Yeon Sun Lee, J Neurol Disord 2016, 4:9(Suppl)
http://dx.doi.org/10.4172/2329-6895.C1.014

Neuroexcitatory effects of dynorphin A

Yeon Sun Lee
University of Arizona, USA

Statement of the Problem: Dynorphin A is an endogenous ligand showing neuro-inhibitory effects *via* opioid related mechanism. However, chronic pain, nerve injury, and inflammation often result in the up regulation of dynorphin A in the spinal column neurotransmitter pathway to the brain and cause neuroexcitatory effects such as motor impairments and hypersensitivity *via* non-opioid mechanism. The purpose of this research is to develop dynorphin A antagonists to modulate the adverse neuroexcitatory effects under pathological conditions.

Methodology & Theoretical Orientation: Systematic structure-activity relationship studies on the non-opioid dynorphin A fragment, dyn A-(2-13) were performed to identify the key structural features for the interaction with the bradykinin receptors, and then structures were refined by examining the effects of different substituents to obtain an antagonist activity. Lead ligands showing a high affinity at the bradykinin receptors were advanced to test their metabolic stability in plasma and anti-hyperalgesic effects in animals.

Findings: Our studies have discovered a novel mechanism of neurotransmission related to pain in which the bradykinin receptors are upregulated and dynorphin A peptides have neuroexcitatory effects that result in hyperalgesia. Our studies have also shown that lead ligand LYS1044 blocks dynorphin A-induced hyperalgesia and motor impairments in naïve animals and inhibits thermal hyperalgesia and mechanical hypersensitivity in a dose-dependent manner in nerve-injured animals. Importantly, the ability of LYS1044 is limited to the CNS and thus can avoid serious cardiovascular effects caused by blocking peripheral bradykinin receptors. However, the ligand showed low metabolic stability in plasma and thus, to improve the stability various modifications were performed. As the result, we could identify a highly stable ligand with retained high affinity at the bradykinin receptors.

Conclusion & Significance: This study presents a new class of ligands based on the unanticipated pathophysiological interaction between the endogenous opioid ligand dynorphin A and bradykinin receptors for the treatment of chronic pain without the toxicities associated with current treatments for these maladies.

Recent Publications

1. Lee Y S, Remesic M, Amos-Colon C, Hall S M, Kuzmin A, Rankin D, Porreca F, Lai J, Hruby V J (2016) Cyclic non-opioid dynorphin A analogues for the bradykinin receptors. Bioorganic Medicinal Chemistry Letter 26:5513-5516.
2. Lee Y S, Kupp R, Remesic M V, Ramos-Colon C, Hall S M, Rankin D, Porreca F, Lai J, Hruby V J (2016) Various modifications of the amphipathic dynorphin A pharmacophore for rat brain bradykinin receptors. Chemical Biology & Drug Design 88:615-619.
3. Cowell S M, Lee Y S (2016) Biphalin: The foundation of bivalent ligands. Current Medicinal Chemistry 23:3267-3284.
4. Remesic M, Lee Y S, Hruby V J (2016) Cyclic opioid peptides. Current Medicinal Chemistry 23:1288-1303.
5. Hall S M, Lee Y S, Hruby V J (2016) Dynorphin A analogues for the treatment of chronic neuropathic pain. Future Medicinal Chemistry 8:165-177.

Biography

Yeon Sun Lee is an Expert in peptide drug discovery area like novel peptide and peptidomimetic ligands for the treatment of pain and neuronal disease. She has been conducting research in identifying key structural features for target receptors including opioid receptors. The goal of her research is to develop new class of ligands modulating serious side effects that are caused by long term administration of opioids to treat chronic pain states, while retaining their high efficacies. Her studies represent a new approach: Drug design for pathological conditions and multifunctional ligands.

yeon@email.arizona.edu