Circadian Biology in Humans

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Introduction

A circadian rhythm is an endogenously generated, rhythm, with a period of approximately 24 hours, which is temperature compensated and can entrain to external cues (Mohawk et al., 2012). Within mammals circadian rhythms are generated by *clock genes* which form a cell-autonomous transcriptional auto-regulatory feedback loop. Due to these clock genes almost every cell in the human body contains a circadian clock (Lowrey and Takahashi, 2004). However, a region of the brain called the hypothalamic suprachiasmatic nucleus (SCN) is the main synchronizing force of circadian rhythms (Sujino et al., 2003). The full extent to which biological processes of humans are governed by circadian rhythms, and what mechanisms drive these rhythms, is active area of research, and this paper will attempt to summarize some of the most significant results to date.

Cell Autonomous Auto-regulatory Transcriptional Feedback Loops

In the core circadian clock of a cell a BMAL1-CLOCK complex within the nucleus activates transcription of the *Period* ($Per1$, $Per2$) and *Cryptochrome* ($Cry1$, $Cry2$) genes. Outside the nucleus the Period and Cryptochrome proteins then form a complex, which then translocates back into the nucleus where is interacts with the BMAL1-CLOCK complex to reduce the expression of the Period and Cryptochrome genes (Lee et al., 2001). In addition to regulating the expression of the Period and Cryptochrome genes, the BMAL1-CLOCK complex also controls the transcription of $Rev-erb\alpha$ and $Rora$, which in turn have an effect on the transcription of BMAL1. While several types of transcriptional feedback loops have been found to generate circadian rhythms in mammals there is also evidence that there are many genes which influence circadian rhythms which are yet to be discovered. There are also many *clock controlled* genes, whose expression are regulated by clock genes, and therefore also possess circadian rhythmicity in their expression (Lowrey and Takahashi, 2004).

The Suprachiasmatic Nucleus

As was mentioned in the introduction the hypothalmic SCN is the master pace-maker for the generation of circadian rhythms in mammals. The mechanism by which the SCN synchronizes itself with the external day is by the use of rod and cone photo-receptors as well as a special type of photo-receptive cell called intrinsically photo-receptive ganglia. When the retina is exposed to light these photo-receptive cells they pass the photic signal directly on to the SCN which uses the light exposure to adjust itself (Mohawk et al., 2012). The SCN is comprised of some $20,000$ neurons, each of which is capable of producing circadian endogenous oscillations. However, the neurons are also coupled with each other which confers extreme precision and robustness to the functioning of the SCN as a network.

A question which follows naturally from the description of the SCN as "the master pace-maker" is how does the SCN keep the rest of the clocks in the body in time? Unfortunately this is, to a large degree, a mystery (Vitaterna et al., 2001). However, experiments with mice have shown that the SCN does indeed play a central role in the circadian behavior of mammals. In one experiment mice which had a mutated clock gene or were missing both cryptochrome proteins, and as a result were lacked circadian rhythmic behavior, received a transplant of fetal SCN tissue. After the transplant circadian rhythmicity was observed in the mice. And since these mice lacked peripheral oscillators it is apparent that the SCN is capable of generating circadian rhythms in other parts of the body and brain (Sujino et al., 2003).

Human Circadian Clocks

In the previous section it was mentioned that when the retina is exposed to light the SCN receives a photic signal, but how exactly does it use this signal to adjust itself? To answer this question many experiments have been conducted to explore how exactly the entrainment of human circadian clocks works. One of these experiments involved keeping humans under constant lighting conditions with an absence of time cues and seeing how their circadian rhythms progressed in the absence of any entrainment. Interestingly the average *free-running* period for humans runs slightly longer than expected at about 24.2 hours (Gentry et al., 2021).

Humans can be classified by *chronotype* which refers to how their circadian clock aligns relative to external time. This is very hard to accurately measure, however, one indicator commonly used is the MSF, which is the average half-way point between sleep onset and wake time. There are four major factors which generally affect an individuals chronotype: genetics, sex, light exposure, and age. Light exposure is a very interesting determinant in chronotype as in evolutionary terms artificial light is very recent. The way in which the circadian clock uses light to regulate itself is by speeding up where it is in it's cycle when exposed to light in the early part of the day, and slowing down when it's exposed to light at night. However, as a result of both industrialization and electrification humans now spend large quantities of time when outside light exposure is high, inside, and when outside light exposure is low there are artificial lights. As a result the SCN receives unreliable information from the photo-receptors about the time of day which can cause internal and external time to differ significantly. This phenomena has prompted chronobiologist Till Roenneberg to say:

> "We have outlived our evolutionary context."

Meaning that the environment that humans have created for themselves is outside the scope of what we evolved to deal with. This dissonance between circadian time and external time can lead to many disorders (Roenneberg and Merrow, 2007).

Pathology of Circadian Clocks

There are six major sleep disorders associated with circadian systems in humans:

1. Advanced sleep phase syndrome (ASPS), a rare condition in which the circadian clock is early relative to external day.
2. Delayed sleep phase syndrome (DSPS), a condition found in about 10% of the population in which the circadian clock is late relative to external day.
3. Non-24-hour sleep-wake syndrome.
4. Irregular sleep wake pattern.
5. Jet lag.
6. Shift work disorder.

And while the immediate effect of these disorders can be significant recent research suggests that they may have much further reaching consequences, including; heart disease, neurodegeneration, cancer, and mental health issues (Gentry et al., 2021).

Conclusion

In conclusion circadian rhythms are ubiquitous not only in nature, but within humans, and have many far reaching consequences. While a vast amount has been learned in a short time there are still many unanswered questions regarding both the mechanisms by which the oscillations are generated, and the consequences of this rhythmic behaviour.

References

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