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Protein biomarkers of mood disorders

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Abstract

Psychiatric evaluation presents a significant challenge because it conceptually integrates the input from multiple psychopathological approaches. Recent technological advances in the study of protein structure, function, and interactions have provided a breakthrough in the diagnosis and treatment of mood disorders (MD), and have identified novel biomarkers to be used as indicators of normal and disease states or response to drug treatment. The investigation of biomarkers for psychiatric disorders, such as enzymes (catechol-O-methyl transferase and monoamine oxidases) or neurotransmitters (dopamine, serotonin, norepinephrine) and their receptors, particularly their involvement in neuroendocrine activity, brain structure, and function, and response to psychotropic drugs, should facilitate the diagnosis of MD. In clinical settings, prognostic biomarkers may be revealed by analyzing serum, saliva, and/or the cerebrospinal fluid, which should promote timely diagnosis and personalized treatment. The mechanisms underlying the activity of most currently used drugs are based on the functional regulation of proteins, including receptors, enzymes, and metabolic factors. In this study, we analyzed recent advances in the identification of biomarkers for MD, which could be used for the timely diagnosis, treatment stratification, and prediction of clinical outcomes.

Keywords

biomarker, cerebrospinal fluid, metabolomics, mood disorder, proteomics, saliva, serum

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Introduction

Proteomics is the study of protein expression and function on a genome-wide scale aimed at collecting data for clinical purposes.[1] However, the application of proteomics in psychiatric research is relatively new. The utilization of genomic, transcriptomic, and proteomic data provides a potential to identify and validate biomarkers of psychiatric disorders. The Research Domain Criteria (RDoC) initiative by the National Institute of Health (NIH) strives to create a more biologically valid framework for understanding psychiatric conditions such as mood disorders (MD) by integrating several levels of objective biological and subjective psychological evidence into a single structural matrix.[1] The RDoC is not intended to replace the Diagnostic and Statistical Manual of Mental Disorders (DSM) in clinical practice, but serves as an aid to facilitate clinical research. In the future, we hope that the increasing use of circulating protein and low molecular weight metabolomic biomarkers would result in creating biological profiles for patients with mood disturbances, which, by comparing them with those for healthy individuals, would help identifying people at risk for MD.[2]

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The aim of this study was to summarize recent achievements in proteomics studies on candidate biomarkers of MD.

Methodology

We performed an extensive search of the Cochrane Central Register of Controlled Trials, MEDLINE (PubMed), and Embase for articles published from January 2010 to January 2016 using the following search terms: mood disorder, major depression or bipolar depression biomarker, proteomics, serum, cerebrospinal fluid (CSF), urine, and saliva. We also examined references from selected articles and included case series with five or more patients, cohort studies, and randomized controlled trials. The data from our own studies were also analyzed.

Results and discussion

Protein biomarkers for early diagnosis of mood disorders and treatment decisions

Nowadays, many studies investigate the biomarkers of MD using multiplex immunoassay systems incorporated into diagnostic devices, which enable the analysis of large numbers of samples and allow a significant degree of modularity. In addition, these assays are fast and cost-effective and do not require bulky equipment. The test developed by scientists in the Fraunhofer Institute in Germany[3] needs just a few drops of blood placed into a small chamber, which is then inserted into a reader the size of a book and the diagnosis score could be obtained in as fast as 15 min.

In their study, Puccini et al.[4] evaluated plasma levels of amyloid-β (Aβ) as a potential diagnostic marker of bipolar depression. They observed that bipolar depressive patients had lower plasma Aβ42 levels and higher Aβ40/Aβ42 ratios compared with the control group. In addition, we found a significant negative correlation between plasma Aβ42 levels and the duration of the disease, and a positive correlation between the Aβ40/Aβ42 ratio and depression relapses.

Frye at al.[5] performed proteomic profiling of serum samples with the aim to identify and differentiate MD. The results indicate that retinol-binding protein 4 (RBP-4), transthyretin (TTR, RBP-4/TTR complex), thyroxine, and vitamin A present in the CSF and involved in brain maturation, cognitive ability, acquisition of concepts, and social behavior, showed a significant difference between psychiatric patients and healthy individuals, implicating these proteins in MD.

Herberth et al.[6] have reported 20 proteins differentially expressed in patients with both bipolar I/II and unipolar depression as well as in presymptomatic bipolar patients compared with controls.

Haenisch et al.[7] showed that 26 proteins, including MMP-7, were differentially expressed in bipolar patients with concomitant depression compared with the control group. The TTR locus 18q12 has been found to be associated with bipolar disorder in a Danish family of bipolar patients.

In the last few years, brain-derived neurotrophic factor (BDNF) became the focus of intensive research. Fuchikami et al.[8] have examined the potential of BDNF epigenetic changes as biomarkers of MD. A comparison of blood samples from healthy participants and unmedicated patients showed that the methylation of BDNF promoter-associated CpG1 correlated with clinical diagnosis

Herberth et al.[6] compared 32 euthymic bipolar patients with healthy controls and identified three differentially expressed proteins, chemokine C-C motif ligand 2, endothelin-1, and macrophage migration inhibitory factor, after correcting for multiple testing. BDNF-6 and insulin-like growth factor 1 (IGF-1) have also been proposed as biomarkers of major depression disorder (MDD); however, their use is limited by insufficient sensitivity and specificity.

Corticotropin-releasing hormone (CRH), also called corticotropin-releasing factor (CRF), is a 41-amino acid peptide distributed in several parts of the central nervous system, where it regulates stress response. Consistent with this notion, Catalan et al.[9] observed a direct correlation between the severity of depression symptoms in depressive disorder and plasma CRF levels. Overall, these data support the contribution of HPA axis activation in the pathogenesis of depression, risk of depression relapse, and suicide, which could have a prognostic value. However, further investigation into the role of CRF in mood disorders is needed, as a recent study reported a decrease in hippocampal levels of CRF mRNA in patients with MDD.[10]

Accumulating data indicate that mediators of neuro-inflammation may play a critical role in triggering depression, as evidenced by the activation

of brain microglia in depressed patients with a greater magnitude in individuals that committed suicide. The role of inflammation in mood disorders is supported by increased mRNA expression of pro-inflammatory cytokines cytokines IL-1α, IL-1β, IL-6, IL-8, IL-10, IFNγ, MIF, and TNFα in these patients compared to controls.[11]

Inflammation is also associated with increased oxidative stress. It has been mRNA expression of genes encoding proteins associated with oxidative stress, including cyclooxygenase-2 (COX -2), myeloperoxidase(MPO), phospholipase A2 (PLA2G2A), purine-rich Box-1 (PU.1), and inducible nitric oxide synthase (iNOS) was increased in peripheral blood of patients with recurrent depressive disorder.[12]

Proteomics in disease prediction and personalized medicine

The assessment of biomarkers prior to depression therapy can help predict the response to antidepressants, thus providing the identification of treatment targets and tailoring therapeutic approaches according to a patient's condition, which is the basis of personalized medicine. In the near future, it would be possible to analyze both protein and small molecule biomarkers and obtain the results during regular hospital visits, which would allow predicting the course of the disease, offering guidelines, and choosing the appropriate treatment.

C-reactive protein (CRP)[13] may help in the selection of the correct antidepressant. As Uher et al.[14] showed, CRP is a common inflammation marker used to determine the response to serotonin and norepinephrine reuptake inhibitors escitalopram and nortriptyline, respectively. Thus, patients with lower CRP levels showed better response to escitalopram than to nortriptyline according to the Montgomery-Åsberg Depression Rating Scale (MADRS). Conversely, patients with higher CRP levels showed greater improvement with nortriptyline than with escitalopram, as evidenced by 3-point higher mean MADRS scores. These data indicate that patients with higher levels of inflammation may benefit more from norepinephrine than from serotonin reuptake inhibitors.

Peripheral mRNA levels of D3 dopamine receptor could be used to predict individual variability in the working memory among patients treated with dopamine agonists. This option is very important for clinical practice, because physicians can use peripheral biomarkers to follow treatment response and identify patients who would most benefit from dopaminergic medications.[15] We observed similar results in studies in rats treated with trimethyltin.[16]

Haenisch et al.[17] reported a number of circulating molecules, including angiotensin-converting enzyme, acute phase protein, BDNF, complement component C4-B, cortisol, growth hormone, superoxide dismutase, and some cytokines, that demonstrate changes correlating with symptom severity in MDD patients exposed to stress and therapeutic agents.

Piccinni et al.[18] showed that BDNF plays an important role in neurogenesis and neuronal plasticity. In their study, BDNF levels were significantly higher in healthy individuals compared to patients with major depressive episodes and mixed episodes ($P < 001$ and $P = 0.022$, respectively). These findings suggest that BDNF is a state marker of MD and may be used in the development of a unitary approach to treat major depression and bipolar depression, and possibly the whole spectrum of manic-depressive conditions.

Neurokinin 1 receptor (NK-1R) plays an important role in MDD, while being less involved in bipolar disorder. Amoruso et al.[19] demonstrated that NK-1R expression was reduced in monocytes from bipolar patients compared to healthy controls ($P < 0.001$).

Cattaneo et al.[20] have observed lower levels of glucocorticoid receptor (GR) mRNA in leukocytes of patients with MDD who did not respond to subsequent antidepressant therapy. Thus, GR could be a good sensitive marker that can distinguish between disorders with overlapping symptoms.

Protein biomarkers for treatment response and patient monitoring

In a clinical trial, Fleming et al.[21] demonstrated that female patients with depressive symptoms receiving a high dose of levothyroxine, a synthetic form of the thyroid hormone thyroxine (T4), showed a significant improvement compared to untreated patients, suggesting impaired function of T4-transporting TTR.

Martins de Souza et al.[22] revealed that saliva levels of norepinephrine metabolite3-methoxy-4-hydroxyphenylglycol sMHPG were higher in

MDD patients compared to the control group. Moreover, individuals demonstrating a good response to SSRIs had higher sMHPG levels compared to non-responders, suggesting that sMHPG could be useful to stratify patients for antidepressant treatment.

Horowitz et al.[23] found that in patients with major depression, venlafaxine and eicosapentanoic acid demonstrated anti-inflammatory activity. Thus, both compounds downregulated the expression of IFN-γ-induced protein 10 (IP-10) and IL-6, while venlafaxine also decreased IL-8 and eicosapentanoic acid reduced IL-15 and IL-1RA, which the authors attributed to the inhibition of NF-κB. However, sertraline and docosahexaenoic acid demonstrated pro-inflammatory properties: sertraline upregulated IL-6 and IFN-α, while docosahexaenoic acid increased IL-15 and IL-1RA. These data suggest that pro-inflammatory mediators should be further investigated as biomarkers of depression disorders.

De Bernardis et al.[24] studied the influence of selective SSRIs, which modulate cytokine production, on both serotonin (5-HT) and norepinephrine and concluded that more extensive investigations will be required for a conclusive explanation.

Meta-analysis of 364 MDD patients performed by Gryglewsk et al.[25] revealed lower 5-HTT levels in the midbrain and amygdale as well as in the striatum, thalamus, and brainstem compared to healthy controls, while no variations were observed in the cerebral cortex.

A decrease in serotonin transporter (SERT) levels, which is considered a compensatory mechanism in the pathophysiology of depression disorders, was found to correlate with the severity of clinical symptoms during psychodynamic psychotherapy by two evaluation systems: Symptom Checklist Global Severity Index and Symptom Checklist Depression Scale.[25] It was demonstrated that the presence of serotonin 2A receptor clusters was higher in therapy-naïve depression patients than in treated patients. These results indicate a state-dependent role of decreased SERT availability in depression disorders, suggesting that it can be used as a biomarker to predict treatment response.

Sanchez et al.[26] demonstrated that a novel antidepressant vortioxetine increased serotonergic, noradrenergic, dopaminergic, cholinergic, histaminergic, and glutamatergic neurotransmission in patients with major depression. Vortioxetine acts as a receptor antagonist of 5HT3, 5HT7, and 5HT1D, partial agonist of 5HT1B, agonist of 5HT1A, and a 5HTT inhibitor. However, vortioxetine and fluoxetine, another serotonergic antidepressant, showed different effects on gamma aminobutyric acid (GABA) neurotransmission, indicating that there are many gaps in the knowledge about GABA involvement in MDD.

Thus, Takebayashi et al.[27] found that plasma levels of fibroblast growth factor (FGF)-2, which upregulates vascular endothelial growth factor (VEGF) were considerably higher in MDD patients compared to controls.

Clark-Raymond et al.[28] demonstrated that by analyzing VEGF levels it was possible to identify remitters and non-responders to escitalopram or quetiapine, for whom VEGF values did not change after 12 weeks of treatment, suggesting that VEGF may predict response to antidepressants and may eventually serve as a biomarker. De Rossi et al.[29] proposed the role of VEGF as a stimulator of postsynaptic responses mediated by glutamate receptors (GluNR), suggesting that it could be a possible target in antidepressant treatment.

The balance between Th1 (cellular) and Th2 (humoral) responses of the adaptive immune system is critical for the treatment of MDD patients. Serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), norepinephrine reuptake inhibitors (nortriptyline, reboxetine), and N-methyl-D-aspartate receptor antagonists (ketamine) promote Th2 response, while the shift to Th1 response causes depressive symptoms. Serotonin and norepinephrine are known to exhibit differential effects on inflammation by mediating Th1 and Th2 shifts, respectively.[30]

The application of protein biomarkers in MD discussed in this previous review are summarized in Table 1.

Conclusion

The aim of this study was to draw attention to biomarkers that signify the risk of developing MD months or even years prior to symptomatic manifestation, thus allowing prediction and prevention of depression. The use of proteomics and/or metabolomics platforms can improve the diagnosis, risk assessment, and monitoring of depression as well

Table 1. Clinical significance of protein biomarkers of mood disorders.

- Early diagnosis and treatment decisions
- Early treatment leads to better patient outcomes and reduces healthcare costs
- Differentiation of depression from other conditions with similar clinical manifestations (dementia and Alzheimer's disease) aids in treatment decisions
- Disease prediction and personalized treatment
- Prediction of responses to specific therapeutic interventions, which enables the selection of patient-specific antidepressants
- Prediction of side effects such as agitation (citalopram) or increase in bodyweight mainly due to visceral fat (mirtazapine)
- Implementation of the most effective prophylactic treatment
- Treatment response prediction and monitoring
- Testing for the normalization of biomarker signature with treatment (efficacy surrogate)
- Testing for the reappearance of signatures on recurrence
- Testing for patient adherence to treatment
- Detection of side effects

as patient stratification according to drug treatment response, although the complexity and large size of the identified protein biomarkers complicate the analysis, precluding quick test results in ambulatory settings. To address this problem, further comprehensive studies on candidate protein biomarkers of MD are required for better understanding of the pathophysiological mechanisms underlying psychiatric conditions and the identification of new drug targets. Our analysis supports the possibility of developing diagnostic tests for depression using validated protein biomarkers, which should facilitate accurate diagnosis and subsequent rapid treatment initiation, ultimately resulting in improved clinical outcomes.

Declaration of conflicting interests

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