Environmental Research 160 (2018) 541–546

Contents lists available at ScienceDirect

Environmental Research

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

The association between p,p′-DDE levels and left ventricular mass is mainly mediated by obesity

M.A. La Merrill[a,*], P.M. Lind[b], S. Salihovic[c,d], B. van Bavel[d], L. Lind[e]

[a] Department of Environmental Toxicology, University of California, Davis, CA, USA
[b] Department of Medical Sciences, Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden
[c] Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
[d] MTM Research Centre, School of Science and Technology, Örebro University, Örebro, Sweden, and Norwegian Institute for Water Research, NIVA, Oslo, Norway
[e] Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Keywords:
P,p′-DDE
Left ventricular hypertrophy
Obesity
Glucose
Hypertension

ABSTRACT

Background and objectives: The pesticide metabolite p,p′-DDE has been associated with left ventricular (LV) mass and known risk factors for LV hypertrophy in humans and in experimental models. We hypothesized that the associations of p,p′-DDE with LV hypertrophy risk factors, namely elevated glucose, adiposity and hypertension, mediate the association of p,p′-DDE with LV mass.

Methods: p,p′-DDE was measured in plasma from 70-year-old subjects (n = 988) of the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS). When these subjects were 70-, 75- and 80- years old, LV characteristics were measured by echocardiography, while fasting glucose, body mass index (BMI) and blood pressure were assessed with standard clinical techniques.

Results: We found that p,p′-DDE levels were associated with increased fasting glucose, BMI, hypertension and LV mass in separate models adjusted for sex. Structural equation modeling revealed that the association between p,p′-DDE and LV mass was almost entirely mediated by BMI (70%), and also by hypertension (19%).

Conclusion: The obesogenic effect of p,p′-DDE is a major determinant responsible for the association of p,p′-DDE with LV mass.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide (Mortality and Causes of Death, 2016). Increased risk of CVD mortality is consistently associated with increased left ventricular (LV) mass and hypertrophy (Levy et al., 1990). LV hypertrophy is also a risk factor for heart failure, stroke and coronary heart disease (Gradman and Alfayoumi, 2006). As such, LV hypertrophy is an important indicator of preclinical CVD. A minority of cases of LV hypertrophy, known as hypertrophic cardiomyopathies, are attributable to genetic risk (Gersh et al., 2011). However, the majority of LV hypertrophy cases without a genetic cause are attributed to hypertension (Gradman and Alfayoumi, 2006). Other metabolic risk factors for LV hypertrophy include elevations in blood glucose (Chen et al., 2015) and adiposity (Chumlea et al., 2009).

The possibility that LV hypertrophy could result from environmental causes is exemplified by salt intake, where a high salt diet is a risk factor for developing both hypertension and cardiac hypertrophy (de la Sierra et al., 1996; Lal et al., 2003). The persistent organic pollutant (POP) 1,1-dichloro-2,2-bis(4-dichlordiphenyl) ethylene (p,p′-DDE), the metabolite of the organochlorine pesticide 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (p,p′-DDT) appears to be another type of environment influence that may serves as a risk factor for cardiac hypertrophy by targeting metabolic abnormalities. Numerous recent systematic reviews and meta-analyses found p,p′-DDE was positively associated with obesity, diabetes mellitus, and hypertension (Evangelou et al., 2016; Park et al., 2016; Song et al., 2016; Tang-Peronard et al., 2011; Wang et al., 2016). Two meta-analyses estimated meta odds ratios (95% confidence intervals) for the association of highest to lowest p,p′-DDE concentration categories and type 2 diabetes of 1.95 (1.44, 2.66) and 2.30 (1.81, 2.93) among studies in North America, Europe, and Asia-Pacific (Evangelou et al., 2016; Song et al., 2016). This was further supported by dose response analysis (Song et al., 2016).

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; LV, left ventricular; LVEDD, left ventricular diameter in end-diastole; LVMI, left ventricular mass index; POPs, persistent organic pollutants; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors

* Correspondence to: One Shields Avenue, Davis, CA 95616, USA.
E-mail addresses: mlamerrill@ucdavis.edu (M.A. La Merrill), monica.lind@medsci.uu.se (P.M. Lind), samira.salihovic@medsci.uu.se (S. Salihovic), bert.vanbavel@oru.se (B. van Bavel), lars.lind@medsci.uu.se (L. Lind).

http://dx.doi.org/10.1016/j.envres.2017.10.031
Received 16 June 2017; Received in revised form 24 July 2017; Accepted 18 October 2017
Available online 26 October 2017

Additionally, a meta-analysis of prospective studies found a positive association between p,p′-DDE exposure and later adiposity (meta-beta = 0.13 BMI z-score (95% CI 0.01; 0.25) per log increase of p,p′-DDE (Cano-Sancho et al., 2017)). Cano-Sancho et al. (2017) classified p,p′-DDE and p,p′-DDT as presumed to be obesogenic in humans based on the human meta-analysis, increased adiposity of two rodent species exposed to p,p′-DDT (and thus p,p′-DDE), and meta-analysis of obesity-related outcomes *in vitro*.

Two studies suggest that p,p′-DDT and p,p′-DDE are also associated with increased left ventricular mass. In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, after adjusting for hypertension, diabetes and obesity, the association between p,p′-DDE and left ventricular mass was no longer significant (Sjoberg Lind et al., 2013), raising the possibility of mediation by these LV hypertrophy risk factors. Indeed, a second study that was performed in mice recently suggested that increased LV mass was a consequence of exposure to technical DDT (La Merrill et al., 2016). These DDT-exposed mice also had elevated blood pressure, adiposity and insulin resistance (La Merrill et al., 2014, 2016), raising the possibility that their increased LV mass was mediated by these metabolic risk factors for LV hypertrophy. Given the mice exposed to technical DDT had circulating levels of p,p′-DDT and p,p′-DDE that were within the range reported in people from North America, Europe, and Africa, their resulting cardiometabolic toxicities could be relevant to human p,p′-DDT and/or p,p′-DDE exposure conditions.

To explore the intricate interplay between p,p′-DDE exposure and LV hypertrophy risk factors on one hand, and p,p′-DDE exposure and LV mass on the other hand, we utilized longitudinal follow-up data from the PIVUS cohort to evaluate whether p,p′-DDE exposure is associated with increased LV mass over time, and explicitly tested whether such an association was mediated by hypertension and metabolic risk factors for LV hypertrophy using structural equation modeling (SEM).

2. Material and methods

2.1. Study Subjects

All subjects confirmed to be living in the community of Uppsala, Sweden according to the register of community living and 70 years old were eligible for this study. The subjects received an invitation by letter within two months of their 70th birthday in randomized order. Of the 2025 invited subjects, 1016 subjects participated (50.1%). Fifty % of the population were female. The baseline investigation was started in April 2001 and completed June 2004 (Lind et al., 2005). The participants were asked to answer a questionnaire about their medical history, smoking and regular medication. All participants were investigated in the morning after an overnight fast. No medication or smoking were allowed after midnight. After five and ten years, all individuals were invited to re-examinations. 826 and 604 subjects participated in the two re-examinations, respectively. The protocol was essentially the same at all investigations, except that serum p,p′-DDE levels were only measured at age 70 years. The study was approved by the Ethics Committee of Uppsala University in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the participants gave written informed consent.

2.2. Metabolic LV hypertrophy risk factors

Blood pressure was measured to the nearest mmHg by a calibrated mercury sphygmomanometer while subjects were in the supine position after at least 30 min of rest, and the average of three recordings was used. In order to avoid misclassification bias associated with blood pressure levels among subjects taking antihypertensive treatment, hypertension was defined as blood pressure > 140/90 mmHg or use of antihypertensive treatment. Given BMI is more strongly associated with LV hypertrophy than other available measures of adiposity (Hu et al., 2015), adiposity was evaluated by body mass index (BMI), defined as height/squared weight as ascertained from clinical measurements. Fasting blood glucose was assessed by the standard hexokinase technique (Lee et al., 2011).

2.3. Echocardiography

A comprehensive two-dimensional and Doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit (Acuson, California, USA) and a 2.5 MHz transducer as detailed previously (Lind, 2008). Briefly, LV dimensions were measured with M-mode on-line from the parasternal projections, using a leading edge to leading edge convention. Measurements included interventricular septal thickness, posterior wall thickness, and left ventricular diameter in end-diastole (LVEDD). LV wall thickness was defined as the sum of interventricular septal thickness and posterior wall thickness divided by LVEDD. LV mass was determined from the Penn convention and indexed for height $^{2.7}$ (LVMI, (Mureddu et al., 2001)).

2.4. Measurement of p,p′-DDE

p,p′-DDE was measured in stored plasma samples. Analyses of p,p′-DDE was performed using a high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS) system (Micromass Autospec Ultima, Waters, Mildford, MA, USA) with some modifications to the method by Sandau et al. (Sandau et al., 2003). The calculated method detection limit was 2.13 ng/g lipid. All subjects had values above that level. All details on the p,p′-DDE analyses have been reported elsewhere (Salihovic et al., 2012a, 2012b). The p,p′-DDE levels were normalized for circulating total lipid levels, which were defined by an established summation formula based on serum cholesterol and serum triglyceride concentrations (Rylander et al., 2006). Thereafter, normalized p,p′-DDE levels were obtained by dividing the wet-weight concentrations of p,p′-DDE by the estimated lipid level.

2.5. Statistical analyses

Variables with a skewed distribution, such as fasting glucose and p,p′-DDE, were natural log-transformed to achieve a normal distribution. In the analyses of the relationships between p,p′-DDE levels and hypertension, BMI and fasting glucose, as well as for the echocardiographical variables, we used all cardiometabolic measurements collected at ages 70, 75, and 80 to evaluate their longitudinal relationship with p,p′-DDE exposure.

Initially, mixed models with random intercepts were used to evaluate possible relationships between p,p′-DDE levels and the well known LV hypertrophy risk factors hypertension, BMI and fasting glucose (Lieb et al., 2014) in separate models using sex as confounder. Linear mixed models (xtmixed) were used for continuous data, while logistic mixed models (xtlogit) were used when the outcome was binary, such as hypertension. Also possible interactions between sex and p,p′-DDE levels regarding the LV hypertrophy risk factors were evaluated.

Potential confounders, such as smoking, education level and alcohol intake were not included in the models since they were not related to p,p′-DDE levels ($p > 0.07$ for all). Therefore, the models were just adjusted for sex (age same in all subjects).

Second, mixed models with random intercepts for subject were used to evaluate relationships between p,p′-DDE levels and the echocardiographical variables LVMI, LVEDD and LV thickness. The first set of models of echocardiographical variables were adjusted only for sex, while the second set of models were also adjusted for hypertension, BMI and fasting glucose. Also possible interactions between sex and p,p′-DDE levels regarding the echocardiographic variables were evaluated. To evaluate if the relationship between p,p′-DDE levels and LVMI was linear or not, predictive margins was used in a model with p,p′-DDE levels on the original scale, also including a squared term for p,p′-DDE levels. A significant squared term is taken as evidence of a non-linear relationship.