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# A Review of animal models of the circadian cycle

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**Abstract.** As society continually develops, humans become increasingly active during the night, which causes a change in their lifestyle and circadian rhythms, leading to more frequent occurrences of diseases such as insomnia, high blood pressure, and depression. By using animal models for circadian disruption, people can have a better understanding of the mechanisms of circadian rhythms as well as their function. Animal models can make it realizable and controllable to find the function of center genes and how regulating circadian rhythms affects human life. This review uses the method of literature review to study the concept of circadian rhythms and introduce three animal models. This review will also sum up the features of three animal models as well as their advantages and disadvantages of them. And then evaluates their help in the study of circadian rhythms and their significance to human circadian rhythms. The paper concludes that mice have the characteristic of rapid propagation, hamsters have the characteristic of easy circadian cycle changes and drosophila have the characteristic of simple genetic manipulation.

**Keywords:** Circadian Rhythm, Animal Models, Mice, Hamster, Drosophila.

## 1. Introduction

Circadian rhythm is a physiological process that is regulated by the circadian clock gene with a cycle of 24 hours. It is also consistent with the external light and dark changes that regulate various physiological activities of the body. The circadian clock enables the host to adapt and adjust to the surrounding environment. If circadian rhythm is disturbed, adverse health consequences arise such as mental diseases, cancer, cardiovascular diseases, or metabolic disorders. It influences important functions in our bodies, such as hormone release, eating habits digestion, and body temperature. Therefore, researchers make a lot of effort to figure out the mechanisms behind the circadian rhyme. Circadian rhyme related to Alzheimer's Disease, Parkinson's, and Down's syndrome diseases is carefully studied by researchers. The results are that a regular and balanced circadian rhythm can provide greater resilience to Alzheimer's Disease [1]. It also helps immunological, metabolic, and behavioral functions. Circadian therapies show their future in helping PD patients. Moreover, fields of traditional Chinese medication, circadian clock genes, cancer, and heart diseases are also investigated with circadian rhythm. Animals are widely used in studies due to their handleability and ease of observation. This review is going to summarize the most common three animal models used in the field of circadian rhythms-mice, hamsters, and fruit flies.

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## 2. Introduction of Circadian rhythm

The history of observation of circadian or diurnal processes dates back to around the 13 century in Chinese medical texts. The first experiment designed to distinguish an endogenous clock from responses to daily stimuli was conducted by a French scientist Jean-Jacques d'Ortous de Mairan. Circadian rhythm is a natural clock that repeats roughly every 24 hours and can be found in many creatures including animals, plants, and microbes. This natural process responds primarily to light and dark stimulation, which can also be affected and changed by light and dark. It orders complex and multiple processes in the body, including alertness, sleepiness, appetite, and body temperature.

## 3. Circadian rhythm of Mice, Hamsters, and Drosophila

### *3.1. Circadian Rhythm of Mouse*

One of the most common animal models used in studying circadian rhythms is mice. In order to study circadian rhythms in mice, we have to remove clock genes in mice. Three genes homological to the Drosophila period existed in the mice and are thought to play an important role in the biological clock. Per1mutant mice appear to be postponed with the expression of clock genes in peripheral tissues. Per1 has a distinct role in regulating the circadian rhythm of mice. It may be involved predominantly in peripheral clocks and in the output pathways of the circadian clock [2].

In another study, the mice model was used to discover the mechanistic basis of schizophrenia and related symptoms to sleep and circadian rhythm disruption. The researchers show that Bdr mice's rest and activity rhythms become fragmented and phase advanced under a day/night cycle. In Bdr mice, the phenomenon of phase advance in SCN and plasma corticosterone appears in the 24-hour rhythms of arginine vasopressin due to the disruption of synaptic connectivity within the SCN [3].

The characteristics of using mice as animal models are they are easy to do genetic manipulation which made the molecular contributors to rhythmicity. Meanwhile, they have a small size which allows the researchers to monitor their behavior and activities in their home cage environment. The mouse genome is 99% similar to the human genome. The mice have the relatively same complex biological systems as humans, such as cardiovascular, skeletal, and immune systems. They are also easy to breed and have high reproducibility. Although mice share many similarities with humans, they don't involve all aspects of human physiology and diseases and can't show them accurately. As a result, the conclusions come from mice can't be used in humans.

In order to study the circadian rhythms in mice, we have to knock off Clock genes. However, after comparing the proliferation rates of fibroblasts derived from WT or Clock mutant embryos. The researchers found that Clock mutation significantly restrains cell growth and proliferation [4].

### *3.2. Circadian rhythm of Hamsters*

Hamsters are also very popular in studying circadian cycles as they don't need to knock off Clock genes. Their circadian rhythms can be changed and regulated by the change of light and dark stimulus. In an experiment of resetting the hamster's circadian system by dark pulses, researchers give three different durations of dark pulses to hamsters. Moderate(3h) and long(6-9h)-duration dark pulses phase reset behavioral rhythms dependently. Also, they increase the wheel running activity on the hamster. This suggests that both locomotor activity and behavioral activation play an important role in the phase-resetting action of dark pulses. In summary, dark pulses are dependent on the circadian phase and stimulus duration to reset circadian rhythms [5]. In another study, the researchers conducted an experiment on the interactions between sleep and circadian rhythms in learning. In the experiment, Down's syndrome model mice and Siberian hamsters are studied. The Down's syndrome model mouse shows severe learning disability due to GABAergic over-inhibition. When hamsters are influenced by advanced and delayed light, they show learning disability as well. These two models show that the circadian system modulates neuroplasticity. Therefore, sleep and circadian systems function as the integrating memory consolidation and have coincident influences [6].

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Hamsters are widely used in the study of circadian rhythm due to their circadian rhythms can be influenced and changed only with the use of light, which means they don't need to knock out genes. This can evade the side effects of knocking down genes that the mice have as the effects may influence their growth and development. They can be in total circadian arrhythmias for life by giving light treatments that have the patterns of a phase advance on one day and a phase delay on the next day. Meanwhile, hamsters also have the advantages that mice have. They have high reproducibility and cost at a low price [7].

However, the genes in hamsters are too complicated for the researchers to study which genes are specifically in charge of circadian rhythms.

### *3.3. Circadian rhythm of fruit flies*

Fruit flies are simple and easy-to-obtain animals. We have already cracked its genes. It has been particularly useful for understanding the molecular basis of circadian rhythms. As a simple model, it has a quantitatively smaller central nervous system (CNS) and genome. Therefore, it becomes relatively easy to unravel interactions that mice and hamsters also other mammalian models. Also, it has a high rate of reproduction and it can produce many offspring in one generation, which makes it inexpensive. Drosophila also has the advantage of its complex behavior. Flies also have the same complex behavior compared to other animal models. They can learn, court, run, fly, and sleep. Another benefit of fruit flies is that people have been focusing on their genetics for a century-long time [8].

For drosophila, it is a popular choice when studying circadian cycles. It shares 75% of the genes that cause diseases in humans. Its small size, short generation time, and easily distinguished features make it easy to operate in circadian studies [9]. One disadvantage of using drosophila is that the hypothesis may work on invertebrate models but doesn't work for vertebrate animals. Also, drosophila have a relatively far relationship with humans, which means that their experiment results can't be directly used in the case of humans. What's more, they are not the ideal model for studying complex behaviors. They can't be used in the area of memory and circadian cycle [10].

## 4. Conclusion

In summary, mice, hamsters, and fruit flies are three of the most common animal models used in the experiments. Mice have the advantage of being easy to remove their genes, but their growth and other behaviors will be influenced. Hamster's circadian cycles can be regulated by light and dark pulses. However, the genes are too complicated to decode and analyze. Firtu fly has the advantages of being a simple and low-cost model which also has relatively complex behavior and an easy genome. These animal models all have the advantages of being easy to obtain and manipulate with a quick reproducing rate. Because of the word limit, this paper can't list all the animal models used in the study of circadian rhythms. It only gives brief summary of mice, hamsters, and drosophila models. Each of them has disadvantages as mice have to knock down genes, and hamsters have complex genomes. Today's study is more focused on discussing the interaction or relation between a single animal model and certain genes. The area of study is widely covered from circadian rhythms and sleep to memory and learning ability. They do give ideas and inspirations of circadian rhythms in humans. However, there are not many researchers who link the result to humans. The future can develop existing research further and link it with the life of humans. In the future, people may also invite more animal models that are more specific to certain experiments. More and more animals may also be included in the field of circadian rhythms to give a wide diversity and more complete knowledge of circadian rhythms.

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