A Novel Multi-Chemokine Receptor Antagonist to Reduce Opioid Use and Break Addiction

Related Problems – Chronic Pain, The Opioid Crisis, and Addiction

Pain relievers, including opioids, do not work well for chronic pain [1], which affects over 40% of Americans, making it one of the most prevalent, disabling and costly health problems in the United States today. A 2011 report from the Institute of Medicine (access here) indicates that chronic pain costs the nation an estimated $565 to $635 billion in treatment costs and lost productivity – more than annual combined costs of heart disease, diabetes and cancer.

Opioids for pain are currently the most widely prescribed class of drug in the United States, with an estimated 245 million prescriptions (not including refills) dispensed in 2014. Opioid analgesics are also highly rewarding, resulting in the diversion and misuse that fuels what is now referred to as the “opioid epidemic” – the magnitude of which has been described as “startling.” [2] Last year 60,000 Americans died of pain-related drug overdoses, resulting in more deaths than at the height of the U.S. AIDS epidemic in 1994-1995.

The decades-old approach to mitigating opioid addiction (e.g. methadone, buprenorphine, and naloxone) has been to identify less addictive opioids [3-5], or after addiction ensues, to block the opioid receptor. Other interventions aimed at the dopaminergic reward pathways themselves or at vaccine antibodies that “soak up” abuse drugs have been explored for decades [3] but have yielded only incremental progress, insufficient for the enormity the problem that exists today.

There is an overwhelming need to develop better pain therapeutics – not just for providing effective pain therapies to those suffering – but as a critical component of a comprehensive approach for solving the current opioid epidemic. Despite this great need, many pharmaceutical companies have exited from pain research. The opioid crisis has become a national tragedy of such consequence that agencies such as the National Institutes of Health and the U.S. Food and Drug Administration have made resolving it a top priority.

Uncontrolled Inflammation Sits at the Crossroads of Chronic Pain and the Opioid Crisis

Neuroinflammation, via activation of specific innate immune chemokine receptors, promotes pain [6-13] by regulating the functional responsiveness of endogenous opioid receptors that mediate analgesia [14-19]. Chemokines (small proteins produced by cells of the immune system released from injured cells during inflammatory processes) both promote pain and reduce the ability of opioid drugs to counteract pain. Chemokines are directly involved in the neurobiology of opioid addiction and psychostimulant abuse [20, 21]. Blocking the actions of chemokine receptors with chemokine receptor antagonists (CRAs) can preserve opioid receptor sensitivity, requiring less opioid, and can “turn off” drug-seeking and addiction behaviors [22, 23]. The primary pharmacological effect of CRAs is to re-sensitize tolerized and non-functional mu-opioid receptors (MOR) [15, 19].
Taking CRAs in combination with opioid drugs can improve pain control and lower the dose of opioid medication, thereby minimizing both undesirable and adverse opioid drug effects and the risk of addiction.

Based on our initial studies with animal models, Creative Bio-Peptides’ lead molecule, an orally bioavailable small peptide CRA with multiple chemokine targets, could deliver superior chronic pain, reduce or eliminate the need for opioids in acute pain situations, thereby reducing or eliminating the risk of opioid addiction.

Our oral peptide R103 is an analog of DAPTA (Dala1-peptide T-amide), which has been shown to target multiple chemokine receptors (CCR2/CCR5/CCR8) that are implicated in chronic neuropathic pain, and in opioid use disorder, and other diseases of chronic inflammation and neurodegeneration. DAPTA has been shown to be safe and effective with no side effects in >600 patients in multiple clinical trials.

Targeting the immune system rather than the nervous system (a very different approach that has not been well explored) suggests that interventions that safely balance brain inflammation will control opioid receptor sensitivity, tolerance, drug-seeking behaviors, and addiction. Thus, by targeting multiple chemokine receptors, our novel peptides could become a safe, effective strategy for treating pain, reducing opioid use, reversing opioid tolerance, and breaking addiction. By being able to reduce the underlying biochemical need for the drug, addiction can be reduced.

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1. REFERENCES