DOI: https://doi.org/10.4038/sljpsyc.v14i2.8487

Review

The association between serum BDNF levels, BDNF polymorphisms, and tardive dyskinesia: A review of current evidence

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Abstract

Background

Tardive Dyskinesia (TD) is a movement disorder that can be potentially permanent and is commonly found among psychiatric patients who are taking anti-psychotics or lithium. Studies have investigated the association between TD and genetics, particularly the impact of Brain-Derived Neurotrophic Factor (BDNF) polymorphisms on TD occurrence and cognitive changes. Among the BDNF polymorphisms studied, Val66Met has been investigated extensively. Nevertheless, the extent to which genetic approaches can contribute to comprehending the susceptibility to TD remains uncertain.

Methods

PubMed was used to search articles systematically. Twenty-seven articles published in the last ten years (2012-2022) were retrieved. Review, meta-analysis, retracted, animal studies, and comment articles were excluded. In addition, only articles in English language were included.

Results

Preliminary results of the study suggest an association between TD occurrence and cognition with specific BDNF polymorphisms and serum BDNF levels.

Conclusions

In conclusion, our study findings suggest a potential relationship between TD and BDNF polymorphisms as well as serum BDNF levels.

Keywords: tardive dyskinesia, brain-derived neurotrophic factor, oxidative stress, schizophrenia, genetics, movement disorders

SL J Psychiatry 2023; 14(2): 15-22

Introduction

Tardive dyskinesia (TD) is a movement disorder common in patients with schizophrenia (SCZ) (Uludag et al., 2021), while Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin, and it has been associated with SCZ (Nieto et al., 2021).

BDNF gene has become a candidate gene for genomics of drugs used in treating SCZ (Rybakowski, 2008). In addition, BDNF may be a trophic factor for dopaminergic neurons (Hyman et al., 1991) and is the most abundant neurotrophin (Tsai, 2018).

In past research, the relationship between serum BDNF levels, BDNF polymorphisms, and psychiatric disorders has been examined, with a focus on potential interactions between these factors. For instance, one specific polymorphism, rs6265, has been found to have no association with serum BDNF levels. This suggests that serum BDNF levels are influenced more significantly by diagnostic effects related to psychiatric conditions rather than genetic factors (kumar et al., 2020). Furthermore, a different study found that met-carriage had an impact on reducing BDNF levels (Ozan et al., 2010). In addition, studies have been made to investigate the association between BDNF and movement disorders such as TD and Parkinsons' Disease. For example, in a study, patients with TD had lower serum BDNF levels than non-TD (Yang et al., 2011). Moreover, different studies investigated that this BDNF-gene Val66Met polymorphism may be related to SCZ pathogenesis (Hong, Yu, Lin, & Tsai, 2003) and TD (Park et al., 2009). These investigations suggest that the Val66Met polymorphism may play a role in the development and manifestation of SCZ and TD, providing further evidence for the complex interplay between BDNF, genetics, and specific psychiatric and movement disorders.

Taken together, systematically investigating the role of BDNF levels and relevant gene polymorphisms in patients with TD is vital.

Methods

PubMed was used to search research articles related to tardive dyskinesia (TD) and BDNF polymorphisms. Twenty-seven articles were retrieved. Among them, review, editorial, meta-analysis, and comment articles were excluded. Studies made after 2004 were included in this review. The review was limited to June 2022. Only articles in English language were included. After the exclusion of articles, only 12 studies were included (Table 1).

The keywords of tardive dyskinesia and "BDNF" were used to investigate relevant studies.

Furthermore, other studies retrieved using Google Scholar were also mentioned to explain the impacts of BDNF according to the inflammatory and oxidative stress (OS) theory of TD. To ensure the review's quality, we employed the use of SANRA.

Table 1. Studies retrieved using PubMed

Author of Study	Title of Study	Goal of Study	Result of Study
(Zai et al., 2009).	Genetic study of BDNF, DRD3, and their interaction in tardive dyskinesia.	Investigating the Association of 15 DRD3 Polymorphisms and Four BDNF Polymorphisms with TD in patients with SCZ.	BDNF markers showed no association, rs3732782, rs905568, and rs7620754 in the 5' region of DRD3 was associated with TD.
(Park et al., 2009)	Genetic association of DNF val66met and GSK-3beta-50T/C GSK-3beta-50T/C polymorphisms with tardive dyskinesia.	The combination of GSK-3beta C/C genotype and the BDNF Val allele is linked to individuals who have SCZ but do not exhibit TD.	The GSK-3β C/C genotype with the BDNF Val allele is associated with patients having SCZ without TD.
(J. Q. Wu et al., 2015)	Altered BDNF is correlated to cognition impairment in schizophrenia patients with tardive dyskinesia.	Examined the BDNF levels, the cognitive function, and the association of BDNF with cognitive function by TD.	Patients with TD exhibited lower levels of BDNF compared to those without TD.
(Q. Wu et al., 2022)	Correlation of blood biochemical markers with tardive dyskinesia in schizophrenic patients.	Investigated the link between blood markers and TD in patients with SCZ.	No difference in the blood level of BDNF between the TD and the SCZ groups.
(X. Y. Zhang et al., 2012)	Brain-derived neurotrophic factor levels and its Val66Met gene polymorphism predict tardive dyskinesia treatment response to Ginkgo Biloba.	Tested if treatment with Ginkgo Biloba would increase serum BDNF levels and reduce TD, among SCZ patients with BDNF Val66Met genotype.	Patients with the potential for greater BDNF release (Val/Val at 66) may have a greater reduction in TD from Ginkgo Biloba.
(Yang et al., 2011)	Decreased serum brain-derived neurotrophic factor levels in schizophrenic patients with tardive dyskinesia.	A study compared BDNF levels in SCZ patients with and without TD and normal controls.	Patients with TD exhibited significantly reduced levels of BDNF in comparison to individuals without TD.

(Continued)

Author of Study	Title of Study	Goal of Study	Result of Study
(Kang et al., 2008)	No association between the brain-derived neurotrophic factor gene Val66Met polymorphism and tardive dyskinesia in schizophrenic patients.	BDNF polymorphism and susceptibility to TD.	BDNF polymorphism does not have a role in the susceptibility to TD.
(Liou et al., 2004)	Association analysis of the dopamine D3 receptor gene ser9gly and brain-derived neurotrophic factor gene val66met polymorphisms with antipsychotic-induced persistent tardive dyskinesia and clinical expression in Chinese schizophrenic patients.	A different study found that the BDNF val66met genetic polymorphism may exert its effect on the phenotypic variability after TD occurrence.	BDNF val66met polymorphism may exert its effect on the phenotypic variability after TD occurrence.
(Lee et al., 2007)	Clinical effectiveness of the Kampo medicine kamishoyosan for adjunctive treatment of tardive dyskinesia in patients with schizophrenia: a 16-week open trial.	No differences in BDNF levels were detected between the TD group and the non-TD group.	No differences in serum BDNF levels were detected between the TD group and the non-TD group.
(Y. Wang et al., 2010)	The Val66Met polymorphism of the brain-derived neurotrophic factor gene is not associated with risk for schizophrenia and tardive dyskinesia in Han Chinese population.	The Val66Met polymorphism of the BDNF gene is not associated with risk for SCZ and TD.	The Val66Met polymorphism of the BDNF gene is not associated with risk for TD.
(Tan, Zhou, & Zhang, 2005)	Decreased plasma brain-derived neurotrophic factor levels in schizophrenic patients with tardive dyskinesia: association with dyskinetic movements	Another study suggests that decreased BDNF may play a role in the pathophysiology of TD.	The reduction in BDNF levels is believed to play a pivotal role in the development and manifestation of TD.
(Bakker et al., 2012)	Candidate gene-based association study of antipsychotic-induced movement disorders in long-stay psychiatric patients: a prospective study.	The study investigated the potential relationship between variation in genes and different subtypes of movement disorders.	Various SNPs reached significance: TD and orofacial dyskinesia with rs6265 and rs988748.

In order to provide a comprehensive analysis, the selected studies included in the review encompassed a diverse range of research designs, such as case-control studies, cohort studies, and cross-sectional studies. These studies explored various aspects related to BDNF polymorphisms and their association with TD.

The included studies examined different populations, including individuals with various psychiatric disorders who were receiving antipsychotic medication, as well as specific subgroups such as patients with SCZ or bipolar disorder.

Furthermore, the selected studies employed different methodologies to investigate the relationship between BDNF polymorphisms and TD, including genotyping techniques like polymerase chain reaction (PCR).

Results

Among the key findings of the study, it was revealed that seven of the studies focused on the genetics of brain-derived neurotrophic factor (BDNF). The remaining studies specifically examined the levels of BDNF in the serum. Notably, the majority of the genetic studies yielded no significant association between the Val66Met polymorphism of the BDNF gene and the risk of developing TD. These findings shed light on the complex relationship between BDNF genetics and TD susceptibility, suggesting the need for further investigation and exploration of additional genetic markers that may contribute to TD risk.

Discussion

Our study found that Tardive Dyskinesia (TD) may be associated with serum brain-derived neurotrophic factor (BDNF) levels and several BDNF polymorphisms. Furthermore, BDNF may lead to TD development through inflammatory and oxidative stress (OS) related mechanisms.

According to the manuscript's preliminary results, seven studies were related to BDNF and genetics. The rest of the studies investigated serum BDNF levels. Most relevant genetic studies found no association between the Val66Met polymorphism of the BDNF gene and risk for TD (Kang et al., 2008). However, they generally confirmed the association between TD occurrence and BDNF levels (J. Q. Wu et al., 2015; Yang et al., 2011), except for a few studies (Lee, Shin, Lee, Park, & Kim, 2007).

Best of our knowledge, there is no previous literature review that investigates the association between the BDNF gene and TD. For instance, the reduction of BDNF can potentially contribute to the development of neurodegenerative conditions affecting motor centers (He, Zhang, Yung, Zhu, & Wang, 2013), while BDNF is an essential factor related to abnormal movements (Mittal et al., 2012) such as TD. Furthermore, genetic studies investigated TD occurrence and the response to antipsychotics (Xu et al., 2010). Moreover, a combination of genetic variants in the BDNF gene might have a role in response to antipsychotics (Xu et al., 2010). Elsewhere, genetic studies investigated the association between BDNF markers and TD risk. One study found that carriers of DRD2 risk haplotypes and the BDNF variants rs6265 and DRD3 haplotypes, were at increased risk of dyskinesia (Kusters et al., 2018). Moreover, BDNF markers showed no association, a haplotype containing rs3732782, rs905568, and rs7620754 in the 5' region of DRD3 was associated with TD diagnosis (Zai et al., 2009). Although a comprehensive literature review investigating the specific link between the BDNF gene and TD is lacking, these aforementioned studies provide valuable insights into the potential involvement of BDNF and genetic factors in TD development. Further research is warranted to elucidate the precise mechanisms and establish a clearer understanding of the association between BDNF gene variations and TD in order to improve diagnosis, treatment, and prevention strategies for TD in clinical settings.

As many confounding factors exist, previous studies are inconsistent concerning the relationship between TD and serum BDNF levels. For example, one study suggests that sex differences in BDNF levels may contribute to sex-related differences in patients with SCZ (Weickert et al., 2019). Additionally, smoking is one of the potential confounding factors as patients with SCZ smoke very frequently (Uludag & Zhao, 2023) while smoking may affect BDNF levels (Jamal, Van der Does, Elzinga, Molendijk, & Penninx, 2014). Furthermore, it is vital to understand approaches related to oxidative stress (OS) and inflammation concerning TD. These factors play a pivotal role in the progression and manifestation of TD symptoms, necessitating a comprehensive examination of their influence.

Brain-derived neurotrophic factor (BDNF) and oxidative stress

A study highlights the interplay between OS parameters and BDNF in the pathophysiology of executive function impairment in patients with SCZ (Wei et al., 2020). In addition, the imbalance between pro-oxidants and antioxidants is partially responsible for cognitive impairment in SCZ (D. M. Wang et al., 2022). In this context, a previous study by our group investigated the association between Superoxide Dismutase levels and relevant genetic polymorphisms concerning cognitive change (Uludag, Wang, & Zhang, 2022).

Another study found that alleviation of OS by BDNF in OGD/RL-exposed slices related to reducing cPLA2 activity, (González-Rodríguez et al., 2019). In addition, OS can interact with the BDNF system to modulate

cognitive function (A. Wu, Ying, & Gomez-Pinilla, 2004), while cognitive impairments may accompany patients with TD (Uludag et al., 2021).

In summary, these studies provide valuable insights into the complex relationship between oxidative stress, BDNF, and cognitive impairments in different scenarios such as SCZ and TD. However, further research is required to fully comprehend the underlying mechanisms involved and explore potential therapeutic approaches that focus on mitigating oxidative stress and targeting BDNF pathways. These endeavors aim to improve cognitive dysfunction in individuals affected by these conditions.

Brain-derived neurotrophic factor (BDNF) and Inflammation

Levels of BDNF and inflammatory markers are altered in psychiatric diagnoses (Carniel & da Rocha, 2021) such as SCZ. A study explains the BDNF-TrkB signaling in the pathology of inflammation-induced depression (J.-c. Zhang, Yao, & Hashimoto, 2016). In another study, evidence implicate BDNF in regulating inflammation (Papathanassoglou, Miltiadous, & Karanikola, 2015). Furthermore, BDNF signal pathway may help to protect against inflammation-related neuronal loss (S.-Y. Wu et al., 2011), which may explain the role of BDNF in cognitive function.

Brain-derived neurotrophic factor and cognitive factors

Research has established an association between BDNF and cognitive impairment in individuals with bipolar disorder (Mora et al., 2019) and SCZ patients (Di Carlo, Punzi, & Ursini, 2019). Another study discussed the role of the BDNF, which may partially mediate neuroplasticity (Calabrese et al., 2014). It has potent effects on synapses (Lu, Nagappan, & Lu, 2014), while reduced levels of BDNF are associated with neuronal loss (Bathina & Das, 2015). A study using mini-mental-state examination and Isaacs' Set Test of Verbal Fluency tests to measure cognitive skills found that BDNF levels positively correlated with cognition in athletes (Belviranli, Okudan, Kabak, Erdo?an, & Karanfilci, 2016). Another study suggests that val66met polymorphism in BDNF can be linked to reduced task performance (Sanchez et al., 2011). In a different study, plasma BDNF is a biomarker of impaired memory in aging women (Komulainen et al., 2008). On the other hand, a meta-analysis study did not find an association between Val66Met BDNF polymorphism and the cognition-related parameters (Mandelman & Grigorenko, 2012). Taken together, the findings suggest that changes in cognitive function and TD may be interrelated, and that BDNF-related mechanisms could potentially serve as a useful biomarker for these conditions.

Limitations

Studies only in English language were included. Heterogeneous variables such as age, sex, age of onset, duration of illness, genetics, epigenetics, antipsychotic dose, drug use, comorbid disorders, and antipsychotic type are the main confounding factors of studies in the literature. We have used only PubMed to search research articles.

Suggestions for further studies

Further studies should investigate other genes (e.g., Superoxide Dismutase, angiotensin-converting enzyme) that might be associated with TD occurrence. Further studies should analyze specific cognitive factors related to changes in serum BDNF levels. These investigations would contribute to a more comprehensive understanding of the underlying mechanisms and potential biomarkers associated with TD, ultimately leading to improved clinical interventions and management strategies.

Future studies can delve deeper into investigating the combined impact of genetic factors on TD susceptibility. Understanding the interplay between different genetic variants and their cumulative effects can provide valuable insights into the complex nature of TD development. For instance, the interplay between BDNF and SOD may have a stronger correlation with the occurrence of TD.

Conclusion

Our study concluded that TD occurrence might be related to specific BDNF polymorphisms and serum BDNF levels. However, the most relevant genetic studies found no association between the Val66Met polymorphism of the BDNF gene and the risk for TD. Further research is necessary to fully understand the complex genetic and molecular mechanisms underlying TD and its relationship with BDNF.

Acknowledgement

Thanks to the authors who made this literature review possible.

Conflicts of interest

There is no conflict of interest to state.

Author statement

K.U. wrote the manuscript.

Funding

K.U. has been granted postdoctoral funding by Shanghai Jiao Tong University.

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