



Major depression induces oxidative stress and platelet hyperaggregability



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ABSTRACT

We have previously demonstrated an impairment of intraplatelet L-arginine-nitric oxide-cGMP pathway in major depression (MD) associated to platelet dysfunction. Here, we evaluated arginase pathway and phosphodiesterase 5 (PDE5) expression in platelets, systemic and intraplatelet oxidative status in untreated MD patients, and their effects on platelet aggregation. Blood samples were collected from 22 treatment naive MD patients (31 ± 2 yr) and 27 healthy subjects (33 ± 2 yr). MD patients presented with an activation of platelet arginase II, which competes with L-arginine for the production of nitric oxide (NO). An increase in protein carbonylation, overexpression of NADPH oxidase and PDE5, an enzyme that inactivates cGMP, was observed in platelets from MD patients compared to controls. In this context, platelet hyperaggregability was found in MD patients. On the other hand, antioxidant enzymes catalase, glutathione peroxidase and superoxide dismutase activities in serum and in platelets did not differ between groups. The increased activation of intraplatelet arginase and platelet aggregability, in addition to an overexpression of PDE5 and oxidative stress may contribute to alterations in L-arginine-NO-cGMP pathway and in platelet function, and consequently to the increased thrombotic risk in MD.

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1. Introduction

Major depression (MD) is considered an independent risk factor for cardiovascular disease (CVD), and depressed patients with pre-existing CVD also present an increased mortality risk (Baghai et al., 2011; Brown et al., 2009; Chrapko et al., 2004; Pinto et al., 2008; Roose, 2000). To date, the exact mechanisms linking MD and CVD are not well known.

It has been suggested that nitric oxide (NO) bioavailability or abnormalities in its signaling pathways may be involved in the occurrence of cardiovascular events in psychiatric diseases (Chrapko et al., 2004; Le Melledo et al., 2004; Pinto et al., 2008). NO

is a potent vasodilator and inhibitor of platelet function, and its synthesis occurs through the conversion of the amino acid L-arginine to L-citrulline and NO by a family of enzymes known as nitric oxide synthase (NOS) (Brunini et al., 2007; Mendes Ribeiro et al., 1999). The majority of NO effects occur through a highly regulated interplay of cGMP formation by NO-induced activation of soluble guanylyl cyclase (sGC) and its degradation by phosphodiesterases (PDE), particularly PDE 5 (Berkels et al., 2001; Brunini et al., 2007).

The cationic amino acid L-arginine is also involved in the urea cycle. It is a substrate for arginase, which hydrolyzes L-arginine into L-ornithine and urea (Mendes Ribeiro et al., 1999; Pereira et al., 2010). Two arginase isoforms have been described: arginase I, present in cytosol, and arginase II, present in mitochondria, but only arginase II has been detected in human platelets (Mendes Ribeiro et al., 1999; Pereira et al., 2010). As arginase competes with NOS for L-arginine, changes in arginase activity can affect NO bioavailability. Moreover, L-ornithine is the principal precursor for production of polyamines required for cell proliferation and differentiation, which is a main feature of atherosclerotic lesions and restenosis (Forte et al., 2011).

Abbreviations: CVD, cardiovascular disease; cGMP, cyclic guanosine monophosphate; GPx, glutathione peroxidase; MD, major depression; NO, nitric oxide; NOS, nitric oxide synthase; PDE5, phosphodiesterase 5; RBC, red blood cells; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase; SOD, superoxide dismutase.

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Oxidative stress is one of the major factors known to reduce NO bioavailability (Valko et al., 2007). It is described as an imbalance between reactive oxygen species (ROS) generation and the biological ability of the body to neutralize them, by means of enzymatic and non-enzymatic antioxidant defence mechanisms. The major antioxidant enzymes include copper–zinc superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), while non-enzymatic antioxidants include bilirubin, uric acid, glutathione, and vitamins A, C, and E (Valko et al., 2007). On the other hand, ROS generation occurs through mechanisms mainly involving NADPH oxidases in the vascular system and in blood cells (Bedard and Krause, 2007). Excessive ROS production, namely superoxide anion, is likely to increase quenching of NO and to activate platelets. Moreover, ROS have direct effect in all stages of platelet activation (Bedard and Krause, 2007), and to our knowledge, there is no report of the oxidative status in platelets from patients with MD.

Platelets are an essential component of the hemostatic process, which happens as follows. In brief, mechanical disruption of blood vessels initiates localized hemostatic responses involving interactions of vascular endothelium, platelets, red blood cells, coagulation and fibrinolysis (Fig. 1). Platelet thrombus formation involves three main steps: platelet adhesion to the damaged endothelium, its activation, and aggregation. Platelet activation involves the generation of intracellular chemical signals that are initiated by platelets through specific surface receptors (e.g. integrins). These signals cause dramatic morphological changes such as the extension of pseudopodia, platelet–platelet aggregation, and granule secretion (e.g. adenosine diphosphate, thromboxane A₂, serotonin), resulting in the generation of platelet thrombus [for an excellent detailed review, please refer to Versteeg et al. (2013)]. Supporting the importance of platelet-dependent thrombosis, the inhibition of platelet activation and aggregation is a common therapeutic target for the acute treatment and secondary prevention of ischemic events (Franchi and Angiolillo, 2015). Platelet dysfunction is a possible mechanism through which depression may increase cardiovascular risk (Celano and Huffman, 2011). In fact, patients with depression have more circulating platelet-leukocyte aggregates compared to controls, indicating a heightened level of platelet activation, which was demonstrated to be directly associated with the severity of depression (Morel-Kopp et al., 2009). In addition, our group has previously demonstrated increased platelet aggregation induced by ADP, associated with an inhibition of intraplatelet L-arginine-NO pathway in patients with MD and bipolar disorder (Fontoura et al., 2012; Pinto et al., 2012).

In the present study, we aimed to improve the biological understanding of the factors that modulate NO bioavailability and platelet dysfunction. Therefore, it was assessed oxidative status, platelet aggregation, arginase pathway and phosphodiesterase 5 expression in platelets from untreated young adults with MD. Biomarkers of oxidative stress were also assessed in serum.

2. Material and methods

2.1. Subjects

The final patient sample consisted of 22 adult patients (18 female and 4 male) with MD recruited from the outpatient clinic of the Department of Applied Psychology of the University of the State of Rio de Janeiro, Brazil. The control group consisted of 27 healthy subjects (17 female and 10 male) recruited from the staff of the University, selected to be demographically and age matched to the depression group. Healthy control subjects did not have a diagnosis of a current or past psychiatric Axis I disorder. Participants were recruited from December 2010 to March 2013.

MD patients were included only if they were treatment naive, therefore they were not under previous or current drug or psychotherapeutic treatment. Furthermore, subjects were excluded if they were smokers, or if they presented past or current CVD, renal failure, mental retardation, diabetes mellitus, infection, or dyslipidemia. This investigation conforms to the principles outlined in the Declaration of Helsinki as revised in 2008. All subjects gave written consent after a full written and verbal explanation of the study. Ethical approval was obtained from the Pedro Ernesto University Hospital Ethical Committee (1436 – CEP/HUPE) before the commencement of the study.

2.2. Assessment instruments

All subjects were assessed using a validated translated Portuguese version of the Mini International Neuropsychiatric Interview (Amorim, 2000) to ensure accuracy and standardization of psychiatric diagnoses, and all patients from the MD group met DSM-IV criteria for major depressive disorder. MD patients that presented anxiety symptoms such as irritability, sleeping problems or nervousness were not excluded, as it is a common co-occurrence of this disease (Kessler et al., 1996). However, none of these subjects presented a diagnostic of anxiety disorder as categorized by DSM-IV.

A validated Portuguese version of the 17-item Hamilton Depression Rating Scale (Moreno and Moreno, 1998) was also administered to assess the severity of MD. According to this scale, depression was considered mild in 37% of patients, moderate in 53%, and severe in 10% of patients.

2.3. Sample preparation and procedures

After a 12-h fasting, 15 mL of blood was collected by venipuncture for usual laboratory testing. In addition, 45 mL blood was collected for the experimental procedures described as follows. The venous blood was anticoagulated with acid-citrate-dextrose (73.7 mM citric acid, 85.9 mM trisodium citrate and 111 mM dextrose, pH 4.5). As described previously (Mendes Ribeiro et al., 1999), platelet-rich plasma (PRP), obtained by centrifugation of

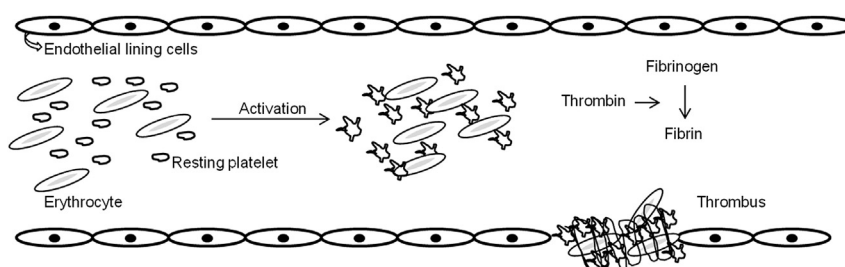


Fig. 1. Platelets during the formation of platelet plug in hemostasis.

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