Cannabinoid receptor 2 agonist attenuates pain related behavior in rats with chronic alcohol/high fat diet induced pancreatitis

Liping Zhang, PhD[1] • Robert Kline IV, MS[1] • Terry Mcnearney, MD[2] • Michael Johnson, PhD[2] • Karin N. Westlund High, PhD[1]

[1]Physiology, University of Kentucky • [2]Neuroscience/Pain, Lilly Research Laboratories, Eli Lilly and Company

19b

Background: Chronic Pancreatitis (CP) is a complex, multifactorial syndrome with dysfunctional pain in a significant number of patients. Drugs developed to treat a variety of pain states fall short of providing effective analgesia, often providing minimal to partial pain relief over time with significant side effects. Cannabinoid receptor 2 (CB2) has emerged as an attractive target for management of chronic pain, as demonstrated in several studies with inflammatory and neuropathic preclinical pain models.

Purpose/Hypothesis: In this study, the analgesic efficacy of a novel, highly selective CB2 receptor agonist, LY3038404 HCl, is investigated in a chronic pancreatitis pain model, induced with an alcohol/high fat (AHF) diet.

Methods: Chronic pancreatitis was induced with a liquid alcohol (6%), high fat (23%) diet for comparison to control rats fed standard lab chow. Weekly behavioral testing was performed during the animal's dark cycle active period (i.e. 0900 h – 1500 h). In week 7-8, LY3038404 HCl powder (10 mg/kg, orally, twice a day for 9 days) was freshly mixed with control rat chow powder (1 g) and drinking water to form a small drug pellet. Pancreas tissues were taken for histopathology and fibrosis at experiment end (week 8).

Results: Rats fed the AHF diet developed visceral pain-like behaviors detectable by week 3 and reached a maximum at week 5 that persists as long as the diet is maintained. Rats were treated with LY3038404 HCl. The treated animals demonstrated significantly alleviated pain related behaviors after 3 days of dosing, including increased paw withdrawal thresholds (PWT), prolonged abdominal withdrawal latencies (ABWL), and decreased nocifensive responses to noxious 44°C hotplate stimuli. Terminal histological analysis of pancreatic tissue sections from the AHF chronic pancreatitis animals demonstrated extensive injury, including a global pancreatic gland degeneration (cellular atrophy), vacuolization (fat deposition), and fibrosis. After the LY3038404 HCl treatment, pancreatic tissue was significantly protected from severe damage and fibrosis. LY3038404 HCl affected neither open field exploratory behaviors nor dark/light box preferences as measures of higher brain and motor functions.

Conclusion: LY3038404 HCl, a potent CB2 receptor agonist, possesses tissue protective and analgesic properties without effects on higher brain function. Activation of CB2 receptors is suggested as a potential therapeutic target for visceral inflammation and pain management.