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C-FOS BRAIN MAPPING OF GLOBAL AND SUBUNIT-SPECIFIC NMDA RECEPTOR ANTAGONISTS: RELEVANCE FOR THEIR POTENTIAL USE AS ANTIDEPRESSANTS

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Introduction: NMDA receptor antagonists as ketamine represent fast-acting alternatives to monoaminergic-based antidepressants. Major drawbacks of these drugs are psychosis-like states and cortical neurotoxicity, effects correlating with potent activation of the cingulated and retrosplenial cortex. The molecular mechanisms underlying these side-effects have not been deciphered yet.

Aims: We aimed to determine potential molecular components of the NMDA receptor implicated in their psychotomimetic action and investigated whether subunit-specific NMDA receptor antagonists also induce similar neurotoxic changes as ketamine.

Method: To investigate deleterious effects of NMDA receptor antagonists, we used brain mapping with the immediate early gene c-Fos. We analyzed the expression pattern of c-Fos in brain areas responsible for deleterious adverse events, after treatment with ketamine and the NR2B subunit-specific antagonist Ro 25-6981, both in wild-type and knockout mice, lacking either the entire NR2A subunit (NR2A ko mice) or its intracellular C-terminus (NR2A deltaC mice).

Results: In contrast to ketamine (10mg/kg), Ro 25-6981, even at high dosages (50mg/kg) does not induce any c-Fos expression in the cingulated and retrosplenial cortex of wildtype mice. However, Ro 65-2981 evokes, both in NR2A ko mice and NR2A deltaC mice, strong c-Fos expression in these areas.

Conclusions: Our data indicate that blockade of both NR2A and NR2B subunits is necessary to induce deleterious effects specific for ketamine. Deletion of the C-terminus of the NR2A subunit is sufficient to disinhibit, together with pharmacological NR2B blockade, neuronal networks associated with psychosis. Therefore, NR2B antagonists may represent safer alternatives to ketamine as potential antidepressants.

https://doi.org/10.1016/S0924-9338(11)72345-8 Published online by Cambridge University Press