Psychoneuroendocrinology 68 (2016) 186–193

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Higher macrophage superoxide anion production in coronary artery disease (CAD) patients with Type D personality

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ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form 28 February 2016
Accepted 29 February 2016

Keywords:
Human macrophages
NADPH oxidase
Superoxide anions
CAD
Type D personality

ABSTRACT

Background: Type D personality (Type D) is an independent psychosocial risk factor for poor cardiac prognosis and increased mortality in patients with cardiovascular disease (CVD), but the involved mechanisms are poorly understood. Macrophages play a pivotal role in atherosclerosis, the process underlying coronary artery disease (CAD). We investigated macrophage superoxide anion production in production in CAD patients with and without Type D.

Methods and results: We studied 20 male CAD patients with Type D (M:66.7 ± 9.9years) and 20 age-matched male CAD patients without Type D (M:67.7 ± 8.5years). Type D was measured using the DS14 questionnaire with the two subscales 'negative affectivity' and 'social inhibition'. We assessed macrophage superoxide anion production using the WST-1 assay. All analyses were controlled for potential confounders. CAD patients with Type D showed higher superoxide anion production compared to CAD patients without Type D ($F(1,38) = 15.57$, $p < 0.001$). Complementary analyses using the Type D subscales 'negative affectivity' and 'social inhibition', and their interaction as continuous measures, showed that both Type D subscales (negative affectivity: ($\beta = 0.48$, $p = 0.002$, $R^2 = 0.227$); social inhibition: ($\beta = 0.46$, $p = 0.003$, $R^2 = 0.208$)) and their interaction ($\beta = 0.36$, $p = 0.022$, $R^2 = 0.130$) were associated with higher WST-1 reduction scores. Results remained significant when controlling for classical CVD risk factors (i.e. body mass index, mean arterial blood pressure), atherosclerosis severity (i.e. intima media thickness, presence of carotid plaques), and psychological factors (depressive symptom severity, chronic stress).

Conclusions: Our results indicate higher macrophage superoxide anion production in CAD patients with Type D compared to those without Type D. This may suggest a mechanism contributing to increased morbidity and mortality in CAD patients with Type D.

1. Introduction

Inflammatory processes play a pivotal role in the progression of coronary artery disease (CAD) and its underlying process atherosclerosis (Libby, 2002). Macrophages are tissue-resident phagocytic immune cells derived from circulating blood monocytes (Lucas and Greaves, 2001). A key initial event of coronary atherosclerosis is the entry of monocytes into the arterial intima, where they mature into macrophages. Intimal macrophages phagocyte oxidized lipoproteins and eventually differentiate into foam cells, a critical and prevalent component of atherosclerotic plaques. Moreover, macrophages are important mediators of inflammation in atherosclerosis (Moore et al., 2013; Robbins et al., 2013).

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http://dx.doi.org/10.1016/j.psyneuen.2016.02.031
0306-4530/

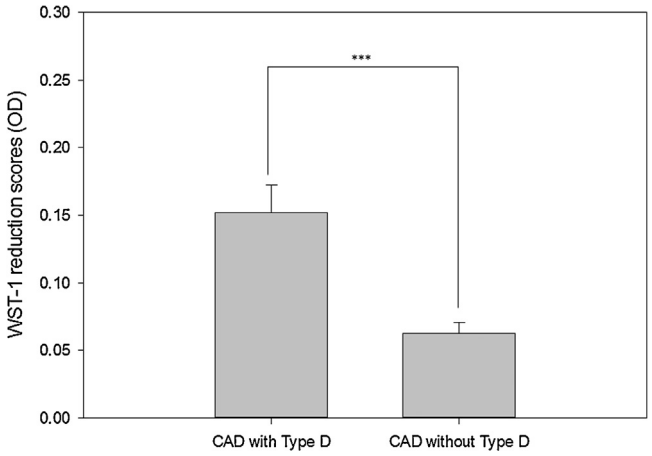

Fig. 1. WST-1 reduction scores in coronary artery disease (CAD) patients with Type D personality (Type D) and CAD patients without Type D (mean ± SEM). CAD patients with Type D had higher WST-1 reduction scores than those without Type D ($p < 0.001^{***}$).

Microbicidal activity, i.e. the killing of microbes, is a key innate immune effector function of classically activated macrophages also known as inflammatory M1 macrophages (Martinez et al., 2008; Mosser and Edwards, 2008). Macrophage microbicidal activity is largely mediated by increased secretion of microbe killing oxidizing agents termed reactive oxygen species (ROS; De Oliveira-Junior et al., 2011; Halliwell, 2006). ROS production in turn derives from activation of the multisubunit enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase located in the phagolysosome and plasma membrane of macrophages. Once activated, NADPH oxidase transfers electrons from NADPH in the cytosol to extracellular or intraphagolysosomal oxygen molecules. These oxygen molecules are then chemically reduced to highly reactive superoxide anions and other ROS subtypes (De Oliveira-Junior et al., 2011; Cathcart, 2004). In particular, superoxide anions are of major importance for the microbicidal activity of macrophages in host defense (Mosser and Edwards, 2008; Nathan and Shiloh, 2000).

Increasing evidence suggests that NADPH oxidase and the resulting production of superoxide anions are likely to play a critical role in the pathogenesis of atherosclerosis. For instance, NADPH oxidase-derived superoxide anions can induce low-density lipoprotein oxidation (Cathcart, 2004; Cai and Harrison, 2000; Griendling et al., 2000) an important cause of endothelial dysfunction as an initial step in atherosclerosis (Libby, 2002; Libby et al., 2011). Indeed, NADPH oxidase-deficient mice developed significantly smaller atherosclerotic lesions (Barry-Lane et al., 2001). Compared with healthy controls, CAD patients had greater NADPH oxidase activation and subsequent superoxide anion production in coronary arteries. This ROS increase was partly related to higher monocyte/macrophage infiltration (Guzik et al., 2006). Moreover, in CAD patients, superoxide anion production by stimulated neutrophils was enhanced with increasing arterial stiffness, a marker of adverse cardiovascular prognosis (Wykretowicz et al., 2005).

Different psychosocial factors significantly relate to the pathogenesis of CAD (Chida and Steptoe, 2009; Rosanski, 2014) and have been identified as risk factors for cardiac events both in healthy subjects and CAD patients (Chida and Steptoe, 2009; Lichtman et al., 2008). Type D ("distressed") personality (Type D) is defined as a tendency to experience negative emotions, and to inhibit their expression in a social context (Denollet et al., 1996). Evidence suggests that Type D is an independent predictor of cardiovascular morbidity and mortality in patients with CAD (Denollet et al., 2013; Grande et al., 2004; O'Dell et al., 2011). However, potential mechanisms underlying poor cardiac prognosis with Type D are unclear and may include inflammatory processes (Denollet et al., 2003; Kupper and Denollet, 2007). Indeed, two studies with chronic heart failure (CHF) patients found Type D to independently predict increased circulating levels of tumor necrosis factor (TNF)-α and TNF-α soluble receptors (Conraads et al., 2006; Denollet et al., 2003). Of note, TNF-α is a pro-inflammatory cytokine involved in atherosclerosis development and progression (Libby, 2002) and also in the pathogenesis of CHF (Aukrust et al., 2005). Furthermore, in CHF patients Type D was associated with increased oxidative stress evidenced by assessing heat shock protein (HSP) 70 and xanthine oxidase (Kupper et al., 2009).

As yet, superoxide anion production in CAD patients with Type D has not been studied. Therefore, the aim of this study was to compare phagocytic NADPH oxidase-derived superoxide anion production by inflammatory M1 macrophages between CAD patients with and without Type D. To rule out potential confounding effects of age on superoxide anion production (Fulop et al., 2004; Shaw et al., 2013), we recruited CAD patients with and without Type D individually matched on age. Given the important role of both superoxide anion production and Type D in the pathogenesis and progression of CAD, we hypothesized that Type D patients would show higher superoxide anion production when compared with non-Type D patients.

2. Materials and methods

2.1. Patients with coronary artery disease

This study was part of a larger project assessing psychobiological mechanisms in patients with CAD. We contacted male patients who were diagnosed with CAD at the Cardiac Prevention and Rehabilitation Clinic, Bern University Hospital, Switzerland, at least 6 months previously. Patients interested to participate were screened by telephone interview using an extensive health questionnaire. Explicit exclusion criteria were: regular strenuous exercise, alcohol and illicit drug abuse, liver and renal diseases, chronic obstructive pulmonary disease, allergies and atopic diathesis, rheumatic diseases, HIV, cancer, psychiatric and neurological diseases, and current infectious diseases. Between December 2012 and June 2015, we enrolled a total of 101 male patients with a diagnosis of CAD who were also assessed for Type D (see below). For every patient classified as Type D, we recruited an age-matched CAD patient without Type D. Given well-known effects of age on various parameters of the immune system (e.g. Fulop et al., 2004; Shaw et al., 2013), we decided for an age-matched design allowing us to minimize potential confounding of macrophage superoxide anion production by age. In total, we identified 20 eligible CAD patients with Type D personality and recruited 20 eligible age-matched CAD patients without Type D. For one 38-year-old CAD patient with Type D, we were unable to recruit an age-matched CAD patient without Type D; instead, we recruited an older control patient. Data of CAD patients were extracted from hospital charts and included the diagnosis of myocardial infarction (MI), left ventricular ejection fraction (LVEF), coronary artery bypass graft surgery (CABG), and the number of diseased coronary vessels (i.e., stenosis of at least 50%). Missing data regarding the number of diseased vessels from 4 patients were estimated using the expectation-maximization (EM) algorithm (Moon, 1996). The project was approved by the Ethics Committee of the Canton of Bern, Switzerland and the study protocol is in accordance with the Declaration of Helsinki. All study procedures were carried out with adequate understanding and written informed consent of all participants.