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The association between norepinephrine and metabolism in patients with major depression

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ABSTRACT

Background: Previous studies indicate that levels of plasma norepinephrine (p-NE) are altered in depressed patients. However, it is unclear whether altered NE metabolism is involved in the pathogenic association between depression and cardiovascular disease. The aim of the present study was, firstly, to investigate if p-NE levels differ between patients with major depression and healthy controls. Secondly, the study sought to assess the associations between p-NE and metabolic variables in all participants. The third and final aim of the study was to assess if the associations between p-NE and metabolic variables are influenced by disease status (depression vs. healthy).

Methods: 108 patients with major depression and 44 healthy controls were tested for levels of p-NE and metabolic variables that affect cardiovascular risk.

Results: The median level of p-NE in depressed patients (DSM-IV) was 2636 pg/ml, (IQR 2094–3143) and 2279 pg/ml (IQR 2007–2562) in non-depressed controls ($p = 0.013$). However, the difference between p-NE levels was non-significant when adjusted for daily smoking ($p = 0.138$). Significant associations ($p \leq 0.05$) were observed between p-NE and p-lipids, mean arterial blood pressure, p-insulin, quantitative insulin sensitivity check index as well as inflammatory markers.

Conclusions: Elevated levels of p-NE observed in patients with major depression were attributable to daily smoking, rather than to the depressive disorder. Important associations were found between p-NE and metabolic variables that affect cardiovascular risk. This is interesting from a clinical point of view, since affected individuals may benefit from simple and inexpensive treatments that influence sympathetic activity. All associations were independent of disease status.

1. Introduction

Depression is a common, serious, and often reoccurring mood disorder considered to be a leading cause of disability adjusted life years (Ferrari et al., 2013). According to the World Health Organization, by 2030 unipolar depression is expected to be the second highest contributing factor to the global burden of disease, making depressive disorders a major global public health concern (Mathers & Loncar, 2006).

Clinical evidence shows a strong bidirectional comorbidity between depression and cardiovascular disease (CVD) (Cuijpers & Smit, 2002; Halaris, 2009; Hare, Toukhsati, Johansson, & Jaarsma, 2014; Kuehl, Penninx, & Otte, 2012). Multiple pathogenic mechanisms appear to contribute to the increased cardiovascular risk in depressed patients, e.g. the effects of depression on lifestyle behaviour (Whooley et al., 2008), on the immune system (Zahn et al., 2013), on platelet activity (Musselman et al., 1996), on endothelial function (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005), on the autonomic nervous system (Carney et al., 2001) and on hypothalamic-pituitary-adrenal (HPA) activity (Pariante & Lightman, 2008). Nowhere in the literature, however, have the effects of these factors been proven sufficient to account for the twofold risk of both CVD incidence and progression that depression appears to confer (Davidson, 2013). Possibly, the pathogenic mechanisms may further increase the risk of CVD when combined, but whether another specific variable is accountable or can be used as a predictor of CVD risk in depressed patients remains unclear (DiVincenzo, Reber, Perera, & Chilian, 2014).

Interestingly, chronic stress has proven to influence and strongly

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precipitate cardiovascular dysregulation and depressive illness (DiVincenzo et al., 2014; Steptoe & Kivimaki, 2012). Stress triggers release of corticotrophin-releasing hormone which plays a role in the pathophysiology of depression by activating the HPA-axis and exciting norepinephrinergic neuronal cell bodies of the locus coeruleus (Bissette, Klimek, Pan, Stockmeier, & Ordway, 2003; Heuser et al., 1998). The latter results in increased activity of the sympatho-adrenal-medullary axis and overall peripheral sympathetic nervous system (SNS) activity (Goldstein, McCarty, Polinsky, & Kopin, 1983; Thornton & Andersen, 2006). Therefore, levels of plasma norepinephrine (p-NE), which represent a useful measure to assess sympathetic neural function, may be altered in patients with depression (Grassi & Esler, 1999).

The effects of excessive catecholamines on metabolism and hemodynamics have been widely studied (Lambert et al., 2013; Mancia et al., 2007; Young & Macdonald, 1992). Hypertension and hypermetabolism characterized by increased lipolysis and glycogenolysis are among the direct effects caused by adrenoceptor stimulation in metabolically active organs and tissues (Petrak et al., 2013). Indirect effects include abnormal glucose metabolism and overproduction of proinflammatory cytokines such as IL-1, IL-6 and TNF-alpha (Morley, Thomas, & Wilson, 2006; Mraz et al., 2011; Schols, Buurman, Staal van den Brekel, Dentener, & Wouters, 1996; Tisdale, 2009). Both the direct and indirect effects of excessive catecholamines dispose individuals for developing the metabolic syndrome, which increases the risk of diabetes mellitus type 2 five times and the risk of CVD and cardiovascular death three times (Nakajima et al., 2013; Stern, Williams, Gonzalez-Villalpando, Hunt, & Haffner, 2004). Furthermore, p-NE has been found to be an independent predictor of prognosis in patients with congestive heart failure (Francis et al., 1993).

Altered levels of p-NE in depressive illness have been the topic of a limited number of studies which, however, yield inconclusive results. The studies are considered inconclusive due to methodological differences and small sample sizes. To the best of our knowledge, no studies have previously examined associations between potentially altered NE metabolism and risk factors of CVD in a large group of non-medicated patients with major depression.

The aim of the present study was, firstly, to investigate if p-NE levels differ between patients with major depression and healthy controls. Secondly, the study sought to assess the associations between p-NE and metabolic variables in all participants. The third and final aim of the study was to assess if the associations between p-NE and metabolic variables are influenced by disease status (depression vs. healthy).

2. Methods

2.1. Study design

The current study was conducted as a matched case-control study with a case group of 108 patients diagnosed with major depression and a matched control group of 44 non-depressed healthy subjects.

2.2. Study participants

We reanalysed the data from 108 depressed patients, who participated in a previous randomized clinical trial (the DEMO-II trial) that evaluated the antidepressant properties of aerobic exercise (Krogh, Videbech, Thomsen, Gluud, & Nordentoft, 2012). Eligible participants were men and women between 18 and 60 years of age, referred from a clinical setting by a physician or a psychologist, and with a diagnosis of major depression (DSM-IV) based on the Danish version of the Mini International Neuropsychiatric Interview (MINI) (Bech, Andersen, & Schütze, 1999). All included depressed participants signed the informed consent statement and scored above 12 on the Hamilton Depression Rating Scale (HAM-D17) (Hamilton, 1960). Exclusion criteria were current drug abuse, antidepressant medication within the last two months, current psychotherapeutic treatment, contraindications to physical exercise, regular recreational exercise over 1 h per week, suicidal behaviour according to the HAM-D17 (item 3, ≥2), pregnancy, or current/previous psychotic or manic symptoms. Out of the 227 potential participants that were referred to the trial site, 112 persons were excluded. The two primary reasons for exclusion were failure to meet the study criteria for depression (n = 32) and declining participation (n = 32). Data from 7 of the depressed participants were not available for assessment due to technical problems, thus 108 participants constitute the group of depressed patients for the current study. Healthy controls (n = 44) were recruited through the media and group matched to the patients with regard to sex, age, and body mass index (BMI). The healthy controls were free of any current or previous psychiatric diseases assessed by the MINI (Bech et al., 1999). Evaluation of patients and healthy controls was commenced in parallel.

2.3. Procedures

2.3.1. Examination

All participants met at the research department between 8:00 and 10:00 a.m. and had beforehand been instructed to refrain from eating and drinking anything except water beginning from midnight prior to the examination day. Furthermore, participants had been instructed not to perform any type of strenuous physical activity prior to the examination. At first, participants were weighed using an electronic scale (Sohnle Medicals, Type 7700, Backnang, Germany). Afterwards, following five uninterrupted minutes of rest in a sitting position, blood pressure was measured using a certified digital blood pressure monitor (Omron M6, Omron Healthcare co. LTD, Kyoto, Japan). Three measurements were performed on each participant, and the average blood pressure was reported. After another 5 min of rest in a sitting position, blood samples were collected through an indwelling venous catheter placed in an antecubital vein. Immediately, the samples were centrifuged at room temperature and stored at −80 °C with light protection until being analysed in the laboratory by automated procedures.

2.3.2. Norepinephrine assay

Quantification of p-NE levels was performed with enzyme-linked immunosorbent assay (ELISA) kits from Whuan EIAab Science Co., LTD, A1710 Guangguguoji East Lake Hi-Tech Zone Wuhan 430074 China. The same batch number was used for the entire experiment. The determination was processed according to the manufacturer´s specifications, and the absorbance was immediately measured at 450 nm (EL 800 Universal Microplate reader, Bio-Tek instruments, INC). The standard curves and the samples (blinded) were run in duplicate. Two controls were included on each plate. The standard curves ranged from 31.2 to 2000 pg/ml NE. The samples were diluted 10 times to be within the range of the standard curve. The intra-assay coefficient of variance for the present study was 7.6%. Therefore, duplicate determinations of absorbency with an intra-assay variance above 7.6% were determined again another day. The average of the duplicates was used in the statistical analyses.

2.4. Outcome measures

2.4.1. Primary outcome

P-NE was measured as stated in Section 2.3.2.

2.4.2. Secondary outcomes

With the purpose of assessing associations between p-NE and metabolism, all participants had the following variables measured: 1) Mean arterial blood pressure (MAP) (measured as stated in Section 2.3), 2) Plasma lipids: HDL, LDL, triglycerides and cholesterol, 3) Plasma glucose, 4) Plasma insulin, 5) Insulin sensitivity (measured by quantitative insulin sensitivity check index (QUICKI)), 6) BMI and waist circumference (used as measures of general and abdominal obesity, respectively), 7) Inflammatory markers: Plasma high-sensitivity CRP