# Control And Coordination Of Mammals' Circadian Cycles

*Emerging Evidence And Evolving Explanations*

## From Insects to Mammals

***Before you start… In column A, list what you have learned about the circadian clocks in Drosophila.***

Studying a single type of organism allows scientists to understand other types of organisms. This is how scientific knowledge about biological clocks has been developed. Discoveries about fruit flies have assisted our understanding of those systems in mammals. One example is the existence of the negative feedback loop in *Drosophila*.

Clock genes in *Drosophila* cause a rise and fall in the manufacture of molecules in the cell. There is a circadian cycle to the concentration of the molecules. The combined activity of the *per* and *tim* genes creates a negative feedback loop. The cycle is sensitive to the local day/night conditions. When exposed to light, a fly's circadian rhythm will shift. As a result, the body chemistry will adjust to different day lengths. This resetting of the clock is called entrainment. The changes in body chemistry control the behaviors of the *Drosophila*.

Learning how genes influence circadian rhythms in fruit flies was an important accomplishment. Fortunately, this knowledge has been useful beyond just fruit flies. Scientists had learned how to look for clock genes that would control circadian rhythms. The activity of different genes could be matched with the behavior of fruit flies. You discovered this yourself in the simulation of *Drosophila* behavior in response to light signals. Scientists have learned that the clock genes of fruit flies and mammals are very similar. What had been learned about an insect guided their thinking when they began working with rats.

## Control Center in Mammalian Brains: The SCN

In a special part of mammalian brains are cells that control circadian rhythms of the entire body (like the sleep/wake cycle). Altogether, this cell cluster is the size of a pinhead. This small but powerful cell bundle is located close to where the two optic nerves cross each other as information from one eye is carried to the opposite brain hemisphere. The name for the control is based upon its location and its structure. It is *above* ("supra" in Latin) the place where the optic nerves *cross* ("chiasma" in Greek). As a clump of cells, it is called a *nucleus* (don't confuse this with the nucleus inside a cell). The technical name for the control center becomes the suprachiasmatic nuclei, which literally means, "cell clusters above the crossing point." It's simpler to just abbreviate this to SCN. When you see or read "SCN" remember this as the brain structure that controls circadian rhythms in mammals.

Scientists in the 1970s found out that the SCN is entrained by signals moving along the optic nerve. Light that strikes the retina creates a nerve impulse that travels through the optic nerve. Even though the SCN is deep within a mammal's skull, its connection to the optic nerve allows it to respond to day/night conditions.

Scientists observed that changes in mammalian behavior followed a daily cycle that was controlled by the SCN. This reinforced the idea that genes control circadian rhythms. In fruit flies this happened within individual cells throughout the organism. In the more complex bodies of mammals, this was controlled by gene activity in the SCN. However, scientists were not sure what was occurring at the molecular level.

Here is what they knew. Electrical activity of the SCN corresponded to changes in environmental light levels. This was evidence that the circadian rhythms in mammalian behavior were controlled by the SCN. But even though the SCN was thought to be the "boss" that kept the body on a daily cycle, it wasn't obvious how this happened. Although the SCN itself seemed to be sensitive to changes in light, somehow this information had to be passed along to other organs. Does the "boss" use nerve impulses to signal the rest of the body? Or does the SCN rely upon chemical messengers (such as hormones) to control physiological activity? The scientists knew that in mammals the SCN regulated various biological processes. But their knowledge was incomplete: they wanted to know *how* the SCN exerted this control.

***Before you go on: In column B of the chart, summarize the information concerning the SCN as the master "boss" clock of mammals***

## Beyond the SCN: Peripheral Clocks

The SCN contains genetic information that operates in a negative feedback loop. This is similar to what you have explored in *Drosophila* cells. The production of certain chemicals rises and falls in an almost 24 hour cycle. This cycle is controlled by the expression of genes and is entrained by exposure to light. The daily cycle was very similar in *Drosophila* cells and mammalian SCN.

Scientists soon discovered that other tissues in mammals also showed a daily rise and fall in chemicals. This means that the SCN is not the *only* place where circadian rhythms occur. While the SCN is viewed as central to circadian rhythms, the clocks in other places in the organism, called *peripheral clocks*, must also play some role.

This doesn't mean that the peripheral clocks are completely independent from the SCN. The SCN has been described as the "boss-clock" that sets the schedule and makes adjustments based upon light levels. This information is then sent to the peripheral clocks that act as if they are "employee clocks." As a result, all the clocks in the body are synchronized. In other words, the SCN *coordinates* the cycles of the peripheral clocks. Once again, scientists are not sure exactly how this is accomplished. It could be through nerve impulses or chemical signals.

In 2000, Yamazaki and a team of other scientists examined the clock genes in several types of rat tissues. These tissues were dissected from the SCN, as well as from other locations like the liver, and kept alive in test tubes. The researchers monitored the activities of the clock genes in these tissue types. They found that while the SCN maintained a strong rhythm for over thirty days, the peripheral clocks weakened within seven days. The scientists then investigated how changing the light/dark cycle affected the tissues. They created a sudden six-hour delay in the light/dark cycle and then measured the clock gene expressions in the various tissues. They observed that the change in the environmental light cycle caused the SCN to shift much more rapidly than the peripheral clocks.

***In column C of the chart, describe the new evidence about peripheral clocks.***

**The Liver as a Peripheral Clock**

The liver plays an important role in digestion. It produces bile to help in the digestion of fats. It also stores and processes newly digested nutrients from food. Researchers have found that the liver doesn't wait to start working until after food arrives. It actually begins working before it is actually needed for digestion. The liver seems to anticipate when food will turn up. The liver times its activity so it is ready to get to work even before the food is present – another example of a biological clock.

Scientists have explained that the liver uses a peripheral clock. Having a peripheral clock in the liver better allows the digestive system to anticipate and set up the physiological conditions for food digestion. In 2001, Stokkan and colleagues measured the activity of liver clock genes of rats. Instead of fiddling with the light/dark cycle, they altered the rats' feeding schedule. They were testing to see whether the availability of food affected the activity of the liver. What they found was that the liver would adjust its cycle to the new feeding times. However, the SCN continued on its normal day/night cycle.

Damiola and her colleagues, in 2001, did a similar study of SCN and liver clocks but used mice. As nocturnal animals, mice do most of their feeding during nighttime. Instead of becoming active when light levels increase, mice become active as it grows dark. As a result, the activities of the SCN and liver correspond to this cycle. When food was made available to the mice during only the daytime, this was the opposite of their normal cycle. When the scientists measured the clock gene activities, they made an interesting discovery. The liver clock was reset so that it was most active during the daytime, better matching when the mice now fed. However, the SCN seemed unaffected. It continued to stay on its previous cycle even though the liver was on the altered schedule.

***In column D of the chart, briefly summarize this recent evidence about liver entrainment.***

## Conclusion

The discoveries scientists make are influenced by what they already know. Recognizing the role of genes on circadian rhythms in *Drosophila* guided the search for biological clocks in mammals. This knowledge about fruit flies also contributed to the discoveries of peripheral clocks. One piece of knowledge influenced how scientists thought about how to solve the next mystery.

Scientists now believe that the circadian rhythm of the liver is controlled by two different sources. Both the SCN and the timing of meals entrain the liver clock. This ability to adjust to both changing light levels and food availability is seen as an adaptive benefit. When day length changes or food is available on a different schedule, mammals' bodies are capable of adjusting. But scientists are still puzzling over how to explain how this happens. It's clear that the SCN has some control over the liver and other tissues and organs. But the way the entrainment signal is carried from the brain to the rest of the body is an incomplete part of the story. What is quite obvious to scientists is that the explanation is not going to be simplistic:

> "In the case of the liver clock, both signals from the SCN and cues from feeding and metabolism contribute to entrainment. The nature of entrainment is [different] for different tissues, which may be adaptive, helping the individual to adjust to different timing of food sources or to changing photoperiod and seasons, or, in modern times, to new time zones or work schedules."

*by Till Roenneberg and Martha Merrow. "The Network of Time: Understanding the Molecular Circadian System" in* <u>*Current Biology*</u>*, volume 13, pp. 198-207, March 4, 2003.*

**Discussion Questions**

Use your chart showing the evolving model of the mammalian circadian system to answer the following questions.

1. How did previous research on *Drosophila* influence scientists' work on the genetic basis of mammalian circadian rhythms?

2. How is the SCN entrained? How does this compare to the entrainment of the liver clock?

3. How does the new evidence from the liver studies affect the boss/employee model used to explain the relationship between the SCN and peripheral clocks?

4. What might be the benefits of an organ (or system) having many entrainment pathways?

5. What is a remaining gap in our understanding about the circadian system in mammals? In other words, what don't we understand yet?

6. Which ideas about the Nature of Science can be found within this article about attempts to explain the circadian system in mammals? Justify your choices with evidence from your chart or the article.
   - ★ Scientific knowledge changes over time to be consistent with evidence and/or new reasoning.
   - ★ Scientific knowledge is reliable because it is continually tested and evaluated.
   - ★ Scientific explanations are often debated, leading to the tentative yet durable nature of science.
   - ★ Evidence and explanations are not the same.
   - ★ Objectivity is an important part of the scientific process.
   - ★ Scientific data must be the result of carefully designed tests and observations and the data must be repeatable.
   - ★ Scientific investigations are based upon an understanding of existing ideas.
   - ★ Because scientists are influenced by what they already know, multiple explanations can be produced from the same set of data