Peptide-Derived Orally-Active Kappa-Opioid Agonist for Peripheral Pain in Rats

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ABSTRACT

Kappa opioid agonists have been particularly efficacious in peripheral pain models but suffer from centrally-mediated effects that limit their development. Derivatives of the tripeptide D-Phe-D-Phe-D-Nle-D-Arg-NH2 (Figure 1), such as CR655, exhibit high peripheral to central selectivity in analogical models when administered by intrathecal injection and benefits patients experiencing visceroskeletal neuropathic pain. However, compounds such as CR655 are not orally active when administered orally. Application of the JT Pharmaceuticals (JT Pharma) non-natural amino acid technology (Figure 2) to CR655 in Phase 1 of this project produced derivatives that exhibit peripheral analgesic activity when dosed orally, but does not promote CNS-based effects. Lead compound JT09 engages the kappa-opioid receptor with EDAK1 in the low nM range, with the highest peripheral selectivity for kappa over other peripheral opioid receptors (mu or delta) was >11,000-200,000-fold. No antagonistic activity was detected. To assess peripheral and central pain modulation, a rat writhing model of peripheral pain and a hot plate model of centrally-mediated pain were performed. Results indicate that JT09 acts as efficacious morphine in alleviating peripheral pain, while failing to produce undesired central activity. In an operant self-administration procedure where rats are required to press a lever to receive an intravenous drug infusion, JT09 targeted to maintain lever responding, indicating no abuse liability. In contrast, highly abused rewards (e.g., sucrose and cocaine) readily maintained lever responding. JT09 did not promote other CNS effects associated with mu or delta opioid receptors (sedation, dysphoria, tolerance, addiction). Thus, we propose that JT09 is a candidate for development as an orally active, peripherally-restricted, kappa-opioid agonist for peripheral pain.

INTRODUCTION

• Pain is the most common symptom that leads people to seek medical intervention in the United States today.
• The most difficult pain to manage successfully is chronic peripheral pain, which includes visceral, thermal, bone, and neuropathic pain, and pain associated with cancer.
• Currently, there are two major types of chronic pain medications in use – opioids and non-steroids – both of which have inherent toxicities (nausea, vomiting, constipation, renal toxicity, depressed breathing, thromboembolic risk, neurotoxicity, tolerance, addiction etc.).
• At this time, there does not exist an analog for the treatment of chronic peripheral pain that does not have side-effects associated with undesired central activity or inadequate receptor selectivity.
• A properly designed opioid receptor agonist could fulfill this role, with requirements that the compound is orally active and targets a specific peripheral pain receptor without crossing the blood brain barrier (BBB) to elicit toxicities mediated by opioid receptors in the central nervous system (CNS).
• The mediation of opioid analgesic effects occurs through three receptors: mu, kappa, and delta.
• Agonists at the mu-receptor are the most used opioid receptor agonists, but suffer from induction of euphoria, addiction, respiratory depression, and GI tract inhibition.
• Kappa-opioid agonists (KOA)s exhibit none of these effects and have been shown in vivo to mediate pain modulation through the peripheral KOA receptors.
• We believe that using the JT Pharma peptide modification technology, orally active peripheral KOAs can be created that will not cross the BBB, constituting a new type of pain medication.

RESULTS

• JT09 is as efficacious as morphine in alleviating peripheral pain, while failing to produce undesired CNS-mediated effects associated with morphine (sedation, dysphoria, tolerance, addiction).
• JT09 does not promote other CNS effects associated with morphine – both of which have inherent toxicities (nausea, vomiting, constipation, renal toxicity, depressed breathing, thromboembolic risk, neurotoxicity, tolerance, addiction etc.).
• JT09 is both orally active and acts as peripherally restricted KOA, thus fitting the criteria of a new pain medication.
• JT09 is a candidate for development as orally available, peripherally-restricted, kappa-opioid agonists for peripheral pain.

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