Office of Technology Management

Modulation of Opioid Analgesics by CaMKII Inhibitors

Technology Reference

CW035

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Field

Biomedical & Therapeutic Sciences

Key Words

Calcium calmodulin dependent protein kinase (CaMKII) inhibitors

Opioid analgesics

Addiction

License Status

Seeking licensing partners

Patent Status

Non-provisional Application Patent filed

Overview

The clinical use of opioids including morphine to treat moderate to severe pain is widely accepted throughout the world. Although opioids are the most effective painkillers, adequate pain management with opioids may require large doses due to the development of tolerance. At high doses, the debilitating side effects of opioids become more troublesome and apparent, which limits their usefulness. Common side effects include nausea, vomiting, respiratory depression, dizziness, and constipation. Chronic use of opioid analgesics at high doses also exposes the patients to higher risk of drug addiction and may alter the immune function and consequently increase susceptibility to developing cancer and infectious disease. Management of adverse effects remains a major clinical challenge.

Vast amounts of published data have linked CaMKII with learning and memory. There has been some speculation that opioid tolerance involves learning and memory. No pre-existing works have studied the direct effect of CaMKII on opioid tolerance, i.e., effects independent of learning and memory process.

Technical Summary

Zaijie Wang discovered that calcium calmodulin dependent protein kinase is a key component in promoting and maintaining opioid tolerance. This hypothesis has been tested in rodent models of opioid tolerance and dependence using commercially available, selective CaMKII inhibitors. Supporting the finding, CaMKII expression is also up-regulated in rats and mice that are tolerant to morphine. Thus, modulation to CaMKII signaling pathways may be used to prevent and reverse opioid tolerance. Currently, there is no therapy or adjuvant therapy available for the prevention or reversal of opioid tolerance. Tolerance to opioids occurs inevitably after prolonged use. Current treatment protocol is dose-escalation, which leads to increased side effects, including higher potential for drug dependence. Often, tolerance occurs so dramatically and so quickly, even with a large dose increase, that pain may not be adequately controlled. The cell and animal models used in these studies can in turn be used to screen for CaMKII inhibitors for their profile in inhibiting CaMKII activity, opioid tolerance and dependence, and chronic pain.

Benefits

- Reversal of tolerance and addition would significantly expand the opioid pain market if proven effective in humans.
- This invention potentially addresses the problem of tolerance, which is a limiting problem in their use, and so potentially could be very beneficial as an adjunctive treatment with opioids.

Areas of Application

- Pain management
- Addiction management
- CaMKII inhibitors have demonstrated in both rat and mouse models with two separate inhibitors to: o "reverse" morphine tolerance o "eliminate" withdrawal symptoms (i.e., elimination of dependence on the opioid) in morphine-addicted mice

Stage of Development

- Animal model completed
- NIH Grant application in process

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