

MAY 29, 1998

Researchers Discover Molecular Pacemakers for Heart and Brain

A single family of genes is responsible for pacemaker activity in both heart and brain, say researchers from the Howard Hughes Medical Institute at Columbia University.

"These genes encode a family of pacemaker ion channels," says Hughes investigator Steven Siegelbaum of Columbia University. "With the identification of these genes it should now be possible to devise genetic screens to identify their role in various inherited cardiac diseases and neurological disorders."

Ion channels are specialized proteins in the membranes of nerve and muscle cells that open and close in response to physiological stimuli. These channels allow sodium and potassium ions to cross the cell membrane and initiate an electrical impulse. Siegelbaum's laboratory discovered the gene family and characterized their function in collaboration with the laboratory of Hughes investigator Eric Kandel, also at Columbia University. Their results are published in the May 29, 1998, issue of *Cell*.

Pacemaker cells generate the rhythmic, spontaneous electrical impulses that power the heart and brain. In the heart, pacemaker activity regulates the heartbeat. In the brain, pacemakers have a wider range of responsibilities, including control of particular behavioral states, including arousal during the sleep-wake cycle; the binding together of the components of perception; and certain rhythmic autonomic functions, such as respiration.

Defective pacemaker activity can lead to inherited or acquired cardiac arrhythmias and may also underlie certain neurological diseases. The existence of pacemakers in the brain and the heart raises the question of whether pacemakers share a common molecular basis. In 1997, Kandel's laboratory discovered the first member of the pacemaker gene family, although they were not completely certain of the protein's true identity at the time.

There were a few obstacles to clear before the group could be sure that they had indeed cloned a pacemaker: First, the gene was present only in brain, and Kandel's team knew that true pacemakers are found in both heart and brain tissue. Second, they had no idea about the functional properties of the protein coded for by the gene, *bcng-1*. Based on the sequence of the gene, however,

they suspected that they had cloned a heretofore elusive pacemaker ion channel.

The break came when Kandel's team, which included Bina Santoro and Dusan Bartsch, in collaboration with Siegelbaum's laboratory, which included Gareth Tibbs, David Liu and Huan Yao, found five additional closely related genes in mice and humans. The teams showed that three of the five genes are expressed in both brain and heart. The HHMI/Columbia researchers also showed that one of the genes codes for an ion channel with electrical properties identical to native brain pacemaker channels and similar to cardiac pacemaker channels providing proof that the genes are fundamental for pacemaking.

The discovery of this new family of genes is likely to aid understanding of a wide range of cardiac and neurological diseases that involve faulty ion channels. "The knowledge of the structure of these ion channels, especially knowing that there are subtle differences between heart and brain pacemaker channels, is likely to aid in the development of new drugs for treating heart arrhythmias and neurological diseases," said Kandel.