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Time of the day dictates the variability of biomarkers of exposure to disinfection byproducts

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ABSTRACT

Non-persistent environmental chemicals (NOPEC) are xenobiotics with short half-lives of elimination (< 7 h). Similar to chronopharmacokinetics, NOPEC metabolism may follow diurnal patterns of cytochrome P450 activity. The role of circadian liver clock in shaping NOPEC metabolism and their concomitant measurements of biomarkers of exposure and effect remains poorly understood in real-life human settings. Metabolic activation (toxication) by CYP2E1 converts trihalomethanes (THM) to harmful metabolites. We investigated the diurnal variation of urinary THM exposures and their metabolism patterns as catalyzed by CYP2E1 redox activity, using the surrogate marker of 4-hydroxynonenal (4HNE). We implemented three time-series trials with adult volunteers conducting specific household cleaning activities at predefined times of a day. Circadia variation of 4HNE was assessed with a cosinor model and its mesor levels increased with THM exposure. The time of exposure within the day dictated the magnitude of urinary THM levels and their toxication effect; in all three trials and relative to urinary THM levels before the activity, lower and higher median THM were measured right after the activity in morning and afternoon/night, respectively. This is consistent with higher reported CYP2E1 redox activity in light/active phase. Population health studies should incorporate time-stamped biomarker data to improve the understanding of chronic disease processes.

1. Introduction

Non-persistent environmental chemicals (NOPEC) are xenobiotics with short half-lives of elimination (< 7 h) commonly associated with a suite of consumer products and related activities, such as personal care products or cleaning or food/water packages (Calafat et al., 2015). These chemicals are ubiquitous in the environment and have been detected in > 90% of biospecimen collected, worldwide (Covaci et al., 2015; Katsikantami et al., 2016). Intermittent daily exposures and random biospecimen sampling during the day could lead to large intra-subject NOPEC variation and inconsistent associations with chronic disease. Similar to drugs, NOPEC metabolism may follow diurnal hepatic patterns of cytochrome P450 activity. Hepatic enzyme activity and blood flow may be influenced by circadian rhythms (Baraldo, 2008). The role of circadian liver clock oscillation effects in shaping NOPEC metabolism remains poorly understood in real-life human settings, since most chronobiology studies operate under constant routine or in forced desynchrony isolation facilities.

Trihalomethanes (THM) are a NOPEC group of xenobiotics formed during water disinfection or household cleaning. Humans are exposed to THM via all routes, including inhalation, ingestion and dermal absorption (Haddad et al., 2006). THM undergo Phase I bioactivation (metabolic activation or toxication), mainly by CYP2E1 in the liver and kidney (Gemma et al., 2003) by generating dihalo-, and trihalo-methyl radicals, free radical species formed primarily due to the CYP2E1 enzyme activity and Phase II conjugation with glutathione (Tomasi et al., 1985). The toxic reactive oxygen species formed during Phase I metabolism of THM have been linked with the generation of lipid peroxidation products especially 4-hydroxynonenal (4HNE) in rodents (Seth et al., 2013). The formation of lipid radicals has a direct correlation with CYP2E1 enzyme activity.

We implemented three time-series panel studies with different young adult volunteers in each study conducting specific disinfecting activities (known to release THM) at predefined times of the day. Therefore, diurnal monitoring of THM and 4HNE as a potential surrogate marker of CYP2E1 redox activity, upon induction via THM exposures was employed. CYP2E1 is the main enzyme driving THM disposition pathways, exhibiting a well-defined circadian rhythm (Tahara

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and Shibata, 2016). The main question of the study was whether the time of THM exposure in the day could dictate the extent of toxicity and thus, the susceptibility to THM, which encompasses both genetic predisposition and circadian clock dependence. Metabolomics tools are often used in human studies that attempt to couple external exposures with corresponding perturbations in the internal metabolome, providing hints regarding specific biological pathways associated with the disease process (Andrianou et al., 2017). As such, metabolomics tools were used here to evaluate the number and type of metabolites associated with the diurnal THM exposures.

2. Methods

2.1. Study design

We collected data from three trials (Fig. S1) on urinary biomarkers of THM exposure, including cortisol measurements before/after four time-stamped (HH:MM) cleaning activities (showering, mopping, bathroom cleaning, and hand dishwashing). 4-Hydroxynonenal (4HNE) was used as a surrogate for CYP2E1 redox activity, since studies have shown that CYP2E1 substrates may cause generation of lipid peroxidation products, namely 4HNE and its generated amount correlates directly with the CYP2E1 activity (Lu and Cederbaum, 2008; Seth et al., 2017, 2013). We intentionally avoided the use of chlorzoxazone as a direct marker of CYP2E1 activity, because of its potential safety and side-effect issues.

The first trial ($n = 6$) consisted of a repeatedly sampled control day and an activity day where only the aforementioned cleaning activities were performed. The second trial ($n = 6$) controlled better for the possible effect of the time of day that THM-related activities have on CYP2E1-catalyzed toxication phenomena. Therefore, the cleaning activities were either concentrated in the morning or in the evening. The third trial (validation) provided participants ($n = 6$) with the same amount of chlorine-containing cleaning agents and they performed the same four cleaning activities. The same dose of the chlorine-containing (hypochlorite salts) disinfectants was provided for use in mopping, dish washing and bathroom cleaning, while showering was done with the participant's own products. The disinfectant-containing cleaning products were freshly opened and provided to the participants the day before the experiment; toilet cleaner with 4.5 g hypochlorite/100, floor cleaner with 1.62 g sodium hypochlorite/100 g and appliance cleaner with < 5% chlorine.

Background THM levels originating from other than those predefined THM exposure sources were anticipated. That is why pairs of pre- and post-activity urine samples were collected and subsequently compared and contrasted. Urinary THM exposure measurements were taken before the activity and 15 min after performing the activities. This urine collection time window was chosen, because urinary THM levels remain constant at least 15 min after the cessation of exposure relevant activities (Caro and Gallego, 2007). Total THM (TTHM) are denoted as the sum of chloroform (TCM) and brominated THM (BrTHM), i.e., bromodichloromethane (BDCM), dibromochloromethane (DBCM), and tribromomethane (TBM). During the sampling period the participants were instructed to perform only the requested activities. Urinary THM measurements are expected to integrate all biologically relevant routes of exposure to THMs. The participants were not offered any water, they were responsible for their own supply. Based on our earlier general population survey, median water consumption rates for tap water, bottled water, and mobile station water sold in vending sites were 0.4, 0.2, and 1.3 L/day/capita/, respectively; mobile station water THM levels were always below detection limit (Charisiadis et al., 2014). Nevertheless, noningestion routes of THM exposures (dermal uptake and inhalation) largely dictate the magnitude of the THM body burden (Charisiadis et al., 2014; Leavens et al., 2007).

For all three trials, young adult volunteers, non-smokers (25–39 years old) were recruited from the university campus. Female to male ratio were 5:1, 3:3 and 4:2 in the respective three trials. All participants lived in the same city, thus, the same tap water supply system was shared by the participants, showing similar background mean tap water THM concentrations (2014 survey: TTHM 32.4 μg/L and BrTHM 21.2 μg/L (Gängler et al., 2017); 2016 survey: TTHM 30.7 μg/L, BrTHM 27.3 μg/L). More details can be found in the SI section.

2.2. Sample analyses

Urine samples were stored at − 80 °C until analyses. Urine samples were analyzed for four THM based on our biomonitoring protocol (Charisiadis and Makris, 2018) using GC–MS/MS (Agilent 7890A GC coupled with an Agilent 7000B triple quadrupole mass spectrometer, Agilent Technologies, Waldbronn, Germany). THM were extracted with MTBE from 15 mL of urine, decafluorobiphenyl was used as surrogate. Sodium sulfate was added to enhance the phase separation for the extraction of the organic phase. We systematically used 10% blanks and QCs in realistic urinary THM concentrations showing acceptable recovery rates for each THM compound, including the extraction recovery of the surrogate compound (82–119%). The limit of detection (LOD) and the limit of quantification (LOQ) (shown in parenthesis) for THM in urine were 30 (90) ng/L for TCM, 17 (50) ng/L for BDCM, 21 (64) ng/L for DBCM, and 15 (45) ng/L for TBM (Charisiadis and Makris, 2018). Analyte concentrations below LOD and LOQ in urine were imputed as half the LOD and half the LOQ. Extraction of THM from passive air samplers was done using carbon disulfide and analyzed for THM using GC–MS/MS using standard procedures. Creatinine measurements were done using the spectrophotometric Jaffe (picric acid based) method (MAK, 2010). 4HNE was determined using immunoassays following the instructions of the manufacturer (Neo Biolabs, USA). An adaption of the method by Moon et al. was used for the determination of urinary cortisol levels (Moon et al., 2009).

2.3. Metabolomics

Metabolomics were performed using GC–MS (Agilent Technologies, Waldborn, Germany) adapting the method of Chan et al. (2011) as described in the Supporting Information, while the spectra processing and workflow were executed as described in Andrianou et al. (2017). QC samples and blanks based on a pooled sample matrix (20 μL of FAME/d27-myristic acid mixture) were frequently analyzed between samples to ensure quality of the analysis (> 20% of the samples). Further processing was done in AMDIS using the default settings, after identifying the highest number of FAME markers and myristic acid-d27. Metabolite identification was done with Fiehn library considering hits with > 80% identification certainty. The peaklist was built in R using the “Metab” package, resulting in 141 different metabolites. Metabolites that occurred in < 75% of the samples were excluded, which lead to a dataset with 55 metabolites. After checking, metabolites identified as Lactulose 1 and 2 were excluded because it is an exogenous compound. Random forest imputation was done for missing metabolites and the data were normalized using probabilistic quotient normalization (Kohl et al., 2012) and log transformed. Relative comparisons were done without scaling whereas for cosinor analysis metabolite areas were Pareto scaled. p-Values were adjusted for multiple testing using the Benjamini-Hochberg procedure (FDR). After assessment of the samples with principal component analysis, four samples were excluded as outliers for metabolomics analysis. Non-unique features due to different derivatization products are indicated with numbers and not merged to one metabolite (Kind et al., 2009).

2.4. Statistical analysis

Statistical evaluation of the data was done using R (version 3.2.5) and the packages “lme4”, “ggplot2”, “car”, “tableone”, “texreg”, “XML”, “gplots”, “ICC”. The measured urinary biomarkers were also

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