

## UCSD Medical Researchers Say Statins, Other Cholesterol-Depleting Agents Affect Hypertension

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**C**holesterol-lowering agents, such as the widely-prescribed statin drugs, and cholesterol-blocking agents may prove to be “novel therapeutic agents to modify cellular calcium that contributes to the development of pulmonary hypertension,” according to Hemal H. Patel, Ph.D., who leads a multidisciplinary team of researchers at the University of California, San Diego (UCSD) School of Medicine.

Presenting his research at the 35<sup>th</sup> Congress of the International Union of Physiological Sciences on Tuesday, April 5 in San Diego, Patel said the team found a previously unappreciated cellular and molecular mechanism for the disease process in idiopathic pulmonary hypertension (IPAH), which was previously called primary pulmonary hypertension. He added that the mechanism found may be amenable to treatment with current and future therapies and might provide more substantial, long-term and efficacious benefit to those who have IPAH.

A severe clinical disease with a poor prognosis, untreated IPHA leads to heart failure and death in two to eight years. Because of limited understanding of the cellular and molecular determinants of the disease process, current therapy is limited and aimed towards symptomatic relief.

Patel, who is a post doctoral fellow in the lab of Paul Insel, M.D., UCSD professor of pharmacology, said two factors that contribute to the disease are dependent on cellular calcium: constriction of vessels, and uncontrolled cell growth resulting in thickening of vessels. The UCSD team sought to determine if IPAH has altered caveolae, which in Latin means “little caves,” on the membrane composed of cholesterol that control the intake of calcium into cells. They also wanted to know if agents that modify cellular cholesterol might limit calcium intake and ultimately limit the two factors (constriction and growth) in vessels that contribute to the disease process. These drugs then might provide for a novel therapy that not merely provides temporary relief of disease symptoms, but helps alleviate the underlying cause of IPAH.

In their research, the team saw that “smooth muscle cells isolated from pulmonary arteries of patients with IPAH indeed had more caveolae on the cell membrane compared to cells from normal individuals, and also that there was a higher calcium intake into the diseased cells,” Patel

reported. Subsequent treatment of the IPAH cells with an agent that depletes cholesterol (methyl-beta-cyclodextrin, or MBCD), or “a statin (in this case, lovostatin, sold as Mevacor by Merck), which blocks cholesterol synthesis, resulted in a disruption of the caveolae and reduced the amount of calcium that entered the cells.

“Additionally, these two treatments also decreased the growth rate of the diseased cells,” Patel said. Taken together, the results “mean that the micro-structure of the cell membrane is involved in controlling the intake of calcium and that the cholesterol modifiers of these structures may serve as novel therapeutics to reduce vessel constriction and cell growth associated with increased calcium intake in IPAH,” Patel stated.

The next steps, Patel explained, are to understand the nature of the proteins located on the caveolae and how these structures communicate with the internal regions of cells to influence calcium intake into the cell. He said the UCSD researchers “already have begun looking at the expression and localization of ion channels into caveolae that may further explain the increased calcium intake into cell.”

In addition to Patel, researchers included Insel and Fiona Murray, Ph.D., UCSD Department of Pharmacology; Shen Zhang, Ph.D. and Jason X-J Yuan, M.D., Ph.D., UCSD Department of Medicine, and Patricia A. Thistlethwaite, M.D., Ph.D., UCSD Department of Surgery. The study was funded by the National Institutes of Health.

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### ***35th Congress of the International Union of Physiological Sciences***

The 35th Congress of the International Union of Physiological Sciences is in San Diego, March 31 - April 5, 2005. The Congress (<http://www.iups2005.org/>) is organized by the six member societies of the U.S. National Committee of the IUPS, [the American Physiological Society](#), [the Society for Neuroscience](#), [the Microcirculatory Society](#), [the Society of General Physiologists](#), [the Biomedical Engineering Society](#), and [the Society for Integrative and Comparative Biology](#), under the auspices of the U.S. National Academy of Sciences.

During the Congress, Patel will present a paper titled “Cholesterol-depleting drugs, including statins, lower intracellular Ca<sup>2+</sup> and inhibit proliferation in pulmonary artery smooth muscle cells in primary pulmonary hypertension,” and will participate in Session 898, “Overview: From organelles to organ,” a featured topic of the IUPS Calcium Signaling Track, beginning at 10:30 a.m. April 5 in the San Diego Convention Center.

The IUPS conference, held every four years, runs concurrently this year with Experimental Biology 2005 at the San Diego Convention Center. The American Physiological Society (APS), which is hosting IUPS, was founded in 1887 to foster basic and applied science, much of it relating to human health. The Bethesda, MD-based Society has more than 10,000 members and publishes

nearly 4,000 articles every year in its 14 peer-reviewed journals. In May, APS received the Presidential Award for Excellence in Science, Mathematics and Engineering Mentoring (PAESMEM).

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