



Letter to the Editor

Neuregulin-1 is increased in schizophrenia patients with chronic cannabis abuse: Preliminary results



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To the Editor,

Plenty of studies have shown that cannabis increases the risk of developing schizophrenia and that chronic cannabis abuse leads to problems in learning, attention and a decrease in brain volume (Van Gastel et al., 2014).

Neurotrophins are proteins that serve as survival factors for selected populations of CNS neurons. Their association with cannabis consumption and schizophrenia was scarcely researched. Jockers-Scherübl et al. (2003, 2004) showed higher levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in cannabis-consuming schizophrenia patients in comparison to controls and non-exposed patients, but BDNF was also increased in patients who abused multiple drugs besides cannabis. Chronic cannabis abusers in the general population had higher levels of NGF, but not BDNF in comparison with non-users (Angelucci et al., 2008). Neuregulin (NRG) has been implicated in cannabis dependence, but it was not previously researched in cannabis-abusing schizophrenia patients (Silveira et al., 2017).

This study aimed to assess the association between chronic cannabis abuse and BDNF, NGF and NRG-1 levels in non-medicated schizophrenia patients.

The sample consisted of 86 (52.3% male) Caucasian patients with a diagnosis of schizophrenia established using the DSM-5 criteria, consecutively admitted to the acute psychiatric unit. Mean age was 40 years (SD = 14.01) and the mean duration of illness was 10.23 years (SD = 12.07). The patients had not used antipsychotics for at least a month prior to admission.

Chronic cannabis consumption was defined as at least 0.5 g per day during at least two years. The exclusion criteria were: regular alcohol consumption, any somatic disease, acute intoxication and withdrawal symptoms.

The patients gave their informed consent. The ethics committee approved the study. The severity of the disease was assessed by the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) with Cronbach alpha 0.81.

Blood samples were taken on the day of admission. BDNF, NRG-1 and NGF were determined using the ELISA procedure.

Analyses were performed with the SPSS 20.0 statistical package and included descriptive statistics, Kolmogorov-Smirnov test, Mann-Whitney *U* test, Spearman's correlations and logistic regression. The significance level was $P < 0.05$.

As the distribution of continuous variables was not normal, Mann-Whitney *U* test was used to compare the group of chronically cannabis-abusing schizophrenia patients and the group of non-abusing patients. Neuregulin-1 was higher in the group of cannabis abusing schizophrenia patients ($U = 462.5$; $p = 0.026$) and members of this group were significantly younger ($U = 482.0$; $p = 0.001$), with a shorter duration of illness ($U = 534.0$; $p = 0.003$). The two groups did not differ in PANSS total and the three main subscales. The levels of BDNF, NGF and NRG-1 were not correlated with PANSS, age or duration of illness. Cannabis consumption was more frequent in males ($\chi^2 = 15.584$; $df = 1$; $p = 0.001$).

Logistic regression with cannabis consumption/non-consumption as the dependent variable and neurotrophic factors, age, gender and duration of illness were included in the model. Male gender, younger age and higher values of NRG-1 were significant predictors of the model presented in Table 1.

Our results suggest that NRG-1 was increased in the group of chronic cannabis-abusing schizophrenia patients in comparison with non-abusing patients. To the best of our knowledge, this is the first study to research the association between NRG and chronic cannabis abuse in schizophrenia.

NRG1 has major functions in synaptic plasticity, myelination processes, migration and differentiation of oligodendrocytes, and modulation of neurotransmitter receptors (D'Souza et al., 2009). In patients with schizophrenia, acute administration of tetrahydrocannabinol (THC) exacerbates symptoms and cognitive impairments, but shows some beneficial effects on cognition. Yücel et al. (2012) have recently found that cannabis abusing schizophrenia patients have superior neuropsychological functioning compared to non-abusing patients, especially with early-onset cannabis use, as was the case in our cannabis-smoking group.

Studies also suggest that NRG-1 influences the endocannabinoid system. NRG-1 modulates the effects of adolescent THC exposure on the expression of CB1 receptors (Silveira et al., 2017).

Table 1

Means, standard deviations, Wald coefficient, statistical significance and 95% CI for Exp (B) for the logistic regression analysis ($df = 1$).

Variable	Cannabis smokers M (SD)	Cannabis non-smokers M (SD)	Wald coefficient	p	95%CI for Exp (B)	
					Lower	Upper
BDNF	4.764(2.53)	4.27(1.00)	2.340	0.125	0.845	3.923
NGF	9.46(4.46)	10.95(13.45)	0.034	0.854	0.890	1.152
NRG 1	5.71(2.71)	4.31(2.56)	7.653	0.006	1.127	2.012
Age	33.06(10.78)	44.07(14.28)	4.579	0.032	0.888	0.995
Gender			7.829	0.005	1.927	41.411
Duration	12.34(12.43)	33.06(10.78)	3.948	0.47	0.825	0.999

M - mean; SD - standard deviation.

In accordance with our results are the findings that propose NRG-1 as a major candidate for the development of cannabis dependence and that genetic predisposition to schizophrenia is associated with increased use of cannabis (Silveira et al., 2017).

Segal-Gavish et al. (2017) implicated that BDNF induction after THC exposure in mice served as a homeostatic response guard to maintain a proper cognitive function against exogenous insult. We may assume that NRG increase, as shown in our study, was an attempt of the brain to amortise the stress of cannabis abuse. Further, Table 1 shows that the values of BDNF and NGF were also increased in patients that abused cannabis, although did not reach statistical significance.

The main limitations of the study are peripheral measurements of BDNF, NGF and NRG and small sample size. However, studies show that neurotrophin serum levels could be an approximated measure of their brain levels (Qin et al., 2017).

Our data, although preliminary, point to the necessity to further research the role of neuregulin in cannabis-abusing schizophrenia patients.

Conflict of interest

The authors declare no conflict of interest.

Contributors

Author Aukst Margetic Branka designed the study, searched the literature and wrote the final version of the manuscript. Author Peitl Vjekoslav took part in study design and literature search, author Vukasovic Ines took part in study design, and performed laboratory analyses. Author Karlovic Dalibor designed the study undertook the statistical analysis and took part in writing of the manuscript. All authors contributed to and have approved the final manuscript.

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