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Association of NMDA receptor (GRIN2B) Gene Polymorphism and Depression in Parkinson's Disease: A Mini Review.

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ABSTRACT

Depressive disturbances are common in patients with Parkinson's disease (PD) and influence many other clinical aspects of the disease. In addition to causing inherent emotional distress, depressive disorders negatively impact quality of life, motor and cognitive deficits, functional disability, and other psychiatric comorbidities in patients with PD. Knowledge of the pathophysiology of PD depression remains limited.Aim of the review is to find the possible association of N-methyl -d-aspartate glutamate (NMDA) receptor gene polymorphism and depression in PD patients. Association of NMDA receptor gene polymorphism and depression may open a new window in therapeutics of PD patients with depression by targeting these particular genes, which in turn may improve their quality of life .

Keywords: NMDA receptor, Parkinson's disease, depression

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BACKGROUND

Introduction To Parkinson's disease

Parkinson's disease (PD) is a disorder diagnosed based on evidence for a movement disorder characterized by tremor, rigidity, and bradykinesia. Clinical management requires care and attention beyond its motor features. Over the course of PD , majority of the patients experience neuropsychiatric disturbances, including depression, anxiety, sleep disturbances, psychosis, and behavioral and cognitive changes [1]. For patients and families, these neuropsychiatric disturbances are often more problematic and distressing than the motor aspects of PD [2]. It is generally accepted that clinically significant depressive disturbances occur in 40–50 % of patients with PD [3]. As such, depression is one of the most frequently reported neuropsychiatric disturbances in PD. In addition to causing inherent emotional distress, depressive disorders negatively impact quality of life, motor and cognitive deficits, functional disability, and other psychiatric comorbidities in patients with PD. Knowledge of the pathophysiology of PD depression remains limited.

NMDA, PD And Depression

N-methyl -d-aspartate glutamate **(**NMDA) receptors are a class of excitatory amino acid receptors, which have several important functions in basal ganglia. These receptors have a crucial role in dopamine-glutamine interactions. NMDA receptor gene polymorphism has been found to have a role in depression. As the concentration of NMDAR is maximum in basal ganglia, it may have a causative role in depression of PD. Hence it is justifiable to study this gene in depressed patients of PD.

In patients with Parkinson's disease (PD), depression is prevalent and disabling, impacting both health outcomes and quality of life. There is a critical need for alternative pharmacological methods to treat depression in PD.

Functional and neuroimaging studies investigating PD depression implicate dopamine and noradrenergic neuronal dysfunction and predominant cortical cholinergic denervation in the setting of dementia. Limited evidence clarifies the role of serotonergic dysfunction. There may be familial susceptibility involved in it. There are several genes which have been studied but none of the genetic mutations associated with PD or depression independently were found to be associated depression of PD.

Mundo et al and Weickert et al reported that the neuronal N-methyl-D-aspartate receptor (NMDAR) play a key role in the pathophysiology of schizophrenia, bipolar disorder, and depression [4,5].The possible role of NMDAR signaling in the pathophysiology of emotional disorders has been supported by various evidences. Coyle and Javitt et al opined that bipolar disorder and major depression disorder are associated with altered levels of central excitation neurotransmitters [6, 7]. Kristiansen et al suggested that expression, distribution, and function of NMDAR are decreased in patients with mood disorders [8]. A study by Ibrahim et al suggested that NMDAR modulator exerts a positive therapeutic effect on patients [9]. Study by Berman et al and Methew et al concluded that antidepressants and mood stabilizers can improve NMDAR function[10,11].Therefore, genes involved in the NMDAR path way might be important genetic regulators of human physiology that consequently influence mood diseases.

The NMDA receptors are composed of a combination of a common NMDA1 subunit and one of four NMDA2 subunits (2A, 2B, 2C and 2D), combined in an undetermined ratio to make up the receptor complex. Charton et al suggested demonstrated that among all the subunits, the NMDA receptor 2B subunit (GRIN2B) is present at the highest concentrations in the basal ganglia which is of particular significance for PD [12]. Such a selective distribution suggests this subunit may be implicated for emotional components and depression associated with PD. It seems reasonable to suggest a possible involvement for the GRIN2B gene in the pathogenesis of depression in PD. Nishiguchi et al. has identified a polymorphism at the 2664th nucleotide of the coding sequence of GRIN2B gene [13].

The NMDAR-NR2B (GRIN2B) gene, consists of 13 exons, located at 12p12, with a size of 419 kb. It is expressed in the hippocampus, basal ganglia and cerebral cortex [14] .It was implicated in the risk or susceptibility of schizophrenia, obsessive-compulsive disorder, Alzheimer's disease and alcohol consumption patterns [15-20]. A polymorphism C2664T of GRIN2B at exon 13, rs1806201, results in a silent mutation where

the codon of ACC is replaced by ACT, both encoding the same amino acid Threonine. Although silent mutations do not alter protein function, they are not always evolutionarily neutral. It may be due to codon usage biases that there is selection for the use of particular codons due to different translational stability. Silent mutations may also affect splicing or transcriptional control. Therefore, the aim of the study is to test the statistical significance of the association for depression of PD and the GRIN2B genetic polymorphism.

In a Chinese study, Tsai et al performed, GRIN2B genotyping and studied a transversion (2664th nucleotide of the coding sequence) affecting codon 888 (tyrosine) of GRIN2B contributing susceptibility to PD [21]. The distribution of the GRIN2B genotypes and alleles did not differ significantly between PD patients and controls. Their negative findings suggest that it is unlikely that the GRIN2B C2664T polymorphism plays a substantial role in conferring susceptibility to PD in the Chinese population. However, the study didn't test with other genetic variations of NMDA subunits, relating either to PD or to the depression in PD. There are several gene polymorphisms that have a role in depression in PD, but association of NMDAR gene polymorphism with depression in PD is least explored, to the best of our knowledge.

Zhang et al studied whether potentially functional polymorphisms of GRIN2B confer risk for major depressive disorder. Their initial findings strengthen the hypothesis that GRIN2B not only confers susceptibility to treatment resistant depression, but also plays a genetic predictor for treatment resistant depression in major depressive disorder patients[22].

However there is a scarcity of literature in this area to the best of our knowledge. Aim of our this mini review was to find the association of NMDA receptor gene (GRIN2B) polymorphism with depression in Parkinson's disease.

NMDA receptors are abundant in basal ganglia and have crucial functions in basal ganglia

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Basal ganglia is affected in PD

↓

Depression is common in PD

↓

NMDA receptors involved in pathogenesis of depression

↓

So NMDA receptor gene polymorphism may be responsible for depression in PD

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Scarcity of literature in this area to the best of our knowledge

Future Research Endeavour

It should be to find the association of NMDA receptor gene (GRIN2B) polymorphism with depression in Parkinson's disease.

Expected outcome

- Such study may throw light on the role of NMDA receptor gene in the causation of depression in PD patients and also on their clinical response to therapy.
- As NMDA receptors are abundant in basal ganglia,they may be important targets for the development of new drugs to treat PD
- NMDA receptor polymorphism if found associated with depression,may be used as a drug target to prevent depression in PD.
- Early prediction and prevention of depression may improve quality of life in PD.

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