SOUTHWESTERN NEWS

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UT SOUTHWESTERN, KOREAN RESEARCHERS LINK BICARBONATE TRANSPORT TO CYSTIC FIBROSIS

DALLAS – March 1, 2001 - Physiology researchers at UT Southwestern Medical Center at Dallas, working with Korean researchers, have connected defects in the transport of bicarbonate with cystic fibrosis. Their findings raise the question about whether delivering bicarbonate to diseased tissues can someday be used to lessen the effects of cystic fibrosis in patients and even extend their lives.

CF is caused by mutations in a protein called CFTR. Until recently, researchers believed cystic fibrosis was always caused by a defect in the transport of chloride by CFTR across cells lining organs such as the lungs and pancreas to their outer surfaces. But in recent years, researchers have identified many mutations that do not prevent chloride transport by CFTR. In those mutations, chloride transport is normal, but cystic fibrosis still results in varying degrees of severity.

In previous studies, the UT Southwestern and Korean researchers found that CFTR transports not only chloride but also bicarbonate. In this current research published in the March 1 edition of *Nature*, they found that mutations in CFTR that do not affect chloride transport actually inhibit bicarbonate transport. They also found a correlation between the extent of this inhibition and the severity of the disease; the greater the inhibition, the more serious the disease.

"This tells us that bicarbonate secretion is very important for the proper functioning of tissues affected in CF," said Dr. Shmuel Muallem, professor of physiology at UT Southwestern. "We know that these tissues secrete very alkaline fluids that contain high concentrations of bicarbonate."

Tissues that secrete such fluids include the vas deferens, pancreas, lungs and intestine. The acidity of those fluids in CF contributes to the precipitation of the mucins, or secretions, that coat the surface of tissues affected in CF and plug the ductal systems of these tissues. This acidity also helps bind harmful bacteria to these precipitated mucins.

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"Plugged ducts destroys the pancreas, and pathenogenic bacteria eventually destroys the lungs of all CF patients," Muallem said. "That leads to death at an early age."

Cystic fibrosis affects about 30,000 Americans and is caused by a defective gene carried by about 5 percent of the population. CF patients' secretory glands produce abnormally thick mucus that obstructs the vas deferens, the pancreas and the airways, resulting in their destruction. The disease's symptoms include salty-tasting skin, persistent coughing, wheezing or pneumonia and bulky stools. Patients usually require frequent hospitalizations and treatments, and while their life expectancy has increased dramatically over the years, few people with the disease live beyond their 20s.

While pointing to defective bicarbonate delivery as a culprit in causing CF in some cases and in facilitating its symptoms, the researchers do not at this time know how to improve delivery of bicarbonate to the surface of affected tissues. This question remains for future research.

"If we can learn how to deliver bicarbonate to the surface of the cells, we may be able to reduce the debilitating effects of cystic fibrosis and lengthen the lives of CF patients," Muallem said.

Other researchers in the study are Dr. Philip Thomas, associate professor of physiology, and Dr. Joo Young Choi, postdoctoral research fellow, both of UT Southwestern; and Dr. Min Goo Lee of Yonsei University in Seoul.

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