Animal Genes Illuminate Human Sleep

A decade-long search through the genes of drowsy dogs has unexpectedly crossed paths with a high-tech survey of the nocturnal activities of mutant mice. These two studies have yielded a dramatic insight into what compels people to spend one-third of their lives in the unconscious state known as sleep.

Scientists have found two related genes, one in dogs and one in mice, that when mutated in these animals produce the sleep disorder narcolepsy. The findings may lead directly to new treatments for people with narcolepsy and may help scientists develop better sleeping pills.

People with narcolepsy tend to fall into a deep sleep suddenly during the day and usually have trouble sleeping at night. Laughter or intense emotions may cause them to abruptly lose all muscle control while still awake, a condition called cataplexy.

This perplexing disorder has long fascinated Emmanuel Mignot of the Stanford University School of Medicine, who maintains a colony of Doberman pinschers that suffer from a canine form of narcolepsy. The dogs inexplicably doze off in the middle of activities and can collapse in cataplexy when they become too excited.

While the genetics of human narcolepsy appears complex, the dog form of the disease clearly stems from one gene. About 10 years ago, Mignot decided to track down this gene, a formidable task since little was known about canine genetics. "Everyone said I was slightly delusional," he recalls.

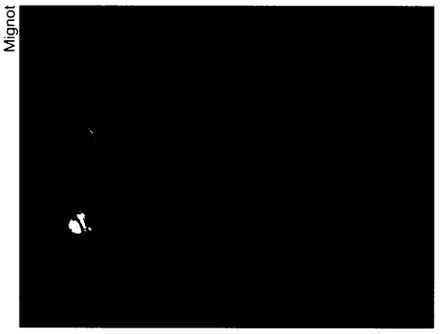
By looking at patterns of DNA sequences inherited by narcoleptic dogs but not unaffected ones, Mignot and his colleagues closed in on a portion of dog chromosome 6 where the putative narcolepsy gene must reside. In the end, they found that Dobermans with narcolepsy have a mutation, an inserted bit of DNA, in a single gene in that small region. Several Labradors with narcolepsy also have a mutation, a deletion, in the same gene.

"The search was excruciating, but the prize was worth it," says Mignot.

As reported in the Aug. 6 CELL, that prize is a gene called *hypocretin receptor 2*, which encodes a protein that sits on nerve cells. This receptor responds to hypocretin 1 and hypocretin 2, recently discovered neurotransmitters formed from a single precursor protein.

The link between the hypocretins and sleep rests on more than Mignot's findings. In the Aug. 20 CELL, scientists from the University of Texas Southwestern Medical Center at Dallas will report that mice lacking the two neurotransmitters develop a condition similar to human and canine narcolepsy.

Mignot



Two narcoleptic dogs experiencing cataplexy, or loss of muscle control.

Masashi Yanagisawa of the Howard Hughes Medical Institute at UT Southwestern has a different name for the hypocretins. He calls them orexins, after the Greek word for hunger, because last year his group found that injecting the chemicals into mice made the animals hungry (SN: 3/7/98, p. 159). His group has now bred mice with a mutation in the gene for the precursor protein of the two neurotransmitters.

The scientists noticed few changes in the mutant animals until they used an infrared video camera to film the rodents at night, when mice are normally most active. "The mice are running around, grooming, eating, whatever, and they stop abruptly, oftentimes falling over to the side. They don't move at all, as if they're dead," says Yanagisawa. "After one or two minutes, [they] resume normal activity, as if nothing happened."

Over a 4-hour period, a mouse might experience as many as 27 of these episodes, which the researchers initially thought were seizures. To address that hypothesis, they implanted tiny electrodes that record the electrical activity of the mouse brain. They learned that mutant mice weren't having seizures. They were suddenly falling into the stage of deep sleep known as REM sleep. Some of the episodes might also be cataplectic events, notes Yanagisawa.

His collaborator Clifford B. Saper of Beth Israel Deaconess Medical Center in Boston has also shown that the brain cells that produce the orexins connect to brain regions involved in wakefulness and sleeping. Moreover, Saper's group discovered that modafinil, a drug prescribed for people with narcolepsy, activates the orexin-making brain cells. "It's very good at keeping you awake, but no one knew how it works," says Saper.

Taken together, the new findings suggest that the hypocretins/orexins help keep animals awake. Do people with narcolepsy have mutations in the genes for the neurotransmitters or their receptors? A few might, says Mignot, but he suspects most have more subtle problems with this neural system.

Still, administering hypocretins/orexins may help treat narcolepsy, he notes. Drugs that block the receptors for the compounds could also prove superior to current sleeping pills, which rarely generate normal REM sleep. "Suppressing the orexin system might lead to a more natural mode of sleep," says Yanagisawa.

Investigators also suggest that these new neurotransmitters will help explain the many documented links between feeding and sleeping. "The orexin cells are probably involved in the arousing aspect of feeding," says Saper. "You've got to be awake to hunt and eat, and there are few things more arousing than food. There are also very few things that make you feel more content and want to go to sleep than a big meal." —*J. Travis*

Seabed slide blamed for deadly tsunami

A year after giant waves swept away 2,200 residents of Papua New Guinea, the disaster has claimed its final victim: the prevailing theory about what causes tsunamis.

Experts on these waves typically attribute them to undersea earthquakes, but evidence collected during marine surveys off the New Guinea coast implicates a submarine landslide or slump, reports the expedition team.

"There is no doubt that there is a shift—a sea change—in interpretation," says David R. Tappin, a coleader of the surveys and a marine geologist with the British Geological Survey in Nottingham.

"This really is one of those big paradigm shifts in science," says team member Philip Watts of Applied Fluids Engineering in Long Beach, Calif., who uses computer models to simulate tsunamis. "We suspect that a lot of the bigger, known tsunamis involved some landsliding."

The Papua New Guinea tsunami, a train of three monster waves, struck the north shore on July 17, 1998 (SN: 10/3/98, p. 221). Ever since then, researchers have struggled to explain how a moderate earthquake, of magnitude 7.1, could have heaved up a tsunami reaching 15 meters tall. Some speculated that the shaking caused an underwater sediment slide large enough to spawn the waves.

In January, a team of researchers boarded a Japanese ship to survey the seafloor. It was the first such intense study after a

tsunami. In this expedition, they mapped the seabed and drilled samples of sediments. In late February, they used a robotic sub to photograph the seafloor.

The scientists described their findings at a July meeting of the International Union of Geodesy and Geophysics in Birmingham, England, and in the July 27 EOS.

The exploration focused on the continental slope, which plummets into a 4-kilometer-deep trench. This chasm marks where a piece of the Pacific Ocean floor crashes into New Guinea. As the Pacific tectonic plate scrapes beneath the island, it creates the deep trench and sparks frequent earthquakes.

The survey found that the extremely steep continental slope bears a thick carpet of sediments. In places, this coating has slid downhill in speedy landslides and slower-moving slumps.

On one dive, the researchers discovered a fresh, amphitheater-shaped scar, created when a giant chunk of sediment slumped downhill. "We know this slope failed sometime in the past," says Watts. "The mystery is, When did it go?"

The researchers also found a 15-km-long fault that showed evidence of recent movement. Faulting of the seafloor can generate tsunamis when one side jumps up and the other side drops, displacing water in the process.

Tappin, Watts, and others who think a slump caused the waves contend that the fault could not be the source. Eyewitness accounts indicate that the first wave struck shore about 20 minutes after the main shock of the earthquake, too long for the tsunami to have originated from subsea faulting during the quake. A slump, however, typically lags several minutes after an earthquake and could explain the delay.

When Watts modeled the tsunami, he obtained better results using an undersea slump than a sea-bottom quake. "I'm convinced that the main part of the tsunami was generated by one giant slump," he says.

Further support comes from a 70-second-long rumble recorded in the middle of the Pacific soon after the earthquake. This sound lasted too long to have come from a small aftershock and may represent a seafloor slide, says Emile A. Okal of Northwestern University in Evanston, Ill.

Some survey participants, however, discount the slump theory. Harry Yeh of the University of Washington in Seattle argues that simulations of a subsea quake can explain the tsunami's size. The team found evidence for small slides but no obvious signs of a giant slump, he says.

Whatever the outcome of the debate, the recent tsunami is forcing researchers to consider slumps as potential sources of giant waves, says Eddie Bernard, coordinator of the National Tsunami Hazard Mitigation Program in Seattle. "I think the good thing that this has done is to open our eyes."

The disaster also suggests that relatively modest quakes, such as the kind that occasionally rock southern California, can trigger giant tsunamis by setting off slides. "This makes the hazard much more dangerous than the scientific community has perceived it in the past," says Bernard. —*R. Monastersky*

Hormone mimics: New assessments air

Dishwashing detergents, pesticides, and even contraceptives contain nonylphenols or compounds that break down into nonylphenols. These chemicals are members of a group that mimic hormones and appear to harm wildlife. Nonylphenols taint waterways throughout the world, especially those downstream of municipal waste treatment plants.

Given half a chance, however, waterborne nonylphenols will take to the air, a new study finds. Their evaporation from water allows the chemicals to travel long distances before settling down again—potentially on land far from water, notes study leader Steven J. Eisenreich of Rutgers University in New Brunswick, N.J.

Using a chemical fingerprinting technique known as gas chromatography, his team identified pollutants in water in the Hudson River estuary and in air nearby. Their work, reported in the Aug. 1 ENVIRONMENTAL SCIENCE & TECHNOLOGY, turned up both water and air pollutants with "an unequivocal match" to the signature of nonylphenols.

The data, the first showing these pollutants in the atmosphere, detected airborne amounts ranging from just above zero to 70 nanograms per cubic meter, which the researchers regarded as a "high concentration." Eisenreich says, "Water was definitely the source of these chemicals in the air."

The Rutgers chemists suspect airborne nonylphenols are "ubiquitous" worldwide. Because nonylphenol concentrations in some European rivers are 10 to 100 times as high as in the Hudson estuary, the airborne chemicals are perhaps even more prevalent elsewhere in the world than in the area studied. The air data raise concern about new routes of human exposure, the scientists say.

Their finding disturbs Susan Sang of the World Wildlife Fund Canada in Toronto, which advocates a phaseout of surfactants that degrade to nonylphenols. When nonylphenol concentrations in water diminish, it has looked like the pollutants were breaking down, Sang says. "It now appears they were just evaporating and moving to where you wouldn't have expected to find them," she says.

Fish exposed to nonylphenols have developed reproductive and other abnormalities (SN: 5/8/99, p. 293). Because of such findings, Sang notes, Canadian officials have recommended that pregnant women avoid nonylphenol exposure.

The Canadian government is also assessing nonylphenol risks. If its findings, due next spring, indicate the pollutants are toxic, the government could require monitoring or even limit nonylphenol release, notes Philippa Cureton of Environment Canada in Hull, Quebec.

Determining whether such pollutants pose risks to people, however, will generally require much more research, concludes a panel convened by the National Research Council (NRC) in Washington, D.C. It released a report of its 4-year assessment of the toxicity of hormonelike chemicals last week.

"We couldn't find any clear evidence that people had been harmed by typical environmental exposures to hormonally active chemicals," observes panel member James C. Lamb IV, a consulting toxicologist in Reston, Va.

Then again, few studies have probed for effects in humans, argues panelist Ana M. Soto of the Tufts University School of Medicine in Boston. A further limitation of the new assessment, she maintains, was its "focus on correlations between one chemical and an effect." Most people face coincident exposures to several hormone mimics—such as nonylphenols, phthalates, and PCBs—and her own studies indicate that the effects can be "at least additive," she says.

When it comes to wildlife, "there was clearly evidence of very negative reproductive effects in populations exposed to chemicals commonly called endocrine disruptors," notes panelist Joanna Burger from Rutgers. The NRC consensus report "doesn't dismiss these findings," she says. Indeed, she notes, it documents many of the hormonal mechanisms that are likely responsible.

Though many pollutants may exhibit hormonal activity, few studies have proved that such hormonal action is responsible for the toxicity of these agents, says panel chair Ernst Knobil from the University of Texas Medical School at Houston. He says that one of his committee's "most radical" actions was to "abandon the term *endocrine disruptor*" to describe hormone mimics.

To Lamb, this decision indirectly challenges the value of a new federal program to screen all commercial U.S. chemicals for hormonal action (SN: 10/17/98, p. 251). He says, "I'm concerned that we'll spend all this money chasing hormones—with no certainty that it will help us predict risks." —*J. Raloff*