

THE CIRCADIAN RHYTHMICITY OF DRUG ADDICTION

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Various aspects of addiction fluctuate on a circadian rhythm. Drug-induced hyperactivity, for example, is stronger in the beginning of the light phase of the circadian rhythm but less strong near the end of the phase. A recently discovered gene, the Clock gene, may play a role in the circadian rhythmicity of drug addiction.

Animal studies reveal that the Clock gene controls the length of a period in a free-running rhythm and it allows an organism to maintain circadian rhythmicity in total darkness. Mutations in this gene can result in a period that is longer than normal (e.g., 26 hours rather than 24 hours) in a free-running rhythm.

In their 1999 animal study, Rozi Andretic et al. unexpectedly found that mutations in genes that control rhythmicity could affect an organism's sensitization to a drug. Sensitization is when an organism becomes increasingly more responsive to the stimulatory effects of a drug with each exposure to the drug. Drug craving and compulsive drug-seeking are examples of responses that occur with sensitization.

Andretic et al. found that mutations in four genes – Period, DoubleTime, Cycle, and Clock – blocked craving for free-base cocaine in fruit flies. This finding caused the researchers to conclude that these genes, which all play a role in circadian rhythmicity, could also regulate sensitization in drug abuse.

The elimination of drug craving appears to be related to the fact that the enzyme tyrosine decarboxylase is not produced in flies that have mutated genes. Normally, tyrosine decarboxylase is produced after exposure to cocaine. This enzyme converts the amino acid tyrosine into the metabolite tyramine which stimulates the release of neurotransmitters such as dopamine from adrenergic nerve terminals while blocking the neurotransmitters' reuptake. This prolongs the actions of the neurotransmitters on the nerve. If the conversion of tyrosine to tyramine does not occur, adrenergic neurotransmitters are not released and, the pleasurable aspects of addiction, as well as drug craving and drug-seeking, are blocked.

Since Andretic's findings, many researchers have sought to more clearly understand the role of the Clock gene in rhythmicity of drug addiction. Researchers Colleen A. McClung et al. examined differences between Clock mice which have a mutated Clock gene and wild mice which have a non-mutated Clock gene. Of special interest to the researchers were: 1) the mice's locomotor activity in response to cocaine; 2) the degree of conditioning for place preference; 3) electrical activity of the ventral tegmental area (part of the brain's reward system; it plays a role in sense of euphoria and well-being); 4) the presence of tyrosine hydroxylase in the VTA; and 5) the presence of deoxyribonucleic acid (DNA) sequences for the Clock gene in the brain.

Each group's activity level was measured every 5 minutes for 2 hours as a baseline. The activity level of both groups of mice was then observed during a circadian day consisting of 12 hours light/12 hours dark. The researchers noted that the Clock mice had a higher activity level than did the wild type mice.

The mice were injected with cocaine once daily at the same time of day for 5 days and then observed for 10 minutes after each dose. The Clock mice increased their level of locomotor activity in response to cocaine (i.e., they were highly sensitive to the effects of cocaine).

McClung and associates placed the mice in a specific chamber each time they gave them cocaine. This was to determine whether they would undergo conditioned place preference response. In this phenomenon, an organism associates the first place where it encountered a drug with the pleasurable feeling and tends to return to that same place to enhance the effects of the drug. The researchers found that the Clock mice developed a stronger conditioned place preference response with smaller amounts of cocaine than did the wild mice.

Measurement of the firing rate of the VTA neurons revealed that the Clock mice had a greater firing rate than the wild type mice. McClung et al. speculate that the increased firing rate may play a role in increased drug sensitization in Clock mice.

McClung et al. found that Clock mice had increased levels of tyrosine hydroxylase in the VTA. Tyrosine hydroxylase is an enzyme which plays a role in the synthesis of dopamine from the amino acid tyrosine. Through the use of antibodies specific to the Clock gene and tyrosine hydroxylase, McClung et al. found that neurons that tested positive for the Clock gene in the VTA also

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continued on page 61



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The Circadian Rhythmicity of Drug Addiction Continued from page 12

tested positive for tyrosine hydroxylase. This suggests that the Clock gene modulates dopamine transmission in the VTA.

Normally, the reward system allows a person to have a sense of satiety, well-being, or pleasure when basic drives such as sex, hunger, thirst, socialization are met. The reward system is a group of neurons found primarily in the VTA located in the upper mid-brain. When stimulated by drugs of abuse (e.g., cocaine, amphetamine), VTA neurons release excessive amounts of dopamine into the synaptic space which in turn causes feelings of euphoria. However, the drugs prevent the reuptake of dopamine back into a neuron so that the neurons become depleted in dopamine and ultimately a person "crashes" (i.e., severe depression sets in). To restore the same sense of euphoria, a person has to take higher and higher doses of a drug. Additionally, repeated use of drugs of abuse can result in a decrease in the size of dopaminergic neurons in the VTA. This can also impair the transmission of dopamine and increase the need for higher and higher dosages of a drug to accomplish the same euphoric effect.

VTA neurons have connections to other areas in the brain such as the nucleus accumbens and the prefrontal cortex, hippocampus, and amygdala. It is these connections which may play a role in some features of drug addiction. The nucleus accumbens plays a role in motivation and reinforcement; in drug addiction, this manifests as the willingness to repeatedly self-administer a drug for its euphoric effect. The prefrontal cortex plays a role in judgment and compulsion; in a drug addicted person, this manifests as a lack of judgment and compulsive drug-seeking. The hippocampus plays a role in long-term memory and spatial navigation; in drug addiction, this manifests as conditioned place preference. The amygdala plays a role in one's sense of danger, avoid-

ance of danger, and negative pleasure (i.e., pleasure associated with aggression); in a drug addicted person, this can manifest as paranoia or engaging in risky behavior to obtain a drug without regard to the danger involved.

People have long noted that addiction "runs in families" suggesting a genetic component to addiction. In looking for "addiction genes," scientists have found that people who suffer from a particular addiction share genetic sequences on certain chromosomes. For example, smokers who find smoking pleasurable share a DNA sequence on chromosome 15 while smokers who struggle greatly from withdrawal symptoms share a DNA sequence on chromosome 6. However, specific areas of a chromosome do not always lead to accurate prediction of an addiction. The area on chromosome 6 which predicts smoking addiction is not associated with an addiction to smoking in Native Americans. Such inconsistencies have prevented mapping "addiction genes" to be of limited use in addiction treatment.

The finding that a connection exists between circadian rhythmicity and addiction may give scientists another way to treat drug addiction. Drugs may be developed which counter the effects of a circadian rhythm gene mutation and in turn block features of drug addiction. For example, a drug which blocks the excessive production of tyrosine hydroxylase in people with Clock mutation could be used to block drug craving. Gene therapy could potentially be used to impact the rhythmicity of drug addiction. When DNA from bacteria that was genetically altered to contain the Clock gene was injected into mice with a mutated Clock gene, the mice had normal circadian rhythmicity like that found in wild mice. In addition to drug therapy or gene therapy, future studies may soon reveal other ways that rhythmicity can be strategically used to combat drug addiction.