Published in final edited form as:

Curr Opin Physiol. 2018 October ; 5: 16–24. doi:10.1016/j.cophys.2018.05.002.

Circadian toxicity of environmental pollution. Inhalation of polluted air to give a precedent

Petra Haberzettl

Diabetes and Obesity Center, Institute of Molecular Cardiology, School of Medicine, University of Louisville, Louisville, KY 40202, USA

Abstract

Exposures to environmental stressors that derive from pollution (e.g. air, light) or lifestyle choices (e.g. diet, activity, 24-hour- $\times$ -7-day) are associated with adverse human health outcomes. For instance, there is evidence that air pollution exposure and changes in sleep/wake pattern increase the risk for vascular and cardiometabolic disorders. Interestingly, air pollution exposure affects pulmonary and cardiovascular functions that follow circadian rhythmicity and increases the risk for pulmonary and cardiovascular events that occur in diurnal patterns suggesting a link between air pollution induced cardiovascular and pulmonary injury and changes in circadian rhythm. Indeed, recent research identified circadian rhythm as an air pollution target and circadian rhythm as factor that increases air pollution sensitivity. Using air pollution exposure as precedent, this review highlights research on how environmental pollution affect circadian rhythm and how circadian rhythm affects the toxicity of environmental stressors.

Introduction

Recent research suggest that urbanization, accompanied by migration to more polluted areas (e.g., light [1^{**}] and air [2] pollution) and our modern 24 h lifestyle (35% adults sleep less than the recommended 7–8 h [3]) could be significant factors fueling into the development of CVD and T2D worldwide [4^{**}]. Exposure to environmental light [1^{**}], air [2], water [5], and food [6] pollution are a major health concern and with intensified industrialization and urbanization [7], its disease burden is likely to increase in the future. For instance, both, exposure to polluted air as well as changes in the day/night cycle have been described to increase the susceptibility for cardiovascular and metabolic injury.

Exposure to ambient air pollution is one of the leading causes of death worldwide that has been linked to 7 million premature deaths per year [2]. Ambient air pollution is a complex mixture of gaseous (i.e. carbon monoxide and dioxide, ozone, nitric oxide, sulfur-dioxide and nitrogen-dioxide), volatile (i.e. hydrocarbons, aldehydes) and particulate matter (PM) components derived from various sources such as industry, traffic, farming, mining, wildfires, volcano eruptions, cigarette smoke, and wood stove burning [8]. While exposure

Corresponding author: Haberzettl, Petra (p0habe02@louisville.edu).

Conflict of interest statement

Nothing declared.

to air pollution increases the risk of many diseases, most (60–80%) premature mortality associated with high levels of particulate matter (PM) air pollution is due to cardiovascular causes [9**]. Acute exposure to increased levels of ambient PM increases the risk of acute myocardial infarction, arrhythmias, and stroke [9**]. Chronically, exposure to PM contributes to lung injury, increases blood pressure and atherosclerotic lesion formation, and induces cardiac remodeling [9**,10,11]. Both experimental and epidemiological data show that exposure to fine particulate matter (PM_{2.5}) air pollution affects systemic insulin sensitivity in human and mice [12–14] and increases the risk for T2D [15,16]. Although the specific mechanism(s) of particle-induced cardiovascular and metabolic injury is ambiguous, it has been suggested that inhaled PM affects cardiovascular and metabolic health by either inducing oxidative stress and inflammation or stimulating sensory receptors in the lung that then extend systemically. In addition it has been suggested that ultrafine/nanosized particles or soluble particle constituents could enter the bloodstream and affect cardiovascular and metabolic health by direct interactions (Figure 1) [8]. This is supported by studies that show for instance the critical role of oxidative stress in mediating PM-induced vascular and metabolic dysfunction [17,18] and our recent studies that show that averting pulmonary oxidative stress prevented PM_{2.5}-induced vascular inflammation and insulin resistance and restored endothelial progenitor cell number and function [13,19].

Similarly, exposure to light pollution and changes in the sleep/wake pattern are indicated to contribute to the development of CVD and T2D [4**]. Circadian rhythmicity controlled by a central clock and peripheral circadian clocks is regulated by external signals such as light, temperature, food, or physical activity, called Zeitgeber (ZT). The central clock or suprachiasmatic nucleus (SCN) in the hypothalamus is the main regulator which resets other organ and tissue clocks in response to light, serotonin and melatonin [20]. Peripheral circadian clocks are reset by the SCN but are also entrained by food, melatonin, insulin and glucocorticoids [21]. Misalignment between SCN and peripheral clocks (e.g., by eating at the wrong time) results in a disorganized circadian rhythm, whereas SCN disruption (e.g., by disturbing the light cycle) leads to dyssynchrony as peripheral clocks keep oscillating without being reset by the SCN and become more and more misaligned (Figure 2) [22]. In humans circadian dyssynchrony has been associated with insulin resistance and increased T2D risk. For instance, it has been shown that extended or shortened sleep duration [23] and increased exposure to unnatural light [24] decrease glucose tolerance, insulin sensitivity and increase the risk for developing T2D. Sleeping >9 h or <5 h per night is associated with an increased T2D risk when compared with 8 h of sleep [25,26]. Moreover, disruption of the circadian rhythm, by changing the light/dark cycle [27,28], surgical ablation of the SCN [29], or genetic disruption of the circadian clock [30,31] increases obesity and induces insulin resistance in mice. Epidemiological as well as laboratory studies also indicate that dyssynchrony is associated with vascular outcomes such as increased blood pressure [32,33]. Depletion of BMAL1 leads to an arrhythmic circadian phenotype that exhibits a high susceptibility to vascular injury characterized by the loss in circadian blood pressure pattern [34,35]. Dyssynchrony has been shown to affect endothelial and cardiac function in mouse models. For instance, mutations in the clock gene *Per2* and genetic ablation of *Bmal1* induce endothelial dysfunction, alter diurnal vasoreactivity, and impair vascular Akt/eNOS signaling, and decrease endothelial progenitor cell function [34,36,37]. Light-induced

disruption of the circadian rhythm impaired wound healing after myocardial infarction and cardiomyocyte-specific depletion or mutation of the clock genes *Bmal1* or *clock* alter diurnal heart function, signaling and metabolism [38–40].

Diurnal changes in the concentration and composition of air pollution

The concentration and composition of man-made air pollution depends on the utilization of its sources (e.g., traffic, industrial processes, smoking) determined by the daily cycle of human activity. Hence, concentration and composition of air pollution show strong correlations to the time of the day exhibiting diurnal pattern. In urban environments, levels of traffic related air pollutant such as carbon monoxide (CO) peak during times of high traffic [41]. Diurnal variations have also been found for the concentration of traffic-related volatile organic compounds such as benzene and toluene that peak during the morning and evening rush hours [42]. In contrast, ambient concentrations of ozone (O₃), formed by a photochemical reaction of ozone precursors such as nitrogen oxides (NO_x) and carbon monoxide (CO) peak later in the noon hours [41,43]. Particulate matter (PM) air pollution is a mixture of different sized particles (coarse particles <10 µm in aerodynamic diameter, PM₁₀, crustal material, source: farming, mining, construction work, volcanic ash, and wood burning; fine particles <2.5 µm in aerodynamic diameter, PM_{2.5}; ultrafine/nano particles <0.1 µm, PM_{0.1}, primarily products of combustion-derived processes, for example, traffic and industrial sources, smoking) that contain organic (OC) and elemental (EC) carbon, sulfate, nitrate, and ammonium, along with many elements such as silica and metals (e.g. Fe, Ni, Al). Not surprisingly, size, concentration and composition of PM air pollution not only vary with geographical, seasonal and meteorological conditions [8], but also with the time of the day. Both, indoor and outdoor PM concentration show diurnal trends. For instance, indoor PM concentrations show daily variations with peaks in the evening and at meal hours that correlate with time for cooking and smoking [44]. Similarly, concentrations of PM_{2.5} are increased during daily train operation hours in European subway tunnels [45] and during traffic hours in downtown Los Angeles [46]. The concentrations of coarse PM follow diurnal pattern as well, showing peak concentrations in the midday to afternoon due to daily meteorological changes (i.e. wind speed) [41,46]. Diurnal changes were also found in the composition of PM. For instance, particle-bound polycyclic aromatic hydrocarbon (PAH) concentrations are shown to be higher at weekdays than at weeknights [47]. The concentrations of water-soluble organic carbons (WSOCs) peak in midday and afternoon and concentrations of redox-active metals such as Fe and Cu peak during the morning rush hour consistent with the observed increase in coarse or fine PM, respectively [48,49]. Both, redox active metals and WSOC have been associated with the production of reactive oxygen species (ROS) [8,50] and not surprisingly the oxidative potential of coarse PM follows diurnal pattern [51].

This is important because recent studies show that the abundance of antioxidant defense mechanisms, needed to fight PM-induced oxidative stress, follow circadian rhythmicity and are regulated by the molecular clocks [52*,53–55,56**,57]. The molecular circadian clock is driven by transcriptional feedback loops. The primary feedback loop contains the transcription factors circadian locomotor-output-cycle-kaput (CLOCK) and muscle aryl hydrocarbon nuclear translocator (ARNT)-like1 (ARNTL or BMAL1) which regulate the

expression of circadian core genes and other non-core target genes. CLOCK and BMAL1 repress their own transcription by initiating the transcription of Period homologs (PER1, 2, 3) and Cryptochromes (CRY1, 2), which negatively regulate CLOCK:BMAL1. A secondary CLOCK: BMAL1 induced feedback loop consists of retinoic acid-related orphan nuclear receptors (REV-ERB- α / β and ROR- α / β / γ) that regulate BMAL1 by activating (ROR α) or repressing (REV-ERB) its transcription [58]. Clock proteins not only control the transcription of core clock genes, but also the expression of other target genes such as antioxidant defense and inflammatory genes. For instance, the pulmonary expression of components of the nuclear factor erythroid-derived 2-like/glutathione (Nrf2/GSH) antioxidant defense pathway follow diurnal pattern. Regulated by CLOCK and BMAL1, NRF2 induces the expression of genes involved in glutathione synthesis and utilization, leading to a time of the day dependent susceptibility to oxidative stress in the lungs [52*]. Similarly, the levels of components of the Nrf2/GSH pathway show diurnal variations in the liver and the highest hepatotoxicity of acetaminophen is found when the levels of GSH are lowest [55]. In addition, circadian rhythmicity has been found for the sensitivity to inflammatory stimuli such as lipopolysaccharides (LPS) that is mediated by the NF- κ B pathway [59]. In line with the circadian variations in the susceptibility to oxidative and inflammatory stimuli, diurnal trends in particle concentrations could increase PM exposure at more vulnerable circadian phases and consequently induce chronotoxic effects. In addition, particle concentration, size and composition are important factors that define particle toxicity [8]. Thus, to develop guidelines and policies to minimize the health effects of air pollutant exposure, it is of high interest to identify, which PM components are subject to diurnal changes and when levels are highest.

Chronotoxicity of air pollution

Recent research makes it apparent that besides of ‘*the dose that makes the poison*’ the timing of the dosing is an important determinant of toxicity. Results from these studies summarized by Dallmann and colleagues [60**] show that circadian timing of drug administration effects toxic and pharmacological outcomes that support the concept of chronotoxicity and chronopharmacology. However, even though Kerr and co-workers emphasized the importance of circadian rhythm on air pollution toxicity [61], the chronotoxic effects of air pollution exposure have not been thoroughly studied, yet. Therefore, to minimize exposures at times of high vulnerability future studies that evaluate the chronotoxicity of air pollution are needed to inform about the time of the highest susceptibility. This is even more important as air pollution exposure has been demonstrated to affect pulmonary, cardiac and vascular functions that follow circa-dian rhythmicity and to increase the risk for pulmonary and cardiovascular events that occur in diurnal patterns. For instance, air pollution exposure changes 24 h blood pressure pattern [62*,63*] and increases the risk for acute cardiovascular events such as acute myocardial infarction and stroke [4**,9**], which are 40–50% higher in the morning [64,65]. Therefore, air pollution exposures in the morning when blood pressure (morning surge) and CVD risk are highest could be more harmful than exposures in the night when blood pressure (nocturnal dip) and CVD risk are lower. In addition, recent research demonstrates that circadian clocks control the diurnal expression of antioxidant defense and inflammatory genes [52*,53–55,56**,59] suggesting that there are timing ‘sweet

spots' at which oxidative stress and inflammation can be managed best. Consequently, air pollution chronotoxicity could be the result of circadian changes in the potential to deal with air pollution-induced oxidative stress and inflammation. On the other hand, recent reports indicate that exposure to polluted air disrupts the circadian rhythm and peripheral circadian clocks supporting the idea that circadian toxicity, could be one mechanism by which the exposure to air pollution leads to adverse health outcomes.

Circadian toxicity of air pollution

Since invention of the electric light our environment has become increasingly brighter at night. Although light at night has its socioeconomic benefits (e.g. productivity increase, more recreational time), it negatively affects our environment. Light pollution has been shown to have detrimental effects on fauna and flora. For instance, some trees fail to regulate seasonal changes and hatching sea turtles as well as migrating birds become disorientated [1^{**}]. Light pollution also has a major impact on human health increasing the risk for developing cancer and other disease [1^{**},4^{**},66^{**}]. Not surprisingly, due to a mutual origin in urbanization and industrialization, maps illustrating the density of light pollution overlap with maps showing concentrations of air pollution [1^{**},15] and light and air pollution seem to be high in areas with an increased risk for developing cardiovascular disease and T2D. Exposure to unnatural light and air pollution are both environmental pollutants that affect circadian rhythmicity. As mentioned earlier, it has been demonstrated that air pollution exposure changes pulmonary, cardiac and vascular functions that follow circadian rhythmicity.

Cardiovascular circadian toxicity of air pollution

In humans, short-term exposures to increased levels of ambient PM₁₀ have been shown to be associated with a higher nighttime (sleeping time) systolic and diastolic blood pressure and a diminished nocturnal systolic blood pressure dip [62^{*}]. This is important, as nondipping, a nocturnal decrease in blood pressure of less than 10% has been associated with increased risk for cardiovascular diseases and mortality especially in hypertension patients [67,68]. Similarly, exposure to second hand smoke increased systolic and diastolic blood pressure with stronger changes during sleeping time (circadian light phase) and a blunted dip of systolic and diastolic blood pressure from the dark (active) to the light (sleeping) phase in rats [63^{*}]. In both, humans and rodents, inhalation of PM₁₀ or second hand smoke and intranasal instillation of benzo[a] pyrene reduced the blood pressure dipping during sleep [62^{*},63^{*},69]. This is important, as blood pressure could be critical to the occurrence of acute cardiovascular events associated with exposure to polluted air [4^{**},9^{**}].

Pulmonary circadian toxicity of air pollution

Exposure to polluted air also has been found to affect circadian rhythmicity of lung function. For instance, exposure to increased levels of ambient air pollution increased the diurnal variability of lung function in asthmatic school children [70]. Interestingly, passive smoking changed the circadian rhythm of peak respiratory flow in children [71], and second hand tobacco smoke exposure altered the circadian clock gene expression in the lungs of mice

[72,73*] suggesting that disruption of the molecular clocks in the lungs could contribute to cigarette smoke induced lung injury. Smoking also increases the risk for developing intervertebral disc degradation and lower back pain and changes in clock gene expression have been also found in the intervertebral disc of second hand smoke exposed rats [74]. Similarly, exposures to electronic cigarette vapors affected the expression of clock genes in the lungs as well as systemically in organs such as kidney, liver and brain in mice [75].

Mechanism of air pollution-induced circadian toxicity

Although recent studies suggest that air pollution exposure could disturb the rhythmicity of clock gene expression by acetylation and degradation of BMAL1 [73*] or methylation of *clock* [76], it is unclear how air pollution exposure disturbs molecular circadian clocks. Because oxidative stress has the potential to directly disrupt the circadian clock by altering clock protein activity, it is possible that air pollution exposures disturb peripheral molecular clocks by inducing oxidative stress. The molecular circadian clock mechanism driven by transcriptional feedback loops is sensitive to oxidative stress as changes in the redox status of clock proteins could alter clock protein activity and the transcription of core clock genes (Figure 3). For instance, the activity of the nuclear orphan receptor REV-ERB- β depends on a reduced dithiol state. The oxidation of thiol groups by reactive oxygen species (ROS) could decrease REV-ERB- β activity, leading to an increase in *bmal1* transcription; and consequently a disruption of the circadian rhythm [56**]. Likewise, oxidative stress could enhance the activity of the CRY1:PER2 complex as oxidation stabilizes the dimer by the formation of a disulfide bond [77]. The nuclear translocation of the transcription factors BMAL1 and CLOCK depend not only on their dimerization, but also on their phosphorylation and acetylation status [78]. CLOCK mediated acetylation of its heterodimer BMAL1 recruits the negative regulator CRY1 suppressing clock gene transcription [79], whereas the deacetylation of BMAL1 by Sirtuin1 (SIRT1) [80] or the S-nitrosylation of BMAL1 by NO [81] seem to upregulate clock gene expression. A recent study shows that in neonatal mice hyperoxia regulates *rev-erb-a* transcription [82], indicating that oxidative stress can directly affect circadian rhythmicity. Thus, oxidative stress induced by the exposure to air pollution has the potential to modify clock protein activity. For instance, air pollution induced oxidative stress could lead to the oxidization of the thiol group of REVERB- β . This would decrease the activity of the transcription factor increasing *bmal1* transcription thereby disturbing the circadian clock.

Conclusion

Although exposure to polluted air and dyssynchrony have been independently shown to increase the risk for pulmonary, cardiovascular and metabolic injury it is not clear whether dyssynchrony affects air pollution toxicity. A study that shows that the depletion of Bmal1 increased the sensitivity to inhaled nanoparticles [83] supports the idea that circadian dyssynchrony increases the sensitivity to air pollution exposure, whereas combined exposure to concentrated PM_{2.5} and dim light at night had no additive neurological affects [84]. However, because the exposure to air and light pollution and changes of our sleep pattern are likely to increase due to increasing urbanization and our modern 24-hour $\times$ 7-day live style choices, it is essential to investigate in future studies whether circadian dyssynchrony

increases the susceptibility to air pollution toxicity. In addition, chronotoxic effects in shift worker have not been studied yet and it is unclear whether shift work-induced circadian dyssynchrony exacerbates the health effects of pollutant exposure although it is known that shift work, which is often accompanied by exposure to pollutants, has acute and chronic health effects [85]. Results from these studies will be essential in assessing whether air pollution exposure exacerbates pulmonary, cardiovascular and metabolic injury in humans with disrupted circadian rhythm. Additional chronotoxicity studies, will inform about specific times in a day when humans are more sensitive to air pollution toxicity. Such studies could help in identifying specific individuals (e.g. those with disrupted circadian rhythms) who might be more sensitive to air pollution exposure and lead to the development of simple and readily implementable preventive strategies (e.g. realigning circadian rhythms) to mitigate against the major harmful health effects of air pollution. They also could lead to targeted approaches that limit air pollution exposures at certain times during the day.

Funding

This work was supported by a grant from the National Institute of Environmental Health Sciences of the National Institutes of Health [R01ES027881] to P Haberzettl.

References and recommended reading

Papers of particular interest, published within the period of review have been highlighted as:

- of special interest
 - of outstanding interest
- 1••. Chepesiuk R: Missing the dark: health effects of light pollution. *Environ Health Perspect* 2009, 117:A20–27. [PubMed: 19165374] This comprehensive review article highlights the effects of light pollution.
 2. <http://www.who.int/mediacentre/news/releases/2014/air-pollution/en/>.
 3. <http://www.cdc.gov/features/dssleep/>.
 - 4••. Bhatnagar A: Environmental determinants of cardiovascular disease. *Circ Res* 2017, 121:162–180. [PubMed: 28684622] This comprehensive review article highlights environmental factors and lifestyle choices that affect cardiovascular health.
 5. Saha N, Rahman MS, Ahmed MB, Zhou JL, Ngo HH, Guo W: Industrial metal pollution in water and probabilistic assessment of human health risk. *J Environ Manage* 2017, 185:70–78. [PubMed: 28029481]
 6. Li AM: Ecological determinants of health: food and environment on human health. *Environ Sci Pollut Res Int* 2017, 24:9002–9015. [PubMed: 26552789]
 7. esa.un.org/unup/CD-ROM/Urban-Rural-Population.htm.
 8. Haberzettl P, Bhatnagar A, Conklin DJ: Particulate matter and oxidative stress–pulmonary and cardiovascular targets and consequences. *Syst Biol Free Radic Antioxid* 2014:1557–1586.
 - 9••. Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA et al.: Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010, 121:2331–2378. [PubMed: 20458016] This comprehensive review article summarizes the cardiovascular effects of air pollution exposure.
 10. Alfaro-Moreno E, Nawrot TS, Nemmar A, Nemery B: Particulate matter in the environment: pulmonary and cardiovascular effects. *Curr Opin Pulm Med* 2007, 13:98–106. [PubMed: 17255799]

11. Wold LE, Ying Z, Hutchinson KR, Velten M, Gorr MW, Velten C, Youtz DJ, Wang A, Lucchesi PA, Sun Q et al.: Cardiovascular remodeling in response to long-term exposure to fine particulate matter air pollution. *Circ Heart Fail* 2012, 5:452–461. [PubMed: 22661498]
12. Brook RD, Xu X, Bard RL, Dvonch JT, Morishita M, Kaciroti N, Sun Q, Harkema J, Rajagopalan S: Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. *Sci Total Environ* 2013, 448:66–71. [PubMed: 22901427]
13. Haberzettl P, O'Toole TE, Bhatnagar A, Conklin DJ: Exposure to fine particulate air pollution causes vascular insulin resistance by inducing pulmonary oxidative stress. *Environ Health Perspect* 2016.
14. Sun Q, Yue P, Deiluiis JA, Lumeng CN, Kampfrath T, Mikolaj MB, Cai Y, Ostrowski MC, Lu B, Parthasarathy S et al.: Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* 2009, 119:538–546. [PubMed: 19153269]
15. Pearson JF, Bachireddy C, Shyamprasad S, Goldfine AB, Brownstein JS: Association between fine particulate matter and diabetes prevalence in the U.S. *Diabetes Care* 2010, 33:2196–2201. [PubMed: 20628090]
16. Kramer U, Herder C, Sugiri D, Strassburger K, Schikowski T, Ranft U, Rathmann W: Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. *Environ Health Perspect* 2010, 118:1273–1279. [PubMed: 20504758]
17. Kampfrath T, Maisseyeu A, Ying Z, Shah Z, Deiluiis JA, Xu X, Kherada N, Brook RD, Reddy KM, Padture NP et al.: Chronic fine particulate matter exposure induces systemic vascular dysfunction via NADPH oxidase and TLR4 pathways. *Circ Res* 2011, 108:716–726. [PubMed: 21273555]
18. Xu X, Yavar Z, Verdin M, Ying Z, Mihai G, Kampfrath T, Wang A, Zhong M, Lippmann M, Chen LC et al.: Effect of early particulate air pollution exposure on obesity in mice: role of p47phox. *Arterioscler Thromb Vasc Biol* 2010, 30:2518–2527. [PubMed: 20864666]
19. Haberzettl P, Conklin DJ, Abplanalp WT, Bhatnagar A, O'Toole TE: Inhalation of fine particulate matter impairs endothelial progenitor cell function via pulmonary oxidative stress. *Arterioscler Thromb Vasc Biol* 2018, 38:131–142. [PubMed: 29191925]
20. Golombek DA, Rosenstein RE: Physiology of circadian entrainment. *Physiol Rev* 2010, 90:1063–1102. [PubMed: 20664079]
21. Saini C, Suter DM, Liani A, Gos P, Schibler U: The mammalian circadian timing system: synchronization of peripheral clocks. *Cold Spring Harb Symp Quant Biol* 2011, 76:39–47. [PubMed: 22179985]
22. Voigt RM, Forsyth CB, Keshavarzian A: Circadian disruption: potential implications in inflammatory and metabolic diseases associated with alcohol. *Alcohol Res* 2013, 35:87–96. [PubMed: 24313168]
23. Yaggi HK, Araujo AB, McKinlay JB: Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006, 29:657–661. [PubMed: 16505522]
24. Leproult R, Holmback U, Van Cauter E: Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 2014, 63:1860–1869. [PubMed: 24458353]
25. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E: Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol* 1985, 2005(99):2008–2019.
26. Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, Speizer FE, Patel S, Hu FB: A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 2003, 26:380–384. [PubMed: 12547866]
27. Fonken LK, Lieberman RA, Weil ZM, Nelson RJ: Dim light at night exaggerates weight gain and inflammation associated with a high-fat diet in male mice. *Endocrinology* 2013, 154:3817–3825. [PubMed: 23861373]
28. Coomans CP, van den Berg SA, Houben T, van Klinken JB, van den Berg R, Pronk AC, Havekes LM, Romijn JA, van Dijk KW, Biermasz NR et al.: Detrimental effects of constant light exposure and high-fat diet on circadian energy metabolism and insulin sensitivity. *FASEB J* 2013, 27:1721–1732. [PubMed: 23303208]

29. Coomans CP, van den Berg SA, Lucassen EA, Houben T, Pronk AC, van der Spek RD, Kalsbeek A, Biermasz NR, Willems van Dijk K, Romijn JA et al.: The suprachiasmatic nucleus controls circadian energy metabolism and hepatic insulin sensitivity. *Diabetes* 2013, 62:1102–1108. [PubMed: 23274903]
30. Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH et al.: Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* 2010, 466:627–631. [PubMed: 20562852]
31. Guo B, Chatterjee S, Li L, Kim JM, Lee J, Yechoor VK, Minze LJ, Hsueh W, Ma K: The clock gene, brain and muscle Arnt-like 1, regulates adipogenesis via Wnt signaling pathway. *FASEB J* 2012, 26:3453–3463. [PubMed: 22611086]
32. Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, Kobayashi E, Nogawa K: Shift work is a risk factor for increased blood pressure in Japanese men: a 14-year historical cohort study. *Hypertension* 2008, 52:581–586. [PubMed: 18625889]
33. Scheer FA, Hilton MF, Mantzoros CS, Shea SA: Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA* 2009, 106:4453–4458. [PubMed: 19255424]
34. Anea CB, Zhang M, Stepp DW, Simkins GB, Reed G, Fulton DJ, Rudic RD: Vascular disease in mice with a dysfunctional circadian clock. *Circulation* 2009, 119:1510–1517. [PubMed: 19273720]
35. Anea CB, Cheng B, Sharma S, Kumar S, Caldwell RW, Yao L, Ali MI, Merloiu AM, Stepp DW, Black SM et al.: Increased superoxide and endothelial NO synthase uncoupling in blood vessels of Bmal1-knockout mice. *Circ Res* 2012, 111:1157–1165. [PubMed: 22912383]
36. Viswambharan H, Carvas JM, Antic V, Marecic A, Jud C, Zaugg CE, Ming XF, Montani JP, Albrecht U, Yang Z: Mutation of the circadian clock gene Per2 alters vascular endothelial function. *Circulation* 2007, 115:2188–2195. [PubMed: 17404161]
37. Wang CY, Wen MS, Wang HW, Hsieh IC, Li Y, Liu PY, Lin FC, Liao JK: Increased vascular senescence and impaired endothelial progenitor cell function mediated by mutation of circadian gene Per2. *Circulation* 2008, 118:2166–2173. [PubMed: 18981300]
38. Young ME, Brewer RA, Peliciari-Garcia RA, Collins HE, He L, Birky TL, Peden BW, Thompson EG, Ammons BJ, Bray MS et al.: Cardiomyocyte-specific BMAL1 plays critical roles in metabolism, signaling, and maintenance of contractile function of the heart. *J Biol Rhythms* 2014, 29:257–276. [PubMed: 25238855]
39. Bray MS, Shaw CA, Moore MW, Garcia RA, Zanquetta MM, Durgan DJ, Jeong WJ, Tsai JY, Bugger H, Zhang D et al.: Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression. *Am J Physiol Heart Circ Physiol* 2008, 294:H1036–1047. [PubMed: 18156197]
40. Alibhai FJ, Tsimakouridze EV, Chinnappareddy N, Wright DC, Billia F, O'Sullivan ML, Pyle WG, Sole MJ, Martino TA: Short-term disruption of diurnal rhythms after murine myocardial infarction adversely affects long-term myocardial structure and function. *Circ Res* 2014, 114:1713–1722. [PubMed: 24687134]
41. Masiol M, Squizzato S, Formenton G, Harrison RM, Agostinelli C: Air quality across a European hotspot: Spatial gradients, seasonality, diurnal cycles and trends in the Veneto region, NE Italy. *Sci Total Environ* 2017, 576:210–224. [PubMed: 27788436]
42. Phuc NH, Kim Oanh NT: Determining factors for levels of volatile organic compounds measured in different microenvironments of a heavy traffic urban area. *Sci Total Environ* 2018, 627:290–303. [PubMed: 29426152]
43. Wei W, Lv Z, Cheng S, Wang L, Ji D, Zhou Y, Han L, Wang L: Characterizing ozone pollution in a petrochemical industrial area in Beijing, China: a case study using a chemical reaction model. *Environ Monit Assess* 2015, 187:377. [PubMed: 26013656]
44. Wallace LA, Mitchell H, O'Connor GT, Neas L, Lippmann M, Kattan M, Koenig J, Stout JW, Vaughn BJ, Wallace D et al.: Particle concentrations in inner-city homes of children with asthma: the effect of smoking, cooking, and outdoor pollution. *Environ Health Perspect* 2003, 111:1265–1272. [PubMed: 12842784]

45. Martins V, Moreno T, Mendes L, Eleftheriadis K, Diapouli E, Alves CA, Duarte M, de Miguel E, Capdevila M, Querol X et al.: Factors controlling air quality in different European subway systems. *Environ Res* 2016, 146:35–46. [PubMed: 26717078]
46. Hasheminassab S, Pakbin P, Delfino RJ, Schauer JJ, Sioutas C: Diurnal and seasonal trends in the apparent density of ambient fine and coarse particles in Los Angeles. *Environ Pollut* 2014, 187:1–9. [PubMed: 24413160]
47. Ringuet J, Albinet A, Leoz-Garziandia E, Budzinski H, Villenave E: Diurnal/nocturnal concentrations and sources of particulate-bound PAHs, OPAHs and NPAHs at traffic and suburban sites in the region of Paris (France). *Sci Total Environ* 2012, 437:297–305. [PubMed: 22947617]
48. Mousavi A, Sowlat MH, Sioutas C: Diurnal and seasonal trends and source apportionment of redox-active metals in Los Angeles using a novel online metal monitor and Positive Matrix Factorization (PMF). *Atmos Environ* 2018, 174:15–24.
49. Cheung K, Daher N, Shafer MM, Ning Z, Schauer JJ, Sioutas C: Diurnal trends in coarse particulate matter composition in the Los Angeles Basin. *J Environ Monit* 2011, 13:3277–3287. [PubMed: 22025084]
50. Ghio AJ, Carraway MS, Madden MC: Composition of air pollution particles and oxidative stress in cells, tissues, and living systems. *J Toxicol Environ Health B Crit Rev* 2012, 15:1–21. [PubMed: 22202227]
51. Cheung K, Shafer MM, Schauer JJ, Sioutas C: Diurnal trends in oxidative potential of coarse particulate matter in the Los Angeles Basin and their relation to sources and chemical composition. *Environ Sci Technol* 2012, 46:3779–3787. [PubMed: 22380575]
- 52•. Pekovic-Vaughan V, Gibbs J, Yoshitane H, Yang N, Pathiranage D, Guo B, Sagami A, Taguchi K, Bechtold D, Loudon A et al.: The circadian clock regulates rhythmic activation of the NRF2/glutathione-mediated antioxidant defense pathway to modulate pulmonary fibrosis. *Genes Dev* 2014, 28:548–560. [PubMed: 24637114] Results of this study demonstrate that in the mouse lung circadian clocks regulate the NRF2/glutathione-mediated oxidative stress defense.
53. Jang YS, Lee MH, Lee SH, Bae K: Cu/Zn superoxide dismutase is differentially regulated in period gene-mutant mice. *Biochem Biophys Res Commun* 2011, 409:22–27. [PubMed: 21549097]
54. Blanco RA, Ziegler TR, Carlson BA, Cheng PY, Park Y, Cotsonis GA, Accardi CJ, Jones DP: Diurnal variation in glutathione and cysteine redox states in human plasma. *Am J Clin Nutr* 2007, 86:1016–1023. [PubMed: 17921379]
55. Xu YQ, Zhang D, Jin T, Cai DJ, Wu Q, Lu Y, Liu J, Klaassen CD: Diurnal variation of hepatic antioxidant gene expression in mice. *PLoS ONE* 2012, 7:e44237. [PubMed: 22952936]
- 56••. Wilking M, Ndiaye M, Mukhtar H, Ahmad N: Circadian rhythm connections to oxidative stress: implications for human health. *Antioxid Redox Signal* 2013, 19:192–208. [PubMed: 23198849] This review article discusses the interactions between the circadian rhythm and oxidative stress.
57. Patel SA, Velingkaar NS, Kondratov RV: Transcriptional control of antioxidant defense by the circadian clock. *Antioxid Redox Signal* 2014, 20:2997–3006. [PubMed: 24111970]
58. Ko CH, Takahashi JS: Molecular components of the mammalian circadian clock. *Hum Mol Genet* 2006, 15 (Spec No 2):R271–277. [PubMed: 16987893]
59. Spengler ML, Kuropatwinski KK, Comas M, Gasparian AV, Fedtsova N, Gleiberman AS, Gitlin II, Artemicheva NM, Deluca KA, Gudkov AV et al.: Core circadian protein CLOCK is a positive regulator of NF-kappaB-mediated transcription. *Proc Natl Acad Sci USA* 2012, 109:E2457–2465. [PubMed: 22895791]
- 60••. Dallmann R, Okyar A, Levi F: Dosing-time makes the poison: circadian regulation and pharmacotherapy. *Trends Mol Med* 2016, 22:430–445. [PubMed: 27066876] This review article summarizes current studies on chronopharmacology.
61. Kerr HD: Diurnal variation of respiratory function independent of air quality: experience with an environmentally controlled exposure chamber for human subjects. *Arch Environ Health* 1973, 26:144–152. [PubMed: 4688853]
- 62•. Tsai DH, Riediker M, Wuerzner G, Maillard M, Marques-Vidal P, Paccaud F, Vollenweider P, Burnier M, Bochud M: Short-term increase in particulate matter blunts nocturnal blood pressure dipping and daytime urinary sodium excretion. *Hypertension* 2012, 60:1061–1069. [PubMed: 22025084]

22868388] Research presented in this article demonstrates the association between short-term exposures to PM and changes in circadian blood pressure pattern.

- 63•. Gentner NJ, Weber LP: Secondhand tobacco smoke, arterial stiffness, and altered circadian blood pressure patterns are associated with lung inflammation and oxidative stress in rats. *Am J Physiol Heart Circ Physiol* 2012, 302:H818–825. [PubMed: 22140051] This animal study by Gentner and Weber shows that in rats exposure to second hand tobacco smoke induces changes in circadian blood pressure that possibly by the induction of pulmonary oxidative stress and inflammation.
64. Cohen MC, Rohitla KM, Lavery CE, Muller JE, Mittleman MA: Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol* 1997, 79:1512–1516. [PubMed: 9185643]
65. Elliott WJ: Circadian variation in the timing of stroke onset: a meta-analysis. *Stroke* 1998, 29:992–996. [PubMed: 9596248]
- 66•. Lunn RM, Blask DE, Coogan AN, Figueiro MG, Gorman MR, Hall JE, Hansen J, Nelson RJ, Panda S, Smolensky MH et al.: Health consequences of electric lighting practices in the modern world: a report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption. *Sci Total Environ* 2017, 607–608:1073–1084. This review article summarizes light exposure induced circadian rhythm disruption and adverse health effects as discussed in a recent toxicology workshop.
67. Peppard PE, Young T, Palta M, Skatrud J: Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000, 342:1378–1384. [PubMed: 10805822]
68. Birkenhager AM, van den Meiracker AH: Causes and consequences of a non-dipping blood pressure profile. *Neth J Med* 2007, 65:127–131. [PubMed: 17452760]
69. Gentner NJ, Weber LP: Intranasal benzo[a]pyrene alters circadian blood pressure patterns and causes lung inflammation in rats. *Arch Toxicol* 2011, 85:337–346. [PubMed: 20848083]
70. Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB, Lin X, Parker EA, Israel BA, Gonzalez L et al.: Air pollution-associated changes in lung function among asthmatic children in Detroit. *Environ Health Perspect* 2005, 113:1068–1075. [PubMed: 16079081]
71. Casale R, Natali G, Colantonio D, Pasqualetti P: Circadian rhythm of peak expiratory flow in children passively exposed and not exposed to cigarette smoke. *Thorax* 1992, 47:801–803. [PubMed: 1481180]
72. Gebel S, Gerstmayer B, Kuhl P, Borlak J, Meurrens K, Muller T: The kinetics of transcriptomic changes induced by cigarette smoke in rat lungs reveals a specific program of defense, inflammation, and circadian clock gene expression. *Toxicol Sci* 2006, 93:422–431. [PubMed: 16870687]
- 73•. Hwang JW, Sundar IK, Yao H, Sellix MT, Rahman I: Circadian clock function is disrupted by environmental tobacco/cigarette smoke, leading to lung inflammation and injury via a SIRT1-BMAL1 pathway. *FASEB J* 2014, 28:176–194. [PubMed: 24025728] The study by Hwang et al. shows that the exposure to second hand cigarette smoke changes circadian clock gene in the lungs by a mechanism that possibly involves the SIRT1-BMAL-1 pathway.
74. Numaguchi S, Esumi M, Sakamoto M, Endo M, Ebihara T, Soma H, Yoshida A, Tokuhashi Y: Passive cigarette smoking changes the circadian rhythm of clock genes in rat intervertebral discs. *J Orthop Res* 2016, 34:39–47. [PubMed: 25939642]
75. Lechasseur A, Jubinville E, Routhier J, Berube JC, Hamel-Auger M, Talbot M, Lamothe J, Aubin S, Pare ME, Beaulieu MJ et al.: Exposure to electronic cigarette vapors affects pulmonary and systemic expression of circadian molecular clock genes. *Physiol Rep* 2017, 5.
76. Romano A, De Giorgio B, Parolini M, Favero C, Possenti CD, Iodice S, Caprioli M, Rubolini D, Ambrosini R, Gianfranceschi L et al.: Methylation of the circadian Clock gene in the offspring of a free-living passerine bird increases with maternal and individual exposure to PM10. *Environ Pollut* 2017, 220:29–37. [PubMed: 27712846]
77. Schmalen I, Reischl S, Wallach T, Klemz R, Grudziecki A, Prabu JR, Benda C, Kramer A, Wolf E: Interaction of circadian clock proteins CRY1 and PER2 is modulated by zinc binding and disulfide bond formation. *Cell* 2014, 157:1203–1215. [PubMed: 24855952]
78. Kondratov RV, Chernov MV, Kondratova AA, Gorbacheva VY, Gudkov AV, Antoch MP: BMAL1-dependent circadian oscillation of nuclear CLOCK: posttranslational events induced by

- dimerization of transcriptional activators of the mammalian clock system. *Genes Dev* 2003, 17:1921–1932. [PubMed: 12897057]
79. Hirayama J, Sahar S, Grimaldi B, Tamaru T, Takamatsu K, Nakahata Y, Sassone-Corsi P: CLOCK-mediated acetylation of BMAL1 controls circadian function. *Nature* 2007, 450:1086–1090. [PubMed: 18075593]
80. Nakahata Y, Kaluzova M, Grimaldi B, Sahar S, Hirayama J, Chen D, Guarente LP, Sassone-Corsi P: The NAD⁺-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell* 2008, 134:329–340. [PubMed: 18662547]
81. Kunieda T, Minamino T, Miura K, Katsuno T, Tateno K, Miyauchi H, Kaneko S, Bradfield CA, FitzGerald GA, Komuro I: Reduced nitric oxide causes age-associated impairment of circadian rhythmicity. *Circ Res* 2008, 102:607–614. [PubMed: 18218984]
82. Yang G, Wright CJ, Hinson MD, Fernando AP, Sengupta S, Biswas C, La P, Dennerly PA: Oxidative stress and inflammation modulate Rev-erb α signaling in the neonatal lung and affect circadian rhythmicity. *Antioxid Redox Signal* 2014, 21:17–32. [PubMed: 24252172]
83. Luyts K, Smulders S, Napierska D, Van Kerckhoven S, Poels K, Scheers H, Hemmeryckx B, Nemery B, Hoylaerts MF, Hoet PH: Pulmonary and hemostatic toxicity of multi-walled carbon nanotubes and zinc oxide nanoparticles after pulmonary exposure in Bmal1 knockout mice. *Part Fibre Toxicol* 2014, 11:61. [PubMed: 25394423]
84. Hogan MK, Kovalycsik T, Sun Q, Rajagopalan S, Nelson RJ: Combined effects of exposure to dim light at night and fine particulate matter on C3H/HeNHsd mice. *Behav Brain Res* 2015, 294:81–88. [PubMed: 26235330]
85. James SM, Honn KA, Gaddameedhi S, Van Dongen HPA: Shift work: disrupted circadian rhythms and sleep-implications for health and well-being. *Curr Sleep Med Rep* 2017, 3:104–112. [PubMed: 29057204]

Figure 1.

Mechanisms of air pollution induced vascular and cardiometabolic injury. Ambient air pollution a complex mixture of gaseous, volatile and particulate matter (PM) components are derived from various natural or man made sources. Inhalation of air pollutant has been suggested to induce vascular and cardiometabolic injury by either the induction of pulmonary oxidative stress and inflammation that spread systemically, the stimulation of the autonomic nervous system, or direct interactions due to systemic translocation of ultrafine/nanosized particles or soluble particle constituents.

Figure 2.

Regulation of the circadian rhythm. The central clock (suprachiasmatic nucleus, SCN) entrained by light regulates the peripheral clocks. Misalignment between SCN and peripheral clocks (e.g. eating at the wrong time) results in a disorganized circadian rhythm, whereas disruption of the SCN leads to dyssynchrony as peripheral clocks keep oscillating without being reset by the SCN and become more and more misaligned.

Figure 3.

Possible mechanism of air pollution-induced circadian toxicity. Inhalation of polluted air induces oxidative stress that could disturb the circadian clocks by changing clock protein activity (e.g. oxidation or changes in nitrosylation and acetylation). Clock proteins not only control the transcription of core clock genes, but also regulate the expression of other target genes such as antioxidant defense genes. Consequently, air pollution exposure, by disruption of the molecular clocks, could disturb the diurnal expression of antioxidant defense genes that could impair the protection against oxidative stress and worsen the adverse health affects of air pollution exposure.