toward higher frequencies, and the short 1450-year cycle leaps above this trend, dominating polar circulation on time scales of 3000 years and less. "It's definitely one of the big players," says Mayewski. "It pins every one of the rapid climate change events," abrupt coolings that chilled Greenland by more than 10°C in less than 10 years at intervals during the last ice age.

Too rapid to be tied directly to the behavior of the sluggish ice sheets, the 1450-year cycle may instead be linked to an inconstant sun, Mayewski says, an idea other researchers have suggested for cycles of 80, 208, 512, and 2300 years found in a variety of other records and now in the GISP2 core. Like these other cycles, he says, the 1450-year one also shows up in tree-ring records of carbon-14, which is produced in the upper atmosphere by cosmic rays that vary with solar activity.

"We have an amazingly close correspondence with the carbon-14 record," says Mayewski, a fact he considers to be strongly suggestive of a solar link. What's more, the GISP2 record of beryllium-10—a more reliable measure of solar activity that is produced along with carbon-14—closely tracks that of carbon-14, says Robert Finkel of Lawrence Livermore National Laboratory, who analyzed the beryllium-10 with Kuni Nishizumi of the University of California, Berkeley.

Still, attributing any climate change to a change in the sun is likely to draw suspicion. Although new studies have fueled a revival in sun-climate links (*Science*, 8 March, p. 1360), such revivals have come and gone before, leaving a hard core of skepticism among many researchers. The beryllium-10 data—which few outside the team have seen yet—will have to be a very good match to win any converts, says Lehman. And some time-series analysts would like to see more statistical work on the identification of the 1450-year cycle, among others. The New Hampshire group's technique "needs to be tested by other methods," says Teresa King of UDP Consulting in Portland, Oregon. And when compared to other types of records, the ice cores don't always yield a perfect match. For example, although Bond sees evidence of Heinrich events in marine sediments, he sees no sign of the 6100-year cycle, for reasons no one can yet explain.

But the 1450-year cycle and others have passed at least one outside test. Pascal Yiou of the CEA-DSM in Saclay, France, applied different statistical methods to the records of a second Greenland ice core, drilled by a European consortium called GRIP, and to the Russian Vostok core from Antarctica and found similar periods as in GISP2. "I don't know if they are real," he says, "but at least they are reproducible." Clearly, the study of climate cycles is on an upswing.

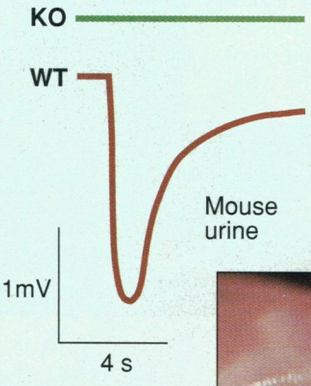
–Richard A. Kerr

NEUROBIOLOGY

Mutant Mice and Worms Help Solve Mysteries of Olfaction

Geoffrey Gold, a physiologist at the Monell Chemical Senses Center in Philadelphia, had wanted for years to put to rest a nagging question: How do odors trigger olfactory neurons to fire off action potentials to the brain? The dogma for the past 5 years had been that odors fall into two categories, each of which acts via a different intracellular messenger molecule. But Gold believed this view was wrong, and that all odors work by increasing the production of the intracellular messenger cyclic AMP (cAMP). One day last spring, Gold got a phone call out of the blue from neurobiologist John Ngai, at the University of California (UC), Berkeley, offering the possibility of answering this question. "It was my dream come true," says Gold.

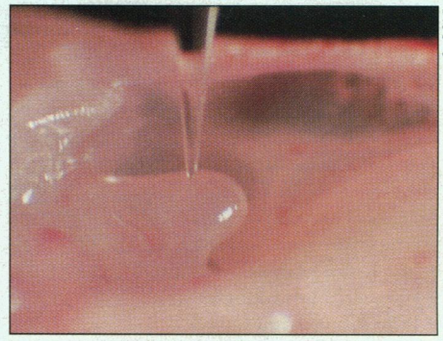
Ngai and his co-worker Lisa Brunet had made knockout mice whose olfactory neurons were missing an ion channel that cAMP must open in order to cause the neurons to fire. He invited Gold to test the mutant animals' response to smells. A month later Gold began the experiment, and the results were stunning—so much so that he thought his equipment wasn't working. "I was getting all these flat traces," he says, "I thought there was something wrong with my setup." But there wasn't anything wrong. The neurons were simply not responding at all to any of the odors Gold tested, implying that the mutant mice couldn't smell a thing. That finding, which is reported in this month's issue of *Neuron*, shows that the cAMP-activated ion channel is essential for the sense of smell. And that, says Gold, means cAMP is in fact the universal intracellular trigger for odor detection in mammals.



While not everyone in the olfaction field agrees with Gold that the case is closed, "the good thing about this [work] is that it activates this controversy and may stimulate people to go back and do more experiments," says Columbia University neurobiologist and olfaction researcher Stuart Firestein. And it has implications that reach far beyond olfaction. "I am excited because it is going to point to the role that these channels play in other organ systems," says neuroscientist William Zagotta, of the University of Washington, Seattle.

Indeed, ion channels activated by cAMP or a related cyclic nucleotide called cGMP may play roles in other sensory systems besides olfaction, and also in embryonic development and heart and brain function. The knockout mice, along with two mutant strains of the nematode *Caenorhabditis elegans* reported in the same issue of *Neuron*, promise to help researchers understand these myriad biological functions. In addition, the complete knockout of smell in the mice will make them useful in answering questions about the role of smell in mammalian behavior.

Ngai and Brunet didn't have such ambitious goals when they began the mouse project. They wanted to study mechanisms of olfaction, including the role of cAMP. Olfactory researchers have known since the late 1980s that many odor molecules raise cAMP levels in olfactory neurons in a variety of animals, and that cAMP can activate an ion channel that causes the neurons to fire. But Heinz Breer and his colleagues at the University of Stuttgart-Hohenheim in Germany had found that some odorants seem to trigger little or no rise in cAMP, and instead cause a burst in concentrations of another intracellular messenger molecule, inositol trisphosphate (IP_3). Breer's finding was complemented by work from Diego Restrepo at Monell and his colleagues, who found an IP_3-activated ion channel in olfactory neurons. That suggested that odor responses fall into two classes, one


G. GOLD

Flat-liner. Electrodes placed in mouse olfactory tissue *(above)* record action potentials from normal mice (WT) in response to odors like mouse urine. Knockout (KO) mice show no response.

that triggers the neurons to fire via IP_3, and the other via cAMP.

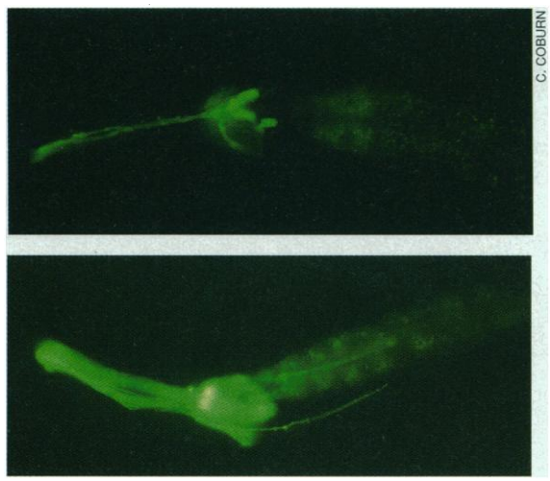
"If you pick up any review dealing with olfactory signal transduction in the past 5 years, the dual-messenger hypothesis is right out there," says Ngai. "But when I compare side by side all the evidence for [the two messengers], I am not satisfied." Ngai and others are not convinced, for example, that the IP_3 increase occurs in the sensory endings of the neurons, where odorant binding takes place, or that it has been reliably shown to open an ion channel. To try to settle the issue, he and Brunet knocked out the gene that codes for the cAMP-activated channel found in olfactory neurons in mice. The mutant animals, they reasoned, should lose the ability to smell odors that depend on cAMP, but remain able to smell any odors that work through IP_3.

Ngai and Brunet sent Gold several mice that were pregnant with mixed litters of mutant and normal pups. When the pups were born, Gold recorded electrical activity from their olfactory epithelium—the surface in the nose that contains the smell-sensing neurons—while exposing the tissue to a variety of odorants, one by one. In epithelium taken from some of the pups, all the odorants produced a normal response, while they produced no responses at all in epithelium from others. And in every case the flat-liners turned out to be the knockouts.

"This would imply that unless there is something very unusual going on, all odorants do in fact mount a cAMP response," says Gabriele Ronnette, an olfaction researcher at Johns Hopkins University. This is in accordance with the thinking of many olfaction researchers that the proposed role for IP_3 made it into review articles and textbooks a little too fast and may be wrong. The Ngai, Brunet, and Gold paper "confirms what most people believe," says Harvard University olfaction researcher Linda Buck, "and that is that [cAMP] is the major pathway" for sending olfactory signals to the brain. While Buck and others agree with Breer that some odors trigger IP_3 production, they suggest that IP_3 may just be modulating the response to those odorants made by the cAMP-activated channels.

But that second-fiddle role for IP_3 "is not the only conclusion that is consistent with the [Ngai team's] data," says Monell's Restrepo, one of the strongest proponents of the dual-messenger hypothesis. He notes that the Ngai team has not checked to see whether the IP_3 signaling pathway is intact in the mutant mice, and proposes that elimination of the cAMP-activated channel might indirectly sabotage IP_3 signaling. That is possible, Ngai admits, but most researchers consider it unlikely. Ngai plans to send knockout mice to Restrepo so he can check IP_3 function.

If the Ngai group's conclusions are correct, cAMP is the central messenger in mouse olfaction. But the same is not true in worms, according to the accompanying papers in *Neuron* by Cori Bargmann and Cara Coburn of UC San Francisco, and Yasumi Ohshima and his colleagues at Kyushu University in Fukuoka, Japan. Bargmann's and Ohshima's teams studied worms that are mutant in a cyclic nucleotide–activated channel similar to the one knocked out in mice by Ngai and Brunet, and found that it is necessary for some—but not all—olfactory responses. They also showed that in worms the channel is needed for other sensations, including taste and temperature sensation.



C. COBURN

Wrong way. In mutant *C. elegans (lower panel)*, a salt-sensing neuron sends its axon in the wrong direction, back toward the animal's tail.

The findings provide the first evidence that a cyclic nucleotide–activated channel plays a role in sensation in worms, says Bargmann, and they establish the first strong parallel between the olfactory systems of worms and mammals. But Columbia's Firestein is more intrigued by the contrast between the two sets of results. While the mice that lack the channel are completely unable to smell, the worms can still smell and respond to some substances. "Clearly you have some sort of a second pathway" that operates in some of the worm's olfactory neurons, he says. There is no indication of what the other signal is, but he suggests it could be IP_3, which has been shown to figure in olfaction in other invertebrates such as lobsters.

Martin Chalfie, who studies sensation in worms at Columbia University, is even more excited about another sensory system implicated in the Bargmann and Ohshima groups' findings: the system for sensing temperature. Temperature sensation is an important sense that "we know very little about" in any species, he says, and the discovery that a cyclic nucleotide–activated channel is involved is an important "breakthrough." It will now be possible to follow up on that lead, he says, and use worm genetics to further dissect the mechanisms of temperature signaling.

There is also evidence, Bargmann says, that the channel mutations in the worms disrupt the development of sensory neurons needed to respond to a taste (salt) and a pheromone that warns the worms of overcrowded conditions. She and Coburn found that as the young worms develop, the axons of those neurons grow abnormally, going past the neurons they should connect with, or heading into "the wrong neighborhood" altogether. She plans to follow up on how the channel helps guide axons to their destinations.

The knockout mice, too, promise to be good tools for exploring neural development. Researchers suspect that the response of olfactory neurons to odors may be needed for the neurons to wire up correctly to the brain. Because the neurons in the mutant mice can't respond to odors, they provide an ideal way to check how that wiring proceeds without olfactory sensation.

Indeed, the fact that the mice can't smell at all makes them useful for another avenue of research that has nothing to do with cAMP—the role of olfaction in behavior. Mice, like other mammals, have two separate systems for sensing volatile chemicals—the olfactory system, and the vomeronasal organ (VNO), which is thought to detect chemicals associated with sexual behavior. To sort out which system is responsible for a behavior, such as the selection or rejection of a mate, researchers can destroy the vomeronasal system, and in this way they have ascribed some behaviors to the VNO and others to olfaction. But it has been hard to check their results with the reciprocal experiment, because it is "very difficult to get 100% elimination of olfaction," says Monell neuroscientist Charles Wysocki. The knockout mice, if they have a normal VNO as researchers expect, will be in demand for behavioral research.

But the broadest use of the mice will be in understanding the various biological roles of the cyclic nucleotide–activated channels, says Washington's Zagotta. Until recently, the channels were known only in the visual and olfactory systems, but they have been popping up recently in many different organ systems, including the pacemaker of the heart and parts of the brain including the hippocampus—a center of learning. As the channels move onto center stage, the mutant mice and worms are going to be hot items for studying them.

–Marcia Barinaga