A metabolically resistant spexin analogue, LIT-01-144, induces potent non-opioid peripheral antinociception in persistent pain via activation of GALR2

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Résumé

Chronic pain affects a significant proportion of the population, with substantial clinical and socioeconomic burdens. Current management largely relies on opioids, which pose risks of dependence and misuse, underscoring the need for alternative therapies. Galanin receptors (GALR1–3) are implicated in pain modulation, but their specific roles remain unclear due to a lack of selective ligands. Recent discoveries identified spexin, a peptide that selectively activates GALR2 and GALR3, offering a novel way to develop pharmacological tools that selectively target these two receptor subtypes. In this study, a modified spexin analog, LIT-01-144, was designed by attaching a fluorocarbon chain to enhance metabolic stability without altering receptor selectivity. In vitro, LIT-01-144 demonstrated high potency toward GALR2 and GALR3 and poor activity at GALR1. Pharmacokinetic studies in mice showed that LIT-01-144 has a significantly longer plasma half-life than native spexin and does not cross the blood-brain barrier. In vivo, LIT-01-144 exhibited potent antinociceptive effects at much lower doses than spexin when administered intracerebroventricularly. While systemic administration had no effect in naïve mice, LIT-01-144 significantly alleviated pain in a model of persistent inflammation induced by CFA. This antinociceptive effect was mediated through GALR2 rather than GALR3 and was independent of opioid pathways. In situ hybridization revealed increased GALR2 expression in dorsal root ganglia of inflamed mice. These results highlight GALR2 as a promising peripheral target for non-opioid pain therapies and establish LIT-01-144 as a valuable pharmacological tool for investigating GALR2-mediated antinociception.

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Mots-Clés: Pain, GPCRs, neuropeptide, pharmacological tool, fluoropeptide