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Association of polybrominated diphenyl ethers in two fat compartments with increased risk of insulin resistance in obese individuals

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HIGHLIGHTS

- PBDE28,47,99&153 are predominant in OM adipose tissues from obese Qatari subjects.
- PBDE28,47&99 in OM adipose tissues are higher in IR obese subjects than IS counterparts.
- PBDE penta congeners are higher in IR obese subjects than IS counterparts.
- Correlations among PBDEs and with mediators of insulin resistance are identified.
- Treatment of OM preadipocytes from IS subjects with PBDE28 triggered IR phenotype.

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ABSTRACT

Background: Polybrominated diphenyl ethers (PBDEs), a widely utilized class of flame retardants in various commercial products, represent a prominent source of environmental contaminants. PBDEs tend to accumulate in adipose tissue, potentially altering the function of this endocrine organ and increasing risk of insulin resistance. The aim of this study was to compare levels of PBDEs in adipose tissues from two metabolically distinct obese groups; the insulin sensitive (IS) and the insulin resistant (IR).
Methods: Levels of 28 PBDE congeners were assessed in subcutaneous and omental adipose tissues from 34 obese Qatari individuals (11 IS and 23 IR) using gas chromatography (Trace GC Ultra) coupled to a TSQ Quantum triple Quadrupole mass spectrometer. Correlations of identified PBDEs and mediators of metabolic disease were established and effects of PBDEs treatment on insulin signaling in primary omental preadipocytes were determined.
Results: Out of 22 detectable PBDEs in subcutaneous and omental adipose tissues, PBDEs 28, 47, 99 and 153 were predominant in omental adipose tissues from obese Qatari subjects. PBDEs 99, 28, and 47 were significantly higher in IR individuals compared to their IS counterparts. Significant positive correlations were identified between PBDEs 28 and 99 in the omental tissues and with fasting insulin levels. When considering PBDEs congeners, penta congeners were also higher in IR compared to IS individuals, while no significant differences were detected in mono, tri, tertra, hexa, hepta and octa congeners between the

Abbreviations: ASE, Accelerated Solvent Extraction; OPLS-DA, An orthogonal partial least squares discriminant analysis; BMI, Body mass index; DBP, Diastolic blood pressure; DCM, Dichloromethane; FPG, Fasting blood glucose; FBS, Fetal bovine serum; HDL, High density lipoprotein; HOMA-IR, Homeostatic model assessment; HOMA-IR, Homeostatic model assessment of insulin resistance; IRS-1, Insulin receptor substrate 1; IR, Insulin resistant; IS, Insulin sensitive; IL-6, Interleukin 6; LDL, Low density lipoprotein; mTOR, Mammalian target of rapamycin; MAP, Mean arterial blood pressure; MRM, Multiple reaction monitoring; OM, Omental; POPs, Persistent organic pollutants; PTEN, Phosphatase and tensin homolog; PBDEs, Polybrominated diphenyl ethers; PBDEs, Polybrominated diphenyl ethers; PLE, Pressurized liquid extraction; PVT, Programmable temperature vaporization; SVF, Stromal vascular fraction; SC, Subcutaneous; SBP, Systolic blood pressure; T2DM, Type 2 diabetes mellitus.

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two studied groups. Treatment of human omental preadipocytes from insulin sensitive individuals with PBDE28 caused inhibition of phosphorylation of GSK3 α/β (Ser^{21}/Ser^{9}), mTOR (Ser^{2448}), p70 S6 kinase (Thr^{389}) and S6 ribosomal protein (Ser^{235}/Ser^{236}) and activation of PTEN (Ser^{380}) phosphorylation, suggesting inhibition of insulin signaling.
Conclusion: This pilot data suggests that accumulation of specific PBDEs in human adipose tissues is associated with insulin resistance in obese individuals. Further investigation of the functional role of PBDEs in the pathology of insulin resistance should help developing therapeutic strategies targeting obese individuals at higher risk.

1. Introduction

Obesity constitutes a major risk factor for cardiovascular disease, hypertension, cancer and type 2 diabetes mellitus (T2DM) (Pi-Sunyer, 2009). However, a subset of obese individuals, known as the insulin sensitive (IS) or metabolically healthy obese (MHO), exhibit less metabolic deregulations compared to their obese insulin resistant (IR) counterparts (Bogardus et al., 1985). The protected IS individuals maintain insulin sensitivity (Bogardus et al., 1985; Samocha-Bonet et al., 2012) and show lower systemic levels of lipids and inflammatory markers (Primeau et al., 2011). During obesity, excess fat accumulates in the adipose tissues within the subcutaneous (SC) and visceral, including the omental (OM), fat compartments. This is often associated with ectopic fat deposition in the liver, skeletal muscle and heart tissues, leading to enhanced risk of insulin resistance and T2DM [9]. Whereas obesity-associated inflammation and oxidative stress were suggested to play a role in the increased risk of obese IR individuals compared to their IS counterparts (Almuraikhy et al., 2016; Elrayess et al., 2017; Jaganjac et al., 2017), the potential role of endocrine-disrupting environmental pollutants in air, water and food in the increased risk of IR-obesity compared to IS-obesity has not yet been investigated.

Evidence linking persistent organic pollutants (POPs) accumulation and development of diabetes was previously described (Magliano et al., 2014). Associations of blood concentrations of various classes of POPs with increased prevalence of diabetes was shown in different populations through increasing risk of insulin resistance (Lee et al., 2007; Pal et al., 2013). Among the studied POPs, polybrominated diphenyl ethers (PBDEs) represent a class of flame retardants that were widely utilized in various commercial products (Birnbaum and Staskal, 2004). Two hundred and nine known PBDE congeners that vary by the extent of halogenations can leak freely into the environment (Chen and Hale, 2010; Ernest et al., 2012). Despite cessation of their manufacturing since 2004, concerns of their bioaccumulation remain (Sjodin et al., 2003; Kelly et al., 2008; Mercado-Feliciano and Bigsby, 2008) due to their high stability in products manufactured before the ban and recycled materials (Birnbaum and Staskal, 2004) as well as their high intake during infancy (Fromme et al., 2016). Deca-BDE were only withdrawn from the N. American market by 2013 as their dehalogenation in environment generates lower-brominated PBDEs. Despite the success of policies in lowering the exposure to some PBDE congeners by eliminating their sources from the markets, exposures continue to rise in North America and may remain abundant in human populations (Hurley et al., 2017; Parry et al., 2018).

Presence of PBDEs in numerous products of daily use increases exposure at home environment (Frederiksen et al., 2009). PBDEs tend to accumulate in adipose tissue owing to their highly lipophilic nature (Stanley et al., 1991). Levels of PBDEs in obese individuals were positively correlated with visceral fat and visceral/subcutaneous abdominal fat ratio (Malarvannan et al., 2013). The bioaccumulation of PBDEs within adipocytes potentially alters their function by increasing lipolysis and decreasing glucose oxidation, causing increased risk of metabolic disease including obesity, insulin resistance and T2DM. Indeed, daily exposure to PBDE71 induced markers of insulin resistance including enhanced lipolysis and reduced glucose oxidation in rat adipocytes (Hoppe and Carey, 2007). The maternal exposure of rodents to PBDE47 predisposed the offspring to increased body weight during early postnatal development and risk of metabolic dysfunction (Suvorov et al., 2009; Wang et al., 2018), whereas PBDE47 exposure during the early postnatal period induced a mild disturbance in glucose metabolism in mice with increased baseline insulin sensitivity (McIntyre et al., 2015). It also triggered significant transcriptomic changes in their gonadal adipose tissue, placing fat tissue as a primary target for PBDE-47 (Abrha and Suvorov, 2018). A positive correlation between serum levels of the PBDE153, metabolic syndrome and visceral fat mass in humans was previously established (Lim et al., 2008). Furthermore, adipogenesis of mouse preadipoctyes was shown to increase in the presence of PBDEs in the absence of glucocorticoids, suggesting a different molecular target than the glucocorticoid receptor (Tung et al., 2014). The versatility of PBDEs function on adipose tissue function, therefore, warrant further investigation.

Despite various studies investigating the association of serum PBDEs with metabolic disease and their potential function on adipocytes, no study has investigated the association of PBDEs within human adipose tissues from IS and IR obese individuals. In this study, we hypothesized that levels of certain PBDEs in human adipose tissues will be associated with incidents of insulin resistance in obese subjects and that PBDEs treatment of cells derived from IS adipose tissues could trigger IR phenotype. In this study, levels of various PBDEs were assessed in subcutaneous and omental adipose tissues from obese IS and IR Qatari subjects and their correlation with mediators of metabolic disease were established together with their impact on insulin signaling in preadipocytes derived from these tissue.

2. Materials and methods

2.1. Chemicals, reagents and other materials

Dichloromethane (DCM) and n-hexane were supplied by Merch (Darmstadt, Germany) or sigma Aldrich (Steinheim, Germany). All solvents were of analytical grade. Silica (200 mm) was supplied by Merch (Darmstadt, Germany). Sulfuric acid was obtained from Sigma Aldrich (Steinheim, Germany). Acidic silica gel (44%) was prepared by adding 44 g of sulfuric acid to 100 g activated silica gel, mixed well for 1 h then stored until used. Certified standards of individual PBDE congeners (3, 7, 15, 17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 138, 153, 154, 155, 166, 181, 183, 190, 203, 205, 206, 207, 209) (EO-5405) and $^{13}C_{12}$-labeled PBDE congeners (15, 28, 47, 99, 153, 154, 183, 197, 206, 208, 209) (EO-5426) were supplied by Cambridge Isotopoe Lab., INC. (Madover, MA, USA). Purified PBDE-