International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Review Article

The Role of N-methyl-D-aspartate Receptor on Late-Life Depression

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A R T I C L E   I N F O

S U M M A R Y

As the life expectancy of general population becomes longer, the prevalence of geriatric mental disorders increases rapidly. Late-life depression (LLD) is the secondly common mental disorders in the elders. LLD has negative impacts on patient's life and is also related to multiple physical diseases, mental problems, and dementia. Treating LLD is important, but there is a substantial proportion of patients with depression who do not show satisfactory therapeutic response or recovery with current antidepressant treatment. Thus, developing new medication is important. Recent studies showed that abnormal activation of N-methyl-D-aspartate receptor (NMDAR) would result in several neurological and psychiatric disorders, such as major depressive disorder, schizophrenia, Alzheimer's disease, and Parkinson diseases. Medication associated with NMDAR is considered to have great potential in treating depression. NMDAR could be activated by glutamate and in turn initiating signaling cascades which are involved in both neural connectivity and neural plasticity. Also, several animal studies suggest that aging alters the expression of NMDAR. The binding functions and intensities of NMDARs decline in aging animal models. Thus, medication involving with NMDARs might take important role in treating depression, especially in the elders. Current medication related with NMDARs includes nonselective NMDAR antagonists (such as ketamine), selective NMDAR antagonists, NMDA agonist and partial agonists, and glutamate release inhibitors. However, more clinical studies should be conducted to investigate the antidepressant effects of these medications.

1. Introduction

LLD is usually defined when a patient develops a major depressive episode after 50 or 60 years of age.[1] In Taiwan, the prevalence of LLD is estimated to be 13–26%.[2] Compared to depression in young adults that is more often related to psychological causes, the pathogenesis of LLD is more related to biological pathway. Also, LLD is often related to multiple physical diseases, cognitive impairment, and dementia.

LLD has negative impacts on patient's life since it would result in decreased quality of life and global function impairment.[1] LLD is also associated with dementia. Depressive patients who also had mild cognitive impairment have at least two folds of risk in developing dementia.[3]

Treating LLD is important for patients, their family and the society.[4] About one-third of patients with LLD are treatment-resistant to current treatment.[5] Patients with LLD are often more vulnerable to the side effects of antidepressants. Even when prescribed with selective serotonin reuptake inhibitors (SSRIs) or other newer generation antidepressants, patients with LLD are often more

sensitive to their side effects.[6] Thus, it is necessary to develop treatment strategies with better efficacy and safety.

2. The relationship between NMDA receptor, glutamatergic system and depression

Glutamate can activate metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). iGluRs are composed of three major families which are N-methyl-D-aspartate receptor (NMDAR) (GluN1, GluN2A-D, and GluN3A-B), kainate receptor (GluK1-5), and α-amino-3-hydroxy-5-methyl-4-isoxazo-lepropionic acid receptor (AMPAR) (GluA1-4).[7] NMDAR is a heteromeric structure which composed of at least one GluN1 and one GluN2 or GluN3, and other binding sites for glycine or D-serine, magnesium, and other polyamines.[8] NMDARs are activated upon concurrent binding of GluN1 to glycine or D-serine and GluN2 to L-glutamate. In resting state, NMDARs contain a magnesium plug which prevents ions from flowing through their channels freely.[9] When NMDARs receive sufficient stimulus, adjacent AMPARs would expel the magnesium plug via cell membrane depolarization, allowing NMDARs to be bound with glycine and glutamate.[8] Upon binding to glycine and glutamate, NMDARs undergo conformational changes which permit subsequent nonselective influx of sodium and calcium ions.[10] Calcium ions, as secondary messengers, initiate sev-

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eral signaling cascades subsequently. These signaling cascades are involved in both neural connectivity and neural plasticity.[11] Thus, abnormal activation of NMDARs would result in several neurological and psychiatric disorders, such as MDD,[12] schizophrenia,[13–15] Alzheimer's diseases,[16–18] and Parkinson diseases.[19] Glutamatergic system plays an important role in the pathophysiology of LLD and dementia.

Increased glutamate level was observed in the prefrontal cortex of postmortem brain samples from patients with MDD.[20] Also, abnormal levels of glutamate were found in blood and cerebrospinal fluid (CSF) of patients with MDD.[21] These suggest that glutamatergic system plays an important role in the pathophysiology of MDD. Significant alterations of NMDARs expression in postmortem samples from patients with mood disorders have also been reported.[22,23] Current literature shows that glutamate, NMDARs, and associated calcium-dependent pathways.[24] Some preclinical studies suggest that NMDARs antagonists have antidepressant effects[25] and might possibly reverse the synaptic disconnection in the impaired cortico-limbic circuit of patients with MDD.[26]

3. The role of NMDA receptor in late life depression

3.1. Inflammation, cytokines, neurotoxicity, and neurodegeneration in major depressive disorder and Alzheimer's disease

Inflammation related to psychological stress is not characterized by classical signs such as redness, warmth, heat, and swelling. Current literature describes this kind of inflammatory response to psychological stress with the term "neuroinflammation."[27] Innate immune cells in brain, such as astrocytes, microglia, and oligodendroglia, are activated to release cytokines when there is an inflammatory stimulus. Whereas an acute infection is usually a protection, chronic infection is usually maladaptive.[28] Microglia is activated in inflammatory state and would initiate a cascade of cytokines and inflammatory responses.[29] This process may occur in aging brains, MDD, or schizophrenia and may be a partial explanation for why the neurodegenerative change in chronic depression may be a prelude to dementia.[30] Astrocytes could regulate synaptic neurotransmitter function, remove the neurotoxins formed by tryptophan-kynurenine pathway, and control the local glutamate concentration.[31] When glutamate concentration is in excess, it would prolong the activation of NMDARs. Astrocytes could convert glutamate into glutamine and transport glutamine into neurons for it to re-synthesize into glutamate. This mechanism occurs in both MDD and schizophrenia and has been shown to be neuroproective.[32]

Current literature suggests that chronic depression may increase the subsequent risk of developing Alzheimer's diseases.[33] In patients with Alzheimer's diseases with previous diagnosis of MDD, the frequency of neurofibrillary tangles and amyloid plaques is greater.[34] Also, neurodegenerative changes is frequently reported in patients with MDD.[35] Since neurodegenerative changes and cognitive deficits are both frequent outcome of MDD, it is important to consider how chronic inflammatory response contributes to such changes.

In conclusion, chronic inflammation is associated with neurodegeneration and change of brain structure, which characterizes depression, and precipitates Alzheimer's diseases.[30]

3.2. Animal studies of the relationship between aging and NMDA receptor

Several animal studies suggest that aging alters the expression of NMDAR. The binding functions and intensities of NMDARs decline in aging animal models.[36] Several studies suggest that the binding of glutamate binding site of NMDARs declines with aging.[37] However, not much studies research for the relationship between aging and NMDARs on human models yet.

4. Current medication related with NMDARs

4.1. Nonselective NMDAR antagonist (ketamine)

Ketamine is a nonselective NMDAR antagonist. Clinical studies suggest that ketamine has antidepressant effects.[38] A single dose of ketamine intravenous infusion is able to relieve depressive symptoms in patients with MDD, with a response rate of 50−70%.[39] Ketamine could also treat patients who do not respond to electroconvulsive therapy and decrease patient's suicide ideation.[39] Although studies suggest that ketamine is effective in treating depression, the long-term effect of ketamine in patient with MDD is still uncertain.

It is hypothesized that ketamine increases the release of presynaptic glutamate, which would activate extracellular signal-regulated kinase (ERK) and Akt signaling.[40] Activation of ERK and Akt signaling would stimulate mammalian target of rapamycin (mTOR) signaling, which phosphorylates p70 S6 kinase (p70S6K) and inhibits 4E binding proteins (4E-BP). The phosphorylation of p70S6K and inhibition of 4E-BP increased downstream synaptogenesis.[40] Ketamine could not only activate mTOR pathway but also stimulate Akt and ERK pathway in the prefrontal cortex of mice.[41] Ketamine could also increase the activity of brain-derived neurotrophic factor (BDNF) and in turn modulate mTOR pathway.[42] Ketamine stimulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and in turn increases the activity of BDNF.[43] In addition, ketamine suppresses the activity of NMDARs and in turn inhibits eukaryotic elongation factor-2 kinase (eEF2K), which increases the translation of BDNF.[44] As described above, increased activity of BDNF would increase synaptogenesis and result in antidepressant effect. Ketamine could also inhibit glycogen synthase kinase 3 (GSK3), a protein which have mood stabilizing function when inhibited, and result in antidepressant effect.[45] Decreased GABA levels are found in the brain of patients with MDD.[46] Ketamine could increase GABA level in animal model and result in antidepressant effect.[47] However, different studies revealed inconsistent results on the association between the antidepressant effect of ketamine and the neurotransmitter alternations. Besides, participants in aforementioned studies mainly received ketamine via intravenous route instead of oral route, and intravenous route may limit ketamine's clinical use.[48] When it comes to long-term use of ketamine in treating depression, there is a concern for its possible psychotomimetic effects, risk of abuse, and cognitive function impairment.[49] Thus, it is important to develop other NMDAR antagonists with better efficacy and safety. However, published data relevant to the relationship between LLD and ketamine is lacking. Whether patients with LLD would benefit similarly to younger patients with MDD is still unclear. It is also not clear whether older patients would develop more side effects, particular in cognitive impairment, than younger patients. More studies should be conducted to answer questions mentioned above.

4.2. Selective NMDAR antagonist

Scientists also target at specific subtypes of NMDARs in order to develop a drug with more specificity and safety. NMDAR subtype 2B (NR2B) is associated with NMDA neurotoxicity and only exists in the

forebrain, so it might be a suitable candidate. Several animal studies reported that NR2B knockout mice develop antidepressant effects which is similar of those treated with ketamine.[50] CP-101, 606 (traxoprodil) is a selective NR2B antagonist. J. D. Graef et al. found that the synaptic activity was increased in the brain of rat after single dose of traxoprodil.[51] However, the development of traxoprodil was discontinued due to the side effect of QTc prolongation.[52] MK-0657 is another NR2B antagonist, and it could be given by oral route. L. Ibrahim et al. reported that MK-0657 monotherapy could improve depressive symptoms in patient with treatment-resistant MDD.[53] Ro25-6891 is another NR2B antagonist which could activate mTOR signaling. Ro25-6891 could prevent long-term depression which is induced by acute stress in rat model.[54] However, most of the studies relevant to selective NMDAR antagonists used animal models or tested on treatment-resistant depression instead of being specific on LLD.[55] It is necessary to conduct more studies for testing the antidepressant effects and safety of MK-0657 and Ro25-6891 on older patients. Memantine, a selective noncompetitive NMDAR antagonist, is used to treat moderate to severe Alzheimer's diseases clinically. EJ Lenze et al. suggested that memantine could reduce depressive and amotivated behavior.[56]

4.3. NMDAR partial agonists

When given at low doses, NMDA partial agonists have agonist effect. When given at high dose, they become antagonists. D-Cycloserine is a NMDA partial agonist which could facilitate synaptic potentials mediated by NMDAR in rat brain slices.[57] GLYX-13 is another NMDA partial agonist whose antidepressant effect could last for 7 days in rat model. GLYX-13 is currently under phase II trial.[58] Similar to drugs mentioned in the previous sections, studies related to NMDAR partial agonists mostly focused on younger patients or treatment resistant depression.[59] Future studies focusing on the antidepressant effect of NMDAR partial agonists on older patients are warranted.

4.4. NMDAR agonists

Sarcosine is an NMDAR agonist which decreases depressive symptoms in both rat and human models. Sarcosine could not only activate mTOR signaling pathway but also decrease depressive-like behavior in rat model.[60]

Sodium benzoate is a D-amino acid oxidase (DAAO) inhibitor, and is able to inhibit reactive oxygen species. DAAO is a flavoenzyme of peroxisomes that could degrade D-serine and D-alanine and raise the level of synaptic D-amino acids.[61] D-amino acid acts as the neurotransmitter for the co-agonist site of NMDAR.[62] Recent research reported that the activation of NMDAR could be enhanced by the inhibition of DAAO.[14] Sodium benzoate could improve the cognition and global function in patients with mild cognitive impairment and early-phase Alzheimer's disease. Previous study reported a better improvement on Alzheimer's Disease Assessment Scale-cognitive subscale in patients with mild cognitive impairment or mild Alzheimer's disease.[16] When sodium benzoate was prescribed to patients with chronic schizophrenia, improvement on both the clinical and cognitive symptoms were reported.[15]

Since LLD is closely associated with dementia, sodium benzoate might also be beneficial for patients with LLD. Furthermore, sodium benzoate also showed anti-oxidative effect,[14] which might play an important role in preventing LLD. Further studies should be conducted to investigate the efficacy and safety of sodium benzoate in patients with LLD.

D-serine, an amino acid, also works as an NMDAR agonist. Previous study reported that D-serine could produce antidepressant effect similar to that of ketamine. D-serine might be a safer target of novel antidepressants comparing to ketamine.[63]

4.5. Glutamate release inhibitors

Riluzole is a glutamate release inhibitor which could not only inhibit glutamate release but also increase glutamate reuptake. Riluzole could also increase AMPAR trafficking and block the activity of NMDAR.[52] Riluzole could decrease depressive-like behavior in animal models.[64] Studies specific on the antidepressant effect of riluzole in LLD is lacking. Further studies with larger sample sizes are necessary to investigate in the antidepressant effect of riluzole.

5. Conclusion

As population aging becomes an important issue throughout the world, LLD deserves more of our concern. LLD would result in decreased quality of life, global function impairment, increased risk of multiple psychiatric and physical disorders, and suicide risk. Furthermore, LLD may increase the subsequent risk of developing dementia, such as Alzheimer's diseases. Thus, treating LLD is important, since that patients, their family, and society would all gain much benefit from it. Unfortunately, about one-third of patients with LLD are treatment-resistant to current antidepressant treatment. Thus, developing treatment strategies with better efficacy and safety is of great importance. Abnormal activation of NMDARs is found to be associated with MDD as well as aging, so that NMDARs may be important therapeutic targets in LLD. Several kinds of drugs with mechanism related to NMDARs are under investigation currently, such as nonselective NMDAR antagonists, selective NMDAR antagonists, NMDAR agonists and partial agonists, and glutamate release inhibitors. Further clinical studies with larger sample sizes are warranted for determining the efficacy and safety of NMDAR-related medications.

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