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Source / Izvornik: **Neuropsychobiology, 2020, 79, 179 - 185**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1159/000504577

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:220:075788

Research Article

Neuropsychobiology

Neuropsychobiology 2020;79:179–185
DOI: 10.1159/000504577

Received: September 3, 2019
Accepted after revision: November 3, 2019
Published online: December 6, 2019

Vitamin D and Neurotrophin Levels and Their Impact on the Symptoms of Schizophrenia

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Keywords
Schizophrenia · Vitamin D · Neuregulin-1 · Brain-derived neurotrophic factor · Nerve growth factor

Abstract
Introduction: Vitamin D is involved in brain development and functioning, as well as in regulation of neurotrophic factors. Changes in the expression of those factors are possibly responsible for morphologic abnormalities and symptoms in patients suffering from schizophrenia. ***Objective:*** The main goal of this research was to investigate the interrelationship between vitamin D, nerve growth factors (NGF, brain-derived neurotrophic factor [BDNF], and neuregulin-1 [NRG1]), and schizophrenia symptom domains. ***Methods:*** This research included 97 inpatients diagnosed with schizophrenia. Schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Blood samples were taken in order to analyze concentrations of vitamin D, BDNF, NRG1, and NGF growth factors. The obtained results were used in a multiple regression analysis. ***Results:*** The vitamin D concentration positively affected the concentration of NRG1 ($F = 8.583$, $p = 0.005$) but not the concentration of other investigated growth factors (BDNF and NGF). The clinical characteristics and symptom domains of schizophrenia seemed to be unaffected by the concentrations of vitamin D, BDNF, and NGF, while the NRG1 concentration significantly affected positive symptom domains of schizophrenia ($F = 4.927$, $p = 0.030$). ***Conclusion:*** The vitamin D concentration positively affected NRG1 levels but not schizophrenia symptomatology as measured by PANSS. The association between the two could be intermediated via NRG1.

Introduction

Aside from its well-known role in calcium homeostasis and bone metabolism, vitamin D has other physiological roles, such as being a neuroactive steroid hormone involved in brain development and functioning [1, 2]. Its involvement in brain functioning became apparent when the presence of vitamin D receptors (VDR) and enzymes included in its synthesis and metabolism was established

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in neurons and glial cells [3]. On that note and according to the available data, vitamin D deficiency may play a predictive role in cognitive functioning, as well as in psychiatric illnesses such as dementia, depression, autism, psychosis, and especially schizophrenia [1]. Furthermore, the vitamin D deficiency hypothesis of schizophrenia was formed as a result of observations that individuals born in winter and in early spring, as well as those living at higher latitudes, with a low exposure to sunlight and who are less involved in outdoor activities, have an increased risk of developing schizophrenia [4]. On that note, there have been reports that neonatal vitamin D levels could be considered a significant risk factor for the development of schizophrenia, considering the fact that VDR regulates the expression of numerous genes, which is an additional epigenetic factor [5, 6].

Although the exact pathophysiological processes are still unknown, it is believed that vitamin D deficiency can influence neurogenesis through protein kinase B, which plays an extremely important role in neuronal growth, differentiation, and migration [7]. Vitamin D is also involved in dopamine neurotransmission through expression of a key dopamine enzyme, i.e., catechol-O-methyltransferase, as well as by direct modulation of tyrosine hydroxylase [8, 9]. Additionally, vitamin D deficiency may reduce γ-aminobutyric acid (GABA) and glutamatergic neurotransmission [10]. It is also involved in the synthesis of neurotrophic factors, which would suggest its neuroprotective effects [11, 12].

It is a well-established fact that neurotrophic factors are directly involved in nerve growth and neuronal differentiation, regulation of synaptic activity, and neurotransmitter synthesis [11]. Hence, changes in their expression may be responsible for characteristic morphologic abnormalities as well as psychopathological symptoms in patients suffering from schizophrenia [13]. Consequently, it has been reported that vitamin D increases the expression of nerve growth factor (NGF), glial cell line-derived neurotrophic factor, brain-derived neurotrophic factor (BDNF), and neurotrophin-3 and reduces the level of neurotrophin-4 [9, 14, 15]. Whether this occurs through direct transcription of the mRNA of certain neurotrophic factors is not completely understood, although there have been reports of such an effect on NGF [9, 16].

Previous research findings suggest abnormal values of NGF and BDNF in those suffering from schizophrenia [17–19]. Although a positive association between BDNF and negative symptoms has been observed, the exact mechanism linking neurotrophic dysregulation and manifestation of symptoms of schizophrenia is still unknown [20]. However, it has already been hypothesized that vitamin D exerts a functional role in the pathogenesis of schizophrenia through neuregulin (NRG) and its tyrosine kinase receptors (ErbB) [21]. Animal models revealed changes in gene expression in NRG pathways in vitamin D deficiency during mouse development [21]. Additionally, NRG1/ErBb4 hypomorphic mice seem to be at an increased risk for behavioral disorders and have a lower quantity of functional NMDA receptors, which corresponds to established brain changes in patients suffering from schizophrenia [22]. Inadequate NRG1 signaling may also lead to a wide range of anatomical abnormalities, altered neurotransmission and expression of psychotic symptoms, and cognitive deficits [22, 23]. Among other things, it is possible that changes in NRG1/ErBb4 signaling affect the deregulation of glutamate, GABA, and dopamine transmission in schizophrenia [6, 24, 25]. Consequently, NRG has for over 2 decades been considered a gene the impaired functionality of which carries a risk of developing schizophrenia [22, 23].

The main goal of this research was to investigate the possible effects of vitamin D concentration on schizophrenia symptom domains, as well as to investigate its potential association with NGF concentrations (BDNF, NGF, and NRG1).

Materials and Methods

Participants

This research was performed in 97 patients suffering from schizophrenia (45 males and 52 females) whose sociodemographic and clinical parameters are presented in Table 1. The inclusion criteria for this study were a diagnosis of schizophrenia using DSM-5 criteria and the absence of any other psychiatric disorder. Participants with any use of psychoactive compounds including alcohol in their medical history were excluded from this study. Participants suffering from any sort of physical or neurologic illness were also excluded from this study, as were those participants who were taking any sort of medicaments or vitamin supplements. All of the subjects were inpatients who at the time of study enrollment were either drug naive (first schizophrenic episode) or off their previously prescribed psychiatric medication (due to lack of treatment adherence and subsequent psychotic decompensation) at least 3 weeks. Informed consent was obtained from all of the included patients after a complete and extensive description of the study profile. This study was approved by Ethics Committee of the University Hospital Centre.

Medical Examination and Study Design

This study included patients who had been admitted for inpatient treatment at the Sestre Milosrdnice University Hospital Center with a diagnosis of schizophrenia in the period from April 2017 to April 2018. During that period, 273 patients were hospitalized with a diagnosis of schizophrenia. After applying the exclusion

criteria, 53 subjects were excluded due to a comorbid physical illness, 22 were excluded due to a comorbid neurologic illness, and 51 were excluded due to the presence of an additional psychiatric disorder and diagnosis. An additional 25 subjects were excluded due to abuse of psychoactive compounds (including alcohol and cannabis) and 21 were excluded because of treatment with various medications (including nonpsychiatric medication), while 4 subjects were excluded for taking vitamin supplements. In the end, 97 patients were enrolled into and completed this study. A structured clinical interview was performed by a psychiatrist, who made the diagnosis using the Structured Clinical Interview for DSM-5 (SCID 5) [26]. The severity of schizophrenia was assessed by the Positive and Negative Syndrome Scale (PANSS) [27]. Variables of disease features (number of episodes and duration of schizophrenia in years) were obtained from the structured clinical interview based on the Mini International Neuropsychiatric Interview (MINI) which was performed by a trained psychiatrist [28].

Biochemical Measurements

Blood samples were taken from patients for analysis of concentrations of vitamin D as well as concentrations of BDNF, NRG1, and NGF growth factors. Blood samples were taken from the cubital vein in vacuumed eprouvettes (Greiner Bio-One, Austria) without an anticoagulant in the morning, after 12 h of fasting, and after a 30-min pause. Research was performed with standard commercial reagents as per the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Vitamin D, as a form of total vitamin (D_2 and D_3), was determined using an immunochemical chemiluminescent method with in vitro diagnostic reagents (Abbott, USA) on an automatic immunochemical analyzer (Architect 18 i2000SR; Abbott). BDNF, NRG1, and NGF growth factors were determined with the enzyme-linked immunosorbent assay (ELISA) procedure using commercial reagents (Abbexa, UK). In our laboratory, the value of the interassay CV was 2.1% for vitamin D, 2.4% for BDNF, 1.5% for NRG1, and 1.9% for NGF.

Data Analysis

A normal distribution was assessed for all measures using the Kolmogorov-Smirnov test. Sociodemographic and clinical characteristics of the patients and concentrations of vitamin D and BDNF, NRG1, and NGF growth factors were described as means (±SD) or frequencies (%), respectively. A normal distribution was confirmed for vitamin D, BDNF, NRG1, and NGF growth factors concentrations. In order to test the predictions of vitamin D concentrations on BDNF, NRG1, and NGF and the severity of the clinical picture as measured by the PANSS, a multiple regression analysis was performed. In addition, a multiple regression analysis was performed in order to test the predictions of BDNF, NRG1, and NGF on PANSS subscales. Because several factors, especially sex and age but also smoking, may affect vitamin D and neurotrophic levels [29–31], we investigated for possible associations. Data analysis was performed using correlation coefficients and Student's *t* tests but revealed no significant findings. Therefore, those variables were not included in the multiple regression analysis. Statistics was performed with SPSS software (SPSS for Windows 17.0; SPSS, Chicago, IL, USA), and the power analysis was performed using G*Power software (http://www. psycho.uni-duesseldorf.de/aap/projects/gpower/).

Table 1. Sociodemographic and clinical characteristics of the schizophrenic patients

Age, years	40.19±14.65
Illness duration, years	10.34±12.09
Hospitalizations, *n*	3.20±1.99
PANSS	22.23±6.21
PS	
NS	24.83±7.89
GPS	47.80±7.78
Total	94.87±16.97
BDNF, ng/mL	4.48±1.78
NRG1, ng/mL	4.70±2.68
NGF, ng/mL	8.73±5.76
Vitamin D, nmol/L	53.56±28.99
Sex	
Male	45 (46.4)
Female	52 (53.6)
Marital status	
Married	62 (63.9)
Single	20 (20.6)
Divorced	15 (15.5)
Education	
Elementary	11 (11.3)
High school	59 (60.8)
University	27 (27.9)

Values are presented as means ± SD or numbers (%).

Results

Sociodemographic, clinical, and other investigated characteristics of the schizophrenic patients who participated in this research are visible in Table 1. We performed a multiple regression analysis in order to establish the influence that vitamin D concentrations exhibit on NGF concentrations (BDNF, NRG1, and NGF) and PANSS scores. The results of that analysis are shown in Table 2. We established that the vitamin D concentration positively affects the NRG1 concentration ($F = 8.583$, $p = 0.005$) but not the concentrations of the other 2 investigated nerve factors, i.e., BDNF ($F = 0.718$, $p = 0.400$) and NGF ($F = 0.002$, $p = 0.961$). In addition, the vitamin D concentration did not affect the PANSS symptomatology variables, i.e., PANSS positive subscale (PS) ($F = 2.279$, $p = 0.136$), PANSS negative subscale (NS) ($F = 0.096$, $p = 0.758$), and PANSS general psychopathology subscale (GPS) ($F = 0.399$, $p = 0.530$). We also performed a multiple regression analysis in order to test the putative influence of NGF (BDNF, NRG1, and NGF) concentrations on schizophrenia symptomatology and severity, as measured by PANSS and its subscales. The results are

Table 2. Influence of vitamin D concentration (in nmol/L) on NGF concentrations and PANSS subscale scores

Dependent variable	B	SE	*t* value	*p* value	95% CI	
					lower limit	upper limit
BDNF (ng/mL)	0.006	0.007	0.848	0.400	–0.008	0.020
NRG1 (ng/mL)	0.030	0.010	2.930	0.005	0.010	0.050
NGF (ng/mL)	0.001	0.023	0.049	0.961	–0.045	0.048
PANSS PS	0.037	0.025	1.510	0.136	–0.012	0.087
PANSS NS	–0.009	0.029	–0.310	0.758	–0.067	0.049
PANSS GPS	0.018	0.028	0.631	0.530	–0.038	0.074

Table 3. Influence of NGF concentrations (in ng/ml) on PANSS subscale scores

Dependent variable	Growth factor	*B*	SE	*t* value	*p* value	95% CI	
						lower limit	upper limit
PANSS PS	BDNF	–0.562	0.398	–1.413	0.162	–1.356	0.231
	NRG1	0.586	0.264	2.220	0.030	0.059	1.113
	NGF	0.074	0.123	0.600	0.551	–0.171	0.318
PANSS NS	BDNF	0.789	0.489	1.613	0.111	–0.187	1.764
	NRG1	0.325	0.325	1.001	0.320	–0.323	0.973
	NGF	0.118	0.151	0.784	0.435	–0.183	0.419
PANSS GPS	BDNF	–0.133	0.461	–0.288	0.774	–1.052	0.786
	NRG1	0.571	0.306	1.865	0.066	–0.040	1.181
	NGF	0.142	0.142	1.000	0.321	–0.141	0.425

B, unstandardized coefficient.

shown in Table 3. They did not reveal a significant influence of BDNF on schizophrenia symptomatology, with the results for each subscale being: positive symptomatology ($F = 1.997$, $p = 0.162$), negative symptomatology ($F = 2.600$, $p = 0.111$), and general psychopathology ($F = 0.083$, $p = 0.774$). On the other hand, we established a significant effect of NRG1 concentration on the expression of positive symptomatology ($F = 4.927$, $p = 0.030$), while the effect was not significant regarding the other 2 investigated parameters, i.e., negative symptomatology ($F = 1.003$, $p = 0.320$) and general psychopathology ($F = 3.478$, $p = 0.066$). Finally, no significant influence of NGF concentration on schizophrenia symptomatology was detected, with the results being: positive symptomatology ($F = 0.360$, $p = 0.551$), negative symptomatology ($F = 0.615$, $p = 0.435$), and general symptomatology ($F = 0.999$, $p = 0.321$).

Discussion

Several studies and meta-analyses have so far reported reduced vitamin D levels in patients suffering from schizophrenia [32, 33], with the focus of research recently shifting towards symptom domains and resulting in conflicting data. For example, the association between reduced vitamin D concentrations and negative symptoms of schizophrenia has been repeatedly confirmed [30, 34–37]. Reduced vitamin D levels have also been associated with cognitive deficits and depressive symptoms in schizophrenia [35, 36], while the association with positive symptoms has been established both in the first psychotic episode and in the chronic phase of schizophrenia [34, 38, 39]. However, we did not reveal a direct association between vitamin D concentrations and schizophrenia symptom domains, which is a confirmation of some previous reports [31, 40].

Taking into account the fact that neurotrophic factors alterations, both at the protein level and at the genetic

level, may contribute to altered brain development, dysregulation of synaptic transmission, and impaired neuroplasticity, it is at least partially possible to explain the individual morphological and neurochemical brain abnormalities identified in those suffering from schizophrenia [13]. Reflecting these findings, reduced peripheral NGF levels (plasma or serum) have been reported in those suffering from schizophrenia compared to healthy individuals [41–43]. Similarly, low BDNF levels are frequently reported in those suffering from schizophrenia, especially in the first psychotic episode [44], along with positive correlations between BDNF levels and positive and negative symptoms of schizophrenia [20, 45]. Also, a significantly increased BDNF concentration has been reported in patients diagnosed with a paranoid subtype of schizophrenia [45]. However, we did not observe and confirm any of these findings in our results.

Several lines of evidence now link vitamin D to various neurotrophic factors, as vitamin D regulates their expression and is considered to be an especially powerful inductor of NGF synthesis while it modulates BDNF levels both in vitro and in vivo [14, 46]. However, it is still not known whether vitamin D genomically affects BDNF expression [9]. In light of those facts, we examined the putative association of vitamin D and neurotrophic factors (BDNF, NGF, and NRG1) but failed to reveal significant associations between vitamin D concentrations and concentrations of BDNF and NGF, while there have been previous reports linking a vitamin D deficit to decreased NGF [47]. Additionally, a nonsignificant association between NGF concentration and the psychopathology of schizophrenia has previously been reported [48]. We did, however, establish a significant positive association between vitamin D and NRG1 concentrations. The effects of the potential association between vitamin D concentration and NRG or NRG1/ErbB signaling in the available literature are largely unknown, although they has been investigated in the cardiovascular system and on animal models. In those models, an active metabolite of vitamin D, i.e., calcitriol, increased NRG1/ErbB signaling [49]. As far as the nervous system is concerned, NRG1 increases the proliferation of neuronal progenitors from embryonic neural stem cells and is involved in a large number of neural development processes, and it plays a role in the etiology of schizophrenia [25]. Additional evidence of a possible role of NRG1 in schizophrenia comes from animal models (NRG1/ErbB4 hypomorphic mice) which revealed abnormal behavior in terms of hyperactivity, social withdrawal, and reduced prepulse inhibition [22]. In this research, we established a significant association between NRG1 and positive symptoms of schizophrenia but not other investigated symptom domains. Although comparable research data is very scarce, it should be emphasized that NRG1 has previously been associated with psychotic symptoms and cognitive deficits seen in schizophrenia (in individuals with a positive hereditary loading for schizophrenia and in those with a high risk of developing schizophrenia) [50]. Finally, only 1 study has previously reported a significant association between NRG1 and schizophrenia (more specifically, with negative symptoms of schizophrenia), whereas 2 studies did not report any significant associations between NRG1 and schizophrenia or symptoms of schizophrenia evaluated by the PANSS [51–53].

This is the first study to address the putative association between vitamin D and several NGF (primarily NRG) and schizophrenia symptom domains, both directly and indirectly. We revealed a positive association between the concentrations of vitamin D and NRG1. We also established a significant association between the concentration of the same neurotrophin and positive symptoms of schizophrenia. Although we did not establish a direct association between vitamin D concentrations and schizophrenia symptom domains, it is possible that it was intermediated through NRG1. Nevertheless, additional research will be needed to clearly confirm this mechanism, while also taking into account the limitations of this research. One of those limitations is the fact that this study was cross-sectional without a prospective design, and thus it was not possible to study vitamin D and NGF dynamics during the clinical course of schizophrenia and/or the influence of psychopharmacological treatment on the investigated parameters. Another limitation is the lack of a control group, as well as that the group of patients suffering from schizophrenia was heterogeneous regarding illness length and number of episodes. In addition, peripheral neurotrophic levels may not indicate their concentrations in the brain. However, it has been reported that neurotrophins could cross the blood-brain barrier via a high-capacity saturable transport system [54] and that serum levels could be an approximate measure of brain levels of neurotrophins [18]. Further research should also include other growth factors (e.g., glial cell line-derived neurotrophic factor) which have previously been linked to schizophrenia and its symptomatology.

Acknowledgment

The authors are indebted to all of the physicians, nurses, and study coordinators who cared for the patients and who kindly provided the data necessary for our analysis.

Disclosure Statement

The authors have no conflict of interests to declare.

Funding Sources

This research was funded by the University of Zagreb's School of Dental Medicine project "Schizophrenia Symptom Dimensions and Serotonin and Dopamine System Gene Polymorphisms."

Author Contributions

Vjekoslav Peitl and Dalibor Karlović contributed equally and should be considered as equals when it comes to assessing this paper. They designed this study, managed literature searches and analyses, revised and corrected this paper, and approved its final version. Dalibor Karlović performed all of the required statistical analyses, while Vjekoslav Peitl wrote the first draft of this paper and supervised all corrections. Ivona Orlović and Branka Vidrih organized sample collection and participant involvement and approved the final draft of this paper. Ivona Orlović also performed the literature search. Danijel Crnković supervised all laboratory and biochemical analyses and approved the final version of this paper. Ante Silić performed the literature search, supervised sample collection, assisted in correction of this paper and approved its final version.

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