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.

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