Neurochemical impact of bisphenol A in the hippocampus and cortex of adult male albino rats

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Abstract
Bisphenol A (BPA), an endocrine-disrupting chemical, is widely used in the manufacture of polycarbonated plastics and epoxy resins and line metal beverage cans. Growing evidence suggests that BPA acts directly on neuronal functions as it is lipophilic and could accumulate in the brain. The present study aims to investigate the effect of two doses of BPA (10 mg/kg for 6 and 10 weeks and 25 mg/kg for 6 weeks) on excitatory (glutamate and aspartate) and inhibitory (γ-aminobutyric acid, glycine, and taurine) amino acid neurotransmitter levels in the cortex and hippocampus. This study extends to investigate the effect of BPA on acetylcholinesterase (AchE) activity and some oxidative stress parameters in the two regions. In the cortex, a significant increase in the excitatory and a significant decrease in the inhibitory amino acids occurred after BPA (10 mg/kg for 10 weeks and 25 mg/kg for 6 weeks). This was accompanied by a significant increase in lipid peroxidation, nitric oxide, and reduced glutathione after 6 weeks of BPA (25 mg/kg). In the hippocampus, a significant increase in the excitatory and inhibitory amino acid neurotransmitters occurred after 6 weeks of BPA. Hippocampal lipid peroxidation increased significantly after BPA exposure and hippocampal reduced glutathione increased significantly after 6 weeks of BPA exposure (10 mg/kg). BPA induced a significant increase in cortical and hippocampal AchE activity. The present neurochemical changes in the cortex and hippocampus suggest that BPA induced a state of excitotoxicity and oxidative stress. This may raise concerns about the exposure of humans to BPA due to its wide applications in industry.

Keywords
Bisphenol A, amino acid neurotransmitters, oxidative stress, cortex, hippocampus, rat

Introduction
Bisphenol A (BPA), an endocrine-disrupting chemical, is an environmental toxicant that has become an issue of controversy. BPA is widely used as an additive during the manufacture of polycarbonated plastics and water bottles. It is also a key ingredient in the manufacture of epoxy resins that are used as dental sealants and more importantly to line metal beverage cans (Kubwabo et al., 2009). BPA from polycarbonated bottles leaches into water at rates ranging from 0.2 to 0.79 ng/h and boiling water increases these rates up to 55 folds (Le et al., 2008).

Most studies on BPA focus on reproductive toxicity as an end point, as BPA is a well-known endocrine disruptor. BPA is an estrogen agonist that binds to both classical nuclear receptors, estrogen receptor α (ERα) and ERβ. It has been suggested that exposure to low doses of BPA might interfere with normal estrogenic signaling (Welshons et al., 2006). Recently, several investigations were carried out to explore the neurotoxic effects of BPA. They showed that BPA causes persistent aberrations in

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spontaneous behavior and in learning and memory in rodents (Yu et al., 2011). Moreover, it has been reported that BPA induces synaptic remodeling in the nervous system and affects the development of higher cognitive functions (Hajszan and Leranth, 2010).

BPA can penetrate the blood–brain barrier (Sun et al., 2002). It has been reported to induce hippocampal neuron apoptosis by increasing oxidative stress and altering microtubule associated regulatory kinase (MARK) signaling (Lee et al., 2008). Obata and Kubota (2000) reported that BPA increased hydroxyl radical formation in rat striatum in an examination using in vivo microdialysis. Pathological conditions induced by BPA may be causally related to the generation of reactive oxygen species and free radical generated by BPA metabolism and/or ER-mediated systems (Kabuto et al., 2003). The study of Kim et al. (2011) showed that BPA has a neurotoxic effect on hippocampal neurogenesis and causes behavioral deficits. Moreover, growing evidence suggests that BPA acts directly on neuronal functions within the central nervous system (CNS), as it is lipophilic and can easily accumulate in the brain where it modifies the activity of neuronal pathways and/or centers involved in nociception and pain (Choi et al., 2007).

Nakamura et al. (2010) reported that BPA disturbs monoamine neurotransmitter levels in certain areas of adult mouse brain, thereby inducing morphological and molecular changes. It is most likely that prenatal and neonatal exposures to BPA induce other behavioral abnormalities associated with alteration of not only the dopaminergic system but also other neurotransmitters (Miyagawa et al., 2007). The authors found that prenatal and neonatal exposure not only to high dose (2 mg/g diet) but also to low dose (30 ng/g diet) of BPA dramatically decreases cholinergic transmission in adult brain, resulting in learning and memory deficits. Several studies have suggested that some neurotransmitter systems such as somatostatin and γ-aminobutyric acid (GABA) are linked to the predominant estrogenic effects of BPA in developing brain (Choi et al., 2007; Facciolo et al., 2005).

L-Glutamate and GABA are the principal excitatory and inhibitory neurotransmitters in the CNS, respectively. Glutamate plays an important role in several physiological functions including learning, memory, and developmental plasticity and it has been implicated in a variety of neurodegenerative disorders (Brann and Mahesh, 1995; Riedel et al., 2003). Glutamate is involved in critical reproductive and endocrine events such as puberty, gonadotropin pulsatility, and preovulatory gonadotropin surge and reproductive behavior (Brann and Mahesh, 1994; Dhandapani and Brann, 2000). It may also participate in reproductive decline associated with aging (Dhandapani and Brann, 2000).

Since glutamate excitotoxicity is linked to the influx of calcium and generation of free radicals and thus the state of oxidative stress, the aim of the present study was to investigate the effect of two doses of BPA (10 and 25 mg/kg) on both excitatory and inhibitory amino acid neurotransmitters in the cortex and hippocampus of adult male albino rats. This work also extended to clarify the link between the state of oxidative stress induced by BPA and the changes in amino acid neurotransmitters and acetylcholinesterase (AchE) activity. Although these doses are 10-fold greater than what we are exposed to due to leaching of BPA from plastics, they may be reached in brain tissues by accumulation during lifetime.

Materials and methods

Animals

Adult male Wistar albino rats weighing 120–180 g (5 ± 0.5 months old) were used as experimental animals. The animals were obtained from the animal house of the National Research Center (Cairo, Egypt). They were maintained on stock diet and kept under fixed appropriate conditions of housing and handling. They were kept at a room temperature of 25 ± 2°C and relative humidity of 60 ± 5%. All experiments were carried out in accordance with the research protocols established by the Animal Care Committee of the National Research Center (Cairo, Egypt), which follows the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Chemicals

Pure BPA powder was purchased from Sigma Aldrich (St Louis, Missouri, USA) and suspended in distilled water. Absolute ethyl alcohol, triethylamine, sulfanilamide, N-(1-naphthylethylene) diamine, thiobarbituric acid, perchloric acid, and trichloroacetic acid were also obtained from Sigma Aldrich. In addition, acetylthiocholine iodide, 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), glutathione, ethylenediaminetetraacetic acid, and phosphate buffers were purchased from Sigma Aldrich. Analytical-grade lithium carbonate, dansyl chloride, glacial acetic acid, and high-performance
liquid chromatography (HPLC)-grade acetonitrile were obtained from Fisher (UK). Free amino acids for standard and HPLC-grade methanol were purchased from BDH (England).

**Experimental design**

A total of 40 animals were divided randomly into 4 groups. Group 1 served as control and received an oral administration of distilled water throughout the experimental period. Animals of groups 2 and 3 received an oral administration of 10 mg/kg of BPA for 6 and 10 weeks, respectively. In group 4, rats were administered orally with 25 mg/kg of BPA for 6 weeks. The doses of BPA were administered five times a week. The higher dose of BPA (25 mg/kg) in this study was chosen on the basis of previous studies (Bian et al., 2006; Richter et al., 2007).

**Handling of tissue samples**

Both treated and control animals were killed 1 h after the last injection after being fasted. A group of the control animals were killed with the treated animals after each time segment. After decapitation, the brain of each animal was transferred rapidly to an ice-cold petri dish where it was dissected to remove the hippocampus and cortex. The brain samples were divided into two equal halves, weighed and kept at −58°C until analyzed. The left half of each brain sample was homogenized in 5% w/v 20 mM phosphate buffer, pH 7.6, centrifuged, and used for the analysis of AchE activity and the levels of malondialdehyde (MDA) as a measure of lipid peroxidation, reduced glutathione (GSH) and nitric oxide (NO). The right half of each brain area was homogenized in 75% ethyl alcohol, centrifuged, and used for the determination of amino acid neurotransmitters.

**Determination of lipid peroxidation**

Lipid peroxidation was assayed in both the hippocampus and cortex by measuring the thiobarbituric acid reactive substances according to the method of Ruiz-Larrea et al. (1994). Thiobarbituric acid reactive substances react with thiobarbituric acid to produce a red-colored complex having peak absorbance at 532 nm. The color was analyzed in a Helios Alpha ultraviolet–visible spectrophotometer (Thermo Spectronic, England).

**Determination of GSH**

GSH was determined by Ellman’s method (1959). The procedure is based on the reduction of Ellman’s reagent by –SH groups of GSH to form 2-nitro-mercaptobenzoic acid. The nitromercaptobenzoic acid anion has an intense yellow color which was measured spectrophotometrically at 412 nm. GSH concentration was calculated by comparison with a standard curve (range from 1 to 6 mmol).

**Determination of NO level**

NO levels, measured as nitrite, were determined using Griess reagent according to the method of Moshage et al. (1995), where nitrite, a stable end product of the NO radical, is primarily used as an indicator for the production of NO. Nitrite is converted to a deep purple azo compound after the addition of Griess reagent. The purple/magenta color developed was read at 540 nm. The quantity was measured by standard curve.

**Determination of AchE activity**

The procedure used for the determination of AchE activity was a modification of the method of Ellman et al. (1961), as described by Gorun et al. (1978). The principle of the method is based on the hydrolysis of acetylthiocholine iodide (substrate) by AchE to produce thiocholine. Thiocholine is allowed to react with the –SH reagent DTNB, which is reduced to thionitrobenzoic acid, a yellow-colored anion whose absorption was read immediately at 412 nm.

**Determination of amino acid concentrations**

The quantitative determination of the amino acids (glutamate, aspartate, glutamine, GABA, glycine, and taurine) was carried out by the HPLC method employed by Márquez et al. (1986). Dansyl derivatization was carried out according to the method of Tapuhi et al. (1981) using 2-aminobutyric acid as an internal standard. The optimization of the dansyl conditions was described by Kang et al. (2006).

The HPLC system consisted of a Wellchrom Mini-star K-501 pump (Knauer, Germany), a column thermostat 5°–85°C with a 20-μl loop injector (Knauer, Germany), a Luna 5 μm -18 reversed-phase column (5 μm particle size, 150 × 4.6 mm² inner diameter) from Phenomenex (Torrance, California, USA), a Wellchrom spectrophotometer K-2600 with variable wavelength (Knauer, Germany), and a chromatography workstation (Eurochrom 2000 Software). The
Table 1. Effect of BPA (10 mg/kg for 6 and 10 weeks and 25 mg/kg for 6 weeks) on cortical amino acid neurotransmitter levels (μmol/g).a

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>BPA for 6 weeks (10 mg/kg)</th>
<th>%D</th>
<th>BPA for 10 weeks (10 mg/kg)</th>
<th>%D</th>
<th>BPA for 6 weeks (25 mg/kg)</th>
<th>%D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine</td>
<td>5.269 ± 0.135b (6)</td>
<td>4.659 ± 0.087c (6)</td>
<td>-11.58</td>
<td>4.687 ± 0.112c (6)</td>
<td>-11.05</td>
<td>4.720 ± 0.140c (6)</td>
<td>-10.42</td>
</tr>
<tr>
<td>Glutamate</td>
<td>6.521 ± 0.161b (5)</td>
<td>6.516 ± 0.147b (6)</td>
<td>-0.07</td>
<td>7.547 ± 0.164c (6)</td>
<td>15.73</td>
<td>7.375 ± 0.203c (6)</td>
<td>13.09</td>
</tr>
<tr>
<td>Aspartate</td>
<td>4.666 ± 0.101b (5)</td>
<td>4.754 ± 0.133b (6)</td>
<td>1.88</td>
<td>5.111 ± 0.090b (5)</td>
<td>9.54</td>
<td>5.245 ± 0.065c (5)</td>
<td>12.41</td>
</tr>
<tr>
<td>GABA</td>
<td>2.296 ± 0.076b (5)</td>
<td>2.319 ± 0.070b (6)</td>
<td>1.00</td>
<td>2.133 ± 0.035c (7)</td>
<td>-7.09</td>
<td>2.022 ± 0.026c (7)</td>
<td>-11.93</td>
</tr>
<tr>
<td>Glycine</td>
<td>1.721 ± 0.025b (5)</td>
<td>1.789 ± 0.053b (6)</td>
<td>3.95</td>
<td>1.466 ± 0.051c (6)</td>
<td>-14.82</td>
<td>1.376 ± 0.067c (6)</td>
<td>-20.04</td>
</tr>
<tr>
<td>Taurine</td>
<td>3.875 ± 0.243b (6)</td>
<td>3.837 ± 0.053b (5)</td>
<td>-0.98</td>
<td>3.415 ± 0.058b (6)</td>
<td>-11.87</td>
<td>3.016 ± 0.092c (5)</td>
<td>-22.17</td>
</tr>
</tbody>
</table>

BPA: bisphenol A; GABA: γ-aminobutyric acid.
aValues represent mean ± SE with the number of animals in parentheses. % D: % difference with respect to control values. Different letters indicate significantly different means p < 0.05. Same letters indicate nonsignificant changes.

The data were expressed as means ± SEM. Data were analyzed by analysis of variance (ANOVA), followed by Tukey’s multiple range test when the F test was significant (p < 0.05). All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) software in a compatible computer. The percentage difference (%D) was calculated as follows:

\[
% D = \left( \frac{\text{Treated value} - \text{Control value}}{\text{Control value}} \right) \times 100.
\]

Results

Table 1 shows the effects of the exposure of male albino rats to different doses of BPA (10 mg/kg for 6 and 10 weeks and 25 mg/kg for 6 weeks, five times a week) on the levels of amino acid neurotransmitters in the cortex of albino rats. The present study revealed that the two control groups at 6 and 10 weeks showed similar results in all the tested parameters. They were thus presented as one group. In the present study, ANOVA revealed significant differences between the three groups of BPA-treated rats and the control group in the analyzed amino acids in the cortex of rats. When rats of group 2 were treated with BPA (10 mg/kg) for 6 weeks, the cortical amino acid neurotransmitters showed nonsignificant changes, except for glutamine that revealed a significant decrease below the control value. The oral administration of BPA (10 mg/kg, five times a week) for 10 weeks (group 3) resulted in a significant decrease in cortical glutamine, GABA, and glycine, whereas a significant increase occurred in glutamate and aspartate levels in comparison with group 1 control rats.

The oral treatment of rats of group 4 with BPA (25 mg/kg) for 6 weeks induced a significant decrease (p < 0.05) in the cortical levels of glutamine, GABA, glycine, and taurine as compared to group 1 control animals. However, glutamate and aspartate showed a significant increase (p < 0.05).

As indicated in Table 2, there were significant differences in the levels of amino acid neurotransmitters in the hippocampus between the different groups of rats.

The treatment of group 2 with BPA (10 mg/kg) for 6 weeks resulted in a significant increase in the levels of the hippocampal excitatory and inhibitory amino acid neurotransmitters above the corresponding group 1 control values. Similarly, rats treated with BPA (25 mg/kg) for 6 weeks (group 4) showed a significant increase in the hippocampal excitatory and inhibitory amino acid neurotransmitters and glutamine above the control values (group 1).

However, nonsignificant changes were recorded in rats of group 3 treated with BPA (10 mg/kg) for 10 weeks.

Figure 1 shows the effect of the oral administration of BPA to different groups of rats on the levels of...
GSH, NO, and MDA in the cortex and hippocampus of rats.

The present findings revealed significant differences in cortical GSH, NO, and MDA levels among groups of animals treated with BPA and control group. When rats were treated with BPA (10 mg/kg), nonsignificant changes in GSH, NO, and MDA levels were recorded. However, rats treated with 25 mg/kg of BPA for 6 weeks (group 4) showed a significant increase in cortical GSH, NO, and MDA levels over control values.

In the hippocampus of rats of different groups (groups 1 to 4), ANOVA revealed significant differences in GSH and MDA levels.
In rats treated with 10 mg/kg of BPA (groups 2 and 3), a significant increase in MDA was evident in the hippocampus of both groups after 6 and 10 weeks, and in GSH levels after 6 weeks (group 3) only as compared to group 1. The oral administration of 25 mg/kg for 6 weeks (group 4) increased hippocampal MDA by 33.81% (p < 0.05) over group 1 control values. However, a nonsignificant decrease in GSH and NO levels occurred.

Moreover, ANOVA revealed significant differences in cortical and hippocampal AchE activity between groups of rats treated with BPA and control group (Figure 2).

A significant increase in cortical AchE activity occurred in all animal groups after the oral administration of BPA, 10 mg/kg for 6 and 10 weeks and 25 mg/kg for 6 weeks, recording 19.47, 46.85, and 41.14% in groups 2, 3, and 4 above group 1 control values, respectively.

Hippocampal AchE activity also showed a significant increase over control after the treatment of rats with BPA, 10 mg/kg (group 2) and 25 mg/kg (group 4), for 6 weeks.

**Discussion**

Humans are widely exposed to endocrine-disrupting chemicals, including BPA which is probably accumulated in lifetime. BPA penetrates the blood–brain barrier (Sun et al., 2002) and could easily accumulate in the brain (Choi et al., 2007).

In the present study, the similarity between the effects of 25 mg/kg for 6 weeks with 10 mg/kg for 10 weeks indicates that BPA has accumulating effects. This in turn may raise the level of warning from the exposure to low levels of BPA during lifetime.

The present data revealed that the cortical and hippocampal changes in amino acid neurotransmitters recorded after BPA administration were accompanied by a state of oxidative stress. This was indicated from the significant increase in lipid peroxidation and NO level in the cortex after 6 weeks of exposure to BPA (25 mg/kg) and lipid peroxidation in the hippocampus after exposure to BPA. The significant increase in the cortical and hippocampal GSH level may represent a compensatory mechanism to mitigate the state of oxidative stress induced by BPA, as GSH is the most important freely available antioxidant (Circu and Aw, 2008). No significant changes were observed in the cortical oxidative stress markers after the lowest dose of BPA (10 mg/kg for 6 and 10 weeks).

The brain is particularly sensitive to oxidative damage, this is because it has a high concentration of unsaturated lipids as well as a high rate of oxidative metabolism (Dringen et al., 2005). It has been suggested that BPA can cause oxidative stress that generates highly reactive membrane toxic intermediates in the brain (Aydoğan et al., 2008). In addition, the brain contains a large amount of phospholipid side chains having a tendency to peroxidation by oxygen-free radicals.

Reactive oxygen metabolites such as hydroxyl radicals, peroxide anions, peroxyl radicals, and hydrogen peroxide are cytotoxic agents, as they cause significant oxidative damage by attacking biomolecules such as membrane lipids, DNA, and proteins in cells (Kabuto et al., 2003). This may explain the significant increase in lipid peroxidation induced by BPA in the present study.

The significant increase in the excitatory amino acids following the exposure to BPA (25 mg/kg for 6 weeks), which was accompanied by a significant decrease in the inhibitory amino acids may result in cortical excitotoxicity. Both glutamate and aspartate stimulate N-methyl-d-aspartate (NMDA) receptors and their prolonged depolarization induces a massive influx of calcium (Ca^{2+}) ions. Prolonged elevation of Ca^{2+} ions is thought to initiate a complex cascade of intracellular events that lead to destruction of neurons (Weber, 2012).

Therefore, the increase in the content of cortical and hippocampal excitatory amino acid neurotransmitters after BPA exposure could underlie the

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**Figure 2.** Effect of BPA (10 mg/kg for 6 and 10 weeks and 25 mg/kg for 6 weeks) on AchE activity in the cortex and hippocampus of rats: ■ control, □ BPA 10 mg/kg for 6 weeks, ● BPA 10 mg/kg for 10 weeks, and ▪ BPA 25 mg/kg for 6 weeks. *Significant change from control. BPA: bisphenol A; AchE: acetylcholinesterase.
generation of reactive oxygen species and inhibition of neuronal progenitor cells and cell death.

Although the exposure of rats to BPA (10 mg/kg for 10 weeks) induced a significant increase in cortical glutamate and aspartate accompanied by a significant decrease in GABA and glycine, there were no changes in cortical oxidative stress markers. It could be suggested that these changes in amino acid neurotransmitters may represent the onset of effects and need to be followed up.

The hippocampus compared to other areas of the brain is characterized by small extracellular space (Green et al., 1970). The limited extracellular space would result in a rapid buildup of extracellular concentrations of potassium ions seen during repetitive neuronal firing, inducing a reduction in neuronal membrane potential, thus increasing neuronal excitability (Fisher et al., 1976). This may explain the rapid effects in amino acid neurotransmitters and oxidative stress markers seen in the hippocampus after 6 weeks of exposure to BPA (10 mg/kg). However, in the hippocampus, the significant increases in the excitatory amino acid neurotransmitters were accompanied by significant increases in the inhibitory amino acids GABA and glycine. This may reflect an attempt to counteract the increased excitability in this particular area. The recovery of the amino acid neurotransmitter levels after 10 weeks of BPA (10 mg/kg) supports this suggestion. However, this attempt did not prevent the damaging effects of the generated free radicals as evident from the increased lipid peroxidation levels obtained after 10 weeks of exposure to BPA (10 mg/kg).

Supporting our findings is the study of Tanabe et al. (2012) who stated that BPA may reach the brain and accumulate without detoxification as judged from no significant conversion of 3H-BPA to other metabolites. Our results are consistent with a significant level of BPA accumulated in the hippocampus of adult male rats.

NMDA receptors, a subtype of glutamate receptor, play a crucial role for normal brain functions. BPA markedly inhibited the expressions of NMDA subunits in the hippocampus of male offspring during postnatal developmental stage and adulthood (Xu et al., 2010). This reported inhibition in the expression of NMDA receptors may be a strategy by which the brain attempts to minimize the state of excitotoxicity induced by BPA as evident from the present data.

BPA has been implicated as an endocrine-disrupting chemical due to its ability to mimic the action of endogenous estrogenic hormones (Paris et al., 2002). Estradiol increased the concentration of glutamate in the arculate nucleus (Blutstein et al., 2009). It could also modulate glutamatergic neurotransmission in various brain regions (Yokomaku et al., 2003) where it increases excitability.

Although the affinity of ERα for BPA is very week (Kuiper et al., 1997), estrogen-related receptor γ is a high-affinity binding protein for BPA (Takayanagi et al., 2006). It has been reported that blocking NMDA receptors by MK-801 abolishes the enhancing effects of estradiol and BPA (Ogiue-Ikeda et al., 2008).

Hence, the increase in the excitatory amino acids in the hippocampus and cortex could be attributed to an endocrine mechanism through the action of BPA on estrogen and estrogen-related receptors (estradiol-like effect).

It has been found that cholinergic fibers were dramatically decreased in several hippocampal regions of mice prenatally and neonatally exposed to low and high doses of BPA (Miyagawa et al., 2007). The authors suggested that chronic exposure to BPA could induce memory impairment associated with reduction in acetylcholine production in the hippocampus. The decrease in acetylcholine could also be attributed to the elevated activity of AchE recorded in the present study as AchE is the enzyme responsible for the breakdown of acetylcholine.

Viberg and Lee (2012) showed that adult mice neonatally exposed to BPA exhibited an abnormal spontaneous behavior to a novel home environment manifested as reduced habituation and hyperactive condition. The behavioral disturbances were long lasting and irreversible. They also suggested that neonatally exposed mice are incapable of processing new sensory information in a novel home environment and integrate it to a normal habituation capacity indicating reduced cognitive capacity.

The prominent neurochemical effects of BPA in the cortex and hippocampus that were evident from the significant changes in amino acid and cholinergic neurotransmission associated with oxidative stress in the present study may be attributed to the deficiency of detoxification mechanisms for BPA in the brain (Doerge et al., 2010, 2011). It has been reported that low-dose exposure to BPA shows rather weak toxic effects on the reproductive or endocrine functions in the peripheral tissues, probably due to the efficient detoxification of BPA by the liver. However, low-dose exposure to BPA may significantly affect brain functions because the detoxification of BPA in the brain is probably very weak due to the extremely low
expression of drug-metabolizing enzymes in the brain (Chinta et al., 2005; Kishimoto et al., 2004).

The present changes induced by BPA could underlie the disturbances in many neuronal functions such as memory, cognitive impairments, hyperactivity, and the inhibition of neuronal progenitor cells proliferation.

According to the present findings, it could be concluded that the exposure to BPA even at low doses may have serious impacts on the brain of adult rats due to its accumulating effects. This may raise concerns about the exposure of humans to BPA due to its wide applications in industry.

**Conflict of interest**
The authors declared no conflicts of interest.

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