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REVIEW

Impact of noise and air pollution on the cardiovascular system through the brain–heart axis

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Abstract

Noncommunicable diseases such as cardiovascular disease (CVD) are becoming more prevalent in urbanized and industrialized societies. Classic risk factors such as hypertension are reinforced by behavioral factors such as smoking and diet, and environmental risk factors such as transportation noise and air pollution. Animal studies reveal that noise causes annoyance and sleep disturbance, promoting stress hormone release. Air pollution damages the lung, causing inflammation and oxidative stress that can spread to the circulation and remote organs. Both noise and air pollution converge at the vascular level, causing dysfunction in vascular signaling and atherosclerotic plaque formation. The complex interplay between environmental risk factors and CVD can lead to synergistic health impacts. The present review focusses on the impact of noise and air pollution on the brain–heart axis. Noise causes its primary health effects on the brain by activating the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis and thereby causes neuroinflammation, cerebral oxidative stress and via stress hormone signaling, and also induces cardiovascular damage. Air pollution activates the stress response as a homeostatic stressor. Uptake of (nano)particles into the brain can proceed by migration along the olfactory nerve. Particles in the brain can cause stress responses similar to neuroinflammation and cerebral oxidative stress due to noise. Understanding the negative effects of noise and air pollution on the cardiovascular system could help protect patients with preexisting CVD.

Keywords: air pollution; noise; brain–heart axis; stress response

Introduction

Air pollution

Air pollution is a term widely used to describe all components of the atmosphere that are toxic to humans, and that encompasses both gaseous components such as ozone, nitric oxides and sulfur oxides, and solid elements, named particulate matter (PM) (Agency 2024*a*). Modern air pollution research started after considerable smog and ozone problems in Los Angeles (California, USA) in the 1950s (Haagen-Smit 1950). A large body of research now describes epidemiological associations of air pollution exposure with various diseases and mechanistic pathways of how air pollution components exert pathophysiological effects. Recent estimates of total global mortality attributed to air pollution range from 6.7 million (WHO (Organisation 2024)), over 8.3 million (Lelieveld *et al.* 2023), and even up to 10.2 million (Vohra *et al.* 2021) yearly deaths, associating air pollution with almost 20% of annual global deaths. PM has recently

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gained more attention due to its recognition as the more detrimental part of air pollution, contributing significantly to the total disease burden and premature deaths (Munzel *et al.* 2018*a*). The most recent Global Burden of Disease (GBD) study showed that particulate matter pollution was the most prominent risk factor by attributable DALYs (disability-adjusted life years) in 2021 (Brauer *et al.* 2024). Interestingly, previous GBD studies have separated PM pollution into household and ambient, ranking them lower, but combined they still represented the number one risk factor for attributable DALYs, even in 1990 (GBD 2019 Diseases & Injuries Collaborators 2020, Brauer *et al.* 2024). PM is usually classified by its size into PM10 (<10 μm), PM2.5 (<2.5 μm) or ultrafine PM (UFPM, <0.1 μm), as its chemical complexity makes it hard to classify by any other parameter. Recent studies have demonstrated that PM size is connected to their detrimental effects, with smaller PM causing more damage due to its ability to penetrate deeper into the lung and translocate into circulation (Pinkerton *et al.* 2000, Kreyling *et al.* 2006, Kuntic *et al.* 2024*b*).

Noise

Due to high urbanization in the modern world, large cities that are often prominent sources of air pollution also have high noise levels. Noise is, therefore, primarily inseparable from air pollution and was not extensively studied as a risk factor for human health until recently (Munzel *et al.* 2021). The close co-localization of noise and air pollution often leads epidemiological studies to overestimate the effects of individual risk factors when not adequately normalized, especially since noise and air pollution were shown to be independent (Chang *et al.* 2015, Heritier *et al.* 2019). Today, transportation noise is prominent in the total noise burden, especially in highly urbanized areas (Munzel *et al.* 2020). Transportation noise was previously linked with many diseases, including cardiovascular, neurodegenerative and neuropsychiatric (Hahad *et al.* 2022). Noise is usually measured as sound pressure level expressed in decibels (dB). Most of the early studies on noise were based on occupational noise, with high sound pressure levels that can cause inner ear damage and loss of hearing (Lie *et al.* 2016). Most of the recent noise research focuses on lower sound pressure levels, which do not cause direct damage or hearing loss but interrupt everyday life due to annoyance, increase in stress and sleep disturbance (Munzel *et al.* 2014). Train and aircraft noise are disturbing due to their intermittent nature and high peak sound pressure levels (Munzel *et al.* 2018*b*). Current guidelines by the WHO state that noise should not exceed 54 dB L_{den} (during the day) and 45 dB L_{night} (during the night), although different sources of noise have even stricter recommendations; for example, aircraft noise should not exceed 45 dB L_{den} and 40 dB L_{night} (Organization 2022). The European Environment Agency suggests that at least 20% of urban population in Europe is exposed to noise exceeding healthy levels, and in many cities, this number can even reach 50% (Agency 2024*b*). Although guidelines are in place and are based on scientific evidence of the detrimental effects of noise, adherence is still lacking.

Brain–heart axis

Traditionally, the brain–heart axis mainly was understood as the autonomic regulation of the heart and the vasculature (Simats *et al.* 2024). Today, we know that the brain–heart axis has many distinct components, some of them neuronal and some hormonal, but different biological pathways can also carry information from the brain to the heart and vice versa. An overview of the brain–heart axis and its components is shown in Fig. 1. The brain–heart axis has two pathway orientations, one from the brain toward the heart (efferent) and one from the heart toward the brain (afferent). The efferent pathway begins with the medial prefrontal and insular cortex, which is responsible for high-level functions. The amygdala and the hippocampus are functionally connected to the prefrontal cortex and are responsible for regulating and processing emotional stress. The paraventricular nucleus (PVN) in the hypothalamus is mainly accountable for hormonal stress response as it controls the activation of the hypothalamic–pituitary–adrenal (HPA) axis. In the brainstem, the rostral ventrolateral medulla (RVLM) increases blood pressure by activating the sympathetic nervous system (SNS). The dorsal vagal nucleus decreases blood pressure by activating the parasympathetic nervous system. The afferent pathway starts with chemoreceptors and baroreceptors, which monitor the blood flow and composition. The signals travel through the brain stem to reach the thalamus, which further relays the signal to the insular cortex, which then processes the hemodynamic information (Pereira *et al.* 2013, Hu *et al.* 2023).

Stress response pathway

The stress response in humans has the function of maintaining homeostasis in the presence of either real or perceived danger. It includes the activation of the HPA axis, and the SNS and is associated with the circadian clock regulation (Russell & Lightman 2019). The stress response starts from the hypothalamus, in the hypothalamic PVN, where corticotropin-releasing hormone (CRH) is secreted. CRH reaches the pituitary gland, where it stimulates the release of adrenocorticotrophic hormone (ACTH), which, through systemic circulation, reaches the cortex of the adrenal glands. When stimulated by ACTH, adrenal glands release glucocorticoids, mainly cortisol, into systemic circulation (Kuntic *et al.* 2024*a*). Glucocorticoids are very important

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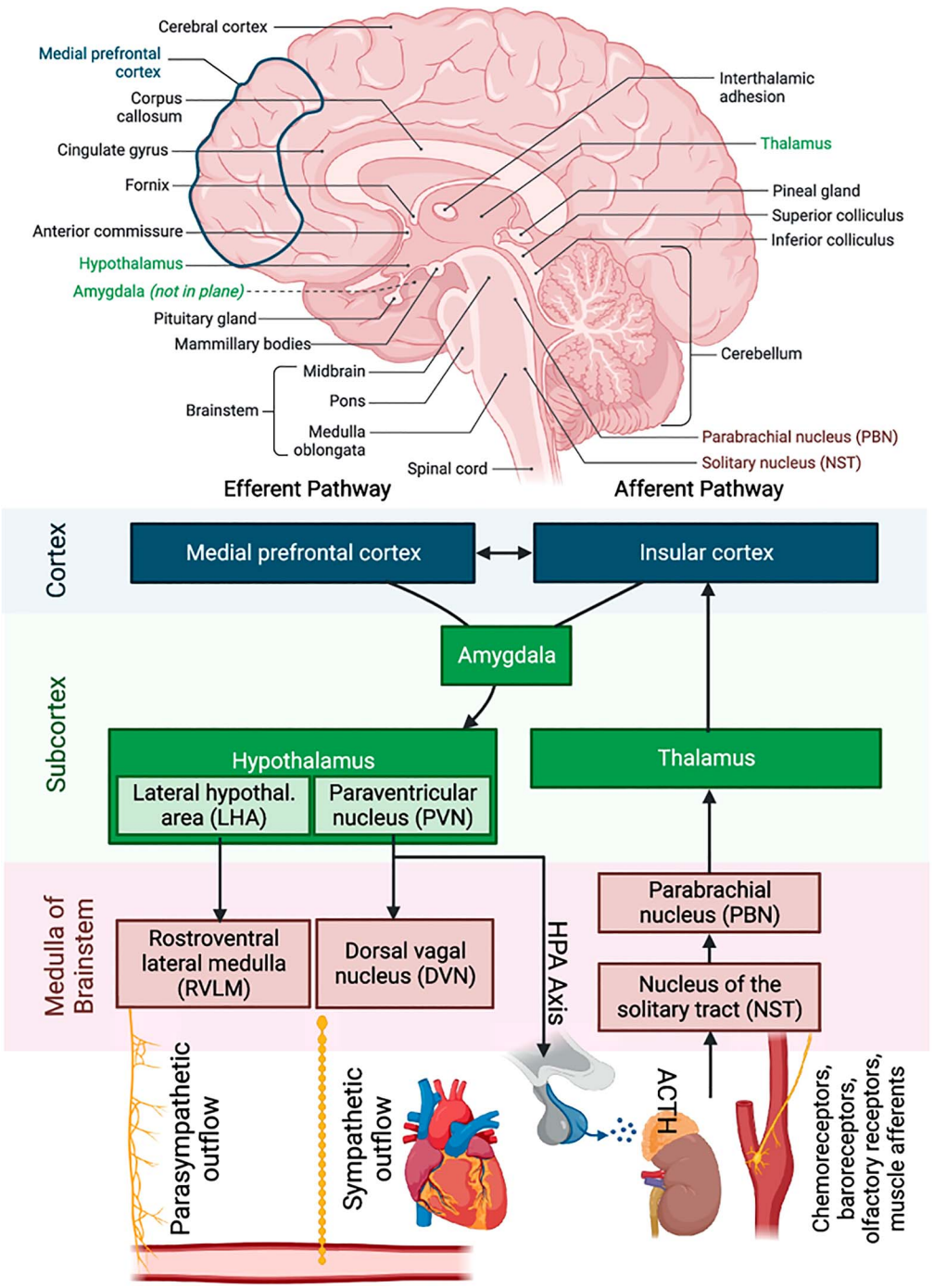

Figure 1

Brain–heart axis and the involved neural pathways. The top-to-bottom (efferent) pathways involve the medial prefrontal cortex and insular cortex, which through the amygdala and the hypothalamus result in the activation of the HPA axis and both the sympathetic and parasympathetic neurons. The bottom-to-top (afferent) pathways start with the input from the chemoreceptors and baroreceptors passing through the thalamus and finishing in the insular cortex. ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal. The figure was reused from Hu *et al.* (2023) with permission.

hormones as they regulate a large number of genes through glucocorticoid receptor binding and further activation of transcription by recognition of glucocorticoid-response elements on the promoter region of target genes (Charmandari *et al.* 2005). Glucocorticoid-activated genes regulate the loss of homeostasis through increased catabolism, lipogenesis, immunosuppression and reduction in reproductive drive

(Charmandari *et al.* 2005, Baschant & Tuckermann 2010). Although glucocorticoids have an anti-inflammatory effect, chronic exposure to high levels of glucocorticoids can lead to the downregulation of their receptors in immune cells, leading to 'cortisol resistance', which promotes inflammation (Vashist & Schneider 2014). Interestingly, there is a difference in how homeostatic and psychological stressors activate the HPA axis. Homeostatic, or reactive, stressors, such as systemic inflammation, hypoglycemia and hypoxia, feed directly to the PVN by monosynaptic relays from sensory organs (Herman *et al.* 2003).

On the other hand, psychological or anticipatory stressors, such as those coming from sensory organs (sight, smell, sound and touch) are subjected to initial activation of the upper limbic structures with the PVN through intermediary nuclei. This allows the organism to gauge the level of severity before activating the HPA axis by having both excitatory and inhibitory neuronal information (Herman *et al.* 2003, Radley & Sawchenko 2011). Both homeostatic and psychological stressors seem to produce the same temporal response, pointing to the importance of the stressor intensity, not the stressor modality (Furay *et al.* 2008).

SNS activation stimulates adrenal medulla and releases catecholamines (adrenaline, noradrenaline, and dopamine) (Pongratz & Straub 2014). Catecholamines, as part of the stress response, bind to the α- and β-adrenergic receptors on the endothelial cells of the vasculature or the cardiomyocytes, where they control the blood pressure and heart rate. Chronic overstimulation of the β receptor can lead to cardiac hypertrophy and fibrosis, mediated through angiotensin 2, endothelin 1 and interleukin 6 release by fibroblast and cardiomyocyte hypertrophy (Reed *et al.* 2014). Catecholamines can have both anti- or pro-inflammatory effects in the immune cells. β-adrenergic receptor has low affinity for catecholamines and produces an anti-inflammatory effect in the presence of large catecholamine concentrations, and α-adrenergic receptor has high affinity for catecholamines and produces a pro-inflammatory effect (mediated by tumor necrosis factor (TNF)) in the presence of low catecholamine concentrations (Pongratz & Straub 2014). Inflammation was previously shown to be associated with perceived stress in humans (Tawakol *et al.* 2017), reinforcing connection within the stress response pathway.

The stress response pathway is both susceptible to and a source of oxidative stress. Both the activated SNS and HPA also lead to the activation of the renin–angiotensin–aldosterone system (RAAS), which leads to the production of angiotensin-II, a potent vasoconstrictor (Correa *et al.* 2022). In addition to its vasoconstrictive properties, angiotensin-II can also activate the NADPH oxidase via protein kinase C inducing oxidative stress through superoxide production (Daiber *et al.* 2020). Oxidative stress is detrimental to the cardiovascular system as many important signaling pathways and functions in the cardiovascular system are redox sensitive. Nitric oxide ($^{\bullet}NO$) signaling, which is of great importance for the maintenance of vascular tone, is sensitive to oxidative stress as superoxide radical can directly scavenge $^{\bullet}NO$ to create peroxynitrite ($ONOO^{-}$). Other oxidative processes can also impair $^{\bullet}NO$ signaling, such as oxidation of the endothelial $^{\bullet}NO$ synthase (eNOS) cofactor tetrahydrobiopterin (BH_4) to the trihydrobiopterin ($^{\bullet}BH_3$) radical by $ONOO^{-}$ or eNOS S-glutathionylation, both of which lead to eNOS uncoupling (Frenis *et al.* 2021*c*). Increase in catecholamine production could lead to increased monoamine oxidase activity and production of H_2O_2 as norepinephrine has been shown to activate the PVN of obese rats exposed to $PM_{2.5}$ (Balasubramanian *et al.* 2013). Increased levels of circulating catecholamines can be oxidized to aminochromes, which are highly reactive quinone compounds that form protein adducts on the cysteine, lysine, and tyrosine residues, causing protein damage and functional alteration in the heart (Dhalla *et al.* 2010).

Evidence from human studies

Effects of air pollution on the stress response pathway

Air pollution acts as a homeostatic stressor as it mostly causes oxidative stress and systemic inflammation, which disturb the homeostasis and elicit a stress response. Translocation of PM from the lung into circulation could also be a signal for homeostatic disturbance, producing direct damage or gaseous constituents of air pollution can act through chemoreceptors sending information to the central nervous system to react via the autonomic nervous system (Perez *et al.* 2015). Although the available literature is lacking direct measurements of either catecholamines or glucocorticoids in association with air pollution exposure, several epidemiological studies have shown positive correlations. A study based on the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed that there is a positive association between urinary epinephrin levels and two air pollution components, NO_x and $PM_{2.5}$ (Hajat *et al.* 2019*a*). The same MESA cohort also produced an association between $^{\bullet}NO_2$ and saliva cortisol levels, pointing to the impact of combustion engine-derived air pollution on the stress response pathway (Hajat *et al.* 2019*b*). Similar results were obtained in a study on pregnant women, where the amount of cortisol in the hair was positively associated with the concentration of $^{\bullet}NO_2$ and black carbon (representing PM) (Verheyen *et al.* 2021*b*). The same group found positive association between hair cortisol levels and PM_{10} and $^{\bullet}NO_2$ exposure in a cohort of adolescent boys,

Redox Experimental Medicine (2025) **2025** e250004
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but not girls (Verheyen *et al.* 2021*a*). Importantly, the study also showed that the total leukocyte count was positively associated with all measured air pollution constituents, $PM_{2.5}$, PM_{10}, $^{\bullet}NO_2$ and black carbon, pointing to the activation of the stress response through systemic inflammation. Another study showed that the increase in saliva cortisol levels and levels of TNF-α promoter methylation are both positively associated with PM_{10} exposure (Dolcini *et al.* 2024). An interventional study showed that exposure to ultrafine PM and ozone decreases peripheral norepinephrine clearance rather than increasing the SNS activity (Heusser *et al.* 2019). Other interventional studies also show increased autonomic activity, but do not report stress hormone concentrations (Brook *et al.* 2014). Reduction in clearance of catecholamines and generally mixed results in the association between air pollution exposure and catecholamines levels possibly imply that air pollution is not a potent stress response activator in acute or low dose exposure conditions. A summary of the mechanistic pathways of air pollution-induced stress response is shown in Fig. 2.

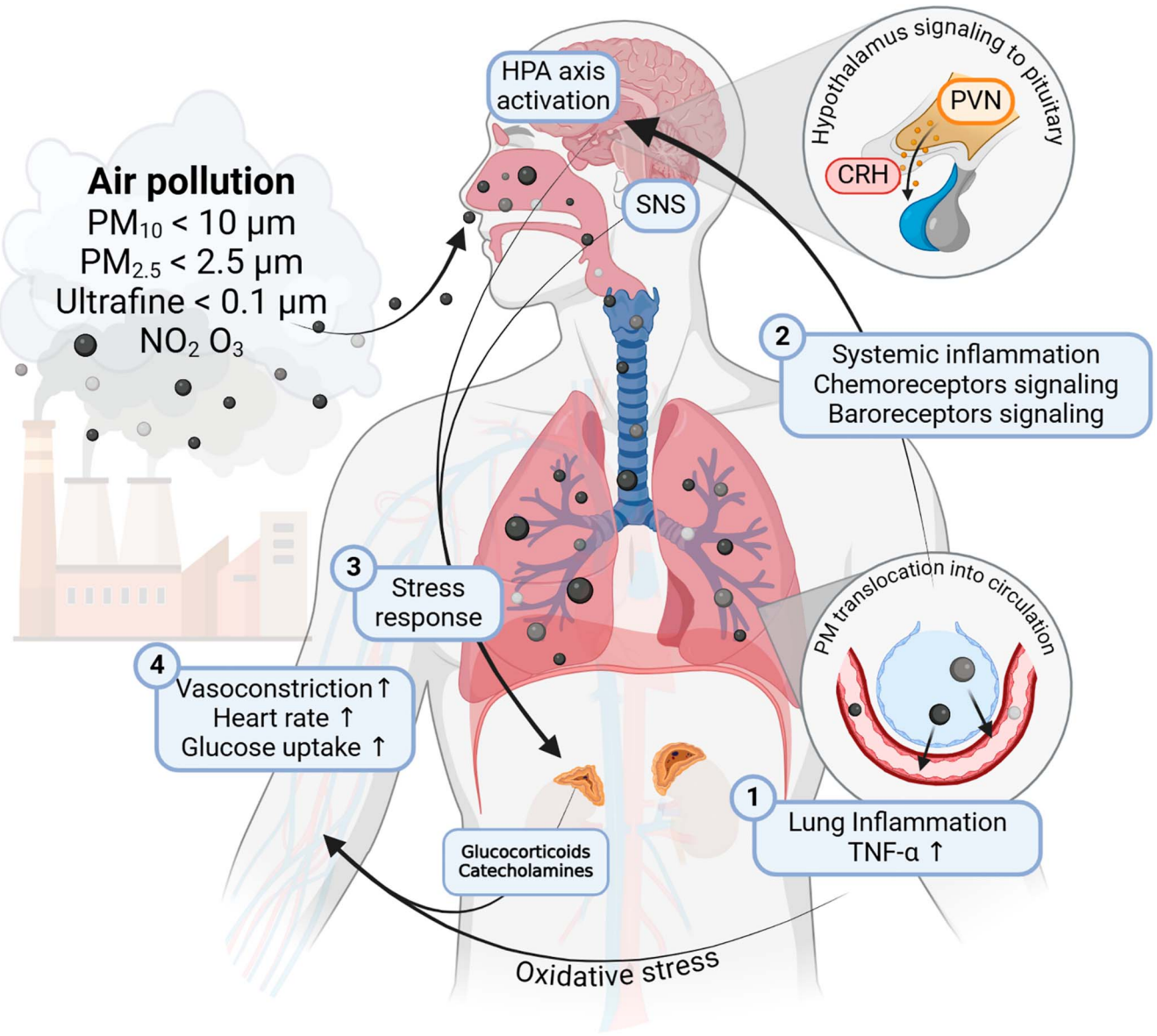

Figure 2

Air pollution induced activation of the stress response. Different components of air pollution enter through the lung, where they activate the resident macrophages, causing local and systemic inflammatory response. PM can also translocate into the circulation, causing direct vascular damage. This homeostatic response signals to the stress response via the activation of the HPA axis and the SNS, resulting in the release of glucocorticoids and catecholamines, which affect the vagal tone and heart rate. $PM_{10/2.5}$, particulate matter of diameter <10/2.5 µm; $^{\bullet}NO_2$, nitrogen dioxide; O_3, ozone; HPA, hypothalamic–pituitary–adrenal; SNS, sympathetic nervous system; PVN, paraventricular nucleus; CRH, corticotropin-releasing hormone; TNF-α, tumor necrosis factor alpha. Created with BioRender.com.

Redox Experimental Medicine (2025) **2025** e250004
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Effects of noise on the stress response pathway

As traffic noise is a major psychological stressor, many studies in humans have looked for the association between noise exposure and stress hormone release, although the results remain inconclusive. A study done on the HYENA (Hypertension and Exposure to Noise near Airports) cohort showed significant association between saliva cortisol and levels of aircraft noise exposure (Selander *et al.* 2009). Interestingly, the association was significant only in women but not in men. Another study measuring saliva cortisol suggested that women have higher cortisol levels than men, but no significant association could be found between road traffic noise levels and cortisol secretion (Wallas *et al.* 2018). Interestingly, the authors note that the levels of annoyance by noise, determined by a questionnaire, correlated with the cortisol levels, indicated that the perceived stress coming from noise is the main driver of the HPA axis activation and not the noise itself. In addition, cortisol is an important mediator of the circadian rhythm, and the lack of association between noise and cortisol levels might arise due to the shift in the cortisol release time, masking the HPA axis activation (Lefevre *et al.* 2017). Activation of the SNS was also observed in epidemiological studies as noradrenaline levels in urine were shown to be associated with noise exposure, but only in the instances where mitigation strategies, such as closing the window, were not available (Babisch *et al.* 2001). An important study correlated transportation noise to arterial inflammation and major adverse cardiovascular events by showing the connection to the heightened amygdala activity (Osborne *et al.* 2020). This landmark study showed both the mechanism of noise induced stress, by showing amygdala activation, and the consequences of noise induced stress, by showing a pathological mechanism, arterial inflammation, resulting in cardiovascular disease. Results from the study are shown in Fig. 3. Several interventional studies have also looked at the direct effects of traffic noise on stress hormone release. In an aircraft noise exposure study, 75 subjects were exposed during nighttime, resulting in the reduction of flow mediated dilation, a marker of endothelial dysfunction, and increase in morning levels of adrenaline (Schmidt *et al.* 2013). Similar observations were made by the same group in the train noise exposure study (Herzog *et al.* 2019), pointing to the activation of the SNS. Both of these studies on aircraft and train noise also showed that administration of vitamin C prevented the negative effects of noise, showing the involvement of oxidative stress.

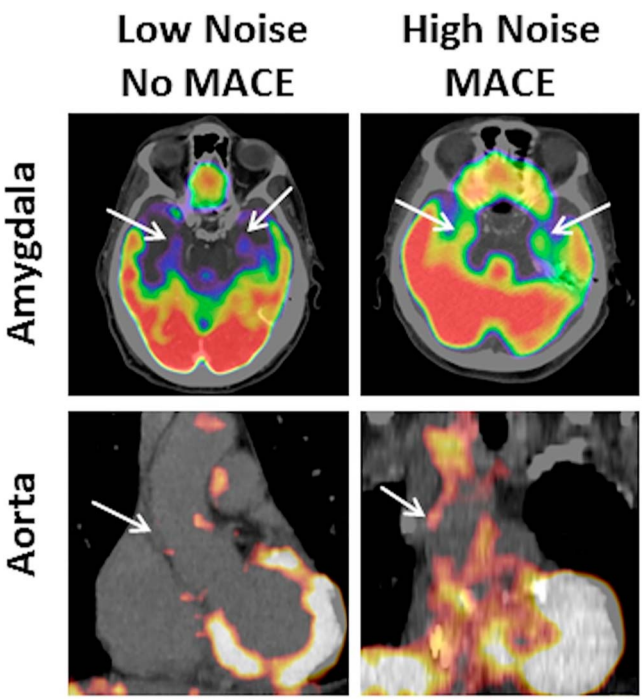

Figure 3

Relationship between noise and vascular inflammation. Positron emission tomography scan of the amygdalar and arterial ^{18}F-FDG uptake, pointing to the noise stress response directly stimulating vascular inflammation. MACE, major adverse cardiovascular events. The figure was reused from Osborne *et al.* (2020) with permission.

Evidence from animal studies

Effects of air pollution on the stress response pathway

Long-term inhalation of airborne pollutants, particularly $PM_{2.5}$, leads to particle accumulation in the deeper lung area, where resident alveolar macrophages phagocytose them (Lehnert 1992) and release cytokines such as IL-6, IL-1β and TNF-α into the systemic circulation, triggering the recruitment of circulating myeloid cells and exacerbating tissue damage (Caceres *et al.* 2024). These cytokines also activate HPA axis to maintain homeostasis under stress and injury (Chen *et al.* 2017). Multiple *in vivo* studies focusing on PM-induced neuroinflammation collectively report an increase in pro- and a decrease in anti-inflammatory markers in the brain (Campbell *et al.* 2005, Liu *et al.* 2020). Mice exposed to ultrafine PM also showed increased pro-inflammatory markers in the whole brain compared to clean air counterparts (Campbell *et al.* 2005). Another study on rats exposed to $PM_{2.5}$ evaluated the mRNA expression of pro- and anti-inflammatory markers in different brain regions between sexes, where females have shown more profound neuroinflammation (Liu *et al.* 2020).

An *in vivo* study on rats sub-chronically exposed to ozone and/or urban PM observed elevated mRNA levels of inflammatory and antioxidant markers in the lungs and in the *Cyp1a1* marker indicative of cardiotoxicity (Thomson *et al.* 2013). The plasma levels of ACTH and corticosterone were increased immediately after exposure and were fully recovered to the control levels after 24 h in both particulate matter and ozone exposed

groups. In another study, the rats were exposed to concentrated air particles (CAPs) containing $PM_{2.5}$ for 8 h with or without ovalbumin-induced asthma model both 2 weeks and 1 h before inhalation exposure (Sirivelu *et al.* 2006). The authors observed an increase of norepinephrine levels in the PVN, indicating the activation of the HPA axis, as PVN accounts for the highest release of CRH. However, dopamine was significantly elevated in the medial preoptic area in the sensitized and inhalation groups only. Corticosterone levels in serum were significantly elevated in all exposed groups even though the plasma was collected 24 h after the 8 h exposure to CAPs. Mice exposed to carbon nanotubes, a surrogate for ultrafine PM, showed a decrease in baroreflex sensitivity (Legramante *et al.* 2009), pointing to the ability of the PM to act as a homeostatic stressor modulating the afferent brain–heart axis pathway. Chemoreceptor modulation was also associated with PM exposure in a mouse model of heart failure, where the authors showed that the cardiac arrhythmias related to exposure to PM were in part due to altered sensitivity of the carotid body innervation (Wang *et al.* 2012). The direct effect on the circadian rhythm was observed in a study in mice, which reported disturbance of rhythmic oscillation in the HPA axis markers upon exposure to chronic ambient $PM_{2.5}$, ultimately disrupting the circadian rhythm (Hu *et al.* 2021). The uptake of particles into the brain is facilitated by migration of particles along the olfactory nerve, leading to neuronal activation (Cheng *et al.* 2016) and potentially adverse signaling via the brain–heart axis.

Studies in animal models showed that air pollution exposure could lead to oxidative stress in the brain and in the cardiovascular system (Park *et al.* 2020, Kuntic *et al.* 2023). Air pollution-derived PM was previously shown to cause oxidative stress through the activation of the NADPH oxidase (Xu *et al.* 2010). NADPH oxidase activation seems to be dependent on toll-like receptor 4 (TLR4) signaling, as *Tlr4* deficient mice showed reduced p47phox phosphorylation, an activation marker of the phagocytic NADPH oxidase (Kampfrath *et al.* 2011). In addition, oxidative stress response through the activation of nuclear factor (erythroid-derived2)-like 2 (*Nrf2*) signaling has been observed in different brain regions of UFPM exposed mice (Guerra *et al.* 2013). *Nrf2* activation, envisaged by increase in heme oxygenase 1 (*Ho1*) and NAD(P)H dehydrogenase [quinone] 1 (*Nqo1*) expression, was also observed in vascular tissue of PM exposed mice (Gao *et al.* 2021). Mitochondrial dysfunction and increased mitochondrial oxidative stress were also observed in urban $PM_{2.5}$ exposed mice (Zou *et al.* 2022).

Effects of noise on the stress response pathway

Recent data from animal studies corroborates the findings that noise causes stress and behavioral changes (Jafari *et al.* 2017, Hahad *et al.* 2022), increases risk factors associated with cardiovascular and cerebrovascular disease (Hahad *et al.* 2020, Chi *et al.* 2021), and exacerbates preexisting health conditions (Chen *et al.* 2016, Luo *et al.* 2024). In a short-term (4 days) noise exposure mouse model, activation of the SNS, RAAS, and HPA axis has been evidenced by elevated plasma catecholamines (particularly norepinephrine and dopamine), angiotensin-II, and renal and plasma cortisol levels (Munzel *et al.* 2017, Sun *et al.* 2021). A study in rats showed that 30 days (4 h per day) of exposure to 100 dB white noise led to the activation of the HPA axis and increased CRH and CRH-R1 in the amygdala (Eraslan *et al.* 2015), which in turn results in the atrophy of brain structures (particularly the hippocampus, prefrontal cortex and amygdala) and a decrease in neuronal density. These morphological changes ultimately lead to cognitive and motor dysfunction (Jafari *et al.* 2018). Interestingly, in the rat pup model, stimulation with moderate noise (~65 dB), a stimulus that does not produce behavioral changes or increases corticosterone concentrations, has been shown to inhibit the induction of long-term hippocampal potential. This, in turn, significantly reduces hippocampal-related learning and memory abilities (Zhang *et al.* 2021). Notably, during a 10-day 30-min per day exposure to loud noise (100 dB), male mice showed a more pronounced HPA axis activation, characterized by elevated and persistently higher ACTH and corticosterone levels than females (Babb *et al.* 2014, Lee *et al.* 2024), possibly due to the protective effects of estradiol (Heck & Handa 2019).

In both the short-term and long-term (28-day) models of aircraft noise exposure, murine subjects demonstrated an increase in both systolic and diastolic blood pressure, endothelial cell dysfunction, blood–brain-barrier hyperpermeability and neuroinflammation (Munzel *et al.* 2017, Frenis *et al.* 2021*b*, Lin *et al.* 2022). Mice were unable to establish noise tolerance, which led to persistent brain–heart axis dysregulation. In rodent models induced by a combination of electric shock and noise, prorenin and its receptor were upregulated in the RVLM. These factors activate the NLRP3 inflammasome in microglia, increasing sympathetic nerve activity (Hu *et al.* 2020, Zhang *et al.* 2020), providing a link between noise exposure and inflammatory response through the activation of the brain–heart axis. Similar studies have found that continuous noise and electric shock stimuli significantly upregulate the expression of $Na_V1.6$ in the RVLM, resulting in SNS activation and elevated blood pressure (Wu *et al.* 2018). In the study using cardiovascular drugs to intervene in aircraft noise-induced cardiovascular disease, the treatment of mice with the beta-blocker propranolol and the alpha-blocker phenoxybenzamine prevented endothelial and microvascular dysfunction, as confirmed by a reduction in levels of inflammation and oxidative stress indicators in heart and brain (summary of the mechanism shown in Fig. 4) (Kuntic *et al.* 2025).

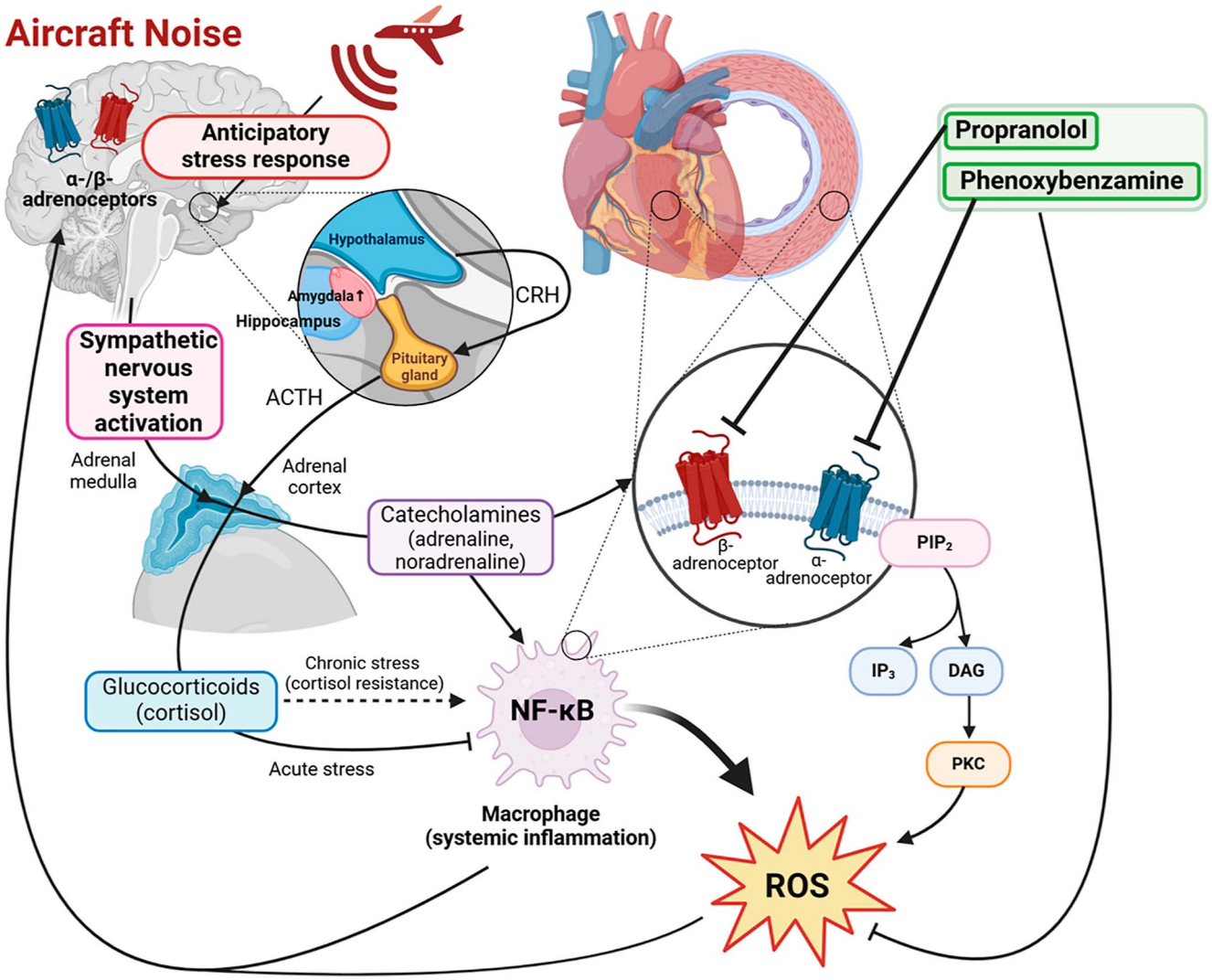

Figure 4

Effects of noise on the brain–heart axis focus on the α- and β-adrenergic signaling. Noise activates both the HPA axis and the sympathetic nervous system, resulting in release of catecholamines that activate the α- and β-adrenergic receptors. This leads to inflammation and oxidative stress in the cardiovascular tissue. α- and β-adrenergic receptors are G protein-coupled receptors that can produce diacylglycerol (DAG) through the activation of phospholipase C. DAG can further activate PKC, which activates NADPH oxidase subunits through phosphorylation, resulting in the formation of the superoxide producing complex. NF-κB can be activated by catecholamines or by prolonged exposure to cortisol in a state called cortisol resistance (acutely, cortisol blocks NF-κB) (Cohen *et al.* 2012). Activation of NF-κB leads to the transcription of pro-inflammatory cytokines and progression of inflammation. Nonspecific α- and β-receptor antagonists (propranolol and phenoxybenzamine) can alleviate the effects of noise on vascular oxidative stress. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, Inositol trisphosphate; PKC, protein kinase C; ROS, reactive oxygen species. Created with BioRender.com and modified from Kuntic *et al.* (2025) with permission.

Similarly, applying α2-adrenoceptor antagonists (beditin and mesedin) has been shown to alleviate the enhanced oxidation of plasma proteins and increased anxiety behavior in rats caused by long-term noise exposure (Manukyan *et al.* 2020).

Activation of the stress response can induce oxidative stress through mechanisms described above. Animal studies have demonstrated that cardiovascular and cerebral oxidative stress can be induced by noise exposure, especially through the activation of the NADPH oxidase (Munzel *et al.* 2017, Frenis *et al.* 2021*a*, Molitor *et al.* 2023). The NADPH oxidase is activated by phosphorylation of the cytosolic subunit p47phox by protein kinase C (PKC), which can be mediated by angiotensin-II, endothelin-1 or by the activation of α- and β-adrenergic receptors (Nguyen Dinh Cat *et al.* 2013, Kroller-Schon *et al.* 2018). Mitochondria were also

observed to be sources of oxidative stress in noise exposure models (Kroller-Schon *et al.* 2018), especially in cardiovascular disease models, where noise was shown to additively increase mitochondrial superoxide levels (Molitor *et al.* 2023). Other sources of oxidative stress, such as the uncoupled eNOS, were also observed to be present in noise exposed animals (Munzel *et al.* 2017, Steven *et al.* 2020, Eckrich *et al.* 2021, Frenis *et al.* 2021*a*).

Conclusion

Air and noise pollution are significant environmental stressors impacting human health. Air pollution, particularly $PM_{2.5}$, contributes to 8.3 million excess deaths annually through systemic inflammation and oxidative stress and by modulating the stress response peripherally. However, some direct contribution of small particles on the brain can be expected by the uptake via the olfactory nerve. Noise pollution, often co-existing with air pollution, acts as a psychological stressor with primarily central effects, activating the HPA axis and SNS, leading to cardiovascular and neuropsychiatric diseases. Both risk factors have a negative effect on the brain–heart axis, share similar pathological mechanisms, and cause additive health damage (Kuntic *et al.* 2023). Despite WHO guidelines, adherence to legal noise and $PM_{2.5}$ limits remains inadequate. Strengthening regulations, improving urban planning, and advancing mitigation strategies are essential to reducing their health burden and protecting public well-being. Urgent action is needed to address these environmental risks effectively.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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