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Effects of bisphenol S, a major substitute of bisphenol A, on neurobehavioral responses and cerebral monocarboxylate transporters expression in mice

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ABSTRACT

Bisphenol A has been restricted in a large variety of products. Bisphenol S (BPS) is its major substitute. Yet, the impacts of BPS on the central nervous system are unknown, especially in vulnerable populations like children. The aim of this study was to investigate the effects of BPS on behavioral performances and the expression of cerebral monocarboxylate transporters (MCTs). Male Swiss mice were exposed to BPS at 100 μg/kg in drinking water for 10 weeks. The protocol started after the lactation period, which is a sensitive period of early social-emotional development. Elevated T-maze and open field tests were used to measure respectively, anxiety-related and activity-related behaviors. Molecular expressions of MCTs isoforms (MCT1, MCT2, MCT4) were determined in the frontal cortex. Data showed that BPS does not affect mRNA expression of MCTs. However, BPS decreases the number of entries into the open arms and the time spent on them for BPS-treated mice. These data reveal an anxiogenic effect of BPS. For locomotor activity and exploratory behavior levels, differences did not reach a statistically significant level in the BPS-exposed group. The effect of BPS on behavioral performances unravels a putative risk for psychopathology development in early childhood and calls for more attention.

1. Introduction

In recent years, a growing concern has emerged about developing behavioral problems, especially in vulnerable populations like children. Indeed, childhood is a sensitive period of early behavioral development. In this regard, endocrine disruptors (EDs) have become a worldwide public health issue. EDs are substances that can interfere with the endocrine system leading to disorders affecting development as well as reproductive, neurological, hormonal and immune systems in both humans and wildlife. Apart from a genetic link and lifestyle factors, early life exposure to EDs is associated with increased risk for developmental psychopathology, including anxious and depressive phenotypes (Schug et al., 2015). In this context, Bisphenol A, a plasticizer largely used in the synthesis of polycarbonate plastic and epoxy resins has been prohibited in many products because of serious risks to human health (Bertoli et al., 2015; Chevalier and Fenichel, 2015; Negri-Cesi, 2015; Rezg et al., 2014). Among human outcomes, particular concerns have been raised about BPA effects on children's cognitive performances and/or behavior. Indeed, neurobehavioral disruptions, including aggressive behavior, attention deficit, hyperactivity disorder, depression, and anxiety were reported frequently in children exposed *in utero* to BPA, suggesting brain alterations during this critical window of development (Mustieles et al., 2015). Also, several studies revealed that BPA induces anxiety- and depressive-like behaviors in rodents of both sexes (Xu et al., 2012, 2015) and can impair learning-memory capacities (Xu et al., 2010). These observations were made after postnatal exposure at different stages of development.

After several reports documenting adverse effects, BPA has been banned and replaced by analogs like Bisphenol S (BPS; 4,4′-sulfonyldiphenol) (Fig. 1). However, despite the use of a “BPA-free” label to promote the safety of new products and reassure the consumer, BPS is suspected to have also deleterious effects (Eladak et al., 2015). Generally, BPS is used in food containers (e.g., vegetables, canned foods, cereals), personal care products (e.g., body lotions and soaps, hair care products, makeup, beauty lotions), paper products (e.g., currency, flyers, tickets, mailing envelopes, airplane boarding passes), manufactured plastics and in numerous other industrial applications (Liao and Kannan, 2014; Liao et al., 2012b, 2012c) (Liao et al., 2012a). In biomonitoring studies, BPS has been identified in several environmental compartments like surface water, sediment, sewage effluent, etc

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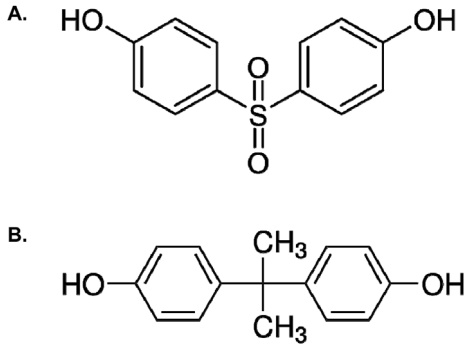

Fig. 1. Chemical structures of bisphenol S **(A)** and bisphenol A **(B)**.

(Chen et al., 2016). In addition, concerning inhalation exposure routes, BPS was detected in indoor dust collected in different countries from Asia, Europe, and North America (Liao et al., 2012b). It is important to highlight that human exposure to BPS is widespread at all life stages from fetal to adult. Indeed, in a recent toxicokinetic study, BPS was detected in maternal plasma, amniotic fluid, fetal urine, and fetal plasma during pregnancy (Gingrich et al., 2018). In addition, BPS was measured in children urine samples from South China aged between 3 and 11 years old (Chen et al., 2018). BPS has been detected also in adult human urine at concentrations and frequencies comparable to BPA in several countries (Japan, USA, China, Kuwait, Vietnam, etc) (Liao et al., 2012a; Zhou et al., 2014). Like BPA, BPS is considered a xenoestrogen, capable of binding to endogenous estrogens receptors (Vinas and Watson, 2013). BPS can also bind to numerous other receptors and proteins to disrupt the functions of thyroid hormones (Wei et al., 2018), testosterone (Ullah et al., 2018), and several neuropeptides in the hypothalamus (Rezg et al., 2018). It has been suggested that BPS and other bisphenols can induce neuroendocrine disruptions through estrogen receptor-dependent mechanisms (Rosenfeld, 2017). Thus, BPS has the potential to alter the function of different physiological systems, but its impact on Human brain and behavior at different life stage remains poorly investigated. Indeed, recently, it has been noted that BPS can affect neurobehavioral capacities in early life stages of zebrafish larvae (Danio rerio) (Gu et al., 2019). The authors reported significant decrease in locomotor behavior with a downregulation in molecular expression of neurodevelopment genes (Gu et al., 2019). Also, in a rodent model, it has been reported that gestational exposure to BPS can alter mouse responses in sociability tests, indicative of anxiety-like behaviors and troubles in social interactions (Kim et al., 2015) and nursing behaviors (LaPlante et al., 2017).

It is now evident that brain development is an organized and constantly adaptive process in which genetic/epigenetic signals allow neurons to differentiate, to migrate and to develop correct connections. Thus, two processes are indispensable to establish the complex network of the developing central nervous system (CNS): 1) Neuronal connectivity via formation and elimination of synaptic contacts, and 2) Adequate number of neurons via loss by apoptosis of neurons that do not uptake enough neurotrophic factors from target neurons at synapses (Stiles and Jernigan, 2010). Such processes require a substantial amount of energy provided in large part by oxidative metabolism. During this period, monocarboxylates (e.g. ketone bodies) represent a large fraction of the energy substrates used to sustain brain development (Nehlig, 2004).

In recent years, the role of monocarboxylates as energy substrates for neurons (in addition to glucose) has attracted increasing attention (Pellerin, 2003). Monocarboxylates such as lactate, pyruvate and ketone bodies play an essential role in brain energy metabolism. Specific transporters for these substances called monocarboxylate transporters (MCTs) have been identified and their cell-specific expression described in the CNS (Pierre and Pellerin, 2005). MCTs belong to a solute carrier family (SLC16A) composed of 14 members. Among the 14 isoforms identified, MCT1–4 have been better characterized. MCT1-4 are expressed in different tissues where they play important roles in inter-organ and intercellular metabolic interactions for both physiological and pathological mechanisms (Halestrap and Wilson, 2012; Perez-Escuredo et al., 2016). For example, their importance for survival and growth in various tumoral tissues makes them significant biomarkers and attractive targets for treating several types of cancers (Pinheiro et al., 2012). In the CNS, MCT1-4 catalyze the passive transport of monocarboxylates through a proton-linked transmembrane transport in and out of brain cells. Among others, MCTs control the distribution of an indispensable energy substrate: lactate, produced by astrocytes and used by neurons. Alterations in MCT expression in brain cells could have important consequences in brain ischemia, epilepsy, learning, and memory as well as neurodegenerative diseases. Indeed, MCT dysfunctions have associated with pathologies of the central nervous system including metabolic disorders and neurobehavioral problems (Perez-Escuredo et al., 2016).

In spite of the importance of MCTs in brain energy metabolism with different physiological implications, there is no information about the putative effects of bisphenols on the expression of these key transporters, especially in the brain. Therefore, in the present study, we investigated the potential effects a post-lactation exposure to BPS on cerebral MCT expression. In addition, we have focused our attention on BPS effects on neurobehavioral performances, including anxiety, locomotor activity, and exploratory behavior, in adolescent mouse offspring.

2. Material and methods

2.1. Chemicals

Bisphenol S was obtained from Sigma-Aldrich (Steinheim, Germany).

2.2. Animals and treatments

Male mice (~10 g) obtained from the Pasteur Institute, Tunisia, were divided into two treatment groups (n = 6). Animals are exposed to BPS in their drinking water at the dose of either 0 (control group) or 100 µg/kg/day (BPS group). The choice of BPS dose is according to NOAEL concentrations (No Observed Adverse Effect Level) for systemic toxicity from studies using rodents as a model (https://echa.europa.eu/). Animals were maintained in a mass air displacement room with a 12-h light-dark cycle at 22 ± 2 °C with a relative humidity of 50 ± 10%. Food and drinking water were given to the animals *ad libitum*. The Standard Diet contained 20.5% crude protein, 4.62% crude fat, and 52.5% nitrogen-free extract (total calories 3.45 kcal/g).

BPS concentration was based on mean daily unadjusted water intake in Swiss Albino mice (about 2 ml/10 g mice) (Bachmanov et al., 2002; Rezg et al., 2018). Animals were treated with the respect of ethics and deontology and all the procedures were carried out in accordance with the Guidelines for Ethical Conduct in the Care and Use of Animals. After 10 weeks of treatment, both treated and control groups were used to evaluate behavioral performances using the elevated plus maze test and the open-field test. Then, the animals were sacrificed. After dissection, frontal cortices were rapidly removed and fixed with RNAlater and stored at −80 °C.

Body weight gain was determined in percentage change from initial body weight by using the following formula: [(weight at the end of the experience – initial weight)/(initial weight)] X 100. The initial weights for control and BPS groups are respectively 9.62 ± 1.6 g and 9.83 ± 1.84 g.

2.3. Behavioral testing

Behavioral analyses including Elevated Plus-maze test (EP) and Open-field test (OF) for mice were performed on control and BPS-treated mice. Testing was conducted from 09:00 to 14:00 under normal lighting conditions. Concerning behavioral assessment, mice were tested alternately (first one control, then one BPS, etc.). All trials were recorded with a video camera attached to a computer and images were stored in a TIFF format. The application used for acquiring and analyzing the behavioral data (Image EP or OF) is based on the public domain Image J program (developed by Wayne Rasband at the National Institute of Mental Health and available at http://rsb.info.nih.gov/ij/), which was modified by Tsuyoshi Miyakawa (available through O'Hara & Co., Tokyo, Japan).

2.3.1. Elevated plus maze

The apparatus used for the elevated plus maze test comprises two open arms (25 x 5 × 0.5 cm) facing each other and perpendicular to two closed arms (25 x 5 × 16 cm) with a center platform (5 x 5 × 0.5 cm). Open arms have a very small (0.5 cm) wall to decrease the number of falls, whereas closed arms have a high (16 cm) wall to enclose the arm. A mouse is placed in the center area of the maze with its head directed toward a closed arm. The elevated plus maze test is recorded using a video camera attached to a computer, which is controlled by a remote device. The number of entries (an entry is defined as the center of mass of the mouse entering the arm), the percentage of open arm entries, the time spent in the open arms (sec) and the percentage of open arm stay time have been recorded. These measurements served as indexes of anxiety-like behavior. Mice were allowed to move freely around the maze for 10 min. Each mouse had one trial in our test series.

2.3.2. Open-field test

Locomotor activity was measured using an open-field test. Each mouse was placed in the corner of the open-field apparatus (40 × 40 × 30 cm). Total distance traveled (cm), and time spent in the center area (20 × 20 cm), were recorded. Experimental areas were wiped clean between trials using a 10% alcohol solution before the next animal was introduced, in order to prevent the possible cuing effects of odors left by previous subjects.

2.4. Quantitative real-time PCR analysis

Total RNA was isolated using RNeasy Protect Mini Kit (#74106, Qiagen, Hombrechtikon, Switzerland). For cDNA synthesis, 200 ng of total RNA were reverse transcribed using Taqman Reverse Transcription Reagents kit (N808-0234, Applied Biosystems, Luzern, Switzerland) with random hexamers according to the manufacturer's instructions in a total volume of 50 µL. Then, 1 µL of cDNA was mixed with the suitable primer (0.3 µM) and the SYBR Green PCR master mix (Applied Biosystems, Luzern, Switzerland) to perform the PCR reaction in a total reaction volume of 10 µL. Each sample was tested in duplicate. Quantitative determination of MCT1 (For, 5′-AATGCTGCCCTGTCCTC CTA-3′; Rev, 5′-CCCAGTACGTGTATTTGTAGTCTCCAT-3′ (Embl NM_009196.3); Microsynth, Balgach, Switzerland), MCT4 (For, 5′-GTGTCGCTGTAGCCAATCCC -3′; Rev, 5′- GGCTGTTTTATCATCACG GGTT -3′ (Embl NM_030696.3); Microsynth, Balgach, Switzerland) and MCT2 (For, 5′-CAGCAACAGCGTGATAGAGCTT - 3'; Rev, 5′ TGGTTGC AGGTTGAATGCTAAT - 3′ (Embl NM_010431.2); Microsynth, Balgach, Switzerland) mRNA expression levels was performed with the StepOnePlus™ Real-Time PCR System or the ViiA™ 7 Real-Time PCR System (Applied Biosystems, Luzern, Switzerland) with *Actin* (For, 5′-GCTTCTTTGCAGCTCCTTCGT-3′; Rev, 5′-GCTTCTTTGCAGCTCCTT CGT-3′ (Embl NM_009735); Microsynth, Balgach, Switzerland) mRNA used as an endogenous control. For data analysis, the raw threshold cycle (CT) value was first normalized to the housekeeping gene for each sample to obtain the ΔCT value. The normalized ΔCT value was then calibrated to the control cell samples to obtain the ΔΔCT value.

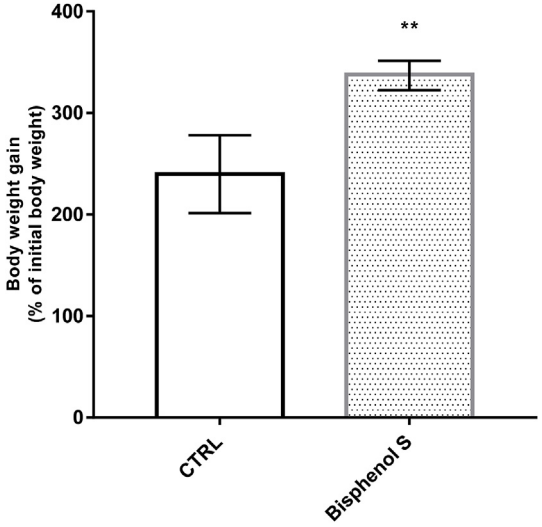

Fig. 2. Effect of BPS exposure on body mass gain. Percentage of body weight gain in mice after an oral administration of water (Control) or BPS exposure to 100 µg/kg/day. Data are medians with interquartile ranges (n = 6/group). **p < 0.01 vs control.

2.5. Statistical analysis

Statistical analysis was performed using GraphPad Prism for Windows (GraphPad Software). Results are expressed as median ± interquartile range. The differences between the groups were compared by nonparametric Mann–Whitney *U* test. Results were considered statistically significant when $p < 0.05$.

3. Results

3.1. Physical observation

No signs of toxicity were observed in treated animals until the end of the experiment. Our results showed that BPS administration causes a significant increase in body weight gain compared to the control group as a percentage of initial body weight; ($p = 0.002$) (Fig. 2).

3.2. mRNA levels of monocarboxylate transporter isoforms (MCT1, MCT2, MCT4) in the frontal cortex

BPS exposure at a dose of 100 µg/kg did not significantly affect mRNA expression levels of all three MCT isoforms as compared to the control group, although a tendency to increase for MCT1 expression ($p = 0.150$) and to decrease for MCT4 expression ($p = 0.309$) was observed (Fig. 3A–C).

3.3. Behavioral responses

Behavioral analyses including the Elevated Plus-maze test (EP) and the Open-field test (OF) for mice were performed on control and BPS-treated mice. Results from the elevated plus maze session are shown in Fig. 4. BPS-treated mice spent less time into the open arms than those of the control group (Fig. 4A) and decrease the percentage of time spent in open arms (Fig. 4B). Additionally, behavioral experiments showed that BPS-treated mice entered less frequently in the open arms than mice from the control group. Thus, chronic BPS exposure decreased the percentage of open arm entries compared to the control group (Fig. 4D). Also, our data revealed a significant increase of the anxious index (AI),

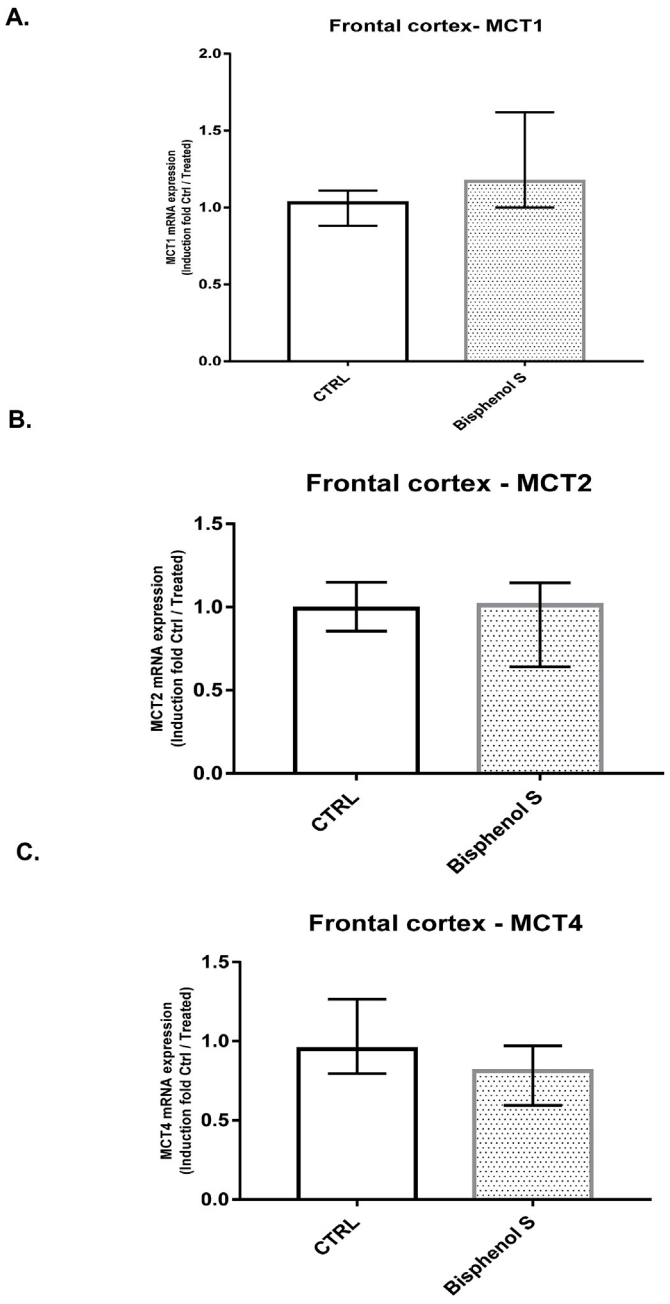

Fig. 3. Effect of ten-week BPS exposure on MCT expression in the frontal cortex. Relative mRNA expression of MCT1 (A) MCT2 (B) and MCT4 (C) in the frontal cortex of mice after oral administration of either only drinking water (Control) or BPS in drinking water at 100 µg/kg/day during ten weeks. Data are medians with interquartile ranges (n = 5/group).

which is calculated as AI = Closed arm entries × 100/Total entries, compared to the control group (Fig. 4E). Results from the Open field session are shown in Fig. 5. No significant effect of BPS has been observed neither in total distance nor total time spent in the center zone.

4. Discussion

BPS is among the most important plasticizer substitutes of BPA. Public and scientific rising concerns have been voiced about the potential implication of BPS in neurobehavioral disorders. Our data with the EP maze reveal that BPS-treated mice exhibit a decrease in the number of entries into the open arms and the time spent in them, reflecting an anxiogenic effect. Indeed, EP is used to assess anxiety-like behavior in rodents. This maze is based on behavior evaluation in novel environments which evokes a conflict between exploratory and fear/defensive behavior. The elevated plus maze is made of two adjacent closed arms perpendicular to two open arms. When rodents are offered to choose between two novel spaces (open and close), closed spaces are preferred. Thus, with this test, compounds that cause anxiety significantly reduce the percentage of entries into, and time spent on, the open arms compared to control animals (Pellow et al., 1985). This test has been validated for use in both mice and rats (Sidor et al., 2010). The distribution of behavior in conflict tests is the most widely accepted index of anxiety.

Data presented in this work are similar to those of several previous studies using experimental animals reporting that BPA also induces an anxiety-like behavior after prenatal or postnatal exposure (Heredia et al., 2016; Kumar and Thakur, 2017; Luo et al., 2013, 2014; Xu et al., 2012). Furthermore, the same observation was reported in humans with several other neurobehavioral problems, including anxiety, attention problems, and/or other cognitive functional impairments, depression, and hyperactivity in children (Harley et al., 2013; Perera et al., 2016). Thus, particular concerns have been raised about the potential influence of early life BPA exposure on children (Mustieles et al., 2015). Considering the similarity in structure between BPA and BPS (Fig. 1), it comes as no surprise that similar concerns can be made with this substitute. Indeed, BPS may potentially constitute a similar health hazard as BPA (Rochester and Bolden, 2015), but whether or not the effects are identical would require further investigations. In addition, it is not clear whether the effects of BPS could be due to a direct influence on cerebral processes or an indirect effect via other systems; but, in the literature, endocrine and/or epigenetic mechanisms have been suggested for neurobehavioral effects of BPA (Mustieles et al., 2015; Wright et al., 2017). Indeed, the influence of BPA on anxiety-like behavior may be partly due to a complex estrogen-mediated mechanism in brain with a predominant implication of the estrogen receptor (ER) subtype alpha-related system (Furuta et al., 2013). It is important to indicate that, at postnatal stage, the brain continues its development with an increase in size and it undergoes structural modifications in both gray and white matter until adulthood. These structural changes correspond to the modifications in the functional organization and resulting behaviors (Stiles and Jernigan, 2010). Thus, BPS like BPA could target these structural changes.

Limited *in vivo* neurotoxicity data exist with BPS. Indeed, to date, few studies have evaluated central BPS effects in animal models. Using zebrafish model, it was shown that BPS can disrupt hypothalamic neurogenesis (Kinch et al., 2015) and can induce hyperactive behavior with a downregulation in the expression of neurodevelopment genes (Gu et al., 2019). In rodents, particularly juvenile female rats, BPS can alter genes involved in neuro-steroidogenesis and dopamine-serotonin systems in the prefrontal cortex after gestational and postnatal exposure (Castro et al., 2015).

In the present study, no significant effect of BPS was observed on the activity level measured in the open field. This test measures hyperactivity and exploratory behaviors. Mice naturally prefer to be near a protective wall rather than exposed to danger out in the open space, but a competing foraging instinct will motivate them to explore. The total distance covered in this maze is an indicator of activity level (Carter et al., 2013). Our results show no significant difference between groups for this parameter. However, a previous study reported in the zebrafish model a significant decrease in locomotor behavior with oxidative stress induction (Gu et al., 2019).

Our study did not reveal a significant effect of BPS on the mRNA expression of MCT isoforms in the frontal cortex. This result may seem surprising, considering the importance of monocarboxylates (i.e. lactate and ketone bodies) as critical energy substrates for brain development during the neonatal period (Nehlig, 2004). However, our study was limited to the frontal cortex. We cannot exclude that significant effects might be detected in other brain regions. For example, the role of the

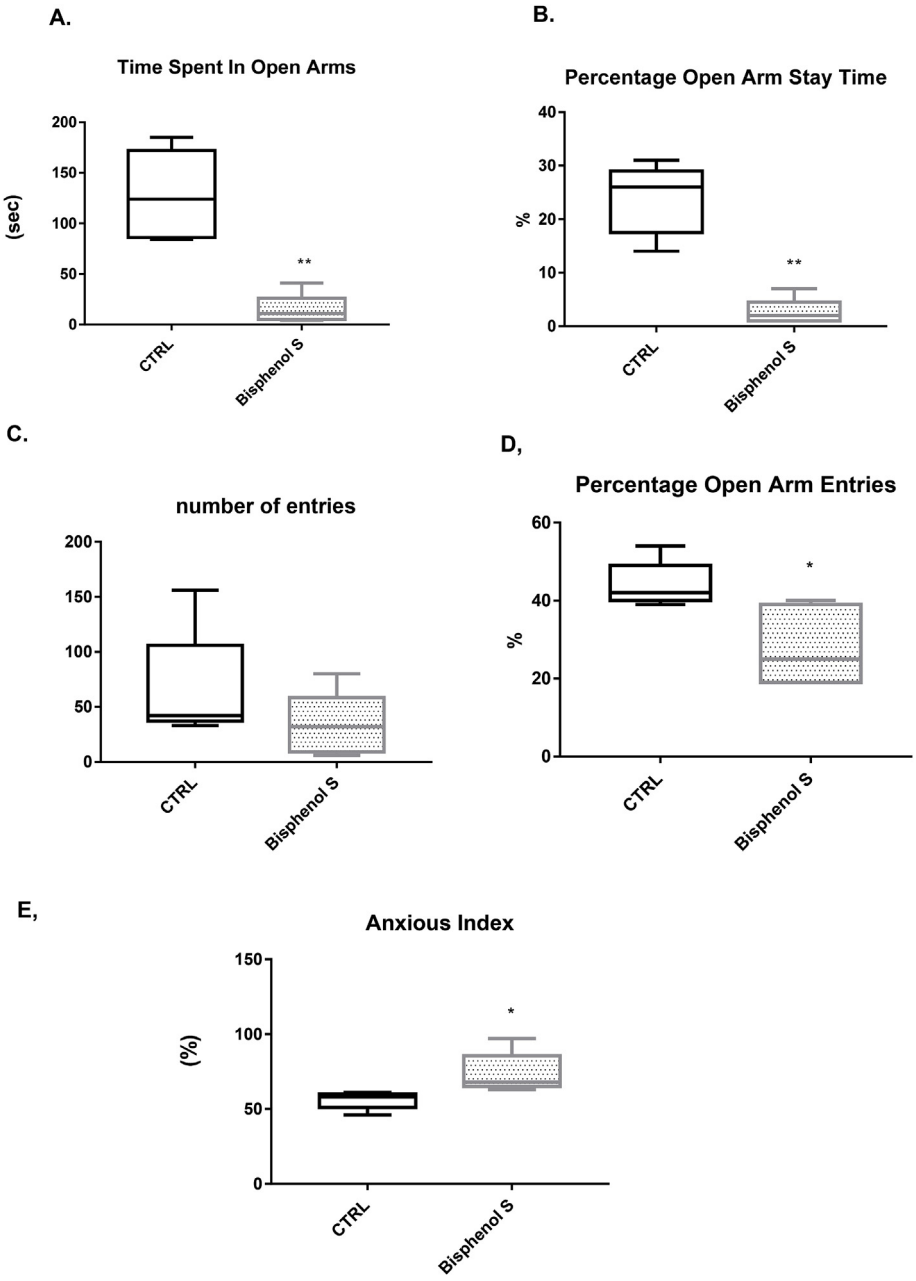

Fig. 4. Results of Elevated Plus Maze (EP): Time spent (A), percentage of stay time (B) in open arms, total entries (C), percentage of open arm entries (D) and anxious index recorded in mice after BPS exposure at 0 or 100 μg/kg/day. Data are medians with interquartile ranges (n = 5/group). **p < 0.01 vs control; *p < 0.05 vs control.

amygdala in anxiety-related behaviors has been well-described (Gilpin et al., 2015). Thus, it would be worth investigating possible alterations in the expression of MCTs in other brain regions that are involved in such behaviors. Another important caveat is that we limited our investigation to the mRNA expression. It would be important to investigate possible changes in expression at the protein level. Indeed, it has been previously, reported that some MCTs are regulated at the translational level (Chenal et al., 2008; Pierre et al., 2003; Robinet and Pellerin, 2010). Brain energy metabolism is multifactorial and very complex in order to guarantee sufficient spatial and temporal delivery of energy substrates (Belanger et al., 2011). Thus, more studies are needed to better assess the impact of BPS on brain energy metabolism, because this xeno-estrogen is strongly suspected of modulating general energy metabolism (Wu et al., 2018). Indeed, it has been reported recently that BPS disrupts glucose transporter expression in the intestinal tissue (Rezg et al., 2019).

5. Conclusion

In summary, this study is the first, to our knowledge, to investigate the impact of a BPS treatment on MCT expression and on neurobehavioral responses in childhood and adolescent male offsprings. BPS-treated mice present an anxiety-like behavior, questioning the safety of its use as a replacement for BPA (and highlighting the fallacy of using a "BPA-free" label on products containing BPS as a safeguard). Other neurotoxicological investigations are needed to better define the safety threshold of these products for human health.

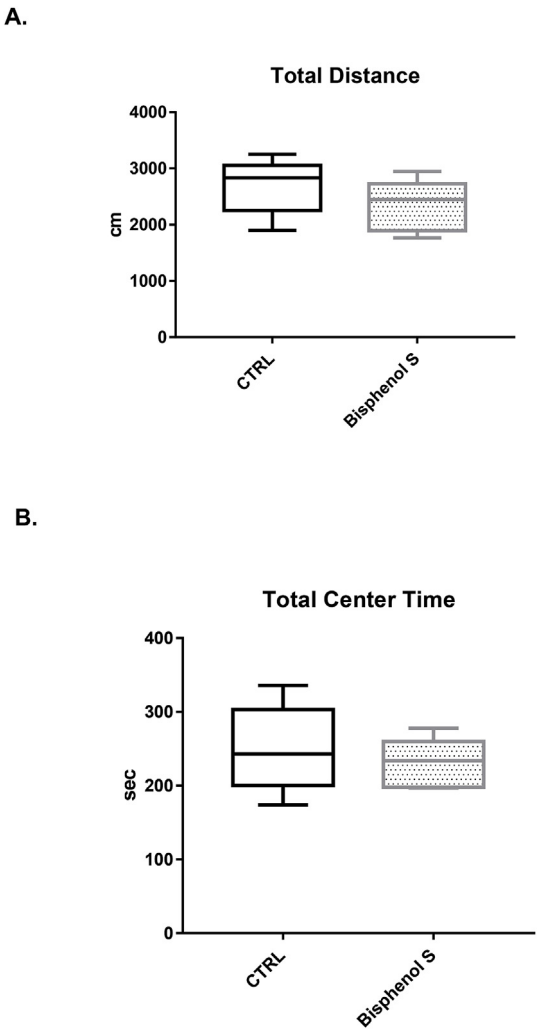

Fig. 5. Results of Open Field Test (OF): Total distance (cm) (A), and total center time (sec) (B) recorded in mice after BPS exposure at 0 or 100 µg/kg/day. Data are medians with interquartile ranges (n = 5/group).

Conflicts of interest

The authors declare no conflict of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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