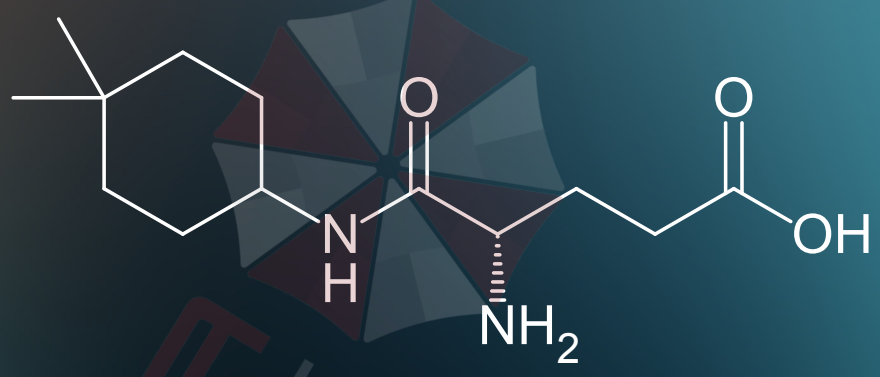

Neboglamine: A Positive Allosteric Modulator of the NMDA Receptor Glycine Site – Preclinical Evidence, Mechanism, and Abandoned Clinical Development

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History

Neboglamine (also known as Nebostinel, CR-2249 or XY-2401) is a drug that was developed from the mid-1990s until the 2010s for the indications of schizophrenia and cocaine abuse. Currently, there are no clinical trials registered and the drug has not been approved in any country, indicating that its development has been abandoned. A synthetic procedure for the production of Neboglamine has been published by one of the earlier papers in 1997.[1]

Mechanism of Action

Neboglamine acts as an allosteric modulator at the NMDA-glutamate receptor in the central nervous system. It increases the physiological function of glycine, which aids glutamate in the activation of the NMDA receptors. [2] It does not bind directly at the glycine site however, still allowing glycine to bind regularly. The NMDA receptor in particular is known the play an important role in learning and memory.

Preclinical Studies

In 2010 Neboglamine was investigated on the hypothesis that it behaves as a potential antipsychotic in a preclinical trial. The authors of the study compared the effects of neboglamine, D-serine and the commonly used antipsychotics clozapine and haloperidol on markers of neuronal activation in rat forebrain. They also studied the effects of these agents on phencyclidine (PCP)-induced behavior in rats, a model predictive of potential antipsychotic activity. Neboglamine, like haloperidol and clozapine, significantly increased neuronal activation. Haloperidol dramatically increased activation (390-fold over control) in the dorsolateral striatum, a brain region in which neboglamine and clozapine had no effect. The pattern of activation induced by neboglamine closely matched that of d-serine, an endogenous agonist at the glycine site of NMDA receptors. Consistent with this finding, neboglamine restored NMDA-mediated neurotransmitter release in frontal cortex punches exposed to the NMDA antagonist PCP. In the behavioral model, all test compounds significantly inhibited PCP-induced hyperlocomotion. Unlike haloperidol and clozapine, neither neboglamine nor d-serine affected the basal levels of locomotor activity. Moreover, oral neboglamine dose-dependently inhibited both the hyperlocomotion and the frequency of rearing behavior induced by PCP. These results, while confirming that the NMDA

glycine site is a feasible target for activating the frontostriatal system, support the clinical evaluation of neboglamine as a functional antipsychotic compound with the potential to treat schizophrenia in humans.[3]

In rats and mice, the effects of Neboglamine on learning and memory were studied in 1996. In this study Neboglamine ameliorated the memory retention deficit produced by scopolamine. Neboglamine was also capable of improving performance in behavioural tests of learning and memory. The activity was determined using different passive and active avoidance behavioural test procedures on rats. Neboglamine was active only when given 45 min before training and did not show any effect when administered immediately after the learning training or before the retention trial. No changes in the general behaviour or motor activity of the animals were observed, indicating that neboglamine effects cannot be attributed to sensory- motor deficit. Microdialysis experiments have shown that neboglamine significantly increased noradrenaline release in the hippocampus. These behavioural results suggest that this new agent has clinical application in memory disorders.[4]

Clinical Trials

There are some second-hand reports in non-scientific sources of clinical trials with neboglamine being conducted. However, no results of such trials have been published, indicating either that these trials have been aborted or that the data was found unsuitable for public release. Specifically, a Phase II study by Rottapharm Madaus was reportedly on hold in 2014.[5,6]

Conclusion

Neboglamine interacts with the NDMA-receptor and increases its activity, which is thought to be responsible for its pharmacological effects. Animal studies suggest it may be useful for treating schizophrenia or addiction and there is limited evidence it may aid in memory enhancement in healthy individuals as well.

It was briefly investigated for potential use in humans, but there has been no news of further development for about a decade as of 2025, and since no published data of these clinical trials exist, the reason for the abandonment of neboglamine remains unclear. There is also no data in the toxicology of the compound, although the fact it reportedly proceeded to Phase II clinical trials suggests that it must have passed previous phase I trials without showing a high toxicity in the trial's participants. Based on animal dosing in preclinical studies, a human dose can be estimated to be around 20-200 mg per dose via subcutaneous injection.[3]

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