Physiology & Behavior 129 (2014) 194–198

Contents lists available at ScienceDirect

Physiology & Behavior

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

Peripheral interleukin-2 level is associated with negative symptoms and cognitive performance in schizophrenia

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HIGHLIGHTS

- Peripheral IL-2 levels correlated positively with performance in tests of working memory and intelligence in patients with schizophrenia.
- IL-2 levels correlated negatively with scores in the negative subscale of PANSS.
- These associations pose IL-2 as a possible marker of cognitive and affective preservation in schizophrenia.

ARTICLE INFO

Article history:
Received 3 August 2013
Received in revised form 7 October 2013
Accepted 12 February 2014
Available online 25 February 2014

Keywords:
Schizophrenia
Interleukin-2
Biological markers
Cognition
Behavioral symptoms

ABSTRACT

Although several studies have pointed to a possible role of interleukin 2 (IL-2) in schizophrenia (SZ), association between IL-2 and the different groups of symptoms has not been explored. The objective of this study was to investigate a possible correlation of peripheral IL-2 levels with symptoms and cognitive performance in patients with SZ. In addition, we compared the plasma levels of IL-2 between patients with SZ and healthy controls. Twenty-nine chronically medicated outpatients with SZ according to DSM-IV were compared with twenty-six healthy controls. The patients were evaluated with the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), the Clinical Global Impression (CGI) and the Global Assessment of Functioning (GAF). All the participants had blood collected into EDTA tubes by venipuncture between 9:00 and 10:00 AM. Plasma concentrations of IL-2 were determined by cytometric bead array. A computerized neuropsychological battery assessed verbal learning, verbal fluency, working memory, set shifting, executive function, inhibition and intelligence. Patients with SZ had lower levels of IL-2 than healthy controls ($p < 0.001$). In the SZ group, IL-2 levels were positively correlated with scores in the digit span test (rho = 0.416, $P = 0.025$) and intelligence (rho = 0.464, $P = 0.011$). We also found a negative correlation between IL-2 and total score in the negative subscale of PANSS (rho = −0.447, $p = 0.015$). Our findings suggest that IL-2 may be involved in the mechanisms related to cognitive deterioration and negative symptomatology in schizophrenia.

1. Introduction

Schizophrenia (SZ) is a chronic, severe and highly prevalent mental disorder that is frequently associated with significant disability [1]. Symptoms of SZ are often divided into two clusters: positive symptoms (hallucinations, delusions, disorganized speech and behavior) and negative symptoms (blunted affect, social withdrawal, loss of volition and alogia) [1]. In addition to the positive and negative syndromes, cognitive impairment is an essential feature of SZ that seems to be directly associated with functional disability in work, poor social functioning and difficulties in daily life activities [2,3]. When compared with healthy individuals, people diagnosed with SZ display deficits in several domains

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http://dx.doi.org/10.1016/j.physbeh.2014.02.032
0031-9384/

of cognition, such as episodic memory, processing speed, attention, inhibition, language and executive functions [4]. Notwithstanding recent advances, causes underlying SZ as well as its different symptomatic manifestations remain largely unknown. Considering the lack of reliable biomarkers, diagnosis, assessment and prognosis of SZ are based on symptomatology alone, which hinders the implementation of personalized treatments [5].

In the last decade, immunological alterations in individuals affected by major mental disorders, such as SZ, have received great attention, as they can aid to further elucidate related pathophysiological pathways [6–9]. One of the most promising approaches to evaluate immune changes in SZ is the measurement of cytokines in serum or plasma [10]. Cytokines are molecular mediators of the immune system. They are involved in a complex and redundant network that communicates immune and non immune cells [11].

Interleukin 2 (IL-2) is a cytokine of 15.5kd discovered more than 30 years ago. First described as a T cell growth factor, IL-2 is mainly produced by T cells after interaction of MHC/antigen/T-cell receptor (TCR) and co-stimulatory molecules. IL-2 acts as an autocrine and paracrine third signal, inducing clonal expansion and effector T and B-cells development. It also plays an important role on innate immunity, leading to activation and proliferation of natural killer (NK) cells [12]. Several studies have pointed to a potential role of IL-2 in SZ, with most studies reporting altered peripheral levels of IL-2 when compared with healthy controls [13,14], as well as a reduction in production of IL-2 by leukocytes after mitogen stimulation [15–18]. Nevertheless, association between IL-2 and different groups of symptoms of SZ, namely positive, negative and cognitive, has not been explored.

The objective of this study was to investigate a possible correlation of peripheral IL-2 levels with symptomatology and cognitive performance of patients with SZ. In addition, we compared serum levels of this cytokine between patients with SZ and healthy controls. We hypothesized that individuals with SZ would exhibit decreased levels of IL-2 when compared to healthy controls. Moreover, we expected to demonstrate that decreased levels of IL-2 are associated with worse psychopathological features and lower cognitive performance.

2. Material and methods

The study protocol was approved by the Ethics Committee of the Universidade Federal de São Paulo (UNIFESP), in São Paulo, Brazil, and all individuals provided their written informed consent before inclusion in the study. This study is part of a large protocol entitled "Prevention of Schizophrenia and Bipolar Disorder from Neuroscience to Community: a Multistaging, Multimodal and Translational Platform to Investigation and Intervention" developed by the Department of Psychiatry of Universidade Federal de São Paulo (UNIFESP). The sample investigated here had already been evaluated regarding other biomarkers and outcomes [8,19].

2.1. Study population

Twenty-nine chronically medicated outpatients were compared with twenty-six healthy controls. The diagnosis of SZ was established according to the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV), using the Structured Clinical Interview for DSM-IV (SCID). The patients were also evaluated with the Positive and Negative Syndrome Scale (PANSS) for severity of psychotic symptoms, the Calgary Depression Scale for Schizophrenia (CDSS) for severity of depressive symptoms, the Clinical Global Impression (CGI) and the Global Assessment of Functioning (GAF) scales for functioning assessment. All patients were under treatment with atypical antipsychotics with stable doses for at least 6 weeks prior to the inclusion. Patients were using Olanzapine ($n = 13$), Clozapine ($n = 10$), Risperidone/Paliperidone ($n = 4$) and Quetiapine ($n = 2$). The healthy volunteers group was matched for age, ethnicity and educational level and had no current or lifetime psychiatric history according SCID, as well as no first-degree relative with history of psychiatric disorders.

Acute and chronic general medical conditions traditionally associated with a significant inflammatory response such as flu-like syndrome, HIV infection, allergies, pregnancy or postpartum period, rheumatologic or immunological conditions were considered exclusion criteria for both groups. Individuals using medications with immunomodulatory effects, such as non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants, were also excluded.

2.2. Collection of blood samples and procedures to biomarker measurement

All the participants had blood collected into EDTA tubes by venipuncture between 9:00 and 10:00 AM. The samples were immediately processed and plasma stored at −80 °C. Plasma concentrations of IL-2 were evaluated using a BD cytometric bead array (BD Biosciences, USA).

2.3. Neuropsychological assessment

A computerized neuropsychological battery assessed the following domains of cognition (for a detailed description of the tests, see previous publication [20]):

2.3.1. Verbal learning: the Hopkins Verbal Learning Test [21];

2.3.2. Verbal fluency: phonemic and semantic verbal fluency;

2.3.3. Working memory: Visual Working Memory [22,23], Keep Track Task [24], Letter Memory Task [25] and the forward digit span of the Wechsler Adult Intelligence Scale [26];

2.3.4. Set shifting (Plus–minus task [27], Number–letter task [28]);

2.3.5. Executive function: Tower of London [29] and Shortened version of the Wisconsin Card Sorting Test [30]);

2.3.6. Inhibition: Computerized Stroop Task [31], Semantic Generation Task [32,33]).

2.3.7. Intelligence: the non-verbal intelligence task (R-1) was used to assess intelligence. This scale allows measures of intelligence in low literacy populations, such as Brazilian schizophrenics. This test highly correlates with the Raven's Colored Progressive Matrices Test ($r = 0.76$, $p = 0.001$) [34].

2.4. Statistical analysis

Statistical analyses were performed using SPSS 20.0 for Mac. All the distributions of quantitative data were tested for normality using the Kolmogorov–Smirnov test. Comparisons of clinical and demographic variables between SZ group and healthy volunteers group were performed using X^2, Student t-test and Mann–Whitney U-test when appropriate. Differences in IL-2 levels between the two groups were evaluated using the Mann–Whitney U-test. Correlation between cognitive tests and biomarker levels was tested using the Spearman correlation coefficient. Statistical significance was set in alpha ≤ 0.05.

3. Results

Clinical and demographic characteristics of the sample are described in Table 1. Comparison of levels of IL-2 demonstrated that patients with SZ had lower levels of this mediator (median = 0.98 pg/mL; mean (M) = 0.699 pg/mL; standard error of the mean (SE) = 0.105) than healthy control (HC) individuals (median = 1.31 pg/mL; M = 1.146 pg/mL; SE = 0.120) (Mann–Whitney test $U = 177.5$, $P < 0.001$).

In order to clarify a possible influence of the difference in marital status on IL-2 levels, we compared IL-2 levels between married (M = 1.084 pg/mL; SE = 0.157) and non-married ($M = 1.110$ pg/mL; SE = 0.220) controls and found no significant differences (Mann–Whitney test $U = 62$, $P = 0.602$). In addition, we compared IL-2 levels between male ($M = 1.212$ pg/mL; SE = 0.180) and female ($M = 1.089$ pg/mL; SE = 0.166) controls and also found no significant differences (Mann–Whitney test $U = 75$, $P = 0.667$). The low number of married and

Table 1
Clinical and demographic characteristics of the sample.

	SZ group $N = 29$	HC group $N = 26$	Test-value	*P*-value
Age in years (mean, SD)	33.17 (9.73)	34.65 (10.64)	0.537*	0.594
Sex (% female)	17.2%	53.8%	8.124**	0.004
Years of education (mean, SD)	10.50 (2.86)	10.10 (3.88)	0.428*	0.671
Ethnic group (%)				
Caucasian	69.0%	47.6%		
Afro-American	3.4%	14.3%	3.134**	0.371
Asian	6.9%	9.5%		
Other	20.7%	28.6%		
Marital status (%)				
Single	93.1%	42.86%		
Married	0%	57.1%	23.075**	<0.001
Other	6.9%	9.5%		
Smoke habit (%)				
Never smoke	46.4%%	42.9%		
Smoke in the past, not currently	7.1%	9.5%	0.121**	0.941
Currently smoker	46.4%	47.6%		
Years of disease (mean, SD)	11.83 (8.43)	–	–	–
PANSS (mean, SD)		–	–	–
PANSS positive scale	13.97 (4.35)	–	–	–
PANSS negative scale	17.14 (5.35)	–	–	–
PANSS general psychopathology	30.28 (7.39)	–	–	–
Total PANSS	61.38 (14.29)			
CDSS (mean, SD)	3.83 (4.22)	–	–	–
GAF (mean, SD)	49.26 (13.51)	–	–	–
CGI (mean, SD)	3.96 (0.99)	–	–	–

PANSS: Positive and Negative Symptoms Syndromes Scale; CDSS: Calgary Depression Scale Schizophrenia; GAF: Global Assessment of Functioning; CGI: Clinical Global Impression.
*Student *t* test.
**X^2 test.

female individuals prevented the possibility of performing this analysis in the SZ group.

Individuals with SZ exhibited deficits in verbal learning (Hopkins test), when compared with healthy subjects. We did not observe differences in other functions such as inhibitory control, working memory, planning, verbal fluency and attention, although differences in verbal fluency were marginally significant.

With respect to performance in the neuropsychological assessment, peripheral IL-2 levels were positively correlated with scores in the digit span test in the SZ group (rho = 0.416, $P = 0.025$). We have also found a positive correlation of IL-2 levels with non-verbal intelligence (rho = 0.464, $P = 0.011$) in this group. We did not find correlations between IL-2 and cognitive performance in the healthy control group.

We also found a negative correlation between IL-2 and total score in the negative subscale of PANSS (rho = −0.447, $p = 0.015$). Specifically, the items of blunted affect (rho = −0.445, $p = 0.016$), poor rapport (rho = −0.411, $p = 0.027$) and difficulty in abstract thinking (rho = −0.493, $p = 0.007$) had statistically significant negative correlations with IL-2. We did not observe correlations with the total PANSS score, the scores in PANSS subscales, depressive symptoms and global severity measured by CGI and GAF.

To assess a possible impact of use of different medications in the included variables, we compared clinical (PANSS total, subscales, CGI and GAF), cognitive variables (digit span, non-verbal intelligence) and IL-2 levels between patients using clozapine and other atypical antipsychotics and found no significant differences in any of the analyses (Mann–Whitney test, all $P > 0.138$). Clozapine is the first choice for refractory schizophrenia and is the only drug with evidence of superior efficacy when compared to other antipsychotics.

4. Discussion

In the present work, we explored, for the first time, the role of IL-2 in several clinical parameters of disease severity in individuals with SZ. We reported that a group of chronically treated SZ individuals had lower plasma levels of IL-2 as compared to HC. In addition, peripheral IL-2 levels were correlated with clinical and cognitive parameters. Individuals with SZ included in this sample were outpatients in a relatively stable condition. This could explain why we did not find significant deficits in most cognitive functions assessed, except verbal learning (Hopkins test), when compared with healthy subjects. Differences in verbal fluency were marginally significant.

Alterations on the IL-2 system have been detected in SZ. Most studies observed lower concentrations of IL-2 in patients when compared with HC, although some studies reported no alterations [6,35–37]. Intriguingly, *in vitro* studies have shown that leukocytes from individuals with SZ when stimulated produce lower levels of IL-2 in comparison to leukocytes from HC [14,38–40]. Our work contributes to the hypothesis of diminished IL-2 levels in SZ. Genetic studies demonstrated that the T allele of −330G/T polymorphism in the IL-2 gene is associated with an increased risk of developing SZ [41,42]. Functionally, the TT and GT genotypes of this gene have been linked to a reduced *in vitro* production of this cytokine [43], providing a possible explanation for the findings of diminished IL-2 levels in SZ. Antipsychotics use could also influence these results. Some studies have shown that this class of medications can affect IL-2 levels, although the results are mostly inconsistent. Quetiapine, risperidone, clozapine and haloperidol have been linked to decreased IL-2 production [40,44]. Contrastingly, other studies pointed to no effect for risperidone, quetiapine and clozapine [45,46] or even an increase with clozapine and chlorpromazine [44].

Interestingly, there was a negative correlation between IL-2 levels and the total score in the negative subscale of PANSS. The statistically significant negative correlations of items of blunted affect, poor rapport and difficulty in abstract thinking with IL-2 indicate that perhaps low levels of this mediator can be specifically associated with negative psychotic symptoms. These findings are in line with those of Bresee and Rapaport [47], reporting a positive association between soluble IL-2 receptor (sIL-2R) and PANSS total scores, negative and general psychopathology subscales, but not the positive subscale. In opposition to IL-2, sIL-2R is increased in individuals with schizophrenia when compared to healthy controls [6].

Regarding neuropsychological assessment, peripheral IL-2 levels were associated with higher performance in tasks of working memory and non-verbal intelligence in the SZ group. IL-2 has been reported to play a role in neuronal proliferation, survival and neuroprotection. Sarder, Saito [48] reported an IL-2 induced increase in neurite branching

and elongation in primary rat brain cultures. Corroborating these neuroprotective effects, Awatsuji, Furukawa [49] showed that IL-2 promoted cell survival in cortical, striatal and septal neurons. IL-2 effects are mediated by binding to its specific receptor (IL-2R). IL-2 receptor is expressed in cerebral areas related to cognition, like the neocortex, cerebellum and hippocampus [50]. We have shown that, in our group of patients, higher IL-2 levels were associated with better cognitive scores, suggesting that IL-2 may be acting as a neuroprotector in SZ individuals.

The results of this study must be interpreted at light of its limitations. First, the relatively small sample size limited the possibility to include more covariates, such as time of illness or current medications. Also, the results could have been influenced by the intergroup differences regarding marital status and sex, although we found no differences in the levels of IL-2 between married and non-married controls and between male and female controls. In addition, the cross sectional design does not allow strong inferences of causality between IL-2 levels and cognitive deficits and symptoms. As all the patients were under antipsychotic pharmacological treatment, we cannot completely rule out its influence on biomarker's levels, which has been previously shown as a potential confounder. On the other hand, we tried to minimize confounders excluding individuals with recent changes in medication regimen and general medical comorbidity. Furthermore, we assessed the possible impact of clozapine use in IL-2 levels, clinical and cognitive variables and found no significant differences between patients using clozapine and those using other atypical antipsychotics.

5. Conclusions

Nevertheless, this study indicates that IL-2 could have a relevant role in the pathophysiology of SZ, being correlated to negative symptoms and cognitive impairment. Although individuals with SZ had lower levels of IL-2 when compared to HC, within the SZ group, higher levels of IL-2 were indicative of less negative symptomatology and a better cognitive performance. Even though we cannot establish a causal relationship, this association poses IL-2 as a possible marker of cognitive and affective preservation in SZ. Considering the complexity of immune responses, additional studies are necessary to further understand the underlying molecular mechanisms of negative and cognitive symptoms in SZ and the relationship of the described IL-2 findings with other relevant inflammatory markers.

Role of funding source

The project was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo. The sponsor had no further role in the study planning, execution or publication.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

No acknowledgements.

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