Progress in Neuro-Psychopharmacology & Biological Psychiatry 48 (2014) 102–111

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

A review of peripheral biomarkers in major depression: The potential of inflammatory and oxidative stress biomarkers

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ARTICLE INFO

Article history:
Received 21 August 2013
Received in revised form 11 September 2013
Accepted 26 September 2013
Available online 5 October 2013

Keywords:
Biomarkers
Inflammation
Major depression
Oxidative stress

ABSTRACT

Biomarkers are regularly used in medicine to provide objective indicators of normal biological processes, pathogenic processes or pharmacological responses to therapeutic interventions, and have proved invaluable in expanding our understanding and treatment of medical diseases. In the field of psychiatry, assessment and treatment has, however, primarily relied on patient interviews and questionnaires for diagnostic and treatment purposes. Biomarkers in psychiatry present a promising addition to advance the diagnosis, treatment and prevention of psychiatric diseases. This review provides a summary on the potential of peripheral biomarkers in major depression with a specific emphasis on those related to inflammatory/immune and oxidative stress/antioxidant defences. The complexities associated with biomarker assessment are reviewed specifically around their collection, analysis and interpretation. Focus is placed on the potential of peripheral biomarkers to aid diagnosis, predict treatment response, enhance treatment-matching, and prevent the onset or relapse of major depression.

Contents

Abbreviations: 8-OHdG, 8-hydroxy-2-deoxyguanosine; 8-oxoGuo, 8-oxo-7,8-dihydroguanosine; BDNF, brain-derived neurotropic factor; BMI, body mass index; COX, cyclooxygenase; CRP, C-reactive protein; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; ESR, erythrocytes sedimentation rate; F2-isoPM, 2,3-dinor-5,6-dihydro-15-F2t-isoprostane; GPx, glutathione peroxidase; **GTP-CH1**, **GTP cyclohydrolase I**; hs-CRP, high sensitivity CRP; IDO, indoleamine 2,3 dioxygenase; IFN, interferon; IL, interleukin; IL-2R, interleukin-2 receptor; KYN, kynurenine; KYNA, kynurenic acid; MDA, malondialdehyde; RA, rheumatoid arthritis; RBC, red blood cell; RNA, ribonucleoside; SOD, superoxide dismutase; SSRI, serotonin reuptake inhibitor; TNF, tumour necrosis factor; TRP, tryptophan; TRYCATs, tryptophan catabolites along the IDO pathway.

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0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.09.017

1. Introduction

Currently the diagnosis of major depression is carried out through a combination of patient interviews, checklists and self-report questionnaires. These generally rely on a list of symptoms derived from the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) and now more recently, its revised 5th edition, DSM-5. Unfortunately, there is debate about the value and objectivity of this symptom-based assessment process (Hilsenroth et al., 2004; Phillips et al., 2012; Stein et al., 2010) particularly around limitations associated with the development of personalised treatment plans.

Biomarkers are indicators of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention that can be measured and evaluated objectively (Biomarkers Definitions Working Group, 2001). They have the potential to overcome some of the issues associated with symptom-based assessments. In medical and pharmaceutical practice, biomarkers are regularly used to support the presence or absence of specific diseases (diagnostic biomarkers), predict optimal treatment options (treatment biomarkers), measure treatment progress (treatment-response biomarkers), and predict the onset of future disease (predictive biomarkers) (Boksa, 2013; Kluge et al., 2011; Schmidt et al., 2011). Unfortunately, progress in biomarker research on depression is hindered by the considerable heterogeneity associated with this disorder. While major depression comprises changes in sleep, appetite, weight, and psychomotor behaviour, these can involve both increases and decreases in symptoms. Complaints about the most debilitating depressive symptom or constellation of symptoms can also vary considerably across individuals. These include variations in the severity of fatigue, worthlessness, suicidal ideation, and effects on memory and concentration. Further complications include the high comorbidity between depression and other medical and psychiatric conditions (Voinov et al., 2013), and factors associated with unique differences across gender, age, lifestyle and other mediating or triggering factors.

In this paper, many of the most commonly researched biomarkers in major depression are reviewed. Only peripheral biomarkers have been selected for review given their suitability and ease of collection in clinical practice. Furthermore, only biomarkers associated with inflammation/immune response and oxidative stress/antioxidant defences have been selected for review as this is an area gaining momentum in depression research (Leonard and Maes, 2012; Maes et al., 2011b; Raison and Miller, 2011).

2. Common oxidative and inflammatory biomarkers measured in depression studies

Several commonly-researched peripheral biomarkers in major depression are listed in Table 1, and pathways associated with their production are detailed in Fig. 2. A brief description of each marker is provided, and they are categorised into inflammatory/immune response biomarkers and oxidative stress/antioxidant defence biomarkers. However, these markers are not mutually

Table 1
Common peripheral biomarkers measured in studies on major depression.

Inflammation and immune response peripheral biomarkers	
C-reactive protein (CRP)	An acute-phase protein found in the blood that rises in response to inflammation.
Cytokines	Immuno-modulating proteins, peptides, or glycoproteins (e.g., interleukins and interferons) secreted by specific cells of the immune system, which carry signals locally between cells, and have an effect on target cells. Cytokines are generally classified by their ability to promote or inhibit inflammatory responses and the type of T-lymphocytes with which they are associated (termed Th1, Th2, and Th17).
Neopterin	Released by macrophages and considered a marker of cell-mediated inflammation activation.
Erythrocyte sedimentation rate (ESR)	A non-specific index of inflammation which measures the rate at which red blood cells sediment in a period of one hour.
TRYCATs (tryptophan catabolites along the IDO pathway)	Production of TRYCATs such as kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid, may be increased following immune activation. An immune response induces indoleamine-(2,3)-dioxygenase (IDO), an enzyme which degrades tryptophan down the TRYCAT pathway, summarised in Fig. 1.
Oxidative stress and antioxidant defence peripheral biomarkers	
Malondialdehyde (MDA)	Product of chemical damage caused by oxygen free radicals to the lipid component of cell membranes.
8-Hydroxy-2-deoxyguanosine (8-OHdG)	A repair product of the oxidation of guanine in DNA, can be used to estimate the rate of oxidative DNA damage.
Isoprostanes	Prostaglandin-like compounds produced by non-enzymatic peroxidation of arachidonic acid.
Superoxide dismutases (SOD)	Important antioxidant defence in nearly all cells exposed to oxygen. Enzymes that catalyse the dismutation of superoxide into oxygen and hydrogen peroxide.
Glutathione peroxidase (GPx)	Enzyme that catalyses the reduction of hydroxyperoxides by glutathione. Main function is to protect against the damaging effect of endogenously formed hydroxyperoxides.
Glutathione reductase	Important cellular antioxidant enzyme that reduces glutathione disulfide (GSSG) to the sulfhydryl form glutathione.
Reduced glutathione	Measure of glutathione status.