Chronic Pain Researchers First to Link Regulatory Protein to Mu Opioid Receptor Signaling

March 7, 2014, Phoenix, AZ -- Researchers found initial confirmation that a novel scaffold protein previously unassociated with the mu opioid receptor (MOR) regulates MOR-induced signaling activation. The MOR is the target of opioid drugs like morphine and is an important mechanism for pain regulation in the body. The research approach was designed to open new avenues to the treatment of chronic pain, a serious public health problem with major economic and societal costs.

Writing in a scientific poster presented today at the 30th Annual Meeting of the American Academy of Pain Medicine, investigators noted that decades of research aimed at discovering new, safer and more effective drugs to treat chronic pain have met with limited success.

“The most surprising result of this study was that we were able to find a novel regulatory protein that no one had ever associated with the MOR or pain, and show in cells that this protein regulates MOR signaling,” said senior study author John Streicher, PhD, assistant professor at the University of New England, College of Osteopathic Medicine, in Biddeford, Maine. “What this finding may allow us to do is design new drugs to target the MOR to produce pain relief with reduced side effects. More broadly, understanding the molecular mechanism of MOR signaling will open up many new strategies for improved drug design.”

Once identified, candidate proteins can be manipulated in cells and the effects on MOR signaling determined, as was done with one candidate protein in this study, Dr. Streicher explained.
Previous research work has validated this basic approach. For example, activation of the kappa opioid receptor (KOR) signaling cascades for analgesic purposes has been limited because of dysphoria; however, this effect may be selectively modulated by developing KOR agonists that are biased toward G protein coupling (associated with analgesia) and away from βarrestin2 recruitment (associated with dysphoria) (Zhou et al, *J Biol Chem* 2013;288(51):36703-16). Though promising, Dr. Streicher said, this approach has been limited so far, because the signaling complex and regulators of opioid receptors have not been defined with sufficient detail, which would be crucial for success.

To identify targets, the investigators applied 2 methods of unbiased screening. The first method (proteomic screen) involved pulling out the receptor and proteins bound to the receptor after drug activation using a technique called co-immunoprecipitation. Once isolated, the receptor and the proteins bound to it may be identified by mass spectrometry.

For the second method, the researchers used a genetic approach that reduces the expression of a specific gene. Using an shRNA library, 15,000 genes were knocked down, 1 in each individual cell. After separating out which cells (each with a knocked-down gene) have decreased or increased MOR signaling, the identity of the knocked-down genes are determined by DNA sequencing.

From these data, the investigators plan to identify a list of potential signaling regulators of the MOR and will further test the candidate proteins for their ability to regulate pain and MOR activity in living animals. The researchers plan to begin studies of this sort in genetically manipulated mice within the next few months with the regulatory protein they have already identified.

“Ultimately, what we hope to accomplish is to develop an array of drugs using different molecular strategies to achieve a desired effect,” Dr. Streicher said. “If successful, patients may one day be able to select specific drugs for difficult-to-treat chronic pain states like neuropathic pain, or to reduce specific -- or all -- side effects.”

The study was funded through a pilot project grant (P20GM103643) from the Centers of Biomedical Research Excellence, a division within the National Institutes of Health.

*Poster 223 – Unbiased Screens for Novel Signaling Regulators of the Mu Opioid Receptor*

### About AAPM
The American Academy of Pain Medicine is the premier medical association for pain physicians and their treatment teams with over 2,500 members. Now in its 31st year of service, the Academy’s mission is to optimize the health of patients in pain and eliminate pain as a major public health problem by advancing the practice and specialty of pain medicine through education, training, advocacy and research. Information is available on the Academy’s website at [www.painmed.org](http://www.painmed.org).

###