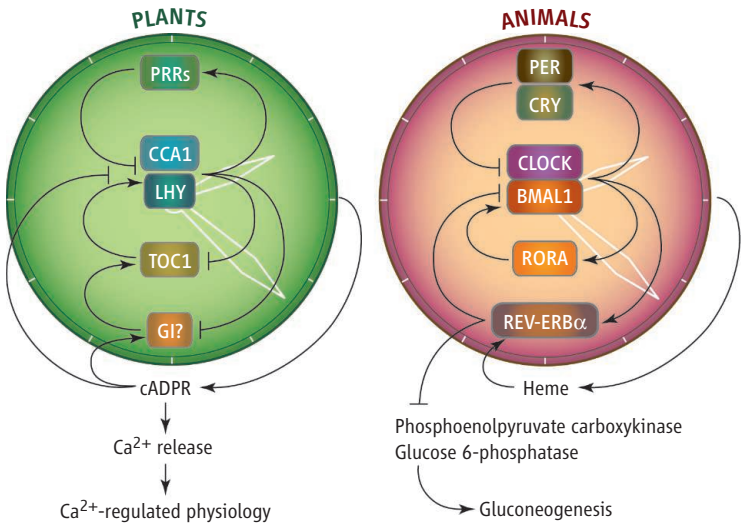
CIRCADIAN RHYTHMS

# Daily Watch on Metabolism

Plants and animals adjust responses to their environments through small molecules, including metabolites, which interact with their circadian clocks

**Takato Imaizumi, Steve A. Kay, Julian I. Schroeder**

Most organisms enhance fitness by coordinating their development with daily environmental changes through molecular timekeepers known as circadian clocks. In eukaryotes, these clocks comprise interlocking loops of transcriptional feedback and protein turnover (*1*). This system of multiple connected loops increases the clock's robustness and provides numerous points of input and output to the clock. Many metabolic pathways are regulated by circadian clocks in plants and animals (*2*, *3*). Two papers in this issue, Dodd *et al.* on page 1789 (*4*) and Yin *et al*. on page 1786 (*5*), provide evidence that clock feedback mechanisms in plants and animals incorporate small metabolites and signaling molecules. This represents yet another complex layer of feedback regulation within circadian networks, and how the clock maintains metabolic homeostasis in response to external conditions.




**Metabolic feedback to clocks.** (**Left**) The plant circadian clock comprises interlocking loops of the clock components CIRCADIAN CLOCK ASSOCIATED 1 (CCA1), LATE ELONGATED HYPOCOTYL (LHY), PSEUDO-RESPONSE REGULATORs (PRRs), TIMING OF CAB EXPRESSION 1 (TOC1), and GIGANTEA (GI). The clock controls the concentration of cADPR, which in turn regulates circadian oscillation in the cytosolic free $Ca^{2+}$ concentration. (**Right**) In the mammalian clock, the CLOCK/BMAL1 heterodimer regulates expression of PERIOD (PER), CRYPTOCHROME (CRY), RORA, and REV-ERBα. REV-ERBα is a heme sensor that forms a transcriptional repressor complex. Heme provides feedback to the circadian clock and influences gluconeogenesis.

In plant and animal cells, the concentration of intracellular free calcium ions ($[Ca^{2+}]_i$) shows a diurnal oscillation (*6*). Because $Ca^{2+}$ is a signaling molecule in various physiological responses, its daily oscillation could encode circadian clock signaling information (*7*, *8*). Analyses in the model plant *Arabidopsis thaliana* suggest that the extracellular $Ca^{2+}$-sensing receptor contributes to generating this oscillation. This pathway involves inositol 1,4,5,-trisphosphate ($IP_3$), which triggers $Ca^{2+}$ release from intracellular stores (*9*). In animal cells, cyclic adenosine diphosphate ribose (cADPR) is another signaling molecule that induces $Ca^{2+}$ release by binding to the ryanodine receptor present on intracellular stores (*10*). Although there is not yet an obvious ryanodine receptor counterpart in plant genomes, cADPR triggers $[Ca^{2+}]_i$ increase in plants as well (*11*, *12*).

Dodd *et al.* determined that cADPR concentration peaks during the early hours of the day. This fluctuation was abolished in plants with defective clock function, indicating that the circadian clock regulates cADPR concentration. cADPR is synthesized from nicotinamide adenine dinucleotide by the enzyme ADP ribosyl cyclase (*10*). Nicotinamide, at 10 to 50 mM concentrations, inhibited ADP ribosyl cyclase and weakened circadian $[Ca^{2+}]_i$ oscillation in plant cells. Dodd *et al*. also found a correlation between the expression of circadian- and cADPR-regulated genes. Moreover, decreasing the cellular concentration of cADPR lengthened the period of circadian gene expression. The authors suggest that circadian-regulated cADPR-derived $Ca^{2+}$ signaling may configure part of the feedback loop that controls the clock (see the figure).

The results of Dodd *et al.* raise interesting questions. The phytohormone abscisic acid, thought to lengthen the clock period (*13*), induces cADPR production (*11*), and cADPR gene expression overlaps with that of genes controlled by abscisic acid (*14*). Does abscisic acid affect the clock partly through cADPR-derived signals? Also, assuming that both $IP_3$- and cADPR-dependent pathways are involved in generating circadian $[Ca^{2+}]_i$ oscillation, do they interact with each other? Dodd *et al.* found that a pharmacological inhibitor (U73122 at 1 μM) of $IP_3$ production did not affect daily $[Ca^{2+}]_i$ oscillation. Because $IP_3$ concentrations were not analyzed, more research is needed to understand the relative roles of both cADPR and $IP_3$. In particular, identification of the plant genes that encode the enzymes that produce cADPR and the proteins that control $Ca^{2+}$ release by cADPR and $IP_3$ are required to analyze the functions of these signaling molecules in plants.

The circadian clock also controls daily metabolic homeostasis in mammals. Indeed, mice with a dominant mutation in *Clock*, the gene that encodes a core clock component, develop various metabolic syndromes (*15*). Many enzymes that catalyze diverse metabolic reactions require heme as a cofactor. The circadian clock regulates the heme metabolic pathway partly by controlling expression of 5-aminolevulinic acid synthase, the rate-limiting enzyme in heme biosynthesis (*3*). Yin *et al.* show that the circadian clock may also monitor heme metabolism through the clock component REV-ERBα. Heme binds to REV-ERBα and regulates its function by promoting its assembly with two proteins that repress transcription—nuclear receptor co-repressor and histone deacetylase 3 complex.

Heme suppresses the expression of genes involved in gluconeogenesis in the liver. Yin *et al.* show that in the presence of heme, REV-ERBα decreased the expression of genes encoding phosphoenolpyruvate carboxykinase and glucose 6-phosphatase, both of which control glucose production, in human hepatoma cells. Heme also augmented transcriptional repression of the core clock gene *Bmal1* by REV-ERBα. Therefore, REV-ERBα couples the circadian clock with glucose metabolism. It would be intriguing to

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study whether REV-ERBα–dependent regulation contributes to the transcriptional regulation of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase genes in *Rev-erbα*–deficient mice.

At first glance, the studies by Dodd *et al*. and Yin *et al*. appear unrelated. However, they propose that both plant and animal clocks possess a mechanism for implementing cellular signaling or redox status in the fine-tuning of daily transcriptional regulation. Thus, a common theme emerges in which small molecules provide feedback mechanisms between the circadian clock network and clock-controlled metabolic pathways to maintain metabolic homeostasis.


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ATMOSPHERIC SCIENCE

# Resolving an Atmospheric Enigma

Data and modeling are helping to explain what drives an important atmospheric oscillation in the tropics.


**Dennis L. Hartmann and Harry H. Hendon**


In 1971, meteorologists Roland Madden and Paul Julian studied weather data from near-equatorial Pacific islands. To their surprise, tropospheric winds, pressure, and rainfall oscillated with a period of about 40 to 50 days (*1*). The oscillation in clouds and precipitation tends to be confined to the tropical Indian and Pacific oceans, but the oscillation in winds and pressure is felt throughout the tropics (see the figure). The search for a single robust theory for this Madden-Julian Oscillation (MJO) continues today.

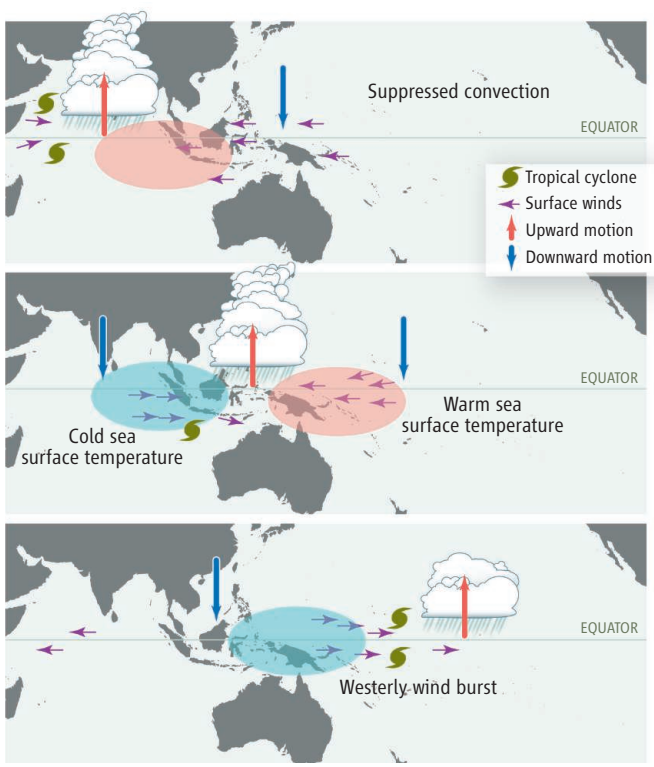
The MJO is not a true oscillation, in the sense that its period varies and its appearance is episodic, but it is the largest source of tropical weather variability on subseasonal time scales, especially in the Indian and Pacific oceans. On page 1765 of this issue, Matthews *et al.* (*2*) use observations from the new Argos system of profiling floats to reveal the deep-ocean response to the MJO. Also in this issue, Miura *et al*. on page 1763 report an advance in modeling the MJO (*3*).

Because of its large amplitude and long period, the MJO affects many people. It causes prolonged dry and wet episodes during the Asian Summer Monsoon and modulates the intensity, frequency, and location of tropical storms in the Indian, Pacific, and Atlantic oceans (*4*, *5*). The strong and persistent surface winds associated with the MJO drive a large response in the upper ocean (*6*). Matthews *et al.* have measured the deep ocean response to wind surges associated with the oscillation. It is as yet unclear what effect this has on the deep ocean. The MJO also influences the onset and intensity of El Niño events and may underlie the very existence of the El Niño–Southern Oscillation (*7*).

In climate models, the MJO is typically weaker and moves faster than is observed. Weather prediction models cannot sustain the MJO. Coupled ocean-atmosphere models tend to produce more realistic simulations, because the MJO interacts strongly with the upper ocean, but this coupling is not essential for the existence of the oscillation (*8*, *9*).

Observations show that a wide range of scales interact within the MJO, ranging from the scale of individual convective cells a few kilometers across and a few hours in duration to the 10,000-km planetary scale of the 40- to 50-day variation (*10*). Similar to a hurricane but on a much larger scale, the release of latent heat in moist convection drives the planetary-scale wind variations of the MJO. The planetary wind variations in turn provide organization to the convective-scale phenomena, suppressing convection in some regions and enhancing it in others.

Because the MJO arises from the interaction of convective and planetary scales, it serves as a probe into our ability to understand and model the interaction of convection and clouds with climate. This interaction remains one of the largest uncertainties in climate projections (*11*). The inability to properly simulate the MJO indicates inaccurate treatment of the interaction between the scale of convection—perhaps 1 km or




**The Madden-Julian Oscillation.** Precipitation first develops in the Indian Ocean and moves eastward with a speed of about 5 m $s^{-1}$. Surface winds converge under the convection, and a burst of eastward surface winds follows the passage of the heaviest rainfall. This burst is an important driver for ocean dynamics. Each panel is separated by ~15 days.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