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Research report

Increased autoimmune responses against auto-epitopes modified by oxidative and nitrosative damage in depression: Implications for the pathways to chronic depression and neuroprogression

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ABSTRACT

Objective: There is evidence that major depression is characterized by oxidative and nitrosative stress (O&NS). The aim of this study is to examine IgM-mediated autoimmune responses against a variety of modified neo-epitopes formed by O&NS damage to self-epitopes in chronic depression.
Methods: Serum IgM antibodies directed against conjugated oleic and azelaic acid, malondialdehyde (MDA), phosphatidyl inositol (Pi), and conjugated nitric-oxide (NO) adducts, i.e., NO-tryptophan, NO-tyrosine, NO-arginine, and NO-cysteinyl, were determined in 33 healthy controls and 74 depressed patients subdivided into 28 patients with chronic (duration >2 year) and 46 without chronic depression.
Results: Serum IgM levels against all neoepitopes were significantly higher in depressed patients than in healthy controls. Moreover, the IgM levels were significantly higher, except Pi, in chronically depressed patients than in non-chronically depressed patients.
Conclusions: Depression is characterized by IgM-related autoimmune responses directed against neo-epitopes that are normally hidden from the immune system but that became immunogenic secondary to damage by O&NS. The results show that the generation of neoantigenic determinants that lead to (auto)immune responses is strongly associated with chronic depression.
Discussion: The damage caused by O&NS to auto-epitopes and the consequent formation of O&NS modified neoantigenic determinants may increase the risk to develop depression and in particular chronic depression through transition to autoimmune reactions. This has implications for understanding the immuno-inflammatory and oxidative-autoimmune pathways that lead to chronic depression and neuroprogression in that illness.

1. Introduction

There is evidence that depression is characterized by an imbalance in the equilibrium between antioxidants and reactive oxygen (ROS) or nitrogen species (RNS), resulting in enhanced oxidative and nitrosative stress (O&NS) that in turn damages fatty acids, proteins and DNA (Maes et al., 2011a; Leonard and Maes, 2012). Under physiological conditions, the production of ROS and RNS is counterbalanced by antioxidants that scavenge free radicals and prevent damage by O&NS. In 2000 (Maes et al., 2000) we reviewed that in depression there is a decreased antioxidant status, as indicated by lowered tryptophan, tyrosine, albumin, zinc and vitamin E levels. Since then many papers have shown lowered levels of key antioxidants and antioxidant enzymes in depression, e.g., vitamin E, glutathione, coenzyme Q10, zinc and glutathione peroxidase (Owen et al., 2005; Ozcan et al., 2004; Kodydková et al., 2009; Maes et al., 2009a, 2011b; Nowak et al., 2005; Szewczyk et al., 2011). Lowered antioxidant defences predispose depressed patients towards increased O&NS and the ensuing damage to fatty acids, DNA and proteins, and apoptosis

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and tissue loss (Maes et al., 2009a, 2011a, 2011d; Ghosh et al., 2011; Lu et al., 2011). Sings of oxidative stress in depression include increased (a) peroxide and xanthine oxidase levels; (b) levels of 8-hydroxy-2-deoxyguanosine, a mutagenic DNA lesion caused by hydoxylation; and (c) lipid peroxidation, as indicated by increased malondialdehyde (MDA), a by-product of polyunsaturated fatty acid peroxidation and arachidonic acid; increased 8-iso-prostaglandin F2α, a byproduct of arachidonic acid peroxidation; and increased levels in the cortex of 4-hydrononenal (HNE), a byproduct generated by peroxidation of ω6 fatty acids (Khanzode et al., 2003; Herken et al., 2007; Dimopoulos et al., 2008; Gałecki et al., 2009; Wang et al., 2009; Maes et al., 2010). Animal models of depression very consistently show lowered antioxidant levels and increased O&NS, in particular lipid peroxidation, while treatments with antioxidants or antidepressants reverse depressive-like behaviours, and lipid peroxidation and lowered antioxidant levels (Song et al., 1994; Maes et al., 2011a). Oxidative stress is associated with shortened telomeres, and mood disorders are associated with shortened telomeres (Watfa et al., 2011; Zhang et al., 2010). Finally, there is a significant association between depression and different single nucleotide polymorphisms (SNPs) of O&NS genes, such as inducible NO synthase, superoxide dismutase, and myeloperoxidase (Gałecki et al., 2010a, 2010b, 2010c, 2011).

During O&NS processes, chemical modifications to lipids and proteins occur that change the natural structure of otherwise ubiquitous epitopes that are normally hidden from the immune system. Consequently, the epitopes are modified to generate new epitopes (neo-epitopes; neoantigenic determinants) that may serve as triggers to bypass immune tolerance (Maes et al., 2006, 2007, 2011c; Geffard et al., 2002). This process in turn may change or abrogate the functions of the epitope and the person may mount autoimmune reactions directed against these neo-epitopes thus further changing the biological activities of the auto-epitopes and causing more inflammatory reactions. In depression, there are data that autoimmune reactions may be mounted against neo-epitopes, including reports of (a) increased plasma IgG antibodies against oxidatively modified LDL epitopes (Maes et al., 2010); and (b) increased IgM-mediated autoimmune responses against conjugated phosphatidyl inositol (Pi), an intracellular component of the cell-membrane that plays a key role in intracellular signaling (Maes et al., 2007), and anchorage molecules including palmitic and myristic acid and *S*-farnesyl-cysteine (Maes et al., 2011c). These findings show that a variety of auto-epitopes are modified by O&NS, making them immunogenic, resulting in autoimmune responses directed against the neo-epitopes. These autoimmune responses are also found in chronic and/or relapsing inflammatory, (auto)immune disorders, such as multiple sclerosis and chronic fatigue syndrome (Maes et al., 2006, 2007; Geffard et al., 2002).

It is understood that depression is quite often a progressive disorder (Moylan et al., 2012). With increased numbers of episodes there is a greater risk of recurrence with recurrence triggered by smaller stressors, and there is a declining probability of response to treatment. There is evidence of progressive neuroanatomical change, as well as of cognitive decline (Maes et al., 2009b, 2011a, 2011b; Catena-Dell'Osso et al., 2011). Concordant with these findings, the staging model has been advanced to integrate these findings into a conceptual framework capable of explaining this process, and guiding treatment (Berk et al., 2007a, 2007b; Moylan et al., 2012). These developments similarly support the importance of prompt diagnosis, active treatment and of early intervention (Berk et al., 2010). It could be hypothesized that the previously outlined autoimmune processes may be core to the process of neuroprogression in the pathophysiology of chronic or recurrent depression (Maes et al., 2012). Neuroprogression is defined as the stage related and potentially progressive process of neurodegeneration, including apoptosis, reduced neurogenesis and neuronal plasticity (Moylan et al., 2012).

The aims of the present study were to examine serum IgM antibodies to a variety of O&NS-modified epitopes in depression and chronic depression, i.e., conjugated oleic acid, an ω9 monounsaturated membrane fatty acid; conjugated MDA and azelaic acid, a saturated C9 dicarboxylic acid that can be derived by oxidation from fatty acids, such as oleic acid; and conjugated NO-adducts, including NO-modified amino-acids, such as NO-tryptophan, NO-tyrosine, NO-arginine and NO-cysteine. Oleic acid and Pi play a role in cell membrane functions and in addition act as neurotrophic factors (Calder et al., 1994; Alberts et al., 1994; Tabernero et al., 2001; Ananthanarayanan et al., 2005). Azelaic acid and MDA are two byproducts of fatty acid peroxidation and thus increased antibody titers directed against these molecules indicate enhanced autoimmunity against oxidized fatty acids (Geffard et al., 2002). Autoimmune responses against NO adducts are non-protein specific but indicate increased autoimmune responses against nitrosatively modified proteins (Maes et al., 2011c).

2. Subjects and methods

2.1. Subjects

One-hundred and seven subjects participated in this study, including 33 healthy controls and 74 depressed outpatients. All patients were admitted to the Maes Clinic, Antwerp, Belgium. The healthy controls were laboratory personnel or their family members. The social-economical level of both groups was comparable, i.e., higher middle class (and this in the Benelux where the differences between the classes are minimal). We made the diagnoses "major depression" using a semistructured interview according to DSM-IV-TR criteria (American Psychiatric Association, 2002). Severity of depression was measured with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The severity of fatigue and physiosomatic symptoms, which are a key component of depression (Maes, 2009), was measured with the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF scale) (Zachrisson et al., 2002). The FF scale measures 12 F&S symptoms, i.e., FF1 muscle pain, FF2 muscular tension, FF3 fatigue, FF4 concentration difficulties, FF5 failing memory, FF6 irritability, FF7 sadness, FF8 sleep disturbances, FF9 autonomic disturbances, FF10 irritable bowel, FF11 headache, and FF12 a flu-like malaise. The sum of the scores on the 12 items was employed as a measure of severity of F&S symptoms.

Patients were classified as suffering from chronic major depression when the actual depressive episode lasted longer than 2 years. The number of previous depressive episodes was registered and examined as the estimated number of episodes or using threshold values, e.g., >2, >3, >4 and >5 episodes. We excluded subjects (a) with medical illnesses, such as diabetes type 1 and 2, essential hypertension, inflammatory bowel disease and rheumatoid arthritis; COPD, neurodegenerative disorders, e.g., Parkinson and Alzheimer's disorder, and multiple sclerosis; (b) who suffered from inflammatory or allergic responses 2 months prior to the study; (c) who had been treated with immunomodulatory drugs, such as glucocorticoids; statins; β-blockers; antioxidant supplements, etc.; and (d) with a body mass index >30 (calculated as weight (kg)/body height (in meter)^2, alcohol abuse and smoking. We did however not control from the menstrual cycle in female healthy controls and depressed patients. Moreover, healthy controls were only included if they had never suffered from any axis-1 diagnoses, or chronic fatigue syndrome, fibromyalgia, and irritable bowel