Channeling new drugs to ischemic hearts

Arteries with poor blood flow can leave the heart muscle starved for oxygen, a condition often foreshadowing a heart attack. For more than a decade, physicians have treated reduced coronary blood supply, or ischemia, with drugs that mimic the body's natural vessel dilation in the aftermath of ischemia. Called calcium-channel blockers, these drugs dilate vessels by blocking the tiny pores that let calcium ions – known to constrict vessels – into the cells of artery walls. But these agents indiscriminately dilate blood vessels throughout the body, causing side effects such as abnormally low blood pressure and flushing.

Another problem plagues clinicians and researchers trying to come up with new treatments for ischemia: the lack of knowledge regarding the molecular changes underlying the disorder. Now, a study of guinea pigs suggests a molecular mechanism for ischemia that explains the action of calcium-channel blockers and may also reveal how some diabetes drugs boost insulin supplies, researchers say. In addition, the findings suggest that new drugs, as well as some already under investigation for other diseases, might dilate narrowed coronary arteries without significantly altering other vessels.

Jurgen Daut, Nikolas von Beckerath and their colleagues at the Technical Institute of Munich say they were motivated by animal studies at the University of Vermont, in which researchers examined certain channels that regulate the flow of potassium ions out of cells. That study, described in the July 14, 1989 SCIENCE, showed that drugs can constrict or dilate abdominal arteries in rats and rabbits by manipulating potassium channels sensitive to adenosine triphosphate (ATP), the fuel that powers cells. If drugs could influence potassium channels to dilate abdominal blood vessels, the West German scientists reasoned, the same drugs might accomplish a similar effect in the coronary arteries.

They verified their hunch using guinea pig hearts, measuring coronary artery dilation elicited by reducing blood supply and oxygen levels. The group found that the hypertension drug cromakalim caused similar dilation, while glibenclamide – a drug used to increase insulin production – prevented dilation. Mark T. Nelson at the University of Vermont College of Medicine in Burlington and his co-workers had used those same drugs to open ATP-sensitive potassium channels.

Von Beckerath calls the link between potassium channels and coronary vessel enlargement surprising, noting that investigators have focused on other possible causes for dilation, including chemicals that react with smooth-muscle cells or the endothelial cells lining blood vessel walls. "It appears that the ATP-sensitive channel regulates over 95 percent of dilation," von Beckerath says.

The ultimate trigger for vessel dilation, he speculates, may be ATP concentration. His team found that even in the presence of oxygen levels that would not normally trigger vessel dilation, drugs that lower intracellular ATP concentrations still open coronary blood vessels.

In the March 16 SCIENCE, von Beckerath and his colleagues propose a Rube Goldberg-type sequence of molecular events to explain how blood vessels enlarge and how calcium channels affect this process. The stress of reduced oxygen or blood flow may deplete ATP concentrations inside arterial smooth-muscle cells, signaling ATP-sensitive potassium channels to open, the team suggests. The resulting departure of potassium ions would increase the negative polarity of cell membranes, which would close voltage-dependent calcium ion channels. The subsequent reduction in intracellular calcium ions would cause the blood vessels to relax and dilate.

Von Beckerath and others note that ATP-sensitive potassium channels in coronary arteries appear more sensitive to vessel-dilating drugs than do potassium channels in other vessels and in heart muscle, suggesting that some dilation drugs could selectively target heart arteries. "There's a wide variety of new drugs and old compounds" to study as candidates, says Nelson. He notes that cromakalim is already under investigation as an agent to lower blood pressure. In addition, he says, glibenclamide's link to potassium channels may help explain its effectiveness in diabetics. *– R. Cowen*

Mapping chemical microscapes of cells

Superman may have had X-ray vision, but he didn't have an eye for the chemicals inside cells. Two chemists at Cornell University do. Using a single instrument that combines the magnifying power of a microscope with the chemical-analysis prowess of a mass spectrometer, they can uncover the identities and cellular locations of elements such as calcium, boron and magnesium.

At last week's Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, held in New York City, George H. Morrison and Subhash Chandra reported adapting the instrument, called an ion microscope, to reveal cellular details of physiological processes.

"More and more biologists are going to see this stuff and come knocking on the door," Morrison says. In fact, they already have. The researchers have received more than 400 reprint requests for a paper they published last year demonstrating the potential of ion microscopy for biological studies.

At the conference, Chandra described more recent studies on the role vitamin D plays in the absorption of calcium into the bloodstream. In these experiments, the chemists injected calcium into the intestines of two sets of chicks, which differed only in the presence or absence of vitamin D in their feed. The team used a stable, heavy isotope of calcium that would stand out from the lighter isotope normally dominant inside cells. By extracting gut tissue at different times after the calcium injections and using the ion microscope to get "snapshots" of the calcium distribution within different cells of the tissue, the researchers could track calcium absorption.

Although they were not surprised to find that chicks lacking vitamin D absorbed calcium poorly at best, Chandra says the ion microscopy study provides graphic data about exactly where and when absorption occurs. And that insight enables scientists who seek more details about the absorption process to rule out many experiments that would likely prove a waste of time. "No other existing technique can localize elements as well at a subcellular level as can ion microscopy," Chandra notes. Other techniques often involve hard-to-handle radioactive chemicals or steps that introduce data-skewing perturbations, he adds.

In their analyses, the researchers first bombard a carefully prepared sample with positively charged oxygen ions. These primary ions sputter secondary ions from the sample surface, and an electric field then accelerates the secondary ions into a mass spectrometer, which sorts them according to the energies they carry and their masses. A special electromagnetic lens system ensures that the secondary ions maintain the spatial relationships they had in the sample surface, and a component known as a charge-coupled device detects and digitizes the spatial pattern of the speeding ions.

Physicists and materials scientists have been using ion microscopy for years to study the elemental distributions of silicon wafers and other materials whose properties depend on trace impurities. The difficulty of adapting the technique for biological samples, which require more complicated preparation, has until now kept ion microscopy from the biologists' tool chest, Morrison says. Adds Chandra: "Now we are applying the technique to real-life situations." *– I. Amato*