Toxicology in Vitro 32 (2016) 205–211

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Involvement of Heme Oxygenase-1 in particulate matter-induced impairment of NO-dependent relaxation in rat intralobar pulmonary arteries

Marjorie Barrier [a,b,1], Marc-Antoine Bégorre [a,b,1], Isabelle Baudrimont [a,b], Mathilde Dubois [a,b], Véronique Freund-Michel [a,b], Roger Marthan [a,b,c], Jean-Pierre Savineau [a,b], Bernard Muller [a,b], Arnaud Courtois [a,b,c,*]

[a] Université de Bordeaux, Bordeaux F-33076, France
[b] Inserm U1045, Centre de Recherche Cardio-Thoracique de Bordeaux, Bordeaux F-33076, France
[c] CHU de Bordeaux, Bordeaux, F-33076, France

ARTICLE INFO

Article history:
Received 11 September 2015
Received in revised form 6 December 2015
Accepted 7 January 2016
Available online 9 January 2016

Keywords:
Particulate matter
Nitric oxide
Pulmonary artery
Heme Oxygenase-1

ABSTRACT

Particulate air pollution exerts deleterious effects on cardiovascular system. We previously described that exposure to urban particulate matter (SRM1648) impairs nitric oxide (NO, a major vasculoprotective factor) responsiveness in intrapulmonary arteries. As Heme Oxygenase-1 (HO-1) is induced by urban particles in some cell types and is known to alter NO-dependent signaling pathway, the objective was to characterize HO-1 involvement in SRM1648-induced impairment of NO-dependent relaxation in intrapulmonary arteries.

Rat intrapulmonary artery rings were exposed or not to Co (III) Protoporphyrin IX Chloride (HO-1 inducer) or SRM1648 in the absence or presence of Cr (III) Mesoporphyrin IX Chloride (HO-1 activity inhibitor). NO-dependent relaxation was assessed with DEA-NOnoate (DEA-NO) on pre-contracted arteries. HO-1 and soluble guanylyl-cyclase (sGC) mRNA and protein expressions were assessed by qRT-PCR and Western blotting, respectively.

SRM1648 or Co (III) Protoporphyrin IX Chloride exposure (24) impaired DEA-NO-dependent relaxation. The SRM-induced alteration of DEA-NO responsiveness was partially prevented by Cr (III) Mesoporphyrin IX Chloride. Co (III) Protoporphyrin IX Chloride induced HO-1 mRNA and protein expressions, whereas SRM1648 only induced HO-1 protein expression without affecting its mRNA level. Exposure to either SRM1648 or to Co (III) Protoporphyrin IX Chloride did not affect the expression levels of sGC.

In conclusion, this study provides some evidence that impairment of NO signaling pathway in intrapulmonary arteries involves HO-1. Therefore it highlights the role of HO-1 in particulate matter-induced detrimental effects in pulmonary circulation.

© 2016 Published by Elsevier Ltd.

1. Introduction

Many epidemiological studies demonstrated a correlation between exposure to particulate matter (PM) pollution and cardiovascular morbidity (Newby et al., 2015; Chen et al., 2014) and mortality (Beelen et al., 2014; Pope et al., 2015). Among cardiovascular adverse effects reported in humans, exposure to PM may induce an increase of blood pressure (Urch et al., 2005), a reduction in heart rate variability via decreased vagal tone (Gold et al., 2000) and may favor atherogenesis (Kunzli et al., 2005). Following inhalation, PM could accumulate in the lung parenchyma, sometimes closed to pulmonary arterial wall (Calderón-Garcidueñas et al., 2001). Thus, in the cardiovascular system, pulmonary vasculature could be primarily targeted by PM. A clinical consequence could be the development of pulmonary hypertension as it was described in mice challenged by a combination of ovalbumin and PM (Grunig et al., 2014), or the exacerbation of pulmonary arterial hypertension in already altered pulmonary vasculature. These data suggest that exposure to PM could exacerbate comorbidities factors, causing or worsening pulmonary hypertension and contributing to right heart failure. In line with this, it was observed an association between exposure to PM and an elevated mean pulmonary arterial pressure in children (Calderón-Garcidueñas et al., 2007).

Thereafter, several hypotheses, which are not exclusive, have been proposed to account for the effect of particles which can deeply penetrate into the lung. First, a local pulmonary inflammation which has

Abbreviations: SRM1648, Standard Reference Materials 1648; HO-1, Heme Oxygenase-1; sGC, soluble Guanylyl Cyclase; NO, nitric oxide; PM, particulate matter.

* Corresponding author at: Inserm U1045, Centre de Recherche Cardio-Thoracique de Bordeaux, 146 rue Léo Saignat, F-33076 Bordeaux, France.
E-mail address: arnaud.courtois@u-bordeaux.fr (A. Courtois).

[1] These authors contributed equally to the work.

http://dx.doi.org/10.1016/j.tiv.2016.01.005
0887-2333/© 2016 Published by Elsevier Ltd.

its own deleterious effect on pulmonary vessels could also trigger a secondary systemic inflammation that could exacerbate cardiovascular dysfunction (Mills et al., 2009). Second, the controversial passage of the finest particles into the blood after inhalation was documented in animals and humans (Kreyling et al., 2002; Nemmar et al., 2002; Wiebert et al., 2006), suggesting direct effects of translocated particles, or of some of their constituents, on remote target tissues. Finally, a growing body of literature described an imbalanced activation of the autonomic nervous system that could explain an increase in blood pressure in response to PM acute exposure (Bartoli et al., 2009; Brook et al., 2009; Cosselman et al., 2012; Ying et al., 2014).

Another factor that could favor the increase in blood pressure is an alteration of the nitric oxide (NO) signaling pathway. Indeed, endothelial NO is a major vasculo-protective agent, participating in the decrease of the vascular tone through activation of cyclic GMP (guanosine 3′,5′-cyclic monophosphate, cGMP) pathway, but also to the inhibition of smooth muscle cell proliferation/migration, and platelet adhesion/aggregation (-Gewaltig and Kojda, 2002). A decrease in endothelial NO production and/or bioactivity has already been observed upon PM exposure (Miller et al., 2009). In addition, we have previously described that PM exposure impairs NO-mediated relaxation, without affecting cGMP-responsiveness. This was attributed to a decrease in soluble guanylyl-cyclase activation (sGC) by NO (Courtois et al., 2008). However the mechanism involved in the decreased activity of sGC remains unknown.

sGC is a heme-dependent enzyme that catalyzes the conversion of GTP into cGMP upon binding of NO to the Fe^{2+} heme moiety. Thus, heme availability may control the responsiveness of sGC to NO and cGMP-dependent relaxation. In cells, the heme level is regulated by Heme Oxygenase (HO) enzymatic system that catalyzes the degradation of heme to an equimolar level of carbon monoxide (CO), biliverdin and Fe^{2+}. Several studies have reported that PM exposure could induce HO expression, either after in vitro exposure in human microvascular endothelial cells (Gong et al., 2007), in rat heart microvessel endothelial cells (Furuyama et al., 2006), in rat alveolar macrophages and epithelial cells (Chin et al., 2003; Li et al., 2003), or after in vivo exposure in rat lung (Ito et al., 2008; Karthikeyan et al., 2013). In several studies, PM exposure-induced HO expression was related to oxidative stress. One study described an alteration of cardiac function and also an increase in pulmonary arterial pressure (Mahne et al., 2012). The precise mechanism involved in this effect was unknown, but the authors observed a hyperplasia in small pulmonary arteries which could explain, at least in part, the increase in pulmonary artery pressure. In that study it was also observed that exposure to PM increased the isoform 1 of HO (HO-1) at the protein level in the left ventricle, and this was considered as an oxidative stress biomarker.

HO activity and heme degradation products are known to inhibit endothelial NO signaling pathway that could be responsible of an alteration of vascular tone (Imai et al., 2001; Koglin and Behrends, 2002; Mingone et al., 2008). Although both induction of HO-1 by PM in vascular cells and alteration of pulmonary artery relaxation were already described, the involvement of HO-1 in pulmonary artery altered relaxation upon PM exposure has not been investigated.

Therefore, the objective of our study was to characterize the involvement of HO-1 system in the PM-induced impairment of NO-dependent relaxation. Indeed, we hypothesized that induction of HO-1 protein level in the vascular wall could alter vascular relaxation and participate to the increase in pulmonary arterial pressure. This study was performed in rat intrapulmonary arteries, which represent a vascular network that could be a target of inhaled airborne pollutants.

2. Materials and methods

2.1. Chemicals

Drugs and reagents were obtained from Sigma Chemical Co. (St Quentin-Fallavier, France), excepted Diethylammonium(Z)-1-(N,N-diethylamino)diazen-1-ium-1,2-diolate (DEA NONOate) which was supplied from Alexis biochemicals (San-Diego, USA); Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, Dinolytic®) and Sodium Pentobarbital from Centravet (Libourne, France); Cr (III) Mesoporphyrin IX Chloride (CrMP) and Co (III) Protoporphyrin IX Chloride (CoPP) from Frontier Scientific (Logan, USA).

2.2. Particulate matter

Standard Reference Materials 1648 (SRM1648) was purchased from the National Institute for Standards and Technology (Gaithersburg, USA). The physical and chemical properties of SRM1648 have been previously described (Becker et al., 1996). SRM1648 has a mean diameter of 0.4 μm, consist in more than 63% inorganic carbon, and 4–7% organic carbon. The minor inorganic constituents (mass fraction in percent) are lead (0.655 ± 0.008), zinc (0.476 ± 0.014) and trace constituents (mg/kg) are arsenic (115 ± 10), cadmium (75 ± 7), chromium (403 ± 12), copper (609 ± 27), manganese (786 ± 17) and nickel (82 ± 3). Major inorganic constituents (mass fraction in percent) according to the National Institute for Standards and Technology data sheet are aluminum (3.42 ± 0.11) and iron (3.91 ± 0.1).

For all experiments, SRM1648 particles were freshly suspended in distilled deionized water at a final concentration of 10 mg/ml.

2.3. Animals, tissue preparation, and exposure to chemicals

Specific pathogen free male Wistar rats (12–14 weeks old; Janvier Labs, Le Genest Saint-Isle, France) were maintained on a 12 h light/dark cycle. Experiments have been carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC), and the investigation conformed to the Guiding Principles for the Use of Animals in Toxicology which were adopted by the Society of Toxicology in 1989. Protocols used were approved by our local ethics committee, and agreement for animal house was obtained from French authorities.

Our study was performed on rat intrapulmonary arterial rings exposed ex vivo to particulate matter (PM), HO-1 inducer or HO-1 inhibitor. After exposure, vessels reactivity, mRNA and protein expression were assessed.

Briefly, rats were first euthanized by lethal injection of sodium pentobarbital. Heart and lungs were removed and placed in physiological salt solution (PSS) containing in mM: 119 NaCl, 4.7 KCl, 1.5 $CaCl_2$, 1.17 $MgSO_4$, 1.18 KH_2PO_4, 25 $NaHCO_3$ and 5.5 Glucose. Intrapulmonary arteries (internal diameter 500–800 μm) were dissected free of connective tissue and cut into segments of 1.6–2 mm length (Leblais et al., 2004). Then, intrapulmonary arterial rings were incubated in DMEM at 37 °C in a humidified atmosphere (95% air/5% CO_2) for 24 h, in the absence (control) or presence of SRM1648 (200 μg/ml) or Co (III) Protoporphyrin IX Chloride (1 or 10 μM), an HO-1 inducer. In some experiments, the HO-1 inhibitor, Cr (III) Mesoporphyrin IX Chloride (1 μM) was added concomitantly to SRM1648 in DMEM for the 24 h incubation period.

The time of 24 h exposure to SRM1648 was chosen because in a previous time course study (Courtois et al., 2008), we observed it was sufficient to alter acetylcholine relaxation as compared to 24 h unexposed arteries.

2.4. Measurements of isometric tension

After 24 h ex vivo exposure to chemicals, arterial segments were mounted in a wire myograph (DMT A/S, Aarhus, Denmark), bathed in PSS maintained at 37 °C, gassed with a mixture of carbogen and placed to their optimal resting tension (Leblais et al., 2004). After equilibration, viability of arteries was evaluated using PSS containing 80 mM KCl (equimolar substitution with NaCl). Preparations developing a wall tension below 1 mN/mm were discarded. A 60 min washout period

Download English Version:

https://daneshyari.com/en/article/5861227

Download Persian Version:

https://daneshyari.com/article/5861227

Daneshyari.com