

Clockwork allergy: How the circadian clock underpins allergic reactions



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Allergic disease is characterized by marked day-night changes in the clinical symptoms and laboratory parameters of allergy. Recent reports suggest that the circadian clock, which drives a biological rhythm with a periodicity of approximately 24 hours in behavior and physiology, underpins a time of day-dependent variation in allergic reactions. New studies also suggest that disruption of clock activity not only influences temporal variation but can also enhance the severity of allergic reactions and even increase susceptibility to allergic disease. These findings suggest that the circadian clock is a potent regulator of allergic reactions that plays more than a simple circadian timekeeping role in allergy. A better understanding of these processes will provide new insight into previously unknown

aspects of the biology of allergies and can lead to the application of clock modifiers to treat allergic disease. Finally, this area of research provides a novel opportunity to consider how modern lifestyles in the developed world are changing the clinical manifestations of allergy as our society quickly transforms into a circadian rhythm-disrupted society in which sleeping, working, and eating habits are out of sync with endogenous circadian rhythmicity. Such findings might reveal lifestyle interventions that enable us to better control allergic disease. (*J Allergy Clin Immunol* 2018;142:1021-31.)

Key words: Circadian clock, period2, allergy, mast cell, chronotherapy

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The circadian rhythm is a biological rhythm with a periodicity of approximately 24 hours and is observed in the behavior and physiology of virtually all living organisms. The word *circadian* is derived from the Latin *circā* (“about”) and *diēs* (“a day”), meaning about a day. Circadian clocks are the endogenous time-keeping mechanisms that drive circadian rhythms.¹⁻³ Circadian clocks generate robust approximately 24-hour rhythms, even in the absence of external inputs, but can adjust their timing in response to environmental cues, such as light, meal timing, exercise, and strong social interactions.

It is well documented that allergic diseases exhibit a circadian oscillation. Many symptoms and laboratory parameters in

Abbreviations used

AD:	Atopic dermatitis
AQP3:	Aquaporin 3
BMAL1:	Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1
CCG:	Clock-controlled gene
CK:	Casein kinase
CLOCK:	Circadian locomotor output cycles kaput
Cry:	Cryptochrome
PCA:	Passive cutaneous anaphylaxis
Per:	Period
SCN:	Suprachiasmatic nucleus
TEWL:	Transepidermal water loss

patients with allergic diseases show marked day-night changes.^{4,5} For instance, in most patients with allergic rhinitis, symptoms worsen overnight or early in the morning (“morning attack”), thereby compromising nighttime sleep and resulting in poor daytime quality of life.⁴ However, until recently, the precise mechanisms underlying these observations have remained enigmatic.

New studies reveal that the immune system is fundamentally connected to the circadian clock system.⁶⁻¹⁰ As a type of immune response, an allergic reaction is also intrinsically under the control of the circadian clock.¹¹⁻¹³ This review summarizes recent advances in our understanding of clock-controlled allergic reactions, the effect of circadian disruption on allergy, and the potential application of clock modifiers to control allergic disease.

MOLECULAR CLOCKS TICK-TOCK INSIDE OF MAMMALIAN CELLS

Virtually all living organisms are subjected to 24-hour periodic changes in their external environment driven by the rotation of the earth. These environmental changes include a light/dark cycle, changes in temperature and food availability, and risk of predator attack. Consequently, organisms have evolved internal timers referred to as circadian clocks that drive daily rhythms in behavior and physiology, enabling them to anticipate and adapt to daily alterations in the environment.¹⁻³

In mammals circadian rhythms are generated from cyclic gene expression controlled by cell-autonomous and self-sustained molecular clocks within each cell.^{2,3} These molecular clocks consist of interlocked transcriptional-translational feedback loops centered on the transcription factors brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK) (Fig 1). BMAL1, which heterodimerizes with CLOCK, binds to E-box motifs throughout the genome and drives transcription of target genes, including their own repressors period 1 (*Per1*), *Per2*, and *Per3* and cryptochrome 1 (*Cry1*) and *Cry2*. PER and CRY proteins form oligomers and enter the nucleus, where they inhibit BMAL1/CLOCK activity. This negative-feedback loop, in conjunction with multiple layers of posttranscriptional regulation, takes approximately 24 hours to be completed, which acts as a molecular oscillator controlling periodic expression of thousands of clock-controlled genes (CCGs) with E-box motifs in the promoter/enhancer regions. Most of the CCGs encode key regulators of various cellular pathways in metabolism and

hormonal, neural, and immune functions. Indeed, Bmal1-deficient mice lack a functional molecular clock, leading to a loss of CCGs oscillation in most tissues and resulting in behavioral and physiologic arrhythmicity.¹⁴

In addition to this core loop, there is a stabilizing loop that regulates the timing and amplitude of Bmal1. This stabilizing loop is provided by the nuclear receptors retinoic acid–related orphan receptor (ROR) α and REV-ERB α (*Nr1d1*). The BMAL1/CLOCK heterodimer activates transcription of ROR α and REV-ERB α , which activates or represses BMAL1 transcription, respectively. Details of transcriptional regulation by the mammalian circadian clock, including dynamic control of chromatin remodeling on a daily basis, have been reviewed elsewhere.^{15,16}

Molecular clocks regulate the timing of cellular activities by controlling a large proportion of CCGs in a cyclic manner. For instance, 1,403 (approximately 8.1%) genes out of a total of 17,308 genes expressed in mouse peritoneal macrophages oscillate in a circadian fashion.¹⁷ These genes include many important regulators of pathogen recognition and cytokine secretion. This results in daily variation in the immune response to bacteria or viruses.⁶⁻¹⁰

Generally, cycling genes are expressed at high levels, and energy needed to synthesize and degrade mRNAs and protein levels of cyclic genes is as much as 2 times greater than that of noncyclic genes.¹⁸ Thus highly expressed genes might be selected to be downregulated in a cyclic manner for energy conservation, and rhythmic gene expression might optimize the metabolic cost of global gene expression.¹⁸

Under constant conditions, molecular clocks autonomously oscillate with a periodicity of around 24 hours (free run, about 23.5 hours in mice), so that the phase needs to be adjusted every day to match the periodic environmental signals. Each component of a molecular clock can be regulated by nonclock proteins, such as nuclear hormone receptors (eg, the glucocorticoid receptor).^{2,3} These regulations result in adjustments to a molecular clock's phase, amplitude, and period in response to inputs from signaling associated with temporally relevant events, such as light and feeding, as discussed below.

MULTICELLULAR CLOCKS ARE SYNCHRONIZED AT THE WHOLE-ORGANISM LEVEL

The human body consists of approximately 40 trillion cells, each having their own clock. How are the numerous cellular clocks coordinated within our body? In mammals the circadian clock system consists of the master oscillator, which is located in the suprachiasmatic nucleus (SCN) neurons of the hypothalamus (the central clock), and peripheral oscillators, which are present in virtually all cell types, including immune cells (peripheral clocks; Fig 2).^{2,3} The SCN receives innervation from the retina, allowing it to be entrained by solar light/dark cycles. Actually, light signaling increases *Per* expression in the SCN neurons and induces phase shifts of the circadian rhythms. In turn, the central SCN clock transmits time-of-day information to peripheral clocks through the hypothalamus-pituitary-adrenal axis and the autonomic nervous system.^{19,20} Thus the main function of the SCN clock is to organize stable phase relationships in the peripheral oscillators. This hierarchically organized system keeps the central and peripheral clocks in phase with each other and synchronizes temporal programs of physiology across many

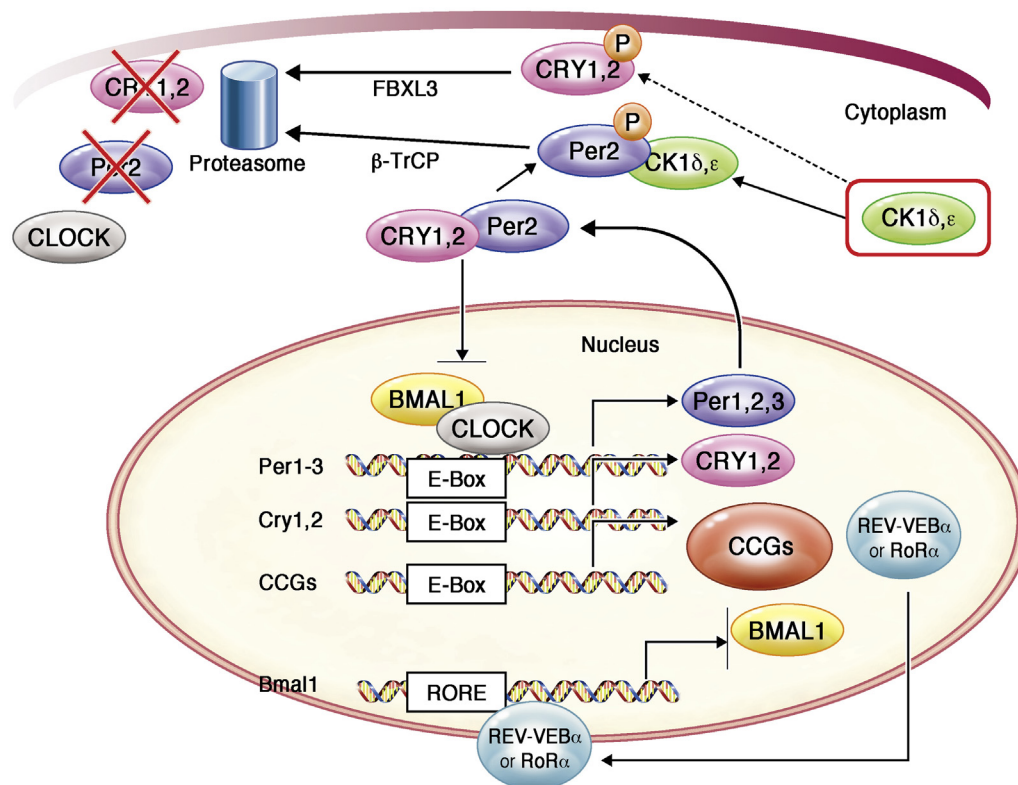


FIG 1. A canonical model of the mammalian molecular clock. In mammals the molecular basis of circadian timing involves a transcriptional-translational feedback loop consisting of several "clock genes" within each cell. The transcription factors Bmal1 and Clock heterodimerize to activate transcription of *Per*, *Cry*, genes encoding ROR α and Nr1d1 (REV-ERB α), and other CCGs with E-box (CANNTG) motifs in their promoter/enhancer regions. The resulting PER and CRY protein dimers translocate into the nucleus and inhibit their own expression by repressing BMAL1/CLOCK activity. This negative feedback loop is also controlled by posttranscriptional regulation through turnover of PER and CRY after phosphorylation mediated by CK1 δ/ϵ . Phosphorylated PER and CRY are actively targeted by using the ubiquitin ligases β -TrCP and FBXL3, respectively, for ubiquitination and proteasome-dependent degradation. Accordingly, the core clock cycle takes approximately 24 hours to be completed and leads to approximately 24-hour rhythms of CCG expression. This core loop is influenced by auxiliary feedback loops by ROR α and REV-ERB α . The BMAL1/CLOCK heterodimer activates transcription of ROR α and REV-ERB α that activates or represses BMAL1 transcription, respectively. PF-670432 is a chemical compound that inhibits CK1 δ/ϵ activity, slows down PER degradation, and lengthens the circadian period. Please note that this model is classical and that recent studies have revealed that the molecular clock consists of a more complex network of clock genes.

and corticosterone in mice) from the adrenal gland exhibits circadian rhythms driven by the SCN and adrenal clocks, with a strong peak before onset of the active phase.²³ Therefore a glucocorticoid surge directed by the SCN can synchronize mast cell clocks at the population level once a day.

Sympathetic nerve activity can mediate numerous effects on immune cells either directly through adrenergic receptors on immune cells or indirectly through regulating blood or lymph flow, modulating the release of neuropeptides, such as substance P, from sensory nerve endings or regulating leukocyte distribution.²⁴ Interestingly, recent studies in mice suggest that norepinephrine released from sympathetic nerve endings can control lymphocyte trafficking to lymph nodes in a circadian manner by synchronizing lymphocyte clocks and maintaining rhythmic expression of promigratory factors on lymphocytes in phase at the population level.^{25,26} Thus the sympathetic nerve activity, under strong control of the SCN, might also act as a timing cue to immune cell clocks through norepinephrine.

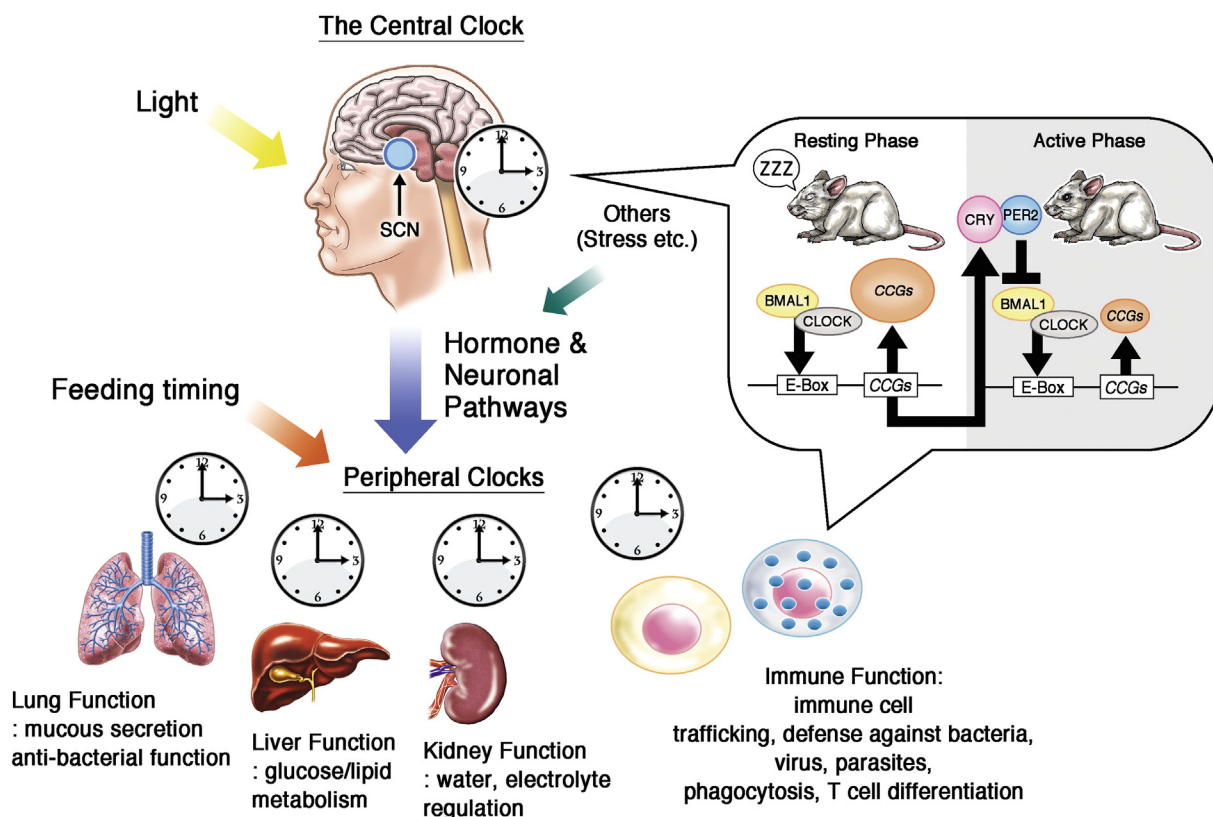


FIG 2. Hierarchically organized circadian clock system in mammals. The mammalian circadian clock consists of the central oscillator, which is located in the SCN of the hypothalamus, and peripheral oscillators present in virtually all cell types, including immune cells. Molecular mechanisms of rhythm generation in the SCN and peripheral cells are cell autonomous and highly conserved as described in Fig 1. The SCN receives innervation from the retina, allowing it to be entrained by solar light/dark cycles. In turn, the SCN transmits time-of-day information to peripheral clocks through the hormonal and/or autonomic nervous system. This hierarchically organized system keeps the central and peripheral clocks in phase with each other and synchronizes temporal programs of physiology across many tissues. Peripheral clocks in each organ or cell regulate local physiology in a circadian manner. Representative functions in each organ or cell under circadian control are indicated. Importantly, peripheral clocks can be entrained independently of the SCN by several nonphotic zeitgebers, such as food timing and social interaction (eg, stress). The core molecular clock machinery in nocturnal mice is shown in the box.

ENTRAINMENT OF THE CIRCADIAN CLOCK BY NONPHOTIC SIGNALS

Entrainment is the process by which circadian clock activity becomes synchronized to a 24-hour periodic environmental cue called “zeitgeber” (German for “timegiver”). As discussed above, light, especially blue-wavelength light, is a strong zeitgeber to which the central SCN clock is entrained and readjusts its timing (phase and period).

Recent studies reveal that peripheral clocks can be entrained by several nonphotic zeitgebers, such as food timing, temperature, exercise, and stress, independently of the SCN.^{27,28} For example, livers of mice fed exclusively during the night (their active phase) or *ad libitum* show a similar phase angle of cyclic liver gene expression. In contrast, feeding during the day almost entirely inverts the phase of liver oscillatory gene expression.^{29,30} This suggests that food intake in opposition to an established circadian rhythm can decouple peripheral clocks from the light-sensitive SCN. The precise mechanisms underlying the entrainment of peripheral clocks by nonphotic cues remain to be determined.

Importantly, such a misalignment of peripheral clocks across the body to the SCN rhythm (internal desynchrony) can

undermine physiologic circadian rhythms, posing a threat to health.³¹ Many epidemiologic studies show that chronic internal desynchrony, as induced by irregular eating times (eg, shift workers), increases the risk of metabolic diseases.^{27,31}

CIRCADIAN NATURE OF ALLERGIC DISEASE

Since the early 1960s, many reports have demonstrated the circadian nature of allergic disease.^{4,5} In patients with allergic rhinitis and asthma, symptoms, nasal or bronchial reactivity, and inflammatory activity are intense nocturnally, during sleep, and in the early morning. Nocturnal pruritus is a typical feature of atopic dermatitis (AD) and is associated with the circadian rhythms related to skin temperature, pH, and transepidermal water loss (TEWL).^{5,32} As a recent example, allergen-induced CD203c expression on basophils (basophil activation test) was shown to exhibit time of day-dependent variation in patients with seasonal allergic rhinitis,³³ although further research is required to confirm these findings.³⁴ Circadian variations found with respect to allergic manifestations suggest that these variations might be an important consideration when managing patients in clinical practice.

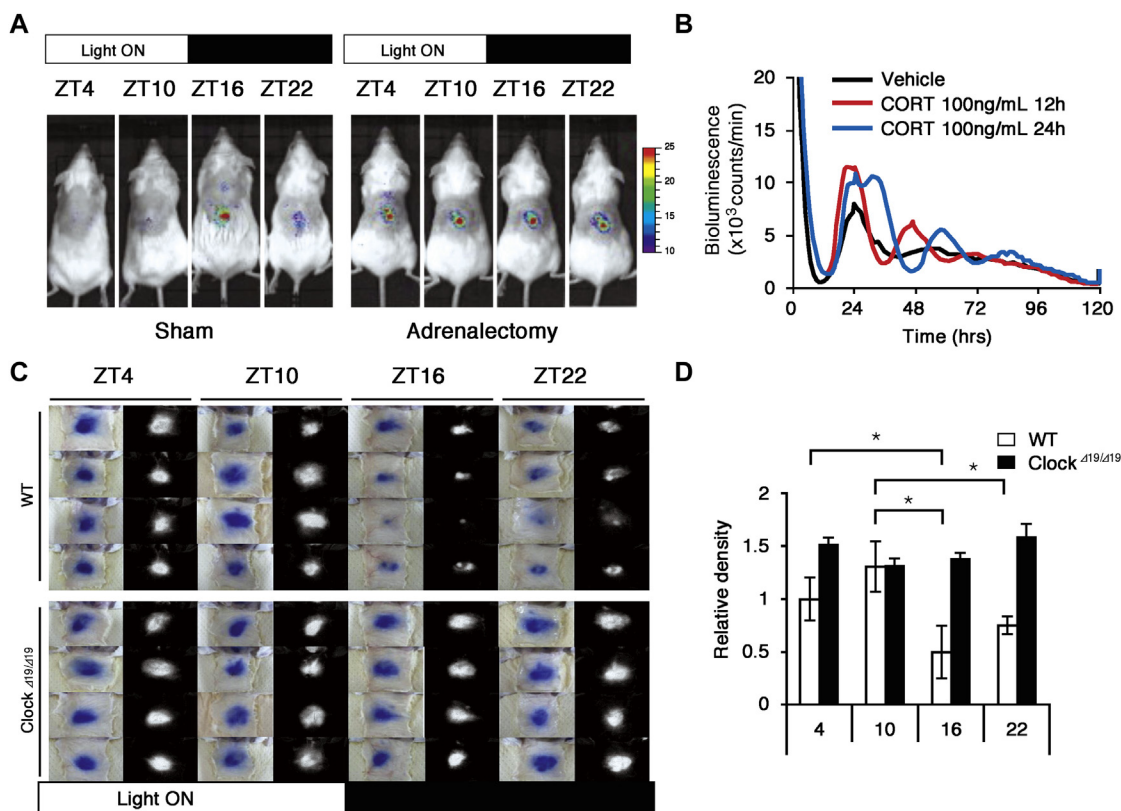


FIG 3. Circadian regulation of the mast cell clock and IgE-mediated mast cell activation. **A**, Mast cell-deficient W/Wv mice were reconstituted by subcutaneous injections of bone marrow-derived mast cells (BMMCs) obtained from PER2:LUC knock-in mice, which express a fusion protein of PER2 and luciferase [LUC]. Mice were housed under 12-hour light/12-hour dark conditions (the light was turned on at 6 AM, which is zeitgeber time [ZT] 0, and the light was turned off at 6 PM, which is ZT12). Representative pictures of *in vivo* imaging of mast cell-deficient W/Wv mice reconstituted with BMMCs from PER2:LUC knock-in mice at the indicated time points are shown. Before *in vivo* imaging, the mice were subjected to a sham operation (*Sham*) or adrenalectomy (*ADX*). The bioluminescence emission from the mice (reflection of PER2 expression in mast cells) showed a time of day-dependent variation in sham-operated mice, with a peak at 10 PM (ZT16), which was absent in adrenalectomized mice. **B**, PER2:LUC bioluminescence of BMMCs obtained from PER2:LUC knock-in mice (PER2:LUC BMMCs) with or without *Clock* mutation (wild-type [WT] or *Clock*^{Δ19}) was monitored over a period of 120 hours. A simple medium change is a trigger to synchronize the circadian clocks in peripheral cells *in vitro*. Rhythms of BMMC cultures indicated by rhythmic PER2:LUC protein expression become asynchronous approximately 72 hours after the medium change because of a lack of oscillator coupling in the dissociated cell cultures, leading to damping of the ensemble rhythm at the population level. Corticosterone (*CORT*) or PF-670432 was added at 72 hours after the media change, as indicated by arrows. When corticosterone or PF-670432 was added to the culture, WT, but not *Clock*-mutated, PER2:LUC BMMCs showed resynchronization of the mast cell clockworks and exhibit daily oscillation of PER2:LUC expression at the population level. **C**, Representative pictures of skin color reactions in W/Wv mice reconstituted with WT BMMCs or *Clock*-mutated BMMCs (*Clock*^{Δ19/Δ19}, left panels) and digitalized images of density value evaluations (right panels) at the indicated time points. Data shown are results from the same group of WT or *Clock*^{Δ19/Δ19} mice challenged at the indicated time points. The extent of PCA reactions showed a time of day-dependent variation in control mice, with a clear nadir around the onset of night (10 PM, which was ZT16). This variation was absent in mast cell-specific *Clock*-mutated mice. **D**, Quantitative analysis of the data in Fig 3, C. Values represent means $\pm$ SDs. **P* < .05. Modified from Nakamura et al.^{21,22}

THE CIRCADIAN CLOCK UNDERPINS RHYTHMIC ALLERGIC REACTION

The mechanisms that underlie these circadian-based allergic manifestations have remained elusive. However, new studies using rodent models of allergies suggest that the circadian clock is primarily responsible for rhythmic allergic reactions by immune cell-intrinsic clocks and/or immune cell-extrinsic clock-dependent mechanisms.

The passive cutaneous anaphylaxis (PCA) reaction is a rodent model of IgE/mast cell-dependent immediate-type allergic

reaction in the skin. The degree of PCA reaction in wild-type mice shows circadian rhythmicity, with a peak during the resting phase and a trough during the active phase.³⁵ The reaction becomes arrhythmic in mast cell-selective *Clock*-mutated mice (Fig 3, C and D), suggesting that the mast cell clock is a primary contributor to the rhythmic PCA reaction.²¹ Specifically, the mast cell clock controls expression of the β subunit of Fc ϵ RI (*Fcer1b*), thereby temporally gating mast cell response to IgE.²¹

Interestingly, a rhythmic PCA reaction is also absent in adrenalectomized mice.³⁵ As discussed above, a glucocorticoid

(corticosterone in mice) likely acts as a timing signal directed by the SCN to synchronize the mast cell clockworks at the population level. Thus the absence of daily rhythms during PCA reactions in adrenalectomized mice can be attributed to a loss of synchronicity of mast cell clockworks likely caused by aberrant release or loss of corticosterone and a subsequent uncoupled mast cell response to IgE at the population level.²¹ Taken together, these data suggest that a rhythmic PCA reaction is likely underpinned by coherence between the mast cell clocks and the central SCN clock through a glucocorticoid.

Scratching and skin barrier dysfunction (eg, enhanced TEWL), pivotal features of AD, show circadian rhythms in patients with AD and NC/Tnd mice, an AD model.^{5,36} In the epidermis of wild-type mice, expression of aquaporin 3 (*Aqp3*), a regulator of water content and TEWL, exhibits circadian rhythms, which become arrhythmic in *Clock*-mutated mice.³⁷ Specifically, mouse *Aqp3* and the human homolog *AQP3* exhibit daily oscillation in mouse skin or human keratinocytes. The oscillation is regulated by molecular clocks. Thus expression of *AQP3* or other key molecules for pruritus and skin barrier function is likely controlled by molecular clocks in skin cells that generate circadian variations in the pathophysiology of AD.

Unfortunately, the circadian nature of asthma has not been recapitulated in experimental rodent models. However, in the ovalbumin model of allergic asthma, mice lacking *Bmal1* in myeloid cells show markedly increased features of asthma when compared with control mice.³⁸ Similarly, *Bmal1*-deficient mice show exacerbation of acute viral bronchiolitis caused by Sendai virus and influenza and common viral triggers of asthma and have much more extensive asthma-like airway changes.³⁹ These results suggest that *Bmal1* in myeloid cells is likely a negative regulator for the development of asthmatic inflammation. Thus daily rhythmic activity of *BMAL1* in the lung might drive the circadian nature of asthma, although the precise mechanisms remain unknown. Interestingly, *Bmal1* expression is reduced in asthmatic patients during the resting phase (night in human subjects) compared with that in healthy subjects.³⁹ When *Bmal1* expression is low, symptoms in asthmatic patients can be exacerbated.

In addition to immune cell clocks, epithelial cell clocks might also play a role in the circadian nature of lung inflammation. LPS-induced lung inflammation varies with the time of day in mice. *Bmal1* in bronchial epithelial cells temporally regulates inflammation by controlling production of *Cxcl5*, a potent neutrophil chemoattractant, from epithelial cells.⁴⁰ Because the LPS response in the lung determines the development and severity of asthma,^{41,42} epithelial cell clock-mediated temporal control of the LPS response in lungs can also contribute to the circadian nature of asthma.

Few studies have reported a circadian nature to food allergy and anaphylactic shock in human subjects. However, in a mouse model of food allergy, antigen challenge during the resting phase induced greater allergic diarrhea and weight loss than antigen challenge during the active phase.⁴³ This is associated with decreased expression of tight junction molecules in the small intestine and increased antigen absorption during the resting phase. In addition, the degree of the passive systemic anaphylactic reaction, a model of IgE/mast cell-dependent systemic anaphylaxis, shows that circadian rhythms in wild-type mice, similar to the PCA reaction, become arrhythmic in SCN-disrupted mice.⁴⁴ Thus the time of food antigen intake

might affect the severity of food allergy symptoms or systemic anaphylaxis, which might be due in part to clock control of tight junction molecule expression and intestinal barrier function.

Collectively, rhythmic allergic reactions likely involve rhythmic expression of key molecules in the pathophysiology controlled by immune cell or residential cell clocks, which is coupled to inputs from the central SCN clock through humoral and neural pathways. Importantly, it appears that disruption of functional clock activity results in loss of suppression of allergic reactions during the active phase (eg, PCA reaction: Fig 3, C and D), suggesting that the clock mechanism principally contributes to suppression of allergic reactions during the active phase.

CIRCADIAN DISRUPTION CAN PROMOTE ALLERGY

Allergy-related peripheral clocks (eg, mast cell clocks) are likely primary drivers for rhythmic allergic reactions. Thus we assume that under a consistent daily pattern of environmental timing cues (zeitgebers), such as normal light/dark and eating/fasting cycle, allergy-related peripheral clocks are properly aligned with the SCN rhythm through humoral and/or neural pathways and drive circadian allergic reactions. Accordingly, any genetic or environmental factors that change allergy-related peripheral clock activity can affect clock-controlled output genes and alter the manifestation of allergic reactions. These include genetic disruption of clock genes or mechanical disruption of the SCN in rodents, mismatched zeitgeber arrivals, aberrant hormone or autonomic nerve activity, and direct perturbation of peripheral clocks. Because the effects of genetic or mechanical disruption of clock genes or SCN, respectively, on allergic reactions are described above, this section discusses influences of other circadian-disrupting factors on allergic reactions.

Mismatched environmental zeitgeber arrivals (eg, irregular circadian light environment or food intake in jet lag or shift work) can make the central clock, peripheral clocks, or both be continuously phase reset, free run, or arrhythmic at the population level. This can undermine circadian rhythmicity of the peripheral clock activity in allergy-related cells, although the detailed mechanisms leading to this response remain to be determined.

Recent studies have shown that aberrant light/dark conditions mimicking jet lag exacerbate virus-induced, asthma-like inflammation.³⁹ In addition, mice housed under a 10-hour light/10-hour dark cycle for 8 weeks, but not mice housed under a normal 12-hour light/12-hour dark cycle, had loss of temporal variations in IL-33- or compound 48/80-mediated mast cell responses (ie, loss of suppression during the active phase), and the inflammatory responses are persistently severe during the entire circadian day.^{45,46} More interestingly, aberrant light/dark conditions abrogate intestinal epithelial barrier function, thereby promoting sensitization to food antigen in mice, and in nurses involved in shift work, a consistent positive correlation is seen between day-shift and night-shift rotation and the incidence of food allergy, suggesting that circadian arrhythmia can play a role in sensitivity to food allergens.⁴⁷ Taken together, these studies suggest that mismatched environmental zeitgeber arrivals can exacerbate allergic reactions or even increase susceptibility to allergic disease.

Hormonal or autonomic nerve activity synchronizes a vast number of peripheral clocks to the SCN rhythm. Thus aberrant hormone secretion or autonomic nerve activity could also

desynchronize peripheral clocks and undermine peripheral clock rhythms at the population level, thereby influencing allergic reactions. For instance, chronic stress would be related to abnormal cortisol levels.⁴⁸ Indeed, mice subjected to chronic restraint stress showed arrhythmicity in *PER2* expression in mast cells associated with the loss of time of day–dependent variation in mast cell activation.⁴⁶ In addition, one can speculate that circadian disruption and arrhythmicity in patients with allergic reactions can occur in allergic patients treated with a long half-life synthetic glucocorticoid because of the loss of physiologic circadian rhythms of glucocorticoids that have a strong synchronizing effect on peripheral clocks, including the lung and nasal mucosa.^{49,50}

Inflammatory or tissue injury factors can directly affect peripheral clock activity. For instance, the phase, period, and amplitude of clock gene and CCG expression in normal lung tissue can be altered by exposure to cigarette smoke, viral or bacterial infection, or inflammatory mediators, such as TNF- α and LPS.⁵¹ In patients with allergic rhinitis, nasal allergen challenge upregulates expression of *Clock* and *Bmal1*, as well as T_H2 cytokines, in the late-phase reaction.⁵² These changes in clock gene expression in peripheral cells could undermine or alter rhythmicity in allergic reactions.

Interestingly, a genome-wide approach investigating circadian gene expression in the lungs of LPS-treated mice revealed that novel cellular and molecular circadian rhythms are elicited in these mice.⁵³ For instance, rhythmic expression of *Nlrp3*, a component of the inflammasome, was observed in the endotoxemic but not normal lung. Thus it appears that peripheral clock activity has plasticity, altering the circadian transcriptome as an adaptive process and thereby optimizing local functions according to environmental changes at the tissue or organ level.

SLEEP DISTURBANCE CAN AFFECT ALLERGY THROUGH CIRCADIAN DISRUPTION

Sleep is an evolutionally conserved behavior in animals from worms and jellyfish to birds and mammals.⁵⁴ Increasing data on fruit flies, zebra fish, mice, and human subjects suggest that the central and peripheral clocks use diverse mechanisms to regulate distinct aspects of sleep.⁵⁴ Perhaps the most compelling evidence that the circadian clock is a dominant controller of the timing of sleep and wakefulness is the observation that mutations in clock genes in mice and human subjects alter the timing of sleep within the circadian day.^{55,56}

Sleep disturbance is common in patients with allergic disease and impairs quality of life. Generally, the severity of allergic symptoms is closely associated with sleep disturbance.^{4,5,13,32,57} Hence the increased frequency of nocturnal symptoms related to disease severity might be a cause of sleep disturbance in allergic patients. However, the pathophysiology of sleep disturbance in allergic patients is poorly understood.³²

In most cases sleep disturbance in allergic patients is associated with altered circadian rhythmicity in physiology, including loss of rhythmic secretion of melatonin.^{32,57} This suggests that sleep disturbance *per se* can induce alteration (or disruption) of normal clock activity in allergic patients. Indeed, the relationship between the circadian clock and sleep is bidirectional. Sleep deprivation can alter the expression and DNA binding activity of core clock genes.^{58–61} Thus there might exist a vicious

cycle: nocturnal allergic symptoms induce sleep disturbance, which in turn affects the central SCN clock activity, leading to alteration of normal circadian rhythms. As a result, alteration of allergy-related peripheral clock activity can occur through modulation of the SCN-controlled neural or hormonal pathways and affect allergic reactions. In this context interventions that restore normal circadian clock activity (eg, melatonin treatment; see below) might be beneficial for sleep disturbance in patients with allergic disease.

However, I would like to emphasize that it is currently very difficult to dissect whether sleep disturbance affects allergy through clock disruption because sleep can influence many pathways that regulate metabolism, hormonal, neural, and immune function irrespective of the circadian clock. Also, it is difficult to know what is chicken and what is egg when looking into reciprocal effects on clock function and sleep.

CLOCK MODIFIERS HAVE THERAPEUTIC POTENTIAL FOR ALLERGY

Allergic diseases are among the most suitable targets for chronotherapy (ie, the practice of delivering drugs in synchrony with the circadian cycle of symptoms). For example, the antihistamine mequitazine exhibits improved efficacy against allergic rhinitis when administered in the evening instead of in the morning.⁶²

Because the circadian clock underpins rhythmic allergic reactions, synthetic compounds capable of modifying the period, phase, or amplitude of clock gene expression can have potential as new antiallergy drugs. Thus far, pharmacologic modulation of 2 circadian components, casein kinase (CK) 1 δ/ϵ and REV-ERB α , are extensively studied as candidates for circadian rhythm disorders, including jet lag, sleep disturbance, metabolic disease, inflammation, and cancer.^{63–66}

CK1 δ/ϵ plays a critical role in the posttranslational modification of molecular clocks. CK1 δ/ϵ phosphorylates the PER protein, leading to its ubiquitin-dependent degradation and determining the intrinsic period of the cellular clock (Fig 1). Therefore inhibition of CK1 δ/ϵ slows down PER protein turnover, decelerates clock progression, and lengthens the circadian period.⁶⁴

In mast cells CLOCK directly controls circadian expression of *FCER1B* and facilitates cellular response to IgE during the resting phase.²¹ Accordingly, PF-670432, an inhibitor of CK1 δ/ϵ kinase (Fig 1), downregulates IgE-mediated mast cell activation when the molecule increases PER2 (a negative regulator of CLOCK activity) expression in mast cells both *in vitro* (Fig 3, B) and *in vivo*.²²

REV-ERB α is a transcriptional repressor that regulates the expression of genes involved in control of circadian rhythm, metabolism, and the inflammatory response. The serum IL-6 response to intraperitoneal LPS challenge in wild-type mice varies with the time of day, which is lost in *Rev-erba*–deficient mice and in macrophages cultured from these animals, despite maintenance of circadian rhythmicity within these cells.⁶⁵ In addition, synthetic REV-ERB α ligands inhibit LPS-induced IL-6 production in human macrophages. Thus REV-ERB α might link the circadian clock to innate immune function, and synthetic REV-ERB α ligands might be beneficial for the treatment of inflammatory diseases including allergy, with minimum adverse effects on systemic clock activity.

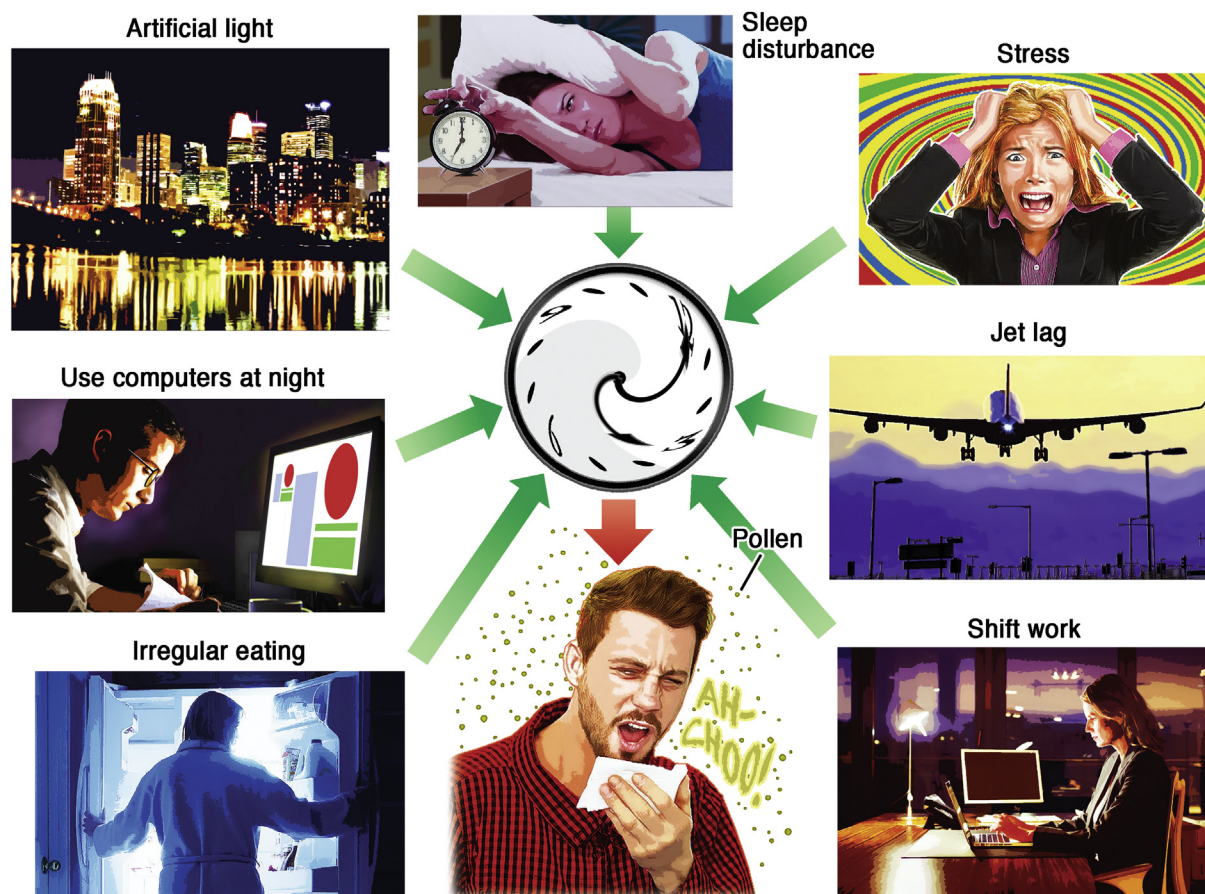


FIG 4. Multiple environmental variables can affect allergic reactions by modulating clock activity. Circadian clock activity is affected by multiple environmental variables, including light/dark cycle, food timing, social interaction (eg, stress), and sleep disturbance. These factors can alter the temporal profile, intensity, and susceptibility to allergic reactions by modulating clock activity and can affect symptoms, laboratory parameters, and optimal timing of treatment in allergic patients. A case of pollinosis is represented in this illustration. In addition to the environmental variables depicted here, the gut microbiome and aging have recently been shown to influence circadian clock activity.^{81,82}

Melatonin is a hormone secreted by the pineal gland in a circadian manner, with a peak in the middle of the night.⁶⁷ Melatonin promotes sleep by directly phase-shifting the central SCN clock or by decreasing the core body temperature, which can induce sleep.⁶⁷ In addition, melatonin has immunomodulatory and antioxidant abilities.³² For instance, melatonin inhibits the development of AD-like dermatitis in NC/Nga mice by suppressing the activation of CD4⁺ T cells.⁶⁸ Based on these properties with minimal adverse effects, melatonin is a promising drug candidate to improve both sleep disturbance and inflammation in patients with allergic disease. Indeed, in a randomized clinical trial melatonin was shown to promote sleep onset and reduce disease severity in children with AD.⁶⁹

As a strong synchronizer of peripheral clocks, glucocorticoids are clock modifiers.⁷⁰ Therefore the effects of synthetic glucocorticoids on allergic disease can be attributed in part to their phase-shift activity on peripheral clocks. Indeed, dexamethasone suppresses IgE-mediated degranulation both *in vitro* and *in vivo* only when dexamethasone increases PER2 levels in mast cells or basophils, similar to PF-670432.²²

Interestingly, dexamethasone does not show these effects in *Clock*-mutated mast cells or basophils, suggesting that functional clock activity is required for glucocorticoid actions.²² Actually,

the relationship between circadian clocks and glucocorticoids is bidirectional. Several clock proteins, such as PER2 or CRY, are required for optimal glucocorticoid signaling.^{71,72} For instance, CRY can interact with the glucocorticoid receptor, and deficiency of Cry vastly decreases gene repression and doubles the number of dexamethasone-induced genes in mouse fibroblasts, suggesting that Cry broadly opposes glucocorticoid receptor activation and promotes repression.⁷² Accordingly, the therapeutic (or also adverse) effects of synthetic glucocorticoids can vary with the time of day, depending on intact clock function in target cells or tissues. An avenue for future research is determining whether regular versus irregular lifestyle schedules affect the efficacy or adverse effects of steroid treatment in allergic patients.

It should be noted that many of the drugs currently used for allergic disease have potential to change circadian rhythms, such as glucocorticoids, β_2 -adrenoceptor agonists, inhibitors of phosphodiesterases that activate cyclic AMP signaling (eg, aminophylline), and histamine H1 receptor antagonists.^{22,73,74} This also suggests close relationships between the circadian clock and allergy. However, the actual physiologic effects on clock activity by such medications given to patients with allergic disease remain to be determined. In addition, this might also become a confounding factor to assess clock importance in patients with allergic disease.

FUTURE DIRECTIONS

A number of questions regarding circadian regulation of allergy remain to be addressed.¹¹ Three important questions in this field are as follows.

First, the mechanisms that link the circadian clock to allergic reactions are not fully understood. Allergy-associated CCGs (eg, *Fcerib*,²¹ *St2*,⁴⁵ *OCT-3*,⁴⁶ *Aqp3*,³⁷ and tight junction molecules^{43,75}) are definitely key genes that connect the clock to allergy. However, the circadian clock is a multimodal system regulating neuronal activity and metabolism, as well as immune cell function.¹⁻³ Neuronal activity and metabolism are now recognized as strong influencers of immunity.^{76,77} Thus it is important to determine to what extent the circadian clock controls allergic reactions by regulating these 2 factors.

Second, there are few epidemiologic and clinical studies on the extent to which circadian clock or circadian disruption, as induced by aberrant environmental light conditions or irregular food intake, influences the predisposition, etiology, maintenance, and progression of allergic disease in human subjects. These studies are clearly needed, although it might be difficult to prove the causal link between the clock and human allergic disease given reciprocal effects on clock function and allergy.

Thus far, to the best of our knowledge, there has been only 1 study related to this subject: the effects of Ramadan fasting on different features in asthmatic patients in a Muslim population.⁷⁸ The study shows that a 1-month Ramadan fasting period has no negative effect on asthma and might have some positive effect on asthma severity with regard to reduction of serum C-reactive protein concentrations and chest wheeze. The findings might be related to a recent study showing that serum IL-5 levels and blood eosinophil counts show circadian rhythms in mice and that mice fasted for 16 hours exhibit suppressed serum IL-5 and blood eosinophils.⁷⁹

Third, local physiology in the nasal mucosa, lung, intestine, and skin exhibits circadian variability, even in healthy subjects. Thus an important question is what makes circadian rhythmicity in the local physiology of allergic patients much stronger than that of healthy subjects (eg, sensitivity to acetylcholine in the airways). In other words, is allergic disease a circadian disorder? To answer this question, it is important to investigate the status of clock gene and CCG expression in patients with allergic lesions and how expression of these genes is altered. Given that most allergic symptoms result from alterations of the nervous system in target tissues/organs,⁸⁰ it might be interesting to examine the kinetics of CCG expression involved in neuronal activity at allergic lesions. Overall, little is known about what happens to circadian regulation at the molecular level in allergic lesions.

CONCLUDING REMARKS

Circadian clock activity is embedded in the regulation of allergic reactions and plays more than a simple circadian timekeeping role in allergy. Accordingly, disruption of the circadian clock strongly affects the temporal profile, intensity, and susceptibility to allergic reactions. Thus research on how the time of day affects allergic reactions, which we can call “chronoallergy,” will become an important field of allergy.

In the developed world most persons live in a society in which daily activities, such as sleeping, working, and eating, are out of sync with endogenous circadian rhythmicity.³¹ This can be especially apparent in shift workers, frequent travelers across

time zones, and extensive users of smartphones or computers that emit strong SCN clock-sensitive blue light at night. Therefore clinicians should devote greater attention to the details of patients' individual lifestyles, such as when they sleep and wake up, when and how many times they eat per day, and their level of psychological stress, because these factors can alter symptoms, laboratory parameters (eg, CD203c expression on basophil activation³³ or serum IL-5 levels and blood eosinophil numbers⁷⁹), and optimal timing of treatment in allergic patients through modulation of the clock activity (Fig. 4).^{81,82} By doing so, clinicians could propose a lifestyle intervention to better control allergies that is tailored to the status of an individual patient.

For instance, we speculate that in patients with allergic rhinitis with irregular eating habits, the mast cell clockwork might show circadian arrhythmicity, leading to persistent IgE/mast cell-mediated symptoms during both the day and night. Simple advice for such patients to have regular eating habits might reduce symptoms during the active phase (day) by restoring normal mast cell clock activity, and then clinicians could reduce dosing of antiallergy medications.

The availability of smartphones and new software applications presents an opportunity to objectively and longitudinally monitor temporal patterns of the sleep/wake cycle and eating or exercise habits of free-living human subjects⁸³ and might help clinicians find a lifestyle intervention to better control allergies. The discovery that the biological clock affects allergy reminds us of the importance of managing allergic patients in the context of their real lives.

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What do we know?

- Allergic diseases show marked day-night changes in symptoms and laboratory parameters and treatment response.
- Rodent studies reveal that rhythmic allergic reactions are underpinned by an internal time-keeping system called the circadian clock.
- Disruption of circadian clock activity not only undermines circadian rhythmicity in patients with allergic reactions but also can enhance or predispose an organism to allergic reactions.

What is still unknown?

- How disruption of circadian clock activity can enhance or predispose an organism to allergic reactions
- To what extent circadian disruption affects allergic disease in human subjects
- What causes the significant differences in circadian clock-controlled local physiology between healthy subjects and allergic patients

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