Study shows new evidence of age-related decline in the brain's master circadian clock

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(Medical Xpress) -- A new study of the brain's master circadian clock — known as the suprachiasmatic nucleus, or SCN — reveals that a key pattern of rhythmic neural activity begins to decline by middle age. The study, whose senior author is UCLA Chancellor Gene Block, may have implications for the large number of older people who have difficulty sleeping and adjusting to time changes.

"Aging has a profound effect on circadian timing," said Block, a professor of psychiatry and biobehavioral sciences and of physiological science. "It is very clear that animals' circadian systems begin to deteriorate as they age, and humans have enormous problems with the quality of their sleep as they age, difficulty adjusting to time-zone changes and difficulty performing shift-work, as well as less alertness when awake. There is a real change in the sleep–wake cycle.

"The question is, what changes in the nervous system underlie all of that? This paper suggests a primary cause of at least some of these changes is a reduction in the amplitude of the rhythmic signals from the SCN."

The SCN, located in the hypothalamus, is the central circadian clock in humans and other mammals and controls not only the timing of the sleep–wake cycle but also many other rhythmic and non-rhythmic processes in the body.

The UCLA research team examined the SCN in mice and found that while critical neural activity rhythms were already disrupted in middle

age, the molecular mechanisms that generate these rhythms were not significantly altered.

"These results indicate that the outputs of the central circadian clock start to decline in middle age and suggest that the same may be true in humans," said study co-author Christopher Colwell, a UCLA professor of psychiatry and biobehavioral sciences who has conducted research with Block for many years. "Before this study, we did not know that the SCN was the site where the decline occurs."

In a technical tour de force, the research team successfully recorded electrical activity from the brain's SCN — not in a Petri dish but in living animals. The research marks the first time this has been achieved in middle-aged animals and the first time scientists have watched the central biological clock of aging animals in action. The study was published July 13 in the Journal of Neuroscience, the journal of the Society for Neuroscience.

The scientists studied young mice, which were just a few months old, and middle-aged mice, which were more than a year old. SCN brain cells are electrically active during the day and electrically silent during the night in younger animals and younger people, the researchers said, but that difference is reduced with aging.

"The changes we observed in the electrical rhythm between the young and middle-aged animals, which are quite dramatic, occur even though we do not see significant changes in the underlying molecular rhythm," Block said. "Our hypothesis is that the age-related changes in the circadian timing system are primarily occurring, at least initially, at the level of the electrical output signaling, perhaps mediated by changes in the cell-membrane properties of SCN clock cells. This is good news, because it points where in the cell to look for the age-related 'lesion' and thus helps inform what type of measures may be available to reduce

these age-related deficits."

Block and Colwell suspect the process is similar in humans.

The SCN keeps the system of multiple distributed circadian oscillators in synchrony, but disruptions in the SCN lead to disrupted sleep, as well as dysfunction in memory, the cardiovascular system, and the body's immune response and metabolism.

The SCN, Block said, can be imagined as a heavy pendulum that controls many light pendulums (oscillators), with rubber bands between them.

"If the central clock weakens, it's effectively like making those rubber bands thinner and weaker," Block said. "When the SCN ages and those rubber bands become weaker, it becomes hard for the SCN to synchronize all of these other oscillators."

In the young mice, the scientists found high levels of activity during the day and much lower activity levels during the night. In middle-aged mice, there was not nearly as large a difference in activity between the day and the night.

"In the middle-aged mice, they still have a circadian rhythm, but the amplitude is reduced," Block said. "During the nighttime, when electrical impulse activity levels are usually fairly low, the levels have increased. Thus, the difference between the highest levels of activity during the daytime and the lowest levels of activity during the nighttime is much smaller in the middle-aged mice."

Large numbers of people over the age of 65 regularly take sleeping pills, but the effects of taking such pills over many years is not known, said Colwell, who hopes the new research will lead to other options for

getting a good night's sleep.

Colwell, Block and their team plan to pursue follow-up research on treatment options that could enhance the function of the circadian system with aging. They are studying the specific membrane channel changes in the SCN that are responsible for the electrical rhythm and also are looking at the circadian regulation of the heart and the mechanisms underlying neural activity rhythms in the SCN.

Their research could potentially lead to new ways of boosting the circadian output. It is possible, Colwell and Block said, that relatively simple approaches could be beneficial, such as exercising early in the morning, getting regular exposure to bright light, eating meals at consistent times and, when traveling, eating meals at the appropriate local time, regardless of whether one is hungry then.

Possible interventions may involve discovering ways to improve the sleep cycle of aging people and their ability to better handle time-zone changes, perhaps by boosting the amplitude of the SCN. New pharmaceutical approaches may be developed, the scientists said. Future research may reveal which approaches are likely to be most effective.

Co-authors of the study included lead scientist Takahiro Nakamura, a former UCLA postdoctoral scholar in Colwell and Block's laboratory, who is currently on the faculty of Japan's Teikyo Heisei University; Takashi Kudo, a UCLA postdoctoral scholar; and Tamara Cutler, a UCLA undergraduate student who works in Colwell and Block's lab.

Implications for patients with neurological disorders such as Parkinson's

In related research, Colwell and his colleagues have documented that

changes similar to those that occur as we age also occur in mouse models of neurodegenerative disorders like Huntington's disease and Parkinson's disease.

"With many neurological disorders, patients have a hard time sleeping during the night and staying awake during the day," said Colwell, who was a postdoctoral fellow in Block's lab in the early 1990s at the University of Virginia. "One of the main clinical complaints of patients with Huntington's disease and Parkinson's disease is they cannot sleep and do not respond well to sleeping pills. We think the same dysfunction we see with normal aging occurs much earlier and more severely with these patients, and we hope that the treatment strategies we develop for aging can be applied to help patients with neurodegenerative diseases as well. If we learn what is going wrong, then we may be able to develop treatments."

Colwell's research on Huntington's disease was published earlier this year in the journal *Experimental Neurology*, and his research on Parkinson's has been accepted for publication in the same journal.

Provided by University of California Los Angeles