



Novel, Safe, Stable

Pain Therapeutics for Animals

Zadina Lab Research and Innovation

The lab of **James Zadina** studies opioids and their role and mechanisms of action in alleviating pain and inducing side effects. Current focus is on development of novel, safer analgesics based on modifications of naturally occurring opioids (endomorphins). One compound is in clinical trials and a second generation of analogs has been shown in animal models to provide analgesia equal to or greater than morphine with substantial reduction or absence of several major side effects. These include: respiratory depression, tolerance, pro-inflammatory responses, and side effects of particular importance for older animals (including motor and cognitive impairment).

Motivation and Development

Opioid painkillers are the gold standard for alleviating pain in humans and animals but are associated with several adverse side effects. Of particular importance, respiratory depression is a cause of death during and after surgery, and motor and cognitive impairment are especially problematic for older animals. Certain analgesics, such as ketamine, are also subject to abuse by humans, to the point that a movement to classify ketamine as a scheduled drug threatens its availability for veterinary uses.

Separation of analgesia from unwanted effects has long been an unmet goal of opioid research, but the most commonly used opioids besides morphine are still based on oxycodone and hydrocodone, discovered nearly 100 years ago. A new approach and new painkillers are desperately needed.

Recently naturally occurring peptides were discovered (endomorphins, EMs) in the brain that act potently and selectively at the mu (morphine) opioid receptor to alleviate pain (Zadina et al., Nature 386:499, 1997). Because the natural EMs are rapidly metabolized, we have developed metabolically stable **EM analogs for use as therapeutics**, that provide analgesia equal or greater than that of morphine, and show significant reduction of side effects. This program has been highly successful.



Lead Compound Identified

The lab identified a lead compound with a favorable profile in multiple tests. At doses providing equal or greater pain relief relative to morphine in the rat, the lead EM analog showed **significantly reduced**: a) respiratory depression, b) impairment of motor coordination, c) impairment of cognitive function, d) tolerance and e) inflammation/glial activation associated with tolerance and pain hypersensitivity. The analogs are very effective at relieving pain in multiple pain models in animals. The results indicate that EM analogs could provide the **gold standard pain relief** typical of currently used opioids like morphine, but with a **remarkably safer profile of major side effects**.

Publications

A publication describing several of these effects has recently been published (*Zadina et al., Endomorphin Analog Analgesics with Reduced Abuse Liability, Respiratory Depression, Motor Impairment, Tolerance, and Glial Activation Relative to Morphine. Neuropharmacology 105:215-227, 2016. doi:10.1016/j.neuropharm.2015.12.024*) Additional publications have been submitted or are in preparation.

Intellectual Property & Development Plan

These compounds are patented under a VA-Tulane University cooperative agreement.

Transition to commercial development is being coordinated in a cooperative effort of the Tulane School of Medicine, Technology Transfer Office and external consultants.

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