Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Modulation of activity of the N-methyl-D-aspartate receptor as a novel therapeutic avenue in major depression: an immunohistochemical evaluation of the mechanism of action and the side-effects profile of rapastinel (GLYX-13) in the rodent brain

Autor: Andrei-Nicolae Vasilescu
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. D. Inta

Major depression represents a growing economic burden. Current therapeutic strategies, which alter the metabolism of monoamines, are confined by prolonged latency to response and by incomplete remission rate. Novel, rapid acting and effective agents rely on modulation of the activity of the N-methyl-D-aspartate-receptor (NMDAR). One such agent is rapastinel, formerly GLYX-13, a positive allosteric modulator with partial agonistic effect on the NMDAR. Aim of our study was to evaluate the potential neuroprotective effect and the activation pattern induced by rapastinel by means of immunohistochemical analysis of molecular markers in relevant brain regions, given that literature to these topics is lacking und thus hampering further understanding and translation of glutamatergic agents.

In order to evaluate the putative neuroprotective effects of rapastinel we made use of an established model of neurotoxicity based on complete NMDAR antagonization induced by MK-801 in 7-day postnatal mice. The effects of rapastinel were compared to those of clozapine, a potent antipsychotic with neuroprotective properties, and of LY354740, an agonist of the metabotropic glutamate receptors 2 and 3, on apoptosis induced by MK- 801 through immunohistological analysis of expression of caspase-3 in brain regions of interest.

Our results showed a robust neuroprotective effect of rapastinel in all examined regions, rapastinel completely inhibited MK-801 induced apoptosis, while clozapine and LY354740 showed only a comparably modest effect.

Cell activation patterns were determined by immunohistochemical analysis of expression of c-Fos in key brain regions of adult mice treated with rapastinel, D-cycloserine, also a positive allosteric modulator of the glycine binding site of the NMDAR, Ro 25-6981, an antagonist of the NR2B subunit of the NMDAR, and/or MK- 801 alone or in combination.

Rapastinel, D-cycloserine and Ro 25-6981 alone did not induce any significant expression of c-Fos. Surprisingly, the two allosteric modulators of the NMDAR rapastinel and D-cycloserine substantially augmented the c-Fos expression induced by MK-801 in all examined brain regions. To what degree this unexpected enhancement represents a compensatory mechanism against the psychotomimetic effects of NMDAR antagonization and what behavioral or clinical significance this finding has remains unclear at present time.

Our findings underscore to our knowledge for the first time the safety profile and the neuroprotective properties of this novel class of agents as well as the complex interactions of glutamatergic substances. Further studies may determine the role of these new and emerging interventions in the treatment or prevention of psychopathology and other brain disorders.