Cardioprotective effect of lipstatin derivative orlistat on normotensive rats submitted to cardiac ischemia and reperfusion

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Abstract

Purpose: To evaluate in vivo animal model of cardiac ischemia/reperfusion the cardioprotective activity of pancreatic lipase inhibitor of the orlistat.

Methods: Adult male Wistar rats were anesthetized, placed on mechanical ventilation and underwent surgery to induce cardiac I/R by obstructing left descending coronary artery followed by reperfusion to evaluation of ventricular arrhythmias (VA), atrioventricular block (AVB) and lethality (LET). At the end of reperfusion, blood samples were collected for determination of triglycerides (TG), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase-MB (CK-MB).

Results: Treatment with ORL has been able to decrease the incidence of VA, AVB and LET. Besides that, treatment with ORL reduced serum concentrations of CK and LDL, but did not alter the levels of serum concentration of TG, VLDL and HDL.

Conclusion: The reduction of ventricular arrhythmias, atrioventricular block, and lethality and serum levels of creatine kinase produced by treatment with orlistat in animal model of cardiac ischemia/reperfusion injury suggest that ORL could be used as an efficient cardioprotective therapeutic strategy to attenuate myocardial damage related to acute myocardial infarction.

Key words: Myocardial Infarction. Arrhythmias, Cardiac. Ischemia. Reperfusion. Biomarkers. Rats.
Introduction

Acute myocardial infarction (AMI) is characterized by ischemic lesions that severely compromise the cardiac structure/function, besides the survival of mammals. Although conventional therapy uses cardiac reperfusion, this procedure increases the cardiac damage caused by ischemia. The increasing prevalence of AMI, especially in the last decade, aroused the interest of pharmacologists in the search for compounds able to attenuate the cardiac damage by ischemia and reperfusion (I/R). These compounds have been classified as cardioprotective drugs. There are now numerous drug therapies available for use, such as lipid-lowering drugs (statins) that are being evaluated. The lipid-lowering effect of statins results from its inhibitory action on the enzyme regulating endogenous cholesterol synthesis. This action promotes the reduction of serum LDL concentration and the intensity of inflammatory processes mediated by LDL.1–4

The molecular mechanisms involved in cardioprotective activity of statins in patients with AMI remains unclear. The elevation of plasma triglycerides (TG) may indicate metabolic disorders, and its dosage is a parameter in the evaluation of arterial hypertension, diabetes, obesity and cardiovascular risk. An elevation in plasma TG levels in patients with diabetes has been related with increased mobilization of lipid storages, increasing the risk of hepatic steatosis and atherosclerosis. However, the cardioprotective activity of lipid-lowering drugs that reduce pancreatic lipase (LP) activity, such as orlistat (ORL), in patients with AMI is still poorly understood.5,6

Since hypertriglyceridemia consists in an important risk factor for AMI, in the present study, we decided to evaluate in vivo animal model of cardiac I/R the cardioprotective activity of pancreatic lipase inhibitor of the ORL.

Methods

Animals were maintained under standard conditions of nutrition, hydration, temperature, light and humidity, and in accordance to normatization approved by Ethical Committee of the EPM/UNIFESP (#0065/12).

Adult male Wistar rats (14 - 16 week-old) weighting between 300 to 340 g were randomized into 4 groups: SHAM-operated (n=10); cardiac I/R (n=40); treatment with vehicle (I/R+VE, n=20) and treated with ORL for 10 days by gavage orally (I/R+ORL, n=20).

Protocol of cardiac ischemia and reperfusion (I/R)

It was used a method to induce cardiac I/R described by our lab.7,8 Rats were anesthetized with urethane (1.25 g/kg), and fixed in the supine position. After intubation (Jelco 14G, USA), rats were mechanically ventilated using a mechanic ventilator Insight model EFF 312 (Insight Equipamentos Científicos, Ribeirão Preto, Brazil). After stabilization for 15 min, thoracotomy was performed to place the vascular tourniquet (4/0 braided silk suture attached to a 10-mm micropoint reverse-cutting needle, Ethicon K-890H, USA) around the left anterior descending coronary artery to produce ischemia. After of 10 min of ischemia, the tourniquet was removed to allow coronary recirculation for 75 min (reperfusion).

The cardiac electrical activity in SHAM-operated and cardiac I/R groups was

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monitored by electrocardiogram (ECG) system using a method to described by our lab\textsuperscript{7,8}. ECG evaluation was performed during all experiment (100 min duration). The ECG was recorded using a biopotential amplifier by means of needle electrodes placed subcutaneously on the limbs\textsuperscript{7,8}. Successful surgical obstruction of the coronary artery was validated by ECG alterations (increase in R wave and ST segment) caused by ischemia\textsuperscript{7,8}. The body temperature was maintained at 37.5ºC with a heated operating platform and appropriate heating lamps, and was evaluated routinely via a rectal thermometer.

**ECG analysis**

The ECG data were recorded using an acquisition system AqDados 7.02 (Lynx Tecnologia Ltda., Brazil), and analysed using the software AqDAnalysis 7 (Lynx Tecnologia Ltda., Brazil). Using this software, were evaluated the heart rates, as well as incidence of ventricular arrhythemias (VA), atrioventricular block (AVB) and lethality (LET), in response to cardiac I/R. The ventricular fibrillation, torsades de pointes, and ventricular tachycardia parameters were considered only as VA. After ECG recording, blood sample were collected from the abdominal aorta artery, and centrifuged (2,500 rpm, for 40 min, at 5ºC) to isolation of serum. The serum was stored at -20ºC for biochemical analysis.

**Biochemical parameters**

For determination of triglycerides by lipoprotein lipase (LPL) enzyme activity in serum, it was performed by measuring enzymatic colorimetric test, measured at 505 nm (Kit VIDA Biotecnologia, Belo Horizonte, Brazil). For determination of serum cholesterol, it was performed by colorimetric test, measured at 505 nm (Kit VIDA Biotecnologia, Belo Horizonte, Brazil). For the quantitative determination of the HDL fraction of Cholesterol in serum, it was performed through Enzyme/Colorimetric test, measured at 570 to 610 nm (Kit VIDA Biotecnologia, Belo Horizonte, Brazil).

Quantitative determination of lactic dehydrogenase (LDH), creatine kinase (CK), and creatine kinase MB fraction (CK-MB) was performed using a kinetic-UV method, measured at 340 nm (Kit Katal Biotecnológica Ind. Com. Ltda., Belo Horizonte, Brazil).

**Data analysis**

Statistical analysis of incidence of VA, AVB, and LET were statistically evaluated using the Fisher's exact test (p<0.05). Statistical analysis of biomarkers of cardiac injury were expressed as mean ± standard error (SE) of the mean, and analysis of variance (ANOVA) was applied, followed by the Tukey post-test (p <0.05). These statistical analysis were performed using Prism 5.0 software (GraphPad, USA).

**Results**

Our results showed that treatment with ORL decreased the percentual incidence of VA (85% to 57%, Figure 1A), AVB (79% to 43%, Figure 1B), and LET (70% to 38%, Figure 1C) in animals.
The treatment with ORL reduced the serum concentrations of the LDL (40.9 ± 4.8 to 10.2 ± 2.7 mg/dL, Figure 2C) and CK (4564.8 ± 470.4 to 2387.2 ± 306.7 U/L, Figure 3B) in animals. In contrast, the ORL effect in I/R group did not alter the levels of serum concentration of the of TG (101.7 ± 7.12 mg/dL, Figure 2A), VLDL (21.38 ± 1.60 mg/dL, Figure 2B), and HDL (35.00 ± 5.01 mg/dL, Figure 2D), such as of the LDH (1653.0 ± 91.9, Figure 3A) and CK-MB (1849.8 U/L ± 221.9, Figure 3C) in animals.

Figure 1 – (A) Incidence of the ventricular arrhythmias (AV). (B) Atrioventricular block (AVB). (C) Lethality (LET) in the SHAM, I/R, I/R+VE and I/R+ORL groups. The results were expressed as mean, and Fisher’s exact test (*p<0.05). A reduced of incidence of the AV, AVB and LET was observed the group of I/R+ORL groups when compared with I/R group. SHAM= simulated group; I/R= cardiac ischemia and reperfusion group; I/R+VE= cardiac ischemia and reperfusion group treated with vehicle; I/R+ORL= cardiac ischemia and reperfusion group treated with orlistat. *Statistically different from the cardiac I/R and SHAM groups.

Figure 2 - Serum concentration of TG (A), VLDL (B), LDL (C) and HDL (D) in the SC, SHAM, I/R, I/R+VE and I/R+ORL groups. The results were expressed as mean ± standard error of the mean, and analysis of variance (ANOVA) was applied, followed by the Tukey post-test (*p<0.05). SC= group without surgery; SHAM= simulated group; I/R= cardiac ischemia and reperfusion group; I/R+VE= cardiac ischemia and reperfusion group treated with vehicle; I/R+ORL= cardiac ischemia and reperfusion group treated with orlistat. *Statistically different from all other groups.
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Figure 3 - Serum concentration of LDH (A), CK (B) and CK-MB (C) in the SC, SHAM, I/R, I/R+VE and I/R+ORL groups. The results were expressed as mean ± standard error of the mean, and analysis of variance (ANOVA) was applied, followed by the Tukey post-test (*p<0.05). SC= group without surgery; SHAM= simulated group; I/R= cardiac ischemia and reperfusion group; I/R+VE= cardiac ischemia and reperfusion group treated with vehicle; I/R+ORL= cardiac ischemia and reperfusion group treated with orlistat. *Statistically different from the cardiac I/R group.

Discussion

Our results showed that treatment of animals submitted to cardiac I/R for 10 days with the pancreatic lipase inhibitor ORL reduced the incidence of VA, AVB and LET, as well as decreased serum levels of CK and LDL-cholesterol.

The metabolic syndrome is a complex disorder represented by a set of cardiovascular risk factors usually related to central fat deposition and insulin resistance. It is important to highlight the association of metabolic syndrome with cardiovascular disease, increasing overall mortality by 1.5 times and cardiovascular mortality by 2.5 times9-13. In this situation, dyslipidemia is characterized by the presence of high levels of LDL-cholesterol and low levels of HDL-cholesterol, and elevated levels of triglycerides5. The drugs capable of reducing the absorption of lipids such as cholesterol may interfere with vascular inflammatory processes, like ezetimibe, a selective inhibitor of intestinal cholesterol absorption by the cholesterol carrier Niemann-Pick C1 Like 1 protein. The ezetimibe is able to block vascular inflammation triggered by oxidative stress, by decreasing serum LDL concentrations, synthesis of monocyte attraction protein-1 chemokine and the expression of the leukocyte-to-endothelial cell adhesion, such as VCAM-1 and transcriptional synthesis of messenger RNA for CD1414.

Elevation of plasma TG may indicate metabolic disorders, and its dosage is a parameter in the evaluation of uremia, diabetes, obesity and cardiac risk. An elevation in plasma TG levels in patients with diabetes is related to increased mobilization of lipid storage areas, increasing the risk of hepatic steatosis and atherosclerosis15.

The ORL binds covalently to the serine portion of the site of action of lipases causing irreversible inhibition of gastrointestinal lipases (gastric and pancreatic lipase)5,6. ORL is a drug partially derived from an endogenous lipstatin produced by Streptomyces toxytricini, and inhibits the pancreatic lipase enzyme, responsible for the hydrolysis of TG ingested from the diet5,6.

When administrated orally, approximately 1 hour before the three main meals, the ORL reduces dietary fat absorption by 30%16 and is used in association with a diet for the treatment of obesity in patients with
body mass index (BMI) greater than or equal to 30 kg/m², or in patients with excess body mass (BMI greater than or equal to 28 kg/m²) who are at risk of disease.

Since hypertriglyceridemia is a risk factor for AMI, we decided to quantify TG plasma concentration in animals and to correlate it with the electrophysiological and cardiac changes in our I/R model. The I/R protocol did not cause a statistically significant change in the TG concentration. Similarly, treatment of rats with ORL was also unable to modify the serum TG value observed in the I/R group. Primary dyslipidemias, such as common hypertriglyceridemia, familial hypertriglyceridemia, combined familial hyperlipidemia, are less important epidemiologically when compared to secondary dyslipidemias observed in diabetes mellitus, obesity and alcoholism, or related to the use of medications such as diuretics, betablockers deprived of ASI, contraceptives and corticosteroids.

The TG is considered important biological markers for other lipid alterations with atherogenic potential, and may indicate alterations such as combined familial hyperlipidemia, decrease in HDL levels and diabetes mellitus. Also, increased serum TG levels increase the risk of thrombogenesis when interacting with coagulation factors and platelets, and its association with other risk factors such as hypertension, smoking, diabetes mellitus, morbid obesity and postmenopausal, increase morbidity and mortality, especially in the case of ischemic heart diseases.

The use of 120 mg of ORL (after 2 hours of ingestion) caused decrease in serum TG levels in patients with familial hypercholesterolemia, as well as the use during 6 months in obese patients, or for 1 year in obese patients, obese with hypercholesterolemia or obese with type 2 diabetes, which favors the reduction the use of oral hypoglycemic agents and insulin. Also, the combination of ORL with Genfibrozil or Statin reduced triglyceride levels by 35% in patients with hypertriglyceridemia.

The ORL in combination with a hypocaloric diet, reduces serum TG levels, an effect associated with a decrease in the intestinal absorption of triglycerides by ORL and widely described in the literature, but this effect was not observed in our study.

Although the elevation of LDL cholesterol is not considered one of the diagnostic criteria for the metabolic syndrome, patients with this syndrome present alterations in the density and particle size of the lipoprotein, predominantly the type B pattern (small and dense LDL). This association is termed atherogenic dyslipidemia. Patients with metabolic syndrome have a high risk of cardiovascular disease when compared to those without metabolic syndrome, and the two first-line medications in the treatment of obesity associated with the metabolic syndrome are sibutramine and ORL.

Biomarkers of myocardial injury have been studied since the 1970s, among them the LDH enzyme. In our study, no change in LDH levels was observed, and others studies using orlistat not have found beneficial effect on the decrease of LDH. The CK constitutes another important biomarker for the diagnosis of AMI, which is an enzyme that regulates the production and use of high energy phosphate in the contractile tissues, like myocardium. The determination of serum levels of total CK and myocardial CK (CK-MB) is important to
diagnosis of AMI.

In our study, we observed a statistical difference in the reduction levels of CK; this may due to the action of ORL on endothelial function and LDL reduction, promoting cardiovascular benefits, and cardioprotection against the I/R. Zhi et al. demonstrated by screening that there is an extremely low degree of systemic absorption for orlistat when administered with a hypocaloric, with small levels in plasma and urine. Therefore, we believe that in spite of presenting a low systemic bioavailability, we propose that ORL after reaching plasma promotes inhibition of the lipoprotein lipase enzyme produced by vasculature from skeletal muscles and adipose tissue, thus exerting in addition to local effects on the gastrointestinal tract and systemic effects.

The treatment with ORL was not reversed the increase in serum CK-MB when compared with I/R group. In the literature was not reported association between the use of the orlist and dosage of CK or CK-MB.

The reduction of VA, AVB, and serum levels of CK and LDL produced by treatment during 10 days with pancreatic lipase inhibitor ORL in animals submitted to cardiac I/R injury clearly indicate the cardioprotective activity of ORL.

■ Conclusions

The reduction of ventricular arrhythmias, atrioventricular block, and lethality and serum levels of creatine kinase produced by treatment with orlistat in animal model of cardiac ischemia/reperfusion injury suggest that ORL could be used as an efficient cardioprotective therapeutic strategy to attenuate myocardial damage related to acute myocardial infarction.

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Erratum

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ORIGINAL ARTICLES

7 - Experimental Surgery

MANUSCRIPT: Cardioprotective effect of lipstatin derivative orlistat on normotensive rats submitted to cardiac ischemia and reperfusion

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