Inhibitory Peptides That Selectively Antagonize Neuropilin 1 (NRP1) for Precise Pain Treatment

Differentiated and precise approach for selectively targeting pain receptors to treat different types of pain effectively and safely without use of opioids.

Technology

The NYU innovators have identified novel therapeutic targets for treating chronic pain and developed inhibitory peptides that show efficacy in mouse models of pain and human nociceptors. The cell surface receptor NRP1 and intracellular adaptor protein G Alpha Interacting Protein Interacting Protein C-terminus 1 (GIPC1) were both identified as essential signal transducers of Nerve Growth Factor (NGF)-induced pain. Importantly, NRP1 and GIPC1, together with the NGF receptor tropomyosin receptor kinase A (TrkA), are enriched in mouse and human nociceptors. Antagonism of nociceptor-enriched NRP1 and GIPC1 prevents NGF-induced pain, likely avoiding the adverse effects (e.g., joint damage) resulting from systemic NGF sequestration with monoclonal antibodies, which prevented regulatory approval. NRP1 was discovered to transduce the pain signals of NGF by 1) binding to NGF as a coreceptor, and 2) by chaperoning TrkA to the plasma membrane and signaling endosomes via the adaptor protein GIPC1. As described in a published paper (Peach et al. *J Clin Invest.* 2024. PubMed PMID: 39589827), NRP1's and GIPC1's mechanism of action was validated through genetic and pharmacological antagonism of NRP1 and GIPC1, in both mouse and human models. Inspection of NGF's structure, molecular modeling of the NGF, NRP1 and TrkA complex, and biochemical studies identified specific amino acids mediating the NGF-NRP1-TrkA interaction. This information was used to design peptide inhibitors (mimicking NGF, TrkA and NRP1 binding regions in the tripartite complex), which inhibit NGF stimulated activation of nociceptors and show therapeutic efficacy in preclinical models of NGF-induced pain, including arthritis pain. These peptides represent promising starting points for further optimization into therapeutic lead candidates for non-opioid treatment of multiple forms of NGF-mediated chronic pain, including arthritis and cancer pain.

Development Stage

NRP1-inhibiting peptides have been designed and validated in mouse models of pain. Ongoing work seeks to improve the efficacy and specificity of these inhibitors by changing the composition (i.e., amino acid sequence and length) of the peptides.

Background

Chronic pain affects at least 20% of the global population; however, adequately treating chronic pain without adverse side effects is a major unmet health need. Opioids and non-steroidal anti-inflammatory drugs, which are the current standard of care, often lack efficacy and frequently cause life-threatening side effects (e.g., opioids cause respiratory arrest and sedation that are

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worsened by addiction; NSAIDs have detrimental actions in the cardiovascular, gastrointestinal, and renal systems). The NGF/TrkA-evoked pain pathway is one of the few alternative chronic pain targets currently validated in humans. NGF, which is produced by injured and diseased tissues, activates the cell surface receptor TrkA on peripheral nociceptors to evoke hyperexcitability and the expression of neuropeptides and ion channels that mediate pain. Previously, anti-NGF monoclonal antibodies showed success in treating pain in osteoarthritis patients; however, this treatment was not FDA approved due to adverse, rapid joint damage observed in some patients, demonstrating that non-discriminate sequestering of circulating NGF with monoclonal antibodies is not a tractable therapeutic strategy for selectively targeting chronic pain. Therefore, innovative approaches with higher specificity, such as targeting the NGF/TrkA/NRP1 axis in nociceptors, are needed to provide effective and safe pain treatment. Because NGF is produced by injured and diseased tissues (e.g., inflamed tissues, cancers), antagonism of its capacity to excite nociceptors provides a more specific way to inhibit disease-relevant pain compared to inhibitors of sodium channels that generally dampen neuronal activity.

Applications

NRP1-inhibiting peptides could be used to treat:

- Chronic pain Inflammatory pain, including arthritis
- Nerve injury pain
- Cancer pain
- Postoperative pain

Advantages

- **Effective pain relief:** NRP1-inhibiting peptides precisely and effectively target NGF/TrkA-evoked pain.
- **Reduced on-target side effects:** NRP1-inhibiting peptides are not expected to cause joint damage and other adverse side effects common to NGF-targeted therapeutics.
- **Non-opioid analgesic:** NRP1-inhibiting peptides are not expected to carry harmful side effects of opioid treatments (e.g., respiratory arrest, sedation, constipation, nausea, addiction).
- **Well-characterized pathway:** the NGF/TrkA-evoked pain pathway is one of the few pain pathways currently validated in humans.

Intellectual Property

NYU has filed a PCT patent application covering the composition of synthetic NGF and TrkA peptides and their method of use for treating different types of pain.

References

1. Chloe J. Peach, et al. , https://doi.org/10.1172/JCI183873