Terapijski rezistentna depresija: nove spoznaje u etiopatogenezi i uloga esketamina u liječenju

/ Treatment-Resistant Depression: New Insights into the Etiopathogenesis and the Role of Esketamine in Treatment

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Terapijski rezistentna depresija (TRD) javlja se u oko 30 % bolesnika koji boluju od velikog depresivnog poremećaja i kod kojih se ne postigne adekvatan terapijski odgovor nakon dvije ili više linija liječenja antidepresivima, uz uvjet da su svaki izabrani antidepresiv uzimali dovoljno dugo i u odgovarajućoj dozi. Brojni su čimbenici povezani s etiopatogenezom TRD, a jedan od značajnih je neurotransmiter glutamat. Glutamat u prekomjernoj koncentraciji u ekstracelularnom prostoru uzrokuje ekscitotoksičnost koja dalje dovodi do otpuštanja proinflamatornih citokina i razvoja neuroupale. To ima za posljedicu oštećenje neurona u područjima mozga koja su odgovorna za emocionalno ponašanje i reguliranje raspoloženja što se klinički može manifestirati kao TRD. Liječenje TRD-a je veliki izazov za kliničare jer unatoč brojnim dosadašnjim farmakološkim i nefarmakološkim metodama liječenja postoji velika potreba za novim učinkovitijim strategijama liječenja. Esketamin je nova terapijska mogućnost u liječenju TRD-a. Za razliku od dosadašnjih antidepresiva djeluje kao antagonist glutamatnih NMDA receptora, primjenjuje se intranazalno i ima akutno djelovanje. Zahvaljujući jedinstvenom mehanizmu djelovanja može biti učinkovit u liječenju TRD-a tako što pojačava signalizaciju neurotrofičnih čimbenika i sinaptogenezu. Esketamin se danas sve više smatra dobrodošlom novom farmakološkom strategijom u liječenju TRD-a, a inhibicija ekscitotoksičnog učinka glutamata stavlja ovaj neurotransmiter sve više u središte znanstvenih istraživanja.

***/** Treatment-resistant depression (TRD) occurs in about 30% of patients with major depressive disorder who have not achieved an adequate therapeutic response after two or more lines of treatment with antidepressants, provided that they have taken each selected antidepressant for a sufficient period of time and at the appropriate dose. Numerous factors are associated with the etiopathogenesis of TRD, one of the significant ones being the neurotransmitter glutamate. In excessive concentrations in the extracellular space, glutamate causes excitotoxicity, further leading to the release of proinflammatory cytokines and the development of neuroinflammation. This results in damage to neurons in brain regions responsible for emotional behavior and mood regulation, which may clinically manifest as TRD. Treating TRD poses a great challenge for clinicians because, despite the numerous current pharmacological and non-pharmacological treatment methods, there is a great need for new and more effective treatment strategies. Esketamine represents a new therapeutic possibility in the treatment of TRD. Unlike traditional antidepressants, it acts as an antagonist to glutamatergic NMDA receptors, it is administered intranasally, and has acute effects. Due to its unique mechanism of action, it can be effective in treating TRD by enhancing the signaling of neurotrophic factors and synaptogenesis. Esketamine is increasingly considered as a welcome new pharmacological strategy in the treatment of TRD, while the inhibition of the excitotoxic effects of glutamate places this neurotransmitter increasingly at the center of scientific research.*

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KLJUČNE RIJEČI / ***KEY WORDS:***
Terapijski rezistentna depresija / *Treatment-Resistant Depression*
Glutamat / *Glutamate*
Neuroupala / *Neuroinflammation*
Esketamin / *Esketamine*

TO LINK TO THIS ARTICLE: https://doi.org/10.24869/spsih.2024.151

UVOD

Značajan udio oboljelih od depresije tijekom liječenja prolazi relativno dugo razdoblje nakon primjene antidepresiva do postizanja vidljivih poboljšanja simptoma. Kada se ne postigne adekvatan terapijski odgovor niti nakon nekoliko linija liječenja (dvije ili više), postavlja se sumnja na terapijski rezistentnu depresiju (TRD) (1).

Povratni (rekurentni) depresivni poremećaj, sukladno MKB-10 klasifikaciji, karakteriziran je povratnim depresivnim epizodama, bez povijesti neovisnih epizoda povišenog raspoloženja ili prekomjerne aktivnosti, što bi ispunjavalo kriterije manije (2) te bez povijesti hipomanih ili mješovitih afektivnih epizoda. Oko 30 % bolesnika koji boluju od povratnog depresivnog poremećaja neće postići adekvatan terapijski odgovor niti nakon dvije ili više linija liječenja antidepresivima, uz uvjet da su svaki izabrani antidepresiv uzimali dovoljno dugo i u odgovarajućoj dozi, te će se kod njih raditi o terapijski rezistentnoj depresiji (TRD) (1). TRD je često udružen s: kroničnim depresivnim raspoloženjem, pogoršanjem cjelokupnog zdravlja i dobrobiti, značajno reduciranim psihosocijalnim funkcioniranjem i povišenim mortalitetom (3). S obzirom na visok udio bolesnika s TRD-om, iznimno ih je važno prepoznati i pružiti odgovarajuću skrb, tj. izabrati odgovarajuću strategiju liječenja.

INTRODUCTION

During their treatment, a significant portion of individuals with depression go through a relatively long period after administration of antidepressants before experiencing visible improvements in their symptoms. When an adequate therapeutic response is not achieved even after several lines of treatment (two or more), suspicion arises of treatment-resistant depression (TRD) (1).

Recurrent depressive disorder, according to the ICD-10 classification, is characterized by recurrent depressive episodes, without a history of independent episodes of elevated mood or excessive activity, which would meet the criteria for mania (2), and without a history of hypomanic or mixed affective episodes. Around 30% of patients with recurrent depressive disorder will not achieve an adequate therapeutic response even after two or more lines of treatment with antidepressants, provided that they have taken each selected antidepressant for a sufficient period of time and at the appropriate dose, thus leading to the diagnosis of treatment-resistant depression (TRD) (1). TRD is often associated with chronic depressive mood, worsening of the overall health and well-being, significantly reduced psychosocial functioning, and increased mortality (3). Given the high proportion of patients with TRD, it

Optimalni ciljevi u liječenju depresije su uspostava pune remisije i potpunog funkcionalnog oporavka bolesnika, dok je realni cilj u svakodnevnoj kliničkoj praksi često postizanje adekvatnog terapijskog odgovora uz zadovoljavajući stupanj funkcionalnog oporavka.

Terapijski odgovor na antidepresive je u brojnim dosadašnjim istraživanjima ocijenjen u četiri stupnja: (4,5):

- nema odgovora: kada je poboljšanje <25 %
- parcijalni odgovor: kada je poboljšanje 25 - 49 %
- odgovor (adekvatan terapijski odgovor): kada je poboljšanje 50 % ili više ali manje od praga za remisiju
- remisija: zadovoljavajući rezultat na ocjenskim ljestvicama za depresiju, npr. rezultat 7 ili manje na MADRS (engl. *Montgomery-Asberg Depression Rating Scale*).

Poznato je da se stopa remisije ne razlikuje značajno nakon prve i druge linije liječenja, ali pada sve više i više nakon treće ili četvrte (na svega 14 do 13 %) (6,7). Treba istaknuti i da se ponekad uzrok terapijske rezistencije nalazi u neodgovarajućoj dozi ili nedovoljnoj duljini primjene antidepresiva, pa je tada riječ o tzv. pseudorezistenciji (8,9). Teško je jednoznačno definirati TRD, a danas je najbolje prihvaćena i najčešće primjenjivana definicija koju najčešće koriste Američka agencija za hranu i lijekove (engl. *US Food and Drug Administration*, FDA) (10) i Europska agencija za lijekove (engl. *European Medicines Agency*, EMA) (11). Prema toj definiciji TRD se može utvrditi ako kod osobe uočimo izostanak adekvatnog terapijskog odgovora na dva ili više antidepresiva, uz uvjet da je svaki izabrani antidepresiv bio propisan u odgovarajućoj dozi i dovoljno dugo, te da je adherencija bila adekvatna (10,11). Osim toga, u zadnje se vrijeme uvodi i pojam ultrarezistentne depresije (URD) kada bolesnik ne odgovori zadovoljavajuće na brojne linije liječe-

is extremely important to recognize them and provide them with appropriate care, that is, to choose an appropriate treatment strategy.

The optimal goals in the treatment of depression include achieving full remission and complete functional recovery of the patient, while the realistic goal in everyday clinical practice is often to achieve an adequate therapeutic response with a satisfactory level of functional recovery. Therapeutic response to antidepressants has been assessed in numerous previous studies through four stages (4, 5):

- Non-response: when improvement is <25%
- Partial response: when improvement is 25 - 49%
- Response (adequate therapeutic response): when improvement is 50% or more, but less than the threshold for remission
- Remission: satisfactory result on depression rating scales, e.g. a score of 7 or less on MADRS (Montgomery-Asberg Depression Rating Scale).

It is known that the remission rate does not differ significantly after the first and second lines of treatment, but it decreases more and more after the third or fourth (to as low as 14 to 13%) (6, 7). It should also be noted that sometimes the cause of treatment resistance lies in an inappropriate dose or insufficient duration of antidepressant use, leading to the so-called pseudo-resistance (8, 9). Defining TRD unequivocally is difficult, and the most widely accepted and commonly applied definition today is the one most often used by the US Food and Drug Administration (FDA) (10) and the European Medicines Agency (EMA) (11). According to this definition, TRD can be diagnosed if a person does not have an adequate therapeutic response to two or more antidepressants, provided that each selected antidepressant was prescribed at an appropriate dose and for a sufficient period of time, and that adherence was adequate (10, 11). Additionally, the concept of ultra-resistant depression (URD) has

nja (uglavnom oko pet različitih linija liječenja) (12).

Cilj ovog narativnog preglednog rada je prikazati nove spoznaje u etiopatogenezi i liječenju terapijski rezistentne depresije, s osvrtom na ulogu esketamina.

NOVOSTI U ETIOPATOGENEZI TERAPIJSKI REZISTENTNE DEPRESIJE

Etiopatogeneza TRD-a još uvijek nije u potpunosti razjašnjena te brojne teorije, od kojih su najznačajnije neuroanatomska, monoaminska, psihoneuroimunološka, psihoneuroendokrinološka i genetička, treba razmotriti u tom kontekstu. Tri najčešća neurotransmiterska sustava istraživana u etiopatogenezi depresije su serotonergički, noradrenergički i dopaminergički, te se upravo putem njih ostvaruje antidepresivni odgovor velikog broja današnjih antidepresiva. U posljednja dva desetljeća glutamatergički sustav, posebice disfunkcija NMDA receptora, zauzima sve značajniju poziciju u etiopatogenezi TRD-a (13). Zbog toga naglašavamo novije aspekte, kao što je uloga glutamata, omjera GABA/glutamat i neuroupale.

Glutamatna hipoteza u zadnje vrijeme je sve više u središtu zanimanja što se tiče razumijevanja, nastanka i liječenja terapijske rezistencije kod oboljelih od depresije. Glutamat je glavni ekscitatorni neurotransmiter u središnjem živčanom sustavu koji je po svom kemijskom sastavu aminokiselina i u tom je svojstvu građevna jedinica za biosintezu proteina (14). Kao neurotransmiter, sintetizira se iz glutamina koji potječe iz glija stanica koje također pomažu u recikliranju i regeneraciji viška glutamata nakon njegovog otpuštanja tijekom neurotransmisije. Nakon otpuštanja iz sinaptičkih vezikula glutamatnog neurona glutamat stupa u interakciju s receptorima i

recently been introduced, and it refers to cases where a patient does not have a satisfactory response to numerous lines of treatment (typically around five different lines of treatment) (12).

The aim of this review article is to present new insights into the etiopathogenesis and treatment of treatment-resistant depression, with a focus on the role of esketamine.

NOVELTIES IN THE ETIOPATHOGENESIS OF TREATMENT-RESISTANT DEPRESSION

The exact etiopathogenesis of TRD is still not fully elucidated, and numerous theories, including the most significant ones such as neuroanatomical, monoamine, psychoneuroimmunological, psychoneuroendocrinological and genetic theories, need to be considered in this context. The three most common neurotransmitter systems investigated in the etiopathogenesis of depression are the serotonergic, noradrenergic and dopaminergic systems, through which the antidepressant response of many current antidepressants is achieved. In the last two decades, the glutamatergic system, particularly the dysfunction of NMDA receptors, has become increasingly important in the etiopathogenesis of TRD (13). Therefore, the focus will be on newer aspects, such as the role of glutamate, the GABA/glutamate ratio and neuroinflammation.

The glutamatergic hypothesis has lately increasingly become the focus of attention in terms of understanding, onset and treatment of treatment resistance in individuals with depression. Glutamate serves as the primary excitatory neurotransmitter in the central nervous system, chemically classified as an amino acid, and in this capacity it represents a building block for protein biosynthesis (14). As a neurotransmitter, it is synthesized from glutamine originating from glial cells which also assist in the recycling

potom se transportira u susjednu gliju preko ekscitatornog aminokiselinskog transportera (engl. *excitatory amino acid transporter*, EAAT). Nakon ponovne pohrane u glija stanice glutamat se konvertira u glutamin posredovanjem enzima glutamin sintetaze. Naime, glutamin se otpušta/transportira iz glija stanica preko specifičnog glijalnog neutralnog aminokiselinskog transportera (engl. *specific neutral amino acid transporter*, SNAT) procesom reverznog transporta, a zatim ga preuzimaju SNAT-ovi na glutamatnim neuronima te posredovanjem mitohondrijskog enzima glutaminaze konvertiraju u glutamat.

U širem smislu, receptori koji reguliraju glutamatergičku neurotransmisiju uključuju: ekscitatorni aminokiselinski transporter (EAAT) koji se nalazi presinaptički i odgovoran je za odstranjivanje viška glutamata iz sinapse, vezikularni transporter za glutamat (vGluT) koji prenosi glutamat u sinaptičke vezikule gdje ih pohranjuje za korištenje u neurotransmisiji te metabotropne glutamatne receptore povezane s G proteinima koji se mogu nalaziti presinaptički ili postsinaptički (15). Tri tipa postsinaptičkih glutamatnih receptora povezani su s ionskim kanalima i poznati su kao kanali otvarani ligandom: NMDA receptori (engl. *N-methyl-D-aspartate*), AMPA receptori (engl. *α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid*) i kainatni receptori.

Ionotropni postsinaptički receptori moduliraju ekscitatornu postsinaptičku neurotransmisiju potaknutu glutamatom. Naročito AMPA i kainatni receptori mogu posredovati brzu, ekscitatornu neurotransmisiju, dopuštajući ulazak natrija u stanicu i posljedičnu depolarizaciju (16). NMDA receptori u stanju mirovanja su normalno blokirani magnezijem koji začepi kalcijev kanal. Da bi došlo do glutamatergičke neutrotransmisije na NMDA receptorima potrebna su tri događaja istovremeno: vezanje glutamata na njegovom veznom mjestu na NMDA receptoru, vezanje glicina ili D-serina

and regeneration of excess glutamate after its release during neurotransmission. After being released from the synaptic vesicles of glutamatergic neurons, glutamate interacts with receptors and is subsequently transported into adjacent glia via excitatory amino acid transporters (EAATs). After reuptake into glial cells, glutamate is converted to glutamine by means of the glutamine synthetase enzyme. Specifically, glutamine is released/transported from glial cells via a specific glial neutral amino acid transporter (SNAT) through a process of reverse transport, and is then taken up by SNATs on glutamatergic neurons, where it is converted to glutamate by means of the mitochondrial enzyme glutaminase.

In a broader sense, receptors that regulate glutamatergic neurotransmission include the following: the excitatory amino acid transporter (EAAT) which is located presynaptically and is responsible for removing excess glutamate from the synapse; the vesicular glutamate transporter (vGluT) which transports glutamate into synaptic vesicles where it is stored for use in neurotransmission; and metabotropic glutamate receptors linked to G proteins which can be found either presynaptically or postsynaptically (15). Three types of postsynaptic glutamate receptors are connected with ion channels, and are known as ligand-gated channels: NMDA receptors (N-methyl-D-aspartate receptors), AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors), and kainate receptors.

Ionotropic postsynaptic receptors modulate the excitatory postsynaptic neurotransmission mediated by glutamate. Specifically, AMPA and kainate receptors can mediate fast, excitatory neurotransmission, allowing sodium entry into the cell and subsequent depolarization (16). NMDA receptors at rest are normally blocked by magnesium, which plugs the calcium channel. For glutamatergic neurotransmission to occur on NMDA receptors, three events need to occur simultaneously: glutamate binding at its binding site on the NMDA receptor, glycine or D-serine

na njegovom veznom mjestu na NMDA receptoru te depolarizacija što omogućuje uklanjanje magnezijevog „čepa“ (17). Neki od značajnih signala koji su posredovani NMDA receptorima koji su aktivirani kada su NMDA kalcijevi kanali otvoreni, uključuju dugoročnu potencijaciju i sinaptičku plastičnost (17,18).

Povećana razina glutamata u sinaptičkoj pukotini odgovorna je za njegovo neurotoksično djelovanje pri čemu se upravo egzocitotoksičnost smatra okidačem terapijske rezistencije. Naime, tri su mehanizma kojima glutamat, točnije rečeno višak glutamata, ostvaruje svoju neurotoksičnost.

S jedne strane, preveliko otpuštanje glutamata dovodi do pretjeranog vezanja na NMDA receptore, što posljedično uzrokuje pretjeranu aktivaciju receptora i utoka kalcija u stanice (19). Višak kalcija intracelularno dovodi do oštećenja stanica, a posljedično i do apoptoze. Stanično oštećenje podloga je za nastanak simptoma depresije. S druge strane, veliki učinak pretjeranog otpuštanja glutamata jest “izljev” viška glutamata u ekstracelularne prostore, a ovo pak dovodi do blokiranja i sinteze i otpuštanja BDNF-a (engl. *brain-derived neurotrophic factor*) (18,19). Do spomenutoga dolazi zbog učinka ekstracelularnih NMDA receptora, koji aktivacijom ekstracelularnim glutamatom dovode do gore navedenog učinka, što ima velike posljedice za normalnu funkciju neurona. Poznato je da je upravo BDNF ključan čimbenik u stvaranju otpornosti ili neurorezilijencije za nastanak različitih poremećaja, djeluje neuroprotektivno te smanjuje neuroinflamaciju. Također, BDNF djeluje kao pozitivni čimbenik neuroplastičnosti (20), a kada je inhibiran dovodi do simptoma anksioznosti i depresije te na taj način doprinosi kliničkoj slici terapijski rezistentne depresije. Konačno, neurotoksičnost glutamata u ekstracelularnom prostoru očituje se u povećanom vezanju na mikroglijalne stanice, što uzrokuje povećano otpuštanje upalnih citokina što se

binding at its binding site on the NMDA receptor, and depolarization, which enables the removal of the magnesium “plug” (17). Some of the significant signals mediated by NMDA receptors that are activated when NMDA calcium channels are open include long-term potentiation and synaptic plasticity (17, 18).

Increased levels of glutamate in the synaptic cleft are responsible for its neurotoxic effects, with excitotoxicity being considered the trigger for therapeutic resistance. Specifically, there are three mechanisms through which glutamate, or more precisely, excess glutamate, exerts its neurotoxicity.

On the one hand, excessive release of glutamate leads to its overbinding to NMDA receptors, subsequently resulting in receptor overactivation and calcium influx into cells (19). Excess intracellular calcium leads to cell damage and, ultimately, apoptosis. Cellular damage serves as the basis for the onset of depressive symptoms. On the other hand, a significant consequence of excessive glutamate release is the “spillover” of excess glutamate into extracellular spaces, leading to blockade, synthesis and a release of brain-derived neurotrophic factor (BDNF) (18, 19). This occurs due to the effect of extracellular NMDA receptors, which, upon activation by extracellular glutamate, lead to the aforementioned effect, having significant consequences for the normal function of neurons. It is known that precisely BDNF is a crucial factor in the development of resilience or neuroresilience for the onset of various disorders, it has a neuroprotective effect and reduces neuroinflammation. Additionally, BDNF acts as a positive factor in neuroplasticity (20), and when inhibited, it leads to symptoms of anxiety and depression, thereby contributing to the clinical presentation of treatment-resistant depression. Finally, the neurotoxicity of glutamate in the extracellular space manifests in increased binding to microglial cells, causing an increased release of inflammatory cytokines, thus further resulting in neuroinflammation (21), which will be discussed further in the text.

dalje očituje neuroupalom (21) o čemu će biti govora u nastavku.

Osim glutamata, u razvoju TRD iznimno je važna i uloga GABA-e. GABA je glavni inhibitorni neurotransmiter središnjeg živčanog sustava (22). GABA i glutamat nalaze se u stanju ravnoteže, što znači da u stanjima kada dolazi do povišene razine GABA-e, kompenzatorno dolazi do povećanja koncentracije glutamata (23). Upravo zbog ovog mehanizma dokazano je da je alkohol, kao sredstvo koje dovodi do pojačanog otpuštanja GABA-e (jer etanol djeluje GABA-ergički), rizični čimbenik koji može dovesti do pogoršanja kliničke slike depresije. Povišene razine GABA-e dovode do kompenzatorno povišene razine glutamata, što uzrokuje glutamatnu ekscitotoksičnost te dolazi do neuroupale koja je okosnica nastanka TRD.

Posebno zanimljive u zadnje vrijeme su i spoznaje proizašle iz istraživanja omjera GABA-e i glutamata u oboljelih od depresije. Studije MR spektroskopijom su pokazale povišenu razinu glutamata i nisku razinu GABA-e u okcipitalnom korteksu oboljelih (24). Nadalje, dokazano je povećanje glutamata u bazalnim ganglijima, što je bilo povezano s anhedonijom i psihomotornom usporenošću. Pretjerano smanjenje omjera glutamata i GABA-e pronađeno je u prefrontalnom korteksu neliječenih osoba, što je pokazalo da omjer ovih dvaju neurotransmitera varira u pojedinim moždanim regijama i potencijalno uvjetuje kakvom će se kliničkom slikom prezentirati pojedinci (24). Konačno, recentna istraživanja u središte zbivanja stavljaju neuroupalu (25,26). Upalni citokini koji se oslobađaju u stanjima upale dvojako dovode do glutamatne ekscitotoksičnosti, koja je prethodno objašnjena. S jedne strane, upalni citokini svojim vezanjem na mikrogliju remete njezinu sposobnost da puferira koncentraciju glutamata, čime dolazi do pretjeranog otpuštanja glutamata iz intracelularnog u ekstracelularni prostor, gdje glutamat djeluje toksično (25). Isto tako, upalni citokini djeluju i na transkrip-

In addition to glutamate, the role of GABA is extremely important in the development of TRD. GABA is the main inhibitory neurotransmitter of the central nervous system (22). GABA and glutamate are in a state of balance, meaning that in conditions where there is an elevated level of GABA, there is a compensatory increase in glutamate concentration (23). Precisely because of this mechanism, it has been proved that alcohol, as a substance that leads to an increased release of GABA (since ethanol acts GABAergically), represents a risk factor that can worsen the clinical presentation of depression. Elevated levels of GABA lead to compensatory elevated levels of glutamate, causing glutamate excitotoxicity and resulting in neuroinflammation, which is central to the development of TRD.

Particularly interesting lately are the findings arising from research on the ratio of GABA to glutamate in individuals with depression. MR spectroscopy studies have shown elevated levels of glutamate and low levels of GABA in the occipital cortex of affected individuals (24). Furthermore, an increase in glutamate in the basal ganglia has been proved, which was linked to anhedonia and psychomotor slowness. Excessive reduction in the ratio of glutamate to GABA was found in the prefrontal cortex of untreated individuals, indicating that the ratio of these two neurotransmitters varies in different brain regions and potentially influences the clinical presentation of individuals (24). Finally, recent studies have focused on neuroinflammation (25, 26). Inflammatory cytokines released during inflammation contribute to glutamate excitotoxicity in two ways, as previously explained. On the one hand, inflammatory cytokines disrupt the ability of microglia to buffer glutamate concentration by binding to them, thus leading to an excessive release of glutamate from intracellular to extracellular space, where glutamate exerts its toxic effects (25). Similarly, inflammatory cytokines also act at the transcriptional level, resulting in an increased expression of glutamate transporters on cells, thus further contributing

tornoj razini dovodeći do povećane ekspresije glutamatnih transportera na stanicama, što dodatno doprinosi prelasku glutamata iz intracelularnog u ekstracelularni prostor (26). Vezanjem na ekstracelularne NMDA receptore glutamat dovodi do stanične smrti i smanjene proizvodnje BDNF-a.

Pravi uzroci nastanka neuroupale do danas nisu u potpunosti razjašnjeni te se etiološki razmatraju genetski i okolišni čimbenici. Također, epigenetika je sve više uključena u etiopatogenetska razmatranja (26). Psihosocijalni stres je veliki okidač neuroupale te djeluje na transkriptornoj razini, najvjerojatnije preko citotoksičnosti uzrokovane glutamatom i na taj način dovodi do smanjene proizvodnje BDNF-a (27). S druge strane, istraživanja su pokazala da dio oboljelih od kronične depresije u DNK svojih astrocita iskazuju uzroke metilacije u obliku promjena u genima uključenima u razvoj kronične upale, poput C-reaktivnog proteina i proinflamatornog citokina IL-6 (28), što se ponovno vraća na epigenetiku kao pozadinu nastanka terapijske rezistencije. Isto se tako trauma i ishemija te upale središnjeg živčanog sustava navode kao potencijalni uzroci (29). Uzroka je mnogo, ali zajednički nazivnik je proces nastanka neuroupale i utjecaj upalnih citokina na glijalne stanice što dovodi do glutamatne ekscitotoksičnosti. Najčešće istraživani i najznačaniji proinflamatorni citokini u etiopatogenezi TRD-a upravo su interleukini IL-1 i IL-6, tumor-nekrotizirajući faktor alfa (TNF-α), kao i njihovi topljivi receptori, te protein akutne faze upale, C-reaktivni protein (CRP). Uz navedene, analiza sline, plazme i cerebrospinalne tekućine oboljelih od terapijski rezistentne depresije otkrila je i povišene razine prostaglandina E2 (30). Nasuprot tome, važno je napomenuti da su neki drugi interleukini, poput IL-8, pokazali suprotno djelovanje te su istraživanja pokazala da djeluju protektivno u oboljelih od depresije i doprinose boljem terapijskom odgovoru (31).

to the transition of glutamate from intracellular to extracellular space (26). By binding to extracellular NMDA receptors, glutamate leads to cell death and reduced production of BDNF.

The true causes of neuroinflammation have not been fully elucidated yet, and etiologically, genetic and environmental factors are considered. Furthermore, epigenetics is being increasingly involved in etiopathogenetic considerations (26). Psychosocial stress represents a significant trigger for neuroinflammation and acts at the transcriptional level, most likely through glutamate-induced cytotoxicity, in this way leading to a reduced production of BDNF (27). On the other hand, studies have shown that some individuals with chronic depression exhibit methylation causes in the DNA of their astrocytes, indicating changes in the genes involved in the development of chronic inflammation, such as C-reactive protein and the proinflammatory cytokine IL-6 (28), which again brings epigenetics to the forefront as the background of treatment resistance. Similarly, trauma, ischemia and inflammations of the central nervous system are cited as potential causes (29). While the causes are numerous, the common denominator is the process of neuroinflammation and the influence of inflammatory cytokines on glial cells, which lead to glutamate excitotoxicity. The most commonly researched and most significant proinflammatory cytokines in the etiopathogenesis of TRD are precisely the interleukins IL-1 and IL-6, tumor necrosis factor-alpha (TNF-α), as well as their soluble receptors, and the acute-phase inflammatory protein, C-reactive protein (CRP). In addition to these, analysis of saliva, plasma and cerebrospinal fluid in individuals with treatment-resistant depression has revealed elevated levels of prostaglandin E2 (30). Conversely, it is important to note that some other interleukins, such as IL-8, have shown opposite effects, and studies have shown that they act protectively in individuals with depression and contribute to a better therapeutic response (31). Understanding the different proinflamma-

Važno je poznavati različite proinflamatorne citokine i njihov različiti utjecaj na etiopatogenezu TRD-a.

NOVOSTI U LIJEČENJU TERAPIJSKI REZISTENTNE DEPRESIJE

Liječenje TRD-a je značajan izazov za kliničare. Prije svega treba isključiti da se ne radi o pseudo-rezistenciji. Kombinirano liječenje može uključivati antipsihotike 2. i 3. generacije te stabilizatore raspoloženja (poglavito litij) kao *add-on* terapiju izabranom antidepresivu (32). Treba spomenuti i augmentativni potencijal tireoidnog hormona (33). Osim toga, u obzir dolaze i nefarmakološke metode liječenja poput repetitivne transkranijske magnetske stimulacije (rTMS) i elektrokonvulzivne terapije (EKT), kao i modernije metode poput fototerapije (34-36).

Inovativna opcija u liječenju TRD-a je esketamin, lijek koji ima svoje posebne indikacije, kontraindikacije, mehanizam djelovanja i nuspojave. Prije uvođenja u kliničku upotrebu primjeni esketamina u liječenju terapijski rezistentne depresije prethodila su brojna istraživanja ketamina (37). Što se tiče razlika u učinku ketamina, lijeka koji nije odobren za liječenje TRD-a, i esketamina, lijeka koji je trenutno u uporabi, studije su pokazale da u usporedbi s intranazalnim esketaminom, intravenski ketamin pokazuje značajniji sveukupni učinak i veći postotak remisije, kao i nižu stopu odustajanja od lijeka zbog nuspojava (37). Također, ketamin je pokazao i bolje kratkotrajne učinke u više kliničkih studija, dok dugoročni učinci nisu dovoljno ispitani (37). Ipak, s obzirom na to da ketamin nije odobren za spomenute indikacije, takva saznanja nisu relevantna za trenutnu kliničku praksu, ali otvaraju vrata za daljnja istraživanja i potencijalnu primjenu lijeka u budućnosti liječenja TRD-a.

tory cytokines and their varied impact on the etiopathogenesis of TRD is important.

NOVELTIES IN THE TREATMENT OF TREATMENT-RESISTANT DEPRESSION

The treatment of TRD poses a significant challenge for clinicians. First, it is necessary to rule out pseudo-resistance. Combined treatment may involve second and third-generation antipsychotics and mood stabilizers (especially lithium) as add-on therapy to the selected antidepressant (32). The augmentative potential of thyroid hormone should also be mentioned (33). Additionally, non-pharmacological treatment methods such as repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT), as well as more modern methods like phototherapy (34-36), should also be considered.

An innovative option in the treatment of TRD is esketamine, a medication with specific indications, contraindications, mechanisms of action, and side effects. Before being introduced into clinical use, the application of esketamine in the treatment of treatment-resistant depression was preceded by numerous studies on ketamine (37). Regarding the differences in the effects of ketamine, a medication not approved for the treatment of TRD, and esketamine, a medication currently in use, studies have shown that compared to intranasal esketamine, intravenous ketamine exhibits a more significant overall effect and a higher percentage of remission, as well as a lower rate of medication discontinuation due to side effects (37). Furthermore, ketamine has shown better short-term effects in multiple clinical studies, while its long-term effects have not been sufficiently investigated (37). However, considering that ketamine is not approved for the aforementioned indications, such findings are not relevant to the current clinical practice, but they open the door for further research and potential application of the medication in future TRD treatment.

Esketamin je S enantiomer ketamina (racemična smjesa R- i S-ketamina), neselektivni, nekompetitivni antagonist NMDA receptora (38,39). Uz spomenuto, svoje djelovanje ostvaruje i indirektnom stimulacijom AMPA receptora postsinaptički (33,34). Isto tako, esketamin potiče aktivaciju neurotrofičnih faktora, kao što su BDNF i vjerojatno VEGF (engl. *vascular endothelial growth factor*) koji su u stanjima kroničnog stresa i depresije sniženi (38,39). Gubitak BDNF i VEGF su povezani s atrofijom neurona u područjima mozga poput prefrontalnog korteksa i hipokampusa u animalnim modelima kroničnog stresa, kao i kod velikog depresivnog poremećaja. Nadalje, smatra se da kronični stres i depresija snižavaju receptore za BDNF i VEGF poznate kao TRKB (engl. *tyrosine kinase 2*) i FLK1 (engl. *fetal liver kinase 1*). Konačno, esketamin djeluje i otpuštanjem dopamina iz presinaptičkih završetaka u strijatumu, međutim, to nije dokazano u humanim istraživanjima (38,39).

Pojačana signalizacija neurotrofičnih faktora i posljedično pojačanje sinaptogeneze nakon uporabe esketamina uočeno je u regijama mozga zaduženima za emocionalno ponašanje i reguliranje raspoloženja (31), što je glavni argument zbog čega je esketamin djelotvoran u liječenju TRD. Naime, njegovo brzo djelovanje može biti povezano s indirektnim učincima na signalizaciju AMPA receptora. Blokada glutamatnih NMDA receptora vodi u brzu aktivaciju AMPA receptora koja pokreće kaskadu signalne transdukcije ERK i AKT puteva, a što dalje direktno stimulira mTORC1 (engl. *mammalian target of rapamycin complex 1*) signalni put, koji regulacijom sinteze proteina stimulira sinaptogenezu i produkciju BDNF-a i drugih trofičkih čimbenika (39). Kao što se može zaključiti, pojačana sinaptogeneza i produkcija BDNF-a djeluju neuroprotektivno i smanjuju simptome depresije.

Esketamin se primjenjuje isključivo u bolničkim uvjetima intranazalno. Brzodjelujući

Esketamine is the S-enantiomer of ketamine (a racemic mixture of R- and S-ketamine), a non-selective, non-competitive antagonist of NMDA receptors (38, 39). In addition to this, its action is also achieved through indirect stimulation of AMPA receptors postsynaptically (33, 34). Likewise, esketamine promotes the activation of neurotrophic factors, such as BDNF and probably VEGF (vascular endothelial growth factor), which are reduced in chronic stress and depression (38, 39). The loss of BDNF and VEGF is associated with neuronal atrophy in brain regions such as the prefrontal cortex and hippocampus in animal models of chronic stress, as well as in major depressive disorder. Furthermore, it is believed that chronic stress and depression downregulate the receptors for BDNF and VEGF known as TRKB (tyrosine kinase 2) and FLK1 (fetal liver kinase 1). Finally, esketamine also acts by releasing dopamine from presynaptic terminals in the striatum, however, this has not been proved in human studies (38, 39).

Enhanced neurotrophic factor signaling and, consequently, increased synaptogenesis following the use of esketamine have been observed in brain regions responsible for emotional behavior and mood regulation (31), which is the main argument for why esketamine is effective in treating TRD. Specifically, its rapid action may be associated with indirect effects on AMPA receptor signaling. Blocking glutamatergic NMDA receptors leads to rapid activation of AMPA receptors, initiating a cascade of signal transduction via the ERK and AKT pathways, which further directly stimulates the mTORC1 (mammalian target of rapamycin complex 1) signaling pathway. This pathway, by regulating protein synthesis, stimulates synaptogenesis and the production of BDNF and other trophic factors (39). As can be concluded, enhanced synaptogenesis and BDNF production have neuroprotective effects and reduce depression symptoms.

Esketamine is administered exclusively in hospital settings via the intranasal route. It is a

je agens koji dovodi do kratkoročnog i dugoročnog poboljšanja depresivnih simptoma kod bolesnika s TRD. Osim toga, posebno je koristan jer je njegova primjena povezana sa smanjenjem suicidalnih ideja kod ove osobito vulnerabilne skupine bolesnika (40,41). Suicidalne ideje predstavljaju značajan problem kod bolesnika s terapijski rezistentnom depresijom i teško se kupiraju bilo kojim dosadašnjim modalitetom liječenja.

Prednosti esketamina su njegova kratkoročna i dugoročna učinkovitost, primjena kao dodatak oralnoj terapiji, bolja podnošljivost u odnosu na ketamin, intranazalna administracija (jednom na tjedan, dva puta na tjedan, svakih dva tjedna) te dostupnost kao terapija u hitnim slučajevima, jer dovodi do brzog smanjenja simptoma (dekompenzacija kod akutno depresivnih) i suicidalnosti. S druge strane, glavni nedostatci su: visoka cijena lijeka, potreba nadziranja primjene lijeka od strane medicinskog osoblja, dostupnost (primjenjuje se samo u posebnim indikacijama), nedovoljno iskustvo psihijatara s esketaminom te, konačno, rizik zloporabe koji se u potpunosti ne može isključiti (42).

Esketamin je značajni inovativni modalitet liječenja TRD-a zahvaljujući svom jedinstvenom mehanizmu djelovanja - inhibiciji ekscitotoksičnog učinka glutamata, indirektno stavljajući glutamatnu hipotezu nastanka TRD-a u sve važniji fokus istraživanja.

ZAKLJUČAK

U današnje vrijeme TRD je veliki izazov u liječenju, a liječenje suicidalnog bolesnika s TRD-om je izrazito kompleksno, zahtjevno i odgovorno.

Epidemiološki gledano, jedan od tri bolesnika s velikim depresivnim poremećajem potencijalno ima TRD. U liječenju ove skupine bolesnika nužan je timski rad, a uz standardnu terapijsku skrb, od ključne je važnosti da su psihija-

fast-acting agent that leads to short-term and long-term improvement of depressive symptoms in patients with TRD. Additionally, it is particularly useful because its use is associated with a reduction in suicidal ideation in this especially vulnerable group of patients (40, 41). Suicidal ideation represents a significant problem in patients with treatment-resistant depression and is difficult to alleviate with any previous treatment modality.

The advantages of esketamine include its short-term and long-term effectiveness, use as an adjunct to oral therapy, better tolerability compared to ketamine, intranasal administration (once weekly, twice weekly, every two weeks), and availability as emergency therapy, as it leads to a rapid reduction of symptoms (decompensation in acutely depressed patients) and suicidality. On the other hand, the main disadvantages are the high cost of the medication, the need for supervision of drug administration by medical personnel, limited availability (used only in specific indications), insufficient experience of psychiatrists with esketamine, and finally, the risk of abuse which cannot be completely ruled out (42).

Esketamine represents a significant innovative modality in the treatment of TRD thanks to its unique mechanism of action - inhibition of the excitotoxic effect of glutamate, indirectly placing the glutamate hypothesis of TRD development in an increasingly important focus of research.

CONCLUSION

Nowadays, TRD represents a significant challenge in terms of treatment, and treating a suicidal patient with TRD is extremely complex, demanding and responsible.

Epidemiologically speaking, one in three patients with major depressive disorder potentially has TRD. Collaborative teamwork is essential in treating this group of patients, and alongside standard therapeutic care, it is of utmost

tri uključeni u liječenje upoznati s najnovijim istraživanjima i terapijskim mogućnostima uključujući primjenu esketamina. Upravo esketamin i ostali lijekovi koji moduliraju glutamatnu aktivnost otvaraju nove mogućnosti u liječenju TRD-a. Iako toksični učinci glutamata ne mogu razjasniti patogenezu kod svih oboljelih od TRD-a, najnovija istraživanja koja u središte stavljaju neuroupalu pokazuju se izrazito obećavajućima.

Može se zaključiti da inovativni sadašnji (poput primjerice esketamina) i budući modaliteti liječenja TRD-a mogu doprinijeti, kako značajnim kliničkim poboljšanjima, tako i poboljšanjima kvalitete života ove terapijski izazovne skupine bolesnika.

importance that psychiatrists involved in the treatment are familiar with the latest research and therapeutic possibilities, including the use of esketamine. Indeed, esketamine and other drugs that modulate glutamate activity open up new possibilities in the treatment of TRD. Although the toxic effects of glutamate cannot explain the pathogenesis in all patients with TRD, the latest research focusing on neuroinflammation appears to be extremely promising.

In conclusion, it can be stated that the innovative current (e.g. esketamine) and future modalities for TRD treatment can contribute to significant clinical improvements, as well as improvements in the quality of life for this therapeutically challenging group of patients.

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