Spinophilin for pain

By Brian Moy, Staff Writer

A major drawback to the use of opioid analgesics is the development of dependence and tolerance. A paper published in *Neuron* suggests that improving the function of spinophilin, a neuronal scaffolding protein that is highly concentrated in dendritic spines and plays a role in synaptic transmission,[1] could optimize the analgesic effects of acute morphine treatment, reduce the development of tolerance and lower the degree of physical dependence.

The challenge is that spinophilin is located in the nucleus accumbens, the ventral portion of the striatum located deep within the brain, and delivering a compound that induces overexpression of spinophilin or mimics its function could prove difficult.

The research, led by scientists at the **University of Crete** and the **University of Texas Southwestern Medical Center**, showed that spinophilin knockout mice had less sensitivity to the analgesic effects of low doses of morphine, methadone and fentanyl than wild-type mice. Moreover, wild-type mice developed tolerance to the analgesic effects of once-daily 20 mg/kg injections of morphine by day 4, whereas spinophilin knockout mice had a lower response to morphine and showed no analgesic response by their second exposure to the drug.[2]

Thus, said Venetia Zachariou, principal investigator and corresponding author of the *Neuron* paper, because spinophilin opposes the consequences of repeated opiate exposure, "the goal is to improve spinophilin function in order to achieve analgesia with low doses of morphine or fentanyl." Zachariou is an assistant professor of pharmacology at the University of Crete School of Medicine.

"The importance of the paper is that it provides a lead into developing analgesics with reduced tolerance and dependence" issues, said Donald Jasinski, a professor of medicine and chief of the Center for Chemical Dependence at **Johns Hopkins Bayview Medical Center**.

Jeffry Vaught, EVP of R&D at **Cephalon Inc.**, said that "while it seems too early to determine the druggability of spinophilin, the paper provides clues into the overall regulation of the μ-opioid receptor and may help identify fundamental causes unlinking analgesia and abuse."

He added that "future research needs to determine if there is a way to manipulate spinophilin to maintain analgesia while avoiding side effects."

"While it seems too early to determine the druggability of spinophilin, the paper provides clues into the overall regulation of the μ-opioid receptor and may help identify fundamental causes unlinking analgesia and abuse."

—Jeffry Vaught, Cephalon Inc.

Special delivery

Both Zachariou and Jasinski think drug delivery will be a key challenge of developing therapeutics that agonize or mimic spinophilin.

Zachariou told *SciBX* that "because spinophilin is a ubiquitous protein affecting the actions of several neurotransmitters, spinophilin function should only be improved in cells expressing the μ-opioid receptor."

Previous studies have shown that morphine tolerance and dependence are closely related to the failure of the bound μ-opioid receptor to be properly processed by the endocytic pathway.[3]

Ongoing research is investigating whether overexpression of spinophilin in the nucleus accumbens is sufficient to improve analgesic responses to morphine and fentanyl or whether it must be overexpressed in multiple brain regions, which affects pain response.

Daniel Carr, CMO at **Javelin Pharmaceuticals Inc.**, said "the high quality of science reported in the paper will certainly extend our understanding of the cellular mechanisms of opiate action and the development of tolerance and dependence."

However, Carr also expressed concern over the near-term feasibility of spinophilin as a target.

"It might be possible to develop a drug that would augment or mimic the desirable effects of spinophilin, but it would be a challenge to deliver that drug to certain brain regions that would benefit while avoiding others where such exposure could be undesirable," he said. "Moreover, spinophilin's particular subcellular localization within the targeted regions poses an additional challenge because achieving drug levels sufficient to produce an effect within dendritic spines may require very high systemic levels, which could produce adverse effects."

Carr also thinks there are "more cost-effective ways to reduce or eliminate requirements for opiates while controlling pain, such as with nonsteroidal anti-inflammatory drugs and local anesthetics. Patients are already relying on multimodal therapies to manage pain."

Javelin's nonopioid development program includes intranasal ketamine, an *N*-methyl-D-aspartic acid antagonist in Phase III testing, and i.v. Dyloject diclofenac, which the U.K. approved last year. The nonselective NSAID inhibits cyclooxygenases (COXs) and is in Phase III testing in the U.S.

Although unsure if it is possible to develop a stable form of spinophilin, Jasinski suggested that "one possible approach would be to look at the distinct domains of the spinophilin protein and then try to develop a compound that mimics its active sites."

He also noted that "future research would need to investigate the chemical characteristics of the receptors impacted by spinophilin in order to develop a therapeutic approach aimed at directly increasing the level of spinophilin expression."

REFERENCES

1. Allen, P.B. *et al. Proc. Natl. Acad. Sci. USA* **94**, 9956–9961 (1997)
2. Charlton, J. *et al. Neuron*; published online April 23, 2008; doi:10.1016/j.neuron.2008.02.006
   Contact: Venetia Zachariou, University of Crete, Crete, Greece
   e-mail: vzachar@med.uoc.gr
3. Edelson, S. *SciBX* **1**(3), 9–10; Feb. 14, 2008

COMPANIES AND INSTITUTIONS MENTIONED

Cephalon Inc. (NASDAQ:CEPH), Frazer, Pa.
Javelin Pharmaceuticals Inc. (AMEX:JAV), Cambridge, Mass.
Johns Hopkins Bayview Medical Center, Baltimore, Md.
University of Crete, Crete, Greece
University of Texas Southwestern Medical Center, Dallas, Texas