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Plasma peptidases as prognostic biomarkers in patients with first-episode psychosis

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ABSTRACT

The plasma activity of nine aminopeptidases was monitored over a year in first-episode psychotic patients. We observed significant differences in aminopeptidase B (APB), aminopeptidase N (APN) and dipeptidyl peptidase IV (DPPIV), but not in puromycin-sensitive aminopeptidase (PSA), prolyl endopeptidase (PEP), cysteine aminopeptidase (Cys-AP), aspartate aminopeptidase (Asp-AP), glutamate aminopeptidase (Glu) or piroglutamate aminopeptidase (PGI) in these patients compared to controls, and also a progressive increase in plasma activity, correlated to changes in scores on clinical scales, Global Assessment of Functioning scale (GAF) and Hamilton Depression Rating Scale (HDRS), at 1 month of follow-up. At 1 month after diagnosis, the median score obtained by patients on the GAF was negatively associated with the plasma activity of APB and PEP measured at the beginning of the psychotic episode, indicating a role as a negative prognostic factor that can predict psychiatric symptomatology. In the case of HDRS, scores at 1 month after diagnosis were found to be positively associated with the initial plasma activity of DPPIV, APN and PSA, indicating that their initial elevation is a negative prognostic factor that can predict subsequent depressive symptomatology. Taken together, these results suggest a pathophysiological involvement of plasma peptidases and indicate that aminopeptidase activity can predict the course of first-episode psychosis patients, acting as a prognostic indicator.

Abbreviations: APB, aminopeptidase B; APN, aminopeptidase N/CD13; DPPIV, dipeptidyl peptidase IV; PSA, puromycin-sensitive aminopeptidase; PEP, prolyl endopeptidase; CYS, cysteine aminopeptidase; ASP, aspartate aminopeptidase; GLU, glutamate aminopeptidase; PGI, piroglutamate aminopeptidase; GAF, Global Assessment of Functioning scale; HDRS, Hamilton Depression Rating Scale; PANSS-P, Positive and Negative Syndrome Scale-Positive scale; PANSS-N, Positive and Negative Syndrome Scale-Negative scale; PANSS-GP, Positive and Negative Syndrome Scale-General Psychopatology scale; PANSS-Global, Positive and Negative Syndrome Scale-Global scale; SCS, Strauss–Carpenter Scale; PRS, Phillips Rating Scale; YMRS, Young Mania Rating Scale; FEPP, first-episode psychotic patients

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1. Introduction

Schizophrenia is a severely debilitating mental illness that, worldwide, is estimated to affect 1% of the population and is among the top 10 causes of disability-adjusted life years, together with depression and bipolar disorder (Rossler et al., 2005). It is clinically complex and, though it is believed to have a neurobiological basis, it currently still diagnosed on the basis of symptom profiles, using standardized criteria (of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-V] or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]). Symptoms are heterogeneous, including cognitive deficits, in working memory, attention and cognitive flexibility, as well as so-called "positive" symptoms, such as hallucinations and delusions and "negative" symptoms, such as avolition and reduced affect (Winchester et al., 2014). These symptoms overlapping with other mental illnesses, in particular bipolar disorder, the appropriateness of the current classification and diagnosis of neuropsychiatric disorders continue to be debated (Craddock and Owen, 2010; Kapur et al., 2012).

Research into cognitive performance of patients in the early stages of schizophrenia is useful for several reasons. In particular, though prodromal symptoms and even very short periods of psychotic symptoms may be associated with cognitive changes, assessing performance at this stage is likely to shed new light on the disorder, most research so far having been done in patients at much later stages. It may be possible to identify cognitive deficits related to neural dysfunction underlying the symptoms, before these are masked by effects of the illness and/or treatment. Indeed, data from the early stages may demonstrate whether some cognitive changes observed later in the course of the disease are attributable to long-term drug treatments. Notably, some studies on first-episode psychosis have grouped patients with a diagnosis of schizophrenia together with those with other psychoses. Since such early-stage diagnoses may change, this inclusive approach has the advantage of not excluding potential schizophrenia cases (Aas et al., 2014).

The aminopeptidase family of proteases is involved in the proteolytic processing of precursor proteins to produce biologically active neuropeptides and hormones (Deng et al., 2013). These include dipeptidyl-peptidase (DPP-IV) (Boonacker and Van Noorden, 2003), prolyl-oligopeptidase (PEP) (Maes et al., 1995) and aminopeptidase N (APN) and aminopeptidase B (APB). In recent years, considerable evidence has emerged for the presence of APN in the brain. The APN receptor has been detected in regions of the mouse hypothalamus, brainstem and cortex (Thundyil et al., 2012). Elevated blood levels of APN have been reported in several brain disorders including bipolar disorder (Breen et al., 2004; Elmslie et al., 2009), mild cognitive impairment and Alzheimer's disease (Une et al., 2011), and schizophrenia (Beumer et al., 2012). DPP-IV selectively removes amino-terminal dipeptides from precursor proteins containing proline or alanine in the second position (Lambeir et al., 2003) and is widely distributed (Mentlein, 1999). It is present as both membrane-bound and circulating forms with indistinguishable protease activity (Drucker, 2003). It is also involved in the processing of bioactive peptides that are involved in regulation of mood and behavior (Maes et al., 1998). Hence, it is relevant to explore the involvement of aminopeptidase activity in synaptic neuropeptide degradation and control to elucidate the neurochemical mechanisms that are on the basis of mental health and neurological diseases, as is the case for aminopeptidase control of opioid peptides (Hui, 2007).

The aminopeptidases have been linked to the pathophysiology of various diseases including neuropsychiatric disorders and metabolic conditions such as type II diabetes mellitus (Drucker, 2003). Although first-episode psychosis is a severe mental disease primarily affecting the brain, it is becoming more apparent that the whole body is involved (Hildebrandt et al., 2000; Brandt and Bonelli, 2008). Studies over the last two decades have shown that many patients with first-episode psychosis have inflammatory, hormonal and metabolic abnormalities, similar to those seen in cardiovascular diseases and diabetes (Hildebrandt et al., 2000).

DPP-IV has been proposed as a diagnostic or prognostic marker for various cancers but also for neuropsychiatric disorders. Specifically, previous studies have indicated that changes in aminopeptidase activity may be involved in neuropsychiatric conditions such as first-episode psychosis (Maes et al., 1998). Further, low serum DPP-IV levels have been associated with neuropsychiatric conditions such as psychosis and anorexia nervosa (Hildebrandt et al., 1999). We considered it particularly interesting to explore whether differences in these enzymatic activities could be used as a means of classifying patients with first-episode psychosis compared to controls. To our knowledge, no previous prospective studies have assessed the value of aminopeptidases as biomarkers in this population.

Given all this, the aim of this study was to analyze plasma samples from a large cohort of patients with first-episode psychosis compared with healthy controls in an attempt to characterize changes in the activities of DPP-IV, APN, APB and other aminopeptidases in this disorder.

2. Methodology

A total of 119 patients (men 78, 65.54%; women 41, 34.45%) with first-episode psychosis (aged between 17–62 years) were included in the study. All of them were inpatients of the Service of Psychiatry, Hospital Universitario de Alava (Basque Health Service/Osakidetza, Vitoria, Spain) admitted between 2009 and 2012 (mean age at initial diagnosis: 30.29 ± 9.94 years). This is a regional hospital that receives referrals of all individuals with acute psychiatric episodes from a geographic area of about 300,000 inhabitants, in the north of Spain. Inclusion criteria were the diagnosis of a first episode of psychosis according to DSM-IV criteria and having provided written informed consent.

A first episode of psychosis was defined as the first time that an individual had hallucinations or delusions for a period for between 1 week and 6 months. The study was approved by the Ethics Committees of UPV/EHU and Hospital Universitario de Alava (Spain).

We excluded patients who had previously taken psychoactive medication (except for benzodiacepines), or who were on non-steroid anti-inflammatories at the time of the episode, and those with mental retardation, neurological diseases, previous craneoencephalic trauma with loss of consciousness, or serious concomitant pathologies (including inflammatory pathologies), as well as any who were pregnant or breastfeeding. The control group ($n=30$) (men 14, 46.66%; women 16, 53.33%) (mean age at initial diagnosis $31.00+10.77$ years), that was not followed-up, was formed by individuals from the same geographic area with no medical history of psychiatric or neurological disorders, cranioencephalic trauma or mental deficiency.

Scores on clinical scales for evaluation of psychiatric symptomatology were the main outcome measure of the study. The battery of clinical scales used in this study included the Global Assessment of Functioning scale (GAF) (Endicott et al., 1976) and the Strauss–Carpenter Scale (SCS) (Strauss and Carpenter, 1972) to assess patient functioning; the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) to evaluate depressive symptoms; the Positive and Negative Syndrome Scale (PANSS-P) (Kay et al., 1987, 1988) to explore psychotic symptoms; the Phillips Rating Scale (PRS) (Harris, 1975) for premorbid adjustment; and Young Mania Rating Scale (YMRS) (Young et al., 1978) for manic symptoms.

Blood samples (10 mL) were taken from healthy controls (baseline only) and patients (baseline, 1 month, 6 months, 12 months) by venipuncture into heparinized tubes, after fasting overnight. Following centrifugation (5000 rpm, for 3 min), plasma samples were separated and stored frozen at -80 °C until analysis of aminopeptidase activity: aminopeptidase B (APB), aminopeptidase N (APN), dipeptidyl peptidase IV (DPPIV), puromycin-sensitive aminopeptidase (PSA), prolyl endopeptidase (PEP), cysteine aminopeptidase (Cys-AP), aspartate aminopeptidase (Asp-AP), glutamate aminopeptidase (Glu-AP), and piroglutamate aminopeptidase (PGI). Total protein content in each sample was determined using the method of Bradford (Bradford et al., 1976). Aminopeptidase activity was detected by spectrofluorimetry, using β-naphtilamide as a chromogenic substrate.

All statistical analyses were performed using the IBM SPSS® Statistics for Windows (version 21). The Shapiro–Wilks test was used to check whether the quantitative data was normally distributed. The baseline characteristics of patients and controls were summarized using descriptive statistics (means and standard deviations) and comparisons were made using Student's *t*-test and ANOVA. Post-Hoc Bonferroni tests were used to detect statistically significant differences.