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Inhalation of polluted air to give a precedent

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Circadian Toxicity of Environmental Pollution. Inhalation of polluted air to give a precedent.

Short Title: Circadian Rhythm and Air Pollution.

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Abstract

Exposures to environmental stressors that derive from pollution (e.g., air, light) or lifestyle choices (e.g., diet, activity, 24-hour-x-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.

Key words: air pollution, cardiovascular disease, circadian rhythm, environment, and oxidative stress

Introduction

Recent research suggest that urbanization, accompanied by migration to more polluted areas (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 world-wide 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- 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 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 [9-11]. 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 obesity and 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 (**Fig. 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 supra chiasmatic 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 (**Fig. 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 >9h or <5h per night is associated with an increased T2D risk when compared with 8h 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, PM_{2.5}; ultrafine/nano particles <0.1 µm, PM_{0.1}, primarily products of combustion-derived processes e.g., 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 hydrocarbons (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 course 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 [52-57]. 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 affects 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 circadian rhythmicity and to increase the risk for pulmonary and cardiovascular events that occur in diurnal patterns. For instance, air pollution exposure changes 24h 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 [52-56,59] 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, obesity 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], while 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 that is sensitive to oxidative stress as changes in the redox status of these clock proteins could alter clock protein activity and the transcription of core clock genes (**Fig. 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 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 REV-ERB- 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 effects [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 x 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.

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Conflict of interest

None declared.

ACCEPTED MANUSCRIPT

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Highlights

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Legends:

Fig. 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.

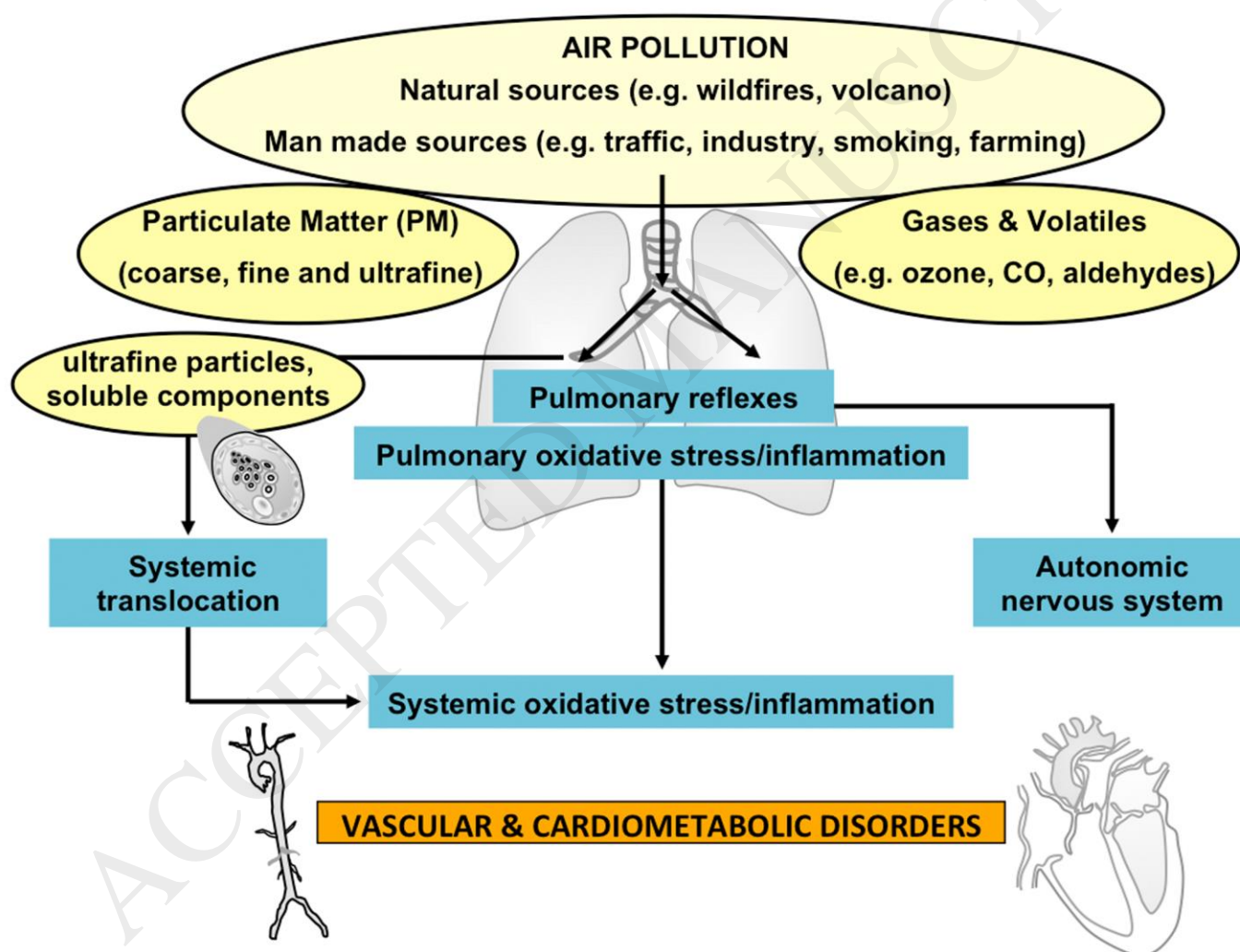


Fig. 2: Regulation of the circadian rhythm. The central clock (suprachiasmatic nucleus, SCN) entrained by light regulates the peripheral clocks. Misalignment between SCN and peripheral clocks (e.g. eating at the wrong time) results in a disorganized circadian rhythm, whereas disruption of the SCN leads to dyssynchrony as peripheral clocks keep oscillating without being reset by the SCN and become more and more misaligned.

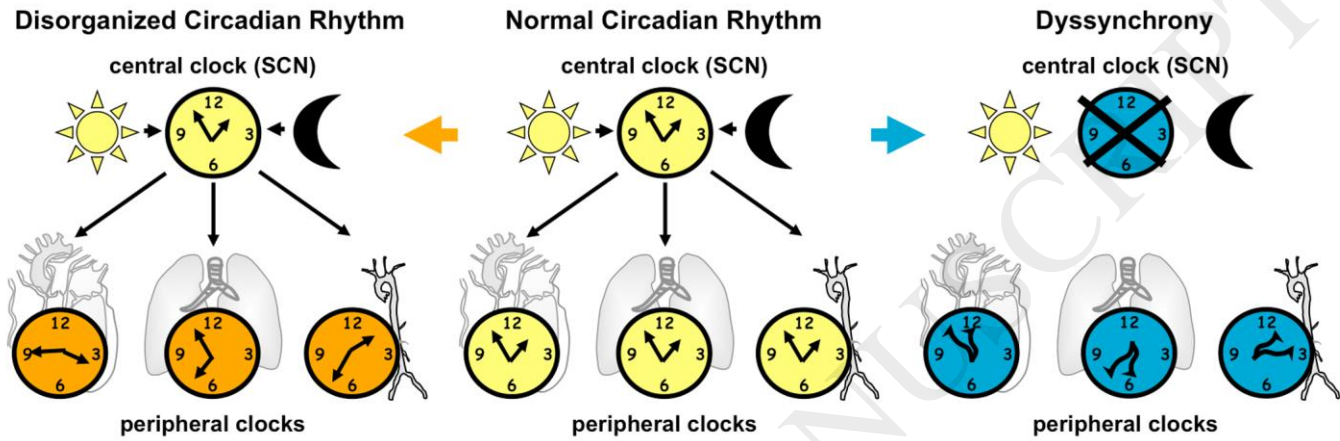


Fig. 3: Possible mechanism of air pollution-induced circadian toxicity. Inhalation of polluted air induces oxidative stress that could disturb the circadian clocks by changing clock protein activity (e.g., oxidation or changes in nitrosylation and acetylation). Clock proteins not only control the transcription 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.

