INHIBITION OF KAPPA OPIOID RECEPTOR PROLONGS KETAMINE ANTI-DEPRESSIVE PROPERTIES IN THE MOUSE MODEL OF DEPRESSION

Ana Živanović*, Miloš Mitić, Iva Lukić, Miroslav Adžić#, Sanja Ivković#

University of Belgrade – Institute of Nuclear Sciences Vinča, Belgrade, Serbia
Shared last authorship

*anazivanovicmb@gmail.com

Major depressive disorder (MDD) is one of the most prevalent and debilitating mental disorders affecting over 300 million people. Classical antidepressants have a slow onset of their therapeutic effects and are not effective in about 30% of MDD patients. Ketamine emerged as a novel and highly effective anti-depressant drug. However, the effects of ketamine are transient and may involve the unwanted side effects. Thus, the enhancement of ketamine-based anti-depressive therapies is essential. The opioid signalization can modulate ketamine antidepressant actions (1), and, the focus was given to kappa opioid receptor (KOR) as it was shown that its inhibition can also exert antidepressive effects (2). Ketamine is a non-competitive NMDAR antagonist acting through the mTORC1 signaling, while the KOR antagonists (such as norbinaltorphimine, NorBNI) induce the activation of c-Jun N-terminal Kinase (JNK). In this study, combined ketamine/NorBNI treatment prolonged anti-depressive-like behavior in adult male mice in the animal stress model of depression. The combined treatment increased the activation of mTOR signaling in the striatum, one of the brain structures affected in depression. In the same time ketamine/NorBNI decreased the activation of JNK confirming the dominant inhibitory effect of ketamine on JNK activation. These molecular alterations could be responsible for the prolonged anti-depressant effect of the ket+NorBNI treatment. Our results strongly suggest that simultaneous modulation of glutamate and opioid signaling can prolong the anti-depressive effects of ketamine in male mice. Therefore, NorBNI can be considered as a possible adjuvant in the ketamine anti-depressant treatment, at least in males.

References

1. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, Hawkins J, Birnbaum J, Lyons DM, Rodriguez CI, Schatzberg AF. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. Am J Psychiatry. 2018;175(12):1205-1215.
2. Carr GV, Bangasser DA, Bethea T, Young M, Valentino RJ, Lucki I. Antidepressant-like effects of kappa-opioid receptor antagonists in Wistar Kyoto rats. Neuropsychopharmacology. 2010;35(3):752-63.

INHIBICIJA KAPA OPIOIDNOG RECEPTORA PRODUŽAVA ANTI-DEPRESIVAN EFEKAT KETAMINA U MIŠJEM MODELU DEPRESIJE

Ana Živanović*, Miloš Mitić, Iva Lukić, Miroslav Adžić#, Sanja Ivković#

Univerzitet u Beogradu – Institut za nuklearne nauke Vinča, Beograd, Srbija
zajedničko zadnje autorstvo

*anazivanovicmb@gmail.com

Klinička depresija (*engl. Major depressive disorder, MDD*) je jedno od najčešćih i najtežih mentalnih poremećaja od koga boluje preko 300 miliona ljudi. Klasični antidepresivi ispoljavaju svoj efekat sa zakašnjenjem i nisu efikasni kod približno 30% MDD pacijenata. Ketamin se nedavno pojavio kao nov i veoma efikasan lek protiv depresije. Međutim, efekti ketamina su prolazni i izazivaju neželjene nuspojave. Stoga je poboljšanje antidepresivnih dejstva ketamina od suštinskog značaja. Pokazano je da opioidna signalizacija moduliše antidepresivni efekat ketamina (1) te je fokus istraživanja usmeren na kappa opioidni receptor (KOR) čija inhibicija takodje deluje antidepresivno (2). Ketamin je nekompetitivni antagonist NMDAR-a i ostvaruje svoje dejstvo preko mTORC1 signalizacije, dok antagonisti KOR-a (na pr. Norbinaltorfiminom, NorBNI) aktiviraju c-Jun N-terminalne kinaze (JNK). U ovoj studiji pokazano je da je kombinovani ketamin+NorBNI tretman produžio antidepresivne efekte ketamina kod adultnih mužjaka u mišjem modelu depresije izazvane stresom. Kombinovani tretman je aktivirao mTOR signalizaciju u strijatumu, moždanoj strukturi značajnoj u patologiji depresije, a u isto vreme, smanjio aktivaciju JNK potvrdivši dominantan inhibitorni efekat ketamina na JNK aktivaciju. Ove molekularne promene bi mogle biti odgovorne za ostvarivanje produženog antidepresivnog efekta ketamin+NorBNI tretmana. Ovi rezultati sugerišu da istovremena modulacija glutamatne i opioidne signalizacije može produžiti antidepresivne efekte ketamina kod mužjaka miša. To znači da NorBNI ima potencijal da bude uključen kao adjuvans ketamina u terapiji depresije, pre svega kod mužjaka.

Literatura

1. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, Hawkins J, Birnbaum J, Lyons DM, Rodriguez CI, Schatzberg AF. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. Am J Psychiatry. 2018;175(12):1205-1215.
2. Carr GV, Bangasser DA, Bethea T, Young M, Valentino RJ, Lucki I. Antidepressant-like effects of kappa-opioid receptor antagonists in Wistar Kyoto rats. Neuropsychopharmacology. 2010;35(3):752-63.