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Long-term exposure to xenoestrogens alters some brain monoamines and both serum thyroid hormones and cortisol levels in adult male rats

Nashwa M. Saied, Wafaa A. Hassan *

Hormone Evaluation Department, National Organization for Drug Control and Research (NODCAR), Giza, Egypt

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Abstract The present study was designed to examine the effect of long-term treatment with the phytoestrogen soy isoflavone [(SIF); 43 mg/kg body weight/day] and/or the plastics component bisphenol-A [(BPA); 3 mg/kg body weight/day] on some monoamines in the forebrain and both serum thyroid hormones and cortisol levels of adult rats. Significant increases in serotonin (5-HT) and norepinephrine (NE) level, and significant decreases in 5-hydroxyindoleacetic acid (5-HIAA) level and 5-HIAA/5-HT ratio, were observed after treatment with SIF or BPA. Level of dopamine (DA) was increased in SIF-treated group and decreased in BPA-treated group. Activity of monoamine oxidase (MAO) was decreased in all treated groups. The level of serum thyroid hormones (fT_3 and fT_4) was increased after treatment with SIF and decreased after exposure to BPA, while cortisol level was increased in all treated groups. It may be concluded that long-term exposure to SIF or BPA disrupts monoamine levels in the forebrain of adult rats through alteration in the metabolic pathways of amines and disorders of thyroid hormones and cortisol levels.

Introduction

Xenoestrogens are natural or synthetic compounds, which are able to mimic and/or interfere with hormone receptors generating as unexpected ligands deleterious effects on animals (Witorsch, 2002; Naciff and Daston, 2004).

Among xenoestrogens, the soy isoflavone (SIF) has been identified as a naturally-occurring and estrogen-like phytoestrogen, which is widely contained in various diets of rodents and humans (Setchell et al., 2001). Soy isoflavones have been suggested as alternative to estrogen replacement therapy in postmenopausal women but might be harmful to the degree that they contribute to carcinogens or other adverse effects (Whitten et al., 1995).

Reports on the effects of SIF on thyroid gland are contradictory. Soy consumption has been shown to have a depressive effect on thyroid function (Doerge,2002; Teede et al., 2004). In contrast some lines of evidence suggested that soy isoflavones have been associated with an increase in the thyroid hormone thyroxine (Lueprasitsakul et al., 1990; Balmir et al., 1996). In another study, soy isoflavones had no effect on thyroid gland size or thyroid hormone levels (Son et al., 2001).

* Corresponding author.

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Previous studies have explored the beneficial and protective effects of soy isoflavone against neuronal death induced by various diseases in both humans and animal species (Chen et al., 2002; Lee et al., 2005; Liu et al., 2008), and in contrast other reports indicated that soy treatment induced neuronal apoptosis and/or DNA fragmentation in neurons of adult rats (Choi and Lee, 2004; Bu and Lephart, 2007). However, the underlying mechanisms involved in these effects of SIF are still largely unknown.

Among other xenoestrogens, the synthetic endocrine disruptor bisphenol A (BPA) deserves particular attention due to its widespread use by humans. It is widely used in the production of polycarbonate plastics and epoxy resins and the largest source for human exposure to it is food containers, beverage cans and medical devices (Geens et al., 2012). Under various conditions, BPA can leach out of plastic containers and pass to the food or beverage which is then a source for human exposure (Kang et al., 2006). BPA is reported to bind to estrogen receptors, and also affects androgen and thyroid hormone systems (Wetherill et al., 2007).

Several authors reported that perinatal exposure of rodents to BPA can induce behavioral alteration by affecting the central nervous system (Miyagawa et al., 2007; Tian et al., 2010; Fan et al., 2013; Matsuda et al., 2013). Other findings also suggested that chronic exposure to BPA in rodents during development may result in extensive physical and mental alterations (Hajszan and Leranth 2010; Wolstenholme et al., 2011).

Various studies have established a definite effect of BPA during perinatal and postnatal stages on monoamine levels (Honma et al., 2006; Matsuda et al., 2010, 2013; Nakamura et al., 2010) and monoamine oxidase activity (Matsuda et al., 2012).

The forebrain included important regions such as the thalamus, hypothalamus and hippocampus; neurotransmitters (DA, NE and 5-HT) in these regions play a key role in the regulation of some brain functions such as emotion and behavior. Neurochemical changes are also involved in chemical neurotoxicity (Tsuga et al., 2002). Moreover, thyroid hormones have been shown to play an important role in regulating central monoaminergic function, not only during brain maturation but also in adult vertebrate brain (Ahmed et al., 2010; Tousson et al., 2012; Hassan et al., 2013a,b).

The hypothalamic–pituitary–adrenal (HPA) axis and the hippocampus are potential targets for estrogen-mediated organizational events (Handa et al., 1994). The limbic-HPA axis circuit is involved in the central regulation of stress response and in addition hypothalamus plays an important role in the regulation of stress (Itoi et al., 2004). During stress response, the hypothalamus secretes corticotropin-releasing hormone, which stimulates the anterior lobe of the pituitary gland to release adrenocorticotropic hormone, which stimulates the cortex of the adrenal gland to release cortisol (O'Connor et al. (2000).

It is important to mention that studies on rats indicated the ability of SIF and BPA to cross the blood–brain barrier into the central nervous system (Sun et al., 2002; Lephart et al., 2004). The present study was undertaken to examine the influence of long-term exposure to SIF and/or BPA on forebrain monoamine levels (DA, NE, 5-HT, 5-HIAA) and 5-HIAA/5-HT ratio in adult male rats. The activity of monoamine oxidase as well as serum levels of both thyroid hormones (fT_3 and fT_4) and cortisol were measured.

Material and methods

Treatments

Soy isoflavones mixture (SIF, 50 mg, genistein, daidzin and saponins, extracted from soy beans) was purchased from Mepaco Medifood Ltd. (Sharkeya, Egypt). SIF was suspended in 1% Tween 80 aqueous solutions. Bisphenol A was bought from Sigma Chemical Co. (Missouri, USA) and dissolved in corn oil.

Animals and experimental design

Forty adult male albino rats of Wistar origin, weighing 180–200 g were used in this study. The animals were obtained from the animal house of the National Organization for Drug Control and Research (NODCAR). They were housed under normal environmental conditions of temperature and humidity and allowed to adapt to the new environment for two weeks before starting the experiment. Animal rooms were maintained on a 12-h light, 12-h dark photoperiods. Animals were provided with food and water *ad libitum*. All experiments were conducted in accordance with the NODCAR Guidelines for the Care and Use of Laboratory Animals.

Rats were randomly divided into five groups, with eight rats in each group

Group 1

Control for soy isoflavone treated rats (C-SIF). Animals received oral administration of 5 ml/kg body weight/day 1% Tween 80 aqueous solution (v/v, the suspension of soy isoflavon) for 8 weeks.

Group 2

Soy isoflavone-treated group (SIF). Rats received oral suspension of soy isoflavone in a dose of 43 mg/kg body weight/day (Khan and Sultana, 2011) for 8 weeks.

Group 3

Control for bisphenol A treated rats (C-BPA). Animals received oral administration of 5 ml/kg body weight/day corn oil (the solvent of bisphenol A) for 8 weeks.

Group 4

Bisphenol A-treated group (BPA). Rats received oral oil solution of bisphenol A in a dose of 3 mg/kg body weight/day (Sakaue et al., 2001) for 8 weeks.

Group 5

Combination of soy isoflavone and bisphenol A group (SIF + BPA). In this group rats received the same dose of

soy isoflavone suspension orally as the SIF group, followed by an oral identical dose of bisphenol A oil solution as the BPA group, for 8 weeks.

Blood samples and tissues preparation

In all experiments done the conditions were adjusted to decapitate the animals between 3.00 and 4.00 pm. Twenty-four hours following the last treatment, rats were sacrificed by decapitation and the trunk blood was collected and allowed to clot, then centrifuged. Serum samples were stored at −20 °C for determination of thyroid hormones [triiodothyronine (T_3) and tetraiodothyronine (T_4)] as well as cortisol levels. Thereafter, the brain was rapidly excised according to the method of Heffner et al. (1980), and transferred to a dry ice-cold glass plate and the forebrain was rapidly excised, plotted dry on a filter paper to remove excess fluid and then weighed. Forebrain samples were stored at −70 °C till taken for an analysis of monoamine content and monoamine oxidase activity.

Determination of serum levels of thyroid hormones and cortisol

Thyroid hormones (fT_3 and fT_4) and cortisol levels were determined in serum samples using ELISA commercial kits (Diagnostic Systems Laboratories INC. USA for fT_3 and fT_4 according to the methods of Wenzel (1981) and Midgeley (2001), respectively) and (Immunospec Corp. USA for cortisol according to the method of Foster and Dunn, 1974).

Estimation of the amine contents

Each tissue sample was homogenized in 10 volumes of cold acidified *n*-butanol using a glass homogenizer; the sample weighing less than 300 mg was homogenized in 3 ml of acidified *n*-butanol (Chang, 1964). The estimation of DA, NE and 5-HT levels in the forebrain of rats was carried out according to the fluorometric method described by Ciarlone (1978) and 5-H IAA level was determined by the method of Miller et al. (1970). 5-HIAA/5-HT ratio was calculated and used as a marker for the turnover of 5-HT.

Determination of monoamine oxidase

Monoamine oxidase enzyme activity in the forebrain homogenate of rats was measured by a fluorometric method described by Olcese and De Vlaming (1979).

Statistical analysis

The values of the parameters determined are expressed as mean ± S.E. Data were analyzed using the SPSS statistical package (version 18). Statistical significance was calculated using a one-way analysis of variance (ANOVA) followed by LSD post hoc test. Values of $p < 0.05$ were considered statistically significant.

Results

The effects of SIF and/or BPA on DA, NE, 5-HT, 5-HIAA levels, 5-HIAA/5-HT ratio and MAO activity as well as fT_3, fT_4 and serum cortisol levels are shown in Tables 1 and 2.

The data expressed in Table 1 indicated that levels of 5-HT and NE in the forebrain of adult male rats were significantly ($p < 0.05$) increased following 8 weeks of treatment with SIF (38.5% and 17.5%, respectively) or BPA (22.7% and 16.9%, respectively) compared with the respective controls. The DA level was significantly increased in SIF-treated group

Table 1 Effect of oral administration of soy isoflavone (SIF) and/or bisphenol A (BPA) for 8 weeks on monoamines (5-HT, 5-HIAA, DA and NE), 5-HIAA/5-HT ratio and monoamine oxidase (MAO) activity in the forebrain of adult male albino rats.

Items	Groups							
	C-SIF	SIF	% difference	C-BPA	BPA	% difference	SIF + BPA	% difference
5-HT (μg/g)	0.39 ± 0.02	0.54 ± 0.02[a]	38.5	0.44 ± 0.01	0.54 ± 0.03[b]	(22.7)	0.46 ± 0.01[a,c,d]	17.9 (4.5)
5-HIAA (μg/g)	0.17 ± 0.00	0.14 ± 0.01[a]	−17.6	0.15 ± 0.01	0.13 ± 0.00[b]	(−13.3)	0.15 ± 0.01[d]	−11.8 (0.0)
5-HIAA/5-HT (ratio)	0.34 ± 0.00	0.26 ± 0.01[a]	−23.5	0.33 ± 0.02	0.24 ± 0.01[b]	(−27.3)	0.32 ± 0.01[c,d]	−5.9 (−3.0)
DA (μg/g)	0.88 ± 0.024	1.08 ± 0.01[a]	22.7	1.02 ± 0.04[a]	0.89 ± 0.02[b]	(−12.7)	0.90 ± 0.02[b,c]	2.3 (−11.8)
NE (μg/g)	0.63 ± 0.041	0.74 ± 0.05[a]	17.5	0.65 ± 0.04	0.76 ± 0.02[b]	(16.9)	0.71 ± 0.03	12.7 (9.2)
MAO (μM/g/h)	9.15 ± 0.46	6.81 ± 0.65[a]	−25.6	9.09 ± 0.17	7.96 ± 0.09[b]	(−12.4)	7.73 ± 0.11[a,b]	−15.5 (−15.0)

Data were expressed as mean ± S.E. The number of animals in each group was eight.
% difference: represent a comparison between C-SIF group and treated groups.
(%) difference: represent a comparison between C-BPA group and treated groups.
[a] $p < 0.05$ vs. C-SIF.
[b] $p < 0.05$ vs. C-BPA.
[c] $p < 0.05$ vs. SIF.
[d] $p < 0.05$ vs. BPA.

Table 2 Effect of oral administration of soy isoflavone (SIF) and/or bisphenol A (BPA) for 8 weeks on both serum thyroid hormones (fT_3 and fT_4) and cortisol levels of adult male albino rats.

Items	Groups							
	C-SIF	SIF	% difference	C-BPA	BPA	% difference	BPA + SIF	% difference
fT_3 (pg/ml)	2.47 ± 0.12	3.00 ± 0.07[a]	21.5	2.63 ± 0.15	2.14 ± 0.04[b]	(−18.6)	2.60 ± 0.06[c,d]	5.3 (−1.1)
fT_4 (ng/dl)	2.70 ± 0.18	3.20 ± 0.11[a]	18.5	3.00 ± 0.15	2.49 ± 0.08[b]	(−17.0)	3.20 ± 0.06[a,d]	18.5 (6.7)
Cortisol (μg/dl)	2.80 ± 0.2	3.37 ± 0.18[a]	20.4	1.44 ± 0.03[a]	1.87 ± 0.05[b]	(29.9)	2.95 ± 0.26[b,d]	5.4 (104.9)

Data were expressed as mean ± S.E. The number of animals in each group was eight.
% difference: represent a comparison between C-SIF group and treated groups.
(%) difference: represent a comparison between C-BPA group and treated groups.
[a] $p < 0.05$ vs. C-SIF.
[b] $p < 0.05$ vs. C-BPA.
[c] $p < 0.05$ vs. SIF.
[d] $p < 0.05$ vs. BPA.

(22.7%), and decreased in BPA-treated group (−12.7%) as compared to their controls. Administration of either SIF or BPA significantly decreased the level of 5-HIAA (−17.6% or −13.3%, respectively) and ratio of 5-HIAA/5-HT (−23.5% or −27.3%, respectively) compared to their corresponding control. Co-administration of SIF and BPA restored the level of 5-HT, NE, 5-HIAA and 5-HIAA/5-HT ratio near the C-BPA group. Activity of MAO was significantly decreased in all the treated groups.

Serum levels of fT_3 and fT_4 were significantly increased in SIF-treated group (21.5% and 18.5%, respectively), decreased in BPA-treated group (−18.6% and −17.0%, respectively) and non-significantly increased in SIF + BPA-treated-group compared to the C-BPA group (Table 2). Serum cortisol level was significantly elevated in SIF, BPA and SIF + BPA treated groups relative to the controls (Table 2).

Discussion

The major findings of the present study were the significant differences in the level of monoamines (DA, NE, 5-HT and 5-HIAA) in the forebrain of adult male rats after long-term exposure to SIF or BPA compared with the respective control, suggesting that SIF or BPA might induce neurotransmitters dysregulation in the adult life. Monoamine oxidase activity, thyroid hormones and cortisol levels were also altered following long-term exposure to these compounds.

Several factors were postulated to explain the disturbances in monoamines following long-term exposure of SIF or BPA. Considering the notion that estrogen regulates the production of monoamines such as 5-HT and DA (Sotomayor-Zarate et al., 2011), and that SIF or BPA have an estrogenic activity, exposure to SIF or BPA might disrupt the level of these amines in the brain, as shown in the present study.

A significant increase in 5-HT level, which was associated with a decrease in its metabolite, 5-HIAA level and 5-HIAA/5-HT ratio (a markers of 5-HT turnover), was found in the forebrain after long-term exposure to either SIF or BPA, suggesting the incidence of an abnormality in serotonin metabolism following exposure to these compounds. However, co-administration of SIF and BPA restored 5-HT and 5-HIAA levels and 5-HIAA/5-HT ratio near to the control values, indicating that no synergistic effect existed between SIF and BPA.

It is important to note that the serotonergic system is regulated by gonadal hormones (Sotomayor-Zarate et al., 2011). Also, Sheng et al. (2004) reported that in the dorsal raphe nuclei of mice, many 5-HT releasing neurons showed estrogen receptor α and/or estrogen receptor β expression. Shimizu and Bray (1993) found that estradiol administration decreased the 5-HIAA/5-HT ratio in the nucleus accumbens of ovariectomized rats. Therefore, the decrease of 5-HIAA level observed in the present study may be related to the estrogenic activity of SIF or BPA. Estrogen replacement for one or five months significantly increased tryptophan hydroxylase (the rate-limiting enzyme for the synthesis of 5-HT) as well as serotonin reuptake transporter (which is important for the regulation of extracellular 5-HT level) in the dorsal raphe region of macaques (Smith et al., 2004).

The results of the present study show that long-term administration of SIF increased DA level; however, administration of BPA or BPA + SIF decreased DA levels. This means that the inhibitory effect of BPA on DA level overcomes the excitatory effect of SIF on the DA level.

The elevated level of DA after treatment with SIF implies that SIF could enhance the DA synthesis or decrease its degradation; this was confirmed by the observed decrease in MAO activity following treatment with SIF. Since SIF is well known to elicit estrogenic function, dietary genistein exposure (a natural isoflavone phytoestrogen present in soybeans) may act similarly to estradiol in augmenting amphetamine-stimulated striatal DA release in male and female rats (Ferguson et al., 2002). Genistein also inhibits DA uptake into the mouse striatum (Simon et al., 1997).

The inhibitory effect of BPA on DA levels may reflect decreased synthesis via decrease in tyrosine hydroxylase enzyme activity, the first and rate-limiting enzyme in the synthetic pathway of catecholamine. This suggestion was confirmed by a previous study of Miyagawa et al. (2007). They recorded a significant decrease in tyrosine hydroxylase-immunoreactive neurons in the hippocampus and substantia nigra of female offspring following maternal as well as early postnatal exposure to BPA. Also, perinatal exposure to BPA disrupted DA receptor

expression and/or function (Mizuo et al., 2004; Narita et al., 2007).

In the present study, NE level was significantly increased following long-term exposure to either SIF or BPA; however, a non-significant increase was recorded following administration of both BPA + SIF group. Honma et al. (2006) found that in neonatal rats, levels of NE in the forebrain and hindbrain were dose-dependently increased following exposure to BPA. The noradrenergic transmission, together with serotonergic transmission in the brain, is considered to play a key role in the behavioral abnormalities (Giorgi et al., 2003; Arias-Carrion and Poppel, 2007). Accordingly, the increase in the level of NE in the forebrain after treatment with SIF and/or BPA recorded in the present study might represent an adverse effect of these compounds on emotion and behavior during adult life. This suggestion was consistent with that of Matsuda et al. (2010).

The present data also demonstrated that treatment with SIF and/or BPA caused a decrease in MAO activity of the rat forebrain. Similarly, Matsuda et al. (2012) reported that perinatal exposure to BPA affects MAO-B in the mouse brain. Taking into consideration that SIF and BPA are well known to elicit estrogenic function, estrogen replacement for one or five months significantly decreased MAO-A, in the dorsal raphe region of macaques (Smith et al., 2004). Moreover, Gundlah et al. (2002) showed that MAO-A and/or -B mRNAs optical densities in some brain areas, including dorsal raphe nuclei, lateral hypothalamus, paraventricular nucleus, preoptic area, and ventromedial nucleus, were significantly decreased in estrogen-treated rhesus monkey.

The observed decreased activity of MAO was accompanied by an increase in the level of 5-HT and NE after treatment with SIF or BPA, and of DA after treatment with SIF. Therefore, it could be concluded that disturbances in monoamine levels in the forebrain of rats exposed daily to BPA and/or SIF for 8 weeks, are a likely consequence of the depressed metabolic processes via a decrease in MAO enzyme activity.

An increase in serum levels of fT_3 and fT_4 was recorded after long-term treatment with SIF, however, a decrease in their levels was observed following BPA exposure. Co-administration of both compounds did not induce any significant change in the level of fT_3 and fT_4 compared to the control values.

It has been reported that thyroid hormones affect 5-HT and DA system of adult rats (Kulikov and Zubkov, 2007; Tousson et al., 2012). Recently, Hassan et al. (2013a) found that hyperthyroidism induced by thyroxine caused an increased level of DA and 5-HT. The elevated levels of thyroid hormones following long-term treatment with SIF were concomitant with a significant decrease in MAO activity. Several authors have also observed an elevation in tyrosine hydroxylase activity following hyperthyroidism (Claustre et al., 1996; Chaube and Joy, 2003). Consequently it appears that hyperthyroidism decreased the enzymatic breakdown or increased the synthetic pathway of biogenic amines, resulting in their increased level. Soy consumption has been shown to have a depressive effect on thyroid function by increased thyroid-stimulating hormone levels (Divi et al., 1997). Other studies have found more modest changes in thyroid function (Teede et al., 2004). Lueprasitsakul et al. (1990) found that at low doses, SIF may increase T_4 levels, perhaps by displacing T_4 from its binding proteins. Because estradiol increases the sensitivity of the thyroid gland to feedback mechanisms mediated through the pituitary (Mazer, 2004), SIF may in part influence thyroid function by disrupting the effects of estradiol.

On the other hand, the decrease in serum levels of fT_3 and fT_4 following long-term exposure to BPA was associated with a decrease in MAO enzyme activity in the forebrain of adult rats. Similarly, Schwark and Keesey (1976) showed that the activity of MAO was decreased in certain brain regions of hypothyroid adult rats. Accordingly, it appears that hypothyroidism induced by BPA may reflect the decrease in enzymatic breakdown of biogenic amines, resulting in an increase in the level of 5-HT and NE. Furthermore, BPA may also interfere with thyroid hormone action, and inhibit thyroid hormone receptor (TR)-mediated transcription by acting as an antagonist in *vitro* (Moriyama et al., 2002). BPA disrupted thyroid hormone function by competing the T_3 for binding with the protein disulfide isomerase, a multifunctional microsomal enzyme, binding sites (Hiroi et al., 2006).

Conversely, the hypothyroid status induced by exposure to BPA was concomitant with a decline in DA level. Recently, Hassan et al. (2013b) found that exposure of adult rats to propylthiouracil, an inhibitor of thyroid hormone synthesis; reduces the DA levels in several brain regions. Tan et al. (2004) reported that dopaminergic dysfunction is associated with thyroid hormone deficiency. These findings indicate that the decline in the DA level induced by exposure to BPA can be mediated by the inhibitory effect of BPA on thyroid hormone levels.

Taken together, the above findings indicate that the changes in monoamines concentration induced by long-term exposure to either SIF or BPA can be mediated not only by the estrogenic action of these compounds, but also through their effects on monoamine oxidase enzyme activity and thyroid hormones level.

Another factor which may explain the disturbances in monoamine levels in the forebrain of rats following treatment with either SIF or BPA is the alteration in serum cortisol level. In the present study, a significant increase in the serum cortisol level in adult rats was observed following long-term exposure to either SIF and/or BPA compared to controls. Intake of lower levels of SIF through diet for a long time increased anxiety and elevated stress-induced plasma corticosterone levels in adult male rats (Hartley et al., 2003). Soy-rich diets also were found to increase aggressive behaviors in nonhuman primates (Simon et al., 2004). Moreover, BPA has been shown to induce stress hyperactive behaviors and increase corticosterone levels through the behavioral tests such as light–dark and Y-maze paradigms (Poimenova et al., 2010).

The hypothalamus plays an important role in the regulation of stress (Itoi et al., 2004) and is responsible for starting the process that leads to the secretion of cortisol by the adrenal gland. Therefore, it could be concluded that the increase in the serum cortisol levels following long-term exposure to SIF and/or BPA might represent an adverse effect of these compounds on stress-like behavior during adult life, resulting in disturbances of transmitter levels.

Poimenova et al. (2010) observed that BPA treatment resulted in an increased serum cortisol level, which could be attributed to the estrogen-mimicking action of this compound on the adrenals, toward increased corticosteroid synthesis (Malendowicz and Mlynarczyk, 1982).

In conclusion, it may be suggested that long-term exposure to SIF or BPA either separately or in combination disrupts monoamine levels in the forebrain of adult male rats, through the estrogen receptor-mediated mechanism, alteration in metabolic pathways of amines, disorders in thyroid hormones and cortisol levels.

References

Ahmed, O.M., Abd El-Tawab, S.M., Ahmed, R.G., 2010. Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: I. The development of the thyroid hormones-neurotransmitters and adenosinergic system interactions. Int. J. Dev. Neurosci. 28 (6), 437–454.

Arias-Carrion, O., Poppel, E., 2007. Dopamine, learning, and reward-seeking behavior. Acta Neurobiol. Exp. (Wars) 67 (4), 481–488.

Balmir, F., Staack, R., Jeffrey, E., Jimenez, M.D., Wang, L., Potter, S.M., 1996. An extract of soy flour influences serum cholesterol and thyroid hormones in rats and hamsters. J. Nutr. 126 (12), 3046–3053.

Bu, L., Lephart, E.D., 2007. AVPV neurons containing estrogen receptor-beta in adult male rats are influenced by soy isoflavones. BMC Neurosci. 8, 13–24.

Chang, C.C., 1964. A sensitive method for spectrophotofluorometric assay of catecholamines. Int. J. Neuropharmacol. 3 (6), 643–649.

Chaube, R., Joy, K.P., 2003. Thyroid hormone modulation of brain in vivo tyrosine hydroxylase activity and kinetics in the female catfish *Heteropneustes fossilis*. J. Endocrinol. 179 (2), 205–215.

Chen, X.C., Chen, Y., Zhu, Y.G., Fang, F., Chen, L.M., 2002. Protective effect of ginsenoside Rg1 against MPTP-induced apoptosis in mouse substantia nigra neuron. Acta. Pharmacol. Sin. 23 (9), 829–834.

Choi, E.J., Lee, B.H., 2004. Evidence for genistein mediated cytotoxicity and apoptosis in rat brain. Life Sci. 75 (4), 499–509.

Ciarlone, A.E., 1978. Further modification of a fluorometric method for analyzing brain amines. Microchem. J. 23 (1), 9–12.

Claustre, J., Balende, C., Pujol, J.F., 1996. Influence of the thyroid hormone status on tyrosine hydroxylase in central and peripheral catecholaminergic structures. Neurochem. Int. 28 (3), 277–281.

Divi, R.L., Chang, H.C., Doerge, D.R., 1997. Anti-thyroid isoflavones from soybean. Isolation, characterization, and mechanisms of action. Biochem. Pharmacol. 54 (10), 1087–1096.

Doerge, D.R., 2002. Goitrogenic and estrogenic activity of soy isoflavones. Environ. Health Perspect. 110 (Suppl. 3), 349–353.

Fan, Y., Ding, S., Ye, X., Manyande, A., He, D., Zhao, N., Yang, H., Jin, X., Liu, J., Tian, C., Xu, S., Ying, C., 2013. Does preconception paternal exposure to a physiologically relevant level of bisphenol A alter spatial memory in an adult rat? Horm. Behav. 64 (4), 598–604.

Ferguson, S.A., Flynn, K.M., Delclos, K.B., Newbold, R.R., Gough, B.J., 2002. Effects of lifelong dietary exposure to genistein or nonylphenol on amphetamine-stimulated striatal dopamine release in male and female rats. Neurotoxicol. Teratol. 24 (1), 37–45.

Foster, L.B., Dunn, R.T., 1974. Single antibody technique for radioimmunoassay of cortisol in unextracted serum or plasma. Clin. Chem. 20 (3), 365–368.

Geens, T., Aerts, D., Berthot, C., Bourguignon, J.P., Goeyens, I., Lecomte, P., 2012. A review of dietary and non-dietary exposure to bisphenol-A. Food Chem. Toxicol. 50 (10), 3725–3740.

Giorgi, O., Piras, G., Lecca, D., Hansson, S., Driscoll, P., Corda, M.G., 2003. Differential neurochemical properties of central serotonergic transmission in Roman high-and low- avoidance rats. J. Neurochem. 86 (2), 422–431.

Gundlah, C., Lu, N.Z., Bethea, C.L., 2002. Ovarian steroid regulation of monoamine oxidase-A and B mRNAs in the macaque dorsal raphe and hypothalamic nuclei. Psychopharmacology 160 (3), 271–282.

Hajszan, T., Leranth, C., 2010. Bisphenol A interferes with synaptic remodeling. Front. Neuroendocrinol. 31 (4), 519–530.

Handa, R.J., Burgess, L.H., Kerr, J.E., O'keefe, J.A., 1994. Gonadal steroid hormone receptors and sex differences in the hypothalamo–pituitary–adrenal axis. Horm. Behav. 28 (4), 464–476.

Hartley, D.E., Edwards, J.E., Spiller, C.E., Alom, N., Tucci, S., Seth, P., Forsling, M.L., File, S.E., 2003. The soya isoflavone content of rat diet can increase anxiety and stress hormone release in the male rat. Psychopharmacology 167 (1), 46–53.

Hassan, W.A., Abdel Rahman, T., Aly, M.S., Shahat, A.S., 2013a. Alterations in monoamines level in discrete brain regions and other peripheral tissues in young and adult male rats during experimental hyperthyroidism. Int. J. Dev. Neurosci. 31 (5), 311–318.

Hassan, W.A., Aly, M.S., Abdel Rahman, T., Shahat, A.S., 2013b. Impact of experimental hypothyroidism on monoamines level in discrete brain regions and other peripheral tissues of young and adult male rats. Int. J. Dev. Neurosci. 31 (4), 225–233.

Heffner, T.G., Hartman, J.A., Seiden, L.S., 1980. A rapid method for the regional dissection of the rat brain. Pharmacol. Biochem. Behav. 13 (3), 453–456.

Hiroi, T., Okada, K., Imaoka, S., Osada, M., Funae, Y., 2006. Bisphenol A binds to protein disulfide isomerase and inhibits its enzymatic and hormone-binding activities. Endocrinology 147 (6), 2773–2780.

Honma, T., Miyagawa, M., Suda, M., Wang, R.S., Kobayashi, K., Sekiguchi, S., 2006. Effects of perinatal exposure to bisphenol A on brain neurotransmitters in female rat offspring. Ind. Health 44 (3), 510–524.

Itoi, K., Jiang, Y.Q., Iwasaki, Y., Watson, S.J., 2004. Regulatory mechanisms of corticotropin-releasing hormone and vasopressin gene expression in the hypothalamus. J. Neuroendocrinol. 16 (4), 348–355.

Kang, J.H., Kondo, F., Katayama, Y., 2006. Human exposure to bisphenol A. Toxicology 226 (2–3), 79–89.

Khan, T.H., Sultana, S., 2011. Antioxidant and hepatoprotective potential of soy isoflavones against ccl4 induced oxidative stress and early tumor events. Indo. Global J. Pharm. Sci. 1 (1), 39–56.

Kulikov, A.V., Zubkov, E.A., 2007. Chronic thyroxine treatment activates the 5-HT2A serotonin receptor in the mouse brain. Neurosci. Lett. 416 (3), 307–309.

Lee, Y.B., Lee, H.J., Sohn, H.S., 2005. Soy isoflavones and cognitive function. J. Nutr. Biochem. 16 (11), 641–649.

Lephart, E.D., Porter, J.P., Hedges, D.W., Lund, T.D., Setchell, K.D., 2004. Phytoestrogens: implications in neurovascular research. Curr. Neurovasc. Res. 1 (5), 455–464.

Liu, L.X., Chen, W.F., Xie, J.X., Wong, M.S., 2008. Neuroprotective effects of genistein on dopaminergic neurons in the mice model of Parkinson's disease. Neurosci. Res. 60 (2), 156–161.

Lueprasitsakul, W., Alex, S., Fang, S.L., Pino, S., Irmscher, K., Kohrle, J., Braverman, L.E., 1990. Flavonoid administration immediately displaces thyroxine (T4) from serum transthyretin, increases serum free T4, and decreases serum thyrotropin in the rat. Endocrinology 126 (6), 2890–2895.

Malendowicz, L.K., Mlynarczyk, W., 1982. Sex differences in adrenocortical structure and function. X. Lipid and corticosterone in the rat adrenal as affected by gonadectomy and testosterone or estradiol replacement. Endokrinologie 79 (2), 292–300.

Matsuda, S., Matsuzawa, D., Ishii, D., Tomizawa, H., Sajiki, J., Shimizu, E., 2013. Perinatal exposure to bisphenol A enhances contextual fear memory and affects the serotoninergic system in juvenile female mice. Horm. Behav. 63 (5), 709–716.

Matsuda, S., Matsuzawa, D., Ishii, D., Tomizawa, H., Sutoh, C., Nakazawa, K., Amano, K., Sajiki, J., Shimizu, E., 2012. Effects of perinatal exposure to low dose of bisphenol A on anxiety like behavior and dopamine metabolites in brain. Prog. Neuropsychopharmacol. Biol. Psychiatry 39 (2), 273–279.

Matsuda, S., Saika, S., Amano, K., Shimizu, E., Sajiki, J., 2010. Changes in brain monoamine levels in neonatal rats exposed to bisphenol A at low doses. Chemosphere 78 (7), 894–906.
Mazer, N.A., 2004. Interaction of estrogen therapy and thyroid hormone replacement in postmenopausal women. Thyroid 14 (Suppl. 1), S27–S34.
Midgeley, J.E., 2001. Direct and indirect free thyroxine assay methods. Theory and practice. Clin. Chem. 47 (8), 1353–1363.
Miller, F.P., Cox, R.H.J.R., Snodgrass, W.R., Maickel, R.P., 1970. Comparative effects of p-chlorophenyl-alanine, p-chloro-amphetamine and p-chloro-N-methylamphetamine on rat brain norepinephrine, serotonin and 5-hydroxy indole acetic acid. Biochem. Pharmacol. 19 (2), 435–442.
Miyagawa, K., Narita, M., Narita, M., Akama, H., Suzuki, T., 2007. Memory impairment associated with dysfunction of the hippocampal cholinergic system induced by prenatal and neonatal exposure to bisphenol-A. Neurosci. Lett. 418 (3), 236–241.
Mizuo, K., Narita, M., Yoshida, T., Suzuki, T., 2004. Functional changes in dopamine D3 receptor by prenatal and neonatal exposure to an endocrine disruptor bisphenol-A in mice. Addict. Biol. 9 (1), 19–25.
Moriyama, K., Tagami, T., Akamizu, T., Usui, T., Saijo, M., Kanamoto, N., Hataya, Y., Shimatsu, A., Kuzuya, H., Nakao, K., 2002. Thyroid hormone action is disrupted by bisphenol A as an antagonist. J. Clin. Endocrinol. Metab. 87 (11), 5185–5190.
Naciff, J.M., Daston, G.P., 2004. Toxicogenomic approach to endocrine disrupters: identification of a transcript profile characteristic of chemicals with estrogenic activity. Toxicol. Pathol. 32 (Suppl 2), 59–70.
Nakamura, K., Itoh, K., Yoshimoto, K., Sugimoto, T., Fushiki, S., 2010. Prenatal and lactational exposure to low-doses of bisphenol A alters brain monoamine concentration in adult mice. Neurosci. Lett. 484 (1), 66–70.
Narita, M., Miyagawa, K., Mizuo, K., Yoshida, T., Suzuki, T., 2007. Changes in central dopaminergic systems and morphine reward by prenatal and neonatal exposure to bisphenol A in mice: evidence for the importance of exposure period. Addict. Biol. 12 (2), 167–172.
O'Connor, T.M., O'Halloran, D.J., Shanahan, F., 2000. The stress response and the hypothalamic–pituitary adrenal axis: from molecule to melancholia. Q. J. Med. 93 (6), 323–333.
Olcese, J.M., De Vlaming, V.L., 1979. Characteristics of monoamine oxidase activity in the hypothalamus of carassius auratus as assayed by a fluorometric technique. Comp. Biochem. Physiol. 62c (2), 213–215.
Poimenova, A., Markaki, E., Rahiotis, C., Kitraki, E., 2010. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A. Neuroscience 167 (3), 741–749.
Sakaue, M., Ohsako, S., Ishimura, R., Kurosawa, S., Kurohmaru, M., Hayashi, Y., Aokil, Y., et al., 2001. Bisphenol A affects spermatogenesis in the adult rat even at a low dose. J. Occup. Health 43 (4), 185–190.
Schwark, W.S., Keesey, R.R., 1976. Cretinism: influence on rate-limiting enzymes of amine synthesis in rat brain. Life Sci. 19 (11), 1699–1704.
Setchell, K.D., Brown, N.M., Desai, P., Zimmer-Nechemias, L., Wolfe, B.E., Brashear, W.T., Kirschner, A.S., Cassidy, A., Heubi, J.E., 2001. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J. Nutr. 131 (Suppl. 4), 1362S–1375S.
Sheng, Z., Kawano, J., Yanai, A., Fujinaga, R., Tanaka, M., Watanabe, Y., Shinida, K., 2004. Expression of estrogen receptors (α, β) and androgen receptor in serotonin neurons of the rat and mouse dorsal raphe nuclei: sex and species differences. Neurosci. Res. 49 (2), 185–196.
Shimizu, H., Bray, G.A., 1993. Effects of castration, estrogen replacement and estrus cycle on monoamine metabolism in the nucleus accumbens, measured by microdialysis. Brain Res. 621 (2), 200–206.
Simon, J.R., Bare, D.J., Ghetti, B., Richter, J.A., 1997. A possible role for tyrosine kinases in the regulation of the neuronal dopamine transporter in mouse striatum. Neurosci. Lett. 224 (3), 201–205.
Simon, N.G., Kaplan, J.R., Hu, S., Register, T.C., Adams, M.R., 2004. Increased aggressive behavior and decreased affiliative behavior in adult male monkeys after long-term consumption of diets rich in soy protein and isoflavones. Horm. Behav. 45 (4), 278–284.
Smith, L.J., Henderson, J.A., Abell, C.W., Betha, C.L., 2004. Effects of ovarian steroids and raloxifene on proteins that synthesis, transport, and degrade serotonin in the raphe region of macaques. Neuropsychopharmacology 29 (11), 2035–2045.
Son, H.Y., Nishikawa, A., Ikeda, T., Imazawa, T., Kimura, S., Hirose, M., 2001. Lack of effect of soy isoflavone on thyroid hyperplasia in rat receiving an iodine-deficient diet. Jpn. J. Cancer Res. 92, 103–108.
Sotomayor-Zarate, R., Tiszavari, M., Cruz, G., Lara, H.E., 2011. Neonatal exposure to single doses of estradiol or testosterone programs ovarian follicular development-modified hypothalamic neurotransmitters and causes polycystic ovary during adulthood in the rat. Fertil. Steril. 96 (6), 1490–1496.
Sun, Y., Nakashima, M.N., Takahashi, M., Kuroda, N., Nakashima, K., 2002. Determination of bisphenol A in rat brain by microdialysis and column switching high-performance liquid chromatography with fluorescence detection. Biomed. Chromatogr. 16 (5), 319–326.
Tan, E.K., Ho, S.C., Eng, P., Loh, L.M., Koh, L., Lum, S.Y., Teoh, M.L., Yih, Y., Khoo, D., 2004. Restless legs symptoms in thyroid disorders. Parkinsonism Relat. Disord. 10 (3), 149–151.
Teede, H.J., Dalais, F.S., McGrath, B.P., 2004. Dietary soy containing phytoestrogens does not have detectable estrogenic effects on hepatic protein synthesis in postmenopausal women. Am. J. Clin. Nutr. 79 (3), 396–401.
Tian, Y.H., Baek, J.H., Lee, S.Y., Jang, C.G., 2010. Prenatal and postnatal exposure to bisphenol A induces anxiolytic behaviors and cognitive deficits in mice. Synapse 64 (6), 432–439.
Tousson, E., Ibrahim, W., Arafa, N., Akela, M.A., 2012. Monoamine concentrations changes in the PTU-induced hypothyroid rat brain and the ameliorating role of folic acid. Hum. Exp. Toxicol. 31 (3), 282–289.
Tsuga, H., Haga, T., Honma, T., 2002. Effects of toluene exposure on signal transduction: toluene reduced the signaling via stimulation of human muscarinic acetylcholine receptor m2 subtypes in CHO cells. Jpn. J. Pharmacol. 89 (3), 282–289.
Wenzel, K.W., 1981. Pharmacological interference with in vitro tests of thyroid function. Metabolism 30 (7), 717–732.
Wetherill, Y.B., Akingbemi, B., Kanno, J., McLachlan, J.A., Nadal, A., Sonnenschein, C., Watson, C.S., Zoeller, R.T., Belcheer, S.M., 2007. In vitro molecular mechanisms of bisphenol A action. Reprod. Toxicol. 24 (2), 178–198.
Whitten, P.L., Lewis, C., Russell, E., NaftoLin, F., 1995. Potential adverse effects of phytoestrogens. J. Nutr. 125 (Suppl. 3), 771S–776S.
Witorsch, R.J., 2002. Endocrine disruptors: can biological effects and environmental risks be predicted? Regul. Toxicol. Pharmacol. 36 (1), 118–130.
Wolstenholme, J.T., Taylor, J.A., Shetty, S.R.J., Edwards, M., Connelly, J.J., Rissman, E.F., 2011. Gestational exposure to low dose bisphenol A alters social behavior in juvenile mice. PLoS One 6, e25448.