



Levels of the potential biomarker p11 in peripheral blood cells distinguish patients with PTSD from those with other major psychiatric disorders

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a severely debilitating anxiety disorder. Over 80% of patients with PTSD also exhibit other psychiatric condition, such as bipolar disorder (BP) or major depression (MDD). Previously, it has been found that p11 mRNA expression was significantly changed in post mortem cortex of patients with PTSD and depression. We hypothesize that p11 mRNA levels in the peripheral blood cells will be a potential biomarker for PTSD with heterogeneity in terms of type of trauma, time since trauma and duration of illness. We examined the peripheral blood mononuclear cell (PBMC) P11 mRNA of patients with PTSD ($n = 13$), major depressive disorder (MDD, $n = 16$), bipolar disorder (BP, $n = 24$), and schizophrenia (SCZ, $n = 12$) or controls ($n = 14$) using quantitative real-time PCR and the circulating levels of cortisol in blood plasma and saliva of PTSD using radioimmunoassay kit CORT-CT2. The Hamilton Rating Scale for Depression (HAM-D) and Anxiety (HARS), the Chinese version of the Davidson Trauma Scale-Frequency (CDTS-F) and the Chinese version of the Davidson Trauma Scale-Severity (CDTS-S), and Impact of Event Scale-Revised (IES-R) were administered. We found that patients with PTSD had lower levels of p11 mRNA than control subjects, while those with MDD, BP and SCZ had significantly higher p11 levels than the controls. P11 mRNA levels were positively correlated with the scores of HAM-D ($r = 0.62$, $p < 0.05$), CDTS-F ($r = 0.71$, $p < 0.05$) and CDTS-S ($r = 0.62$, $p < 0.05$), while they did not correlate with scores of HARS and IES-R. Basal levels of plasma and salivary cortisol of PTSD patients were not statistically different from those of controls. Our findings suggest that PBMC p11 mRNA expression levels may serve as a potential biomarker to distinguish PTSD from BP, MDD and SCZ.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating anxiety disorder commonly comorbid with major depressive disorder (MDD) and with symptom overlap and also often comorbid with bipolar disorder (BP), and schizophrenia (SCZ). The National Comorbidity Study found exceedingly high rates of psychiatric comorbidity in respondents experiencing PTSD, with 88.3% having one or more comorbid Axis I diagnosis (Henderson et al., 2000; Kessler et al., 1997). Individuals with PTSD are 8–14 times more likely to have a second lifetime diagnosis of psychosis after the

development of PTSD, with 50–80% of those being affective and anxiety disorders (Kessler et al., 1997). PTSD is more common among depressed primary care patients than previously thought (Campbell et al., 2007), and 62% of individuals diagnosed with PTSD have suicidal ideation (Henderson et al., 2000). However, at present, there is no biological tool for differentiating PTSD from other psychiatric disorders. Diagnosis for these psychiatric diseases is established on the basis of clinical history and mental status examination, using a clinically structured interview, symptom checklist or patient self-report. It is often difficult to distinguish PTSD from other psychiatric disorders, resulting in difficult treatment decisions or under-diagnosis. The current clinical assessment would benefit substantially from a more objective means to identify PTSD patients and to differentiate PTSD from other psychiatric disorders.

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P11, a member of the S-100 family may be a valuable candidate for identifying several psychiatric disorders, including PTSD (Zhang et al., 2008). P11 (annexin II light chain) was first described by Gerke and Weber (1985), who identified and characterized p11 as a member of the S-100 family. Recently, Svenningsson et al. provided compelling data supporting the association of p11 down-regulation in cortical tissue of patients with depression (Svenningsson et al., 2006), while Zhang et al. (2008) demonstrated that p11 was up-regulated in the prefrontal cortex of individuals with PTSD (Zhang et al., 2008). These contrasting results suggest that p11 may differentiate the two conditions. The possible role of p11 in depression has been further supported by the finding that p11 knockout mice exhibited a depression-like phenotype and had reduced responsiveness to 5-HT_{1B} receptor agonists (Svenningsson et al., 2006). Furthermore, p11 over-expression increased localization of 5-HT_{1B} receptors at the cell surface and enhanced 5-HT_{1B} receptor function (Svenningsson et al., 2006).

In regards to PTSD, expression of p11 in the prefrontal cortex of rats was up-regulated by both the stress-related hormone glucocorticoid (GC) and inescapable tail shock (Zhang et al., 2008). In addition, we found that p11 mRNA was over expressed in the post-mortem brain of patients with PTSD (Zhang et al., 2008). The molecular mechanism of GC-induced over-expression of p11 occurs through glucocorticoid response elements (GREs) within the p11 promoter, which can be attenuated by either a glucocorticoid receptor antagonist, RU486 or by mutating two of the three glucocorticoid response elements (GRE2 and GRE3) in the p11 promoter (Zhang et al., 2008). However, whether changes in p11 expression are specific to one psychiatric disorder and whether the changes observed in the postmortem brain tissue of PTSD and BP subjects are also reflected in the peripheral blood mononuclear cells (PBMC), thus serving as a potential and useful biomarker, remain to be determined. We hypothesize that p11 mRNA levels in PBMCs serve as a potential biomarker for PTSD with heterogeneity in terms of type of trauma, time since trauma and duration of illness. In this study, we measured p11 mRNA expression in PBMCs of patients with PTSD, MDD, BP and SCZ, and compared these results to non-psychiatric control subjects. To determine the role of glucocorticoid in PTSD, we also quantified the circulating levels of cortisol in blood plasma and saliva, and the expression levels of glucocorticoid receptor mRNA in PBMCs of patients with PTSD and controls. These results provide support for specific role of p11, as well as GR in PTSD and suggest that they may be differential biomarkers for PTSD.

2. Material and methods

2.1. Subjects

79 subjects, including those exhibiting PTSD ($n = 13$), MDD ($n = 16$), BP ($n = 24$), SCZ ($n = 12$) and controls ($n = 14$), were included for the p11 mRNA study at the Division of Psychiatry, Faculty of Medicine, National Yang-Ming University and Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan. The available clinical records, including inpatient and outpatient, were reviewed and all subjects were carefully interviewed regarding psychiatric history, family history of mental disorders and history of substance abuse. Diagnoses were established by two psychiatrists using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and DSM-IV for all study subjects. All patients met DSM IV diagnostic criteria for PTSD, MDD, BP or SCZ. Exclusion criteria were current medical problems, significant physical illness, neurological diseases, history of head trauma with loss of consciousness, and history of substance abuse and current alcohol abuse (within 6 months). Non-psychiatric control

group was recruited from local advertisement and was selected in randomly in the same geographic location and during the same time frame when the PTSD patients were being enrolling into the study. The ethics committee of the Hospital approved the research and all subjects provided a written informed consent after the study design had been fully explained and prior to undergoing psychiatric evaluation and blood collection. Over 77% of patients with PTSD in this study exhibit other psychiatric conditions. The psychiatric comorbidity for other clinical groups is as follows: major depressive disorder (MDD, $n = 16$), dysthymia (41%), panic disorder (27.6%), social phobia (17.6%), generalized anxiety disorder (GAD) (24%) and suicidality (11.8%); bipolar disorder ($n = 24$), panic disorder (8.3%), social phobia (4.2%), PTSD (4.2%), GAD (25%) and suicidality (4.2%) and schizophrenia ($n = 12$), dysthymia (25%).

2.2. Symptom ratings

To quantify the clinical outcome of mood and anxiety symptoms, the Hamilton Rating Scale for Depression (HAM-D), and Anxiety (HARS) were used, respectively (Hamilton and White, 1959). For severity and frequency of PTSD symptom measurement, the Chinese version of the Davidson Trauma Scale-Frequency (CDTS-F) and the Chinese version of the Davidson Trauma Scale-Severity (CDTS-S) (Davidson et al., 1997), and Impact of Event Scale-Revised (IES-R) (Horowitz et al., 1979) were administered.

2.3. Blood samples

Heparinized and unheparinized blood samples (10 mL each) were collected by venipuncture in Vacutainer tubes. A part of the whole heparinized blood (50 mL per tube) was used. Peripheral blood mononuclear cells (PBMCs) were separated by centrifugation on Ficoll-Hypaque (Invitrogen) density gradient. The serum for determination of cortisol concentration were stored at -80°C .

2.4. Serum cortisol determination

All serum samples were collected at 8:00 AM. Serum cortisol concentration was determined by the radioimmunoassay kit CORT-CT2 (CIS bio international). All samples were analyzed in duplicate following the manufacturer's protocol. The sensitivity of the assay was $0.17\ \mu\text{g}/100\ \text{mL}$, and the intra- and interassay coefficients of variation were less than 6% and 8%, respectively.

2.5. Saliva cortisol assay

Salivary samples were assessed at four times (8:00 AM, 10:00 AM, 4:00 PM and 10:00 PM) during the day. The study subjects were instructed to collect 5 ml of saliva into a plastic tube by direct spitting at 8 AM (fasting after midnight), 10 AM, 4 PM and 10 PM. Saliva samples were separated by centrifugation and stored at -80°C until analysis. Cortisol levels was measured by radioimmunoassay (RIA). The cortisol RIA was performed using an antiserum supplied by IgG Corp. (Nashville, TN) and cortisol-3-(O-carboxymethylloximino-[2-¹²⁵I]iodohistamine) from Amersham (Aylesbury, UK). All samples were assayed in duplicate. The antiserum reacts fully with cortisol and cross-reacts 9.4% with dihydrocortisol, 5.9% with 11-deoxycortisol, 1.7% with corticosterone, and <1% with tetrahydrocortisol. The sensitivity of the assay (ED₁₀) was 10 pg/tube. Intra- and interassay coefficients of variation were 3% and 6%, respectively (Weems and Carrion, 2008).

2.6. Real-time PCR analysis of p11 or GR gene expression

RNA was extracted from human blood lysates using PAXgen blood RNA validation Kit (PreAnalytiX, Qiagen/BD, Valencia, CA).

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