Effect of NMDA receptor antagonists on behavioral impairment induced by chronic treatment with dexamethasone

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Abstract:
Severe and prolonged stress but also long-term treatment with glucocorticoids (GCs) have been described to cause brain damage (especially hippocampal and striatal neurons) in humans as well as in animals. GCs potentiate stress or ischemia-induced accumulation of excitatory amino acids (EAA) in the extracellular space of the hippocampus. It was shown that EAA play a major role in various neurologic disorders with cognitive dysfunction. Many authors suggested the neuroprotective effect of N-methyl-D-aspartate (NMDA) glutamate receptor antagonists in some acute or chronic neurodegenerative diseases. On the other hand, many NMDA receptor antagonists produce highly undesirable side-effects at the doses within their putative therapeutic range. The aim of the present study was to evaluate the behavioral effects (memory performance, motor coordination, lethality and body weight) of MK-801 or memantine (MEMAN, non-competitive NMDA receptor antagonists) (at the doses of 25 and 50 μg/kg/day or 2.5 and 5.0 mg/kg/day, respectively) on neurotoxicity induced by dexamethasone (DEX) administered chronically at the doses of 40 or 80 mg/kg/day in mice. It was shown that prolonged treatment (for 10 days) with DEX at the dose of 80 mg/kg/day (but not at 40 mg/kg/day) significantly decreased the retention time in the memory task in mice and impaired the motor coordination in “chimney” test. Neither MK-801 nor MEMAN (at the both doses used) were able to counteract the behavioral impairment induced by DEX administration. Moreover, the potentiation of the body weight reduction and lethality induced by DEX were noted in mice co-treated with MK-801 or MEMAN. The above findings suggest that MK-801 or MEMAN at the doses used have no neuroprotective effect. On the contrary, both NMDA receptor antagonists potentiate the toxicity of DEX given chronically.

Key words:
NMDA receptor antagonists, MK-801, memantine, dexamethasone, neurotoxicity, mice