

## Zinc deficiency attenuates the Antidepressant response of NMDA receptor antagonists in the Restraint Stress Model in Mice



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### Abstract

The latest trend in modern pharmacology of depression is the search for compounds with rapid onset of action and long-term therapeutic effects. One of such compounds, ketamine, is effective in clinical settings while the NMDA receptor antagonist, Ro 25-6981, is effective in animal studies. Clinical and preclinical studies have shown that dietary zinc may play a crucial role in the development and treatment of depression. For instance, people with depression and low blood zinc levels respond poorly to treatment and have more severe symptoms. In such individuals, zinc supplementation improved the response to classical antidepressants. Thus, our research sought to evaluate whether reduced zinc levels can alter the therapeutic response to atypical compounds with potential antidepressant activity. Using a zinc-deficient diet (3mg Zn/kg/3 weeks), mice were subjected to chronic restraint stress (CRS, 3-hours immobilization/ day/3 weeks). CRS is a well-known and proven animal stress model that leads to biochemical and physiological changes that resemble human depression. After the stress period, mice were injected with ketamine (10mg/kg), Ro 25-6981 (10mg/kg), or with a combination of a single dose (2.5mg/kg) of hyperforin (TRPC6 receptor agonist) and lanicemine (NMDA receptor antagonist). All substances were administered once, i.p. To verify the effectiveness of treatment, behavioral tests: tail suspension test (TST), forced swim test (FST), and sucrose preference test (SIP) were carried out at various time points to examine both fast and long-term antidepressant effects. We showed that ZnD weakens the antidepressant response of ketamine and Ro 25-6981 in mice simultaneously subjected to CRS. These effects were observed in two behavioral tests (SIP and TST). Under these conditions, only hyperforin plus lanicemine treatment exhibited fast and long-lasting antidepressant activity. Our data thus indicate that low zinc levels could be a marker of the therapeutic response to atypical fast-acting compounds with antidepressant activity.

### Biography

Bernadeta Szewczyk has completed her PhD at the age of 29 years from Institute of Pharmacology, Polish Academy of Sciences in Krakow, Poland. She is the Assistant professor and the Head of Laboratory of Trace Elements Neurobiology of Maj Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland. She has 95 publications that have been cited 2300 times, and her publication H-index is 30. Her research focuses on the role of the NMDA receptor, serotonergic receptors, as well as zinc deficiency in the pathophysiology and therapy of depression.

### Publications

1. Hyperforin Potentiates Antidepressant-Like Activity of Lanicemine in Mice
2. Nitric Oxide Synthase Inhibitor Attenuates the Effects of Repeated Restraint Stress on Synaptic Transmission in the Paraventricular Nucleus of the Rat Hypothalamus
3. Zinc homeostasis and neurodegenerative disorders
4. Investigational NMDA receptor modulators for depression.



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