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Review

NMDA Receptors Subunits, Medical Conditions Involved in, and Their Roles as Drug Targets

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ABSTRACT

In the 1960s, Jeff Watkins and colleagues discovered N-methyl-d-aspartate (NMDA) receptors, and since then, it has been a pharmacodynamic target for many neurological and psychiatric drugs. NMDA is a glutamate receptor and ion channel protein located in nerve cells. There are many subunits for the NMDA receptor. They are all working together in a harmonic pattern to regulate the calcium permeability and the voltage-dependent sensitivity to magnesium influenced by the binding of glutamate as a neurotransmitter. In this paper, a light will be shed on glutamate ionotropic receptor NMDA subunits. There are several names for the GRIN gene, such as GluN. It is proven that GRIN has a significant influence on memory and learning abilities. Interestingly, part of how GRIN executes its function by interacting with other receptors. For example, GRIN counteracts the role of the cAMP response element-binding protein (CREB) receptor, while its function modulated by dopamine D1 receptors. Therefore, Hypo-functioning and mutation of this gene play a pivotal role in developing neurodevelopmental disorders wither it was with or without hyperkinetic movements and with and without seizures, besides several psychotic disorders such as schizophrenia. Hence, NMDA receptors subunits have been a target for therapeutic development for the last years. With the advancements in the genetic and genomic science, investigators are trying to find the alternative splicing of GRIN, understanding location and the distribution of NMDA subunits with deeper lucidity than it is currently. However, that is faced by some challenges. Modifying the NMDA receptor subunits to treat one condition can lead to potential harm effect in another condition because, sometimes, NMDA works complicatedly inversely with many other receptors and neurotransmitters, which will have an impact on the investigators to find the appropriate way to cause no harm.

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1. INTRODUCTION

NMDA is an ion-channel receptor usually present in excitatory synapses, which is a part of the nerve structure that transmits the action potential from the presynaptic structure to the postsynaptic structure. NMDA receptor is

activated by glycine and glutamate, and that leads to influxes of calcium. This ionic activity regulates the function of many parts of the central and peripheral neuron system [1]. NMDA receptor is structured from three subunits: GRIN1, GRIN2, and GRIN3. These subunits are architected in the form of three domains: extracellular, transmembrane, and intracellular [2]. NMDA receptor mal

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functionality has an implication in the development of several diseases. For example, overexcitation of the NMDA receptor can lead to stroke; therefore, it has been found that NMDA receptor suppression can be neuroprotective. However, that was not entirely practical because of the excess side effects of the NMDA antagonist drugs [3]. Conversely, downgrading NMDA receptor functionality by the overuse of the antagonists leads to overactivation of the nervous system structures that are regulated by dopamine, and subsequently causes behavioral symptoms to resemble the ones that come with schizophrenia [3]. Other researches findings have linked the NMDA receptors with pain disorders, Alzheimer's disease, Huntington Disease, Parkinson's disease, Depression, White matter injury, Autism spectrum disorders, cognitive impairments, and Anti-NMDAR encephalitis [4].

As mentioned, the NMDA receptor is composed of three subunits. A certain gene encodes each of these units. Each gene is located in a specific site on the DNA. GRIN1 located in chromosome 9q34.3 [5]. GRIN2A, 2B, 2C and 2D are placed respectfully at 16p13.2, 12p13.1, 17q25.1, 19q13.33 [5]. GRIN3A and 3B are pinpointed at 9q31.1 and 19p13.3 [5]. These subunits have been therapeutics targets for many diseases. For instance, GRIN2B antagonist is used in cerebral ischemic disorders, traumatic brain injury, Alzheimer's disease, Parkinson's disease, Depression, and pain disease management. GRIN2C antagonist is deployed to treat white matter injury [4].

2. MATERIAL AND METHODS

A literature search and reviews conducted utilizing literature screening through different research websites, including Ohio State University library website, pubmed.com, and the online mendelian inheritance in man website, genenames.org, and google.com. After reviewing each literature, extracting data, analyzing it, then arrange the most critical information to the paper numerically concerning NMDA receptor subunits. After that, I matched the information of each disorder with subunits involved in its pathogenesis. The following step was to search the available drugs or the prototypes with its antagonism to the NMDA receptors in general, and their action on the subunits in particular.

3. RESULTS

3.1. NMDA RECEPTOR STRUCTURE, LOCATION, GENE INVOLVED AND FUNCTION

NMDA receptors consist of an extracellular domain that looks like a clamshell and has the amino-terminal domain. This domain contains the subunits assembly. The other domain is called the agonist-binding domain. This domain

binds with the neurotransmitter glutamate. The third domain is the transmembrane domain. In some diseases, this domain is affected by a mutation in a gene that is responsible for the receptor protein trafficking.

Each NMDA receptor subunit is encoded by a specific gene and located at a particular chromosome. Subunit GRIN1 locates on chromosome 9q34.3; it is HGNC gene ID is 4584. Subunit GRIN2A sets at chromosome 16p13.2, and its HGNC gene ID is 4585. Subunit GRIN2B is defined at chromosome 12q13.1, and its HGNC gene ID is 4586. Subunit GRIN2C is defined at chromosome 17q25.1, and its HGNC gene ID is 4587. Subunit GRIN2D is found at chromosome 19q13.33, and its HGNC gene ID is 4588. Subunit GRIN3A is marked at chromosome 9q31.1, and its HGNC gene ID 16767. Subunit GRIN3B is located on chromosome 19p13.3, and its HGNC gene ID is 16768 [5]. Although, not all these subunits are present in the same receptor, yet its existence determines the function of NMDA receptors. Intriguingly, the subunit composition is not static as well, but it is dynamic based on the response to neuronal activity [5].

The NMDA receptor subunits spread differently though out the nervous system, furthermore, their development is distinct form subunit to subunit. GRIN1 locates almost throughout the nervous system and among all the CNS development stages. Conversely, GRIN2B is numerous in the early developmental stages but it starts to slump later on, whilst, GRIN2A is scarce in the early stages then it increases in numbers in the adulthood. GRIN2C is absent at the early stage, however, it becomes predominant in the cerebellum. GRIN2D is abundant in the thalamus, hippocampus, and brainstem [6].

Regarding the physiology of the NMDA receptors, the NMDA receptors are Ion- channel receptors. They are activated by glutamate binding and co-agonist (glycine or D-serine) as a secondary neurotransmitter. When it is activated, it becomes highly permeable to Ca. However, it is activation cessed by unbinding of glutamate and by voltage-dependent block by Mg. This harmonic functionality is determined by the subunit composition [7].

3.2. MEDICAL CONDITION AND ITS PATHOGENESIS

NMDA receptor dysfunction is involved in the development of many diseases. Each disease is caused by mutation or alteration of the gene that encoded one of the subunits that formed the NMDA receptor. For example, alteration in the gene that encodes GRIN2B causes excessive activation of NMDA receptors and subsequently leads to rising the extracellular glutamate level, which in turn that heads to consuming the ATP reservoir of the neuron cell and its damage. Also, the genetic alteration can cause overexpression of GRIN2A and 2B, and then have an implication on the nerves that conducting the pain sensation [4].

Alzheimer's disease is another commonly known medical condition that is connected form some reasons with the alteration in the genetic structure that encodes GRIN2B. It

has been found that the energizing of GRIN2B mediates amyloid-B formation, which brings about synaptic plasticity, synaptic loss, enhanced production of tau-induced excitotoxicity (Tau is a protein formed from the malfunction of GRIN subunits that formed NMDA receptor) [4].

Herman F. and Lynn R mentioned in their book "NMDA Receptors and Huntington's Disease," an Excitotoxic Hypothesis in Huntington Disease. They said that among several studies contained transgenic HD mouse models showed that there was a decrease in the striatal GRIN2A and 2B gene expression while enhancing in GRIN1. However, they concluded that the lack of the apparent evidence connection between the NMDA receptor subunits and HD, that might be attributed to the failure of the mouse models to produce a similar connection that might be found in the human [6].

Parkinson's disease is a progressive neurodegenerative disorder. Up till now, there is a belief based on research findings and that Parkinson's happens because of the loss of the dopaminergic neurons of the Substantia Nigra Pars, which locates in the basal ganglia in the midbrain. A research study has linked the malfunction of the NMDA receptor with the pathogenesis of Parkinson. It demonstrated that through the effect of the excessive glutamate substance at the afferents. This exorbitant glutamate availability takes place after an imbalance between the GRIN1A and GRIN2B from one side and the GRIN2A. This imbalance appears in the form of abundance in GRIN1A, GRIN2B, and reduction in GRIN2A. This appears in the form of dyskinesia symptoms that comes along Parkinson's disease [8].

NMDA receptor dysfunction has also implications on psychiatric and cognitive disorders. Published in 2014, a study showed that although the implication of the different NMDA receptor subunits in depression and schizophrenia are still poorly grasped, the authors studied a preliminary drug called MK-80. They investigated the effect of this drug as a non-selective antagonist. They found that both GRIN2A and 2B subunits have an influence in inducing stereotypies, which might be suggestive of potential psychotomimetic effects in humans; meanwhile, inhibition one of them can lead to adverse events manifested as depression. This is emphasized that the imbalance between these subunits leads to appear these symptoms [9].

Furthermore, NMDA receptors have been found to have an implication in many neurodevelopmental disorders; interestingly, Autism spectrum disorders (ASDs) are associated with multiple genetic dysfunctions; however, a study revealed that a de novo mutation in GRIN2B has a high probability of being linked with ASDs. The author found that this mutation caused extirpating the NMDA-dependent Ca influx because it decreases the cellular trafficking of the receptor's protein [10].

3.3. AVAILABLE DRUGS: HOW THEY WORK, THEIR EFFECTIVENESS, CHANGE IN THE PROGNOSIS, AND THE COST

Drug discovery and development is going in fast pace along with revealing how NMDA receptors subunits integrated into the pathogenesis of many diseases. In preclinical studies, blocking GRIN2B has shown some positive results in protecting against stroke, whereas it as found that NMDR receptor blockade within an hour of ischemia. Nonetheless, these hops started to diminish when NMDA receptor agonists failed to prove that in the clinical trial [11]. Similarly, a study showed that NMDA receptor antagonist such as Amantadine has a modest effect in reducing neuropathic pain, especially after surgeries, however, the same study affirms that intravenous ketamine still has a superb effect on the postoperative pain than Amantadine [12].

One of the most known NMDA receptor antagonist drugs in curing Alzheimer's disease is memantine. However, a study conducted by a group of investigators to search and compare various types of drugs obtainable for Alzheimer's patients showed that, as clinical effectiveness, memantine is not preferable than other drugs certainly for moderate and severe cases, likewise the cost-effectiveness of memantine dose not stand well among others [13]. The cost of memantine is around 40 to 95 dollars. Furthermore, Huntington's disease can be cured by targeting the NMDA receptor in general, or GRIN2B subunits in specific. Kathryn Gorgas revealed in her study that targeting GRIN2B subunit and knocking down mRNA that responsible for this subunit has shown a result in reducing the neuropathic pain that related to Huntington's diseases [14].

In 2014, Dr. Young Dang and his team conducted a study to review the effect of ketamine on depression disorder. Ketamine is a non-competitive NMDA receptor antagonist. It has a rapid action of AMPA and mTOR signaling pathways following blocking the NMDA receptor. Its effect on mTOR signaling pathways leads to an effect on the mRNA of GRIN2 and 3. Furthermore, it has been found that ketamine antagonism has also demonstrated some effect on the level of GRIN1 and synapsin 1, which is a presynaptic protein [15]. Ketamine costs around 160 to 210 dollars. In contrast to depression, Schizophrenia disorder does not have approved medication that works on antagonizing the NMDA receptor. However, there is a recent study that illustrates the potential role of NMDA antagonism in treating schizophrenia. The investigator explains his hypothesis through modulating neurotransmitters sites, such as glycine, D-Cycloserine at a high dose, D-Serine, at the NMDA receptor. Furthermore, the author cited that the antagonism can occur by using an inhibitor to these neurotransmitters, such as sodium benzoate, which is an inhibitor to D-serine, sarcosine, which inhibits glycine transporter-1[16].

4. DISCUSSION

It is evident that the NMDA receptors' mechanism of action is very complicated. There is no solo function for each subunit, and it is clear that NMDA receptors work together simultaneously; nonetheless, any of the subunits can take the prime role based on the neuron condition. This role is not permanently assigned for that subunit, which means that another subunit can take over the central role at any level.

Furthermore, there are other influential factors that impact the NMDA receptor subunits' function. Some of these factors have been discovered. For instance, neurotransmitters like glutamate and glycine affect the activity of these subunits, some proteins like serine affect the activity of these neurotransmitters themselves, as well as the availability of the ion (like Ca) dose some impact as well.

Although this dynamicity carries tremendous potential therapeutic targets, it still is a source of complexity. It presents various challenges to the researchers, not only because these subunits affect each other, but also the NMDA receptors and its operating system if we can call it like that, is a part of a bigger and deeper system which might have implications either positively or negatively on the therapeutics that target NMDA receptors.

5. CONCLUSIONS

As cited, the NMDA receptor contains three subunits. They involve in neurodevelopment and cognitive disorders. Although NMDA receptor subunits GRIN1 and 3 are potential therapeutic targets, apparently, GRIN 2 B has shown that it has the most substantial pharmacological effect. Moreover, targeting NMDA receptors is still underdeveloped. It needs further investigations to reveal the mechanism of the function of these receptors, their subunits, the neurotransmitters that are reacting with them, and the proteins that affect these neurotransmitters. Definitely, the results of these investigations will have an impact on directing this therapeutics and aid the cost-effective analysis of them.

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