significant reduction in infarct size only by the concentration of 5 mM ALC (Cui et al., 2003). Our results are consistent with the results of Cui et al. in the case of infarct size reduction quality only. However, in contrast to their results, all the used concentrations of ALC in our model significantly reduced infarct size even the lowest concentration (0.375 mM). In addition, our results showed that ALC not only lowered VF incidence in reperfusion time, but also decreased the number and duration of VT, number of VEBs, duration and incidence of total VF in both ischemia and reperfusion time, and incidence of reversible VF in both ischemia and reperfusion phase, when it was used throughout I/R. We suggested that the existence of some methodological differences between the above studies (i.e. type of ischemia and duration of ALC perfusion into the heart) caused different results by low concentrations of ALC. However, other studies, such as the work done by Rosenthal et al (2005), have also demonstrated the same differences that ALC does not promote clinically measurable neuroprotection if administration is significantly delayed following restoration of spontaneous circulation. Thus, in order to maximize the chances of effective neuroprotection, they postulate that for optimal neuroprotective benefit, ALC should be administered as shortly as possible following resuscitation, most definitely within 30 min of reperfusion (Rosenthal et al., 2005). It seems that the potential cardioprotective mechanisms of action of ALC are very similar to those of L-Car (the parent compound of ALC).

5.2.6 Uses of ALC in other diseases

5.2.6.1 Cerebral metabolism

ALC can cross the blood–brain barrier through the γ-amino butyric acid (GABA) uptake system (Burlina et al., 1989). In studies on short-term treatment with ALC in aged rats, the molecule was found to improve some behavioural and biochemical parameters and normalize the age-related impairment in membrane phospholipids metabolism (Aureli et al., 1990), and shown to reduce the sphingomyelin and cholesterol accumulation in the aged rat brain (Aureli et al., 1994a). ALC treatment was also reported to enhance brain energy metabolism and to decrease lactate levels following transient cerebral ischemia (Aureli et al 1994b). In addition, ALC is involved in acetyl group trafficking among different intracellular compartments, and to be a precursor of different lipogenic acetyl CoA pools in rat brain (Ricciolini et al., 1997). Studies on the effects of ALC on cerebral metabolism reported a significant increase in brain phosphocreatine levels, which was associated with a reduction in tissue content of lactic acid and inorganic phosphate (Aureli et al., 1990). ALC administration immediately after 20 min of severe cerebral ischemia has also been demonstrated to induce a faster recovery of cerebral ATP and a strong decrease in tissue lactic acid levels during early post-ischemic reperfusion in the rat (Aureli et al., 1994b). The reduction in cerebral glucose oxidative metabolism associated with the increase in newly synthesized glycogen, suggests that treatment with ALC may modulate cerebral substrate oxidation. Researches showed that the relative flux through pyruvate carboxylase and pyruvate dehydrogenase pathways was not affected by ALC. These findings appear to suggest an overall metabolic effect of ALC on both neurons and glial cells (Tommaso et al., 1998).

5.2.6.2 Aging processes and Alzheimer's dementia

ALC was reported to ameliorate the spatial memory performance of rats exposed to neonatal anoxia (Dell et al., 1997) and improvement of spatial memory. In aged rats it could be achieved only in intermediate but not in good or poor classes of spatial learning performance (Taglialatela et al., 1996). Data shows that improvement could be achieved for novel but not for familiar environments (Caprioli et al., 1995). In the Alzheimer's disease (AD), brain is under extensive oxidative stress and evidenced by significant protein oxidation, lipid peroxidation, and DNA oxidation and is characterized by deposition of amyloid β (Aβ) peptide (Butterfield et al., 2003). Aβ induces lipid peroxidation in ways that are inhibited by free radical antioxidants (Butterfield & Lauderback, 2002). ALC improves neuronal energetic and repair mechanism, decreases the level of lipid peroxidation in the aged rat brain (Kaur et al., 2001), is involved in mitochondrial metabolism (Hagen et al.,1998), and may have antioxidant properties (Poon HF at al., 2006; Kaur J et al., 2001). However, the precise mechanism of action by which ALC may be neuroprotective in aging and neurodegeneration, is not known.

5.2.6.3 Chemotherapy-evoked neuropathic pain

Neurotoxicity is the dose-limiting side effect for chemotherapeutics in the taxane and vinca alkaloid classes, and in many cases the nerve damage is accompanied by a chronic painful peripheral neuropathy (Cata et al., 2006; Dougherty et al., 2004). Impaired mitochondrial function suggests that there might be an energy deficit that compromises the neuron's ability to operate ion transporters. This would lead to membrane depolarization and the generation of spontaneous action potentials. Recent evidence suggests that treatment with ALC, an agent known to ameliorate mitochondrial dysfunction (Virmani et al., 2005; Zanelli et al., 2005), prevents and reverses chemotherapy-evoked pain in rats (Flatters & Bennett GJ, 2006; Ghirardi et al., 2005a, b).

5.2.6.4 Diabetic neuropathy

Studies show that prevention and correction of the metabolic, functional, and structural abnormalities characterizing the neuropathy in the diabetic rat after ALC administration. In addition, the same treatment showed a promoting effect on suppressed nerve fiber regeneration in diabetic rats. In addition, ALC treatment appears to have a sustained beneficial effect on vasoactive prostanoid analogues, possibly counteracting the deleterious effects of decreased endoneurial blood flow in diabetic nerve (Sima et al., 1996).

5.2.6.5 HIV infection

HIV-infected patients on nucleoside analogue therapy commonly experience peripheral neuropathy as an adverse effect of the medications. Patients taking stavudine, zalcitabine or didanosine may have to discontinue therapy as a result. Some studies have suggested ALC as well as recombinant human nerve growth factor may be beneficial in managing this condition (Moyle & Sadler, 1998).

5.2.6.6 Fatigue

Patients with chronic fatigue syndrome show reduced exercise tolerance, and post exercise fatigue induced by minimal physical activity, suggesting decreased muscle function, is considered as one of the causes of this syndrome (Jones et al., 2005). Abnormal mitochondria

have been observed in muscle of some elderly patients with fatigue, suggesting some underlying abnormalities in muscle mitochondrial energy production (Behan et al., 1991). The ALC treatment reduced significantly both physical and mental fatigue and improved physical activity and cognitive status (Malaguarnera et al., 2007). The improvement of energetic metabolism in myocardial tissue and in muscular-skeletal tissue is probably the factor that reduces the presence and the severity of physical fatigue in treated subjects. Also researches show that ALC is better tolerated and more effective than amantadine for the treatment of multiple sclerosis-related fatigue (Tomassini et al., 2004).

5.2.6.7 Immune enhancement

ALC has been found to be a powerful immune enhancer. This is due to its ability to promote the health of the nervous system, which in turn governs the activity of the immune system (Scarpini et al., 1997).

5.2.6.8 Effect on cataract

Cataract accounts for most cases of treatable blindness worldwide. Hence, it is important to identify factors that contribute to cataractogenesis with a view to developing novel therapeutic and preventive strategies. It has previously shown that ALC exhibits anticataractogenic activity in an in vitro and in vivo model of selenite cataractogenesis by maintaining antioxidant enzymes at near normal levels and by controlling lipid peroxidation (Geraldine et al., 2006). These observations suggest a novel use for ALC as a possible cataract-preventing drug (Elanchezhian et al., 2009).

5.2.6.9 Male infertility

L-Car and ALC are highly concentrated in the epididymis and are important for sperm metabolism and maturation. In a double-blind, cross over trial of 100 infertile patients, receiving either L-Car or placebo, a significant improvement in sperm quality was observed in the L-Car group. In addition, combination therapy with both L-Car and ALC was given to 60 infertile men and similar outcomes were observed (Movassaghi & Turek, 2008).

5.2.7 Adverse effects of ALC

ALC may cause gastrointestinal disorders and a change in body odor, which can be reduced or eliminated with lower dosages. Less frequent side effects include diarrhea, abdominal pain, nausea, and vomiting (David et al., 2000). ALC may interfere with thyroid metabolism. In individuals with seizure disorders, an increase in seizure frequency and severity has also been reported. ALC also increase agitation in some Alzheimer's disease patients (Hendler & Rorvik, 2001). Overdosing can produce severe muscle weakness, though some have experienced only mild diarrhea with doses as high as 26,000 mg /day (David et al., 2000). With long-term (one year) administration, the most common adverse reactions noted have been agitation, nausea, and vomiting (Spagnoli et al., 1991).

5.3 Propionyl-L-carnitine (PLC)

PLC is a natural short-chain derivative of L-Car and it has a higher transport rate into the myocardium than L-Car (Sayd-Ahmed et al., 2000).

5.3.1 Structure of PLC

PLC is chemically similar to carnitine, but is more efficient (Ferrari et al., 2004). Chemical structure of PLC is shown in fig. 3 (molecular formula: C10H19NO4).

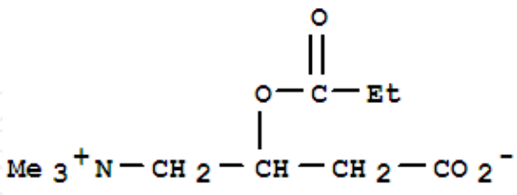

Fig. 3. Chemical structure of PLC

5.3.2 Pharmacokinetics of PLC

PLC is formed via carnitine acetyltransferase from propionyl-CoA, a product of methionine, threonine, valine, and isoleucine, as well as of odd-chain fatty acids (Ferrari et al., 2004). PLC has higher affinity for the plasma membrane transport system. It is more lipophylic and penetrates myocytes faster than L-Car (Lango et al., 2001). Pharmacokinetic studies demonstrated that, in humans, plasma concentration of PLC increases following intravenous administration and then decreases to baseline values within 6 to 24 h. This life span varies with dosage (Ferrari et al., 2004). The plasma concentrations of endogenous PLC in placebo-treated subjects averaged 1.28 nanomol/ml, over the 24 h period of observation. Intravenous PLC has a short elimination half-life (1 h), a small volume of distribution (18 l) and a clearance of about 11 l/h; the renal clearance of PLC increases as the intravenous dose of PLC hydrochloride is increased; and, based on urinary excretion data, L-Car is a major metabolite of intravenously administered PLC hydrochloride. The corresponding value for the estimate of creatinine clearance, which is assumed to be equal to GFR, was 6.08 l/h. Because PLC does not bind to plasma proteins, these data indicate extensive tubular reabsorption of PLC (about 95%). The renal handling of PLC in humans involves saturable tubular reabsorption. The results of in vitro studies have found that PLC is stable to hydrolysis in whole blood, but readily undergoes hydrolysis to L-Car on exposure to hepatic and renal homogenates. The L-Car formed from PLC was likely to have been converted to ALC, resulting in the observed increases in the plasma and urinary levels of the acylated product (Pace et al., 2000).

5.3.3 Mechanism of action of PLC

PLC is an energy source, and it stimulates the Krebs cycle as a precursor of succinyl-CoA, decreases oxidative stress in various systems, and improves cardiac dysfunction in rodent models (Vermeulen et al., 2004). It is now generally agreed that I/R injury in the heart is associated with accumulation of long chain acylesters. The increase of long chain acylesters and depletion of free L-Car in the myocardium have been suggested to damage the cardiac cell membrane and impair the electrical and contractile activities of the heart. It has been shown that PLC administration improves the recovery of mechanical function of the ischemic-reperfused hearts. PLC administration to rats with pressure-overload heart

hypertrophy and volume overload heart hypertrophy has been reported to improve cardiac function. Furthermore, PLC was found to exert beneficial effects on myocyte performance and ventricular dilatation in rats subjected to MI (Sethi et al., 1999). PLC increases plasma and cellular carnitine content, thus enhancing FFA oxidation in carnitine-deficient states, as well as increasing glucose oxidation rates. During the reperfusion of previously ischemic hearts, PLC stimulated glucose oxidation and significantly improved the functional recovery. This supported the theory that carnitine's beneficial effects on ischemic myocardium are the result of its ability to overcome the inhibition of glucose oxidation that is induced by increased levels of fatty acids (Ferrari et al., 2004). PLC enhances the propionyl group uptake by myocardial cells. This is important because propionate can be used by mitochondria as an anaplerotic substrate, thus providing energy in the absence of oxygen consumption. Note that propionate alone cannot be administered because of its toxicity. Because of the particular structure of the molecule with a long lateral tail, PLC has a specific pharmacologic action that is independent of its effect on muscle metabolism; this result in peripheral dilatation, positive inotropic effects and coronary vasodilatation with reduced oxygen extraction. It is clear that typical inotropic agents, such as digitalis, calcium, and adrenergic compounds, cause a decline in the phosphocreatinine (PCr)/Pi ratio; this suggested that they place the heart in a supply/demand imbalance. This was not the case for PLC. Thus, all of the cardiovascular actions of PLC can be attributed to its pharmacologic properties rather than to its role as a metabolic intermediate. Energy metabolism remained unchanged despite the increase in myocardial performance (Ferrari et al., 2004). It seems that PLC improved skeletal muscle metabolism in patients with idiopathic dilated cardiomyopathy by increasing pyruvate flux into the Krebs cycle and decreasing lactate production. This effect, which occurs in the absence of major hemodynamic and neuroendocrine changes, may underlie the ability of PLC to increase exercise performance in patients with CHF. It was reported that, when PLC was given to patients with severe heart failure (NYHA IV), it was able to reduce the increase in tumor necrosis factor-α (TNF-α) and, in particular, its soluble receptor that is elevated in CHF, and that is responsible for intracellular signaling of the effects of TNFα. An increased TNF was implicated in the skeletal muscle changes of patients with CHF (Ferrari et al., 2004). Similar to L-Car, PLC have also been proposed to alleviate the noxious effects of oxygen free radicals in the reperfused hearts and to delineate cardiac cells more resistant to I/R damage by stabilizing cellular membranes (Calvani et al., 2000). Endothelial cellular membranes are better protected by PLC against Fe2 and Fe3 ions induced peroxide production, the protection being possibly due to ion chelating (Lango et al., 2001). Finally, attenuating defects in the sarcolemmal membrane may be the other mechanism of PLC and thus may improve heart function in CHF due to MI (Sethia et al., 1999).

5.3.4 Uses of PLC in cardiovascular health and diseases

PLC has shown efficacy in the treatment of a number of cardiovascular disorders including ischemic heart disease, CHF and hypertrophic heart disease. PLC efficacy on cardiac performance is greater than that observed with L-Car (Calvani et al., 2000). Because of PLC's characteristics, it was hypothesized that it could provide adjuvant benefit over standard therapy by specifically improving impaired metabolism of skeletal and heart muscle in

patients with CHF (Ferrari et al., 2004). The effects of PLC in a number of models of CHF are particularly evident under conditions of high-energy demand that is induced by increases in workload. Therefore, it seems likely that PLC is able to correct some metabolic steps of the process that leads to heart failure. Besides its effect on the heart, PLC could be helpful in CHF for a specific action on peripheral heart muscle. In CHF, exertional fatigue is not simply the result of skeletal muscle under perfusion. In most patients, there is a decrease in flow responses to exercise as a result of an abnormality of arterial vasodilatation, evidenced by a failure of leg vascular resistances to decrease during exercise. The use of PLC improves the walking capacities of patients with peripheral arterial disease, suggested that PLC could specifically improve metabolism and function of skeletal muscle in patients with CHF. There are several studies on the effects of PLC in peripheral artery disease (Ferrari et al., 2004). PLC hemodynamic effect was evaluated in patients with CAD with normal LV function. When PLC was intravenously administered at 15 mg/kg, it improved the stroke volume and reduced the ejection impedance as a result of decreased systemic and pulmonary resistances and increased arterial compliance. Total external heart power improved with a proportionally smaller increase in the energy requirement; this suggested that PLC has a positive inotropic property. PLC increased the performance of the aerobic myocardium independent on changes of peripheral hemodynamics or coronary flow when administered chronically to the animals several days before the isolation of the heart (Ferrari et al., 2004). PLC used in doses of 15 mg/kg caused a slight decrease in peripheral vascular resistance in patients with stable coronary disease, but due to a simultaneous increase in stroke volume, no decrease in arterial blood pressure was observed. A similar dose administered to patients with ischemic heart disease caused in a short time (5 min) a 43% increase in lactate uptake by myocardium and increase in stroke volume by 8% (Lango et al., 2001). The protective effect of PLC in perfused rat hearts is dose-dependent and also depends on the time of administration, provided it is administered before post-ischemic reperfusion begins. From the accumulated results, it seems that positive biological effects observed after PLC are more evident than those after L-Car administration. Better penetration into myocytes and supplying a substrate for the citric acid cycle can explain this observation in short-term supplementation (Lango et al., 2001). In isolated rat hearts that were subjected to global low-flow ischemia, the group that was treated with PLC exhibited significantly greater recovery of all hemodynamic variables during reperfusion. In a similar preparation, 1 mmol PLC had no protective effect, whereas 5.5 and 11 mmol improved the recovery of cardiac output. The beneficial effect is greater than that of L-Car on a molar basis. PLC was also found to directly improve postischemic stunning. Specific experimental studies were conducted on the efficacy of this agent with respect to CHF. In particular, treatment with PLC (50 mg/kg, intra-arterially) for 4 days significantly improved the hemodynamics of pressure overloaded (by constriction of the abdominal aorta) in conscious rats. In another study, papillary muscles were isolated from rats that had been treated with 180 mg/kg PLC for 8 weeks, starting from weaning. Aortic constriction was performed at 8 weeks of age and lasted for 4 weeks. The papillary muscles of untreated animals showed increased time-to-peak tension and a reduced peak rate of tension rise and delay. PLC normalized all of these parameters. In an infarct model of CHF, chronic administration of PLC (60 mg/kg orally given for 5 months) positively influenced ventricular remodeling; it was equally as effective as the ACE inhibitor, enalapril (l mg/kg orally), in limiting the

magnitude of LV dilatation estimated by pressure-volume curves. PLC limited the alterations in ventricular chamber stiffness that was induced by infarction at low and high filling pressures. In isolated myocytes obtained from infarcted rats, PLC increased peak systolic calcium, peak shortening, and velocity of cell shortening to a greater extent than in normal cells (Ferrari et al., 2004).

5.3.5 Experimental and clinical findings on beneficial effects of PLC against cardiac arrhythmias

The antiarrhythmic effect of PLC was evaluated in the guinea-pig isolated heart; arrhythmias were induced with hypoxia followed by reoxygenation and by digitalis intoxication. PLC 1 μm, was found to be the minimal but effective antiarrhythmic concentration against reoxygenation-induced VF. The antiarrhythmic action of L-PC on reoxygenation-induced arrhythmias is not correlated with its direct electrophysiological effects studied on normoxic preparations. No antiarrhythmic effect was observed against digitalis induced arrhythmias. D-Propionyl carnitine and propionic acid did not exert antiarrhythmic effects. During hypoxia and reoxygenation, PLC consistently prevented the rise of the diastolic left ventricular pressure, and significantly reduced the release of the cardiac enzymes creatine kinase (CK) and lactic dehydrogenase (LDH) (Barbieri et al., 1991).

5.3.6 Uses of PLC in other human diseases

5.3.6.1 Cisplatin induced nephrotoxicity

It is well known that Cisplatin induced nephrotoxicity is the most important dose-limiting factor in cancer chemotherapy. Cisplatin therapy is usually associated with cardiotoxicity including electrocardiographic changes, arrhythmias, myocarditis, cardiomyopathy and congestive heart failure. Combinations of Cisplatin with other anticancer drugs as methotrexate, 5-fluorouracil, bleomycin and doxorubicin are associated with lethal cardiomyopathy. PLC has potential protective effect against Cisplatin-induced cardiac damage with no interfere with the antitumor activity of anticancer drugs. PLC mechanism of action in this case may be due to membrane stabilization by the L-Car portion of PLC with the consequent decrease in release of cardiac enzymes or due to its antioxidant activity (Al-Majed et al., 2006).

5.3.6.2 Sickle-cell anemia

Sickle-cell anemia erythrocytes are under oxidative stress which contributes to some modifications observed in these cells. PLC by antioxidant activity is able to stabilize damaged cell membranes and is also able to decrease the formation of thiobarbituric acid reactive substances. Thus it may be beneficial in maintaining the normal shape of sickle-cell anemia erythrocytes at low oxygen tension and in decreasing the peroxidative damages which accumulate during the life of red blood cells (Ronca et al., 1994).

5.3.6.3 Peripheral arterial disease

PLC stimulates energy production in ischemic muscles by increasing citric acid cycle flux and stimulating pyruvate dehydrogenase activity. Also PLC improves coagulative fibrinolytic homeostasis in vasal endothelium and positively affects blood viscosity. Improvements in maximum walking distance (MWD) correlated positively with increased mitochondrial oxidative ATP synthesis in patients with intermittent claudication. Oral PLC

therapy was associated with significant improvements in quality of life in patients with a baseline MWD < 250m (Wiseman et al., 1998). In comparison with pentoxifyllin, PLC had the better effect in the treatment of critical ischemia (Milio et al., 2009; Signorelli et al., 2001). In patient with Leriche-Fontaine stage II peripheral arterial disease of lower limbs LPC showed improvement on circulatory reserve of the ischemic limb without any effect on heart rate and arterial blood pressure. The effect of LPC on the hyperemic response to stress, mainly on halftime of hyperemia, was possibly due to a drug-induced increase of ATP utilization by the ischemic tissues (Corsi et al., 1995).

5.3.6.4 Chronic fatigue syndrome

The symptoms of chronic fatigue syndrome by treatment of PLC showed considerable improvement in 63% of the patients (Vermeulen et al. 2004).

5.3.7 Adverse effects of PLC

PLC may cause some transient and mild gastrointestinal side effects. These adverse effects include nausea, vomiting, abdominal pain, cramps and diarrhea. PLC also may cause seizures in susceptible individuals because of its close structural resemblance to L-Car. Some patients with pre-existing seizure disorders have reported an increase in the number or frequency of seizures upon using PLC. A study mentions that L-Car, a chemical component of PLC, is a peripheral antagonist of the action of thyroid hormones on the body. This means that the circulating L-Car in the blood opposes the action of the thyroid hormones at their site of action. For patients suffering from decreased thyroid function, this could aggravate their condition. PLC could cause other rare side effects such as a body odor, fishy smell of urine and stool and increased appetite. Such adverse effects are more common upon administration of doses as high as 3 grams of PLC. Decreasing the dose usually eliminates these untoward side effects (Nnama, 2010).

5.4 Ranolazine

5.4.1 Structure of ranolazine

Ranolazine is a substituted piperazine compound similar to Trimetazidine (Morin et al., 2001). It is a racemic mixture and chemically described as 1-piperazine acetamide, *N*-(2, 6-dimethyl phenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]. Its empirical formula is C24H33N3O4 with following chemical structure (Bhandari & Subramanian, 2007):

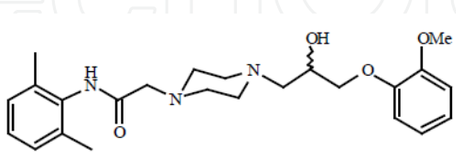

Fig. 4. Chemical structure of ranolazine.

5.4.2 Pharmacokinetics of ranolazine

Peak plasma concentrations (Cmax) are observed within 4-6 hours of administration with extended-release tablets. In case of oral solution or immediate release (IR) capsule, Cmax is achieved in an hour. After administration of radiolabelled ranolazine, 73% of administered

dose was excreted in urine with <5% excreted unchanged in both urine and feces. Bioavailability of ranolazine is 35-50% and food does not interfere with its absorption. It is primarily metabolized by cytochrome P450 (CYP) 3A enzyme. Pharmacokinetics of ranolazine is not affected by sex, but existence of marked gender difference in ranolazine pharmacokinetics in rats has been demonstrated. Pharmacokinetics is unaffected in the presence of concomitant illnesses like CHF and diabetes mellitus. Dose adjustments are required in renal failure (Bhandari & Subramanian, 2007).

5.4.3 Mechanism of action of ranolazine

Ranolazine is a partial fatty acid oxidation (pFOX) inhibitor that directly inhibits fatty acid β-oxidation and thus reduces inhibition of PDH by fatty acid oxidation (Sabbah & Stanley, 2002). This metabolic switch increases ATP production per mole of oxygen consumed, reduces the rise in lactic acid and acidosis, and maintains myocardial function under conditions of reduced myocardial oxygen delivery. This mechanism of action of ranolazine may explain its antiischaemic action, in the absence of any hemodynamic effects (without reduction of heart rate or blood pressure or increases of coronary blood flow) in human and animal models (Zacharowski et al., 2001; Cairns, 2006). In addition, blockade of a late sodium current that facilitates calcium entry may play a role in the action of ranolazine (Hume & Grant, 2007). Reducing reactive oxygen species (ROS) concentration by decreasing lipid oxidation could be another possible mechanism of action of ranolazine (Bhandari & Subramanian, 2007).

5.4.4 Experimental and clinical findings on beneficial effects of ranolazine in cardiovascular diseases

Ranolazine has shown cardiac antiischemic and antianginal activity in several in vitro and in vivo animal models and clinical trials (Morin et al., 2001). Results of a study demonstrated that ranolazine behaves as a weak β1- and β2-adrenoceptor antagonist in the rat cardiovascular system (Létienne et al., 2001). In dogs with experimentally-induced heart failure, acute intravenous administration of ranolazine, improved LV ejection fraction as well as other indexes of LV performance. In contrast, ranolazine had no effect on LV function in normal dogs, suggesting that this agent was devoid of any classical cAMP-mediated positive inotropic effects. Ranolazine also improved LV systolic function without increasing coronary blood flow or myocardial oxygen consumption. These studies suggest that pharmacologically switching the oxidative fuel of the heart away from fatty acids towards carbohydrate can improve mechanical efficiency of the failing heart (Sabbah et al., 2002). Previously, we demonstrated that ranolazine reduced number and incidence of VT and the time spent for reversible VF in the ischemic-reperfused isolated rat heart (Najafi & Eteraf Oskouei, 2007). Dhalla et al. tested the effect of ranolazine on ventricular arrhythmias in an ischemic model using two protocols. In protocol 1, anesthetized rats received either vehicle or ranolazine (10 mg/kg, iv bolus) and were subjected to 5 min of LAD occlusion and 5 min of reperfusion with electrocardiogram and blood pressure monitoring. In protocol 2, rats received either vehicle or three doses of ranolazine (iv bolus followed by infusion) and 20 min of LAD occlusion. With both protocols, occurrence and duration of VT and incidence of VF significantly reduced in ranolazine-treated rats. Ranolazine also reduces

experimental ST segment elevation and myocardial infarct size and enhances function of stunned myocardium in the peri-infarct area (Dhalla et al., 2009). In isolated canine ventricular myocytes and arterially perfused left ventricular function, ranolazine have shown to produce antiarrhythmic activity along with antianginal actions. Ranolazine produces ion channel effects similar to those observed after chronic exposure to amiodarone. Although ranolazine have shown to cause modest prolongation of the QT interval and action potential duration, but this prolongation is not associated with early after depolarization, triggered activity or polymorphic ventricular activity. Torsades de pointes arrythmias were not observed spontaneously and even on stimulation at concentration as high as 100 micromol/L. Rather, ranolazine is found to possess significant antiarrhythmic activity and suppress the arrhythmogenic effects of other QT-prolonging drugs (Bhandari & Subramanian, 2007). After several clinical trials, ranolazine was approved in the United States and Europe for the treatment of chronic angina pectoris (Dhalla et al., 2009). Because ranolazine prolongs the QTc, the FDA approval is limited to patients who have not responded to other antianginal drugs, and its use in combination with amlodipine, beta-blockers, or long-acting nitrates is recommended. The daily dose should be limited to 1,000 mg and precautions are advised regarding QTc prolongation (Cairns, 2006). Clinical trials also demonstrate the ability of ranolazine to decrease the incidence of VT, supraventricular tachycardia, and ventricular pauses. These antiarrhythmic effects likely arise from the ability of ranolazine to inhibit the late Na^+ current. The antiischemic and antiarrhythmic effects of ranolazine are not mutually exclusive, as they occur at similar concentrations (Lopaschuk et al., 2010). Non-insulin-dependent diabetes mellitus is characterized by elevated fatty acids (FA) levels due to diminished action of insulin in inhibiting FA release from adipocytes. FA may contribute to hyperglycemia by stimulating gluconeogenesis in the liver in the post absorptive state. It also attenuates glucose disposal in skeletal muscle in the fed state. FA oxidation inhibitors may be helpful in controlling hyperglycemia by reducing glucose production in humans. Protective role of the metabolic agents in diabetes with ischemic cardiomyopathy with trimetazidine have been demonstrated. However, the potential usefulness of ranolazine in diabetic patients is expected, but clinical trials are still awaited (Bhandari & Subramanian, 2007).

5.4.5 Adverse effects of ranolazine

The most common adverse effects are dizziness, nausea, asthenia and constipation. Postural hypotension, syncope, headache, dyspepsia and abdominal pain are also reported. Ranolazine should not be administered along with CYP3A inhibitors like ketoconazole, verapamil, diltiazem etc. Ranolazine itself is a weak inhibitor of CYP3A and increases Cmax for simvastatin. By inhibiting P-glycoprotein, it increases plasma concentration of digoxin. Ranolazine should be avoided in liver disease, hypokalemia, or if there is a personal or family history of Long QT syndrome (Bhandari & Subramanian, 2007).

5.5 Trimetazidine

Trimetazidine is likely to stimulate carbohydrate oxidation by directly inhibiting the β-oxidation of fatty acids and secondarily activating PDH (Hara et al., 1999).

5.5.1 Structure of trimetazidine

Trimetazidine [(1-(2,3,4-trimethoxy-benzyl)-piperazine dihydrochloride] with molecular formula: C14H22N2O3 (Fig. 5) is a well-established drug which has been extensively used since 1961 in the treatment of ischemia in angina pectoris and during heart surgery (Tanaka et al., 2005; Ancerewicz et al., 1998).

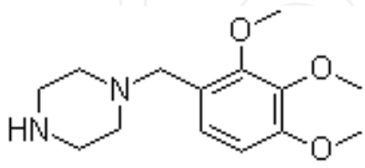

Fig. 5. Chemical structure of trimetazidine.

5.5.2 Pharmacokinetics of trimetazidine

Trimetazidine is absorbed through the intestinal mucosa with a Tmax of 5.4 hours. The Cmax is 89 microgram/L. The bioavailability is 87%, slightly inferior with trimetazidine modified release than with the immediate-release formulation, explaining the increase in the dose of trimetazidine. The bioavailability is not influenced by food. The steady state is reached 2 to 3 days after starting the treatment. The volume of distribution, unaffected by the modified-release formulation, is 4.8 L/kg which means good tissue diffusion. Protein binding affinity is low (16%), with equal binding to albumin and alpha-glycoprotein. No uptake of trimetazidine in red blood cells was observed. The major drug related component observed in plasma and urine was unchanged trimetazidine. In addition to the parent drug, 10 metabolites were detected in urine. Seven routes of metabolism have been identified in man: 2 phase I oxidation and 5 phase II conjugation routes. Trimetazidine and its metabolites are predominantly eliminated in urine. A small proportion of trimetazidine is excreted in the faeces (about 6% of the administered dose). The renal trimetazidine clearance is 350 ml/min and is independent of the urine and plasma concentration of the drug, whereas it is correlated with renal creatinine clearance. That is why the elimination half-life is shorter in the healthy patients as compared with the elderly patients (7 and 12 hours, respectively). Trimetazidine can be safely prescribed without adapting the dose in elderly patients and in case of renal insufficiency (if creatinine clearance remains above 15 ml/min) (http://www.cipladoc.com/therapeutic/pdf_cipla/trivedon_mr.pdf).

5.5.3 Mechanism of action of trimetazidine

Trimetazidine has been shown in numerous trials to be a moderately effective prophylactic antianginal agent. The exact mechanism of antiischemic effect of trimetazidine remains controversial, but its efficacy cannot be accounted for on the basis of purely hemodynamic changes (Horowitz et al., 2010). Trimetazidine has no negative inotropic or vasodilator properties. It is thought to have direct cytoprotective actions on the myocardium (Kantor et al., 2000). The experimental finding that trimetazidine inhibits the enzyme long-chain 3-ketoacyl-CoA thiolase (3-KAT) has led to its being categorized as a partial fatty acid oxidation inhibitor (Horowitz et al., 2010) and a stimulation of glucose oxidation (Kantor et

al., 2000). Recent clinical studies have supported this suggestion, demonstrating that trimetazidine inhibits myocardial fatty acid oxidation and augments glucose utilization. Importantly, trimetazidine is also free of the potential to induce tissue phospholipids accumulation with associated toxicity (Horowitz et al., 2010). The relatively low potency of trimetazidine as a carnitine palmitoyltransferase-1 inhibitor makes the mechanism of inhibiting of long-chain fatty acid oxidation and increasing myocardial oxygen utilization, and explains its therapeutic antiischemic effect (Kennedy et al., 1998). Trimetazidine is clinically utilized as an antianginal therapy throughout Europe and in over 90 countries. By inhibiting fatty acid β-oxidation, trimetazidine causes a reciprocal increase in glucose oxidation, thereby decreasing the production of H^+ arising from glycolysis uncoupled from glucose oxidation. Interestingly, in the setting of pressure-overload cardiac hypertrophy, where the rates of fatty acid β-oxidation are depressed, trimetazidine confers cardioprotection independently of alterations in fatty acid β-oxidation. Rather, trimetazidine attenuates the elevated rates of glycolysis and increases glucose oxidation to limit the production of H+ attributed to glucose metabolism. The inhibition of glycolysis coupled with the increase in glucose oxidation, or the partial inhibition of fatty acid β–oxidation and the parallel stimulation of glucose oxidation, can limit ischemia-induced disturbances in myocardial ionic homeostasis. Specifically, the improved coupling of glucose metabolism attenuates intracellular acidosis as well as Na^+ and Ca^{2+} overload during ischemia and subsequent reperfusion and improves the recovery of post ischemic cardiac function. Trimetazidine also affects on cardiac myocyte Ca^{2+} handling that can limit ischemic myocardial injury, including reductions in Ca^{2+} current, prevention of elevated$[Ca^{2+}]i$, and preservation of SR Ca^{2+}-ATPase activity that may limit or prevent cytosolic Ca^{2+} overload. Therefore, the metabolic effects of trimetazidine are permissive to increasing cardiac efficiency by sparing ATP hydrolysis from being utilized to correct ionic homeostasis, and making it available to fuel contractile work (Lopaschuk et al., 2010). Trimetazidine also enters brain tissues in low concentrations. Since oxygenated free radicals are believed to play a major role in both I/R injury and neurodegenerative diseases (Alzheimer and Parkinson's disease), it was suggested that trimetazidine might possess antioxidant properties (Ancerewicz et al., 1998).

5.5.4 Experimental and clinical findings on beneficial effects of trimetazidine in cardiovascular diseases

Trimetazidine is efficacious in the treatment of angina, MI and heart failure. The antiischemic effects of trimetazidine in the treatment of angina include an increased time to 1-mm ST segment depression and decreased weekly nitrate consumption disease (Lopaschuk et al., 2010). Trimetazidine has also been shown to significantly improve exercise-induced anginal symptoms in patients with CAD without eliciting any of the classic antiischemic effects of traditional therapies such as a decrease in heart rate, coronary vasodilation, or a decrease in arterial blood pressure (Sabbah & Stanley, 2002). In acute MI, the cardioprotective effects of trimetazidine are evident as a reduction in reperfusion arrhythmias and a more rapid resolution of ST segment elevation. The addition of trimetazidine to treatment regimens also improves NYHA functional class, LV end-diastolic volume, and ejection fraction in patient with heart failure and ischemic cardiomyopathy, as well as idiopathic dilated cardiomyopathy. Thus, the partial inhibition of fatty acid β-

oxidation, via the reversible, competitive inhibition of 3-KAT attenuates several consequences of various forms of ischemic heart disease (Lopaschuk et al., 2010). It was reported that trimetazidine therapy was associated with QTc interval shortening in patients with ischemic heart failure (Zemljic et al., 2010). In the ischemic cardiomyopathy, despite treatment with conventional agents, a high proportion of patients continue to have symptoms and a substantial proportion shows progressive contractile dysfunction leading to LV enlargement and heart failure. Thus, there is a need for new treatments for ischemic cardiomyopathy that apply mechanisms other than those already addressed by conventional agents. There are many evidences suggesting that in patients with ischemic cardiomyopathy, LV dysfunction progress in consequence of alterations in substrate metabolism. Trimetazidine, which acts on myocardial metabolic pathways, appears to protect the heart from the deleterious effects of ischemia, and it has been shown to enhance LV contractility in patients with stunned or hibernating myocardium. Trimetazidine has been shown to improve symptoms and LV ejection fraction and to have a beneficial effect on the inflammatory profile and endothelial function in these patients. These results suggest that trimetazidine is a useful adjunct to the current treatments for the patients with ischemic cardiomyopathy (Bertomeu-Gonzalez et al., 2006). Muscle's metabolic and vascular effects of trimetazidine add new interest in the use of trimetazidine in type 2 diabetic patients with ischemic cardiomyopathy (Monti et al., 2006). It has shown improvement in LV function, symptoms, glucose metabolism and endothelial function in such patients (Bhandari & Subramanian, 2007). Despite beneficial uses, trimetazidine can induce some adverse effects including parkinsonism, gait disorder and tremor (Martí Massó et al., 2005).

5.6 Etomoxir

5.6.1 Structure of etomoxir

Etomoxir {2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate} is an irreversible inhibitor of carnitine palmitoyl transferase I (CPT-I) that was initially introduced as a potential anti-diabetic agent based on its hypoglycemic effects (Lee et al., 2004, Lopaschuk et al. 2010).

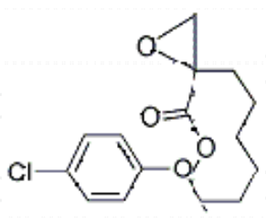

Fig. 6. Chemical structure of etomoxir.

5.6.2 Mechanism of action of etomoxir

Etomoxir inhibits CPT-I, the key enzyme involved in fatty acid uptake by the mitochondria (Baetz et al., 2003), and alters the balance between myocardial fatty acid β-oxidation and glucose oxidation. It leads to reduced fatty oxidation rates, increased glucose oxidation rates and improved myocardial energy efficiency. Although etomoxir has been investigated as a treatment for heart failure, it has not yet been studied as an antianginal agent (Lam A & Lopaschuk, 2007).

5.6.3 Experimental and clinical findings on beneficial effects of etomoxir in cardiovascular diseases

In experimental models of I/R, etomoxir improves the recovery of ventricular function following ischemia. In palmitate-perfused ischemic rat hearts, etomoxir reduced oxygen consumption during ischemic recovery and also prevented depression of myocardial function. In pressure-overloaded, hypertrophic, and failing rat hearts, etomoxir led to an improvement in indices of left ventricular dysfunction (Lee et al., 2004). In isolated rat hearts, perfusion of etomoxir-enriched K/H solution significantly decreased the incidence of ischemic VT and the time spent for reversible VF (Najafi & Eteraf Oskouei, 2007). This cardioprotective effect is also afforded to the postischemic diabetic heart and may suggest the possible clinical utility of etomoxir in patients with diabetic cardiomyopathy. The protective effects of etomoxir in the postischemic period are accompanied by increased rates of myocardial glucose oxidation and an increased production and utilization of ATP for contractile work due to the stimulation of the cardiac PDH complex (via the Randle cycle). Although clinical experience with etomoxir is very limited, its potential beneficial effects on heart function have been assessed in a small (15 patients) uncontrolled, open-label study of patients with NYHA class II heart failure. Following 3 months of etomoxir treatment (80 mg), there was an improvement in LV ejection fraction, cardiac output at peak exercise, and clinical status; however, this trial was not able to assess the long-term safety of etomoxir treatment. More recently, etomoxir for the recovery of glucose oxidation (ERGO) study had to be stopped early as several patients with NYHA class II-class III heart failure in the treatment group were found to have elevated liver transaminase enzyme levels. This adverse effect may be related to the irreversible inhibition of CPT-1 in response to etomoxir, an effect that may allow toxicity to manifest from its excessive accumulation. This study did not detect any significant improvement in the etomoxir group (40 and 80 mg) as compared with placebo (likely due to limited power); however, there was a trend to increased exercise time (Lopaschuk et al. 2010).

5.7 Dichloroacetate (DCA)

DCA is a PDH activator (Liu et al., 2002) and stimulates carbohydrate oxidation through direct inhibition of PDH kinase and reduces fatty acid oxidation through inhibition of fatty acid uptake by mitochondria (Hara et al., 1999).

5.7.1 Structure of DCA

DCA is a compound with formula $CHCl_2COOH$ and below chemical structure (Fig. 7). (http://en.wikipedia.org/wiki/Dichloroacetic_acid).

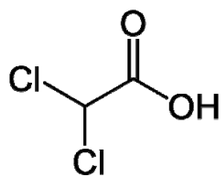

Fig. 7. Chemical structure of DCA.

5.7.2 Pharmacokinetics of DCA

DCA is completely absorbed following oral dosing and about 20% is bound to human plasma proteins. In all species examined, the first dose is cleared from plasma more rapidly than subsequent doses, although the mechanism for this effect is unknown. Glyoxylate is an intermediate in DCA metabolism, and oxalate and CO2 are terminal end products. Neither glyoxylate nor oxalate stimulates PDC activity. However, because the actions of DCA in humans often persist for several days after its clearance from plasma, it is possible that other reactive intermediates of DCA accumulate intracellularly at active sites and bind covalently to target proteins, or that DCA (or a metabolite) induces enzymes responsible for its pharmacodynamic effects. DCA is excreted with little of the dose unchanged (Stacpoole et al., 1998).

5.7.3 Mechanism of action of DCA

DCA exerts multiple effects on pathways of intermediary metabolism. It stimulates peripheral glucose utilization and inhibits gluconeogeneis, thereby reducing hyperglycemia in individuals with diabetes mellitus. It decreases circulating lipid and lipoprotein levels by inhibing lipogenesis and cholesterolgenesis, in patients with disorders of lipoprotein metabolism. DCA facilitates oxidation of lactate and decreases morbidity in lactic acidosis by stimulating the activity of PDH. The drug improves cardiac output and LV mechanical efficiency under conditions of myocardial ischemia or failure, probably by accelerating myocardial metabolism of carbohydrate and lactate as opposed to fat (Stacpoole, 1989). DCA promotes myocardial glucose oxidation at the expense of myocardial fatty acid β-oxidation; however, unlike trimetazidine and ranolazine, DCA stimulates the mitochondrial PDH complex by directly inhibiting the activity of PDH kinase. Experimental studies have demonstrated the ability of DCA to enhance the postischemic recovery of cardiac function in vitro as well as in vivo. An increase in cardiac efficiency, and an improved coupling between glycolysis and glucose oxidation, accompany the cardioprotective effects of DCA (Lopaschuk et al., 2010). DCA may also increase regional lactate removal and restoration of brain function in the cerebral ischemia. DCA appears to inhibit its own metabolism, which may increase the duration of its pharmacologic actions and lead to toxicity. DCA can cause a reversible peripheral neuropathy that may be related to thiamine deficiency and may be ameliorated or prevented with thiamine supplementation. Despite its potential toxicity and limited clinical experience, DCA and its derivatives may be useful in the acute or chronic treatment of several metabolic disorders (Stacpoole, 1989).

5.7.4 Experimental and clinical findings on beneficial effects uses of DCA in cardiovascular diseases

When myocardial carbohydrate oxidation is acutely increased in heart failure patients by activating PDH with intravenous DCA, there is a rapid improvement in LV performance (Sabbah & Stanley, 2002). Clinical experience with DCA is limited; however, in a small clinical trial, DCA increased LV stroke volume and myocardial efficiency, effects accompanied by increased lactate utilization. As the metabolic effects of DCA are similar to those of trimetazidine and ranolazine, it may be relevant in the therapeutic management of angina pectoris; however, its antiischemic efficacy has yet to be established in such a setting (Lopaschuk et al., 2010).

5.8 Perhexiline

Perhexiline has similar metabolic and antianginal effects which are found with inhibition of CPT-I using such as ranolazine (Sabbah & Stanley, 2002).

5.8.1 Structure of perhexiline

Perhexiline is 3 2-(2,2-dicyclohexylethyl) piperidine (Dawson et al., 1986) with following structure (Fig. 8).

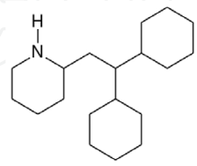

Fig. 8. The chemical structure of perhexiline (http://en.wikipedia.org/wiki/Perhexiline).

5.8.2 Pharmacokinetics of perhexiline

Perhexiline has only ever been available as an oral formulation, thus its bioavailability is unknown. However, it has been reported that in a small group of volunteers receiving 400 mg of perhexiline daily for 14 days, 24 h recoveries of unchanged perhexiline in faeces on days 12, 13 or 14 averaged 7.7% (range 0–32.5%), suggesting good absorption from the gastrointestinal tract. The major determinant of perhexiline clearance appears to be hepatic metabolism, since in humans only approximately 0.1% of a dose is eliminated as unchanged drug in urine. Perhexiline forms two primary monohydroxy (OH) metabolites, cis-OH-perhexiline and trans-OH-perhexiline, which can undergo further secondary metabolism to dihydroxy metabolites, as well as glucuronide conjugates. Formation of the major primary metabolite, cis-OH-perhexiline is catalysed by CYP2D6, and this metabolic pathway is thought to give rise to both the saturability and genetic polymorphism in perhexiline clearance (Sallustio et al., 2002).

5.8.3 Mechanism of action of perhexiline

Although initially designated as a calcium-channel blocker, it has no significant calcium channel blocking activity at therapeutic concentrations. Perhexiline is not negatively inotropic and does not change systemic vascular resistance within therapeutic concentrations and it is well tolerated by patients with combined angina and LV systolic dysfunction. It acts by shifting myocardial substrate utilization from fatty acids to carbohydrates through inhibition of CPT-1 following in increased glucose and lactate utilization (Lee et al., 2004). It seems that, inhibition of CPT-1 then decreasing fatty acid β-oxidation is an effective therapeutic approach in various types of ischemic heart diseases (Lopaschuk et al., 2010).

5.8.4 Experimental and clinical findings on beneficial effects uses of perhexiline in cardiovascular diseases

Perhexiline was developed as a prophylactic antianginal agent approximately 40 years ago. It was initially thought to be a coronary vasodilator, although in fact its vasomotor effects

are minimal – later its weak L-type calcium channel blocking effects were thought to underlie its effects. This was inherently implausible, because the observed antianginal effects of perhexiline were extraordinary, with relief of otherwise intractable symptoms in many patients. Despite its antianginal efficacy, perhexiline induced substantial toxicity, which caused a decline in its therapeutic uses from 1980. It was shown that the toxicity of perhexiline was preventable, and that the toxicity were observed in patients in whom plasma perhexiline levels were elevated beyond 600 μg/ml whereas dosage titration to achieve steady-state levels between 150 and 600 μg/ml, serious toxicity was turned away. These findings have permitted a reevaluation of the therapeutic role of perhexiline in severe angina, and an extension to possible therapeutics of other conditions such as heart failure and inoperable aortic stenosis (Horowitz et al., 2010). Of importance is the fact that the hepatic toxicity of perhexeline is due to the inhibition of the hepatic isoform of CPT 1. In vitro studies clearly demonstrate that the cardiac isoform of CPT 1 is more sensitive to inhibition by perhexeline, an effect that allows for the use of dose titration to avoid or limit adverse effects. Several clinical trials have demonstrated the beneficial effects of perhexeline in aortic stenosis, heart failure, and angina pectoris (Lopaschuk et al., 2010).

5.8.5 Adverse effects of perhexiline

Long-term therapy with perhexiline frequently induced both hepatotoxicity and neurotoxicity by phospholipidosis in hepatocytes and Schwann cells with this agent. Other side effects are nausea, dizziness or both, and hypoglycemia in diabetics. These effects were later demonstrated to occur most commonly in patients who are slow hydroxylators, bearers of a genetic variant of the cytochrome P-450 enzyme family. These patients are slow metabolisers of perhexiline due to saturation of hepatic metabolic pathways, which leads to accumulation of the drug and toxicity. The mechanism for toxicity appears to be due to phospholipids accumulation, which is a direct consequence of CPT-1 inhibition. Hence, this is a potential side effect of any drug that inhibits CPT-1, including amiodarone, which exhibits weak CPT-1-inhibitor properties. This is thought to be the mechanism responsible for the peripheral neuropathy and hepatitis occasionally seen with amiodarone use (Lee et al., 2004).

6. Conclusion

Alterations in fatty acid β-oxidation have important implications on cardiac function in both heart failure and IHD. Of importance is that emerging evidence suggests that inhibition of fatty acid β-oxidation may be a useful approach to improve heart function in the setting of obesity, diabetes, heart failure, and IHD. Metabolic agents modulate fatty acid and glucose utilization by the myocardium during I/R to protect the heart from I/R injuries such as arrhythmias. Some of the agents have well-documented antiischemic and antiarrhythmic effects against I/R-induced cardiac arrhythmias.

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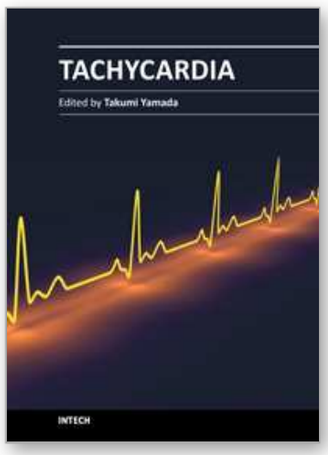

Tachycardia
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Heart rates are normally controlled by a natural pacemaker, the sinus node, and normal heart rhythm is called sinus rhythm. Tachycardia is defined as a faster heart rhythm than normal sinus rhythm. Tachycardias can cause symptoms such as palpitations, chest pain, shortness of breath and fatigue, which reduce the quality of life. Fast tachycardias can cause hemodynamic collapse and sudden cardiac death. The causes, mechanisms, and origins of tachycardias are various. The diagnosis of tachycardias is made by electrocardiograms and electrophysiological testing. Tachycardias can be managed and treated by pharmacological and non-pharmacological approaches. This book covers these concerns from basic and clinical points of view and will lead to a further understanding and improvement in the clinical outcomes of tachycardias.

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