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Brain-derived neurotrophic factor levels in first episode of psychosis: A systematic review

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Data sharing: Technical appendix, statistical code, and dataset are available from the at Dryad repository, who will provide a permanent, citable and open-access home for the dataset.

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Abstract

AIM: To systematically review studies measuring peripheric brain-derived neurotrophic factor (BDNF) levels on first-episode psychosis patients and variables related to them.

METHODS: A systematic search was made of articles published in the Medline database from 2002 up to June 2014. Included are original studies that report enzyme-linked immunosorbent assay measurement of BDNF levels in serum or plasma in patients with a diagnosis of first episode psychosis (FEP) and age- and gender- matched healthy controls.

RESULTS: Of the initially identified 147 articles, only 18 satisfied the inclusion criteria. Of this, 15 found a significant reduction in patients with FEP compared with age- and gender - matched controls.

CONCLUSION: Peripheral BDNF levels are generally reduced in FEP patients. There are some factors that may influence BDNF levels that need to be further studied. Furthermore, a future meta-analysis in this topic is needed.

Key words: Brain-derived neurotrophic factor; Psychosis

Core tip: Brain-derived neurotrophic factor (BDNF) has an important role during brain development and various studies have reported altered peripheral BDNF levels in schizophrenia, but findings are inconsistent. Some studies have been carried out specifically in first episode patients to address this issue. In the present study we have systematically reviewed studies measuring BDNF levels in first episode psychosis (FEP) patients compared to healthy controls and variables related to them. Most studies report reduced BDNF levels in FEP patients but some factors that may influence BDNF levels need to be further studied.

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INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system and is highly expressed in the hippocampus and the prefrontal cortex (areas implicated in schizophrenia symptoms[1]. BDNF has an important role during brain development as it is implicated in many essential functions, including neurogenesis, neuronal differentiation, survival and normal maturation of neurodevelopmental pathways[2]. BDNF also has a significant role in the adult brain, regulating neuronal integrity, promoting synaptic plasticity, modulating synthesis, metabolism and release of neurotransmitters (dopamine, γ-aminobutyric acid, serotonin and glutamate), and moderating neuroplasticity processes[3].

As abnormalities in brain development and plasticity have been related to the pathophysiology of schizophrenia, there is a growing interest in understanding the role of BDNF in this disease. Interestingly, BDNF crosses the blood-brain barrier and serum concentrations strongly correlate with brain levels[4]. Low serum BDNF levels have been associated with decreased hippocampal volume, an area that has been strongly related to schizophrenia[5]. A meta-analysis conducted by Green *et al*[6] in 2011 indicated that BDNF levels were altered in patients with schizophrenia, with numerous studies, but not all, reporting reduced levels. They concluded that peripheral BDNF levels were moderately reduced in schizophrenia samples, including drug naïve and medicated patients, when compared with age-matched healthy controls. They also found an accelerated decrease with age, although they observed a high heterogeneity in BDNF levels between the different studies. Furthermore, their results could not support the greater decrease in men than in women that had previously been observed. The reasons for the heterogeneity in BDNF levels between different studies could be due in part by the fact that some patients were evaluated while on antipsychotic treatment. Atypical antipsychotics may increase, whereas treatment with conventional antipsychotics may decrease, peripheral BDNF levels[7]. Moreover, they did not take into account illness characteristics, such as illness stage. BDNF alterations throughout the course of illness are still unclear.

Identifying BDNF alterations in first episode psychosis (FEP) is a preliminary step to understanding the role of BDNF in schizophrenia pathophysiology, as first episode patients are not affected by medication effects (in some cases), or other factors related with chronicity[8]. Several studies have been carried out in FEP patients to identify peripheral BDNF alterations. Therefore, the aim of the present study was to systematically review these studies measuring peripheral BDNF levels in FEP (drug-naïve or medicated) patients and analyze the variables related with them.

MATERIALS AND METHODS

Search strategy

A systematic search was made of articles published in the Medline database using the following keywords: "schizophrenia", "psychosis", and "first episode" in combination with "bdnf", "serum", "plasma", and "peripheral". Articles in both English and Spanish published from 2002 up to June 2014 were selected. Indexed references in the retrieved articles that met the inclusion criteria were manually searched for additional relevant studies.

Inclusion/exclusion criteria

Included in the systematic review are original studies that report enzyme-linked immunosorbent assay measurement of BDNF levels in serum or plasma[6] in patients with a diagnosis of FEP and age- and gender-matched healthy controls. We excluded studies reporting data for patients with comorbid neurologic disorders or other psychiatric illnesses. We also excluded studies that reported peripheral BDNF levels in chronic schizophrenia patients and studies that only reported BDNF genetic data.

From the included studies, we assessed age and gender characteristics. We analyzed statistical differences in age and gender percentage between studies with lower BDNF levels than controls and those that did not with a *t*-test.

Statistical analysis

A statistical review has been performed by a biomedical statistician.

RESULTS

A diagram describing the selection of studies is presented in Figure 1. Of the initially identified 147 articles, only 18 satisfied the inclusion criteria[5,9-25]. Characteristics of these studies are described in Table 1. Seven articles reported BDNF levels in plasma and 11 studies reported levels in blood serum. Moreover, 13 articles reported BDNF levels only in drug-naïve patients and 5 studies reported BDNF levels in medicated patients (the most used antipsychotics were olanzapine, risperidone, quetiapine, aripiprazole and clozapine). When a study measured blood BDNF levels at two different time points, such as the studies that reported BDNF levels in schizophrenia patients before and after antipsychotic treatments, we included only data from the baseline without treatment. A detailed description of the results from the included studies is summarized in Table 2.

Of the 18 articles that measured BDNF levels at

Table 1 Characteristics of the included studies

Ref.	Sample	Age (yr)	Matched for	Illness duration (yr)	Medication	BDNF measurement
Jockers-Scherübl *et al*[9]	157 FEP 72 Ctl	31.8 32.3	Age, gender	Not reported	Drug naïve	Serum
Zakharyan *et al*[10]	25 FEP 105 Ctl	25.3 ± 9.2 37.3 ± 11.3	Age, gender	18.4 ± 7.2	Drug naïve	Plasma
Murphy *et al*[11]	15 FEP 15 Ctl	18.6 ± 3.3 18.5 ± 3.1	Age, gender	Not reported	Quetiapine	Serum
Sotiropoulou *et al*[12]	50 FEP 50 Ctl	29.84 ± 8.20 31.36 ± 7.96	Age, gender	Not reported	Drug naïve	Serum
Ruiz de Azua *et al*[13]	47 FEP 47 Ctl	24.3 ± 8.5 24.0 ± 8.8	Age, gender, education level	Not reported	Drug naïve, Rsp, Olz	Plasma
Yoshimura *et al*[14]	50 FEP 50 Ctl	30.8 ± 5.3 32.3 ± 7.1	Age, gender	Not reported	Apz	Plasma
Rizos *et al*[5]	20 FEP 21 Ctl	30.8 ± 10.5 34.0 ± 4.7	Age, gender, education level, employment	Not reported	Drug naïve	Serum
González-Pinto *et al*[15]	18 FEP 18 Ctl	24.39 ± 6.53 25.19 ± 5.95	Age, gender	Not reported	Drug naïve[1]	Plasma
Rizos *et al*[16]	37 FEP 22 Ctl	26.81 ± 9.22 26.59 ± 4.47	Age, gender	Not reported	Drug naïve	Serum
Jindal *et al*[17]	41 FEP 41 Ctl	22.40 ± 5.47 22.31 ± 5.67	Age, gender	Not reported	Drug naïve	Serum
Goto *et al*[18]	18 FEP 18 Ctl	29 ± 11 30 ± 11	Age, gender	9.4 ± 6.8	Drug naïve, Rsp/ Olz/Apz	Serum
Pillai *et al*[19]	34 FEP 36 Ctl	32.19 ± 8.74 38.30 ± 1.26	Age, gender	Not reported	Drug naïve	Plasma
Rizos *et al*[20]	31 FEP 22 Ctl	26.81 ± 9.22 26.81 ± 9.22	Age, gender, education level, employment	Not reported	Drug naïve	Serum
Chen da *et al*[21]	88 FEP 90 Ctl	29.2 ± 9.6 29.8 ± 9.8	Age, gender, education level, smoking	23.4 ± 19.1	Drug naïve	Serum
Rizos *et al*[22]	14 FEP 15 Ctl	25.4 ± 5.8 26.6 ± 5.0	Age, gender, education level, employment	Not reported	Drug naïve	Serum
Buckley *et al*[23]	15 FEP 14 Ctl	21.00 ± 8.83 25.00 ± 5.72	Age, gender	25.2 ± 33.0	Drug naïve	Plasma
Palomino *et al*[24]	48 FEP 43 Ctl	23.7 ± 1.0 25.5 ± 0.8	Age, gender	Not reported	Atypical, mood stabilizers	Plasma
Pirildar *et al*[25]	22 FEP 22 Ctl	27.81 ± 9.54 25.7 ± 5.8	Age, gender	15.2 ± 13.0	Drug naïve[1]	Serum

[1]BDNF levels were also assessed after antipsychotic treatment (Olz, Rsp, Cloz) but not included in the review. Data are presented as mean ± SD. Apz: Aripiprazole; BDNF: Brain-derived neurotrophic factor; Cloz: Clozapine; Ctl: Controls; FEP: First episode psychosis; Olz: Olanzapine; Rsp: risperidone.

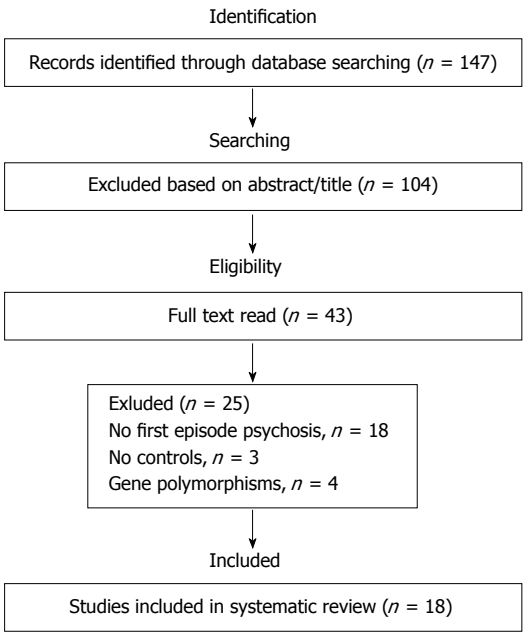

Figure 1 Flow diagram describing the selection of studies.

baseline, 15 found a significant reduction in patients with FEP compared with age- and gender-matched controls.

There were no statistical differences in mean age between those studies that found lower BDNF levels in patients than those that did not (26.18 ± 3.89 *vs* 29.11 ± 3.50, $P = 0.24$) The percentage of men was lower in the studies that found decreased BDNF levels in patients compared to those that did not (47.89% *vs* 54.71%, $P = 0.36$).

DISCUSSION

We found 15 out of 18 articles found a reduction in BDNF levels compared to age- and gender-matched controls. It is important to note that 13/18 studies included only drug-naïve patients and 2 included drug-naïve and medicated patients. Televe out of 15 studies that found a decrease were conducted in drug-naïve patients whereas two of the three studies that found no alteration in BDNF included medicated patients.

Table 2 Basal levels of brain-derived neurotrophic factor

Ref.	FEP (ng/mL)	Controls (ng/mL)	Results	Effect size d (CI)
Jockers-Scherübl *et al*[9]	13.1 ± 5.9	13.2 ± 0.2	No difference	0.10 (-0.18-0.38)
Zakharyan *et al*[10]	0.176 ± 0.014	0.24 ± 0.3	↓ in FEP	1.21 (0.75-1.67)
Murphy *et al*[11]	Missing data	Missing data	No difference	-
Sotiropoulou *et al*[12]	12620 ± 1860	14520 ± 2180	↓ in FEP	0.64 (0.23-1.04)
Ruiz de Azua *et al*[13]	6.09 ± 3.70	9.19 ± 4.21	↓ in FEP	0.66 (0.24-1.07)
Yoshimura *et al*[14]	0.7 ± 0.4	Missing data	↓ in FEP	0.43 (0.03-0.82)
Rizos *et al*[5]	9.76 ± 4.61	15.33 ± 6.34	↓ in FEP	0.99 (0.34-1.64)
González-Pinto *et al*[15]	4.09 ± 2.31	5.80 ± 2.66	↓ in FEP	-
Rizos *et al*[16]	18.87 ± 8.23	29.20 ± 7.73	↓ in FEP	0.72 (0.17-1.26)
Jindal *et al*[17]	0.09 ± 0.03	0.117 ± 0.04	↓ in FEP	0.54 (0.10-0.99)
Goto *et al*[18]	Missing data	Missing data	No difference	0.38 (-0.28-1.04)
Pillai *et al*[19]	Missing data	Missing data	↓ in FEP	0.53 (0.05-1.00)
Rizos *et al*[20]	Missing data	Missing data	↓ in FEP	-
Chen da *et al*[21]	9.0 ± 4.2	12.1 ± 2.2	↓ in FEP	0.92 (0.61-1.23)
Rizos *et al*[22]	23.90 ± 5.99	30.00 ± 8.43	↓ in FEP	0.83 (0.07-1.59)
Buckley *et al*[23]	0.017 ± 0.003	0.049 ± 0.007	↓ in FEP	1.37 (0.56-2.18)
Palomino *et al*[24]	4.19 ± 2.26	7.55 ± 4.31	↓ in FEP	0.56 (0.13-0.97)
Pirildar *et al*[25]	14.2 ± 8.1	26.8 ± 9.3	↓ in FEP	1.07 (0.93-1.7)

Data are presented as mean ± SD. FEP: First episode psychosis.

These results are consistent with some studies pointing out normalization in BDNF levels with treatment. However, other additional factors may influence BDNF alterations.

Another factor that could affect BDNF levels is the mean age of patients, as a greater reduction in peripheral BDNF in schizophrenia was reported with increasing age in Green *et al*[6]. We did not find statistical differences in mean age between those studies that found lower BDNF levels in patients than those that did not. However we must take into account that our age variance was much smaller than in Green *et al*[6] study.

On the other hand, although some articles have described a greater reduction in BDNF in males than females with schizophrenia[6], this does not appear to be a factor in the present analysis, even after taking into account the size effect (results upon demand). This results are in agreement with Green *et al*[6] who found no a reduction in both men and women in BDNF after excluding an outlier.

Patients clinical characteristics, could also affect BDNF levels. It would be interesting to conduct a prospective study on high risk psychosis patients through different illness stages to clarify this issue.

Another important variable to consider is substance use, particularly cannabis use. Cannabis use is very common in first episode patients, with a prevalence ranging from 30% to 60%[26]. Moreover, in non-psychotic patients, it has been described that acute cannabis use can initially increase, whereas chronic use can decrease, peripheral BDNF levels[27]. However, cannabis use was an exclusion criterion in most studies, but not in all. Specifically, the article by Jockers-Scherübl *at al*[9] compared BDNF levels between FEP patients and controls that used and did not use cannabis[9]. They found increased BDNF levels in FEP cannabis-users than non-users and controls. These results are in disagreement with a more recent study[27]. Further research should therefore be performed to clarify the effects of cannabis use on BDNF levels in FEP patients. The effect of the val66met BDNF polymorphism and the interaction between this polymorphism and cannabis use could also affect BDNF levels. A Val to Met substitution at codon 66 of the BDNF gene, is known to result in less efficient intracellular trafficking and decreased activity-dependent BDNF secretion and has been related to psychosis emergence[28]. Furthermore a study has described an interaction effect between cannabis, this polymorphism and gender, on the risk of psychosis emergence[29].

Other environment factor should also affect BDNF levels. A history of childhood trauma has been related to a reduction of BDNF levels[30].

Limitations

A limitation of this type of systematic review is that some relevant studies, including those that are unpublished, may be overlooked. Another limitation is the marked heterogeneity of the articles included in the review in relation to the sample size, the mean age of the patients, the proportion of men/women, the illness duration (only reported in six studies), the medication type (in patients receiving treatment), and the type of symptomatology patients were presenting. Furthermore, we did not take into account the effect of the BDNF polymorphism, and it could have multiplicative on lower BDNF levels.

Peripheral BDNF levels are generally reduced in FEP patients. However, there are some factors that may influence BDNF levels that need to be further studied, which will help to resolve inconsistencies in the literature. Furthermore, a future meta-analysis on

this topic would help to clarify BDNF alterations in FEP.

COMMENTS

Background

Altered brain-derived neurotrophic factor (BDNF) levels have been described in schizophrenia, and have been related to brain abnormalities, but findings are still inconsistent. Moreover, BDNF alterations throughout the illness course are still unclear.

Research frontiers

Neuroimaging in schizophrenia; neurodevelopment in schizophrenia; neuroplasticity in schizophrenia; neurodegeneration in schizophrenia.

Innovations and breakthroughs

This is the first work that systematically reviews studies measuring peripheric BDNF levels in first episode patients, a group of patients not affected by cronicity.

Applications

Comprehending BDNF alterations in first episode patients is a preliminary step to understanding the role of BDNF in schizophrenia pathophysiology and brain structure alterations.

Terminology

Neurotrophic factors are a family of proteins that are responsible for the growth and survival of developing neurons and the maintenance of mature neurons.

Peer-review

This is an interesting manuscript.

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