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Review article

Oxidative stress and inflammation contribute to traffic noise-induced vascular and cerebral dysfunction via uncoupling of nitric oxide synthases

Andreas Daiber[a,b,*], Swenja Kröller-Schön[a], Matthias Oelze[a], Omar Hahad[a,b], Huige Li[c], Rainer Schulz[d], Sebastian Steven[a], Thomas Münzel[a,b,*]

[a] Center for Cardiology, Molecular Cardiology, University Medical Center, Mainz, Germany
[b] Partner Site Rhine-Main, German Center for Cardiovascular Research (DZHK), Langenbeckstr. 1, 55131, Mainz, Germany
[c] Department of Pharmacology, University Medical Center, Mainz, Germany
[d] Institute of Physiology, Justus-Liebig University, Giessen, Germany

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ABSTRACT

Environmental pollution and non-chemical stressors such as mental stress or traffic noise exposure are increasingly accepted as health risk factors with substantial contribution to chronic noncommunicable diseases (e.g. cardiovascular, metabolic and mental). Whereas the mechanisms of air pollution-mediated adverse health effects are well characterized, the mechanisms of traffic noise exposure are not completely understood, despite convincing clinical and epidemiological evidence for a significant contribution of environmental noise to overall mortality and disability. The initial mechanism of noise-induced cardiovascular, metabolic and mental disease is well defined by the „noise reaction model" and consists of neuronal activation involving the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathetic nervous system, followed by a classical stress response via cortisol and catecholamines. Stress pathways are initiated by noise-induced annoyance and sleep deprivation/fragmentation. This review highlights the down-stream pathophysiology of noise-induced mental stress, which is based on an induction of inflammation and oxidative stress. We highlight the sources of reactive oxygen species (ROS) involved and the known targets for noise-induced oxidative damage. Part of the review emphasizes noise-triggered uncoupling/dysregulation of endothelial and neuronal nitric oxide synthase (eNOS and nNOS) and its central role for vascular dysfunction.

1. Introduction

Environmental stressors such as air pollution, noise, mental stress or climate changes are increasingly recognized as important determinants of our health. According to health experts, environmental exposure to stressors (the „exposome") even outcompetes genetic health determinants and joins classical health risk factors such as obesity and diabetes in their health impact [1,2]. As concluded by the Lancet Commission on pollution and health „Pollution is the largest environmental cause of disease and premature death in the world today. Diseases caused by pollution were responsible for an estimated 9 million premature deaths in 2015 – 16% of all deaths worldwide - three times more deaths than from AIDS, tuberculosis, and malaria combined" [3]. These data are also supported by recent World Health Organization (WHO) reports [4,5]. The numbers are even more dramatic for the global burden of non-communicable chronic diseases since all forms of pollution cause an estimated 268 million disability adjusted life years annually (consisting of 254 million years of life lost and 14 million years lived with disability) [6]. With respect to disability adjusted life years in Europe, noise ranks second to air pollution in the list of environmental triggers, and outcompetes lead, ozone and dioxins [7]. In spite of this growing evidence, noise is not mentioned in any global health action plans, with only occupational noise being mentioned as a significant environmental health risk factor in the Global Burden of Disease (GBD) Study [8]. Traffic noise exposure is a clearly underestimated environmental risk factor, and contributes substantially to the development of cardiometabolic complications such as ischemic heart disease, hypertension, heart failure, and thereby also to global mortality and disability

Abbreviations: BH4, tetrahydrobiopterin; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; L-NAME, L-N^G-nitro-arginine methyl ester; NOS, nitric oxide synthase; NOX, NADPH oxidase; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SOD, superoxide dismutase

* Corresponding author. Universitätsmedizin der Johannes Gutenberg-Universität Zentrum für Kardiologie 1 – Labor für Molekulare Kardiologie, Geb. 605 – Raum 3.262, Langenbeckstr. 1, 55131, Mainz, Germany.
E-mail addresses: daiber@uni-mainz.de (A. Daiber), tmuenzel@uni-mainz.de (T. Münzel).

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adjusted life years [9–11]. This review provides mechanistic insights on noise-induced mental stress reactions, inflammation, oxidative stress and neuronal/vascular damage with an emphasis on the uncoupling of nitric oxide synthases (NOS).

2. Noise research and noise reaction model

The majority of noise research relates to the direct adverse effects on the auditory system, which is documented noise-induced hearing loss, and is not further discussed in this review. A mechanistic similarity between noise-induced hearing loss (typically observed upon noise exposure to sound pressure levels ≥ 100 dB(A)[1]) and the non-auditory effects of noise (typically studied with sound pressure levels ≤ 80 dB (A)) is that both harms are accompanied by increased production of reactive oxygen species (ROS) [12]. Thus, hearing loss was improved by antioxidant treatment in experimental models [13] and noise-induced non-auditory effects such as endothelial dysfunction were improved by vitamin C infusion in healthy subjects [14].

The non-auditory effects of noise rely mainly on a neuronal component and the individual perception of noise exposure, and their health consequences were reviewed in a monograph “Effects of Noise in Man” by Karl D. Kryter in 1970 [15]. This monograph discusses the effects of noise on work performance, sleep, pain sensitivity, vision and blood circulation. Kryter postulated that noise initiates secondary reactions by stimulation of the neuronal system including the autonomic/reticular nervous systems and (sub)cortical brain centers. A detailed overview on historic development of noise research can be found in Ref. [12].

The modern noise reaction model for non-auditory noise effects was established by Babisch, which comprises an “indirect pathway” based on the disturbance of sleep, communication and activity that is mainly triggered by low level noise exposure (even by sound pressure levels of 50–60 dB(A)) thereby causing changes of emotional and cognitive parameters and annoyance, followed by the adverse health effects described above [16,17]. The contribution of noise-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathetic nervous system response to these stress reactions leads to a chronic release of stress hormones such as cortisol and catecholamines as well as the subsequent induction of inflammation (with increases in interleukin [IL]-6, IL-1β and proinflammatory monocytes) [18,19] and oxidative stress [14,20,21] (Figs. 1 and 2). Noise also triggers anxiety disorders and depression [22] as well as annoyance and atrial fibrillation [23]. The severe adverse health impact of noise-induced mental stress is documented by cases of stress-induced cardiomyopathy (so called Takotsubo Syndrome or broken heart disease) [24], which has been described as a consequence of a nighttime aircraft noise exposure [25]. The increase of glucocorticoid levels by mental stress also leads to endothelial dysfunction characterized by reduced vascular endothelial nitric oxide synthase (eNOS) function and nitric oxide (˙NO) bioavailability [26] as well as increased sensitivity of the vasculature to vasoconstriction action of the sympathetic nervous system [27].

Some molecular links between mental stress induced by noise exposure (HPA axis, sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activation) and the induction of vascular and cerebral inflammation as well as oxidative stress are illustrated in Fig. 1 (also reviewed in Ref. [19,20]). Severe life stress, including sleep deprivation as induced by noise exposure during sleep, leads to cerebral oxidative stress, which is mediated by angiotensin-II signaling and NADPH oxidase isoform 2 (NOX-2) activation and microvascular as well as neuronal inflammation [28]. Increased circulating levels of angiotensin-II is an important stress biomarker in noise exposed animals [21,29]. Mental stress induced by sleep deprivation and frequently interrupted sleep impairs the cerebral redox balance and leads to abnormal (manic-like) behavior and memory impairment, which is improved by treatment with the antioxidant quercetin or TEMPOL [28,30,31]. Oxidative stress in turn activates the sympathetic nervous system in human [32] and animal studies [33,34]. In addition, administration of catecholamines induces oxidative stress in rats, probably by serving as substrates for monoamine oxidases (MAO) [35] or activation of astrocytes, microglia and NOX-2 [36]. Inhibition of NADPH oxidase (several NOX isoforms) activity in hypertensive mice (RAAS activation model) decreases blood pressure and circulating concentrations of angiotensin-II and noradrenaline [37], whereas AT1-receptor blockers and angiotensin-converting enzyme inhibitors decrease cardiovascular oxidative stress [38,39], clearly indicating an interaction of the RAAS and ROS levels.

3. Traffic noise exposure activates ROS sources and causes oxidative damage

3.1. Noise-triggered inflammation and activation of immune cells – role of phagocytic NADPH oxidase (NOX-2)

Low levels of road traffic noise cause immunological alterations (e.g. higher IL-12 levels and lower natural killer cell populations/activity) that are associated with increased circulating cortisol levels, noise sensitivity and the health status of affected individuals [40]. Traffic noise also increases high-sensitivity C-reactive protein (hsCRP) levels [41]. Train noise induces plasma proteome changes in healthy subjects leading to a pro-inflammatory, pro-oxidant and pro-atherothrombotic phenotype [42]. These data are in good harmony with the established correlation between acute psychological stress conditions, hormone levels, recruitment/activation of immune cells and impaired cardiovascular function in humans, where the highest cardiovascular event rates were associated with most pronounced immunological changes [43,44]. Noise exposure augments neuroinflammation and Alzheimer's disease pathology in rodent studies [45], which is in keeping with our recent observations in mice indicating that low level noise exposure (mean sound pressure level 73 dB(A)) increases circulating cytokines, aortic inducible nitric oxide synthase (*iNOS)*/monocyte chemoattractant protein-1 (*MCP*-1, CCL2) mRNA levels and vascular infiltration of immune cells [21,46]; this was accompanied by neuroinflammation characterized by astrocyte activation and higher cerebral *CD68*,[2] *IL-6* and *iNOS* levels [46] (Fig. 2).

In addition, the activation of immune cells by noise as measured by an oxidative burst (a parameter for leukocyte NOX activity) was more pronounced [46] and there was a greater abundance of NOX-2 in the vasculature of noise-exposed mice [21], leading to increased vascular and cerebral ROS formation as well as vascular (endothelial) dysfunction. The concept that ROS from inflammatory cells are responsible for noise-induced oxidative stress is further supported by a marked reduction of noise-induced systemic oxidative stress (e.g. aortic superoxide formation as measured by HPLC analysis of 2-hydroxyethidium)

[1] The sound pressure level is measured in the dimension Decibel (dB) on a logarithmic scale. It is interconvertible to the sound pressure that is measured in the dimension Pascal (Pa). A whisper has a sound pressure of 0.000063 Pa, which is equivalent to a sound pressure level of 10, whereas the traffic on a highway may reach a sound pressure of 0.2 Pa, which is equivalent to a sound pressure level of 80 dB. The sound pressure level is expressed by either dB or dB (A), where dB(A) means Decibel A-weighted and accounts for the different frequency sensitivity of the human ear (e.g. reduced sensitivity for low audio frequencies). The Decibel A-weighted value compensates for this variation in the human hearing sensitivity and most commercial acoustic measurement devices express the sound pressure level as dB(A).

[2] CD68 (Cluster of Differentiation 68, macrosialin) is a protein that is highly expressed by cells in the monocyte lineage (e.g. monocytic phagocytes, osteoclasts), by circulating macrophages, and by tissue macrophages (e.g. Kupffer cells, microglia). CD68 is involved in cell adhesion and recruitment and activation of macrophages for phagocytosis or removal of cell debris.

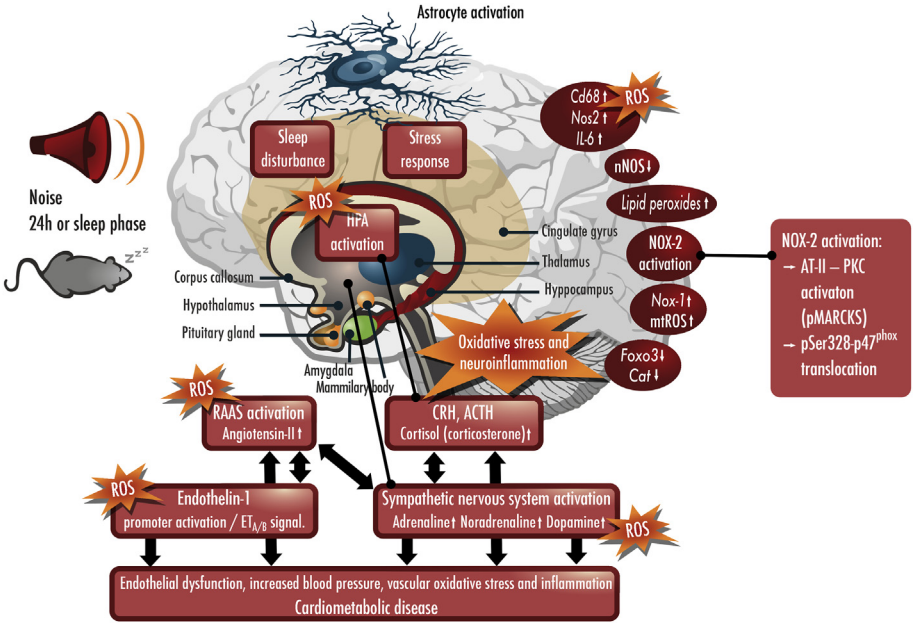

Fig. 1. Noise exposure induces neuronal activation. First line neuronal events in response to noise exposure are sleep disturbance (when exposed during the sleep phase) and stress response reactions via activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. This leads to release of stress hormones (glucocorticoids and catecholamines) and secondary activation of the cerebral (and systemic) renin-angiotensin-aldosterone system (RAAS) as well as endothelin-1 expression. These potent triggers of inflammation and oxidative stress will cause activation of NOX-2 via protein kinase C (PKC) and $p47^{phox}$ phosphorylation in the brain, expression of markers of inflammation, increased lipid peroxidation, down-regulation of neuronal nitric oxide synthase (nNOS) and loss of antioxidant genes such as catalase (*Cat*) and forkhead box O3 (*Foxo3*) transcription factor. All of these changes induce a neuroinflammatory phenotype with increased cerebral oxidative stress. These stress hormones and vasoconstrictors lead to similar adverse changes in the cardiovascular (and pulmonary) system, finally resulting in cardiometabolic disease. The HPA axis, sympathetic nervous system, RAAS, endothelin-1 expression and neuroinflammation are redox regulated and vice versa can induce oxidative stress via NOX-2 activation and other sources. AT-II, angiotensin-II; CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotrophic hormone; CVD, cardiovascular disease.

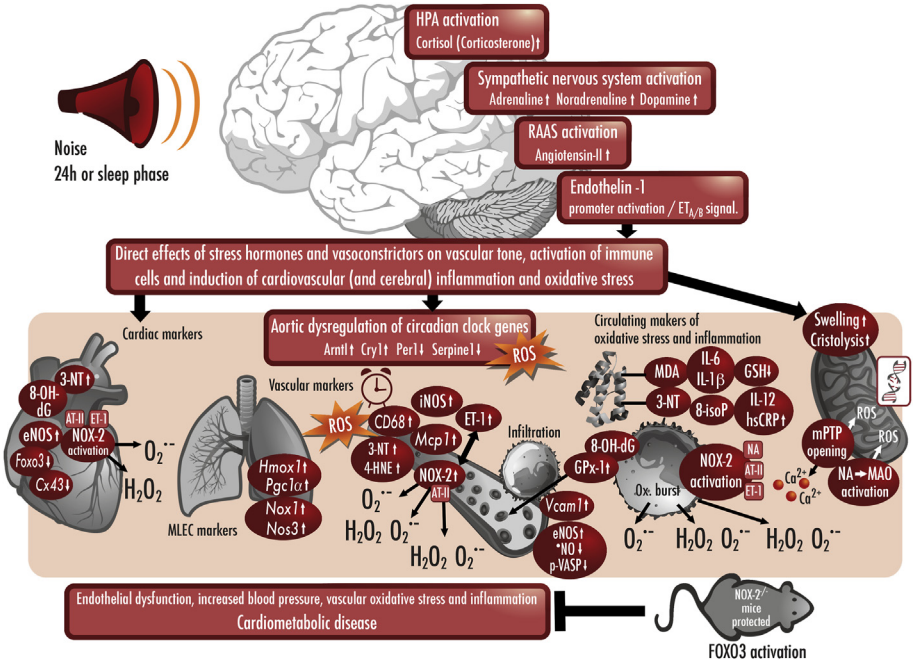

Fig. 2. Noise-induced neuronal activation induces cardiovascular ROS sources and oxidative damage as well as inflammation (summary of animal and human data). The stress hormones and vasoconstrictors have direct effects on the vasculature, the heart and immune cells via their receptors. Noise-induced sleep deprivation causes dysregulation of the circadian clock (e.g. changes in expression of period and cryptochrome genes), in part by adverse redox regulation of clock genes, which negatively affects inflammation and redox balance. In the heart, noise upregulated markers of oxidative stress (3-NT and 8-OH-dG), eNOS and NOX-2 activity, whereas noise down-regulated the antioxidant factor *Foxo3* and the structural component connexin43 (Cx43), all of which indicated cardiac remodeling and fibrosis. In endothelial cells isolated from mouse lungs (MLEC), antioxidant defense genes (*Hmox1* and *Pgc-1α*) as well as *Nox1* and *Nos3* (*eNOS*) were upregulated in the noise group suggesting counter-regulatory mechanisms. In the aorta, noise increased oxidative protein damage (3-NT and 4-HNE), markers of inflammation (e.g. iNOS, *Cd68*, *Mcp1* and *Vcam1*) and NOX-2 activity. While eNOS expression was upregulated in aortic tissue of noise-exposed animals, ˙NO bioavailability was decreased as well as phosphorylation of the vasodilator-stimulated phosphoprotein (P-VASP), which is a read-out of the ˙NO/cyclic guanosine-3',5'-monophosphate (cGMP)/protein kinase G (PKG) signaling cascade. Also aortic oxidative stress was directly measured and immune cell infiltration (mainly $CD11b^+$ cells, not shown in the scheme) was quantified - both were increased upon noise exposure. Circulating markers of oxidative stress (MDA, 3-NT, 8-isoP) and inflammation (IL-6, IL-1β, IL-12, hsCRP) were increased upon noise exposure, whereas levels of reduced glutathione (GSH) were decreased. Circulating white blood cells had more oxidative DNA damage (8-OH-dG), compensatory increase in glutathione peroxidase 1 (GPx-1) and displayed more pronounced oxidative burst in noise exposed animals or subjects. Mitochondria of noise exposed animals showed increased swelling of the membranes, cristolysis and mtDNA damage, impaired function of the mitochondrial permeability transition pore (mPTP) and calcium handling as well as monoamine oxidase (MAO) activation by high noradrenaline (NA) levels due to noise exposure. Direct impact of hormones besides vasoconstriction is mentioned in the text boxes. The adverse redox changes and inflammatory signaling by noise promote the development of cardiometabolic disease. Pharmacological activation of FOXO3 and genetic Nox2 deletion largely prevent noise-induced adverse health effects. AT-II, angiotensin-II; ET-1, endothelin-1; 3-NT, 3-nitrotyrosine; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; 8-isoP, 8-isoprostane; 8-OH-dG, 8-hydroxy-2′deoxyguanosine; hsCRP, high sensitivity C-reactive protein.

by genetic deletion of the *Nox2* gene ($Nox2^{-/-}$) or pharmacological inhibition (GSK2795039) of the NOX-2 protein [46]. In the brain of around-the-clock noise exposed mice, protein kinase C (PKC) activity (as measured by higher phospho-MARCKS levels) and PKC-dependent $p47^{phox}$ phosphorylation at serine 328 were increased, which is a marker for enhanced translocation of cytosolic $p47^{phox}$ to the membrane reflecting increased NOX-2 activity [46] (Fig. 1). The activation of PKC is most likely due to higher circulating (and cerebral) levels of

angiotensin-II in response to noise, leading to enhanced formation of diacylglycerol (upon activation of the angiotensin II type 1 (AT1)-receptor), a potent PKC activator [47]. In addition, PKC can be activated by oxidative modifications of the zinc-sulfur complex in the phorbol ester/diacylglycerol binding domain [47]. Importantly, inflammatory pathways and immune cell activation are triggered by oxidative stress (e.g. by redox changes in central players of inflammatory cascades such as NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) and high mobility group box 1 (HMGB1) protein) as extensively reviewed previously [48–50].

Aircraft noise increases the expression of endothelin-1 (ET-1) in the aorta of mice and enhances sensitivity to ET-1 mediated vasoconstriction [21,46] (Fig. 2). Of note, ET-1, in addition to being a potent vasoconstrictor, also increases NOX-2 activity [51,52]. Likewise, oxidative stress and NOX-2-derived ROS activate the ET-1 promoter to increase its expression [53,54], so initiating a self-promoting crosstalk between NOX-2 and endothelin-1 [55]. ET-1 also interacts with the RAAS, as demonstrated by increased vascular expression of ET-1 in angiotensin-II induced hypertensive rats [56] or by reduction of blood pressure and circulating angiotensin-II levels in bosentan ($ET_{A/B}$ receptor blocker)-treated animals with fructose-dependent hypertension [57]. Increased ET-1 signaling is also proposed to contribute to the unique susceptibility of Alport ($Col4a3^{-/-}$) mice to noise toxicity, a model of glomerular disease associated with hearing loss [58].

3.2. Noise triggers ROS production by mitochondria or vascular NOX isoforms

Mitochondria which represent a central pharmacological target for the therapy of (ischemic) heart disease [59,60], are also ROS-producing organelles generating interest in noise research. Rats exposed to low-frequency noise ($\geq$90 dB(A), < 500 Hz) have enlarged cardiac mitochondria and reduced connexin 43 content, indicating mitochondrial damage, and cardiac fibrosis [61] (Fig. 2). Importantly, mitochondria also contain connexin 43 [62] and changes in mitochondrial connexin 43 content affects ROS formation [63]. Moreover, loud noise (100 dB(A)) induces mitochondrial DNA damage, swelling of mitochondrial membranes, matrix dilution and cristolysis, which may be associated with higher noradrenalin levels, MAO activity and disturbed mitophagy [64], all of which may contribute to a dysregulation of mitochondrial permeability transition and calcium handling [65]. Other specific mitochondrial ROS producing systems, e.g. $p66^{Shc}$ [66,67] or the mitochondrial NOS system [68], have so far not been studied with respect to noise-induced oxidative stress. Our recent studies also reported activation of cerebral mitochondrial ROS formation on day 4 of around-the-clock noise that persisted upon deletion of *Nox2* [46], indicating additional mechanisms beyond the crosstalk between NOX-2- and mitochondria-derived ROS as reported in various disease conditions [55]. Sleep phase noise exposure also induced more pronounced mitochondrial ROS formation than awake phase noise (measured by mitoSOX fluorescence microtopography) [46]. Dysfunctional/damaged mitochondria provide one explanation for the substantial impact of traffic noise exposure on cardiovascular disease in general and ischemic heart disease in particular [10], as (oxidative) damage of mitochondria plays a central role in cardiovascular health and disease [69]. Additional ROS sources include NOX-1 and xanthine oxidase. In isolated lung endothelial cells and in the brain, aircraft noise increased *Nox1* mRNA [21,46]. The protective effects of allopurinol on noise (125 dB(A), 2–3 kHz)-induced hearing loss also suggests a partial contribution of xanthine oxidase to overall ROS generation in noise-exposed animals [70].

3.3. Noise-triggers oxidative damage of biological structures and redox-regulation of biological pathways

Rats exposed to high levels of white noise (80–100 dB(A), 8–16 kHz) have higher malondialdehyde levels, lower superoxide dismutase (SOD) activity and increased plasma nitrite/nitrate levels (probably from iNOS) that was associated with higher plasma concentrations of corticosterone, catecholamines and endothelin-1 [71]. Cardiomyocytes isolated from rat hearts upon exposure to white noise (> 100 dB(A)) have oxidative damage, including DNA damage, providing an explanation for cardiovascular dysfunction in response to noise [72]. White noise exposure of rats for up to 30 days (100 dB(A) for 4h/d) also induced cognitive impairment that was associated with upregulation of SOD and more lipid peroxidation in the brain as well as higher plasma corticosterone levels associated with lower glutathione concentrations [73] (Fig. 1). Exposure of mice for 4 weeks to white noise (90 dB(A) for 5h/d) increased circulating stress hormone levels and 8-hydroxy-2′deoxyguanosine (a marker of oxidative stress induced DNA damage) [74]. Other related studies and reports of noise-induced imbalance of redox state in developing animals have been reviewed, although it should be noted that most of these studies used extremely high sound pressure levels of more than 95 dB(A) [75]. Noise exposure of humans (46 dB(A) mean sound pressure levels) caused oxidative damage of biomolecules used as redox biomarkers (including 3-nitrotyrosine and 8-isoprostane), which were substantially increased in the plasma [46]. In addition, factory workers exposed to loud noise (at least 85 dB(A)) had markedly greater oxidative DNA damage in peripheral blood mononuclear cells, higher GPx-1 levels and higher blood pressures compared to office workers with exposure to lower noise levels (40–50 dB(A)) [76] (Fig. 2). As summarized previously, noise-induced oxidative stress is mainly mediated via redox-sensitive kinases (e.g. c-Jun N-terminal kinase) that can be prevented by antioxidant therapies (e.g. natural antioxidants, synthetic ROS scavengers, cardiovascular drugs or genetic Nrf2 activation) and can be mitigated by physical exercise [77]. Of note, noise can also induce epigenetic changes as shown by substantial redox-triggered alterations of microRNA networks in the setting of hearing loss [78].

Previous studies by our group demonstrated that aircraft noise exposure (mean sound pressure level 73 dB(A) for 4d) increased oxidative stress, as indicated by higher levels of oxidative damage markers such as 4-hydroxynonenal-positive proteins in aortic tissue [21] and malondialdehyde-positive proteins in plasma as well as 3-nitrotyrosine-positive proteins in plasma and heart tissue [21,46]. We also observed oxidative DNA damage (8-hydroxy-2′deoxyguanosine) in aorta of aircraft noise-exposed mice (Kvandova et al., in press in *Free Radical Research*). Oxidative stress in turn provoked upregulation of antioxidant defense systems including the stress-response protein heme oxygenase-1 or the protective peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) in isolated lung endothelial cells [21], which may have protective effects on eNOS coupling state (Table 1) and prevent noise-induced endothelial dysfunction. Using next generation sequencing we also demonstrated a down-regulation of genes encoding for antioxidant systems (e.g. intracellular superoxide dismutase [*Sod1*], forkhead-box-protein O3 [*Foxo3*]), whereas pro-apoptotic/cell death factors were upregulated (e.g. *caspases, Fas, p38*) [21]. Next generation sequencing also revealed dysregulation of the circadian clock system as central clock genes were significantly up- or down-regulated (e.g. *Per1, Bmal1 (Arntl), Cry1, Npas2* (paralog of *Clock*) and *Rora* [46], which may be related to impaired FOXO3 signaling and adverse redox regulation of cysteine residues in central circadian clock proteins (e.g. cryptochrome) by noise-induced oxidative stress as reviewed in detail [64]. A disturbance of the circadian rhythm in response to “nighttime noise” is associated with multiple adverse health effects, such as cardiometabolic disease [64], characterized by increased plasma glucose and leptin levels in noise-exposed mice [46]. The HPA axis activity and thus cortisol levels are largely controlled by the circadian clock [18]. Noise-dependent dysregulation of gene expression measured by next generation sequencing was confirmed for selected genes by RT-PCR [46]. Impaired FOXO3 signaling is likely a key mechanism in our noise animal model since the activation of FOXO3 by the calcium antagonist bepridil

Table 1
eNOS uncoupling by S-glutathionylation in disease models (literature before 2012 reviewed in Ref. [47,104,105]).

Adverse regulation and uncoupling of eNOS (leading to superoxide formation) by S-glutathionylation at cysteine residues Cys689 and Cys908 in the reductase domain.	[86,106]
eNOS uncoupling by S-glutathionylation was detected in mice with lung injury after lipopolysaccharide challenges.	[107]
eNOS uncoupling by S-glutathionylation and endothelial dysfunction in hypertensive mice was prevented by pharmacological (SfA and CsA) or genetic ($CypD^{-/-}$) inhibition of mitochondrial permeability transition pore opening.	[108]
eNOS uncoupling by S-glutathionylation was found in mice with atherosclerosis induced by carbamylated low-density lipoprotein treatment.	[109]
eNOS uncoupling by S-glutathionylation was aggravated in mice with cardiac pressure-overload, whereas N-acetylcysteine treatment improved the phenotype.	[110]
eNOS uncoupling by S-glutathionylation and endothelial dysfunction in mice was aggravated by aging and genetic glutathione peroxidase 1 deficiency ($Gpx1^{-/-}$).	[111]
Pressure overload induced by transverse aortic constriction was associated with eNOS uncoupling by S-glutathionylation in mice, which was prevented by physical exercise.	[112]
Pharmacological induction of eNOS uncoupling by S-glutathionylation and endothelial dysfunction by isosorbide-5-mononitrate treatment of mice.	[113]
eNOS uncoupling by S-glutathionylation was associated with erectile dysfunction in rats with type 2 diabetes mellitus.	[114]
eNOS uncoupling by S-glutathionylation was aggravated by doxorubicin treatment leading to cardiomyopathy in mice and was normalized by antioxidant therapy with folic acid.	[115]
Exposure of mice to aircraft noise caused eNOS uncoupling by S-glutathionylation, endothelial dysfunction and hypertension.	[21,46]
A knock-in mouse with C101A-eNOS mutant (impaired dimer formation due to disrupted $Zn(Cys)_4$ complex) displayed eNOS S-glutathionylation and higher superoxide formation rate and tyrosine nitration levels.	[116]
Human aortic endothelial cells showed pronounced eNOS S-glutathionylation upon challenges with ultrafine particles (air pollution).	[117]
Cultured endothelial cells had increased eNOS S-glutathionylation and decreased BH4 levels in response to ischemia/reperfusion.	[118]
eNOS S-glutathionylation can be reversed by glutaredoxin-1 making this eNOS dysregulatory mechanism a reversible redox regulatory pathway.	[119]
eNOS S-glutathionylation and a role for glutaredoxin-1 were demonstrated in mice with necrotizing enterocolitis.	[120,121]
Experimental fibrosis is linked to altered glutathione synthesis and enhanced eNOS S-glutathionylation.	[122]
eNOS S-glutathionylation and BH4 deficiency are obviously interconnected and predict eNOS uncoupling.	[123]
eNOS S-glutathionylation is correlated with nNOS activity.	[124]
Placental eNOS S-glutathionylation is a hallmark of preeclampsia.	[125]
Kruppel-like factor 2 (KLF2) protects endothelial function by activation of the Nrf2/HO-1 pathway and normalizing eNOS S-glutathionylation and BH4/BH2 ratio in cultured endothelial cells upon ischemia/reperfusion.	[126]
Treatment of hypertensive mice with the glucagon-like peptide analog liraglutide normalized oxidative stress, endothelial function and eNOS S-glutathionylation.	[127]

significantly improved several key parameters such as endothelial dysfunction and vascular/cerebral oxidative stress [46]. White noise exposure at similar sound pressure levels as compared to aircraft noise (73 dB(A)) did not cause any of the above described adverse vascular/cerebral effects produced by noise, clearly identifying that it is not only the loudness of the noise but rather also the sound pattern/characteristics such as irregular breaks, the frequency of the noise, and the crescendo or descrescendo nature determine the detrimental effects of noise [21,46]. Of importance is our recent demonstration of increased oxidative stress in the vasculature and the plasma within 24h at low noise exposure levels that is very different from older reports, where oxidative damage was established by exposure to very loud white noise (90 dB(A) for 5h/d for 4 weeks) [74], which is far greater than the sound levels used for aircraft noise in our recent studies [21,46].

4. NOS uncoupling by traffic noise exposure and cardiovascular/cerebral consequences

4.1. Noise-mediated impairment of vascular (endothelial) function

Early evidence for the systemic effects of noise exposure on the circulation was based on blood pressure increases in noise-exposed monkeys [79] and rats [80]. Of note, these increases in blood pressure were not associated with hearing loss. Exposure of rats to loud white noise for up to 4 weeks (100 dB(A) for 4h/d) caused endothelial dysfunction (measured with acetylcholine-dependent relaxation) and increased sensitivity to vasoconstriction by serotonin [81,82]. These observations in animals were extended to human studies which revealed that even exposure to low-level traffic noise (mean sound pressure levels of 46 (aircraft) or 54 (train) dB(A)) for one night induced endothelial dysfunction (measured by flow-mediated dilation, FMD) in healthy subjects or patients with established coronary artery disease. Impaired FMD was associated with impaired sleep quality and/or increased stress hormones [14,83], markers of inflammation/thrombosis [42] and oxidative stress (3-nitrotyrosine, 8-isoprostane and interleukins in plasma samples of exposed subjects) [46]. According to our observations, exposure of mice to aircraft noise induced endothelial dysfunction, increased blood pressure [21,46], increased circulating levels of neurohormones and induced a supersensitivity to vasoconstrictors such as endothelin-1 and noradrenalin [46].

4.2. Noise-mediated uncoupling/dysregulation of eNOS

As a potential explanation of noise-induced endothelial dysfunction, we observed diminished vascular $^{\bullet}NO$ bioavailability in the aorta of noise-exposed mice (measured by electron paramagnetic resonance [EPR] spectroscopy) [21]. This is likely a consequence of a more pronounced oxidative break-down of $^{\bullet}NO$ by a rapid reaction with superoxide to form a highly reactive intermediate peroxynitrite [84], which in turn may be responsible for a dysfunctional eNOS [55,85] (Fig. 3). Higher rates of formation of ROS (including superoxide) by aircraft noise exposure were discussed above, but eNOS S-glutathionylation represents another mechanism for uncoupling of the eNOS protein [21,46]. S-glutathionylation of eNOS suggests an altered electron flow in the reductase domain and the transfer of these electrons to molecular oxygen and thus superoxide formation [86], a pathomechanism established for numerous diseases (see Table 1 and reviewed in Ref. [87]). Other mechanisms of eNOS dysregulation that were previously not reported for noise exposure but that are conceivable include: PKC or protein tyrosine kinase 2 (PYK-2) dependent adverse phosphorylation at Thr495 and Tyr657, respectively, or accumulation of asymmetric dimethylarginine, oxidative disruption of the zinc-sulfur-complex at the dimer binding interface and oxidative tetrahydrobiopterin (BH4) depletion (all explained in detail in Refs. [47,87] and summarized in Table 2). Another method to detect eNOS-dependent endothelial ROS formation in aortic tissue of noise-exposed mice is the quantification of endothelial dihydroethidium by cryo-staining [21,46]. Inhibition of this signal by the eNOS inhibitor L-N^G-nitro-arginine methyl ester (L-NAME) indicates substantial uncoupling of eNOS protein [88]. In contrast, identical sound pressure levels of white noise increased rather than decreased endothelial dihydroethidium fluorescence signal in the presence of L-NAME, pointing to a functional (coupled) eNOS protein [21]. Importantly, aircraft noise increased *eNOS* mRNA in isolated lung endothelial cells and eNOS protein in aorta suggesting a compensatory upregulation in response to the oxidative uncoupling/dysregulation of eNOS protein [21].

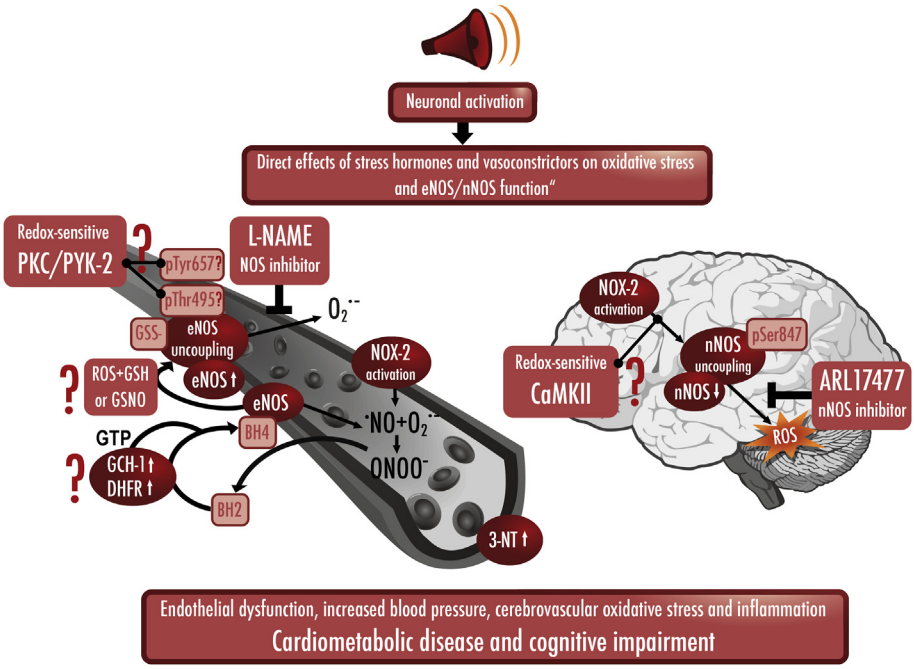

Fig. 3. Noise exposure causes eNOS and nNOS uncoupling. Superoxide formation induced by noise (e.g. NOX-2 activation) causes oxidative break-down of $^{\cdot}$NO leading to peroxynitrite formation and providing an explanation for increased protein tyrosine nitration (also iNOS-derived $^{\cdot}$NO contributes) as well as impairment of $^{\cdot}$NO/cGMP signaling. Despite upregulation of eNOS and the tetrahydrobiopterin (BH4)-generating enzymes GTP-cyclohydrolase 1 (GCH-1) and dihydrofolate reductase (DHFR), diminished $^{\cdot}$NO bioavailability was observed in aorta of noise-exposed mice. BH4 is an essential cofactor of eNOS (but also of iNOS) and oxidative depletion by ROS (e.g. peroxynitrite) to dihydrobiopterin (BH2) causes uncoupling of all NOS isoforms. BH4 levels were not measured upon noise exposure but upregulation of GCH-1 and DHFR obviously cannot compensate for the loss of function of eNOS in this setting. Therefore, eNOS was found to be dysfunctional or uncoupled, which was supported by S-glutathionylation (GSS-modification) by either ROS/GSH or S-nitrosoglutathione (GSNO) reaction. eNOS S-glutathionylation is an accepted marker of eNOS uncoupling (see Table 1) and uncoupled eNOS after noise exposure was detected at the molecular level by endothelial ROS formation that was sensitive to inhibition by the NOS inhibitor L-NAME. Although not measured in tissues of noise-exposed animals so far, the inactivating phosphorylation of eNOS at threonine 495 or tyrosine 657 (see Table 2), mediated by redox-activated protein kinase C (PKC) and protein tyrosine kinase 2 (PYK-2) respectively, would be conceivable under noise-induced oxidative stress conditions. In the brain, oxidative stress induction (e.g. NOX-2 activation) by noise caused nNOS uncoupling as envisaged by cerebral ROS formation that was sensitive to inhibition by the selective nNOS inhibitor ARL-17477 as well as phosphorylation at serine 847 (previously reported for uncoupled nNOS). Phospho-Ser847 in nNOS is introduced by calcium/calmodulin-dependent protein kinase (CaMKII) that is activated by ROS. The adverse redox regulation of eNOS and nNOS by noise induced oxidative stress promote the development of cardiometabolic disease and cognitive impairment that were previously reported for noise exposure for clinical/epidemiological studies.

The enzymes responsible for the synthesis and recycling of BH4 are GTP-cyclohydrolase-1 and dihydrofolate reductase [89]. In the setting of increased oxidative stress, oxidative conversion of BH4 to the $^{\cdot}$BH3 radical and finally to dihydrobiopterin (BH2) leads to depletion of this essential eNOS cofactor and causes eNOS dysfunction [89–91]. The observation that aircraft noise increases the expression of GTP-cyclohydrolase-1 and dihydrofolate reductase points to a compensatory (however futile) upregulation of these enzymes to overcome eNOS uncoupling and endothelial dysfunction [21] (Fig. 3). Although redox-dependent proteasomal degradation of GTP-cyclohydrolase-1 and dihydrofolate reductase have been reported [92], the upregulation of GTP-cyclohydrolase-1 and dihydrofolate reductase under inflammatory conditions can also known the cofactor BH4 for iNOS activity [93]. The consequences of eNOS uncoupling in response to noise are decreased $^{\cdot}$NO bioavailability (due to eNOS dysfunction/uncoupling as well as direct oxidative break-down of $^{\cdot}$NO by enhanced superoxide formation) and increased vasoconstrictor sensitivity of the vasculature to noradrenaline, endothelin-1 and angiotensin-II, all of which contributes to endothelial dysfunction. Of note, exposure to "white noise" with identical mean sound pressure levels did not induce these adverse vascular effects, indicating that it may not only be the loudness (quantity) of a specific noise but rather also its characteristics (quality such as frequencies, pattern) that determine its harmful effects [21].

4.3. Noise-mediated uncoupling/dysregulation of nNOS

Aircraft noise caused nNOS downregulation and uncoupling in the brain of mice as evidenced by increased phosphorylation at serine 847 of the enzyme [46] (Fig. 3); this phosphorylation site was previously shown to cause uncoupling of nNOS [94]. In addition, ROS formation in brain tissue sections from noise-exposed mice was prevented by the highly specific nNOS inhibitor ARL-17477, implicating nNOS-derived cerebral ROS formation (nNOS uncoupling) [46]. Thus, downregulation and uncoupling of the nNOS protein leads to a cerebral deficit of the neurotransmitter $^{\cdot}$NO, resulting in enhanced neuroinflammation, downregulation of *Foxo3* and increased cerebral oxidative stress [46].

Table 2
eNOS uncoupling/dysregulation by other mechanisms (reviewed in detail in Ref. [47,87]).

Oxidative depletion of tetrahydrobiopterin (BH4) is the most prominent and well accepted mechanism of eNOS uncoupling and was reported for hypertension, diabetes and atherosclerosis.	[90,128–132]
GTP-cyclohydrolase-1 (GCH-1), the major enzymatic source for BH4, is an important regulator of eNOS activity and endothelial function. eNOS/GCH-1 ratio determines proper NO synthesis.	[131,133]
Dihydrofolate reductase (DHFR) represents the "salvage pathway" and is responsible for recycling of oxidized BH2 back to BH4.	[134,135]
Oxidative disruption of the zinc-sulfur-complex ($ZnCys_4$) in the binding region of the eNOS dimer is another mechanism of eNOS uncoupling and described in diabetic animals and men. This oxidative damage of eNOS is most-likely mediated by HOCl and peroxynitrite.	[136–138]
Phosphorylation at Thr495 and Tyr657 by PKC and protein tyrosine kinase 2 (PYK-2), respectively, cause at least dysfunction of eNOS and were observed in models of hypertension, aging and nitrate tolerance.	[111,139–141]
The formation and degradation of the potent endogenous eNOS inhibitor (and maybe uncoupling agent), asymmetric dimethylarginine (ADMA), is regulated by protein arginine methyltransferases and by dimethylarginine dimethylaminohydrolases (DDAH) that are both redox-regulated	[105,142,143]
L-arginine deficiency may contribute to uncoupling of eNOS as shown by a case report on a patient with impaired ADMA due to genetic inefficiency of y^+LAT-1 (amino acid transporter)-dependent ADMA export from endothelial cells. This patient had severe angina pectoris and substantial eNOS uncoupling that was improved by high dose L-arginine therapy driving the ADMA export via the cationic amino acid transporter.	[144,145]

Cerebral nNOS down-/dysregulation and concomitant NOX-2 upregulation can also account for the impaired cognitive development (including memory and learning) of noise exposed children [95], which is also supported by the established role of NOX-2 dependent ROS formation for learning and memory impairment in female adult rats [96]. Redox-regulation of adverse (uncoupling) nNOS phosphorylation at serine 847 by the redox sensitivity of calcium/calmodulin-dependent protein kinase [94] provides another important mechanism for NOX-2 dependent cognitive impairment.

5. Conclusions and outlook

Exposure to aircraft noise in humans and experimental animals activates the sympathetic and HPA systems, leading to increases in stress hormones such as catecholamines, angiotensin-II, endothelin-1 and cortisol. These changes contribute to the direct activation of phagocytic NADPH oxidase, causing oxidative stress and thus oxidative depletion of $^{\bullet}NO$, and eNOS uncoupling e.g. by S-glutathionylation [21,46]. Likewise, noise-induced cerebral oxidative stress causes nNOS downregulation and uncoupling the consequences of which include immune cell activation/infiltration (potentiating the oxidative damage in cardiovascular/cerebral tissues) and enhanced vasoconstriction. Moreover, decreased nNOS activity contributes to changes of gene expression towards pro-inflammatory and pro-oxidative conditions (including impaired circadian clock or dysregulated FOXO signaling) [46]. These vascular and cerebral (oxidative) alterations caused by aircraft noise-exposure of mice are mostly due to eNOS and nNOS dysregulation acting as central players that contribute to the development of cardiometabolic disorders such as arterial hypertension and diabetes mellitus [21,46] and which are also confirmed by human studies [9,97]. The key role of oxidative stress for the harms to health caused by noise is further supported by the demonstration of impaired antioxidant defenses and the prevention of noise inflicted damage by treatment with exogenous antioxidants or the activation of endogenous antioxidant pathways [75]. Taken together, the major pathomechanisms of noise exposure are the induction of endothelial dysfunction, oxidative stress and inflammation (e.g. by activation of the NADPH oxidase and by eNOS uncoupling).

These mechanisms are strikingly similar to those reported for classical cardiovascular risk factors such as diabetes [98], hypertension [99] and hypercholesterolemia [100]. It remains to be established whether treatment with AT1 receptor blockers, ACE-inhibitors, antidiabetic agents and also statins could prevent noise-induced adverse cardiovascular health effects, as these cardiovascular drugs possess potent antioxidant and anti-inflammatory pleiotropic properties [101,102], and thereby could interfere with the major pathomechanisms of noise-induced health harms. Confirmation of established cardiovascular drugs as efficient preventive measures against noise-inflicted damage would be important, since patients in need of those drugs (e.g. those with preestablished cardiovascular diseases) may represent a population of high noise-dependent vulnerability [83]. Other populations of high noise-dependent vulnerability may be children at developmental stage, who showed cognitive impairment in response to noise [95], as well as elderly, who showed an increased risk of metabolic syndrome in response to noise [103].

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Declaration of competing interest

The authors declare that they have no conflicts of interest with the contents of this article.

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