Circadian rhythms in fruit flies

Sofía Polcowñuk explains how the fruit fly helps us to understand the internal biological clocks that are found in most, if not all, organisms

Circadian rhythms

Circadian rhythms are crucial for co-ordinating an organism's physiological and behavioural activities with environmental change, such as daily changes in light and temperature. The term 'circadian' is derived from *circa*, meaning about, and *diēm*, meaning day. Circadian rhythms are controlled by internal clocks that regulate biological processes. They do not require input from the environment in order to generate their cyclical activity, although they do rely on external signals to synchronise their output with environmental changes.

Why the fly?

The fruit fly *Drosophila melanogaster* is an excellent model organism for investigating circadian rhythms. Its genome has been sequenced, and many mutant strains are available that show changes in both physiology and behaviour. This allows precise genetic manipulation and functional analysis of specific genes. Like humans, *Drosophila* exhibits well-defined behaviours that are controlled by circadian rhythms. Researchers can observe these circadian responses, identify the genes involved, and analyse related neuronal activity in the laboratory.

The fruit fly *Drosophila melanogaster*

A molecular clock

Drosophila has been used to study the molecular mechanisms underlying the internal circadian clock, specifically the cyclical transcription of certain genes – clock genes – and the synthesis and degradation of the proteins they encode. One way to identify genes associated with circadian rhythms is to study the locomotor activity of mutant fly strains compared with control flies, under continuous dark conditions. When the external cue of light is absent, daily changes in the locomotor activity of the flies are controlled solely by their internal circadian clock.

In *Drosophila*, key clock genes include *period* (*per*), *timeless* (*tim*), *clock* (*clk*), *cycle* (*cyc*) and *cryptochrome* (*cry*). These genes and associated proteins form complex molecular feedback loops (see Figure 1). The interplay of clock genes and their protein products orchestrates the rhythmic expression of many other downstream genes, ultimately governing circadian behaviour and physiology.

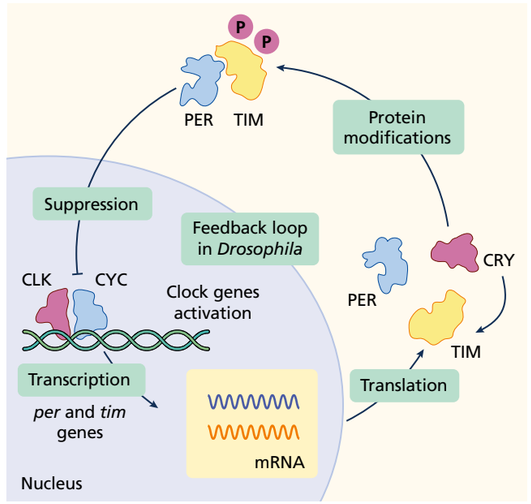


Figure 1 A simplified version of the *Drosophila* circadian feedback loop. The proteins CLK and CYC together activate the expression of *per* and *tim* genes. After translation in the cytoplasm, other proteins interact with PER and TIM, resulting in PER and TIM interaction, phosphorylation of TIM (P), and transport into the nucleus, where they suppress the activity of CLK and CYC, and hence repress expression of *per* and *tim*

Neuronal communication

Neurones that form the circadian clock communicate with each other in the control of co-ordinated behaviour. This is where the gene *pdf*, and the PDF protein it encodes, play a crucial role. PDF is produced by a sub-group of 16 clock neurones (see Figure 2). It acts as a messenger that allows the central clock to communicate timing information within the brain, enabling synchronisation between different neurones. The production and release of PDF changes throughout the day, and this is accompanied with changes in the shape of the axons of these neurones and the synapses they form with others.

Studying *Drosophila*'s circadian rhythms provides insights into fundamental biological processes that are relevant to human health. **Dysregulation** of these rhythms is linked to sleep, metabolic and mood disorders. By exploring the molecular mechanisms, researchers may identify novel **therapeutic targets**.

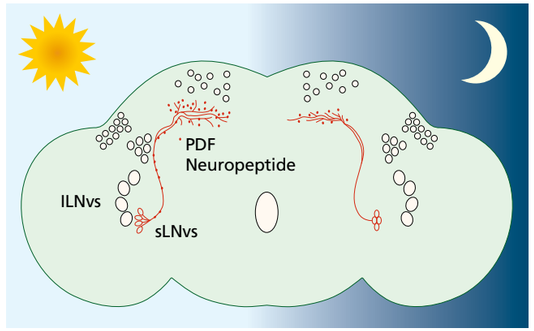
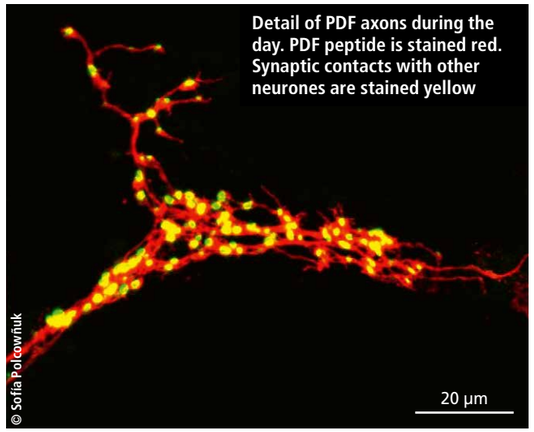
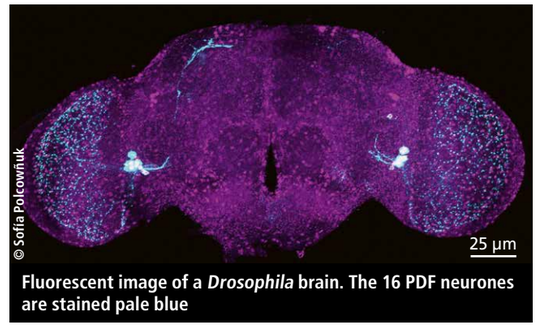


Figure 2 Diagram of a *Drosophila* brain, showing the main clock neurones. The sLNvs and lLNvs (small and large lateral neurones) express PDF peptide. The axons of the sLNvs become more extensive during the day, and less so at night.



Tiny brains

The *Drosophila* brain comprises only around 100 000 neurones. Approximately 150 of these contain the core components of the clock. These neurones can be visualised using fluorescently labelled antibodies that bind to protein products of the clock genes.



Fluorescent image of a *Drosophila* brain. The 16 PDF neurones are stained pale blue

TERMS EXPLAINED

Circadian rhythms Biological processes that oscillate with a period of approximately 24 hours.

Dysregulation Abnormal function of a biological process.

Therapeutic target In the context of medicine, a molecule or mechanism that plays a key role in the development or progression of a disease.

RESOURCES

More on circadian rhythms: **https://tinyurl.com/circadian-rhythms**
A YouTube video describing research into *Drosophila* neurones: **https://tinyurl.com/Drosophila-neurones**

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