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Oxidation of apolipoprotein B-containing lipoproteins and serum paraoxonase/arylesterase activities in major depressive disorder

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Abstract

Major depressive disorder (MDD) is blaimed to play a role in the onset of coronary artery disease (CAD). The aim of the present study was to investigate serum paraoxonase/arylesterase activities and oxidation of apolipoprotein B-containing lipoproteins in patients with MDD. Oxidation of lipoproteins plays an important role in atherogenesis and the enzyme paraoxonase, has been shown to prevent lipoprotein oxidation. Furthermore, low paraoxonase activity was suggested to predict CAD. Eighty-six patients who fully met the fourth Diagnostic and Statistical Manual of Mental Disorders criteria for MDD and 36 healthy control subjects were included in the study. Serum paraoxonase and arylesterase activities were determined spectrophotometrically. Malondialdehyde (MDA) levels of apolipoprotein B-containing lipoproteins were determined before (basal) and after incubation with copper-sulphate, that yielded basal- and Δ-MDA values, respectively. Serum paraoxonase/arylesterase activities were significantly reduced in the post-treatment group compared with the pre-treatment group. Basal–MDA (MDA) level was significantly higher in the MDD group compared with the control group. Δ-MDA level of the severe MDD group was significantly higher than that of the control group. There was a positive correlation between the oxidizability of apolipoprotein B-containing lipoproteins and the severity of the disease. Total cholesterol, HDL-cholesterol, LDL-cholesterol, apolipoprotein B levels were significantly higher and apolipoprotein AI levels were significantly lower in the MDD group compared with those of the control group. The findings of the present study suggest that: 1) antidepressant treatment might reduce serum paraoxonase activity/mass; 2) oxidation and oxidizability of apolipoprotein B-containing lipoproteins seem to be increased in MDD.

Keywords: Aylesterase; Coronary artery disease; Lipid; Lipoprotein oxidation; Major depressive disorder; Paraoxonase

1. Introduction

Evidence is accumulating that mental health diseases, in particular depression contribute to the development of coronary artery disease (CAD) (Joynt et al., 2003; Lett et al., 2004; Rozanski et al., 1999; Wulsin and Singal, 2003). Depression is associated with poor health behavior, maladaptive coping style, social isolation and chronic life stress (Lett et al., 2004; Rozanski et al., 1999). Smoking, low physical activity, poor diet, and failure to adhere to medical recommendations are the behavioral risk factors that mediate the relationship of depression with CAD (DiMatteo et al., 2000; Ziegelstein et al., 2000). However, data from several studies demonstrated a significant increase in symptomatic and fatal ischemic heart disease after controlling for known medical risk factors (Barefoot and Schroll, 1996; Pratt et al., 1996). Some authors suggested that major depressive disorder (MDD) could be an independent, major and modifiable risk factor for CAD (Frasure-Smith and Lesperance, 2005; Wulsin, 2004). Several mechanisms by which depression may predispose to CAD have been proposed. Nervous system activation, cardiac rhythm disturbances, inflammation and hypercoagulability are the potential mechanisms mediating cardiovascular threat in depression (Joynt et al., 2003; Lett et al., 2004; Rozanski et al., 2005). However, the biological mechanisms of the association between MDD and CAD remain to be clarified.

Abbreviations: AE, arylesterase; CAD, coronary artery disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; hsCRP, high sensitive C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MDA, malondialdehyde; MDD, major depressive disorder; PON 1, paraoxonase; VLDL, very low density lipoprotein.

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It is well known that oxidation of low density lipoprotein (LDL) (Witzum, 1994) and other apolipoprotein B-containing lipoproteins play an important role in the initiation and progression of atherosclerosis (Jong et al., 2000; Zhang et al., 1993). Paraoxonase (PON 1) is an high density lipoprotein (HDL) associated enzyme, whose physiological role and substrate are not known. PON 1 exerts paraoxonase and arylesterase activities, since the enzyme hydrolyzes organophosphates (such as paraoxon) and aromatic esters (such as phenyl acetate) (Gan et al., 1991). PON 1 has been shown to prevent LDL and HDL oxidation and has also been proposed to stimulate cholesterol efflux, the first step in reverse cholesterol transport (Aviram et al., 1998; Mackness et al., 1993). Mounting evidence suggests that human serum paraoxonase activity is a predictor of CAD (Jarvik et al., 2000; Mackness et al., 2003). Low serum paraoxonase activity was reported in patients with CAD and in situations that are associated with enhanced atherogenesis, such as hypercholesterolemia and diabetes (Mackness et al., 1991).

Studies investigating the mechanisms underlying the association between depression and CAD are scanty. Furthermore, it is not clear whether successful treatment of MDD reduces the onset of CAD or the progression of existing CAD. So, understanding the biological mechanism underlying the association between MDD and CAD is critical. The aim of the present study was to test if serum paraoxonase activity was altered in depression and modified in response to treatment. For this purpose we determined serum paraoxonase and arylesterase activities, oxidizability of apolipoprotein B-containing lipoproteins and lipid profiles of patients with MDD. We also measured levels of serum high sensitive C-reactive protein (hsCRP) and homocysteine that are suggested to play role in both MDD and CAD (Anisman and Merali, 2002; Miller et al., 2005; Empena et al., 2005; Severus et al., 2001).

2. Methods

2.1. Subjects

Eighty-six patients diagnosed as having MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994) were included in the study. Patients with an Axis I disorder other than MDD or with an Axis II disorder, as well as patients having MDD with psychotic features, bipolar, cyclothymic, dysthymic or anxiety disorder or patients at significant suicide risk were excluded by a semi-structured psychiatric interview. Healthy controls (*n*: 36) were recruited from the hospital-university staff and were also assessed by a semi-structured psychiatric interview. The patients and the controls were examined by 2 independent specialists in psychiatry. All subjects were screened for any major health problems. Laboratory examinations, including complete blood count, serum electrolyte assay, liver function tests, thyroid function tests, urine analyses and electrocardiography were performed to all subjects. The patient group consisted of 62 women and 24 men (mean age±S.D.: 40.5±10.5, range: 20–55) and the control group consisted of 26 women and 10 men (mean age±S.D.: 37.2±7.3, range: 24–55). The MDD group was classified according to the Hamilton Depression Rating Scale (HDRS) scores as mild MDD (HDRS: 15–18, *n*: 33), moderate MDD (HDRS: 19–22, *n*: 35) and severe MDD (HDRS: 23 and more, *n*: 18). The patients had been drug-free for at least 3 weeks. Exclusion criteria for the patients were: having a physical or psychiatric disease other than depression as judged from their clinical and laboratory examinations. The patients were treated by various antidepressant drugs in standard antidepressant doses and, after 6 weeks of treatment, a decrease of 50% in HDRS was accepted as the response to treatment. Fifty-eight of the patients responded the treatment. After 6 weeks of treatment, blood samples from the 77 of the MDD patients, could be obtained.

2.2. Sample preparation

Blood was withdrawn from the antecubital vein in the fasting state. Serum triglyceride, total cholesterol, HDL-cholesterol, apolipoprotein AI and B, lipoprotein (a) and hsCRP levels were measured the same day that the blood was collected. Plasma obtained for determination of apolipoprotein B-containing lipoprotein oxidation was kept at 4 °C and assayed within 24 h. Serum aliquots for paraoxonase/arylesterase and homocysteine measurements were kept at −80 °C and analyzed within two months. The same procedures were performed for the samples obtained after the 6 weeks of treatment.

2.3. Analysis

Serum levels of the total cholesterol, HDL-cholesterol and triglyceride were determined using enzymatic assays on an Aeroset autoanalyzer (Abbott Laboratories. Irving, Texas, USA). LDL-cholesterol concentrations were calculated according to Friedewald's formula (Friedewald et al., 1972). Apolipoprotein AI, apolipoprotein B, lipoprotein (a) and hsCRP were assayed by immunonephelometry (Dade Behring Marburg GmbH, Germany). Homocysteine levels were determined using fluorescence polarization immunoassay on an Axsym autoanalyzer (Abbott Laboratories. Irving, Texas, USA).

Paraoxonase assays were performed in the absence (basal activity) and presence of NaCl (salt-stimulated activity). The rate of hydrolysis of paraoxon (diethyl-*p*-nitrophenylphosphate) was measured by monitoring the increase in absorbance at 412 nm at 25 °C. The amount of *p*-nitrophenol generated was calculated from the molar absorptivity coefficient at pH: 10.5, which was 18290 M^{-1} cm^{-1} (Eckerson et al., 1983). Phenylacetate was used as a substrate to measure the arylesterase activity. Enzymatic activity was calculated from the molar absorptivity coefficient 1310 M^{-1} cm^{-1} (Haagen and Brock, 1992).

The phenotype distribution of paraoxonase was determined by a double substrate method, which calculates the ratio of salt-stimulated paraoxonase activity and arylesterase activity (Adkins et al., 1993).

In order to study oxidizability of apolipoprotein B-containing lipoproteins, this fraction was precipitated with dextran sulphate-magnesium chloride and then EDTA was removed as described by Zhang et al. (1993). Cholesterol concentration of