HYPERTENSION

Possible New Path for Blood Pressure Control

High blood pressure may well be the most common disease of the industrialized world, affecting an estimated 50 million people in the United States alone. And the consequences are severe: Elevated blood pressure, or hypertension, boosts the risk of stroke, heart attack, congestive heart failure, and kidney failure. But despite years of study, researchers still don't fully understand how the body normally regulates its blood pressure or why that regulation so often goes awry. Results described on page 1107 now provide an important new clue to both those puzzles.

Molecular geneticist Richard Lifton of Yale University School of Medicine and his colleagues have identified two related genes, either of which can, when mutated, cause a rare hereditary form of high blood pressure known as pseudohypoaldosteronism type II (PHAII). Seven other genes have been linked to hypertension, many by the Lifton team. The new genes, however, appear to be part of a previously unknown pathway that helps control blood pressure by regulating ion movements in the kidney.

In tight. This composite confocal image of a kidney section shows that WNK4 (stained red) occurs with the tight junction protein ZO-1 (stained green).

"This work clearly breaks new ground; it's not just a 'me-too' finding," says Theodore Kurtz of the University of California, San Francisco. And although it remains to be seen whether mutations in the genes can cause the common type of hypertension, Kurtz and others say that even if they don't, the pathway should still be an excellent target for new drugs for treating high blood pressure.

Lifton has been tracking the genes involved in PHAII for 7 years. Although genetic linkage studies had pointed to PHAII genes on chromosomes 1, 12, and 17, the genes have proved elusive, he says. Then Lifton and his colleagues found a new PHAII family whose disease gene appeared to be located near the end of chromosome 12.

At that point, he recalls, "we got lucky." Yale's Rick Wilson found that affected family members, but not normal ones, carry a deletion in that chromosomal area. When the researchers then showed that the deletion lies at the beginning of a gene called *WNK1*, and that another PHAII family has a similar deletion, they had their gene. Discovered just last year by Melanie Cobb's group at the University of Texas Southwestern Medical Center in Dallas, *WNK1* encodes one of the cell's many kinases, enzymes that regulate the activity of other proteins, but its function was otherwise unknown.

Lifton and his colleagues then searched the databases for *WNK1* relatives and found one, designated *WNK4*, that turned out to lie in the chromosome 17 region thought to carry a PHAII gene. The team also found that patients whose PHAII is linked to chromosome 17 have mutations—single-base changes—in *WNK4*.

To probe how the mutations might lead to high blood pressure, Lifton's team determined where the two genes are expressed. The kidneys of PHAII patients "absorb too much salt and excrete too little potassium and hydrogen ions," Lifton explains. Consistent with that, the researchers found the WNK1 and WNK4 proteins in the distal renal tubules, the kidney structure that plays a key role in maintaining the body's salt and water balance. What's more, whereas the WNK1 protein is in the cytoplasm of the tubule cells, WNK4 is located in a membrane structure called the tight junction that controls ion movements through the cell layer forming the tubule lining.

Lifton therefore proposes that *WNK* gene products are part of a pathway regulating chloride ion uptake by the kidney. If so, overexpression or increased activity of the genes could cause the kidney to retain extra chloride ions. To balance that, the kidney would have to retain excessive amounts of sodium ions, resulting in water retention and increased blood volume and thus high blood pressure. Potassium and hydrogen ion excretion would also be impaired.

That hypothesis is not yet proven. But however the genes work, there's at least a hint that *WNK4* mutations may contribute to the more "garden variety" hypertension seen in the general population. Genetic studies of the large population in the Framingham Heart Study, conducted by Richard Myers of the National Heart, Lung, and Blood Institute and Boston University and his colleagues, including Lifton, show an association between blood pressure and the chromosome 17 area where *WNK4* is located. The *WNK4* discovery is "particularly interesting because it may provide insight into the mechanisms of commonly occurring variations in blood pressure," Myers says.

And beyond that, the finding opens the door to a better understanding of kidney physiology generally. Says blood pressure expert Friedrich Luft of the Max Delbrück Center for Molecular Medicine in Berlin, Germany: "The novelty here is the discovery of new pathways that will generate a whole line of investigation into how the [kidney] works."

–JEAN MARX

ASTROPHYSICS

Smooth X-rays Fill the Milky Way's Disk

X-rays from the plane of our galaxy have exposed a hot spine of energy sizzling among the stars. But like radiologists puzzling over unusual smears on their films, astrophysicists are mystified by blurs that point to processes they don't yet understand.

Astronomers have known for 2 decades that x-rays stream from the galaxy's ridge, a band less than 1000 light-years thick that bisects the lenslike cross section of the Milky Way like a layer of cream cheese in a sliced bagel. Early satellites couldn't resolve the origin of the most energetic radiation, called "hard" x-rays. Most scientists felt that run-of-the-mill interstellar gas was too cool and diffuse to churn out so much hard radiation, so speculation centered on swarms of familiar objects, such as flaring stars. However, according to a report published online this week by *Science* (www.sciencexpress.org), new telescopes trained on the region haven't spotted any obvious x-ray sources speckling the ridge. "The apparently difficult scenario has come true," says astrophysicist Kazuo Makishima of the University of Tokyo in Japan.

The new observation comes from a team led by astronomer Ken Ebisawa of NASA's Goddard Space Flight Center in Greenbelt, Maryland, using the Chandra X-ray Observatory. In February 2000, Chandra stared for 25 hours at a nondescript patch of sky in the constellation Scutum. The patch, less than half the size of the full moon, sits on the galaxy's midsection but contains no bright x-ray sources. Chandra's exposure revealed at least 36 pinpricks of x-ray light. That's about the number of distant galaxies that Chandra resolves when it points at any swatch of space the same size. Because hard x-rays pierce the Milky Way, Ebisawa's team deduced that most of the pinpricks originated far beyond the galaxy, not within it.

The rest of the x-rays—about 90% of the

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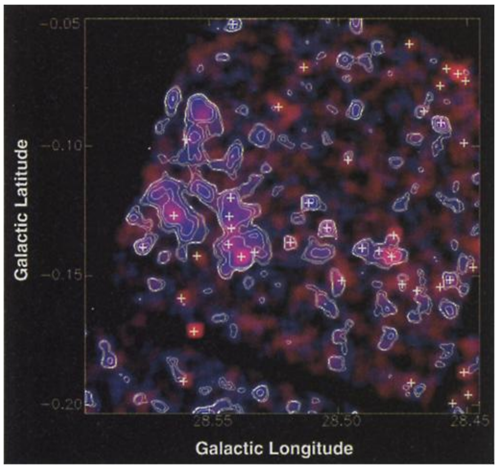


It's a gas. Most hard x-rays (blue) from the galaxy's disk stream from a smooth plasma, not from point sources (crosses).

energy in Chandra's field of view—formed a hazy fog. "We finally obtained an ability to see almost all of the sources of x-rays in the galaxy. The ridge emission is diffuse," Ebisawa says.

The details of Chandra's images leave little doubt, most reviewers say. "Their claim is clear and convincing," says astrophysicist Yasuo Tanaka of the Max Planck Institute for Astrophysics in Garching, Germany. However, astrophysicist Koji Mukai of NASA Goddard holds out hope that some of the emission may stream from quiescent dwarf novae: dim white dwarf stars that periodically flare in x-rays. "The debate will continue until we know more about the luminosities of dwarf novae," Mukai says.

Still, most researchers agree that the focus will shift to figuring out why the rarefied matter drifting among the stars glows so brightly in x-rays. "This component of the interstellar medium is not just a little thing," says astrophysicist Richard Mushotzky of NASA Goddard. "It dominates the pressure and the energy balance, and it's been completely ignored."

Several explanations have been proposed, each with its adherents and its problems. Makishima thinks the galaxy's rotation spawns magnetic fields in the interstellar medium that twist, snap, and reconnect in a large-scale, tenuous process akin to flares on the sun. If so, such magnetic torquings could heat plasma to tens of millions of degrees, the temperatures needed to produce hard x-rays. Astrophysicist Kotsuji Koyama of Kyoto University in Japan thinks frequent supernova explosions may suffice to heat the gas. However, other theorists say that the hot plasma would disperse too quickly to stay in the galaxy under either model.

Astrophysicist Azita Valinia of NASA headquarters in Washington, D.C., has another idea: low-energy cosmic rays. Electrons launched by supernovae may zing through the interstellar medium and ionize heavy atoms. Those interactions would spit out the right mix of energetic x-rays, Valinia believes. "You don't have to have strong magnetic fields or a very hot gas, which we don't know how to produce," she notes. Still, no one knows whether enough such cosmic rays exist, as the solar wind keeps them away from Earth.

Longer exposures might favor one model by unveiling patterns in the galaxy's x-ray haze, although it will be tough to get that much time on Chandra or its European counterpart, XMM-Newton. Meanwhile, expect theorists to have a field day. Says Mushotzky: "This raises all sorts of issues about the interstellar medium that people had been trying to suppress."

–ROBERT IRION

CREDITS: (TOP TO BOTTOM) K. EBISAWA *ET AL.*/CHANDRA X-RAY OBSERVATORY CENTER; JPL/NASA

2002 BUDGET

Fall Fight Looms Over Space Science Funding

Congressional lawmakers are at odds with each other and with the new Administration over which U.S. space science efforts should be funded—or cut—in 2002. The high-stakes legislative game affects plans for several important space projects, from Mars exploration to a successor for the Hubble Space Telescope. The politicians also want to shunt hundreds of millions of dollars into pork programs—a move likely to increase the pressure on NASA's strained budget.

The opening bids are laid out in vastly different 2002 spending plans that the House and Senate approved before leaving town last week for a monthlong break. Legislators will try to reach a compromise when they return, in time for the 1 October start of the 2002 fiscal year. "There are very dramatic differences, and there won't be a lot of money added in the end" to give both sides what they want, says Representative James Walsh (R–NY), who chairs the panel that funds NASA and the National Science Foundation. The sluggish economy and vanishing surpluses, he adds, are putting the screws on government spending for next year.

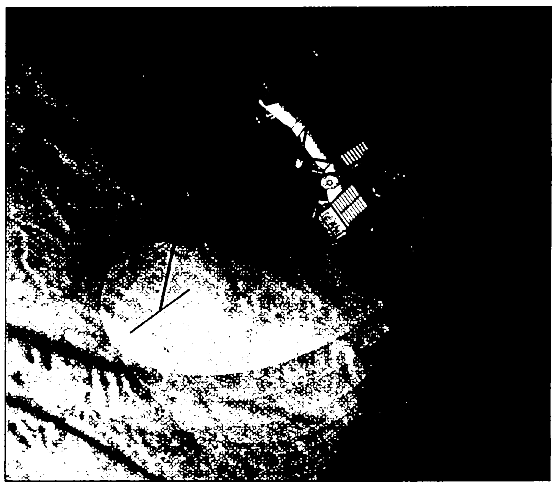
In the meantime, lawmakers have stacked up their NASA bargaining chips. The House chopped funding for programs such as the Next Generation Space Telescope favored by the Senate; the Senate, in turn, slashed spending for efforts such as Mars exploration backed by the House. And both chambers have their own beefs with the White House: The House wants to spend more money for research on the space station (*Science*, 20 July, p. 408), while the Senate approved $25 million to keep a Pluto mission on track that NASA canceled last year due to budget constraints (*Science*, 17 November 2000, p. 1270).

The Senate figure for Pluto isn't enough, says NASA space science chief Ed Weiler, who estimates that a 2004 launch will cost at least $75 million. Weiler also must contend with the Senate's decision to cut $49 million from NASA's request for an orbiter to visit Jupiter's moon Europa and put most of that money into a comprehensive outer planets program which would include a competed Europa mission.

The Europa effort currently is being handled by NASA's Jet Propulsion Laboratory (JPL) in Pasadena, California, which has been under fire for its Mars failures and high program costs. "We've already spent a lot of money on [Europa] planning," complains one NASA official, who adds that the technical challenges make JPL the best choice to build the necessarily complex craft. But competitors like such as Applied Physics Laboratory (APL) in Laurel, Maryland—in the home state of Senate spending subcommittee chair Barbara Mikulski—are eager for a shot at such a big endeavor.

Mikulski's panel also added $20 million to NASA's request for $40 million to develop a series of spacecraft to monitor the sun—which APL will have a significant hand in developing—and cut $50 million from the requested $431 million for Mars exploration. The Senate also wants NASA to move more of its spacecraft operations to contractors—a move that the Senate bets will save money but which could cost JPL hundreds of jobs. "I don't like it," says Weiler about the proposed transfer.

Despite their differences, the Walsh and Mikulski panels agree that NASA's budget is a good mechanism to fund unrelated pro-



Target. Senate wants labs to compete for a mission to Jupiter's moon Europa, under scrutiny here by proposed JPL orbiter.