Journal of Dermatological Science 78 (2015) 51–60

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

The impact of urban particulate pollution on skin barrier function and the subsequent drug absorption

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ARTICLE INFO

Article history:
Received 22 September 2014
Received in revised form 8 December 2014
Accepted 20 January 2015

Keywords:
Particulate matter
Skin
Barrier function
Stratum corneum
Tight junction
Drug absorption

ABSTRACT

Background: Ambient particulate matters (PMs) are known as inducers that adversely affect a variety of human organs.
Objectives: In this study, we aimed to evaluate the influence of PMs on the permeation of drugs and sunscreens via the skin. The role of skin-barrier properties such as the stratum corneum (SC) and tight junctions (TJs) during the delivery process was explored.
Methods: This work was conducted using both in vitro and in vivo experiments in pigs to check the responses of the skin to PMs. PMs primarily containing heavy metals (1648a) and polycyclic aromatic hydrocarbons (PAHs, 1649b) were employed to treat the skin.
Results: According to the transepidermal water loss (TEWL), 1649b but not 1648a significantly disrupted the SC integrity by 2-fold compared to the PBS control. The immunohistochemistry (IHC) of cytokeratin, filaggrin, and E-cadherin exhibited that 1649b mildly damaged TJs. The cytotoxicity of keratinocytes and skin fibroblasts caused by 1649b was stronger than that caused by 1648a. The 1649b elicited apoptosis via caspase-3 activation. The proteomic profiles showed that PMs upregulated Annexin A2 by >5-fold, which can be a biomarker of PM-induced barrier disruption. We found that the skin uptake of ascorbic acid, an extremely hydrophilic drug, was increased from 74 to 112 μg/g by 1649b treatment. The extremely lipophilic drug tretinoin also showed a 2.6-fold increase of skin accumulation. Oxybenzone and dextran absorption was not affected by PMs. The in vivo dye distribution visualized by fluorescence microscopy had indicated that 1649b intervention promoted permeant partitioning into SC.
Conclusions: Caution should be taken in exposing the skin to airborne dust due to its ability to reduce barrier function and increase the risk of drug overabsorption, although this effect was not very marked.
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1. Introduction

Airborne pollutants, especially particulate matters (PMs), represent elements of significant environmental exposure adversely influencing human health [1]. The World Health Organization (WHO) claims that PMs result in 8×10^5 premature deaths every year, ranking PMs the 13th leading cause of mortality worldwide [2]. PMs are complex mixtures containing metals, minerals, organic toxins, and/or biological materials. Most of the studies involved relating to PMs have focused on respiratory and cardiovascular injuries. The ambient air pollution elicits oxidative stress and inflammation on lung tissues, causing epithelial barrier function degradation, cytotoxicity, and even cancer development [3]. The epidemiological evidences demonstrate a correlation between PM exposure and cardiovascular disorder-related morbidity and

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http://dx.doi.org/10.1016/j.jdermsci.2015.01.011
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mortality [4]. Along with the oral and respiratory routes, the skin is the common pathway through which the xenobiotics or chemicals enter the body. The skin contributes to the important interface between the environment and the body. Alteration of the skin barrier function has resulted in the development of various cutaneous diseases [5]. PMs have been proved to induce skin, aging, allergic reactions, and delay the wound healing of the skin by topical exposure [6–8]. Until now, investigations pertaining to PMs' impact on the skin have been far less abundant as compared to those pertaining to the respiratory and cardiovascular systems. The integrity of the skin barrier is always unideal in environmental and occupational situations [9]. The purpose of this work was to explore the effect of airborne pollution on the skin barrier, including the stratum corneum (SC) and tight junctions (TJs), both of which form a functional skin barrier.

The contents of PMs that receive the most attention for causing health problems are heavy metals and polycyclic aromatic hydrocarbons (PAHs) [10]. In this study, we employed two standard reference materials predominantly composed of heavy metals (1648a) and PAHs (1649b), respectively, issued by National Institute of Standards and Technology (NIST) of the USA. The 1648a urban PMs are the microparticles (average diameter = 5.85 μm) with soluble metal contents such as Cu, Mn, Ni, Pb, and Ti [11]. The 1649b PMs are the urban dusts with an average diameter of about 11 μm. The constituents of 1649b include PAHs, polychlorinated biphenyl (PCB) congeners, pesticides, and dioxins. SC and TJs function as a permeation barrier against the penetration of molecules [12]. The permeation barrier deterioration by PMs may accelerate drug delivery into the skin, augmenting the risk of overabsorption. The second purpose of this study was to assess the permeation profiles of some permeants via PM-treated skin. We had selected four permeants frequently used to prevent cutaneous aging or to treat skin disorders. The permeants utilized herein were ascorbic acid, oxybenzone, tretinoin, and dextran. These permeants have various molecular sizes and lipophilicities that are advantageous for comparison of permeation profiles. The traditional rodent models always overestimate the skin penetration of drugs although they are easily handled and cost-effective. In order to approximate the condition of humans, we used the pig as the animal model.

2. Materials and methods

2.1. Materials

The standard reference materials 1648a and 1649b were supplied by NIST (Gaithersburg, MD, USA). Ascorbic acid, oxybenzone, tretinoin, fluorescein isothiocyanate (FITC)-conjugated dextran (4 kDa), and rhodamine B were purchased from Sigma–Aldrich (St. Louis, MO, USA).

2.2. Animals

Male Landrace × Yorkshire × Duroc pigs (8 weeks old) were obtained from Doctor Pig Animal Technology (Miaoli, Taiwan). The pigs were used to test the in vitro/in vivo topical PM application, physiological parameters, histology, and proteomic analysis. The animal experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Chang Gung University. All animals used in this work were treated under the institutional guidelines. A laboratory diet and water were given ad libitum. The total numbers of pig used were 11.

2.3. Topical application of PMs on pig skin

The pigs were anesthetized by intramuscular injection of Stresnil® (Jenssen Pharmaceuticals, Titusville, NJ, USA) at a dose of 1 ml/kg. After 15 min, Zoletil® 50 (Virbac, Carros Cedex, France) was injected intramuscularly at a dose of 50 mg/kg. The 1648a or 1649b was dispersed in phosphate buffered saline (PBS) at a concentration of 0.1 μg/ml. This vehicle was spread on a nonwoven polyethylene pad (3 M, Taipei, Taiwan) with an area of 2 cm × 2 cm and then applied to the pigs' dorsal region. The dose of PMs on the skin was 100 μg/m^2. The pad was fixed by Tegaderm® adhesive dressing (3 M, St. Paul, MN, USA) and gauze. Then a Silkypore® elastic adhesive gauze (Alcare, Tokyo, Japan) was used to cover the pad. The cloth was replaced with a new one every 24 h. After 5 days of consecutive application, the cloth was withdrawn, and the treated area was cleaned for a subsequent examination. Fig. 1A illustrates the procedures of PM application.

2.4. Gross observation

The gross imaging of pig skin treated with or without PMs in PBS was observed using a handheld digital microscope (Mini Scope-V, M&T Optics, Taipei, Taiwan). A magnification of 200× was used for imaging capture.

2.5. Physiological parameters

This evaluation aimed to evaluate the change of macroscopic condition of skin by PMs. Immediately after a 5-day application of PMs, the pig skin was examined for physiological parameters, including TEWL, skin surface pH, and erythema (a*). A Tewameter® (TM300, Courage and Khazaka, Köln, Germany) was employed for measuring TEWL (g/m^2/h). The pH was determined by Skin-pH-Meter® PH905 (Courage and Khazaka). A spectrocolorimeter (CD100, Yokogawa, Tokyo, Japan) was used to quantify cutaneous erythema.

2.6. Histological analysis

The dorsal skin was excised from the pig after sacrifice by isoflurane. The skin species were immersed in a 10% buffered formaldehyde using ethanol, embedded in paraffin wax, and sliced at a thickness of 3 μm. The samples were stained by hemoxylin and eosin (H&E) and imaged under light microscopy (IX81, Olympus, Tokyo, Japan).

For immunohistochemical (IHC) observation, primary anti-cytokeratin, anti-filaggrin, and anti-E-cadherin antibodies were incubated with the skin specimens at room temperature for 1 h. The skin sections stained with cytokeratin and filaggrin were visualized by light microscopy. On the other hand, the samples stained with E-cadherin were monitored by fluorescence microscopy. Immunoreactivity was detected with an Alexa Fluor 594 goat anti-rabbit immunoglobulin antibody (Invitrogen, Carlsbad, CA, USA).

2.7. Two-dimensional gel electrophoresis (2DE) and image analysis

Functional proteomics serve as a platform to explore the cellular process at the protein level and characterize the target proteins in the process. The skin samples (250 μg) extracted from the skin with or without PM treatment were thawed and diluted in immobilized pH gradient sample buffer containing 7 M urea, 2 M thiourea, 2% 3-[3-(cholamidopropyl) dimethylammoniol]-propanesulfonate (CHAPS), 65 mM dithiothreitol, and 1% IPG buffer to a volume of 350 μl. After rehydration for 12 h at 30 V, isoelectrofocusing (IEF) was conducted with a total of 75 kVh. Following IEF separation and equilibration, electrophoresis was performed on acrylamide gels at 40 mA. Proteins were observed by silver staining and subsequently scanned by an image scanner (Amersham Bioscience, Buckinghamshire, UK). The protein spot amounts were presented as the volumes. The spot volumes were calibrated

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