

Designing Systemically Active Galanin Analogs for the Treatment of Epilepsy and Pain

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For a substantial number of patients with epilepsy and chronic pain, the currently available therapies are often not effective in controlling their symptoms. The neuropeptide galanin and its associated receptors play an important role in controlling neuronal excitability in the CNS. Direct administration of galanin to the brain has been found to possess anticonvulsant and antinociceptive properties in rodent epilepsy and pain models. In this respect, galaninergic receptors represent a novel molecular target for therapeutic manipulation. In the present investigation, a number of galanin-based analogs that display systemic bioavailability, increased metabolic stability, and penetrate the blood-brain-barrier were synthesized and evaluated in a battery of well-established animal seizure and pain models. The prototype compound NAX-5055, retains nanomolar affinity for galanin type 1 and 2 receptors and displays potent activity following i.v., i.p. or s.c. administration in the 6 Hz psychomotor seizure test. Unlike several of the established anticonvulsant drugs, NAX-5055 retains potent efficacy across a range of stimulus intensities (i.e., 22, 32, and 44 mA) in the 6 Hz test. NAX-5055 is also active in the corneal kindled mouse and hippocampal kindled rat models of partial epilepsy. In addition to its anticonvulsant activity, NAX-5055 displays pronounced antinociceptive activity in the mouse and rat formalin pain model. It is also effective in the mouse abdominal constriction model of pain and the rat sciatic nerve partial ligation model of chronic pain. As the prototype compound, NAX-5055 has provided the necessary proof-of-principle to support the further development of a galanin-based therapeutic for the treatment of epilepsy and pain. Ongoing structure-activity-relationship studies are focused on optimizing NAX-5055 in the search for the most effective and safe IND candidate. Supported by grants from the Epilepsy Therapy Project, The Epilepsy Foundation of America, and the NINDS, NIH (R21 NS059669).