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Effects of Ethanol or Naltrexone after Ethanol Exposure on Plasma Levels of Hepatic Enzymes, Lipid Profile and Apolipoprotein in Rats

Silvânia M. M. VASCONCELOS * [1], Paula M. SOARES [1], Natália M. LIMA [1], Roberto F. PEREIRA [2], Renata S. ALVES [2], Maria Gorette R. QUEIROZ [2], Danielle S. MACEDO [1], Rivelilson M. FREITAS [1], Francisca Cléa F. SOUSA [1], Marta Maria F. FONTELES [1], Glauce S. Barros VIANA [1]

[1] Department of Physiology and Pharmacology, Federal University of Ceará, Rua Cel. Nunes de Melo 1127, 60430-270, Fortaleza, Ceará, Brazil.
[2] Department of Clinical and Toxicological Analyses, Federal University of Ceará, Rua Cel. Nunes de Melo 1127, 60430-270, Fortaleza, Ceará, Brazil.

Abstract

This work studied the effects of ethanol and naltrexone on plasma levels of hepatic enzymes, lipid profiles and apoprotein (APO-A1). Rats were treated daily with ethanol for 7 days and, after ethanol discontinuation, they received naltrexone up to the 14th day. The results showed increased alanine aminotransferase (ALT) and aspartate aminotranferase (AST) activities, as well as total cholesterol (TC), triglycerides (TGI) and high density lipoprotein cholesterol (HDL-C) levels after ethanol. Naltrexone alone significantly increased APO-A1 and TGI levels and significantly decreased TC concentrations. Naltrexone treatment after ethanol exposure leads to a significant increase in both ALT (48%) and AST (34%). While no changes were seen in HDL-C levels, naltrexone blocked the increase in TC levels induced by ethanol. However, TGI as well as APO-A1 levels were maintained at higher values as compared to controls and similar to those observed to the naltrexone group without ethanol treatment. The work indicates that the hypolipaemic effect of naltrexone after ethanol exposure is a favorable point to the use of this opioid antagonist in the treatment of alcoholism.

* Corresponding author: Tel.: +55(85)3366-8337; Fax: +55(85) 3366-8337.
E-mail: silvania_vasconcelos@yahoo.com.br (S. M. M. Vasconcelos).

Key words

Ethanol • Naltrexone • Hepatic enzymes • Lipid profile • Apoproteins.

Introduction

Liver disease is the most common complication from ethanol abuse [1]. It is estimated that 15 to 30% of chronic heavy drinkers eventually develop severe liver diseases. Alcoholic fatty liver may progress to alcoholic hepatitis and finally to cirrhosis and liver failure [2]. In the USA, chronic alcohol abuse is the leading cause of liver cirrhosis and the need for liver transplantation [3]. On the other hand, it has been shown that alcohol consumption may protect against severe coronary atherosclerosis, but the mechanism through which alcohol might exert its protective effect remains unclear [4].

High-density lipoprotein cholesterol unlike other lipids shows a dose-dependent relationship to alcohol intake. Because HDL-C is thought to play an important role in preventing atherosclerosis [5], it has been proposed that alcohol protection occurs via increasing HDL-C. Other results also show that apoprotein A1 (APO A1) levels rise with alcohol consumption, and this may protect against atherosclerosis even better than HDL-C does [6]. APO A1 is considered to be a protective, anti-atherogenic particle found in the HDL-C. Sillanaukee and coworkers [7] showed that all lipid values, except low density lipoprotein cholesterol (LDL-C), positively correlated with self reported alcohol consumption.

Despite suggestions that anti-atherogenic effects of moderate alcohol consumption may be explained by its effects on plasma HDL-C levels, alcohol effects on low density lipoproteins LDL-C, the major atherogenic lipoproteins, are not clear [8]. An earlier work [9] showed that daily consumption of alcohol at dinner resulted in increased post-prandial plasma triglyceride levels and decreased LDL-C. In contrast, HDL-C levels were raised at all time points analyzed. Also, alcohol consumption resulted in a raised HDL-C/APO A1 ratio, at 5 and 9 p.m. These alcohol dependent effects on plasma HDL-C and LDL-C, during the post-prandial

phase, are considered anti-atherogenic, and may contribute to the observed protection against coronary heart disease, by moderate alcohol consumption.

It has been repeatedly reported that endogenous opioid pathways play an important role in ethanol drinking behavior. Clinical trials suggest that opioid antagonists may be effective in the treatment of alcoholism [10, 11] and most of the work in the literature points out to the beneficial effect of naltrexone on alcoholism treatment [12–14]. The opiate antagonist naltrexone suppresses ethanol-reinforced behavior in animals, and decreases ethanol intake in humans. Gonzales and Weiss [15] found that naltrexone suppressed significantly ethanol self-administration, and prevented ethanol-induced increases in dialyzed dopamine levels. Their results suggest that suppression of ethanol self-administration by opiate antagonists is the result of interference with dopamine-dependent aspects of ethanol reinforcement. Naltrexone is an opioid antagonist which effectively blocks heroin effects, but there is insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for treatment of opioid dependence [16].

The objectives of the present work were to study the effects of the repeated ethanol or naltrexone administrations as well as naltrexone after ethanol exposure on plasma levels of hepatic enzymes, lipid profiles and apoproteins, in rats.

Experimental

1. Animals

A total of 35 male Wistar rats (150-200 g) were used. Animals had free access to a commercial diet (Purina, Brazil) and water, and were housed in groups of 5-6 in a room with a 12 h on-and-off lighting schedule. All experiments were performed according to the Guide for the Care and Use of Laboratory Animals, from the US Department of Health and Human Services.

2. Drugs

A twenty percent ethanol (Vetec, RJ, Brazil) solution in distilled water was administered orally (2 ml/kg body weight, corresponding to 4 g/kg, p.o.). Naltrexone

(Revian, 50 mg pill from Cristália Laboratory, Brazil) was grounded, suspended in distilled water, and administered orally at the dose of 10 mg/kg, p.o. All other drugs were of analytical grade.

3. Treatment

Ethanol (Etha), naltrexone (Nalt) and distilled water (controls) were administered by gavage. Treated animals as well as those from control groups were maintained on a normal diet and water *ad libitum*. The maintainence of controls on normal diet instead of isocaloric diet is also a procedure followed by others [17, 18]. Animals were treated daily with ethanol for 7 days and, at the 8^{th} day, ethanol was discontinued, and the group received only naltrexone, which was administered up to the 14^{th} day (Etha + Nalt). Groups treated with ethanol (4 g/kg, p.o., 7 or 14 days), naltrexone (10 mg/kg, p.o., 7 days) or distilled water (controls; 7 days) were also included.

4. Biochemical analyses

For biochemical analyses, blood samples were collected from each group in the morning, 48 h after the last drug administration. A minimal amount of blood (1 ml) was collected from the orbital sinus into tubes containing separator gel (from Vacuette, Brazil). Serum was separated by centrifugation at 3500 rpm for 10 minutes and immediately used for biochemical assays. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) transaminase were determined according to Bergmeyer et al. [19] and total plasma apoprotein AI (APO A1) was determined by quantitative immunoturbidimetric methods [20]. Concentrations of plasma TGI, TC and HDL-C were measured by standard enzymatic methods [20, 21] with a spectrophotometer Selectra II model from Winner.

5. Statistical analyses

All results are presented as means ± SEM. ANOVA and Student-Newman-Keuls as a *post hoc* test were used to compare results among treatments, and Student's t-test for comparison between two means. The significance level was set at $p<0.05$.

Results

The table 1 shows the results of ethanol (4 g/kg, p.o., 7 or 14 days) and naltrexone alone or after ethanol exposure on serum levels of ALT and AST, in rats. Although ethanol after daily administration for 7 days produced no effects on ALT and AST levels, it increased significantly in 53 and 39% ALT and AST levels respectively, with a prolonged treatment (14 days), as compared to controls (ALT:48.6±2.5; AST: 83.6±7.0). Naltrexone did not alter serum levels of these hepatic enzymes. In the naltrexone treated group, after ethanol exposure (Etha + Nalt), increases ranging from 48 and 34% were observed in ALT levels as compared to controls and ethanol 7 days respectively, and of 34 in AST levels as compared to controls.

Tab. 1. Effects of ethanol, naltrexone or, naltrexone after ethanol exposure, on serum levels of ALT and AST in rats. Animals were treated daily with distilled water (controls, 7 days), ethanol (Etha, 4 g/kg, p.o., 7 or 14 days) or naltrexone (Nalt, 10 mg/kg, p.o., 7 days). In the group Etha + Nalt, animals were treated daily with ethanol for 7 days and, at the 8th day, treatment continued only with naltrexone up to the 14th day. In all groups, 48 h after the last drug administration, 1 ml of blood was collected from the orbital sinus from each animal for biochemical analyses. The results were expressed in U/L and numbers represent means ± SEM of groups of animals (in parentheses). $p<0.05$, **a** and **b** as compared to controls and Etha 7 days respectively. (ANOVA and Student-Newman-Keuls as the *post hoc* test).
ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Group	ALT (U/L)	AST (U/L)	ASL/ALT
Control	48.6±2.5(5)	83.6±7.0(5)	1.7
Etha 7d	52.2±5.1(5)	103.8±8.3(5)	1.9
Etha 14 d	74.5±6.5(6) **a,b**	116.1±7.3(6) **a**	1.5
Naltrexone	58.5±2.9(6)	92.0±3.5(6)	1.5
Etha+Nalt	71.8±4.8(6) **a,b**	112.0±6.4(6) **a**	1.5

While ethanol did not alter APO A1 concentration, significant increases of 79% were detected in triglyceride levels, after 14 days ethanol treatment. This group also presented increases of 49 and 36% in TC and HDL-C levels respectively. Naltrexone increased APO A1 (68%) and TGI levels (107%) and decrease TC level (37%) as compared to controls. On the other hand, naltrexone did not alter HDL-C level as compared to same group. The APO A1 levels were also increased in 68 in the naltrexone group previously exposed to ethanol (Etha + Nalt) as compared to control group (Table 2).

In the naltrexone group previously exposed to ethanol (Etha + Nalt), TC concentrations were decreased when compared to controls, ethanol 7 days and 14 days and increased as compared to naltrexone. In the same group, APO A1 levels were significantly increased by 68% as compared to controls. Finally, HDL-C concentrations in the Etha + Nalt group were not significantly altered, except for a 34% decrease when compared to ethanol 14 days (Table 2).

Discussion

Although epidemiological studies concerning the effects of alcohol consumption on cardiovascular risk are still a controversial matter, this question seems to be partially explained by the relationship of several biochemical parameters associated to atherosclerosis and the amount of alcoholic beverages consumed [21, 22].

In the present work, we showed that ethanol significantly increased AST and ALT levels, as well as triglycerides, total cholesterol and HDL-C concentrations. However, except for the increased AST/ALT ratio after ethanol 7-day, no other difference was detected among groups. Other works also demonstrated a significant increase in the AST/ALT ratio after the intravenous infusion of ethanol to rats [23] or human [24]. These authors concluded that the ratio AST to ALT might be a useful index for acute alcohol intoxication. Similarly to our data, others [25] also found increased HDL-C levels in subjects consuming more than 100 g of

Tab. 2. Effects of ethanol, naltrexone or, naltrexone after ethanol exposure, on serum levels of apolipoprotein and lipoprotein concentrations in rats. Animals were treated daily with distilled water (controls, 7 days), naltrexone (Nalt, 10 mg/kg, p.o., 7 days) or ethanol (Etha, 4 g/kg, p.o., 7 or 14 days) daily for 14 days. In group Etha + Nalt, rats were treated with ethanol for 7 days and, at the 8th day, ethanol was discontinued and treatment continued with the naltrexone up to day 14. In all groups, 48 h after the last drug administration, 1 ml of blood was collected from the orbital sinus from each animal for biochemical analyses. The results were expressed in mg/dl and numbers represent means ± SEM of groups of animals (in parentheses). $p<0.05$, **a**, **b, c** and **d** compared to controls, Etha 7 days, Etha 14 days and Naltrexone, respectively (ANOVA and Student-Newman-Keuls as the *post hoc* test). APO= apolipoprotein; TGI= triglycerides; TC= total cholesterol; HDL= high density lipoproteins.

Group	APO A1 (mg/dl)	TGI (mg/dl)	TC (mg/dl)	HDL (mg/dl)
Control	0.95±0.07(13)	36.9±5.1(5)	49.0±3.9(6)	19.3±1.8(5)
Etha 7d	1.1±0.04(5)	51.9±2.3(5)	52.9±3.1(5)	22.1±1.1(5)
Etha 14 d	1.06±0.06(5)	65.9±5.6(5)**a**	72.9±1.6(5)**a,b**	26.2±0.7(5)**a**
Naltrexone	1.6±0.37(6)**a**	76.5±4.9(6)**a,b**	30.7±1.8(6)**a,b,c**	***18.4±0.7(6)****c*
Etha+Nalt	1.6±0.14(6)**a**	55.0±10.8(5)	40.3±1.7(6) **a,b,c,d**	17.4±1.7(6)**c**

alcohol per week as compared to non-consumers. Moderate alcohol intake is associated with lower atherosclerosis risk, presumably due to increased HDL-C concentrations [26] which occur in a dose-dependent fashion associated with and possibly caused by an increase in the transport rate of HDL apolipoproteins. As a matter of fact, this increase in high-density lipoprotein associated with alcohol intake appears to account for approximately half of the cardioprotective effect of alcohol [27].

Several works have also shown that alcohol increases HDL-C [28, 29] and may decrease LDL-C in blood [27, 30]. The enzyme activities of ALT, AST and

gama–glutamyltransferase (GGT) are considered to be a sign of alcohol abuse and are in general increased with alcoholism [31, 32]. Nemesanszky et al. [33] found a significant increase in serum AST activity, but no change in ALT activity, in moderate drinkers abstained from alcohol for 4 weeks and immediately after an ethanol challenge dose of 1 g/kg. Similarly, Nanji et al. [34] found an increased AST/ALT serum ratio, in the presence of cirrhosis, which may reflect a more severe liver damage.

It has been shown [35] that alcohol intake increases HDL-C in a dose-dependent fashion, associated with and possibly caused by an increase in the transport rates of HDL apolipoproteins APO A1 and AII. It was observed that the heterozygosity for a novel APO A1 mutation underlies a detrimental lipoprotein profile associated with enhanced coronay artery disease (CAD), indicating the pivotal role of APO A1 in the protection against CAD [36]. A data reported increased serum APO A1 and HDL-C concentrations, after 3 weeks of moderate alcohol consumption [37].

Although naltrexone is currently used as part of a treatment regimen for alcohol-dependent patients [38–40], most of the works in the literature, on its effect in the treatment of alcoholism, are related to ethanol-induced behavior alterations produced by this compound [41, 42]. Thus, studies on the potential benefit of the use of naltrexone to revert ethanol induced liver injury are rare. Although naltrexone seems to be efficacious in reducing alcohol consumption, its specific role in the alcoholism treatment remains to be more clearly defined [12]. The suppressive effect of opioid antagonists such as naltrexone, on ethanol intake, seems to be based on the interference with ethanol-induced stimulation of DA release in the nucleus accumbens. An earlier work [43] showed that mean plasma levels of hepatic enzymes did not show significant modification, in the course of long-term treatment with naltrexone.

In the present work, we observed that naltrexone had no effect on the hepatic enzymes, ALT and AST. However, it increased ALT and AST levels after previous exposure to ethanol and this is probably a consequence of the ethanol effect itself.

APO A1 levels increased in ethanol plus naltrexone group as related to controls and, as compared to ethanol groups, APO A1 levels showed a tendency to increase.

Although there are a great number of studies on the treatment of alcohol-dependence by naltrexone, only a few reports emphasize the beneficial effects of naltrexone on reversing plasma lipid alterations caused by ethanol. Earlier work showed that, in rats fed with a cholesterol-cholic acid supplemented diet, morphine elevated total plasma cholesterol, raised low density lipoprotein cholesterol and very low density lipoprotein (VLDL) cholesterol, and lowered HDL-C levels. The resulting increase of the atherogenic index was accompanied by enhanced aortic cholesterol deposition, and these alterations were prevented by daily naltrexone administration [44]. Also, preliminary investigation showed that treatment of alcohol dependence with naltrexone appeared to be feasible and effective [45]. Some studies using humans found a decreasing [46] or unaltered [47] levels of hepatic enzymes (ALT and AST) supporting that naltrexone did not induce hepatotoxicity.

Stressful stimuli are known to elevate total plasma cholesterol levels and activate the endogenous opioid system. Thus, in cholesterol-cholic acid fed rats, immobilization stress increased levels of low plus very low density lipoprotein cholesterol, and reduced levels of high density lipoprotein cholesterol. Pretreatment with the opiate antagonist naltrexone prevented stress induced changes. Morphine administration duplicated the cholesterol alteration seen in immobilized rats [48].

It has been also shown that naltrexone decreased significantly serum total cholesterol and triglyceride concentrations in alcohol-dependent patients, during withdrawal therapy [49]. The authors concluded that naltrexone by its hypolipaemic effect could be useful for withdrawal therapy in alcoholic patients, because it may decrease the cardiovascular risk in abstinent patients with alcohol dependence, by lipid mechanisms. In the present work, possible beneficial effects of naltrexone might be related to increased levels of APO A1 associated with decreased levels of cholesterol. Although TGI levels were highly elevated after naltrexone

administration, these values were reduced by naltrexone administered after ethanol exposure.

Our results indicated that ethanol effects undergo the influence of multiple variables such as dose, time of drug exposure and withdrawal, and also animal species. The beneficial hypolipaemic effect of naltrexone administration, followed by ethanol pretreatment, evidenced by the decreased triglycerides and total cholesterol levels, could be used as a favorable factor in the pharmacological treatment of alcoholism.

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