Biology

Proteins that produce hunger . . .

Masashi Yanagisawa recently went fishing with 50 different lures. The scientist landed some prize catches: two proteins whose function in the brain is apparently to stimulate feeding. Yanagisawa, a Howard Hughes Medical Institute investigator at the University of Texas Southwestern Medical Center at Dallas, and his colleagues named the proteins orexins, after orexis, the Greek word for hunger.

The lures cast in their fishing expedition were receptors, proteins on the surface of cells that transmit signals into a cell when a molecule binds to them. Seeking the unknown binding partners for so-called orphan receptors, Yanagisawa and his team engineered cells to overproduce the cell surface proteins and then exposed the cells to extracts from brain tissue.

The researchers could tell when an orphan receptor had hooked a molecule by monitoring signaling events, such as waves of calcium ions, in the cells. They describe in the Feb. 20 CELL how this method eventually identified the orexins, both fragments of the same larger precursor molecule.

These catches were largely a mystery until the group determined where in the brain the protein's receptors are displayed. They show up primarily in a region called the lateral hypothalamus. "That was the first real clue," says Yanagisawa, noting that when this area is damaged, animals eat less and almost starve to death.

When the investigators injected the orexins into the brains of mice, the animals became voracious. Moreover, the gene encoding the orexins' precursor molecule became more active when animals were denied food, implying that the brain was trying to stimulate eating by making the orexins.

Yanagisawa's collaborators at SmithKline Beecham Pharmaceuticals in King of Prussia, Pa., are searching for possible appetite suppressants that would work by blocking the activity of the orexins.

Investigators expect that many brain proteins responsible for regulating feeding behavior remain at large. "There is little reason to suspect that the last of the important actors has been discovered, and so fishing expeditions will be trolling the hypothalamic waters in search of more big trophy catches," observe Jeffrey S. Flier and Eleftheria Maratos-Flier of Harvard Medical School in Boston in an accompanying commentary. —*J.T.*

. . . and a gene that causes hair loss

Hair loss can disturb the male psyche, but it's even more upsetting for women. No wonder Angela M. Christiano put her education to use when she was diagnosed with alopecia areta, a hair loss condition affecting more than 2 million people nationwide.

While the effort may not have resolved why she loses hair, Christiano, a geneticist at Columbia University, has now identified the first gene associated with human hair loss. She and her U.S. colleagues teamed up with scientists in Pakistan to study a family whose members frequently have alopecia universalis, a rare condition that results in no scalp or body hair growth after birth.

While closing in on the location of the responsible gene, the investigators began to wonder whether it might be the human version of a mouse gene that, when mutated, results in hairless rodents. Using the DNA sequence of the mouse gene, they found the human version in the chromosomal region they had targeted. In the Jan. 30 SCIENCE, the researchers reveal that the gene harbors a mutation in family members afflicted with alopecia universalis.

The gene encodes a transcription factor, a protein that regulates the activity of other genes. Christiano and her colleagues hope that their discovery will lead to the identification of more genes involved in human hair growth. Ultimately, such research may suggest new treatments to stem or reverse hair loss. —*J.T.*

Environment

Radon–lung cancer risk high for smokers

For 2 decades, scientists have been homing in on the lung cancer risks posed by chronic exposure to radon, a radioactive gas emitted by rocks and soil. Now, a blue-ribbon panel convened by the National Research Council in Washington, D.C., to review the most recent studies of radon's effects on health has confirmed earlier estimates.

In the United States alone, residential exposure to this ubiquitous gas causes between 15,000 and 22,000 lung cancers annually—or 12 percent of all such malignancies. Indeed, radon is second only to smoking as a source of lung cancer, the NRC stated in its report, released Feb. 19.

Cancer risk climbs with lifetime exposure to radon's toxic decay products, which are themselves radioactive. In the absence of any confounding risk factors, a doubling of exposure will double risk, the report says. However, cigarette smoking greatly magnifies any such risk. In fact, the new analysis finds that all but about 2,000 to 3,000 radon-related cancers in the United States each year occur among current or former smokers.

This suggests that "radon reduction may benefit smokers more than nonsmokers because of the strong combined effects of smoking and radon," observes Jonathan M. Samet, an epidemiologist at Johns Hopkins University in Baltimore and head of the NRC review.

Radon tends to build up in confined spaces, such as caves, mines, and houses. The Environmental Protection Agency has set 4 picocuries of radon per liter (pC/l) of air as the concentration at which homeowners should consider installing special ventilation equipment to flush out the gas. The new analysis finds that 30 percent of all radon-related lung cancers occur among people living in homes that exceed that concentration—and another 40 percent occur in dwellings where radon averages only 1.25 to 4 pC/l.

While there are uncertainties about whether radon poses additional hazards—such as the development of fibrous tissue in the lung—the NRC concludes that radon's carcinogenicity has been "convincingly documented." —*J.R.*

Fine-tuning federal water policies

Also on Feb. 19, President Clinton unveiled his Clean Water Action Plan, a strategy for protecting the nation's waters and cleaning up polluted aquatic areas. The plan, which calls for more than 100 new and expanded programs, requires no new legislation, explains Environmental Protection Agency spokesperson Robin Woods. However, enacting the proposed changes will demand a boost in the nation's water protection budget. Clinton will be asking Congress for $2.3 billion over the next 5 years.

Among key elements is a recommendation to unify or coordinate programs affecting a common watershed—such as the Chesapeake Bay—that may now be fragmented among many federal agencies. At present, runoff of fertilizer and pesticides from farms might be managed by one program, efforts to control air pollution raining into the bay might be handled out of another, logging of erodible lands upstream might be regulated by a third, and safeguarding threatened or endangered fisheries might be coordinated by a fourth.

The plan also seeks to reduce pollutants and parasites—from methyl mercury to *Pfiesteria*—that threaten the safety of fish and shellfish, to establish new quantitative limits on pollutants that can enter specific waterways, to develop 100,000 additional acres of wetlands per year by 2005, and to remove or relocate 5,000 miles of roads each year that foster erosion of stream banks or carry pollution from motor vehicles into waterways.

Finally, the plan recommends a host of new research ventures, including a national survey of contaminants in fish and shellfish by 2000. —*J.R.*