Correlation between antibodies to bisphenol A, its target enzyme protein disulfide isomerase and antibodies to neuron-specific antigens

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ABSTRACT: Evidence continues to increase linking autoimmunity and other complex diseases to the chemicals commonly found in our environment. Bisphenol A (BPA) is a synthetic monomer used widely in many forms, from food containers to toys, medical products and many others. The potential for BPA to participate as a triggering agent for autoimmune diseases is likely due to its known immunological influences. The goal of this research was to determine if immune reactivity to BPA has any correlation with neurological antibodies. BPA binds to a target enzyme called protein disulfide isomerase (PDI). Myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) are neuronal antigens that are target sites for neuroinflammation and neuroautoimmunity. We determined the co-occurrence of anti-MBP and anti-MOG antibodies with antibodies made against BPA bound to human serum albumin in 100 healthy human subjects. Correlation between BPA to PDI, BPA to MBP, PDI to MBP and PDI to MOG were all highly statistically significant ($P < 0.0001$). The outcome of our study suggests that immune reactivity to BPA-human serum albumin and PDI has a high degree of statistical significance with substantial correlation with both MBP and MOG antibody levels. This suggests that BPA may be a trigger for the production of antibodies against PDI, MBP and MOG. Immune reactivity to BPA bound to human tissue proteins may be a contributing factor to neurological autoimmune disorders. Further research is needed to determine the exact relationship of these antibodies with neuroautoimmunities. Copyright © 2016 The Authors Journal of Applied Toxicology Published by John Wiley & Sons Ltd.

Keywords: Bisphenol A; Protein Disulfide Isomerase; Myelin Basic Protein; Myelin Oligodendrocytic Glycoprotein

Introduction

Bisphenol A (2, 2-bis(4-hydroxyphenyl) propane [BPA]) is a synthetic monomer used widely in many forms, from plastic food containers, toys, medical products, lining of tin cans and even thermal receipts (Rochester, 2013). BPA can be leached when heated or when exposed to food products that have low pH (Welshons et al., 2006). Exposure to BPA-containing products leads to increased BPA levels in animals and humans (McLachlan, 2001). BPA is one of the most commonly prevalent chemicals to which humans are exposed. The practice of heating food items in plastic or storing acidic liquids in BPA such as vinegar and soda increase the bioavailability of BPA (Careghini et al., 2015). Researchers have reported that more than 90% of the population in the United States has detectable levels of BPA in their urine samples (Calafat et al., 2008). Human urinary and tissue biomonitoring studies have confirmed increased levels of BPA worldwide (Vandenberg et al., 2012).

Current accumulated evidence suggests that BPA is an endocrine disruptor and has the potential to impact fetal, child and adult health (Mikolajewska et al., 2015). BPA has been found specifically to bind to hormone receptors such as those for estrogen and impact signaling as both an agonist and antagonist, thereby interfering with normal functioning (Bonefeld-Jorgensen et al., 2007). There is currently limited research done on the autoimmune impact of BPA, particularly in humans. The potential for BPA to participate as a triggering agent for autoimmune diseases is very high due to the known immunological influences BPA has with estrogen receptors, T-cell receptors and aryl hydrocarbon receptors (Kharrazian, 2014).

Although there have been limited human studies linking BPA to autoimmune, a number of animal studies have connected BPA exposure to the development of various autoimmune diseases. In one study, maternal BPA exposure in utero of pregnant mice and lactating mice through dam drinking water induced increased incidence of spontaneous diabetes development in offspring of non-obese diabetic mice and increased severity of pancreatic islet cell insulitis (Bodin et al., 2014). An earlier study also found that long-term BPA exposure accelerates insulitis development in diabetes-prone non-obese diabetic mice (Bodin et al., 2013). These two mouse studies demonstrated the direct role of BPA exposure both through drinking water and the role they play in autoimmune pancreatitis leading to type 1 diabetes in mice (Brinkmeyer-Langford et al., 2014).

Researchers have also investigated the role that BPA exposure may have on virus-induced demyelination associated with multiple sclerosis in a mouse model. They found that perinatal
BPA exposure combined with viral infections resulted in accelerated onset of autoimmune demyelination symptoms, increased inflammation in both the spinal cord and digestive tract, and amplified immune-related gene expression changes. These animal studies provide some early evidence that BPA has the potential to both trigger and intensify autoimmune reactivity and autoimmune disease.

Many immunological mechanisms exist for BPA to induce autoimmunity, such as altered hepatic biotransformation, pituitary lactotrophic cell activation to synthesized prolactin, estrogen receptor endocrine disruption, altered cytokine expression, lipopolysaccharide-induced nitric oxide promotion, altered antigen-presenting cell reactivity, altered immunoglobulin activity, molecular mimicry and T-helper (Th)17 aryl hydrocarbon receptor activation, which have all been shown to be induced by BPA exposure in animal and human studies. All of these mechanisms have also been found to play a role in autoimmune development (Kharrazian, 2014).

BPA as a synthetic compound monomer alone is unlikely to trigger immunological antibody reactions or exert such diverse influences unless it can bind to enzymes or proteins leading to new antigenic epitopes. It exerts a diverse list of physiological effects on the endocrine system, thyroid hormones, nervous system and immune system, including estrogenic activity, anti-androgenic activity leading to xenoestrogen activity, inhibition of steroidogenesis, thyroid hormone receptor antagonist, modulation of dopamine release, upregulation of immune Th1 and Th2 responses, and disruption of immune regulation (Elsworth et al., 2013; Gentilcore et al., 2013; Kimura et al., 2015; Panchanathan et al., 2015; Robinson & Miller, 2015; Romano et al., 2015; Weng et al., 2010; Youn et al., 2002; Zhang et al., 2011).

Researchers have found that BPA binds to a key target enzyme molecule called protein disulfide isomerase (PDI) (Hiroi et al., 2006). PDI is an enzyme in the endoplasmic reticulum in eukaryotes that catalyzes the formation and breakage of disulfide bonds between cysteine residues within proteins as they fold; it therefore acts to catalyze protein folding. PDI has been isolated from rat brain synaptosome fractions and has been named as a BPA-binding protein (Hiroi et al., 2006). It is also known as a binding protein of thyroid hormone (T3) and estrogen (E2) (Hashimoto & Imaoka, 2013; Hashimoto et al., 2010; Youn et al., 2015; Weng et al., 2015; Kimura et al., 2013; Gentilcore et al., 2013; Kimura et al., 2015; Panchanathan et al., 2015; Robinson & Miller, 2015; Romano et al., 2015; Weng et al., 2010; Youn et al., 2002; Zhang et al., 2011).

We previously demonstrated that BPA can bind to human serum albumin (HSA) forming a new antigenic epitope that could potentially play a role in the mechanism by which environmental chemicals can induce autoimmunity reaction. We found that 13% (IgG) and 15% (IgM) of random blood donors presented with antibodies to BPA bound to HSA (Vojdani et al., 2015). In this current study, we investigated if the immune reaction to BPA bound to HSA co-occurs with antibody against PDI and if this immune reaction against BPA and PDI has any correlation with myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), the known targets of neuroautoimmunities.

Materials and methods

Blood samples

Sera from 100 random human donors aged 18–65 were purchased from Innovative Research Inc. (Southfield, MI, USA). The samples were registered as healthy human subjects. Before shipping, each blood sample was tested according to FDA guidelines for the detection of hepatitis B surface antigen, antibodies to HIV, antibodies to hepatitis C, HIV-1 RNA, hepatitis C RNA and syphilis. All units yielded non-reactive/negative results for each test performed. The subjects were divided equally between men and women and 60% of the samples were white, 20% were African American and 20% were Hispanic and other races. The distribution of sample by age, sex and race attempted to reflect the distribution of the healthy adult population in the United States.

Proteins and chemicals

BPA, HSA, bovine serum albumin, MBP and MOG were all purchased from Sigma Aldrich (St. Louis, MO, USA), and PDI was purchased from BioSynthesis (Lewisville, TX, USA) to develop antigen-coated enzyme-linked immunosorbent assay (ELISA) plates.

Preparation of bisphenol A binding to human serum albumin

Preparation of BPA bound to HSA (BPA) was conducted by measuring 1 g of HSA that was dissolved in 100 ml of 0.01 M phosphate-buffered saline (PBS) pH 7.4, to which 40 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCL was added and kept on the stirrer for 10 min. In a separate tube, 100 mg of N-hydroxysulfosuccinimide sodium salt was dissolved in 10 ml distilled water and was added dropwise to the mixture. One hundred milligrams each of BPA was dissolved in 10 ml of 0.01 M PBS pH 7.4, each was separately added dropwise to the protein mixture. The mixtures were kept for 1 h at room temperature and then 4 h at 4°C. The unreacted small molecules were removed by dialysis using a molecular cutoff of 8 kDa. Conjugation of BPA binding to HSA was confirmed by sodium dodecyl sulfate gel electrophoresis and shift in band configuration. In addition, spectrographic analysis of the conjugate was undertaken until there was an increase in absorption from 230 to 260 nm that indicated that BPA was covalently linked to the HSA or to a protein carrier.

Preparation for enzyme-linked immunosorbent assay

BPA, PDI, MBP and MOG were dissolved in PBS at a concentration of 1.0 mg ml⁻¹, then diluted 1: 100 in 0.1 M carbonate–bicarbonate buffer, pH 9.5 and 100 μl were added to each well of a polystyrene flat bottom ELISA plate. Plates were washed with 1% HSA-TBS and then washed three times with 200 μl Tris-buffered saline (TBS) containing 0.05% Tween 20, pH 7.4. The non-specific binding of immunoglobulins was prevented by adding a mixture of 1.5% BSA and 1.5% gelatin in TBS, and incubation overnight at 4°C. Plates were washed as described above, and then serum samples diluted 1: 100 in 0.1 M PBS Tween containing 2% BSA were added to duplicate wells and incubated for 1 h at room temperature. Sera from patients with neuroimmune disorders, with known high titers of antibodies, were used as positive controls. Plates were washed and then alkaline phosphatase goat antihuman IgG, IgM or IgA F (ab)2 fragments (KPI, Gaithersburg, MD, USA) optimal dilution of 1: 400–1: 2000 in 1% HSA-TBS was added to each well; plates were incubated for an additional 1 h at room temperature. After washing five times with TBS-Tween buffer, the enzyme reaction was started by adding 100 μl of paranitrophenylphosphate in 0.1 ml diethanolamine buffer 1 mg ml⁻¹ containing 1 mM MgCl₂ and sodium azide, pH 9.8. The reaction was stopped 45 min later with 50 μl of 1 N NaOH. The optical density was read at 405 nm by means of a microtiter reader. To detect non-specific binding, several control wells contained all reagents except human serum, or wells were coated with different tissue antigens, such as liver.
and kidney. Human serum and all other reagents were added and used in each assay.

Statistical analysis
Statistical analysis was performed to study the relationships of BPA, PDI, MBP and MOG. Analysis was conducted separately for three immunoglobulins: IgG, IgA and IgM. The determination of the presence of statistically significant correlative relationships was conducted with Pearson’s coefficients, Kendall’s tau and Spearman’s rho. These measures are invariant to any monotonic transformation. A standard $P$ value of 0.05 and a confidence interval of 95% were used. Correlative analysis and the magnitude of the relationship were reported. STATA software package was used to conduct all inferential and descriptive analysis.

Results
Using ELISA we measured the levels of IgA, IgG and IgM antibodies against BPA-HSA and PDI in serum to identify any relationship between these antibodies with MBP and MOG antibodies. Descriptive statistical analysis is summarized for immunoglobulins A, G and M separately with scatter matrix plots to demonstrate optical density outcomes of ELISA results with expression measured at 405 nm. Correlative analysis relationship is presented as scatter plots. Pearson’s, Kendall’s tau and Spearman’s rho correlations coefficients are listed to identify the coefficient of determination.

Relationship between bisphenol A-human serum albumin and protein disulfide isomerase
Two-way scatter plot evaluation for BPA-HSA and PDI for IgA, IgG and IgM immune reactivity all demonstrate a strong positive monotonic relationship (Fig. 1). Statistical analysis using Pearson’s correlation coefficient, Kendall tau rank correlation and Spearman’s rank correlation were both highly statistically significant ($P < 0.0001$). Pearson’s correlation coefficient for IgA demonstrated a moderate correlation of 0.62. Kendall tau rank correlation for IgA demonstrated a weak correlation of 0.37. Spearman’s rank correlation for IgA demonstrated a moderate correlation of 0.53. Pearson’s correlation coefficient for IgG demonstrated a substantial positive correlation of 0.82. Kendall tau rank correlation for IgG demonstrated a moderate correlation of 0.58. Spearman’s rank correlation for IgG demonstrated a substantial correlation of 0.78. Pearson’s correlation coefficient for IgM demonstrated a substantial correlation of 0.89. Kendall tau rank correlation for IgM demonstrated a moderate correlation of 0.68. Spearman’s rank correlation for IgM demonstrated a substantial correlation of 0.86.

Relationship between bisphenol A-human serum albumin and myelin basic protein
The two-way scatter plot evaluation for BPA-HSA and MBP for IgA immune reactivity demonstrates a weak positive relationship (Fig. 2). Pearson’s correlation coefficient for IgA immune reactivity for BPA-HSA and MBP is minimally statistically significant ($P = 0.01$) with a weak correlation of 0.25. Kendall tau rank correlation for IgA immune reactivity for BPA-HSA and MBP is statistically significant ($P = 0.003$) with a weak correlation of 0.24. Spearman’s rank correlation coefficient for IgA immune reactivity for BPA-HSA and MBP is statistically significant ($P = 0.003$) with a weak correlation of 0.30.

The two-way scatter plot evaluation for BPA-HSA and MBP for IgG and IgM immune reactivity demonstrates a strong positive monotonic relationship (Fig. 2). Statistical analysis using Pearson’s correlation coefficient, Kendall tau rank correlation and Spearman’s rank correlation were both highly statistically significant ($P < 0.0001$). Pearson’s correlation coefficient for IgG demonstrated a weak correlation of 0.45. Kendall tau rank correlation for IgG demonstrated a moderate correlation of 0.58. Spearman’s rank correlation for IgG demonstrated a moderate correlation of 0.61. Pearson’s correlation coefficient for IgM demonstrated a substantial correlation of 0.92. Kendall tau rank correlation for IgM demonstrated a moderate correlation of 0.67. Spearman’s rank correlation for IgM demonstrated a substantial correlation of 0.86.
Relationship between bisphenol A-human serum albumin and myelin oligodendrocyte glycoprotein

The two-way scatter plot evaluation for BPA-HSA and MOG for IgA, IgG and IgM immune reactivity demonstrates a positive monotonic relationship (Fig. 3). Statistical analysis using Pearson's correlation coefficient, Kendall tau rank correlation and Spearman's rank correlation were all highly statistically significant \((P < 0.0001)\). Pearson's correlation coefficient for IgA demonstrated a moderate correlation of 0.60. Kendall tau rank correlation for IgA demonstrated a weak correlation of 0.29. Spearman's rank correlation coefficient for IgA demonstrated a weak correlation of 0.44. Pearson's correlation coefficient for IgG demonstrated a moderate correlation of 0.58. Kendall tau rank correlation for IgG demonstrated a weak correlation of 0.45. Spearman's rank correlation for IgG demonstrated a moderate correlation of 0.61. Pearson's correlation coefficient for IgM demonstrated a substantial correlation of 0.92. Kendall tau rank correlation for IgM demonstrated a moderate correlation of 0.67. Spearman's rank correlation coefficient for IgM demonstrated a substantial correlation of 0.86.

Relationship between protein disulfide isomerase and myelin basic protein

The two-way scatter plot evaluation for PDI and MBP for IgA immune reactivity demonstrates a moderate positive correlation (Fig. 4). Pearson's correlation coefficient for PDI and MBP is not statistically significant \((P = 0.09)\). Kendall tau rank correlation for PDI and MBP is minimally statistically significant \((P = 0.04)\) with a weak correlation of 0.16. Spearman's rank correlation coefficient for PDI and MBP is minimally statistically significant \((P = 0.03)\) with a weak correlation of 0.22.

The two-way scatter plot evaluation for PDI and MBP for IgG and IgM immune reactivity demonstrates a strong positive monotonic correlation (Fig. 4). Statistical analysis using Pearson's correlation coefficient, Kendall tau rank correlation and Spearman's rank correlation were all highly statistically significant \((P < 0.0001)\). Pearson's correlation coefficient for IgG demonstrated a moderate correlation of 0.66. Kendall tau rank correlation for IgG demonstrated a moderate correlation of 0.50. Spearman's rank correlation coefficient for IgG demonstrated a moderate correlation of 0.69. Pearson's correlation coefficient for IgM demonstrated a substantial correlation of 0.77. Kendall tau rank correlation for IgM demonstrated a moderate correlation of 0.63. Spearman's rank correlation coefficient for IgM demonstrated a substantial correlation of 0.82.

Relationship between protein disulfide isomerase and myelin oligodendrocyte glycoprotein

The two-way scatter plot evaluation for PDI and MOG for IgA, IgG and IgM immune reactivity demonstrates a strong positive monotonic correlation (Fig. 5). Statistical analysis using Pearson's correlation coefficient, Kendall tau rank correlation and
Spearman's rank correlation were all highly statistically significant ($P < 0.0001$). Pearson's correlation coefficient for IgA demonstrated a substantial correlation of 0.83. Kendall tau rank correlation for IgA demonstrated a moderate correlation of 0.66. Spearman's rank correlation coefficient for IgA demonstrated a substantial correlation of 0.85. Pearson's correlation coefficient for IgG demonstrated a moderate correlation of 0.64. Kendall tau rank correlation for IgG demonstrated a weak correlation of 0.49. Spearman's rank correlation coefficient for IgG demonstrated a moderate correlation of 0.65. Pearson's correlation coefficient for IgM demonstrated a substantial correlation of 0.91. Kendall tau rank correlation for IgM demonstrated a substantial correlation of 0.75. Spearman's rank correlation coefficient for IgM demonstrated a substantial correlation of 0.91.

**Discussion**

Autoimmunity is a growing epidemic that afflicts between 7 and 10% of the world's population (National Institutes of Health, 2005). Chemicals have been identified as potential triggers that elicit and perpetuate autoimmune disease, according to systemic review and meta-analysis of the literature (Barragán-Martínez et al., 2012). Based on the 2003–2004 National Health and Nutrition Examination Survey conducted by the Centers for Disease Control and Prevention, detectable levels of BPA were found in 93% of 2517 urine samples from tested subjects 6 years of age and older. A current review of the literature shows limited research on the autoimmune impact of BPA with humans.

In one of our previous publications we demonstrated that BPA can bind to human albumin, leading to potentially new immune reactive epitopes, resulting in the production of IgG and IgM antibodies in 13% (IgG) and 15% (IgM) of random human blood donors (Vojdani et al., 2015). In this current study, we attempted to correlate IgA, IgG and IgM immune reactivity between the BPA-HSA antibody, its target protein (PDI) and the neural antigens MBP and MOG, known targets of brain autoimmunity. We found weak-to-high degrees of correlation between the levels of IgM, IgG and IgA antibodies against BPA-HSA with PDI, MBP and MOG antibodies (see Table 1). The most significant correlation was shown by the IgM antibodies. Earlier studies have established that immune response to haptenic chemicals results in the production of more IgM antibodies than IgG or IgA (del Guercio et al., 1974; Onoue et al., 1965). This is in agreement with our own very significant IgM results for BPA-HSA to PDI (0.89), BPA-HSA to MBP (0.83), BPA-HSA to MOG (0.92), PDI to MBP (0.77) and PDI to MOG (0.91). The IgG antibody levels were the second most significant, with IgA being the least insignificant.

**Table 1.** Pearson's correlation between IgA, IgG and IgM antibodies against BPA, PDI, MBP and MOG

|                | IgA | IgG | IgM |
|----------------|-----|-----|-----|
| BPA to PDI     | 0.62| 0.82| 0.89|
| BPA to MBP     | 0.25| 0.85| 0.83|
| BPA to MOG     | 0.60| 0.58| 0.92|
| PDI to MBP     | –   | 0.66| 0.77|
| PDI to MOG     | 0.83| 0.64| 0.91|
| BPA, bisphenol A; MBP, myelin basic protein; MOG, myelin oligodendrocytic glycoprotein; PDI, protein disulfide isomerase. |

Although there are many other neuron-specific antigens, for this study we specifically focused on MBP and MOG. These myelin proteins are the immunological target site for neuroinflammation and neurological autoimmune diseases, and are directly associated with disease such as neuropathy and multiple sclerosis (Correale & Tenenbaum, 2006; Mir et al., 2015; Vassall et al., 2015).

Anti-MBP and anti-MOG were found in 78.5% of autistic children and were insignificant in normal subjects (Mostafa & Al-Ayadhi, 2013). A recent publication found that metabolomics analysis showed the correlation between metabolite concentrations and total BPA was three times greater with subjects diagnosed with autism spectrum disorder than the controls, and the number of absolute partial correlations for percentage bound BPA was 15 times higher with autism spectrum disorder (Stein et al., 2015). Anti-MBP were also found significantly higher in 100 mothers of children with autistic disorder compared to 100 age-matched unaffected children, leading to the possibility that there may be placental transfer of maternal antibodies in autism (Singer et al., 2008). Besides autism, anti-MOG and anti-MBP are key serum biomarkers to identify multiple sclerosis and have been found to be key predictive biomarkers for identifying future demyelinating events after onset of the disease (Berger et al., 2003).

In acute autoimmune inflammatory conditions, there is evidence that anti-MOG and anti-MBP are also found in chronic neurodegenerative disease. One study found increasing anti-MBP levels in patients with Parkinson's disease; anti-MBP may be a valuable marker to monitor the progression of the disease (Papuc et al., 2014). This study found that between 4 and 9% of our healthy serum samples demonstrated elevations of MBP and MOG that may predict future disease process and determine active neuroinflammation. This percentage was irrespective of any demographic consideration.

The outcome of our study indicates that IgM immune reactivity to BPA-HSA and PDI, MBP and MOG has a high degree of statistical significance. This suggests that BPA may be a trigger for the production of antibodies against PDI, MBP and MOG. How were these antibodies generated in a subgroup of healthy subjects? One possibility is that our subject individuals with high levels of antibodies may have had disruptions of the blood–brain barrier, which can be affected by stress, toxic chemicals or other factors in the environment, causing the release of PDI, MBP and MOG into the blood, where BPA was able to bind to them (Abdel-Rahman et al., 2002; Seelbach et al., 2010). We acknowledge that our study has limitations, as the measured levels of BPA-HSA antibodies and their co-occurrence with PDI, MBP and MOG antibodies in the blood only provide indirect evidence for BPA being the cause of the production of these antibodies. This study, therefore, does not provide any direct proof of BPA binding to PDI, MBP or MOG in the brain. We also acknowledge that while BPA has been previously detected in the urine, blood and tissue of the majority of the population, we have no information on the chemical exposure of our purportedly healthy subjects. Whereas this was not the objective of this study, proof of the penetration of the blood–brain barrier by BPA and its subsequent binding to brain proteins would be useful information for the diagnosis or prevention of neurological and autoimmune diseases, and merits further research. It is recommended that individuals with high levels of antibodies against BPA-HSA, PDI, MBP and MOG should be monitored for many years to determine whether these antibodies have any pathological roles in neuroautoimmune disorders.
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Conflict of interest
The authors did not report any conflict of interest.

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