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Alcoholism: Clinical & Experimental Research

The body's biological clock: alcohol may lead to physiological anarchy

Circadian rhythms refer to biological phenomena that oscillate within a 24-hour cycle, in keeping with the earth's rotation. A review in the August issue of *Alcoholism: Clinical & Experimental Research* summarizes new findings on interactions between alcohol and the "clock genes" that underlie circadian rhythmicity.

"The human body, like many other mammals and some bacteria, displays changes in functions and behavior that wax and wane through the cycle of day and night," said Dipak K. Sarkar, director of the endocrinology program and biomedical division of the Center of Alcohol Studies at Rutgers University, and corresponding author for the study. "These rhythms are not simply a response to 24-hour changes in the physical environment but instead arise from a timekeeping system or 'biological clock' within the body. An individual has more than 100 circadian rhythms that are unique and influence various aspects of body functions, including heart rate, blood pressure, body temperature, hormone levels, pain threshold and even the ability to fight against harmful invaders like bacteria and virus. Almost no area of our body is unaffected by these rhythms."

"This review shows that alcohol exposure can alter biological rhythmicity and, as a result, have deleterious consequences on a number of important physiological systems," noted Robert J. Handa, professor of neuroscience at Colorado State University. "The fact that alcohol intake may influence the molecular underpinnings of circadian rhythmicity is an emerging concept with potentially important biomedical ramifications.

Although a majority of these studies have been performed in rodent models ' observations of humans correlate with the animal studies and imply that similar types of pathology are associated with alcohol intake."

Some of the review's key findings were:

The chronobiological disruptions observed in human alcoholics appear to be partially due to alcohol-induced disruption of fundamental biological timing processes, and partially due to genetic associations.

"Generally speaking," said Handa, "fluctuations in physiological function are synchronized to the 24-hour day by a 'master' clock which resides within the suprachiasmatic nucleus (SCN) of the brain's hypothalamus. The SCN collects temporal information from the retina and elsewhere, passing it to various physiological systems of the body. By disrupting the ability of the 'master clock' to synchronize physiological systems across the 24-hour day, or by rendering individual physiological systems unable to respond to the signals of the master clock, alcohol intake may result in what could be considered 'physiological anarchy.' The pathology resulting from such generalized disorder could be widespread."

Handa added that it is still unknown whether the genetics underlying alcohol preference drives the circadian dysregulation, or whether the genetics of circadian dysregulation is what drives alcohol preference. "Presumably it is the latter," he said. "In animals where there is a genetic predisposition to weakened circadian rhythmicity, the stress associated with the absence of physiological order results in alcohol preference. This could also be the case in some human conditions, such as Seasonal Affective Disorder."

Sarkar concurred. "Alcohol-preferring rats have an altered light response in their central clock, and alcoholic humans have abnormality in the expression of *Period* genes that regulate the biological clock," he said. "We cannot say that people are genetically predisposed to drinking through their circadian rhythmicity, but one could interpret the data to mean that if an individual's biological clock does not function properly, they may have increased motivation to consume more alcohol."

Chronic alcohol administration appears to significantly alter central and internal clocks that govern neuroendocrine functions.

"Both 'central clocks' in the SCN, and 'internal clocks' in many neuroendocrine and other cells, depend on the coordinated expression of specific 'clock genes,'" said Sarkar. "Animal models have shown us that chronic alcohol drinking hampers the daily expression of these clock genes, which can disrupt the circadian release of neuroendocrine hormones that govern stress reactivity, food intake and various other body functions."

Alcohol consumption may influence immune function by altering an individual's central and internal clock activities.

"It is well known that immune function can be influenced by stress hormones and that stress hormones undergo daily rhythmic fluctuations," said Handa. "As a result, immune function possesses a circadian component. A new twist on this story, however, is that the immune system is not just a passive partner responding to circadian signals, but possesses an intrinsic clock of its own that is synchronized to an individual's central clock via hormonal and autonomic signals."

There may be a molecular basis for greater alcohol consumption among shift workers and people suffering from jet lag.

"In both cases," said Handa, "the activity of the individual and the physiological requirements for such activity are at odds with the regulatory timing cues provided by the SCN. For example, in the case of the individual working the late shift, light signals providing synchronizing information to the SCN are normal, yet the individual is active during a period when physiological rhythms are normally set for rest. Such activity resets peripheral rhythms away from that of the master clock and disorder ensues until activity rhythms are realigned with that of the SCN."

Alcohol may interact with different human physiological systems that are subject to circadian rhythmicity.

"Alcohol can directly alter the molecular clock machinery in different cell types, such as neuroendocrine cells and immune cells, and the molecular components of the central clock in the hypothalamus that coordinates the circadian rhythms in physiology and behavior," said Sarkar. "In addition, chronic alcohol consumption may also affect the synchronizing signals by which clocks in different tissues talk to each other."

In summary, said Sarkar, new discoveries in the emerging field of Chronobiology of Alcohol Abuse indicate that alcohol consumption has long-term adverse effects on the body's internal clocks, that altered circadian rhythm due to rotating shift work and traveling over time zones may increase the propensity of alcohol-drinking behavior, and that chronic drinking may increase the risk for sleep disturbances, depression, compromised immune function, and increased incidence of certain forms of cancers.

"We are now conducting studies using laboratory animals to understand *how* alcohol drinking in the adult alters the molecular machinery governing the body's biological clock," said Sarkar. "We are also determining the negative health consequences of maternal alcohol abuse on the offspring's circadian neuroendocrine and immune system functions."

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Alcoholism: Clinical & Experimental Research (ACER) is the official journal of the Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism. Co-authors of the ACER paper, "Alcohol Consumption and the Body's Biological Clock," were: Rainer Spanagel of the Department of Psychopharmacology at the Central Institute of Mental Health in Germany; Alan M. Rosenwasser of the Department of Psychology at the University of Maine; and Gunter Schumann of the Department of Psychiatry and Psychotherapy, and the Department of Addictive Behaviour and Addiction Medicine, at the Central Institute of Mental Health in Germany. The review was funded by the National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism, and several European research funding agencies.