SOUTHWESTERN NEWS

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NEW FINDINGS ON CELLULAR "GREASE" MAY LEAD TO MORE EFFECTIVE HEART DRUGS

DALLAS — Aug. 16, 1996 — By revealing a function of a "very special piece of grease," researchers at UT Southwestern Medical Center at Dallas have identified a potential target for new drugs that regulate heart contractions.

UT Southwestern professor of physiology Dr. Donald W. Hilgemann and instructor of pharmacology Dr. Rebecca Ball reported their finding in the Aug. 16 issue of the journal *Science*.

This "piece of grease," actually a lipid or molecule of fat known as phosphatidylinositol-4,5-biphosphate or PIP_2, helps calcium move out of heart cells in an orderly fashion. PIP_2 attaches to a transport protein that carries calcium out of the cells and stimulates their activity.

The ratio of calcium in and around the cell is important. Calcium is found in large quantities outside the cell membrane and in very limited quantities inside the cell. The buildup of calcium inside the cell signals the heart muscle to contract.

"The muscle reads the calcium signal — or buildup of calcium — with each heartbeat," Hilgemann explained. If too little calcium builds up inside the heart cell it won't contract. If too much calcium builds up inside the cell, it generates irregular heartbeats, or arrhythmias.

"We became convinced that the cell signal going to the protein that transports calcium was something unusual in the membrane itself," he said.

To uncover the mechanism of calcium transport, Hilgemann had to control the movement of molecules across the cell membrane. He developed a technology that "gives us complete control of the factors that may influence the things that move across the membrane," he said. The cardiac membrane patches he developed let him study calcium

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transport from both inside and outside of the membrane.

Hilgemann examined the cell membrane to identify the target molecule and found PIP_2. "We also learned that not only is PIP_2 connected to other cell-signaling molecules but also may be a cell signal itself," he said.

That finding raises additional questions, Hilgemann said. "We still don't know much about how PIP_2 is controlled in cells or how it works at a molecular level."

Hilgemann said the research will also give scientists a handle on how the heart can regulate the strength of its contractions. While the hormone adrenalin affects the pace of contractions, it is possible that PIP_2 regulates the strength of contractions without changing the frequency of the heartbeat.

Medications are available that specifically alter the strength of heart contractions, but Hilgemann said they are difficult to use. PIP_2 could be a potential target for drugs that would regulate the strength of heart contractions more effectively with fewer side effects. "This might be a step in that direction," he said.

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