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Beyond The Glutamate N-methyl D-aspartate Receptor in Major Depressive Disorder: The mTOR Signaling Pathway

Beata Karolewicz[1], Mesut Cetin[2], Feyza Aricioglu[3]

ÖZET:

Majör depresif bozuklukta glutamat N-metil-D-aspartat reseptörlerinin ötesi: mTOR sinyal yolağı

Serotonin ve/veya noradrenalin üzerinden etki yapan geleneksel antidepresanlar depresif hastaların yaklasık yarısında etkisiz kalmakta ve etkin olmaları durumunda da etkilerinin başlaması geç olmaktadır. Glutamaterjik sistemin majör depresif bozukluğun nöropatolojisinde ve tedavisinde önemli rol oynadığına dair kanıtlar giderek artmaktadır. Yakın zamanda ketaminin tek doz uygulanmasıyla hızlı ve uzun süren antidepresan etki sağladığı gösterilmiştir. Ketamin, glutamat ile taşınan sinirsel iletiyi alan N-metil-D-aspartat reseptörlerini (NMDARs) bloke eden, insan ve hayvanda anestezik olarak kullanılan bir ilaçtır. Çok yakın zamanda Yale Üniversitesi'nde yapılan ve Science dergisinin Ağustos sayısında yayınlanan bir çalışmada ketaminin etki mekanizması tam olarak aydınlatılmıştır. Sıçanlarda yapılan çalışmalarda temel bilimciler ketaminin sinirlerde sinyal iletimini sağlayan bir çok yolaktan biri olan "rapamisinin memelilerdeki hedefi" diye adlandırılan ["mammalian target of rapamycin" (mTOR)] yolağı hızla aktive ettiğini göstermişlerdir. Bu yeni yaklaşım depresyon tedavisinde devrim olarak yorumlanabilir ve antidepresan ilaç geliştirilmesinde yeni terapötik hedeflere yol açabilir.

Anahtar sözcükler: Glutamat, N-metil-D-aspartat reseptörü, ketamin, mTOR

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ABSTRACT:

Beyond the glutamate N-methyl D-aspartate receptor in major depressive disorder: the mTOR signaling pathway

Conventional antidepressants acting through serotonin and/or noradrenaline fail to help about half of depressed patients and even when effective, they have a delayed onset of therapeutic response. Accumulating evidence suggests that the glutamatergic system plays an important role in the neuropathology and treatment of major depressive disorder (MDD). Recently it has been shown that ketamine has a rapid and long lasting antidepressant activity after a single dose. Ketamine has been used as a human and animal anesthetic. It acts on the human brain by blocking the N-methyl-D-aspartate receptors (NMDARs), which receive nerve signals carried by glutamate; however, in a very recent Yale University study, published in the August issue of Science, the exact mechanism of ketamine's action has been identified. In studies with rats, basic researchers demonstrated that ketamine rapidly activates the so called "mammalian target of rapamycin" (mTOR) pathway, one of many such pathways that perform signal transduction in neurons. This new approach may be a revolutionary break-through in the treatment of depression and it might lead to novel therapeutic targets for antidepressant drug development.

Key words: Glutamate, N-methyl-D-aspartate receptor, ketamine, mTOR, mammalian target of rapamycin

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[1]Ph.D., Assistant Professor of Pharmacology The University of Mississippi Medical Center, Division of Neurobiology and Behavior Research, Department of Psychiatry and Human Behavior, Jackson, MS-USA.
[2]M.D., Professor of Psychiatry, Editor -in-Chief, Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Pychopharmacology, GATA Haydarpasa Training Hospital, Department of Psychiatry, Istanbul-Turkey
[3] Ph.D., Professor of Pharmacology, Marmara University, School of Pharmacy Department of Pharmacology and Psychopharmacology Research Unit, Istanbul-Turkey

Yazışma Adresi / Address reprint requests to: Feyza Aricioglu, Ph.D., Professor of Pharmacology,Marmara University, School of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul-Turkey

Telefon / Phone: +90-216-418-9573

Faks / Fax: +90-216-345-2952

Elektronik posta adresi / E-mail address: feyza.aricioglu@gmail.com

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Major depressive disorder (MDD) is a common, chronic, recurrent mental illness that affects about 17% of the population worldwide and is one of the leading causes of total disability and economic burden. In the past fifty years, depression research has focused on the contribution of the monoamines (noradrenaline, serotonin, dopamine) to the pathophysiology and treatment of depression. Various groups of antidepressants have been developed successfully, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants. These medications are effective and beneficial. Their major limitation is the delayed onset of therapeutic response, resulting in non- compliance, and dramatically increasing the risk for suicidal behavior. Moreover, only about one-third of depressed patients respond to the first medication prescribed, increasing disability rates and the corresponding economic burden (increased health care costs, unemployment, etc.) (1).

Rapidly accumulating evidence suggests that the glutamatergic system plays an important role in the neuropathology and treatment of MDD (2,3). Glutamate (L-glutamic acid) is the major excitatory neurotransmitter

in the central nervous system and exerts its action through ionotropic (iGluRs) and metabotropic receptors (mGluRs). Ionotropic glutamate receptors are highly permeable for Na+ and Ca+2 and are principal mediators of fast excitatory neurotransmission in the central nervous system. These receptors include three subfamilies: alpha-amino-3-hydroxy-5-methylisxazole-4-propionic acid (AMPA), kainate, and N-methyl-D-aspartate receptors (NMDARs). To date, eight metabotropic glutamate receptors (mGluR1-8) have been described in the mammalian brain and are classified into three groups with respect to their sequence homology, neuronal signaling, and pharmacological properties. NMDARs have received the most attention with respect to the biology of depression and its treatment (4,5). Drugs that modulate NMDAR function have demonstrated antidepressant-like properties in animal screening procedures (4,5). Interestingly, NMDARs are endowed with multiple extracellular regulatory sites that recognize ions or small molecule ligands, some of which are likely to regulate receptor function in vivo. These allosteric sites, which differ from agonist-binding and channel-permeation sites, provide the means to modulate NMDAR activity, either positively or negatively (Figure 1). Although preclinical studies support the glutamatergic system's role in the mechanism of antidepressant action, ultimately it will be studies conducted with NMDAR modulators in patients with MDD that will prove this system's relevance in antidepressant action.

The search for new antidepressant medications took a really interesting turn in 2006, when a team of scientists affiliated with the National Institute of Mental Health published a study looking at the effects of the NMDAR antagonist, ketamine, on 17 severely depressed patients, all of whom had failed to respond to standard treatments (6). Ketamine traditionally has been used as a general anesthetic, but researchers found that, in lower doses, the drug produced fast relief from depression. In this study, a single intravenous dose of ketamine produced a fast (within 110 min) and long lasting (up to one week) antidepressive effect in treatment resistant depressed patients. No other pharmacological intervention, that consistently produces results in such a rapid manner, has been reported so far. The authors note that ketamine has also been tested as a rapidly effective means to treat people with suicidal thoughts, a benefit usually not seen for weeks with traditional antidepressant treatments; however, clinical use of ketamine has been limited because it has to be delivered intravenously under medical supervision and in some cases can cause short-term psychotic symptoms (5-6).

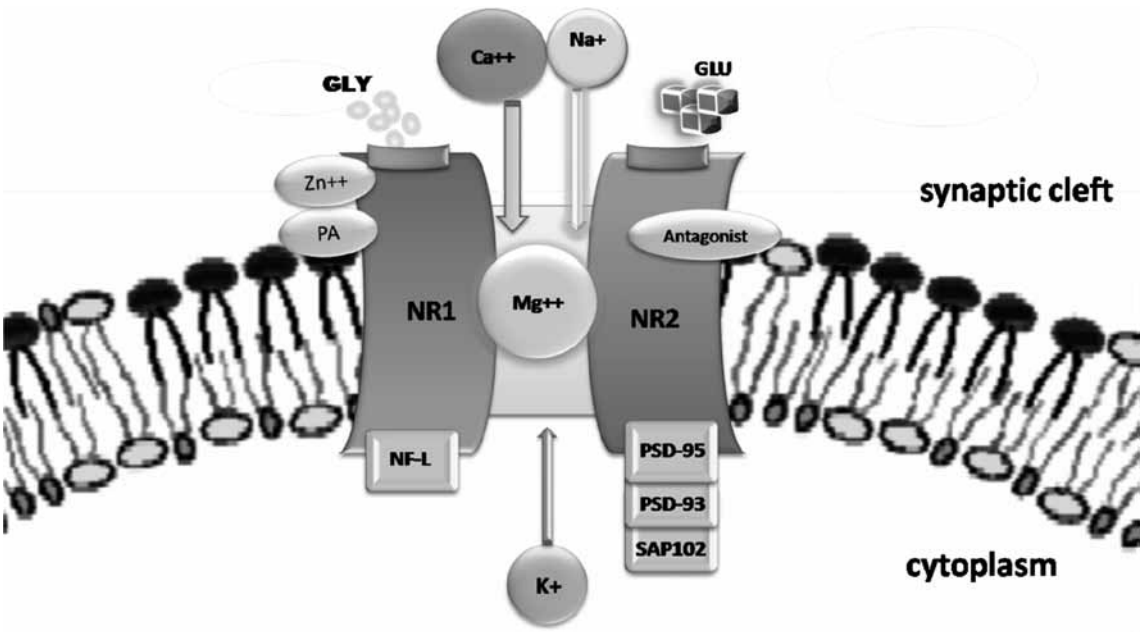

Figure 1: NMDA receptor structure. The NMDA receptor consists of two subunits; NR1 and NR2. NR1 subunits bind the co-agonist glycine (GLY) and NR2 subunits bind the neurotransmitter glutamate (GLU). The postsynaptic density proteins PSD95, PSD93 and, SAP102 contain regions that bind the NR2 and NF-L interacts with NR1 subunits. The ion channel is responsible for calcium permeability, and voltage-dependent magnesium block.

The observation that antidepressant activity of the NMDAR antagonist, ketamine, could be achieved within hours, instead of weeks, is one of the most important neuropharmacological findings in recent years considering that all of the currently available antidepressants exhibit a delayed onset of antidepressant response and are not effective in one-third of depressed patients. The molecular underpinnings of ketamine's antidepressant activity, however, have not been fully investigated. The elucidation of the molecular mechanisms underlying the rapid antidepressant action of ketamine has the potential to revolutionize the care of many millions who suffer from depression. Researchers at Yale University have turned to the mammalian target for the rapamycin signalling pathway (mTOR) for answers (7).

mTOR, an atypical Ser/Thr kinase, is a central controller of cell growth that is structurally and functionally conserved in all species and controls protein synthesis required for new synaptic connections. Protein synthesis is a highly regulated process that can be separated into three general phases: initiation, elongation and termination (8). The majority of known translational regulation occurs at the level of translation initiation (9) and central to the regulation of translation initiation and long-lasting synaptic plasticity is the activity of a ubiquitously expressed kinase, mTOR (8-11). Four major inputs control mTOR activity: nutrients, such as amino acids; growth factors, such as insulin; cellular energy levels, such as the AMP/ATP ratio; and stress, such as hypoxia. mTOR controls cell growth by the positive and negative regulation of several anabolic and catabolic processes, respectively, that collectively determine cell size (12). The involvement of mTOR signaling in dendritic protein synthesis has been recently characterized (13). Several components of this pathway (Figure 2) are present in dendrites and are enriched at postsynaptic sites (11). mTOR function is influenced by the activity of neuronal surface receptors including NMDAR, mGluR5, and neurotrophic tyrosine kinase receptors (TrkB) which are vital for the induction of synaptic plasticity. It is generally accepted that mTOR acts as a node of convergence downstream of the aforementioned receptors and several signaling pathways, including phosphoinositide dependent kinase-1 (PDK1), phosphoinositide-3-kinase (PI3K), and Akt/protein kinase-B (Akt/PKB) (8,9). Previously, a significant decrease in Akt activity has been reported in the prefrontal cortex (PFC) of suicide victims (14) and schizophrenics (15) indicating an association between dysregulation of Akt/mTOR signaling and psychiatric disorders. mTOR controls the efficiency of protein translation within cells via its downstream targets, including 70-kDa ribosomal protein S6 kinase (p70S6K), eukaryotic initiation factor 4E- binding protein (4E-BP), small ribosomal protein 6 (S6), eukaryotic translation initiation factor 4B (eIF-4B), and eukaryotic translation initiation factor 4E (eIF-4E).

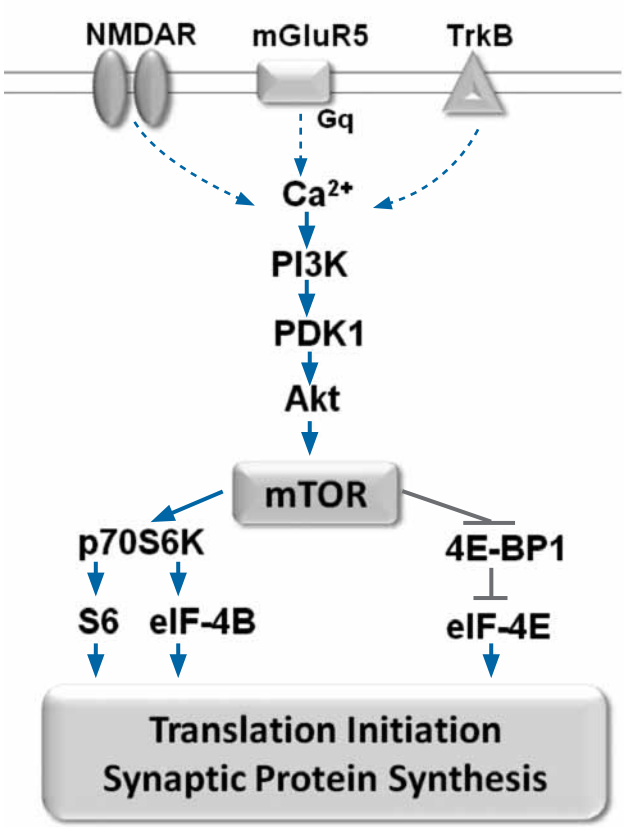

Figure 2: The mTOR signaling pathway. Neuronal receptors (NMDAR, mGluR5, TrkB) increase intracellular [Ca^{2+}], and in turn activate PI3K, PDK1, Akt/PKB, and mTOR. Activated mTOR phosphorylates p70S6K followed by p70S6K-induced phosphorylation of S6 and eIF-4B, which promotes the initiation of protein translation. mTOR also phosphorylates and inactivates 4E-BP, reducing its affinity for eIF-4E and releasing eIF-4E to facilitate translation initiation. Abbreviations: N-methyl-D-aspartate receptor (NMDAR), metabotropic glutamate receptor 5 (mGluR5), tyrosine kinase-B receptor (TrkB), phosphoinositide-3-kinase (PI3K), phosphoinositide-dependent kinase 1 (PDK1), Akt/protein kinase-B (Akt/PKB), mammalian target of rapamycin (mTOR), 70-kDa ribosomal protein S6 kinase (p70S6K), small ribosomal protein 6 (S6), eukaryotic translation initiation factor 4B (eIF-4B), eukaryotic initiation factor 4E- binding protein 1 (4E-BP1), eukaryotic translation initiation factor 4E (eIF-4E). The blue lines denote stimulatory regulation and the gray lines denote inhibitory regulation. Constructed using information from references (8-11).

There is abundant evidence linking mTOR signaling to synaptic change, memory, and neurological disorders (9); however, there are no studies indicating the involvement of mTOR in the pathology of MDD or antidepressive activity. Recently, Dr. Duman's group at Yale University using animal models demonstrated that the antidepressant effects of NMDAR antagonists, including ketamine and Ro-25-6981, are mediated by activation of the mTOR-dependent translation initiation pathway leading to increased synaptic signaling proteins and increased number and function of new spine synapses in the PFC in rats (7). In these studies ketamine and Ro-25-6981 produced rapid antidepressant effects, which were blocked by preinfusion of rapamycin, a potent inhibitor of mTOR signaling (7). Moreover, blockade of mTOR signaling with rapamycin completely blocked ketamine induction of synaptogenesis. The activation of mTOR and related proteins was also observed after treatment with another NMDAR antagonist, MK-801 in rat frontal cortex (16). Interestingly, chronic, but not acute, treatment with the selective serotonin reuptake inhibitor, fluoxetine, was shown to induce the hyperphosphorylation of eIF4E, which is a key regulator of protein translation in the brain, suggesting that regulation of the translational machinery was involved in the mechanism of action of chronic fluoxetine administration (17). The activation of the mTOR pathway, therefore, may be related to the common effect of NMDAR antagonists and antidepressants.

It has been previously demonstrated that stress and depression can cause atrophy of PFC neurons in rodent models and in the postmortem tissue of depressed subjects (18,19), and brain-imaging studies report a decrease in PFC volume in MDD (20). It might be possible that atrophy of cortical neurons, such as smaller soma size, is related to smaller dendritic trees, abnormal morphology of synaptic contacts or deficits in synaptic proteins in MDD. Recent postmortem studies show a significant reduction in the expression of prominent synaptic proteins such as NMDAR subunits (NR2A, NR2B), mGluR5 and their anchoring/scaffolding postsynaptic density protein (PSD-95) in the PFC of depressed subjects (21,22). Alterations in glutamate receptor expression can be a consequence of altered glutamate levels in the brains of depressed subjects. In fact, several lines of evidence indicate abnormal levels of glutamate in various brain regions in depression (23-25). Previous postmortem studies have revealed a reduction in cellular size and density in the PFC in depression (19,26,27). Neuronal pathology detected in the cortical layers of the dorsolateral PFC and anterior cingulate cortex in depression (18,19) is associated with pathology of glutamatergic pyramidal neurons that express NMDARs (28). It has been established that activation of synaptic NMDARs promotes neuronal survival, and enhanced expression of brain derived neurotrophic factor (BDNF) (29). Thus, it is likely that disturbances in the NMDAR system in depression may underlie impairment in cellular plasticity and resilience, and may contribute to the cellular pathology consistently detected in the PFC in depression (30,31). Further studies are required to elucidate whether aberrations in the NMDAR complex are the reason for or consequence of the cellular changes detected in depression.

Our postmortem studies demonstrate region specific abnormalities in NMDAR expression in MDD (21,22). Based on these observations it is tempting to hypothesize that ketamine produces its rapid antidepressant responses by correcting these abnormalities in a "here and now" manner in critical neuronal circuits. Moreover, based on these observations, it is plausible to hypothesize that optimal levels of NMDAR activation are essential for proper PFC function and could be required for antidepressant activity. It is also plausible to suggest that deficits in glutamate receptors and other postsynaptic proteins in the PFC (21,22) are linked to reduced mTOR-dependent mRNA translation rates in the PFC in MDD. Thus, these studies could indicate an association between marked deficits in postsynaptic proteins and dysregulation of the mTOR signaling pathway in MDD. Taken together, all these findings support the hypothesis that MDD might be characterized by a disruption of mTOR-dependent translation regulation; therefore, the deficits in the mTOR-dependent translation initiation pathway may contribute to the molecular and structural pathology seen in the PFC in MDD and a rapid reversal of these abnormalities may underlie the antidepressant activity of NMDAR antagonists.

No significant paradigm shift in the psychopharmacology of MDD has occurred in the past several decades, due to a poor understanding of disease pathogenesis, imprecise delineation of phenotypic boundaries, and the limitations of animal models (32). As the search for treatments in depression continues, it is crucial to change the way we understand and conduct drug development. As with other

areas of medicine, our gradual understanding of the pathophysiology of depression and the mechanism of action of antidepressants indicates that an antidepressant response that occurs within hours is now an achievable goal. The work described above provides direct evidence that rapid response is possible. While serendipity will continue to play a role in drug discovery in psychiatry, advances in animal and human genetics, molecular biology, and brain imaging will likely promote the discovery of biomarkers and identify plausible endophenotypes for subgroups of patients with these illnesses. A major thrust of future drug discovery in MDD will enhance efforts to identify the molecular basis of rapid and sustained antidepressant actions, thereby minimizing disorder morbidity and mortality during the critical weeks between initial symptom expression and drug efficacy.

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