First Molecular Pathway Known to Regulate Rest and Wakefulness

By Stephen Bradt

Working with sleep-deprived fruit flies, scientists at the University of Pennsylvania have uncovered the first molecular pathway, in any species, implicated in the shift between rest and wakefulness.

The findings, from a team led by **Joan C. Hendricks** of Penn's Center for Sleep and Respiratory Neurobiology were reported in the November issue of the journal *Nature Neuroscience*. The work indicates that a *Drosophila melanogaster* gene known as CREB — evolutionarily conserved in species from flies to humans — plays a role in rest's rejuvenating effects, apparently permitting sustained wakefulness.

Anyone who's ever pulled an all-nighter knows by the next morning that sleep is essential, and sleep's status as a behavior found in organisms ranging from fruit flies to frogs to humans underscores its importance as a biological process. But 50 years after the discovery of REM sleep, scientists still know little, on a molecular level, about why sleep is needed and the exact benefits conferred by a daily period of rest.

The Penn researchers say that in addition to offering answers to such fundamental questions, the new work could help improve the efficacy and safety of the ways people alter their sleep patterns.

"If we can get at basic mechanisms of how sleep is normally controlled, and what it does for us, we can start to think of how to control, manage and improve sleep," said Hendricks, the Corinne R. and Henry Bower Professor of Medicine at the School. "This would be helpful for people subjected to changes in sleep schedules and for people with sleep disorders."

Hendricks' group first described *Drosophila* sleep in a paper published last year in the journal *Neuron*. Rest in flies shares numerous similarities with human sleep, including prolonged immobility, decreased sensory responsiveness and a need to compensate after sleep deprivation. Fruit flies spend about six to 10 hours a day resting, mostly at night.

"The sleeping flies lie prone in a quiet corner, unresponsive to stimuli, for bouts averaging about 45 minutes but sometimes lasting up to two-and-a-half hours," Hendricks said. "These sessions are interspersed with very brief, one- to two-minute interruptions, during which they eat and groom and then settle back down."

The Penn researchers' new findings indicate that the activity of CREB, short for cyclic AMP response element binding protein, is inversely related to the physiological urge for rest. The need for sleep after a phase of deprivation — attained through the mechanical agitation of fly habitats roughly every 15 seconds for as long as six hours — surged in flies whose CREB activity was blocked. In normal flies, CREB activity remains elevated for some 72 hours after such a prolonged period of wakefulness; CREB mutants slumber even longer than normal flies in the aftermath of deprivation.

CREB, which is evolutionarily conserved in species from slugs to mice to humans and already known to function in cyclic AMP signaling, is also known to play an important role in learning in fruit flies. Hendricks' work could strengthen the link that many researchers believe exists between rest and the consolidation of memory.

The Penn group is continuing its studies of how CREB is turned on, as well as the target genes affected by its activity. They suspect that CREB activation during rest may somehow optimize the function of the central nervous system during waking hours.

Hendricks' co-authors on the *Nature Neuroscience* paper are **Julie A. Williams**, **Karen Panckeri**, **David Kirk** and **Amita Sehgal**, all of Penn, and Marcela Tello and Jerry C.-P. Yin of the Cold Spring Harbor Laboratory in New York. Their work is funded by the National Institute of Heart, Lung and Blood and the Howard Hughes Medical Institute.

Director of Development for VHUP Appointed

Donna M. Carlson has been appointed director of development for VHUP.

Ms. Carlson served as director of development for Eagleville Hospital for three years. Previously she was in several positions over a six-year period at Holy Family College. She received her undergraduate degree in economics from Holy Family College. Donna owns a great Pyrenees and has been a VHUP client.

Cystinuria Study in the Maned Wolf

Dr. Paula Henthorn, associate professor of medical genetics, received a three-year grant from the Morris Animal Foundation to continue studies of cystinuria in the maned wolf. The maned wolf, a threatened South American canid species, has a high incidence of this hereditary disease that results in cystine stone formation. The study is an extension of the ongoing studies of cystinuria in dogs. The preliminary studies were carried out by **James Kehler, V'02**, a student in the School's V.M.D./Ph.D. program. It is worth noting that **Dr. Kenneth Bovee** studied cystinuria in the maned wolf back in the 1970's and 1980's, and that the Metabolic Screening Laboratory in the Section of Medical Genetics has been providing urine screening for the past 20 years as a service for North American zoos and wildlife sanctuaries that maintain maned wolves. The current studies are an extension these previous studies, and we can now use molecular genetics approaches to understanding the disease.