Bisphenol A glucuronidation in patients with Parkinson’s disease

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Article history:
Received 29 March 2017
Received in revised form 17 September 2017
Accepted 18 September 2017
Available online 20 September 2017

Keywords:
Bisphenol A
Parkinson disease
Glucuronidation

ABSTRACT

Background: Bisphenol A (BPA) is a widely distributed estrogen-mimetic molecule, with well-established effects on the dopaminergic system. It can be found in canned food, dental sealants, thermal paper, etc. BPA undergoes liver conjugation with glucuronic acid and is subsequently excreted in the urine.

Objectives: In the present study we quantified the concentration of free and conjugated Bisphenol A in blood of patients affected by Parkinson Disease, using their spouses as controls.

Methods: An interview was performed to determine possible confounders in BPA exposure. Free and conjugated BPA were quantified by gas chromatography coupled with mass spectrometry.

Results: Parkinson’s Disease patients carried a statistically significant lower amount of conjugated Bisphenol A compared to controls. The two populations were mostly homogeneous in terms of exposure to possible Bisphenol A sources. The only exceptions were exposure to canned tuna and canned tomatoes PD patients consumed significantly more of both (p < 0.05). Moreover, no difference in Bisphenol A glucuronidation was found after stratification by typology of anti-Parkinson’s drug taken and after conversion to the Levodopa Equivalent Daily Dose.

Conclusion: BPA glucuronidation was decreased in patients with Parkinson disease. The possible unique mechanisms underlying Bisphenol A metabolism in PD patients deserve further elucidation. Moreover, further study is needed to assess a possible BPA role in Parkinson’s Disease pathogenesis, due to its documented dopaminergic toxicity.

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1. Introduction

Bisphenol A (BPA) is a ubiquitous organic monomer, used in plastic (polycarbonates and epoxy resins) and plastic additive synthesis. BPA is used in the production of bottles, dishes, compact discs, purchase-receipt paper, self-adhesive labels, fax paper and dental sealants. Moreover, epoxy resins are used as the internal coatings of metal products (e.g., food and beverage cans) and in water pipes. Diet is the main source of human exposure, through the contamination of food and beverages contained in both polycarbonate bottles and coated cans (Cwik-Ludwicka and Ludwicki, 2014; Hoekstra and Simoneau, 2013). Potential contamination is also determined by the nature of the contained food (acid or base) or by exposure to high temperatures, including microwave heating (Le et al., 2008; Welshons et al., 2006). In the liver, BPA is conjugated with glucuronic acid and, to a lesser extent, with sulfate, generating BPA glucuronide and BPA-sulfate (Matsu-moto et al., 2002). The two conjugates are devoid of biological activity, and eliminated in urine.

BPA belongs to the class of endocrine disrupters, i.e. molecules able to interfere with the endocrine system by mimicking, antagonizing, or altering endogenous steroid levels (Frye et al., 2012).

Specifically, BPA interacts with low affinity to nuclear estrogen α and β-receptors, and with high affinity to membrane estrogen receptors (Wolstenholme et al., 2011). Takayanagi et al. (Takayanagi et al., 2006) first described a high affinity binding to estrogen-related gamma nuclear receptor (ERR-γ).
Exposure to BPA has been associated with a wide range of reproductive, metabolic, and developmental adverse effects in humans (Rochester, 2013).

Because estrogen increases dopamine (DA) release from GABAergic neurons (Yoest et al., 2014), the potential indirect effects of BPA are particularly interesting. Several studies have documented the effects of BPA on the central nervous system. For example, it has been demonstrated that estrogen exposure may affect tyrosine hydroxylase (TH) expression in DA neurons, as well as DA receptor expression (Jones and Miller, 2008). Ishido et al. (Ishido et al., 2007) found that postnatal BPA exposure caused decreased TH immune reactivity in rats. Similarly, in vitro studies show that BPA exposure may cause dopamine transporter (DAT)-mediated dopamine efflux and increased DAT trafficking in pheochromocytoma cell line 12 (PC12) (Alyea and Watson, 2009a), an effect described as depending on estradiol exposure as well (Alyea and Watson, 2009b); similar results were obtained by Yoneda et al. (Yoneda et al., 2003), showing that PC12 cells exposure to BPA caused DA release, in a G-protein and Ca**+ channel-dependent manner. Additionally, in vitro studies show that, when activated, ERRs α, β and γ are transcriptional activators of the enzymes monoamino oxidase (MAO) A and B, with subsequent stimulation of reactive oxygen species (ROS) generation and toxicity (Ren et al., 2011). Thus, the potential indirect effects of BPA are wide and varied.

Parkinson Disease (PD) is the second most frequent neurodegenerative disorder, characterized by a progressive loss of the dopaminergic neurons projecting from substantia nigra to the basal ganglia. Its cardinal motor signs are rest tremor, bradykinesia, rigidity and loss of postural reflexes (Jankovic, 2008). Clinical diagnosis, according to the UK Brain Bank Criteria (Hughes et al., 1992), attempts to discern idiopathic PD from secondary forms of Parkinsonism, i.e. those caused by hydrocephalus, cerebrovascular disease, neuroleptics, and from atypical Parkinsonisms, such as progressive supranuclear palsy, multiple system atrophy, cortico-basal degeneration, Lewy body dementia. The current view regarding PD etiology is that a genetic basis interacts with environmental factors, causing the disease (Chin-Chan et al., 2015).

Mitochondrial dysfunction has been implicated in the pathogenesis of the disease (Nakamura et al., 2011). BPA-induced mitochondrial toxicity, i.e. a decreased activity of mitochondrial enzymes and an increased ROS generation, has been described in rats (Khan et al., 2015). A relationship between BPA exposure and substantia nigra degeneration has been shown by Ishido and Masuo (Ishido and Masuo, 2014), who treated adult rats with either a massive dose of 20 μg of Bisphenol A injected in the substantia nigra, or 3 mg/kg/day subcutaneously for 28 days. Both treatments led to substantia nigra degeneration.

The present study is the first to explore the association of BPA metabolism and Parkinson’s Disease. The possible role of this molecule was investigated by quantifying free and conjugated BPA in the blood of Parkinson’s patients and their spouses, and by assessing working and food habits, and the presence of dental sealants, as an estimation of exposure.

2. Methods

2.1. Participants

Blood samples were collected during 2013 at the Parkinson centers in Naples and Salerno University Clinics, in a BPA-free BD vacutainer blood collection red tube (without additives) and immediately frozen to –20 °C until analysis. A structured interview was performed by a medical doctor in order to collect information about socioeconomic characteristics (e.g., occupation, education), lifestyle habits and BPA exposure (e.g., smoking, passive smoking, dental fillings, canned food consumption and professional exposure), and environmental exposition to toxicants suspected to be involved in the genesis of PD, such as pesticides and metals. Questions were chosen according to the main sources of these molecules, as they are described in literature (EFSA CEF Panel, 2015; Krieter et al., 2013; Lakind and Naiman, 2011; Lorber et al., 2015; Mariscal-Arcas et al., 2009; Mikolajewska et al., 2015; Racette et al., 2012; van der Mark et al., 2012; Vandenberg et al., 2007). This questionnaire was used in order to eliminate any possible confounder regarding massive exposure to established sources of BPA and toxic agents. Human tissue collection strictly adhered to the guidelines outlined in the Declaration of Helsinki and the study was approved by the ethics committee. All participants signed an informed consent.

2.2. Patients

Parkinson’s patients (Campania region) were enrolled during visits for routine medical assessment. Inclusion criteria were: a diagnosis of idiopathic PD following the UK Brain Bank Criteria, voluntary participation in the study. Exclusion criteria were: suspected or diagnosed secondary Parkinsonian syndrome or atypical Parkinsonism. Clinical assessment of motor impairment and disability was scored according to the third section of Unified Parkinson’s Disease Rating Scale (UPDRS III) and the Modified Hoehn and Yahr Scale (H&Y scale), both of which are validated scales universally used for the clinical assessment of Parkinsonian patients (Goetz et al., 2004). The total number of Parkinson’s patients enrolled in the study was 86 (31 women, 55 men; Table 1)

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 86)</th>
<th></th>
<th>Controls (n = 42)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Median (Lower-Upper Quartile)</td>
<td>Min-Max</td>
<td>Median (Lower-Upper Quartile)</td>
<td>Min-Max</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>66.0 (62.0–71.0)</td>
<td>43–83</td>
<td>65.0 (56.0–69.0)</td>
<td>49–80</td>
</tr>
<tr>
<td>Duration of disease (year)</td>
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<td>1–29</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Women</td>
<td>31 (36.05%)</td>
<td>–</td>
<td>31 (73.81%)</td>
<td>–</td>
</tr>
<tr>
<td>Men</td>
<td>55 (63.95%)</td>
<td>–</td>
<td>11 (26.19%)</td>
<td>–</td>
</tr>
<tr>
<td>Height (Kg)</td>
<td>75.0 (65.5–84.0)</td>
<td>46–130</td>
<td>65.0 (56.0–69.0)</td>
<td>50–100</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>167.5 (161.0–172.0)*</td>
<td>149–185</td>
<td>161.0 (156.0–165.0)</td>
<td>150–180</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>103.0 (94.5–109.0)</td>
<td>68–138</td>
<td>98.0 (89.0–109.0)</td>
<td>72–121</td>
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<tr>
<td>BMI (Kg/m²)</td>
<td>26.33 (24.22–29.38)</td>
<td>15.37–44.98</td>
<td>25.80 (23.95–29.04)</td>
<td>19.53–35.43</td>
</tr>
<tr>
<td>UPDRSIII</td>
<td>18.5 (12.0–26.0)</td>
<td>2–67</td>
<td>–</td>
<td>–</td>
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<tr>
<td>H&amp;Y Stage</td>
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<td>1–4</td>
<td>–</td>
<td>–</td>
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<tr>
<td>LDD (mg/day)</td>
<td>800.0 (600.0–1135.0)</td>
<td>52–2352.5</td>
<td>0</td>
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