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FORUM REVIEW ARTICLE

Redox Regulatory Changes of Circadian Rhythm by the Environmental Risk Factors Traffic Noise and Air Pollution

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Abstract

Significance: Risk factors in the environment such as air pollution and traffic noise contribute to the development of chronic noncommunicable diseases.
Recent Advances: Epidemiological data suggest that air pollution and traffic noise are associated with a higher risk for cardiovascular, metabolic, and mental disease, including hypertension, heart failure, myocardial infarction, diabetes, arrhythmia, stroke, neurodegeneration, depression, and anxiety disorders, mainly by activation of stress hormone signaling, inflammation, and oxidative stress.
Critical Issues: We here provide an in-depth review on the impact of the environmental risk factors air pollution and traffic noise exposure (components of the external exposome) on cardiovascular health, with special emphasis on the role of environmentally triggered oxidative stress and dysregulation of the circadian clock. Also, a general introduction on the contribution of circadian rhythms to cardiovascular health and disease as well as a detailed mechanistic discussion of redox regulatory pathways of the circadian clock system is provided.
Future Directions: Finally, we discuss the potential of preventive strategies or ''chrono'' therapy for cardioprotection. *Antioxid. Redox Signal*. 37, 679–703.

Keywords: environmental risk factors, external exposome, air pollution, traffic noise exposure, circadian clock, oxidative stress, cardiovascular risk

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Introduction

Environmental risk factors, disease burden, and global mortality

In the recent past, the global burden of disease primarily consisted of infectious, perinatal, and nutritional diseases. With the advent of modern medicine and accompanying great extension to life expectancy, the burden of disease has shifted toward noncommunicable diseases of age, lifestyle, and environment, such as cardiovascular disease, cancer, *etc.* The industry advanced alongside medicine and yielded potential new cardiovascular risk factors: air pollution (130, 157) and traffic noise (from road, aircraft, and railway) (105).

We are coming to understand the role that the physical environment plays in the genesis of noncommunicable diseases (125). Association and interventional studies demonstrate that these novel cardiovascular risk factors are associated with cardiovascular, metabolic, and mental diseases, including hypertension, heart failure, myocardial infarction (MI), diabetes, arrhythmia, stroke, depression, and anxiety disorders. Epidemiological evidence highlights the shift in disease burden and illustrates a serious impact on public health by environmental factors.

Pollution-caused diseases were responsible for an estimated 9 million premature deaths in 2015—16% of all deaths worldwide. These deaths account for three times more deaths than from acquired immunodeficiency disorder syndrome (AIDS), tuberculosis, and malaria combined and 15 times more than from all wars and other forms of violence. Exposure is highly variable, but in the worst-affected regions pollution-related disease is responsible for more than one death in four (125).

Though these risk factors are relatively newly identified, there is some insight into the pathophysiological mechanisms: Chronic stress reactions lead to increases in stress hormones cortisol, adrenaline, and noradrenaline, which, in turn, promote the generation of oxidative stress and activation of inflammatory pathways, leading to the initiation of cardiovascular disease (155). Here, we shift the focus to circadian clock dysregulation as a potential down-stream pathomechanism of environmental risk factors *via* environmentally triggered adverse redox regulation and oxidative stress.

The exposome as the totality of all environmental exposures

Christopher P. Wild coined the term ''exposome'' in 2005 to describe the sum of all environmental exposures on human physiology. Addends of the exposome sum are not only environmental stressors such as UV radiation, climate, and pathogens, but also more sociologically based factors, such as lifestyle, socioeconomic status, and the urban environment as well as different environmental pollutants (''pollutomes'') and mental stress factors such as anxiety or noise exposure (Fig. 1) (206, 244). The sum of these exposures defines the ''external exposome.''

The exposome is deeply rooted in the individual situation, can vary greatly from person to person, and is measurable through correlational studies between the internal environment (transcriptome, epigenome, proteome, metabolome, and microbiome) and the external environmental factors that are independently correlated with health risks, disease burden, or mortality. Insight into both the internal and the external environment allows for bioinformatical mapping, which could reveal an overlap between the environmental components of the exposome and classical cardiovascular, metabolic, and neurodegenerative risks, which eventually initiate disease.

Though there is certainly an overlap between the exposome and classical risk factors for disease, it has been speculated that the exposome may carry more weight than even genetic factors in the propagation of chronic diseases (190).

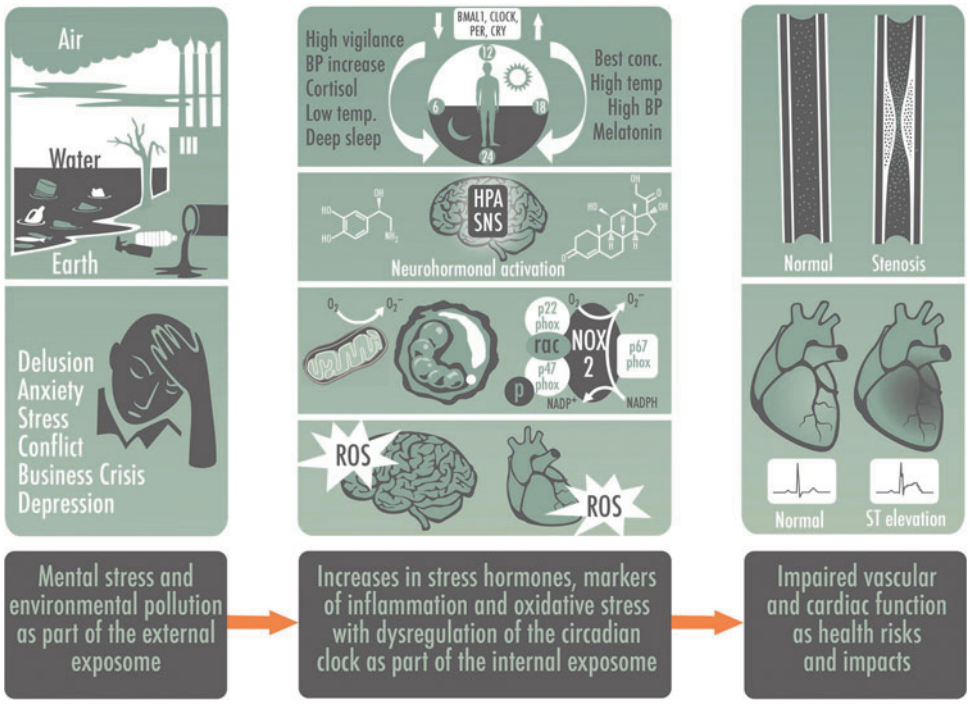

FIG. 1. The exposome concept. The external exposome (*e.g.*, mental stress and environmental pollution) confers changes of the internal exposome (*e.g.*, altered circadian clock by forward/backward shift, stress hormones, inflammation, and oxidative stress), leading to health risks and disease conditions (*e.g.*, atherosclerosis, vascular stenosis, and myocardial infarction). Adapted from Li *et al.* (133) with permission. BMAL1, brain and muscle arnt-like protein-1; CLOCK, circadian locomotor output cycles protein kaput; CRY, cryptochrome; NADPH, nicotinamide adenine dinucleotide phosphate; PER, period; ROS, reactive oxygen species.

Influence on the circadian rhythm and stress responses represents a physiological impact on the ''internal exposome'' (changes of biochemical pathways, for example, proteome, transcriptome, metabolome) by the external exposures, which is further linked to cardiovascular complications. We will discuss these links between the external and internal exposome, physiological responses, and cardiovascular complications through the lens of dysregulation of the circadian clock, as there is crosstalk with the external environment that can directly affect the behavior of the organism in terms of diet, activity, sleep, and cognitive function.

Circadian Rhythms

The master clock of the body lies within the hypothalamus: a group of 20,000 neurons in the suprachiasmatic nucleus (SCN) that communicate with peripheral clocks that reside in nearly every mammalian tissue to autonomously control certain physiological processes (Fig. 2A) (24). The central and peripheral clocks allow organisms to respond to routine environmental fluctuations over the course of a 24-h period (41). The circadian rhythm refers to the endogenous ''circa 24 h'' rhythm that also pertains in constant darkness. These endogenously generated circadian rhythms are synchronized to the day–night (light–dark) cycles *via* light signals/circadian photoreceptors.

However, though they are often used interchangeably, the terms circadian rhythm and diurnal rhythm have discrete definitions. Circadian rhythms are self-sustaining biological responses that occur without external cues from the environment, whereas diurnal rhythms occur as responses to the environment (195). The stimuli that provide feedback to the circadian pathways are called Zeitgebers or time-keepers, the primary of which is light but food, exercise, and social cues are also considered Zeitgeber signals. Peripheral clocks are tissue-specific circadian drivers that are controlled independently within the system they reside (*e.g.*, cardiovascular, reproductive, endocrine, *etc.*) *via* transcriptional–translational feedback loops on a 24 h cycle (149, 195), which is also the case for the cellular molecular clocks (152).

These clocks are influenced by the central clock, but they largely regulate their respective tissues endogenously *via* mammalian clock core genes, including circadian locomotor output cycles protein kaput (*Clock*), period 1, 2, and 3 (*Per1*, *Per2*, and *Per3*), cryptochrome 1 and 2 (*Cry1* and *Cry2*), and brain and muscle aryl hydrocarbon receptor nuclear translocator (*Arnt*)-like protein-1 (*Bmal1* and *Bmal2*). Proteins CLOCK and BMAL1 (or its paralog neuronal PAS domain-containing protein 2 [NPAS2]) positively regulate the expression of clock proteins by heterodimerizing, translocating to the nucleus, and binding to the E box promotors of *Per* and *Cry*, causing the initiation of gene transcription of their own inhibitors (Fig. 2B) (149, 195).

Translated PER and CRY proteins inhibit the transactivation of BMAL1 and CLOCK and in doing so, also inhibit their own expression. The feedback loops between *Clock/Bmal1* and *Per/Cry* are further connected to the rhythmic expression of *Rev-erbα* and *Rorα*, the determinants of *Bmal1* expression (149, 152).

Recent data from human and animal studies revealed significant sex-specific differences in the mechanisms that establish circadian rhythms with substantial consequences

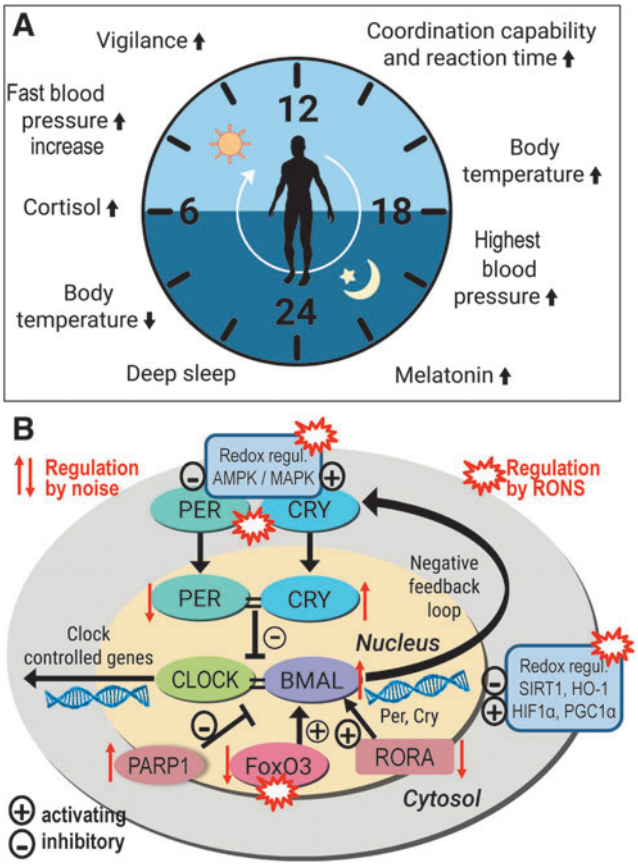

FIG. 2. Circadian clock (dys)functions and molecular components. (A) The circadian clock regulates a number of essential biological functions such as sleep, body temperature, appetite, cognitive functions *via* time-dependent hormone release such as cortisol or melatonin, and it largely contributes to cardiovascular health (41, 238). Modified and redrawn from ''Press release. NobelPrize.org. Nobel Media AB 2021. Tue. 16 Feb 2021. https://www.nobelprize.org/prizes/medicine/2017/press-release/.'' **(B)** The clock core components consist of the positive regulators CLOCK and BMAL that directly control circadian gene expression as well as the negative regulators PER and CRY (238). Numerous components are redox regulated [reviewed in Li *et al.* (133)] and modified by aircraft noise exposure of mice (117). AMPK, AMP-activated protein kinase; FBXL3, F-box/leucine rich-repeat protein 3; FOXO, Forkhead box O; HIF-1α, hypoxia-inducible factor 1α; HO-1, heme oxygenase-1; MAPK, mitogen-activated protein kinase; PARP-1, poly(ADP-ribose) polymerase-1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; RONS, reactive oxygen and nitrogen species; SIRT1, sirtuin 1.

for health and resilience to changes in sleep pattern (3). The SCN acts as a master regulator of ubiquitously expressed gonadal steroid receptors and these systems, in a sex-specific manner, also control other central systems such as the hypothalamic-pituitary-gonadal axis, the hypothalamic-pituitary-adrenal (HPA) axis, and sleep-arousal systems (11).

When subjecting rats to a shift work model (light–dark shifts) and ischemic stroke, the light–dark shifted male rats displayed a more pronounced mortality, whereas circadian desynchronization produced significant increases in stroke-induced infarct

volume and sensorimotor deficits in the surviving female rats (56). These sex-specific differences in circadian pathways may also help to explain the differential onset of cardiovascular, metabolic, and tumor disease in men and women (247), which represents an opportunity of significant advance of gender-specific medical approaches (192).

The circadian clock in cardiovascular cells

In the heart, ~13% of genes and 8% of proteins shows circadian rhythmic expression throughout the day (236), illustrating a strong influence on cardiovascular function. Oscillating circadian genes influence the activity of endothelial cells, fibroblasts, and vascular smooth muscle cells (VSMCs) (234) and help to maintain normal cardiovascular physiology.

In the vasculature, cells forming all layers of the blood vessel display rhythmic expression and regulation of circadian genes. A study done in mice has shown that Bmal1 and Cry1 demonstrate periodic expression in aortas that have been harvested at different time points during the day (180). Rhythmic expression of Per1 in the vasculature was confirmed through measurement of Per1-luciferase activity in transgenic rats (49). In vascular endothelial cells, as many as 229 genes were found to be regulated by the Clock/Bmal2, showing that many functions of the endothelium are rhythmically regulated (234).

Also, polymorphisms in Bmal1 cause endothelial cells to become more susceptible to injury, which then increases the risk of developing hypertension (252). Animal studies have shown that mice with mutations in *Per2* display endothelial dysfunction, decreased production of nitric oxide and vasodilatory prostaglandins, and increased production of vasoconstrictors (241). There is also a vital crosstalk between the circadian clock and the endothelin system (51). Smooth muscle cells are also influenced by the expression of the circadian clock genes. A study on cultured VSMCs demonstrated that mPer2 and Bmal1 were expressed with circadian oscillation and that cultured VSMCs can be used as models for circadian clock regulated gene expression research (33, 168).

Circadian clock genes in cultured fibroblasts display oscillations without any input from a master clock (162, 249). Also, the oscillation of blood coagulation markers such as thrombomodulin seems to be under the control of a peripheral clock, as oscillations were altered both in clock mutant mice and also by temporal feeding restriction (234).

Cardiomyocytes were shown to conserve the circadian gene expression even in culture (55). Isolated cardiomyocytes also react to stimuli such as β-adrenoceptor agonists, which is known to increase heart rate and contractility and to amplify Per2 circadian rhythm (16). This implies that even heart rate, which is regulated by neurohumoral input, is under the influence of the circadian clock. This was demonstrated by using radiotelemetry to show that cardiomyocytes in clock mutant mice are bradycardic, also placing heart rate under a peripheral clock control (20).

Further, cardiac power was higher in wild-type mice in comparison to cardiomyocyte clock mutant mice without being associated with mitochondrial dysfunction (20). Functioning circadian rhythms also play a part in protecting the heart from stress-induced damage. Noradrenaline functions as a Zeitgeber for cardiomyocytes; it induces the expression of dehydrogenase kinase isozyme or uncoupling protein-3 in a circadian manner, providing cardiomyocytes with protection against reactive oxygen species (ROS) and stress-induced myocardial damage (246). The molecular circadian clock was also present in cardiac progenitor-like cells, indicating that all of the cells belonging to the cardiovascular system are under the influence of the peripheral clock (53).

Disturbed circadian rhythms in cardiovascular pathophysiology

Synchronous circadian rhythms are essential for the normally functioning cardiovascular system (41). There is ample experimental and clinical evidence connecting the disruption of circadian rhythms and cardiovascular disease, one of the leading causes of morbidity and mortality in the world (187); however, we are still discerning what causes these disruptions. There is growing epidemiological evidence that suggests that environmental factors are contributing factors in the development of cardiovascular disease. Depression, anxiety, social isolation, shift work, and noise and air pollution can activate oxidative stress, increase autonomic response, and cause vascular dysfunction, culminating in the onset of cardiovascular disease.

Blood pressure displays a diurnal rhythm, peaking mid-morning and decreasing slowly throughout the day, a pattern that is essential for maintaining a normal cardiac physiology (67). Importantly, a blunted or absent nighttime blood pressure dip (a fall in pressure around 10–20% is considered normal) is associated with altered cell communication in the heart, thereby leading to an increased risk of cardiovascular events [for review see Yano and Kario (257)].

Sleep pattern disturbance often presents in shift workers and people suffering from sleep apnea, who are more likely to develop cardiovascular diseases *via* circadian misalignment due to alternation of the heterodimerization pattern of *Bmal1-CLOCK* (194). Resynchronized blood pressure rhythms in shift workers may occur 24 h after a shift rotation (35). The presence of sleep apnea is commonly found in airline crew and shift workers and changes in the circadian autonomic system activity in these populations were shown to increase the risk of stroke, heart attack, ischemic heart disease, and sudden death (19, 70).

Importantly, some cardiovascular diseases have known diurnal variations. MI, ventricular arrhythmia, and sudden cardiac death have outcomes that are somewhat related to the time of onset (194). More precisely, acute myocardial infarction (AMI) is more likely to occur in the early waking hours (233) due to the state of the central and peripheral clocks at this time and due to the control they have over the physiology of the organism (*e.g.*, heart rate, blood pressure, peak cortisol in blood). A similar chronobiological pattern exists for the rupture and dissection of aortic aneurysms (139, 147, 242), as well as for ischemic and hemorrhagic stroke (140), which is unexpected as these events represent completely different clinical entities but obviously all of them share the same circadian mechanisms (143, 219).

Likewise, a meta-analysis of 31 studies indicated a circadian pattern in stroke onset, with a pronounced risk in the morning hours (57). Heart rate and blood pressure are elevated in the morning, accompanied by a higher level of

vasoconstriction of blood vessels, leading to an increased energy demand and decreased blood flow to the heart (119). Also, right ventricular function and heart rate variability is under circadian control (230). However, it is important to mention that not all conducted studies find an association between cardiac events.

The seasonal shift from winter to summer time also disrupts the circadian rhythm, illustrating that environmental factors can also influence AMI incidence. The quality and amount of sleep is affected and AMI incidence is increased 3 weeks after the time reset, with a more pronounced difference in women than in men (98), findings that were also supported by a subsequent meta-analysis (141). However, the quality and amount of sleep may not be the only determinants for the observed higher cardiovascular risk as also the general environmental condition, gender, and individual preference in circadian rhythms (chronotype) may play a role (142).

Chronic desynchronization of light–dark cycles in hamsters with cardiomyopathies lowers the chance of survival (179). Disturbed diurnal rhythm by reduction of the light–dark cycle from 24 to 20 h in mice resulted in adverse outcomes in response to a pressure overload cardiac hypertrophy model displaying abnormal end-systolic and diastolic dimensions, reduced contractility, and impaired left ventricular remodeling post-MI, with rescue by diurnal resynchronization (145). In mice, clock mutants exhibit altered immune cell infiltration after AMI alongside decreased blood vessel formation one week post-MI in the proliferative phase and worsened outcomes (2). A cardiomyocyte-specific *Bmal* knockout model proved an integral role of the cardiomyocyte circadian clock in maintaining rhythmicity of the transcriptome (260).

Mitochondria are both susceptible to changes under environmental stress conditions and also a central player in cardiovascular disease development, especially in ischemia–reperfusion injury (84). The adverse effects of particulate matter (PM) on mitochondrial function were reviewed in detail (47). In isolated rat hearts, contractile performance, carbohydrate oxidation, and oxygen consumption were greatest in the middle of the night, with little variation in fatty acid oxidation (261). Similarly, the most abundant and efficient hydrogen peroxide-eliminating enzyme in mitochondria, peroxiredoxin III, and sulfiredoxin undergo antiphasic circadian oscillation in mitochondria (198).

Therefore, disturbing the diurnal cycle caused increased lipid peroxidation, reduced activity of antioxidant system enzymes, and reduced activity of the enzymes involved in adenosine triphosphate synthesis in mitochondria (118). Cardiac deletion of *Bmal1* in mice resulted in mitochondria with impaired respiratory complexes and a decrease in the expression of genes within the fatty acid oxidative pathway, the tricarboxylic cycle, and the mitochondrial respiratory chain. These mice develop severe progressive heart failure with age. The changes in gene expression can also be emulated through repeated light–dark cycle reversal in wild-type mice (115).

Oxidative Stress, Redox Regulation, and Circadian Clock

Oxidative stress arises as a consequence of an imbalance between the production and clearance of free radical species, which can be due to an overproduction of ROS, deficient antioxidant activity, or both. There are many physiological sources of ROS, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, the mitochondrial respiratory chain, and uncoupled endothelial nitric oxide synthase (eNOS). These sources of ROS and oxidative stress, in general, have been linked to environmental stressors, including mental stress (253), traffic noise (156), air pollution (157), heavy metal- (39) or pesticide exposure (52, 150), and all forms of smoking (73, 158).

Oxidative imbalance is found in all environmental exposures (155) and is an important feature of the exposome to be studied. As such, in this review, we focus primarily on studies of the mammalian/murine circadian clock and the effects of oxidative stress; however, we do discuss selected studies in *Drosophilia*.

Redox-regulatory mechanisms in the circadian clock

The crystal structures of mammalian/mouse cryptochrome 1 (mCRY1) and *Drosophila* cryptochrome (dCRY) have revealed two separate manners by which circadian clocks are regulated (42). dCRY is a blue-light photoreceptor with a key redox component for light synchronization. dCRY possesses three cysteine residues (Cys337, Cys416, Cys523) that enable both the flavin-adenin-dinucleotide (FAD)-dependent photoreaction and the phototransduction of FAD to the regulatory protein tail. The electron transfer relies on tryptophan and cysteine residues and potentially on nearby methionine residues, which can all be modified under conditions of oxidative stress.

The mammalian homologues, mCRY1 and mCRY2, however, have a different mechanism of action, participating in a negative feedback loop with the mCLOCK/mBMAL1 heterodimer, which then results in the fundamental basis of circadian activity. As such, the stability of mCRY1 and mCRY2 is tightly regulated *via* interaction with mammalian period 1 (mPER1), mammalian period 2 (mPER2), or the E3-ligase component F-box/leukine rich-repeat protein 3 (FBXL3) [reviewed in Merbitz-Zahradnik and Wolf (149)].

The crystal structure of mCRY1 illustrates redox-dependent characteristics, wherein AMP-activated protein kinase (AMPK) phosphorylates CRY1 at Ser71 and Ser280 in response to the metabolic and redox state of the cell (Fig. 3) (42). Phosphorylation of mCRY1 by AMPK enhances complex formation with FBXL3, leading to its proteasomal degradation (122). AMPK also activates casein kinase I, which leads to the degradation of PER proteins *via* TrCP E3 ligases (102, 129). As CRY and the CRY-PER complex are essential for BMAL1/CLOCK repression, their proteasomal degradation enhances BMAL1/CLOCK activation and thereby affects circadian cycling.

Notably, AMPK itself is known to be both an important stress and antioxidant response protein and redox regulated (97, 216), offering a route for redox regulation of the mammalian cryptochromes. There is also a mitogen-activated protein kinase (MAPK) phosphorylation site at Ser247 in mCRY1. MAPK-dependent phosphorylation of mammalian CRY proteins (Ser247 of mouse mCRY1, Ser265 of mCRY2) negatively regulates transcriptional repression of circadian clock mediated gene expression (208). Thus, the MAPK pathway represents another possibility for stress response

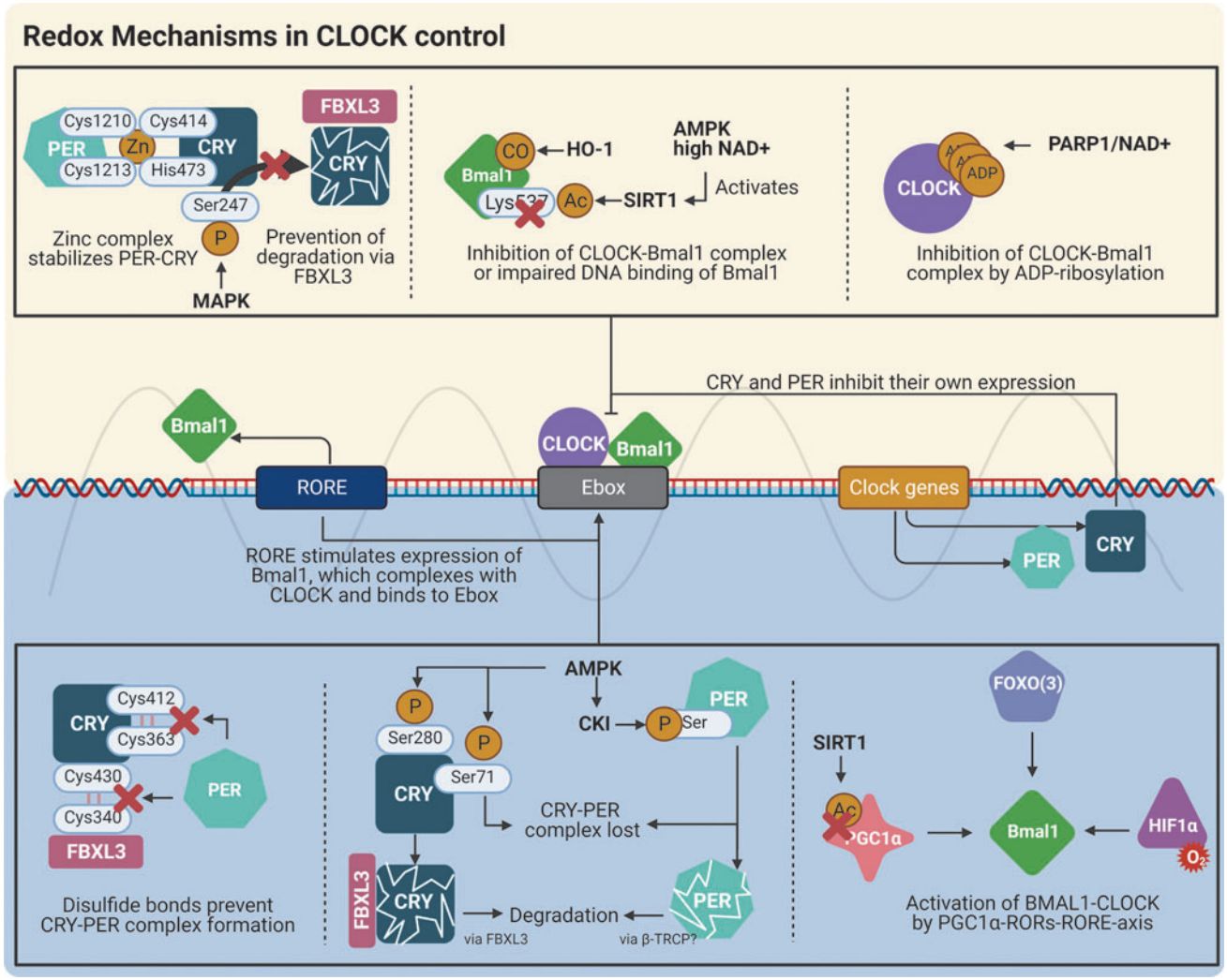

FIG. 3. Proposed mechanisms of redox regulation of the circadian clock. The circadian clock is affected by a number of redox-sensitive processes that ultimately lead to repression (*top*, *yellow*) or activation (*bottom*, *gray*) of the central transcription factor complex BMAL1/CLOCK. Redox-sensitive cysteine thiol groups (C363 and C412, *bottom left*) and a zinc-sulfur center (C1210 and C1213 of PER2, C414 and H473 of CRY1, *top left*) were identified in mammalian CRY1 and PER2 that act as redox switches (*via* disulfide bond formation) controlling CRY-PER interactions and thereby the activity of the CLOCK/BMAL1 complex (149, 173, 211). The scheme also contains other redox-sensitive pathways in the regulation of circadian rhythm, such as redox-sensitive kinases AMPK or MAPK. AMPK phosphorylates S71 and S280 to affect the affinity of CRY1 for the E3 ligase FBXL3 and thereby CRY stability (42, 122). AMPK *via* CKI phosphorylates PER to cause proteasomal degradation *via* β-TRCP (102, 129) (*bottom middle*). The MAPK phosphorylates S247 to affect CRY-dependent transcriptional repression of BMAL1/CLOCK (42, 208) (*top left*). Further, stress-response proteins such as PARP-1 (8, 102) (*top right*), HO-1 (*top middle*), HIF-1α (193), PGC-1α (129), FOXO3 (36, 266) (*bottom right*), and the histone deacetylase SIRT-1 (7, 129, 164) (*bottom right and top middle*) affect the circadian clock by modifying the transcriptional activity of BMAL1/CLOCK. Vice versa, the expression of several antioxidant and ROS-producing enzymes is controlled by the circadian clock and thereby contributes to cellular redox homeostasis (110, 196). Summarized from the respective references in this legend using BioRender.com. CO, carbon monoxide; OS, reactive oxygen species.

regulation of the circadian clock as MAPK are activated under cellular stress conditions and by redox modifications, and they are involved in survival pathways and apoptosis (204).

The impact of MAPK phosphorylation sites in mCRY1 was demonstrated not only by the attenuation of mCRY1 transcriptional repression activity toward BMAL1/CLOCK on mutation of Ser247 to Asp in mCRY1 (208), but also by the suppression of FBXL3 binding to mCRY1 (S247D) in U2OS cells (42).

The structure of the mCRY1/mPER2 complex has also been resolved, yielding essential but unexpected data regarding possible redox regulation of the complex by cysteine oxidation and thereby the regulation of mCLOCK/BMAL1 (211). Cys1210/Cys1213 residues in mPER2 and Cys414/His473 residues in mCRY1 form a zinc interface; a tetrahedral zinc complex, which stabilizes the mCRY1/mPER2 complex (Fig. 3) and prevents the formation of a nearby located disulfide bond between Cys412 and Cys363 of mCRY1 (211).

Also, zinc incorporation in the mCRY1/PER2 complex, by changing the intracellular pool of ''free'' zinc ions, may contribute to circadian redox regulation (173). Interestingly,

mice overexpressing a zinc binding deficient mCRY1(C414A) mutant protein showed a long 28 h circadian period, abnormal entrainment behavior, as well as symptoms of diabetes, including reduced cell proliferation and insulin secretion (hypoinsulinemia) (171). Notably, the Cys412-Cys363 disulfide bond is observed in mCRY1 (42), but it is absent in the CRY1-PER2 complex (211).

Hence, the intramolecular disulfide bridge between Cys363 and Cys412 of mCRY1 represents another direct redox regulation pathway of the circadian clock, leading to a conformational change in a PER2-binding loop of mCRY1 and thereby also affecting formation of the repressive CRY1-PER2 complex, in addition to the zinc interface (42, 211). Likewise, an intermolecular disulfide bridge between Cys430 of CRY2 and Cys340 of FBXL3 was reported, further supporting the significant redox regulation of mammalian clock proteins (254) (Fig. 3). Together, the structural analyses of mouse cryptochromes and mutational *in vivo* studies in mouse models suggest an important role of cysteine redox modifications and of a zinc–sulfur complex for the general regulation of circadian clock-dependent gene expression by temporal redox oscillations observed in most tissues.

Other redox-regulatory mechanisms in the circadian clock are based on NAD^+- and AMPK-dependent sirtuin 1 (SIRT1) activation, where AMPK enhances SIRT1 activity by increasing intracellular NAD^+ levels (129). SIRT1 and high NAD^+ levels affect BMAL1/CLOCK-dependent circadian gene activity *via* deacetylation of BMAL1–K537, histone H3 K9/K14 (164), and PER2 (7). Also, deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) by SIRT1 causes activation of the CLOCK/BMAL1 complex *via* the PGC1α-RORs-RORE-axis (129).

Further, DNA-binding activity of CLOCK-BMAL1 is inhibited by poly ADP-ribosylation of CLOCK by poly(ADP-ribose) polymerase-1 (PARP-1) in an NAD^+-dependent reaction, where PARP-1 activity is controlled by oxidative stress (8, 102). In addition, the DNA-binding activity of the CLOCK(NPAS2):BMAL1 heterodimers is also inhibited by an excess of oxidized $NAD(P)^+$ over reduced NAD(P)H (205).

As shown by *foxo* mutants, the sensitivity of the central clock to oxidative stress is also modulated by the antioxidant forkhead box O (FOXO) transcription factors, which are insulin- and redox-regulated (processes highly affected by aging), thereby controlling antioxidant gene expression (266). Deletion of *foxo3* caused irregular circadian clock oscillation and higher period variability (36). This may be explained by reports on a BMAL1 binding site for FOXO3 and is further supported by dysregulation of circadian clock gene expression by FOXO3 downregulation in a murine model of aircraft noise exposure (117).

Finally, several other redox-regulated enzymes such as hypoxia-inducible factor 1α (HIF-1α) or heme oxygenase-1 [HO-1 *via* carbon monoxide (CO)-dependent attenuation of DNA binding of the CLOCK(NPAS2):BMAL1 complex (112)] contribute to the control of the circadian clock (193) (Fig. 3).

Association of the circadian clock with the cellular redox state in health and disease

The circadian clock regulates the expression of many genes, including some involved in ROS production or antioxidant defense, resulting in cyclic redox transcriptional oscillations after the circadian rhythm. In astrocytes, activation of nuclear factor erythroid 2-related factor (NRF2) is an essential neuroprotective process required for antioxidant protection of dopaminergic neurons from ferroptosis. The activation of NRF2 is carried out by brain-derived neurotrophic factor (BDNF) in a circadian fashion *via* astrocyte tropomyosin-related receptor kinase type B (TrkB.T1), a truncated isoform of BDNF, and neurotrophin receptor p75 ($p75^{NTR}$), where the latter is a CLOCK/BMAL1-dependent gene required for consistent clock oscillation (94).

BDNF, in turn, serves as the major neurotrophin of the rodent brain with active roles in neuronal survival, differentiation, and synaptic plasticity (94). Further, an important neuroprotective antioxidant process is the regulation of intracellular glutathione levels, which is also a circadian-controlled process (110). Glutathione synthesis and clearance, alongside antioxidant response (in the form of superoxide dismutases, catalase, glutathione peroxidase/peroxiredoxin/thioredoxin transcription), have a regulatory network of microRNAs in common with the circadian clock, which manifests as a clear oscillation of antioxidant and/or ROS-producer gene expression (110). ''Redox oscillations'' can also be seen in the rhythmic changes in the redox state of peroxiredoxin (*e.g.*, reduced thiols, disulfide, sulfenic, sulfinic, and sulfonic acid content) (196).

The relationship between the cellular redox state and the circadian clock is not unidirectional: it has been proposed that there is a ''redox control of cellular timekeeping,'' which does not contradict previously discussed insights on the redox-regulatory mechanisms within the circadian clock (184). In much the same way that the expression and inhibition of core clock genes create feedback loops, it is likely that although regulation of metabolism is the output, the nutrient, energy, and redox cellular state provide feedback to reinforce rhythmicity. As each peripheral clock is responsive within its native tissue, this effect both allows the tissue to adapt to temporal challenges and can also cause targeted dysfunction (193).

Redox signaling is important in the conductance of vascular smooth muscle contraction, which can be interrupted by ROS. The translation of both ROS-producing and ROS-degrading enzymes is influenced by the circadian rhythm, as demonstrated by the presence of increased oxidative stress and subsequent endothelial/vascular dysfunction in animals (mostly mice) with deletions of critical clock components (5, 40, 241).

Beyond endothelial dysfunction, mice with high fat diet-induced nonalcoholic steatohepatitis (NASH) were found to have disrupted regulation of circadian clock genes (*Clock, Bmal1, Cry2, Per2*), which impaired the clock-dependent regulation of lipid metabolism proteins (*via* nuclear receptor subfamily 1, group D, member 1 [Rev-Erbα or NR1D1], RAR-related orphan receptor alpha [RORα]) and sterol regulatory element-binding transcription factor 1 [SREBP1c]) and it thereby exacerbated the development of fatty liver (23). It is likely that the NASH exacerbation was facilitated by the circadian dysregulation, which caused altered redox balance and reduction of SIRT1 and SIRT3 activity.

Redox regulation of circadian clock genes has been strongly tied to chronic airway diseases (229) as well as cardiac hypertrophy (262), diabetes (263), and hypertension

(163). A hallmark feature of all these diseases is the presence of endothelial dysfunction and increased vascular oxidative stress (48). The vascular redox state is also interconnected with the circadian variation in blood pressure and vascular contraction (200). Disturbance of this diurnal rhythm causes changes in gene expression and increased left-ventricular end-systolic/diastolic dimensions, which are early signs of cardiac hypertrophy (145).

Connection of Noise Exposure (Mental Stress), Circadian Clock Dysregulation, and Cardiovascular Disease

Stress response concept

Hans Selye, the founder of the ''stress theory,'' or the hypothesis that stress could result in nonspecific symptoms of illness, described the stress reaction in three parts: ''The three stages of the stress syndrome are (i) the alarm reaction, in which adaptation has not yet been acquired; (ii) the stage of resistance, in which adaptation is optimum; and (iii) the stage of exhaustion, in which the acquired adaptation is lost again'' (214). In his pioneering work, he detailed the first biochemical underpinnings of stress reactions and a guideline how to measure stress conditions.

Since the founding of the stress theory, research has linked chronic mental stress, for example, in the form of traffic noise exposure, to cardiovascular risk factors, including increased blood pressure, blood viscosity and blood glucose, as well as dyslipidemia and activation of blood clotting factors in humans (10). More insight on oxidative stress and inflammation within the scope of mental stress is provided in (217), and the link between social isolation and cardiovascular disease is discussed in (253). External stressors cause increases in adrenocorticotrophic hormone (ACTH) and glucocorticoids (GCs) release during the inactive phase (87), and translational models have given evidence that all these have effects on peripheral clocks (87, 114, 232).

The GCs are known to regulate the expression of several circadian genes *via* binding to glucocorticoid response elements in promotor regions of these genes (231). Supporting data show that injections of dexamethasone for 3 days at Zeitgeber time (ZT)4 induced phase entrainment of PER2 rhythms in the liver, kidney, and submandibular gland (232), which demonstrates that GCs are not simply ''stress hormones,'' but also have important roles in maintaining peripheral clocks (231).

The GR dimers are formed after nonclassical signaling and can lead to activation of kinases such as phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), or MAPK independent of genomic events (114). Although there is much still unknown regarding the mechanisms in stress-induced circadian effects, it is suspected that the sympathetic nervous system and the HPA axis are involved (231). The GCs are the output of the adrenal glands and ACTH of the pituitary, so interference in these pathways intuitively points toward a downstream interference in circadian pathways as well. Also, monoamines such as norepinephrine or epinephrine can also induce circadian gene expression (235). In mice, phase advance of bioluminescent rhythms in peripheral tissues was observed after treatment with norepinephrine or epinephrine (232).

Noise exposure studies on cardiovascular health effects in animals and men

Molecular links between noise-induced stress and the induction of vascular and cerebral inflammation as well as oxidative stress are reviewed in (45, 46). Regarding the sequence of events, acute noise exposure for 30 min (85 dB) has been demonstrated to increase the adrenocorticotropic hormone corticosterone in a dose-dependent manner (25, 27). In addition, corticotropin-releasing hormone and its receptor type 1 was upregulated at the mRNA level in amygdala in response to chronic noise exposure of rats (59).

In monkeys, noise with a mean sound pressure level of 85 dB(A) caused a blood pressure increase by 30 mmHg (181). Subsequent translational studies of traffic noise exposure in mice have established endothelial dysfunction and blood pressure elevation in association with higher levels of cortisol and catecholamines (117, 156); effects that were abrogated in NADPH oxidase isoform 2 (*Nox2*)-knockout mice, indicating that they were oxidative-stress driven in nature. Noise exposure during sleep also appears to contribute more to the phenotype of vascular pathology than exposure while awake, as effects in mice exposed to noise only during sleep were more pronounced than counterpart mice, also resulting in substantial neuronal activation, cerebral oxidative stress, and neuro-inflammatory phenotype (117).

The uncoupling of eNOS and neuronal nitric oxide synthase was observed (117, 156), partly explaining the noise-induced endothelial dysfunction and the impairment of cognitive/memory function in humans (212, 213, 225). We also identified substantial changes in gene expression by RNA sequencing, for example, dysregulated antioxidant and stress response (antioxidant and DNA repair genes), aggravated cell death pathways, and impaired vascular signaling (156), all of which were associated with dysregulated circadian clock pathways and FOXO signaling (117). We also established additive impairment of cerebral and vascular oxidative stress, inflammation, and endothelial dysfunction by noise and angiotensin II treatment in mice (226).

Noise also induced oxidative burst of blood leukocytes and other markers of oxidative stress such as oxidative DNA damage (8-oxoguanine) and enhanced NOX-2 expression as well as inflammation in C57BL/6 mice, with further increases in 8-oxoguanine glycosylase knockout ($Ogg1^{-/-}$) mice (DNA-repair deficient 8-oxoguanine glycosylase knockout) (120).

Aircraft noise also causes endothelial dysfunction in healthy subjects (213) and increased blood pressure in patients with established coronary artery disease (212) and elevations in overnight urinary cortisol in children living in noisier areas, indicating a translational relevance (60). Similarly, exposing healthy subjects to 30 or 60 train events during nighttime decreased quality of sleep and impaired flow-mediated dilation of the brachial artery significantly and the latter was improved by acute vitamin C infusion, indicating a role for oxidative stress (88).

Targeted proteomic analysis detected in plasma proteins within redox, pro-thrombotic, and pro-inflammatory pathways was significantly impacted versus controls (88). A molecular link between neuronal activation, coronary inflammation/atherosclerosis, and higher incidence of major adverse cardiovascular events (*e.g.*, MI) was recently provided in subjects with higher noise exposure undergoing

positron emission tomography-scan (172). This human mechanistic evidence was also supported by epidemiological outcome studies, indicating a higher risk of ischemic heart disease in people with higher traffic noise exposure (105).

Also, higher risk of obesity, diabetes, and hypertension in association with traffic noise exposure was suggested by epidemiological data (99, 185, 222). Induction of arterial stiffness and dysregulation of DNA methylation patterns are other hallmarks of traffic noise exposure in Switzerland (62, 68).

Traffic noise effects on circadian clock

A prospective study of 3350 participants of the of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults by Eze *et al.* demonstrated a significant modification of the relationship between residential nighttime road traffic and subsequent 8-year change in glycated hemoglobin values (HbA1c) among diabetic participants by a genetic risk score of six common circadian-related melatonin receptor 1B (MTNR1B) variants (MGRS) after adjustment for diabetes risk factors and air pollution levels (61).

The strongest interaction was found for rs10830963, an established diabetes risk variant also implicated in melatonin profile dysregulation. Sørensen *et al.* suggest lower melatonin due to decreased sleep in people exposed to nighttime traffic noise to be a potential mechanism to explain the increased risk of breast cancer (223), but this effect, if it exists at all, may be also explained by concomitant light exposure, which usually coexists in the setting of nighttime traffic noise exposure (82).

However, there is ample evidence from human studies demonstrating a link between traffic noise exposure and impaired sleep (14), thus providing at least indirect evidence for a relationship between traffic noise exposure and circadian dysregulation.

As noise exposure during the night mediates its detrimental effects mainly *via* sleep deprivation and fragmentation (159), sleep disorders may effectively reflect the pathophysiology of noise-triggered health effects. Circadian misalignment is a phenomenon often seen in shift workers, who have a higher prevalence of obesity, type II diabetes, hypertension, coronary heart disease, and ischemic stroke (114). Connections between circadian disruption and cardiovascular disease pathogenesis have also been made (154, 238). In studies of short-duration circadian misalignment in humans (28 h day for 8 days), increases in blood glucose, insulin levels, and blood pressure were observed (209).

Data for noise exposure in humans are heavily reliant on association studies and epidemiological data due to their highly variable nature in both level of exposure and degree of cognition by the subject. For this reason, animal models of noise exposure are a critical component in understanding the molecular mechanisms by which noise affects the organism. In mice, a self-sustaining peripheral clock was found to be present in the cochlea, implying that even sensitivity to noise was rhythmically controlled (148).

The neurons located within the inferior colliculus, an important structure in the brain for sound processing, also have their own CLOCK-dependent rhythmic expression. Further, this study found that exposure to noise caused notable transcriptional changes, resulting in oscillation abnormalities in isolated neurons from the murine inferior colliculus (175). Taken together, it appears that not only sensitivity and cognition of noise is regulated rhythmically, but also transcriptional rhythm itself can be disrupted by noise.

Studies applying noise differentially between light and dark cycles found anxiety-like behavior, memory and learning impairments, as well as physiological effects such as reduced brain volume, hippocampal volume, and neural density alongside HPA axis activation (95). We have found significant dysregulation of multiple circadian genes in the aorta and kidney of mice (minor changes in the heart) that are compatible with sleep deprivation by around-the-clock aircraft noise exposure (Fig. 4) (117).

Most prominent were reductions in the expression of *Per1* and *Foxo3* and upregulation of *Cry1* and *Arntl* in the aortas of mice exposed to noise either around the clock or during their sleeping phase, but not during their waking phase (117), forging a link between circadian disruption and consequences borne of noise exposure.

Noise exposure exerts its effects both centrally and peripherally, though it is possible that these occur by different mechanisms. There appears to be crosstalk between the pineal and adrenal glands, wherein peak corticosterone occurs at light–dark transition (in nocturnal animals), causing arousal entrained by the SCN (43). Corticosterone, in turn, enhances melatonin production. However, in times of stress or immune challenge, night melatonin content in plasma is reduced, an effect rescuable by adrenalectomy (66).

These connections between HPA axis activation and circadian expression could offer explanation for the effects previously mentioned in the circadian pathways after noise exposure and the well-characterized inflammatory phenotype that arises. A previous study reported increased blood pressure and inflammatory markers after 3 days of 12 h inversion of environmental and behavioral cycles (154). Also, a study in mice exposed to noise at 95 decibels showed increases in plasma interleukin-6 (IL-6), tumor necrosis factor (TNF)-α, and oxidative stress markers (136), and our own work shows increases in inflammatory parameters in blood, vascular tissue, and brain, which exacerbate preexisting phenotypes and are accompanied by aggravated stress hormone levels (45, 226).

It is becoming clearer that the circadian clock has a regulatory role in the vascular redox state and thereby endothelial function in mice (178), which is also diurnally regulated in part *via* eNOS, whose phosphorylation seems to be cyclic in nature (177). eNOS was found to be upregulated after 60 h of noise in both cytosol and mitochondria of various cell types in guinea pigs (86). Related, the critical eNOS cofactor tetrahydrobiopterin displays circadian-dependent expression (5). Other studies in rats demonstrated morphological alterations of the heart followed by exposure to noise at 100 dB(A), including the development of myocardial and perivascular fibrosis and a reduction of cardiac connexin 43 content (6).

Enlarged mitochondria and the presence of lipofuscin granules were also observed, indicating some degradation of the mitochondria (6). In another study, the enlarged mitochondria found that postnoise showed calcium accumulation and were less calcium tolerant, as opening of the mitochondrial permeability transition occurred more rapidly (207). In rat cardiomyocytes, 12 h of exposure to loud noise caused

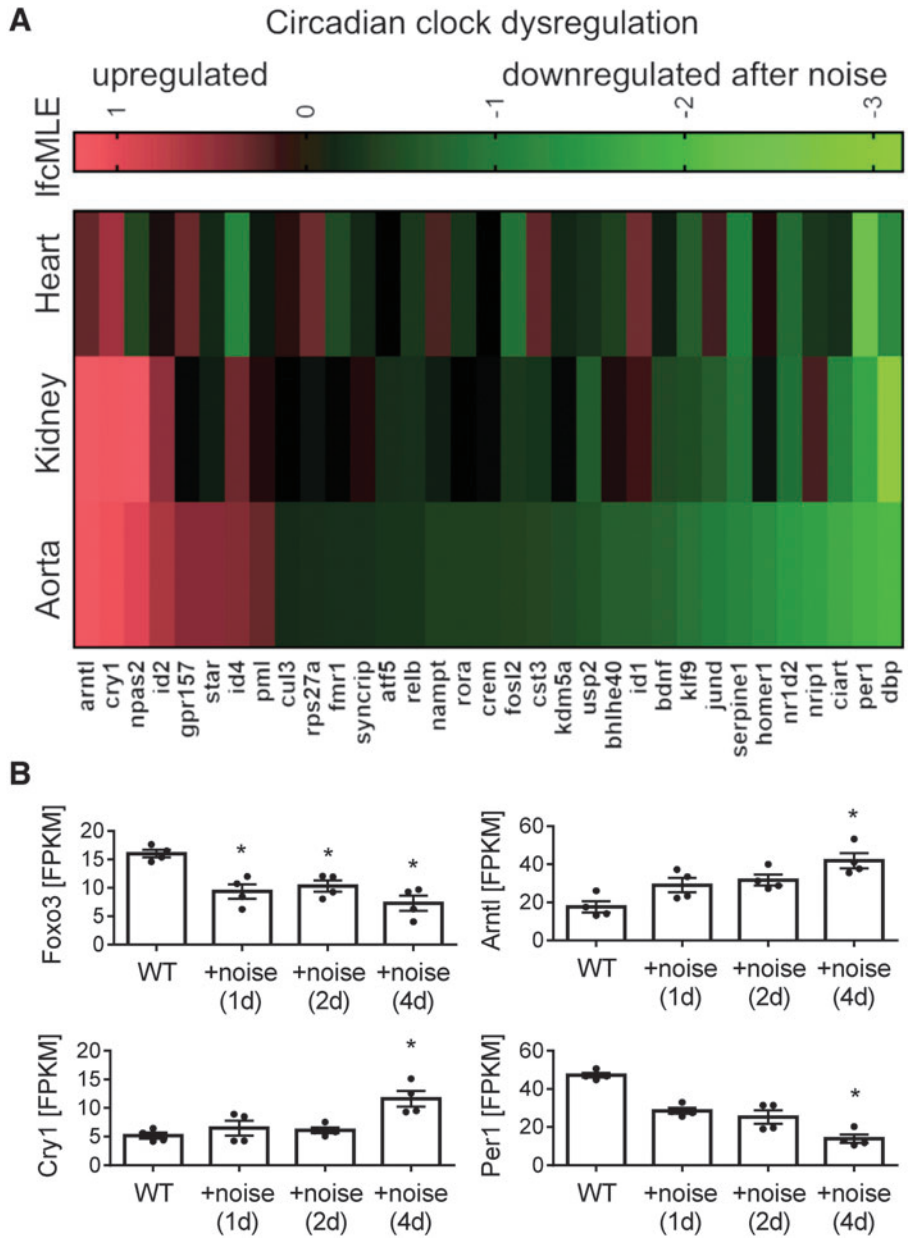

FIG. 4. Mouse studies on noise effects on the circadian clock. (A) Noise (mean sound pressure level 72 dB(A) for 12 h/day for 1, 2 and 4 days) caused substantial dysregulation of the expression of circadian clock genes in the aorta and kidney, as revealed by Illumina RNA sequencing (see heat map) (117). **(B)** In particular, aortic gene expression of the transcription factor *Foxo3* and *Per1* was downregulated, whereas *Arntl* and *Cry1* were upregulated by noise. FoxO3 has a binding site in BMAL1 and thereby contributes to the regulation of circadian rhythm. *, $p < 0.05$ versus WT group. Adapted from Kroller-Schon *et al.* (117) with permission. WT, wild-type.

significant DNA damage alongside swelling of mitochondrial membranes, dilution of the matrix, cristolysis, and increased noradrenaline levels and utilization (131).

Although a definitive all-encompassing mechanism has yet to be uncovered, studies in animal models have highlighted clear effects on the circadian rhythm by traffic noise exposure and have led to interesting correlations between sleep, behavior, vascular function, inflammation, and mitochondrial function.

Connection of Air Pollution, Circadian Clock Dysregulation, and Cardiovascular Disease

Cardiovascular health effects by general environmental pollutants

As previously outlined, there is substantial evidence from epidemiological and experimental data suggesting that heavy metals and air pollution can contribute to cardiovascular disease (39). Also, other environmental chemicals such as pesticides are cardiotoxic (150). The links between environmental pollutants and oxidative stress imply that there would be a redox connection with the circadian clock. In terms of terrestrial pollutants, heavy metal exposure also has impacts on redox balance; an overview of these mechanisms was recently published (176).

Briefly, in rats, cadmium induced alterations in the cells of the circadian pacemaker (201) and disruption of the circadian rhythm by cadmium was partially prevented by antioxidant co-therapy, supporting the links to a role of oxidative stress (121). Copper overload also has adverse effects on the circadian clock (81). Toxicity studies in *Drosophilia* have demonstrated that the median lethal dose (LD_{50}) value of pesticides varied by time of day and correlated with the diurnal expression profiles of genes responsible for metabolizing xenobiotics (15, 91).

The preclinical and clinical evidence for a crosstalk between environmental organic chemicals and circadian pathways as well as the underlying mechanisms [*e.g.*, involvement of aryl hydrocarbon receptor-dependent detoxification (79)] can be found in detail (135, 183). Of note, these environmental chemicals may be also attached to the surface of airborne PM and significantly affect their biological effects.

Air pollution by PM effects on oxidative stress and cardiovascular health/disease

Air pollution in the form of PM is recognized by the American Heart Association and other cardiac societies as cardiovascular risk factors (22) and further, it is well accepted to induce cardiovascular oxidative stress (188, 251). Exposure to PM exerts well-characterized effects on the vasculature: endothelial dysfunction, inflammation, and strong ties with the pathogenesis of atherosclerosis (189) as well as increases the sensitivity to vasoconstrictors (258).

An in-depth review of the oxidative stress pathways and inflammation induced by PM and diesel exhaust can be found in (157). It was also recently reported that around 7% of nonfatal MIs and 18% of sudden cardiac deaths could have been triggered by exposure to traffic-derived pollution. These numbers are equivalent to those arising from traditional lifestyle risk factors such as smoking, poor diet, and obesity (39).

The importance of air pollution as a cardiovascular risk factor is supported by data from the short-term reductions in traffic, and industrial air pollution during the 2008 Beijing Olympic Games resulted in a 13–60% reduction in the concentrations of air pollutants, which perfectly corresponded with similar effects on the biomarkers of inflammation, oxidative stress, and thrombosis in healthy adults (92, 111, 199, 203). Once restrictions were lifted, however, the beneficial effects quickly dissipated, indicating that long-term mitigation of air pollution is necessary.

Between 2003 and 2012, the city of Tokyo made efforts to decrease diesel emissions, leading to a 44% decrease in PM from traffic. Osaka introduced similar laws in 2009. Comparisons of mortality rates between Osaka and Tokyo revealed a striking decrease in cardiovascular mortality by 11% among Tokyo's population, which was mainly due to a 10% decrease in ischemic heart disease mortality (259).

Magnetic air pollution particles deriving from combustion and friction were discovered inside mitochondria in ventricular myocytes, as well as in the endoplasmic reticulum (ER), mitochondria-ER contact sites, and intercalated disks of human hearts, resulting in the upregulation of left-ventricular prion protein (26), which is believed to contribute to cardiac adverse effects (264). In dogs exposed to high concentrations of air pollutants, including ultrafine PM, mitochondria possessed fragmented or missing cristae, with intramitochondrial lucent areas and an increase in the fusion of multiple mitochondria producing giant mitochondria and the presence of nanoparticles; a vastly different morphology from the uniform and linear mitochondria of control samples. (240).

In vitro studies utilizing 24-h exposure to nano-PM resulted in increases in mitochondrial DNA oxidation and a decreased mitochondrial oxygen consumption rate (21). Mitochondrial oxidative capacity was also altered after exposure to diesel exhaust *via* interference with complex I of the respiratory chain after repeated exposures (104).

Air pollution effects on circadian clock

Air pollution has been directly linked to disruption of the circadian clock. In an untargeted analysis of the transcriptome and methylome of primary human bronchial epithelial cells exposed to PM, it was shown that genes associated with circadian system are not only differentially regulated, but also DNA methylation associated with them changed significantly in comparison to the nonexposed controls (89).

In an experiment exposing both pregnant and offspring rats to air containing PM, the downregulation of key clock genes *Per1, Per2, Per3, Rev-erbα*, and *Dbp* and upregulation of *Bmal1* was found versus filtered-air-exposed controls (220). As recently reviewed, air pollutants have also been linked to changes in sleep–wake pattern, which was then seen to increase risk for vascular and cardiometabolic diseases due to several cardiovascular and even pulmonary functions that are rhythmically regulated (80).

Air pollution is also mentioned as a factor of chronobiologic aspects of venous thromboembolism (63). Chronic exposure to ambient particles with an aerodynamic diameter of <2.5 μm (PM2.5) was also found to accelerate the development of atherosclerotic plaques (227), and to exacerbate vascular oxidative stress and inflammation (103). In addition to effects on redox balance and clock gene expression, PM2.5 exposure was found to increase levels of stress hormone metabolites, 18-oxocortisol, and 5a-tetrahydrocortisol, and it altered the levels of circadian rhythm biomarkers, including melatonin, retinol, and 5-methoxytryptophol (255).

Rats exposed to PM2.5 exhibited pathological changes and ultra-structural damage in hearts, which included mitochondrial swelling and cristae disorder accompanied by significantly increased mitochondrial fission/fusion genes (optic atrophy protein 1, mitofusin 1, dynamin-related protein 1, and fission-mediator protein 1) expression (134). Similar to previously discussed data, on exposure to PM, rats did not display inhibition of mitochondrial function basally but manifested greater myocardial mitochondrial swelling and fusion after ischemia and reperfusion (75). In male Sprague-Dawley rats, exposure to PM caused a significant increase in mitochondrial transition pore opening, leading to decreased mitochondrial function (167). TNF-α antibody infliximab alleviated the impairment in mitochondrial function in residual oil fly ash-exposed mice (144).

A study in mice explored the influence of PM2.5 on the hepatic lipid metabolism and found that peroxisome proliferator-activated receptor alpha (*pparα*)-mediated genes responsible for fatty acid transport and oxidation were upregulated (267). In addition, expression of *Bmal1* was enhanced at ZT 0/24. Dysfunction in white and brown adipose tissue, as demonstrated by downregulation of adipokines, was accompanied by disruption in expression patterns of *Sirt1*, *Sirt3*, and *Ucp1* in PM2.5 exposed mice, which could be detrimental since disturbance in the lipid metabolism is tightly linked to cardiovascular disease (65).

Cigarette smoke derived PM was shown to shift circadian clock gene expression by up to 9 h in rat intervertebral disks (169). Altered regulation of circadian clock genes *Bmal1* and

Clock was also observed in the lungs of mice exposed to shisha and electronic cigarette derived PM (108). Knockout mice for Rev-erbα, an important circadian clock component, showed increased susceptibility to inflammation after exposure to cigarette smoke-derived PM (228). Natural physiological rhythms of mice did not recover even 4 weeks after cessation of smoke exposure (239). Also, altered methylation of the Clock gene was found in blood cells of free-living birds in dependence of PM10 exposure (202).

Circadian-dependent cardiovascular functions, including blood pressure (in the form of nocturnal dipping), daytime urinary sodium excretion (237), and nocturnal heart rate variability (128), were found to be affected by PM levels. Chen *et al.* demonstrated short-term PM2.5 exposure to be associated with lower pulse pressure, decreased maximum rate of left-ventricular pressure rise, and increased systemic vascular resistance in subjects with nighttime blood pressure dip of <10%, whereas no hemodynamic changes were observed in subjects with nighttime blood pressure dip of ≥10%, indicating that individuals with circadian-dependent dysregulations are more susceptible to PM-related cardiovascular risks (37).

Outside of cardiovascular complications, evidence demonstrating a role for airborne PM in alteration of the circadian molecular clocks *via* redox regulation was found in chronic airway diseases (229) and complementary findings were reported after exposure to ambient reactive gases (*e.g.*, ozone), where authors proposed that maintaining an intact circadian clock was protective against damage to skin and keratinocytes (17). In asthmatic school children, exposure to PM2.5 and PM10 was shown to increase the diurnal variability of lung function (132).

Further, exposure to secondhand smoke led to changed circadian rhythm of peak respiratory flow in children (29). A relationship between environmental arsenic exposure, which can be found in PM, and changes in circadian genes was revealed by data mining and interaction network analysis of sources related to human bladder cancer (182). An inverse relationship between occupational indoor PM2.5 exposure and heart rate variability was found in a study by Chuang *et al.*, with a pronounced decrease in heart rate variability of the participants during nighttime working hours compared with daytime periods of work (38).

Bisulfite sequencing of 407 newborns revealed epigenetic regulation of circadian genes in dependence of the regional PM2.5 exposure levels of their mothers during gestation (165). Epigenetic regulation was observed by altered placental methylation of CpG sites within the promoter regions of circadian genes *Npas2*, *Cry1*, *Per2*, and *Per3*, suggesting that PM2.5 exposure might affect placental processes and fetal development.

Approaches Related to Environmental Risk Factors and "Chrono" Therapy for Cardioprotection

Classical risk factors, comorbidities, and comedications undeniably play an important role in cardiovascular detriment or cardioprotection (4, 64). However, it is becoming clearer that this is not a ''complete picture'' and that these concepts are complemented by the contribution of environmental factors and a properly maintained circadian clock. Lifestyle is crucial in predisposing individuals to developing cardiovascular diseases not only through its ''classical'' contributions (*e.g.*, diet and exercise), but also in its role impacting circadian rhythms.

When an individual is ''phase shifting,'' there the change in *Per1* and *Per2* expression is faster than that of *Clock,* thereby causing desynchrony (109). Mutations in genes such as *Bmal1, Cry1*, *Cry2*, *Rora*, and *Clock* can alter sleep patterns (113). Shift workers show disturbances in circadian rhythms that result in disturbed blood glucose control and as a result, insulin resistance (76). Another factor, obesity, has been linked with *Cloc*k (96), *PER2* (58), and *Bmal1* (250) mutations, observable in both human and mouse models. Accordingly, chronotherapy is the method of administering therapy at specific points in the circadian rhythm in the hopes of improving efficacy and tolerance to drug therapy (Fig. 5) (265). Typical examples of human and animal studies are listed in Table 1.

Many factors can be influenced within the circadian pathway by environmental risk; however, the common denominator is the resultant dysregulated release of melatonin, a hormone from the pineal gland that plays an important role in maintaining regular circadian rhythm, antioxidant clearance, and is an anti-depressor (137). Melatonin is also believed to be cardioprotective and reduces infarct size while decreasing ventricular fibrillation after ischemia–reperfusion, although clinical results have been conflicting (137).

More time-targeted therapy may have given different results, and treating individuals with dysregulated circadian rhythms due to depression, jet lag and sleep disorders can re-regulate circadian rhythms to help prevent the development of cardiovascular events (224). A study carried out in Maastricht has shown that introducing light therapy to patients resulted in improved sleep patterns in cardiac patients (72). Animal studies reinforce this finding with complementary evidence: Altering the diurnal environment worsens their outcomes and increases inflammation in the infarct zone after an MI (215).

The administration of dexamethasone, a synthetic GC, at different times of day showed varying efficacy in protecting mice from acute noise trauma. Specifically, efficacy was only found when administered during daytime, when circulating GCs are already low, highlighting the benefits of chronotherapy (31). Noise is also part of a murine model of stress known as ''chronic mild stress.'' In this model, the administration of melatonin nocturnally was found to alleviate stress-induced behaviors (83).

Since air pollution is known to exacerbate inflammation (188), chronotherapy could be a useful tool to modulate additional burden in patients suffering from chronic inflammatory conditions. The peptide hormone adropin is known to regulate glucose homeostasis (71). It was recently suggested that adropin could be used in chronotherapy (116). Glucose levels and impairment of glucose homeostasis have been positively correlated to ambient air pollution exposure (71), and therapy in patients without metabolic disease could benefit from giving medications such as adropin during specified times of the day. Circadian rhythm is also linked to autophagy, apoptosis, and necrosis (187).

These cell death pathways are regulated differently during different times of the day, and air pollution is known to trigger them (44, 170). Chronotherapy of different cardiovascular diseases that can benefit from alterations to these

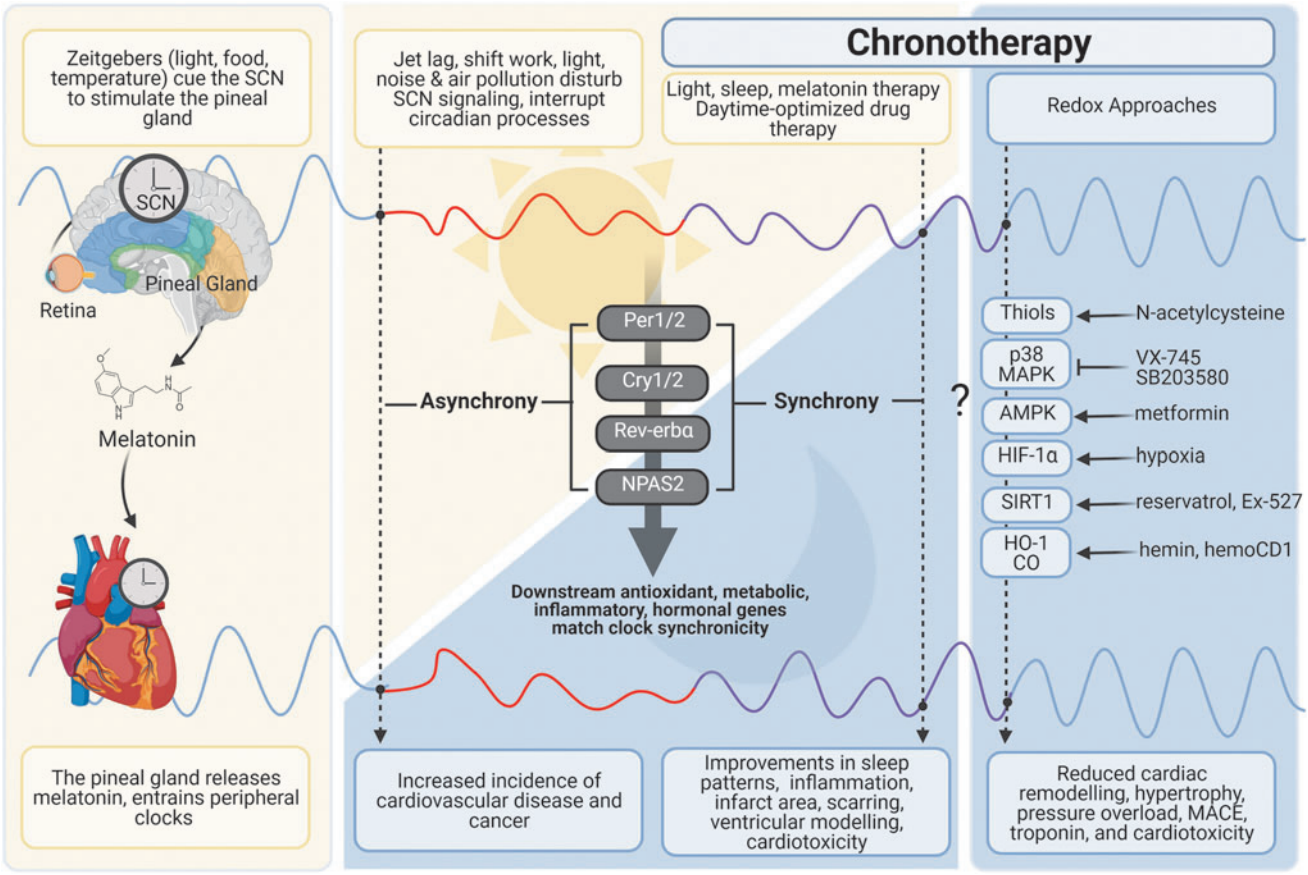

FIG. 5. Approaches related to environmental risk factors and "chrono" therapy for cardioprotection. *Left:* The central clock is controlled by different zeitgebers, leading to the release of melatonin *via* the pineal gland and the entrainment of peripheral clocks, for example, in the heart (40). *Middle:* Lifestyle and environmental risk factors were shown to disrupt circadian rhythms, causing asynchrony in circadian gene/protein expression patterns and thereby increase the risk of developing cancer and cardiovascular diseases. *Right:* Chronotherapy is believed to reduce side effects and to increase the efficacy of classical cardiovascular or chemotherapeutic drugs (133). Chronotherapy by sleep/light therapy, melatonin administration, and optimization of temporal drug administration/surgical interventions can improve clinical outcomes after a cardiovascular event in both human and animal models. In addition, preclinical redox approaches modulating circadian gene/protein expression or activity, and restoring synchrony, may help improve cardiovascular outcomes in patients, when applied in the optimal concentration range. Created with BioRender.com. MACE, major adverse cardiovascular events; NPAS2, neuronal PAS domain-containing protein 2; Rev-Erbα, nuclear receptor subfamily 1, group D, member 1; SCN, suprachiasmatic nucleus.

pathways might be promising since autophagy is an important pro-survival mechanism that protects cells from environmental insult such as air pollution (126).

As discussed in detail earlier and previously reviewed in detail (157, 160, 161), air pollution and traffic noise exposure induce oxidative stress. Accordingly, drugs acting on the earlier mentioned redox regulatory pathways of the circadian clock may normalize dysregulated rhythms in various disease conditions triggered by air pollution and traffic noise exposure, at least in preclinical models (Fig. 5). The AMPK activating drug metformin affected the circadian clock and metabolic rhythms in different tissues of healthy mice (12) and opposed the deleterious changes in core clock protein expression in white adipose tissue of genetically obese db/db mice (30).

The treatment of cultured chick pineal cells with SB203580, a selective and reversible inhibitor of p38 MAPK, had effects on the period and phase of the circadian rhythm of the melatonin release (85) and the inhibition of p38 MAPK activity with VX-745 led to cell-type-specific period changes in the molecular clock in different cancer cell lines (74). Hypoxia-induced pathways (*e.g.*, *via* HIF-1α) may not only harbor great therapeutic potential of normalizing impaired circadian signaling in cardiovascular diseases (13) but also contribute to the cardiovascular complications observed due to hypoxic episodes in obstructive sleep apnea (243).

The impact of SIRT1 on circadian clock and cardiac health is a two-edged sword, with low activity being cardioprotective and higher activity leading to cardiac hypertrophy (221), which is also supported by differential effects of SIRT1 activation by resveratrol and inhibition by Ex-527 on rhythms in neonatal cardiomyocytes (54). Selective chemical removal of endogenous CO by hemoCD1 in mice caused disruption of rhythmic expression of the clock genes and promoted the binding of NPAS2 and CLOCK to DNA (E-box) in the murine liver, resulting in upregulation of the E-box-controlled clock genes (Per1, Per2, Cry1, Cry2, and Rev-erbα) (151).

Table 1. Examples of Chrono Therapy Approaches in Humans and Animals

Author, year	*Type of study*	*Major finding*	*Reference*
Human evidence			
Wang, 2016	Pharmacokinetic study in 12 healthy subjects	Melatonin metabolism is inhibited in people whose diets are rich in coumarins	(245)
Carlson, 2019	Study in 12 healthy male subjects	Exercise in the morning has reparative effects on circadian rhythm *via* beneficial effects on melatonin signaling, compared with afternoon exercise	(28)
Bonten, 2014	Study in 14 healthy subjects	Administration of aspirin in the evening reduces platelet reactivity the next morning, which could reduce the overall risk of developing MI	(18)
Rezvanfar, 2017	Study in 76 patients with T2DM	Melatonin administration (6 mg/12 weeks) lowers fasting glucose and HbA1c levels in patients with type 2 diabetes mellitus	(197)
Raygan, 2019	Study in 60 patients with diabetes and CHD	Favorable effect of melatonin (10 mg/12 weeks) on glycemic control in diabetic patients with coronary heart disease	(191)
Doosti-Irani, 2018	Meta-analysis of 12 randomized controlled trials	Melatonin administration reduces fasting glucose levels, whereas insulin and HbA1c levels are not affected by melatonin	(50)
Celinski, 2014	Study in 74 patients with NAFLD	Administration of melatonin (5 mg/2 times per day/ 14 months) reduces LDL cholesterol and triglycerides in patients with nonalcoholic fatty liver disease	(32)
Wang, 2016	Study in 63 healthy subjects	Cigarette smokers display reduced free fatty acids, markers of inflammation and endothelin-1 after 2 weeks of melatonin administration (3 mg/kg)	(248)
Akbari, 2019	Meta-analysis of 8 randomized controlled trials	Melatonin administration is associated with decreased systolic and diastolic blood pressure in patients with metabolic disorders	(1)
Scheer, 2004	Study in 16 men with untreated essential hypertension	Administration of 2.5 mg/day of melatonin for 3 weeks lowers both systolic and diastolic blood pressure	(210)
Review articles			
Jiki, 2018	Mechanistic review	Dietary melatonin can increase the blood levels of melatonin and improve circadian rhythm	(101)
Imenshahidi, 2020	Mechanistic review	Beneficial effects of melatonin on cardiometabolic risk factors such as diabetes, dyslipidemia, and hypertension	(93)
Pandi-Perumal, 2017	Clinical and mechanistic review	Beneficial effects of melatonin on blood pressure regulation, circulating catecholamines, and vascular reactivity in healthy subjects	(174)
Animal evidence			
Lamont, 2011 & 2015	Mouse and rat studies	Chronic and moderate consumption of melatonin or resveratrol at dietary doses reduces infarct size in rats/mice subjected to MI	(123, 124)
Maarman, 2015	Rat study	Chronic and moderate consumption of melatonin at dietary improves cardiac function in rats with pulmonary arterial hypertension	(138)
Qiu, 2018	Rat study	Exercise has positive effects on melatonin signaling in a model of hypertension	(186)
Martino, 2011	Mouse study	Angiotensin-converting enzyme inhibition has more beneficial effects on cardiac remodeling when administrated during sleep time in a model of pressure overload hypertrophy	(146)
Wang, 2016	Rat study	Cigarette smoke induced higher levels of inflammatory markers, endothelin-1, and impaired metabolic pathways, which were normalized by melatonin administration (10 mg/kg)	(248)
Yaekura, 2020	Mouse study	Cytokine blocker Baricitinib reduces IL-6, interferon-γ, TNF-α, and granulocyte–macrophage colony-stimulating factor most efficiently during the period of increased cytokine expression in a mouse model of collagen-induced arthritis	(256)

IL-6, interleukin-6; MI, myocardial infarction; TNF-α, tumor necrosis factor-α.

Vice versa, the overexpression of HO-1 decreased the binding of NPAS2 and CLOCK to E-box, leading to downregulation of the clock genes. Pharmacological induction of HO-1 by hemin caused dose-dependent and reversible dampening of PER2 rhythms in the hypothalamic tissue of mice (78). The antioxidant N-acetylcysteine prevented alcohol- or hydrogen peroxide-induced increases in intestinal cell CLOCK and PER2 expression levels as a model of alcohol-induced intestinal hyperpermeability (69).

Of note, not all processes that are detrimental for the heart have been so far explored for chronotherapy. Although NFkB appears to interact with the circadian system (90) and is known to play a role in the inflammation associated with cardiovascular diseases, a few studies have explicitly probed this association. In support of this notion, myocardial ischemia–reperfusion injury was associated with higher NFkB levels that were most efficiently suppressed by a combination therapeutical approach of ischemic postconditioning and melatonin (9).

Likewise, many targets that play an important role in cardioprotection were not yet investigated in full detail with respect to circadian regulation (*e.g.*, PTEN, mitochondrial permeability transition pore, dipeptidyl peptidase-4, Toll-like receptors, or cardioprotective microRNAs), and therefore, they have not been deeply explored for chronotherapy so far (218). Circadian regulation of these processes should be considered in light of the substantial knowledge on the importance of time of the day for cardioprotective interventions (153), although not all studies confirmed a daytime dependence of elective cardiac surgery and clinical outcome (77, 107, 166).

Conclusions and Clinical Implications

In conclusion, the circadian rhythm is susceptible to alterations from lifestyle and environmental factors, which, in turn, influence the development and onset of cardiovascular disease. Considerations for these factors in regulatory and therapeutic undertakings could yield beneficial results in the considerable burden generated by cardiovascular disease. Anti-stress therapy, chronotherapy, and melatonin treatment alongside tighter regulations against air and noise pollution could reduce circadian rhythmic desynchronization and prevent the development of cardiovascular diseases.

Normalizing the cellular redox state arising from the dysfunctional mitochondria or improving mitochondrial function itself could also represent a possible strategy for abrogating the subclinical symptoms of developing cardiovascular and even neurological disease. Though the current research is somewhat inconsistent, this can be overcome through careful translational approaches and targeted clinical data to make chronotherapy a practicable therapeutic option.

As a final consideration, it is important to note that young animals are more resilient to changes in the environment than older animals (34), which makes age of the specimen an important consideration when conducting *in vivo* studies. Preclinical animal studies are usually performed during the day with the lights turned on; therefore, experiments performed on mice should be interpreted as their inactive phase, which does not directly translate to the times of the highest ''cardiovascular circadian risk'' in humans.

To gain insights translationally, data should be gathered during the night or the mice could be phase-shifted (127). Light settings could also be adjusted to coincide with the seasons in the outside environment (100). Therefore, when designing a study to assess the cardioprotective potential of a new therapy, it is important to take the time of day into consideration to improve the efficacy and tolerability of the treatment.

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Author Disclosure Statement

The authors certify that there is no conflict of interest with any financial organizations regarding the materials discussed in the article.

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Abbreviations Used

ACTH = adrenocorticotrophic hormone
AKT = protein kinase B
AMI = acute myocardial infarction
AMPK = AMP-activated protein kinase
ARNTL = aryl hydrocarbon receptor nuclear translocator-like protein
BDNF = brain-derived neurotrophic factor
BMAL1 = brain and muscle arnt-like protein-1
CLOCK = circadian locomotor output cycles protein kaput
CO = carbon monoxide
CRY = cryptochrome
dCRY = *Drosophila* cryptochrome
eNOS = endothelial nitric oxide synthase
ER = endoplasmic reticulum
FAD = flavin-adenin-dinucleotide
FBXL3 = F-box/leucine rich-repeat protein 3
FOXO = Forkhead box O
GCs = glucocorticoids
HbA1c = glycated hemoglobin levels as a long-term measure of blood glucose levels
HIF-1α = hypoxia-inducible factor 1α
HO-1 = heme oxygenase-1
HPA = hypothalamic-pituitary-adrenal
IL-6 = interleukin-6
MACE = major adverse cardiovascular events
MAPK = mitogen-activated protein kinase
mCRY1 = mammalian cryptochrome 1
MGRS = MTNR1B variants
MI = myocardial infarction
mPER1 = mammalian period 1
mPER2 = mammalian period 2
MTNR1B = melatonin receptor 1B
NADPH = nicotinamide adenine dinucleotide phosphate
NASH = non-alcoholic steatohepatitis
NOX2 = *NADPH oxidase isoform 2*
NPAS2 = neuronal PAS domain-containing protein 2
NRF2 = nuclear factor erythroid 2-related factor
PARP-1 = poly(ADP-ribose) polymerase-1
PER = period
PGC1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K = phosphatidylinositol 3-kinase
PM = particulate matter
Rev-Erbα (or NR1D1) = nuclear receptor subfamily 1, group D, member 1
ROR-α = RAR-related orphan receptor alpha
ROS = reactive oxygen species
SCN = suprachiasmatic nucleus
SREBP1c = sterol regulatory element-binding transcription factor 1
SIRT1 = sirtuin 1
TNF-α = tumor necrosis factor-α
VSMCs = vascular smooth muscle cells
WT = wild-type
ZT = Zeitgeber time