HYDRA BIOSCIENCES News

Hydra Biosciences Announces Data Revealing the Crucial Role Played by the TRPA1 Ion Channel in a Standard Model of Pain Receptor Activation

-- Study to be published online in the *Proceedings of the National Academy of Sciences* highlights ion channel's potential as an analgesic drug target --

Cambridge, MA, August 7, 2007 – Hydra Biosciences today announced data revealing a key role of the Transient Receptor Potential ion channel, TRPA1 in the formalin pain model, a standard model for the development of pain drugs. The data overturn long-standing views of how formalin induces pain and advance TRPA1 as an attractive target for analgesic drug development. The results will be published in the online edition of *Proceedings of the National Academy of Sciences (PNAS)*.

Hydra is investigating TRPA1 as part of its Ion Channel Program, its leading research and development effort focused on the Transient Receptor Potential (TRP) family of novel non-selective cation channels. TRP channels account for ~20% of all the VGL Superfamily channels. They respond to a variety of stimuli, and may act as multimodal signal integrators in a number of tissues, including sensory neurons. Because the members of the TRP family have low homology to each other and to other classes of ion channels, Hydra sees significant opportunity for developing drugs that can potently and selectively target individual TRPs for the treatment of important medical conditions (e.g., pain, inflammation, pulmonary disorders, hypertension, and renal disease).

"For decades it was believed that the pain induced in the formalin model was based on generalized tissue damage and inflammatory response generated by formalin," said Russell Herndon, President and CEO of Hydra. "These PNAS-published results show that the acute pain induced by formalin is actually due to activation of the TRPA1 ion channel. These data should cause the pain research community to take a new view of data obtained from the formalin model over the last 30 year. This study represents a strong validation of our novel approach toward developing possible new treatments for pain while reinforcing our leadership position in TRP research."

"The formalin test is a widely used and validated model for pharmacologic and genetic studies of nociception and pain, and has been cited in the literature hundreds of times. Understanding its underlying biology is a crucial step in drawing a more detailed picture of the physiology of acute and chronic pain at the molecular level," said David Julius, Ph.D., Morris Herzstein Chair in Molecular Biology and Medicine, Professor and Chair of the Department of Physiology, University of California, San Francisco, a member of Hydra's ion channel advisory board, the National Academy of Sciences, and communicating author on the study.

Dr. Julius continued, "These data uphold an important role of the TRP family, including TRPA1, in pain perception, and provide us with an avenue for the development of new drugs for pain management."

About the Study

With this combined *in vitro* and *in vivo* study, researchers at Hydra and UCSF set out to determine whether TRPA1 activation could account for formalin's ability to activate pain receptors. The active component of formalin, formaldehyde, is similar in structure and reactivity

to pain-inducing irritants found in air pollutants (e.g. acrolein), and in mustard oil (i.e., allyl isothiocyanate, or AITC), which are known activators of TRPA1.

The research team found that formalin activated cells expressing human or rat TRPA1, but not cells lacking the ion channel. These responses in TRPA1-positive cells could be attenuated with a selective TRPA1 inhibitor identified at Hydra, HC-030031.

The researchers also found that while sensory neurons isolated from normal mice responded to formalin exposure with increased intracellular Ca^{2+} concentrations, those from mice engineered to lack TRPA1 did not. Rat neurons treated with Hydra's TRPA1 inhibitor, HC-030031 were similarly resistant to formalin stimulation.

Treatment with HC-030031 also substantially reduced formalin-mediated pain responses in rats. This decrease in pain response was not only apparent during the early phase (Phase I) of the formalin response, but also persisted in the later phase (Phase II). Phase I is thought to reflect the acute pain response while phase II is proposed to be caused by central sensitization. Phase I and II formalin responses were also reduced in mice lacking functional TRPA1, providing further confirmation of the channel's role in pain receptor activation.

Citation: McNamara CR, Mandel-Brehm J, Bautista DM, Siemens, J, Deranian KL, Zhao M, Hayward NJ, Chong JA, Julius D, Moran MM, Fanger CM. (2007) TRPA1 mediates formalin-induced pain. *Proc Natl Acad Sci USA*.

About Ion Channels

Aberrant ion channel activity has been implicated in many diseases, including hypertension, cardiac arrhythmias, gastrointestinal disorders, cystic fibrosis and pathological pain. Many drugs on the market today act on ion channels, either directly or indirectly, including calcium channel blockers for hypertension and angina, and sodium channel blockers for pain. Hydra's TRP channel discovery program has identified numerous modulators predicted to impact diseases such as pain and inflammation, hypertension, and pulmonary diseases. Many of these modulators have been shown to be efficacious in animal models of disease. In addition, ion channels have been successful drug targets, with modulators of ion flux representing up to 17% of world pharmaceutical sales.

About the Pain Therapeutics Market

Over 50 million people suffer from inflammatory pain, including osteoarthritis and rheumatoid arthritis. Millions more suffer from post-operative, back and diabetic neuropathic pain. The total worldwide market for all pain indications is estimated to be $20 billion.

About Hydra Biosciences

Hydra Biosciences, a biopharmaceutical company based in Cambridge, Massachusetts, develops drugs to treat pain, inflammation, cardiovascular and other diseases using its expertise in novel ion channels. Hydra's proprietary high throughput screening platforms enable the company to identify and develop drug candidates that address significant unmet medical needs. More information about Hydra Biosciences is available at: www.hydrabiosciences.com.

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