

To sleep, perchance to rest (in the daytime)

A newly identified compound selectively blocks receptors for the protein that narcoleptics lack. The drug has the apparent capacity to put wakeful people to sleep.

For years, researchers interested in the regulatory mechanisms of the sleep-wake cycle have studied narcolepsy, a disorder of excessive daytime sleepiness that occurs in some mammals, including dogs, rats, and humans. Investigators led by François Jenck at Actelion Pharmaceuticals (Allschwil, Switzerland) found the drug, known as ACT-078573, after screening new compounds for the ability to block orexin receptors. Orexins are neuropeptide hormones produced by certain neurons in the brain—neurons that degenerate in human narcoleptics. One role of orexins is to regulate wakefulness, although these proteins have also been associated with modulating addictive behavior.

In separate trials, Jenck's group administered the drug orally to rats, dogs, and humans during periods of normal wakefulness (*Nat. Med.*, February). In effect, the drug put the subjects to sleep in a

dose-dependent manner. One common phenomenon associated with narcolepsy is cataplexy, a state of muscle paralysis often induced by intense emotion—mirth or fright, for instance—but no signs of cataplexy were observed in any of the study's subjects. Moreover, other side effects commonly associated with some sedatives, such as feelings of drunkenness or 'abnormal coordination', were rarely associated with the drug's use in humans.

Despite its ability to induce sleep, the drug does not appear to be a good candidate for insomnia treatment. Orexins are produced primarily during normal waking hours, and although the drug caused sleepiness when administered to dogs and rats during normal waking time, there was no such effect during normal sleep periods. Nevertheless, the drug may prove to be effective in helping



shift workers, sufferers of jet lag, and others who try to sleep during daytime hours.

In addition, the drug holds promise for addicts because orexins have been implicated in addiction-associated pathways. In some studies, mice that lack orexins resist overeating and some of the behaviors typical of morphine addiction. Although this connection between orexins and addiction is still not well understood, it presents the possibility that a drug blocking the orexin receptors may be therapeutic for addicts.

Owen Young

TO CATCH A KILLER GENE

Combining genetic screening with pathogenicity testing in mice, a recent study reports the progress of a research group seeking to tap the mysteries of *Burkholderia pseudomallei*—and may lead to a vaccine or other treatment against this deadly bacterium.

The developing world is rife with infectious pathogens all but unknown in the United States and other developed nations. *B. pseudomallei* is one such dangerous pathogen, for which there is no vaccine, no reliable treatment, and a dearth of information about its pathogenesis. *B. pseudomallei* causes melioidosis in mammals, a disease endemic to Southeast Asia and characterized by symptoms that vary from fever, pneumonia, and body aches to parotid abscesses and neurological abnormalities. Many experts believe that *B. pseudomallei*'s ability to colonize most of the body's organs, coupled with its intrinsic resistance to many antibiotics, make it a natural candidate for bioterrorism. The physiological sources of the bacterium's virulence are still largely unknown.

For that reason, Brendan Wren at the London School of Hygiene and Tropical Medicine (London, England) and his colleagues modified a technique called signature-tagged mutagenesis (STM) to aid in the identification of virulent genes in the *B. pseudomallei* genome. In essence, STM uses transposons to

randomly insert short gene sequences into a bacterial genome, creating mutants that researchers screen for pathogenicity. Presumably, mutants with attenuated virulence have transposon inserts in genes involved in the pathogenesis of *B. pseudomallei*.

Wren and his coworkers created 892 such mutants in *B. pseudomallei* and tested these mutants for virulence in female BALB/c mice (*Infect. Immun.*, March). They identified 39 attenuated mutants, of which one had a transposon insertion in the *aroB* gene, which encodes an enzyme in the shikimate metabolic pathway. Wren's group then attempted to vaccinate mice with this attenuated mutant strain of *B. pseudomallei*—dubbed mutant 13B11—against wildtype *B. pseudomallei*. Although this novel vaccine did not ultimately protect the mice against *B. pseudomallei* infection, the treatment did increase the survival time of the vaccinated mice.

Such progress is encouraging, but hopefully only the first steps of many. "We continue to study the protective efficacy of other mutants identified as live attenuated vaccines during our study," Wren tells *Lab Animal*. "The shikimate pathway," he continues, "is missing in mammals, meaning that drugs targeting dehydroquinate synthase (the product of the *aroB* gene disrupted in mutant 13B11) may be of use in the treatment of melioidosis."

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