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## Two Oscillators Are Better Than One: A Circadian Pacemaker Escapes from the Light

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Continuous light exposure can suppress circadian rhythms. In this issue of *Neuron*, Murad et al. demonstrate that, under certain genetic conditions, a novel cluster of pacemaker neurons can drive rhythmic behavior in constant light. Surprisingly, these neurons are distinct from those thought to drive rhythms in constant darkness.

Circadian clocks are imperfect time-keepers, running with a periodicity a little slower or faster than 24 hr. The daily rhythm of sunlight synchronizes these clocks to the 24 hr environment. Unfortunately, you can get too much of a good thing. Continuous light exposure (constant light; LL) can suppress circadian rhythms in many organisms, including mammals and insects. Here, Murad and colleagues examine how *Drosophila* circadian clocks can “escape” from this light suppression (Murad et al., 2007).

To understand the destructive aspects of light, one first needs to understand the inner workings of the circadian clock. Genetic studies in fruit flies and mice have revealed a remarkably conserved, cell-autonomous molecular clock. In *Drosophila*, clocks consist of a primary transcriptional feedback loop in which the CLOCK/CYCLE dimer activates *period* (*per*)

and *timeless* (*tim*) transcription (reviewed in Hardin, 2005). PER represses CLK/CYC, leading to robust transcriptional oscillations. Phosphorylation of these components, most notably PER, appears to contribute to protein stability and feedback repression to modulate the periodicity of molecular and behavioral oscillations.

How does light impact this molecular circuit? Unlike their mammalian counterparts, flies have a cell-autonomous photoreceptor, CRYPTOCHROME (CRY). Cryptochromes are blue-light photoreceptors related to UV-dependent DNA repair enzymes (photolyases). Light triggers both CRY and CRY-dependent TIM degradation, resetting the molecular clock (see Busza et al., 2004, and references within). Under constant light conditions, *cry* mutants are rhythmic (Emery et al., 2000a), although reports of splitting, i.e., two rhythmic components with different

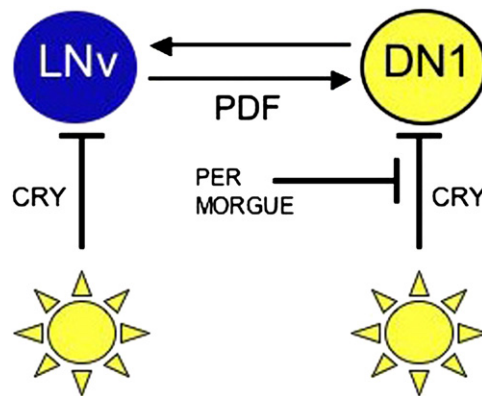
periods, have also been made (Yoshii et al., 2004). In mammals, CRYs (CRY1 and CRY2) appear to be the principal transcriptional repressors rather than photoreceptors.

The work of Murad et al. highlights the role of a network of clock neurons in the fly brain. While *Drosophila* is revered for its arsenal of molecular genetic tools, tremendous progress has been made in revealing the neuronal network that rhythmically modulates fly behavior. In mammals, circadian behavior is driven by the hypothalamic suprachiasmatic nuclei, a complex and heterogeneous network consisting of approximately 20,000 neurons. The fly circadian pacemaker is a model of efficiency, accomplishing comparable timekeeping tasks with only about 100 pacemaker neurons, and under certain genetic conditions, behavioral rhythms are observed with just a small fraction of functional pacemaker

neurons (Grima et al., 2004; Helfrich-Forster, 2005). This relative simplicity has eased the characterization of these neurons and their projections. They can be divided into six interconnected clusters: small ventral lateral neurons (sLNv), large ventral lateral neurons (lLNv), dorsal lateral neurons (LNd), and three groups of dorsal neurons (DN1, DN2, and DN3; Figure 1). The LNv uniquely express the neuropeptide PIGMENT DISPERSING FACTOR (PDF) that is essential for coordinating molecular rhythms between these neuronal pacemakers.

Distinct clusters are responsible for distinct aspects of circadian behavior. Under light-dark conditions (12 hr light:12 hr dark by convention), flies exhibit a morning burst of activity that begins prior to lights-on and an evening burst preceding lights-off. It is this anticipation of these environmental transitions that is a hallmark of clock function under natural conditions. Distinct pacemaker clusters direct each of these bursts. The PDF-containing LNv (most likely the sLNv) drive morning behavior, while the LNd, a subset of DN1, and/or a single PDF<sup>-</sup> LNv drive evening behavior (Grima et al., 2004; Stoleru et al., 2004). The sLNv subset also appears to be especially important in driving rhythmic behavior under constant darkness conditions. Manipulating circadian period selectively in the LNv alters periodicity in other pacemaker clusters (Stoleru et al., 2005), suggesting that the LNv are a master pacemaker for circadian behavior.

The studies described by Murad et al. were initiated by the surprising observation that PER overexpression throughout the pacemaker network resulted in flies that were rhythmic in LL, albeit with lengthened periods (Murad et al., 2007). Thus, primary changes in the core clock (not just light input pathways) can also release flies from clock suppression by light. As rhythms in constant darkness are likely driven by the LNv and CRY function in the LNv is important for responses to brief



**Figure 1. A Simplified Network Model for Circadian Function in Constant Light**

The ventral lateral neurons (blue) mediate rhythms in constant dark, increases in morning activity, and are coupled to DN1 (yellow), which in turn may drive increases in evening activity. Constant light (sun symbol) suppresses pacemaker function through the CRYPTOCHROME (CRY) photoreceptor. Overexpression of *per* or *morgue* can impair the effects of constant light in the DN1 but not the LNv, allowing rhythmic DN1s to drive rhythmic behavior. See text for details.

light pulses (Emery et al., 2000b), it was assumed that LL rhythms would also be driven by the same cluster. Surprisingly, selective expression of PER in PDF<sup>-</sup> but not PDF<sup>+</sup> pacemaker neurons resulted in LL rhythmicity (Murad et al., 2007). Similar results were found when similarly overexpressing a second gene, *morgue*, identified in an overexpression screen for blockers of light-induced arrhythmicity (Murad et al., 2007). These results suggested that PDF<sup>-</sup> neurons may be responsible for driving rhythms in constant light. To determine which, if any, of these cells are responsible, they measured the levels of a clock marker and component of a second feedback loop, PDP1, that demonstrates a robust circadian oscillation in all pacemaker neuron clusters. Consistent with their hypothesis, oscillations were observed in a subset of PDF<sup>-</sup> DN1 neurons but not in the PDF<sup>+</sup> LNv (Murad et al., 2007). It is not clear why *per* and *morgue* can rescue DN1 but not LNv or other pacemaker neurons from LL-induced arrhythmicity (Figure 1).

If the DN1 subset of neurons is driving rhythmic behavior, then are the PDF<sup>+</sup> LNv mere bystanders or slaves to the DN1 master? To test this hy-

pothesis, Murad et al. examined the LL effects of *morgue* overexpression in a *pdf*<sup>01</sup> mutant background. *pdf* mutants display poor rhythms with slightly short periods under DD conditions (Renn et al., 1999). These *morgue*-expressing *pdf*<sup>01</sup> flies demonstrate LL rhythms that are better than their *pdf*<sup>01</sup> counterparts, but not as good as *morgue*-expressing flies (Murad et al., 2007). Clearly, *morgue*'s ability to suppress light effects does not require PDF. On the other hand, PDF still plays a role in enhancing LL rhythmicity, at least under these conditions, suggesting that PDF is still in the loop (Figure 1). Consistent with this idea, rescue of *cry* mutants only in the LNv does partially suppress LL rhythmicity. In these LNv-rescued *cry*<sup>b</sup> mutants, the suppression is only partial,

suggesting that non-PDF neurons may be mediating rhythms (Murad et al., 2007). An examination of PDP1 oscillations also finds robust oscillations only in a subset of DN1 neurons in these flies (Murad et al., 2007).

Thus, Murad et al. demonstrate that a subset of DN1 neurons is capable of driving behavior in constant light under specific genetic conditions. This adds to accumulating evidence for a dual oscillator system in *Drosophila* that drives rhythmic behavior. The preponderance of evidence supports the following model: the morning LNv appear to mediate the nighttime rise in activity before dawn and free-running rhythms in the dark. On the other hand, a subset of DN1 may contribute to the daytime rise in activity before dusk and here a subset drives free-running rhythms in the light. A caveat is that it is unclear whether these two DN1 subsets overlap. Nonetheless, it is notable that the majority of DN1s are undetectable in *glass* mutants in which all known fly photoreceptors fail to develop (Klarsfeld et al., 2004). Thus, some DN1s may be developmentally programmed to function during the day. These two oscillators appear to be interconnected, but, as

these experiments suggest, may have distinct properties. The data presented here suggest that the presence of a second pacemaker (the DN1) fortifies the network, allowing behavioral rhythms to persist under conditions that would suppress individual oscillators. The network organization of the fly circadian pacemaker, and that of mammals, is likely critical to maintain rhythms under a variety of environmental conditions, such as different seasons. Given the potential importance of rhythms in health and disease, this is no small feat.

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## Reconstructing the World: Switching from Segmentation to Integration Allows Neurons in Area MT to Make “Sense” of the Visual Scene

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Huang et al. in this issue of *Neuron* show that primate area MT neurons exploit contextual cues to adequately interpret motion information. MT neurons switch from segmentation to integration when motion arises from single rather than multiple objects. This switching may help solve the aperture problem and bind distant object components into a perceptual whole.

The visual world, as projected onto our retinas, is fraught with continuously changing ambiguous signals. The brain is faced with the formidable challenge of extracting meaning from these signals and generating an image of the external world that contains the information necessary for survival. In the process, the external world is *reconstructed* from the two-dimensional, unstable and moving input from the retina, where detail is signaled by millions of neurons that view the world through small “windows”: their receptive fields. Although signals from these receptive fields are pooled at subsequent stages of visual processing, neurons in mid-level visual

areas still suffer from “seeing” only a restricted part of the visual world, a phenomenon which results in the so-called aperture problem (Wallach, 1935). This problem arises if a moving contour is viewed through an aperture (Figure 1B). Under those circumstances, motion direction and speed are impossible to determine unless additional information is provided. Since every individual neuron has a limited window to the world, it is regularly confronted with this problem. In order to overcome it and assign appropriate meaning to object parts within these apertures, the content within must be appropriately influenced by the content without—vision is hence an act

of interpretation, whereby segments of the visual scene are interpreted in light of the larger context within which they appear. Fortunately, objects and scenes often occur and move in statistically predictable ways in our visual environment. Consequently, the visual system frequently has “reason to believe” that a particular feature is present at a particular location, because of the spatial structure of the current scene, the temporal structure of its evolution over time, and prior knowledge of the spatiotemporal structure of the visual world (Kersten et al., 1996). Vision as an act of integration and interpretation is exemplified in Figure 1A. The artist has painted 2D