Behind The Scenes in Pharmacognosy

A Mint and So Much More

by Amy Keller

In June of 2006, the *Journal of Natural Products* awarded the Jack L. Beal Award to "Synthesis of Salvinorin A Analogues as Opioid Receptor Probes", authored by Kevin Tidgewell and others in the laboratory of Dr. Tom Prisinzano. Dr. Prisinzano graciously answered our questions regarding this fascinating area of research.

Peter Katavic, Matt Schmidt, Kevin Tidgewell, Herky the Superhawkeye, Anthony Lozama, Denise Simpson, and Tom Prisinzano (left to right). Not pictured: Wayne Harding, Kushal Shah, Pavitra Kannan, and Howard Cobb.

How did you become interested in *Salvia divinorum* and salvinorin A?

I first heard about salvinorin A when I was a graduate student in the School of Pharmacy at Virginia Commonwealth University. Bill Devane was a new assistant professor in the Department of Pharmacology and was going to try and characterize its mode of action. He said it was a hallucinogen, but I was very skeptical since I was working in the laboratory of Richard Glennon, who was one of the world experts on the medicinal chemistry of hallucinogens, and it looked nothing like other hallucinogens. Then as a postdoctoral fellow at the National Institutes of Health (NIH), my mentor Kenner Rice asked me to purify salvinorin A he had inadvertently contaminated for a paper he was working on. I was then in the process of starting to find a job as a professor. After reading the 2002 PNAS paper by Roth et al (including my mentor Kenner Rice), which described the opioid activity of salvinorin A, I asked Kenner if he knew anyone doing structure-affinity relationships (SAR) on salvinorin A. His quote to me was, "No, but I think this would be a great project for you to work on." The rest of the story remains to be written.

Who in your laboratory carried out the research?

The research was carried out by my graduate students Kevin Tidgewell, Anthony Lozama, my postdoctoral fellow Wayne Harding, undergraduate research assistants Pavitra Kannan and Kushal Shah, and a PharmD student Howard Cobb. In addition, our collaborators Chris Dersch performed the binding studies on the salvinorin A analogues in Richard Rothman's lab at the National Institute of Drug Abuse (NIDA) and the X-Ray crystal structure in the paper was done by Damon Parrish and Jeff Deschamps at the Office of Naval Research.

Could you provide a brief explanation of the work and results in your own words? In what way are the data in your paper new?

Recently, salvinorin and several related compounds were shown to have affinity and activity at opioid receptors, the sites in the brain where morphine and other opioids work. There was little information as to how a diterpene interacts with receptors that previously had only been shown to interact with alkaloids and related amines. To begin to better understand how this is possible, we explored the SARs of salvinorin A and related diterpenes at opioid receptors. With one exception, all of the compounds in the paper were new derivatives of salvinorin A. The binding affinities and X-ray structure were also newly carried out. This work also indicates that salvinorin A and related analogues may not be binding in an identical manner to opioid receptors.

What impact does this research have, and your research in general?

Opioids, like morphine, are highly effective analgesics but are accompanied by side effects such as respiratory depression, constipation, tolerance, and dependence which limit their clinical usefulness. In addition, there are few medications available for the treatment of drug abuse. By researching salvinorin A and salvinorin related molecules, we may find novel treatments for pain without these side effects, as well as medications to treat drug dependence and other CNS disorders.