Nitric Oxide Nitric oxide (NO) has also been reported to be involved in ketamine's antidepressant effects.ACKNOWLEDGMENTS This study was supported by Young Investigator grants from the Brain & Behavior Research Foundation (to J.-W.K., 30254; to K.S., 27733), grant 21153MFDS601 from the Korean Ministry of Food and Drug Safety (to J.-W.K.), National Research Foundation of Korea (NRF) grant RS-2023-00212118 funded by the Korean government (MSIT) (to J.-W.K.), Japan Society for the Promotion of Science KAKENHI grant 22K20697 (to K.S.), and National Institutes of Health grants MH070727 and MI081060 (to L.M.M.) and MH066198 (to E.T.K.).The NMDA receptor activates neuronal nitric oxide synthase to produce NO. In a recent report, NO synthesized by NMDA activation S-nitrosylated glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and stimulated the binding of the nitrosylated GAPDH to Rheb, a stimulator for mTOR signaling (91).Moreover, although selective serotonin reuptake inhibitors (SSRIs) rapidly increase serotonin levels in brain regions such as the mPFC and dorsal raphe (99, 100), the antidepressant responses appear 2 to 4 weeks after initiation of drug treatment in patients with MDD (101).In-depth endeavors are ongoing to ascertain the specific pharmacological targets) responsible for the antidepressant effects of ketamine and determine whether it is possible to separate the beneficial effects from the side effect such as abuse potential heart Problems and dissociation thesestudies will be important in contributing to improved treatment outcomes as well as sustained antidepressant action.In animal studies, ketamine restored active stress-coping behaviors in the learned helplessness test by restoring dopaminergie activity and synaptic plasticity in the mesolimbic dopaminergic circuit (94, 95).www.muarvicas.org o The dutidepresunt Action of Kecamine 137 In addition, ketamine treatment increased the activity of Drdl+ neurons in the mPFC, with chemogenetic activation of Drdl+ neurons in the mPFC relieving the helpless behavior.Similarly, depletion of serotonin by injecting p-chlorophenyl alanine, a serotonin synthesis enzyme inhibitor, abolished the antidepressant .(effects of ketamine, although the effect depended on the study condition (31, 96

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