Scientific Letters

Poster Communication 32

Ketamine and the glutamatergic system: A systematic review of NMDA receptor modulation

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Abstract

Background: Ketamine was first synthesized in 1962 by Calvin Stevens as an alternative to phencyclidine. Its effects stem primarily from glutamatergic modulation, particularly from the antagonism of *N*-methyl-*D*-aspartate receptors (NMDAR) [1]. **Objective:** This study aims to systematically review the pharmacodynamics of ketamine, with particular attention to its effects on the glutamatergic system. **Methods:** The bibliographic search was conducted using books and scientific databases (PubMed and ScienceDirect), using the following terms: "ketamine", "NMDA receptors", "ketamine pharmacology". Only articles published in English from 2000 to 2025 were considered. A total of 7 articles were included. **Results:** Both enantiomers of ketamine, (*S*)-ketamine and (*R*)-ketamine, are noncompetitive antagonists of NMDARs; however, (S)-ketamine has an affinity/potency for NMDARs that is approximately four times greater [2]. In Xenopus oocytes expressing recombinant NMDAR GluN2A–D subunits, in the absence of Mg^{2+}, ketamine shows a higher affinity for NMDARs-GluN2B subtype [3]. However, the affinity depends not only on the subunits that constitute the receptor but also on Mg^{2+} levels and affinity for the receptor [4]. *D*-serine acts as a coagonist of ketamine by binding to the $glycine_B$ site of NMDARs. In PC-12 cells, ketamine influences intra- and extraneuronal levels of *D*-serine: (*S*)-ketamine increases intraneuronal levels and reduces extraneuronal levels, while (*R*)-ketamine decreases both. Furthermore, studies in rats have demonstrated that ketamine modulates the transcription of the gene encoding for serine racemase (*Srr*), increasing *Srr* mRNA levels in the striatum, hippocampus and cortex, but decreasing them in the forebrain [5]. **Conclusions:** The glutamatergic system plays a major role in short-term memory retention and consolidation, as well as in cognition [6]. Interference with this system leads to decreased memory retention, cognitive impairment, and dissociation [1]. Ketamine exerts both direct and indirect effects on the glutamatergic system, which explains the characteristic effects of its use. These effects underlie its use in recreational contexts [1] and as a facilitator drug in sexual assaults [7].

Keywords: ketamine; *N*-methyl-*D*-aspartate receptors; glutamatergic system; psychoactive effects

Funding

This work was supported by FCT - Fundação para a Ciência e Tecnologia, I.P., in the scope of the project UID/04378/2025 (DOI identifier 10.54499/UID/04378/2025), and UID/PRR/04378/2025 (DOI identifier 10.54499/UID/PRR/04378/2025), of the Research Unit on Applied Molecular Biosciences – UCIBIO and the project LA/P/0140/2020 (DOI identifier 10.54499/LA/P/0140/2020) of the Associate Laboratory Institute for Health and Bioeconomy - i4HB, and by CESPU – Cooperativa de Ensino Superior Politécnico e Universitário under the grant "DeTTeCaK-GI2-CESPU-2025".

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