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NMDA and sigma receptors in psychiatry

Sucharita Mandal, Deepanjali Medhi[1]

Senior Resident, Department of Psychiatry, Burdwan Medical College Hospital, Burdwan, West Bengal, India

[1]Associate Professor, Department of Psychiatry, Gauhati Medical College Hospital, Guwahati, Assam, India

Abstract

Hypoactive N-methyl-d-aspartate (NMDA) receptors lead to mesolimbic dopamine (DA) hyperactivity associated with positive symptoms of psychosis. If NMDA receptors are hypoactive then mesocortical DA pathways also become hypoactive explaining cognitive, negative and affective symptoms of schizophrenia. NMDA receptor hypofunction in glutamatergic corticostriatal and corticoaccumbens projections reduces the excitatory drive on gamma aminobutyric acid (GABA) neurons that create the thalamic filter which can lead to excess sensory information escaping to the cortex. Drugs antagonising NMDA receptor have antidepressant effect. D-cycloserine facilitates glutamate release thus GABA inhibition is strengthened which is the predominant fear extinction pathway. Acamprosate acts as anticraving by binding with NMDA receptor. NMDA receptors play a role in the development of kindled state. Memantine is NMDA antagonist, blocks NMDA receptor and prevents neurodegenaration. Initially reported as opioid receptor but when it could not be blocked by naltrexone and naloxone, later termed as sigma receptor. Functions of sigma receptors include modulation of calcium release, modulation of cardiac myocyte contractility and inhibition of voltage gated potassium channel. Association between sigma receptor 1 gene (SIGMAR1) with susceptibility to schizophrenia has been found. Interaction of sigma 1 receptor with NMDA receptor modulates spatial memory in rats. Most conventional neuroleptics showed a significant affinity to sigma receptors.

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Correspondence: hereismon@gmail.com

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Introduction

Glutamate is the principal neuroexcitatory transmitter that acts like a "master switch." It is present in synaptic and nonsynaptic regions of neurons. Two general classes of receptors are ionotropic i.e. glutamate gated ion channel permeable to cations and metabotropic i.e. G protein coupled receptors (mGLUR). N-methyl-d-aspartate (NMDA) receptors are ligand gated ion channels having three subunits – NR1, NR2 and NR3. NR1 is the core subunit; NR2 and NR3 are modulatory components. Presently seven sites are recognised. NMDA receptors have three characteristic features: at resting potentials, it remains blocked by magnesium; during activation, calcium enters the cell; neurotransmission occurs slowly and lasts for a prolonged period. Sigma receptor is a transmembrane protein situated in endoplasmic reticulum.

Role in psychiatry

Glutamate pathways

The cortical brainstem glutamate projection is a descending pathway that projects from cortical pyramidal neurons in the prefrontal cortex (PFC) to brainstem neurotransmitter centres (raphe, locus coeruleus, ventral tegmental area [VTA], substantia nigra) and regulates neurotransmitter release. Another descending glutamatergic pathway projects from the PFC to the striatum (corticostriatal glutamate pathway) and to the nucleus accumbens (corticoaccumbens glutamate pathway) and constitutes the "corticostriatal" portion of cortico-striatal-thalamic loops. Thalamocortical glutamate pathways are pathways that ascend from the thalamus and innervate pyramidal neurons in the cortex. Corticothalamic glutamate pathways descend from the PFC to the thalamus. Intracortical pyramidal neurons can communicate with each other via the neurotransmitter glutamate. These pathways are known as corticocortical glutamatergic pathways.[1]

NMDA receptor hypofunction hypothesis of schizophrenia

The cortical brainstem glutamate projection communicates with the mesolimbic dopamine (DA) pathway via a gamma aminobutyric acid (GABA) interneuron in VTA. Excitatory glutamate stimulates NMDA receptors on the interneuron causing GABA release and GABA in turn inhibits release of DA from the mesolimbic DA pathway; thus the descending glutamatergic pathway normally acts as a brake on the mesolimbic DA pathway. If NMDA receptors in the cortical brainstem glutamate projection are hypoactive then the downstream effect of tonic inhibition of the mesolimbic DA pathway will not occur leading to

hyperactivity in this pathway. This is the theoretical biological basis for the mesolimbic DA hyperactivity thought to be associated with the positive symptoms of psychosis.

The cortical brainstem glutamate projection communicates directly with the mesocortical DA pathway in the VTA normally causing tonic excitation. If NMDA receptors in cortical brainstem glutamate projections are hypoactive, tonic excitation here is lost and mesocortical DA pathways become hypoactive, potentially explaining the cognitive, negative and affective symptoms of schizophrenia. [1]

Sensory gating

Pyramidal glutamatergic neurons descend from the PFC to the striatum where they terminate on GABA neurons that project to the thalamus. The release of GABA in the thalamus creates a sensory filter that prevents too much sensory information traveling through the thalamus from reaching the cortex including the feedback thalamocortical glutamate neurons that project back to the original cortical pyramidal neuron.

DAergic input to the nucleus accumbens via the mesolimbic DA pathway has an inhibitory effect on GABA neurons. Thus DA input reduces the stimulatory glutamatergic input to these neurons from the PFC and thereby reduces the effectiveness of the thalamic sensory filter since less GABA is released by GABA neurons projecting from the nucleus accumbens to the thalamus. This means that more sensory input can escape from the thalamus to the cortex.

A thalamic filter for sensory input to the cortex is set up by glutamate neurons projecting to nucleus accumbens, stimulating GABA release in the thalamus. When effective, this inhibitory GABA filters out most sensory input arriving in the thalamus so that only selected types of sensory input are relayed to the cortex.

Too much DA activity in the nucleus accumbens reduces GABA output to the thalamus thus greatly reducing the effectiveness of the thalamic filter. When this occurs, more sensory input gets through the thalamic filter and increases the amount of cortical activation by ascending thalamocortical glutamate neurons. This definitely causes increased cortical activation and could potentially even cause overload in the PFC and positive symptoms of schizophrenia.

NMDA receptor hypofunction in glutamatergic corticostriatal and corticoaccumbens projections reduces the excitatory drive on GABA neurons that create the thalamic filter which can lead to excess sensory information escaping to the cortex. When this NMDA receptor hypofunction is coupled with hyperactivity of mesolimbic DA neurons, this can cause the thalamic filter to fail to the point where so much sensory information reaches the cortex that positive symptoms of psychosis occur.[1]

Corticocortical glutamate pathway

Cortical pyramidal neurons utilise glutamate and NMDA receptors to communicate back and forth. When NMDA receptors are hypofunctional, there is dysregulation of the loops resulting in symptoms of schizophrenia.

Depression

Drugs antagonising NMDA receptor have antidepressant effect. Selective serotonin reuptake inhibitor (SSRI)/serotonin norepinephrne reuptake inhibitor (SNRI)/tricyclic antidepressant (TCA) increase cyclic adenosine monophosphate (cAMP) causing increased protein kinase activity resulting in increases of cAMP response element binding (CREB) protein and brain derived neurotrophic factor (BDNF). NMDA antagonist decreases NMDA receptor function. Both these actions decrease NMDA receptor subunit expression which has antidepressant action.

Posttraumatic stress disorder

When an individual encounters a stressful or fearful experience, the sensory input is relayed to the amygdala where it is integrated with input from the ventromedial prefrontal cortex (VMPFC) and hippocampus so that a fear response can be either generated or suppressed. The amygdala may “remember” stimuli associated with that experience by increasing the efficiency of glutamate neurotransmission so that on future exposure to stimuli, a fear response is more efficiently triggered. If this is not countered by input from the VMPFC to suppress the fear response, fear conditioning proceeds. Fear conditioning is not readily reversed but it can be inhibited through new learning. This new learning is termed fear extinction and is the progressive reduction of the response to a feared stimulus that is repeatedly presented without adverse consequences. Thus the VMPFC and hippocampus learn a new context for the feared stimulus and send input to the amygdala to suppress the fear response. The “memory” of the conditioned fear is still present, however.[1]

Cognitive behaviour therapy (CBT) using exposure methods trigger fear extinction learning. D-cycloserine facilitates glutamate release thus GABA inhibition is strengthened which is the predominant fear extinction pathway.

Substance abuse

Ethanol, by increasing GABAergic and decreasing glutamatergic activity, upregulates NMDA receptors and calcium channels; thus increases susceptibility of withdrawal seizure. Acamprosate acts as anticraving by

binding with NMDA receptor; inhibits glutamate and enhances GABA function – "artificial alcohol."

Epilepsy

Animal models show that focal application of glutamatergic agonist at NMDA receptor produces seizure. Gradual induction of a hyperexcitable neuronal state can occur by repetitive subconvulsive stimulation of the hippocampus, amygdala and other brain areas known as kindling. Studies have shown that NMDA receptors play a role in the development of kindled state. NMDA receptor antagonists can prevent this phenomenon.

Long term potentiation (LTP): Persistent increase in synaptic strength following high frequent stimulation of a chemical synapse occurs in cerebral cortex, cerebellum and amygdala.

Long term depression (LTD): It is a process which selectively weakens specific synapses to make constructive use of synaptic strengthening caused by LTP. Decrease in postsynaptic receptors or decrease in neurotransmitter results in persistent weak synaptic stimulation causing reduction in the efficacy of synapses. It facilitates the coding of new information.

Spectrum of excitation

A major hypothesis for the pathophysiology of neurologic and psychiatric disorders that run a neurodegenerative course is that glutamate may cause neuronal damage or death by a process of normal excitatory neurotransmission run amok called excitotoxicity. The spectrum of excitation by glutamate ranges from normal neurotransmission which is necessary for such neuronal activities as LTP, memory formation and synaptogenesis; to an excessive amount of excitatory neurotransmission that may occur while a patient is experiencing pathologic symptoms such as psychosis, mania or panic; to excitotoxicity that results in damage to dendrites but not neuronal death; to slow progressive excitotoxicity resulting in neuronal degeneration of many neurons over an extended period of time as occurs in Alzheimer's disease or possibly schizophrenia; to sudden and catastrophic excitotoxicity causing neurodegeneration leading to loss of a large number of neurons at once as in stroke.[1]

NMDA-glutamate hypothesis of cognitive deficiency

In Alzheimer's disease, toxic plaques from amyloid precursors are produced. Plaques use to downregulate glutamate transporter. There is steady leak of glutamate which initially interferes with memory and learning problems; later on damages neurons. Memantine is NMDA antagonist, blocks NMDA receptor and prevents neurodegenaration.

Future directions

Glycine is an allosteric modulator. Serine is agonist at glycine site of NMDA receptor. Sarcosine is glycine transporter inhibitor. Cycloserine is agonist at glycine site. Results in treating positive, negative and cognitive symptoms of schizophrenia have been modest and inconsistent; needs more research.[2,3] Memantine can be used to check the progression of Alzheimer's disease. Studies are coming up showing the antidepressant efficacy of ketamine.

Sigma receptors

In 1976, it was reported that sigma receptor is a type of opioid receptor. N-allylnormetazocine interacts with sigma receptor which mediates psychomimetic actions. It was designated as a type of opioid receptor. Later on, it was seen that this opioid receptor could not be blocked by naltrexone and naloxone. Then the concept was changed and later on termed as 'sigma' receptor.

It is a transmembrane protein situated in endoplasmic reticulum. There are three types e.g. sigma 1, sigma 2 and recently developed sigma 3 receptor. Well studied receptor is sigma 1.

Functions: Modulation of calcium release, modulation of cardiac myocyte contractility and inhibition of voltage gated potassium channel.

Agonists and antagonists: Agonists are amphetamine, cocaine, citalopram, fluvoxamine, phencyclidine, morphine, lamotrigine and afobazole-selective 1 receptor; rimcazole, BD-1047-selective at sigma and BMY-14802 are antagonists.

Physiological effects of sigma receptors: Hypertonia, tachycardia, tachypnoea, papillary dilatation, convulsion and antidepressant.

Implications in psychiatry

Schizophrenia

Preclinical studies: Sigma receptor antagonists like BMY-14802 and NE-100 are found to be effective in reducing abnormal behaviour in animal model. BMY-14802 prevents methamphetamine induced psychosis.[4] NE-100 blocks phencyclidine (PCP) induced cognitive dysfunction.[5]

Binding studies: Sigma receptors are expressed densely in mesolimbic and mesocortical areas of cortex and hippocampus where structural abnormalities were reported in schizophrenia brains.[6]

Postmortem studies: Reduced sigma receptor density in the brain of schizophrenia patients is found compared to that of controls.[7]

Clinical trials: Selective antagonists like SL 82.0715 and panamesine showed successful therapeutic effects in schizophrenia.[8,9] Most conventional neuroleptics showed a significant affinity to sigma receptors. Haloperidol showed a most potent affinity to sigma receptors.

Genetic studies: Association between sigma receptor 1 gene (SIGMAR1) with susceptibility to schizophrenia has been found. Gene for sigma receptor 2 has not been cloned yet, the possibility remains that genetic variance of sigma 2 or unknown subtypes could precipitate the development of schizophrenia.

Patients with schizophrenia show nonpsychotic and nonspecific prodromal symptoms for several years preceding the onset of frank psychosis. Studies have shown that atypical antipsychotics in people with prodromal symptoms may reduce the risk of subsequent transition to schizophrenia. In a recent study,[10] authors proposed a hypothesis that selective serotonin reuptake inhibitors (SSRIs) with sigma 1 receptor (e.g. fluvoxamine) may reduce the risk of subsequent transition to schizophrenia.

There is rapid modulation of the serotonergic system in dorsal raphe nucleus and the glutaminergic transmission in the hippocampus. Onset of action is fast. Fluvoxamine is most potent. Sigma receptor has antiamnestic properties. It has role in neuroprotection and neuronal plasticity. Interaction of sigma 1 receptor with NMDA receptor modulates spatial memory in rats.[11] There is reduction in sigma 1 receptor density in PFC in Alzheimer's disease. Lu 28-179, a sigma 2 receptor agonist, has anxiolytic property in rodents.

Conclusion

Sigma-1 receptors may be associated not only with the psychomimetic actions of PCP but also with regulation of the NMDA receptor. However the exact physiological functions of sigma receptors and how they may modulate NMDA receptor functioning remain poorly characterised; thus sigma-1 receptors remain in many ways the "sigma enigma."[1]

Further Reading

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