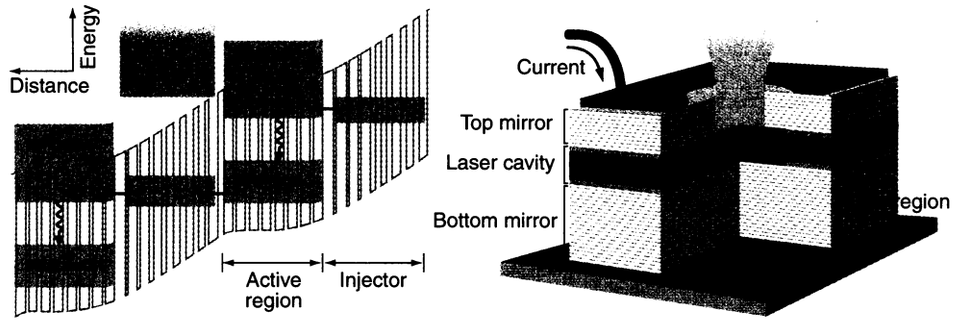


Recent advances in laser technology. The VCSEL laser **(right)** emits light perpendicular to the device; traditional lasers emit light from the edges. The QC laser **(left)** exploits quantum confinement of electrons in ultrathin layers of semiconductors.

lasers (*1*) describes operation at or below room temperature (300 K), and their epitaxial structure was designed for good performance at room temperature. But results were obtained with pulsed operation at a low duty cycle, because the total instantaneous current and power injected into the laser are typically 2 A and 16 W, respectively. Although these values may not seem large, the power density, with an active area of about 0.04 mm^2, is nearly half a gigawatt per square meter.

The electrical power density level in (*1*) is much less than the optical pumping levels involved in (*2*) and (*3*). The provision of an adequate thermal management scheme even for 16 W is nontrivial and not easily justified on cost, weight, and complexity grounds. So it is quite plausible that practical QC lasers either will use low duty-cycle operation at an average drive power level of a few milliwatts, rising to 0.6 W at a maximum duty cycle of 4%, or will operate continuously in more compact device structures with the same threshold current density. Because they were concerned with obtaining electrical tunability, Müller *et al.* used a three–quantum well combination that gives a substantial quantum-confined Stark effect (*1*). By using a two-contact configuration, they could control the emission wavelength and the output power level of the laser independently while avoiding the temperature changes caused by continuous operation.

The "engineering" issues of design, construction, and operation of new semiconductor lasers discussed above are hardly the stuff of revolution, but the devices described are likely to be important for a variety of applications. Both types of lasers allow high power densities. QCs will, for example, allow high-resolution mass spectrometry over much of the IR spectrum, and the blue VCSELs will find application in high density optical storage. A recent paper on quantum dot emitters embedded in high-Q resonant cavities (*7*) may lead to even more sophisticated combinations of light generation and cavity structure. This device, in which a selectively oxidized nanocavity contains a quantum dot, may allow photon emission events to be controlled individually, even at usefully high power levels. Such control is not only of physical interest but also has the potential to radically transform the nature of fiber-optical communications.

References

1. A. Müller, M. Beck, J. Faist, U. Oesterle, M. Illegems, *Appl. Phys. Lett.* **75**, 1509 (1999).
2. I. L. Krestnikov *et al.*, *Appl. Phys. Lett.* **75**, 1192 (1999).
3. T. Someya *et al.*, *Science* **285**, 1905 (1999).
4. S. Nakamura and G. Fassol, *The Blue Laser Diode* (Springer-Verlag, Berlin, 1997).
5. B. Gil, *Group III Nitride Semiconductor Compounds* (Clarendon, Oxford, 1998).
6. J. Faist *et al.*, *Science* **264**, 553 (1994).
7. C. Ell *et al.*, *IEEE-LEOS Newsl.* **13**, 8 (August 1999).

PERSPECTIVES: NEUROBIOLOGY

The CRYs of Flies and Mice

Paul E. Hardin and Nicholas R. J. Glossop

Essentially all organisms (microbes, plants, and animals) use an endogenous timekeeping system, termed the circadian clock, to control daily rhythms in physiology and behavior. In each organism studied thus far, the clock's timekeeping mechanism, or oscillator, is characterized by an intracellular feedback loop in which expression of a group of genes results in production of proteins that then switch off the expression of those genes. The circadian feedback loops of the fruit fly *Drosophila* and mice (see the figure) are similar in that they are controlled by a homologous set of transcriptional activator proteins (CLOCK and BMAL1 in mice; dCLK and CYC/dBMAL1 in *Drosophila*) and inhibitors that block these activators (mPER 1, 2, and 3 and maybe mTIM in mice; PER and TIM in *Drosophila*) (*1*). In addition to keeping circadian time, the feedback loop maintains synchrony with environmental light-dark cycles by shifting phase in response to light. Discovery of the blue light receptor CRYPTOCHROME (CRY) in *Drosophila* and mice fueled speculation that this protein would mediate circadian photoreception in both species (*2*). Although this turned out to be the case in *Drosophila* (*3*), on page 2531 of this issue Okamura and colleagues now provide strong evidence that mouse CRYs (mCRYs) act as transcriptional inhibitors within the circadian feedback loop and not as circadian photoreceptors (*4*).

Although the *Drosophila* and mouse circadian feedback loops have similar components, they function at opposite phases of the circadian cycle and mediate light-dependent phase resetting through different mechanisms. In *Drosophila*, transcription of the *per* and *tim* genes is activated by dCLK-CYC protein dimers late in the day and inhibited by PER and TIM proteins late at night (*1*). In contrast, transcription of *mPer1*, *mPer2*, and *mPer3* is activated by CLOCK-BMAL1 dimers early in the day and repressed by the mPER proteins and perhaps mTIM late in the day (*1*). Despite these phase differences, *Drosophila* and mice show similar responses to light pulses administered during the dark phase. In both, light administered early in the dark phase causes phase delays, whereas light administered late in the dark phase causes phase advances. The mechanisms by which light resets the clock are, however, vastly different in *Drosophila* and mice. In *Drosophila*, light leads to the degradation of TIM protein (*5*). In mice, light causes the rapid induction of *mPer1* and *mPer2* transcription (*6*). Hence, light acting during the early night causes a phase delay due to prolonged high levels of *mPer1* and *mPer2* transcripts, whereas light acting during the late evening prematurely produces *mPer1* and *mPer2* transcripts that advance the clock.

A key issue in both *Drosophila* and mice is the identity of the circadian pho-

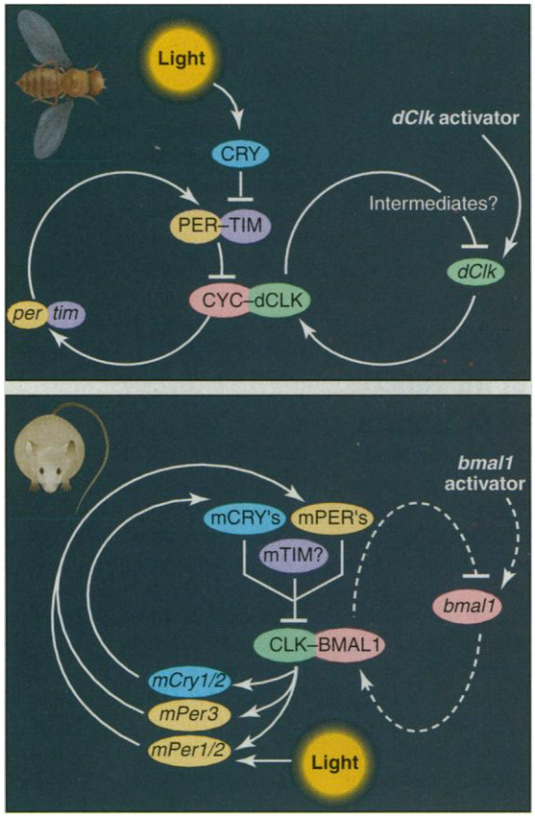
The authors are in the Department of Biology and Biochemistry and Biological Clocks Program, University of Houston, Houston, TX 77204, USA. E-mail: phardin@uh.edu

toreceptor, which initiates phase shift responses upon stimulation by light. In *Drosophila*, CRY acts as a circadian photoreceptor, resetting the clock through light-dependent interactions with TIM (*3*). The identification of two mouse *Cry* genes (*mCry1* and *mCry2*) provided a likely candidate for the mouse circadian photoreceptor (*2*). In mice genetically engineered to be deficient in mCRY1 or mCRY2 there is a significant shortening or lengthening, respectively, of the free-running period (that is, wheel running rhythms in constant darkness). In contrast, animals that are deficient in both proteins are arrhythmic under free-running conditions (*7, 8*). These results show that the *mCry* genes are required for circadian clock function, but they do not preclude a possible role for these genes in circadian photoreception.

Recent in vitro studies reveal that mCRY1 and mCRY2 play two critical roles within the circadian feedback loop itself. First, both proteins promote translocation of mPER1, 2, and 3 into the nucleus (*9*). Second, once in the nucleus, mCRY proteins effectively inhibit transcription (mediated by CLOCK and BMAL1) of reporter genes coupled to the *mPer1* promoter (*9*). This inhibition of *mPer1* is more potent than inhibition by any of the mPER proteins or mTIM, and neither the ability nor the degree of *mPer1* inhibition is dependent on light (*9, 10*). If mCRY proteins play a major role in blocking CLOCK-BMAL1–mediated transcription in vivo, then *mPer1* levels should be relatively high in the suprachiasmatic nucleus (SCN; the site of the central circadian oscillator) of mice deficient in both mCRY1 and mCRY2. Consistent with earlier results (*8*), Okamura and colleagues now show that *mPer1* and *mPer2* mRNA levels are indeed high in the double knockout mice (*4*). The lack of mCRY proteins does not result in a desynchronization of rhythmic SCN cells, because *mPer1* transcripts are elevated in each cell (*4*). Thus, mCRY proteins are core components of the mouse circadian feedback loop and repress CLOCK-BMAL1–activated transcription.

If mCRY proteins also function as circadian photoreceptors in mice, their absence should abolish light-dependent induction of *mPer1* and *mPer2* transcription. Although *mPer1* and *mPer2* mRNA levels are already high in mice lacking both mCRY1 and mCRY2, a light pulse (30 min) produces induction of *mPer1* and *mPer2* of the same magnitude as in wild-type mice (*4*). Thus, the results of Okamura's group indicate that mCRY proteins are dispensible for light-induced phase shifting of the circadian clock.

Although recent advances have provided a molecular framework for the mouse circadian feedback loop, important questions remain. First, what is the circadian photoreceptor in mice? The mouse circadian photoreceptor is present in the eye, yet elimination of essentially all rod and cone cells in the retina fails to abolish circadian photoentrainment (that is, the ability to synchronize the oscillator to external environmental light-dark cycles) (*11*). The only other clue to the identity of the circadian photoreceptor is that it appears to be a vitamin A–based photopigment (*12*). Second, is the mammalian circadian oscillator composed of interlocked feedback loops? The *Drosophila* circadian oscillator consists of a *per/tim* feedback loop, which is activated by dCLK-CYC dimers and repressed by PER-TIM dimers, and a *dClk* feedback loop, which is repressed by dCLK-CYC and derepressed by PER-TIM (*13*). These feedback loops are interlocked because the interaction of PER-TIM with dCLK-CYC simultaneously inhibits *per/tim* transcription and releases *dClk* repression, thus enabling *per/tim* and *dClk* mRNA to cycle in opposite phases (*13*). In mice, *mCry1* and *2* and *mPer1*, *2*, and *3* are activated by CLOCK and BMAL1 and repressed by mCRY and mPER (*4, 9, 14*), thus forming a feedback loop in which *mCry* and *mPer* transcripts peak during mid- to late day. Because the transcript encoding BMAL1 cycles in antiphase to the *mCry* and *mPer* transcripts (*15*), it is possible that there is an interlocked *bmal1* loop analogous to that of *dClk* in *Drosophila*. Third, what is the relationship between CRY-dependent and mPER-dependent repression? Although CRY1 and 2 and mPER1, 2, and 3 mediate varying degrees of repression in cell culture, it will be important to know how well these proteins repress in vivo and whether there is any target gene specificity. While many questions about clock function remain, it is clear that entrainment of the mouse circadian oscillator is no longer a CRY in the dark.



The CRYing game. Circadian oscillators in flies and mice. **(Top)** Model of the *Drosophila* circadian oscillator showing the *per/tim* loop **(left)** and *dClk* loop **(right)**. **(Bottom)** Model of the mouse oscillator showing the *mCry/mPer* loop **(left)** and a putative *bmal1* loop **(right)**. Key: yellow, *per* and *mPer1, 2,* or *3* genes, PER and mPER proteins; purple, *tim* gene, TIM and mTIM proteins; green, *dClk* gene, dCLK and CLOCK (CLK) proteins; pink, *bmal1* gene, CYC and BMAL1 proteins; blue, *mCry1* and *2* genes, CRY and mCRY proteins. Arrows, positive regulation; blunt-ended lines, negative regulation; dashed lines, putative regulatory interactions.

References and Notes

1. J. C. Dunlap, *Cell* **96**, 271 (1999).
2. A. R. Cashmore *et al.*, *Science* **284**, 760 (1999).
3. R. Stanewsky *et al.*, *Cell* **95**, 681 (1998); P. Emery *et al.*, *Cell* **95**, 669 (1998); M. F. Ceriani *et al.*, *Science* **285**, 553 (1999).
4. H. Okamura *et al.*, *Science* **286**, 2531 (1999).
5. M. Hunter-Ensor *et al.*, *Cell* **84**, 677 (1996); C. Lee *et al.*, *Science* **271**, 1740 (1996); M. P. Myers *et al.*, *Science* **271**, 1736 (1996); H. Zeng *et al.*, *Nature* **380**, 129 (1996).
6. U. Albrecht *et al.*, *Cell* **91**, 1055 (1997); L. P. Shearman *et al.*, *Neuron* **19**, 1261 (1997); Y. Shigeyoshi *et al.*, *Cell* **91**, 1043 (1997); T. Takumi *et al.*, *Genes Cells* **3**, 167 (1998); M. J. Zylka *et al.*, *Neuron* **20**, 1103 (1998).
7. R. J. Thresher *et al.*, *Science* **282**, 1490 (1998); G. T. J. van der Horst *et al.*, *Nature* **398**, 627 (1999).
8. M. H. Vitaterna *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 12114 (1999).
9. K. Kume *et al.*, *Cell* **98**, 193 (1999).
10. E. A. Griffin Jr. *et al.*, *Science* **286**, 768 (1999).
11. M. S. Freedman *et al.*, *Science* **284**, 502 (1999).
12. J. S. Takahashi *et al.*, *Nature* **308**, 186 (1984); I. Provencio and R. G. Foster, *Brain Res.* **694**, 183 (1995).
13. N. R. J. Glossop *et al.*, *Science* **286**, 766 (1999).
14. N. Gekakis *et al.*, *Science* **280**, 1564 (1998); J. B. Hogenesch *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 5474 (1998); A. M. Sangoram *et al.*, *Neuron* **21**, 1101 (1998).
15. S. Honma *et al.*, *Biochem. Biophys. Res. Commun.* **250**, 83 (1998); K. Oishi *et al.*, *Biochem. Biophys. Res. Commun.* **253**, 199 (1998).

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