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REVIEW ARTICLE

Differential blood-based biomarkers of psychopathological dimensions of schizophrenia☆

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Abstract Symptomatology of schizophrenia is heterogeneous, there is not any pathognomonic symptom. Moreover, the diagnosis is difficult, since it is based on subjective information, instead of markers. The purpose of this study is to provide a review of the current status of blood-based biomarkers of psychopathological dimensions of schizophrenia. Inflammatory, hormonal or metabolic dysfunctions have been identified in patients with schizophrenia and it has attempted to establish biomarkers responsible for these dysfunctions. The identification of these biomarkers could contribute to the diagnosis and treatment of schizophrenia.

PALABRAS CLAVE
Biomarcadores;
Esquizofrenia;
Cognición;
Síntomas positivos;
Síntomas negativos

Biomarcadores sanguíneos diferenciales de las dimensiones psicopatológicas de la esquizofrenia

Resumen La sintomatología de la esquizofrenia es heterogénea, no existiendo ningún síntoma patognomónico de la misma. Además, su diagnóstico presenta dificultades, ya que se basa en información subjetiva en lugar de en marcadores. El propósito de este estudio es ofrecer una revisión del estado actual de los biomarcadores sanguíneos de las dimensiones psicopatológicas

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de la esquizofrenia. En pacientes con esquizofrenia se han observado disfunciones inflamatorias, hormonales o metabólicas y se ha intentado establecer los biomarcadores responsables de esas disfunciones. La identificación de estos podría contribuir al diagnóstico y tratamiento de la esquizofrenia.

Introduction

Schizophrenia is a severe, complex and multifactor mental disorder that is characterised by its broad phenotypic variation, heterogeneous aetiology and fluctuating evolution. It commences in late adolescence or early adulthood and includes symptoms that are positive, negative, affective and cognitive. It affects at least 0.7% of the population.[1,2]

The symptoms of schizophrenia are heterogeneous, and it has no pathognomic symptom. It is also hard to diagnose, given that this is based on subjective information supplied by the patients themselves, or on the skill of the clinician in drawing inferences, rather than on markers such as laboratory tests or neuroimaging techniques. Due to this, current research centres on seeking markers which would make it possible to evaluate results in a more sensitive and precise way. Biological as well as neurophysiological markers were therefore studied, together with the psychiatric phenotype. Chan et al. reviewed a selection of studies of blood biomarkers in schizophrenia, bipolar disorder and major depression patients, to emphasise the importance of implementing valid biomarkers that not only make diagnosis and effective treatment possible, but which also improve the prognosis for patients.[3] The National Institute of Mental Health, in turn, has commenced the Research Domain Criteria Project,[4] the aim of which is to increase knowledge about the brain–behaviour relationship and to introduce this information about neural dysfunction in clinical practice, so that more effective treatments can be developed.

This study reviews the current status of blood biomarkers in the psychopathological dimensions of schizophrenia.

The positive dimension

There are no problems respecting the positive dimension of schizophrenia, as the instruments traditionally used measure it sufficiently well. The 2 most widely used scales in research as well as clinical practice are the Scale for the Assessment of Positive Symptoms[5] and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS).[6–8]

Respecting the biomarkers for the positive dimension, a significant relationship has been detected between triglyceride levels in serum and the positive symptoms evaluated using the positive scale of the PANSS.[9] Additionally, a statistically significant inverse relationship has been detected between the plasma glucose levels and the positive symptoms evaluated using the PANSS, showing that an altered glucose metabolism may be associated with the pathogenesis and symptoms of schizophrenia in the early stages of the disease.[10] These authors conclude that the factors which best predict glucose levels in schizophrenia patients are insulin resistance, insulin and the positive symptom score in the PANSS.[10] Weight gain during antipsychotic treatment, in turn, predicts an improvement in the psychotic syndrome and positive symptoms.[11]

Alterations have also been detected in several inflammatory parameters: the levels of interleukin (IL)-1β seem to increase during acute phases[12] and the initial stages of the disease,[13] while levels of TGF-β and IL-6 also increase during acute phases.[12] Increased positive symptoms (hallucinations and deliria) seem to be associated with interleukin expression in schizophrenia patients;[14] thus for example, Dimitrov et al.[15] found a positive association between IL-6 levels and the positive symptoms evaluated using the PANSS. Tumour necrosis factor (TNF)-α has also been associated with the severity of the positive dimension,[16] as well as the number of hospitalisations and episodes of imbalance that reflect greater severity,[17] indicating the possibility that it may be a specific biomarker for this dimension. All of these data show the existence of state-specific markers, i.e., during the first psychotic episodes and acute relapses a series of inflammatory and associated immune processes arise.[12,18] Likewise, a positive relationship has been detected between peripheral levels of PCR and the severity of positive symptoms.[19]

Finally, the endocannabinoid system has been described as an endogenous anti-inflammatory neuroprotector system, and certain markers of this system, such as raised levels of anandamide, have been associated with positive symptoms.[20]

The negative dimension

The negative dimension of schizophrenia has traditionally been measured using the Brief Psychiatric Rating Scale,[21] the Scale for the Assessment of Negative Symptoms[22] and the PANSS.[6,22] Additionally, Marder et al. established the negative factor of the PANSS by means of factorial analysis. Nevertheless, the PANSS and even the negative factor obtained by Marder et al.[23] have important conceptual and psychometric limitations.[24,25]

This negative dimension has become of greater interest in recent years due to the diagnostic and therapeutic challenge it involves, together with the great impact of its cognitive symptoms on the functioning of individuals with schizophrenia.[24] Negative symptoms show minimum response to antipsychotic medication, and they are