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Melatonin Modulates Bisphenol S Induced Alterations in Metabolic Status and Ovarian Functions in Adult Golden Hamster, *Mesocricetus auratus*

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Abstract

Over the past few years, there has been a significant increase in miscellaneous female reproductive disorders that have highlighted the growing concern towards compromised female reproduction. Among various contributing factors, exposure to environmental contaminants such as bisphenols, phthalates, polychlorinated biphenyls and microplastics has been implicated in the disruption of reproductive pathophysiology. Bisphenol S (BPS), earlier believed to be a safe substitute for Bisphenol A (BPA), is established as a potent endocrine disruptor causing adverse health effects. Hence, in the present work, we have demonstrated the pernicious outcome of BPS exposure on peri-gonadal white adipose tissue and ovarian functions, along with the ameliorative potential of melatonin in adult female golden hamsters. BPS was found to induce dyslipidemia as evidenced by the altered serum lipid profile, while melatonin supplementation normalised the effect. Exposure to BPS has also been found to cause hypertrophy of adipocytes in the peri-gonadal region. Further, BPS treatment disrupted ovarian functions by decreasing the expression of BMP-15 and increasing degenerative follicles. However, melatonin treatment reduced the adipocyte dysfunctions and ovarian anomalies. Therefore, from the present study, we can conclude that BPS exposure causes alterations in serum metabolic parameters, adipocytes and ovarian functions, while melatonin ameliorated the negative impacts of BPS.

Keywords: Bisphenol S, Lipid Profile, Ovary, BMP-15, Melatonin, White Adipose Tissue

1. Introduction

Bisphenol S (4,4'-Sulphonyldiphenol) (BPS), a widespread environmental contaminant, is a major substitute of its hazardous analogue Bisphenol A (BPA)[1]. Earlier regarded as a safer alternative, BPS has been associated with increased risk of cancer, metabolic disorders, liver damage, obesity, endocrine disruption, and reproductive malfunctions[2-4]. Indeed, BPS was found in various human samples, including breast milk, urine and serum, conferring about its ubiquitous presence[5-8]. Along with its endocrine-disrupting properties, BPS produces similar effects as BPA, influencing female reproductive health[9]. It has been suggested that BPS exposure induces ovarian dysfunctions, uterine abnormalities, reduced pregnancy rates and nursing issues, developmental disorders and breast tumours that have a significant impact on female reproductive strength[10-13].

Over the years, obesity sets an intimidating remark to human health, and is considered a contributing factor for the surging of various diseases like type 2 diabetes, dyslipidemia, hypertension, osteoarthritis, cardiovascular diseases, *etc*[14,15]. Obesity is also associated with reproductive disorders, especially in women. It is reported to cause anovulation, menstrual disturbances, miscarriages and difficulties in pregnancy outcomes[16].

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The marked alterations in the adipokines, leptin and adiponectin are implicated in hormonal disturbance, ovarian function and endometrial receptivity, expediting infertility[17,18]. Besides, dyslipidemia, accompanying obesity, is further marked by increased Triglycerides (TGA) and free-fatty acids (FFA), increased Low-Density Lipoprotein (LDL) and a striking decrease in high-density lipoprotein (HDL)[19,20]. There have been several findings suggesting that altered lipid metabolism is associated with hormonal imbalance, ovarian and uterine malfunctioning influencing female fertility[21,22].

Among various factors contributing to obesity, exposure to a number of Endocrine Disrupting Chemicals (EDCs) such as bisphenols, phthalates, polychlorinated biphenyls, per- and polyfluoroalkyl substances, *etc*., is among the main contributors[23]. Some studies revealed that BPS exposure can cause hypertrophy of peri-gonadal White Adipose Tissue (WAT)[24,25]. Hypertrophy of WAT can result in hyperinsulinemia, insulin-resistant conditions and ovarian metabolic alterations[26]. Also, BPS is further found to be associated with altered lipid metabolism and obesogenic effects[24,27].

Ovarian folliculogenesis is a prominent feature in female reproduction and is controlled by various paracrine and autocrine factors. Among these factors, BMP-15 (bone-morphogenetic protein 15) plays an essential role in the growth and differentiation of ovarian follicles[28,29]. Alterations in the expression of BMP-15 can be related to various ovarian dysfunctions, especially premature ovarian insufficiency[30].

Melatonin, an amphiphilic hormone synthesised by the pineal gland and extra-pineal sources, including the ovary, has wide ameliorating properties[31]. Melatonin actions in the ovary, mainly via the MT-1 receptor present on the granulosa cells, bring about follicular growth and development[11,32]. It acts as a potent anti-inflammatory, anti-apoptotic, free radical scavenger and a metabolic regulator[33-35]. Melatonin has direct effects on ovarian functions, including steroidogenesis, oocyte maturation, ovulation, and folliculogenesis[36]. Additionally, melatonin modulates obesity by circadian control governing lipid and glucose metabolism[37]. Therefore, our study explored the BPS-induced alterations in lipid metabolic status and ovarian dysfunctions along with the protective effects of melatonin.

2. Materials and Methods

2.1 Animal Procurement and Maintenance

Syrian adult female hamsters were obtained from Central Drug Research Institute (CDRI), Lucknow, India, and maintained in the departmental animal house facility (Reg. NO.1802/Re/S/15/CPCSEA) of Banaras Hindu University, Varanasi, India. The animals were accommodated in polypropylene cages with rice chaff as a bedding material in a properly aerated room maintained at a temperature of 25 ± 2℃ with a 12.5h/ 11.5 h dark light/ dark cycle[34]. They were fed with commercially available food pellets and drinking water in glass bottles *ad libitum*. The animal experimentation used in this study adhered to the principles of the Institutional Animal Ethics Committee (IAEC) of BHU (IAEC Approval Reference No. BHU/DoZ/IAEC/2022-2023/005) under the purview of the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Government of India.

2.2 Chemicals and Reagents

Reagents for animal experimentation, Bisphenol S (CAS no. 80-09-1) and melatonin (CAS #73-31-4), were procured from Sigma Aldrich Chemicals, St. Louis, USA. Lipid profile (total cholesterol, triglyceride, LDL and HDL) kits were purchased from Erba Mannheim, Germany. For Western blotting, Nitrocellulose membrane (product code: #162-0115; 0.45µm), Trans-Blot Turbo 5X transfer buffer (product code: 10026398) and Clarity Western ECL Substrate (product code: #1705061) were acquired from Bio-Rad laboratory, Germany/USA. All routine chemicals used in the current investigation were bought from HiMedia, SRL and Merck Ltd.

2.3 Experimental Design

Adult female hamsters *Mesocricetus auratus* (PND 90) were allocated to four experimental groups (n=7/per group)

Group I: Control (vehicle-treated);

Group II: Melatonin-treated (3 mg/kg BW/ alternate days);

Group III: BPS-treated (150 mg/kg BW/day); and

Group IV: Melatonin and BPS-treated (3 mg/kg BW/alternate days and 150 mg/kg BW/day, respectively).

Melatonin (100 µL) was administered intraperitoneally (i.p.) at a dose of 3 mg/kg BW/alternate day, while BPS (200 µL), dissolved in corn oil, was administered through the oral route at a dose of 150 mg/kg BW/day, every day between 10:30 am and 11:30 am for 28 days. The dosage of both BPS[38] and melatonin[39,40] was selected based on previous findings[11]. Melatonin treatment was started 24 h prior to BPS administration. Melatonin was prepared fresh by dissolving it in ethanolic saline.

2.4 Sample Collection and Processing

Before sacrifice, the body weight of all the animals in each experimental group was measured and sacrificed after 24 hours of the last treatment. To minimise hormonal variability, the oestrous cycle stage was monitored during the experimentation, and animals were sacrificed during the diestrus phase. Blood was collected, and serum was separated and stored at -80°C for further analysis of various parameters. Peri-gonadal white adipose tissue and ovaries of one side were dissected out, weighed and then quickly immersed in aqueous Bouin's solution for fixation, while ovaries on the other side were kept at -80°C for western blotting.

2.5 Histological Analysis

Ovary, and white adipose tissues from each group were fixed in Bouin's fixative for 24 hours at room temperature, dehydrated in different grades of ethanol, cleared in xylene and embedded in paraffin wax. Sections were cut at 7 µm in a microtome (RM2245 semi-automatic microtome, Leica, Germany), spread on 2% gelatin pre-coated slides and maintained at 37°C for 1 week. Staining of deparaffinized sections was done using hematoxylin and eosin. Tissues were then observed under a research microscope for histopathology and morphology (Nikon Eclipse E200, Tokyo, Japan). Histomorphometric analysis was done in randomly selected five sections per slide (n=3 slides/per group), with NIS Element D software.

2.6 Serum Lipid Profile Assessment

Levels of circulatory cholesterol (Erba- 120194), triglycerides (Erba- 120211), LDL (Erba- BLT00043) and HDL (Erba- BLT00029) were measured using the kits as per the manufacturer's details.

2.7 Western Blot Analysis

10% (w/v) ovarian tissues were homogenised with RIPA buffer that includes mixtures of various protease inhibitors, which was then resolved on 12% SDS-polyacrylamide gel electrophoresis (PAGE) for BMP-15 (Cat. No. #PA5-34401). The sample was loaded (65µg/per group) and the proteins were separated based on their size. For each protein targeted n=3 was used as a biological replicate for western blotting. Proteins were further transferred to a nitrocellulose membrane and incubated with the primary antibody overnight (details of antibodies provided in Table 1). Detection was done using HRP-tagged specific secondary antibodies and then visualised using the ECL kit. The relative band intensity was observed by Alpha Imager 2200 software (Alpha Innotech) when β-actin was used as an internal loading control.

Table 1. Details of antibody used in Western Blotting

Antibody	Host species	Dilution	Catalogue no.	Source
BMP-15	Rabbit	1:500	PA5-34401	Invitrogen
β-actin	Mouse	1:2000	A-2228	Sigma-Aldrich
Secondary:				
Rabbit IgG	Goat	1:1500	32 067	GeNei
Mouse IgG	Goat	1:2000	SACO0000083	GeNei

2.8 Statistical Analysis

Statistical analysis was carried out using GraphPad Prism 8 (USA) software with One-way Analysis of Variance (ANOVA) followed by post-hoc Tukey's multiple comparison test for the determination of the levels of significance of the difference between the groups. The differences were considered statistically significant when $p<0.05$.

3. Results

3.1 Effect on Body Weight and Serum Lipid Profile

A significant ($p<0.001$) increase in body weight was documented upon BPS administration, while there was a significant ($p<0.001$) decrease in the body weight of hamsters upon melatonin supplementation (Figure 1A). Serum lipid profile exhibited dyslipidemia in BPS-treated hamsters as apparent by a significant ($p<0.001$) increase in cholesterol, triglycerides and LDL levels, besides a significant ($p<0.05$) decline in HDL level. However, melatonin, along with BPS-treated animals, showed a significant decrease in cholesterol ($p<0.001$), triglycerides ($p<0.01$), and LDL ($p<0.001$) levels as compared to BPS-exposed animals (Figure 1B-E).

3.2 Effect on Histoarchitecture of WAT

The histoarchitecture of peri-gonadal white adipose tissue unveiled a significant ($p<0.001$) increase in diameter and area of adipocytes in BPS-treated female hamsters. However, upon melatonin treatment to BPS-exposed hamsters, a significant ($p<0.001$) decrease was observed in both diameter and area of adipocytes (Figure 2A-F).

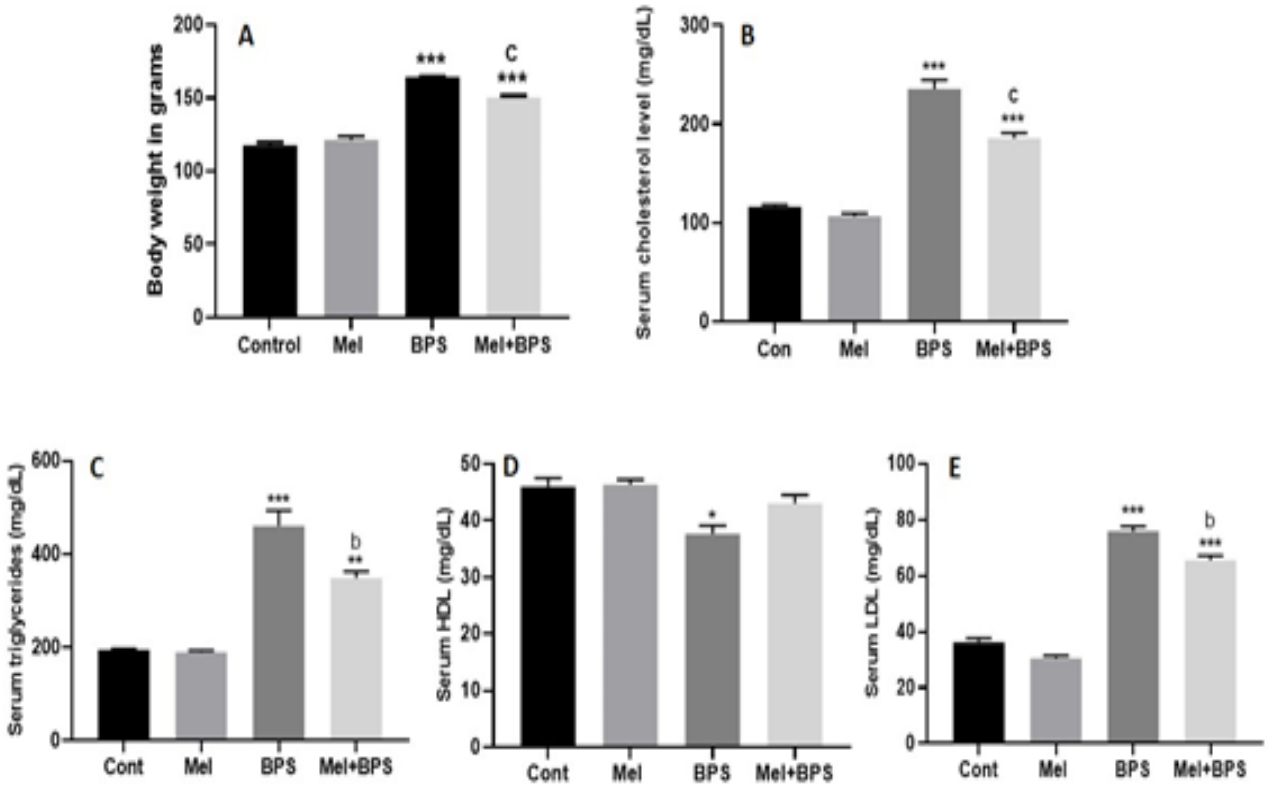


Figure 1. Effect of BPS and melatonin administration on **(A)** Body weight, **(B)** and **(C)** on serum cholesterol and triglycerides level, respectively, **(D)** and **(E)** representing serum HDL and LDL levels. Data are represented as mean ±SEM, where $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ control vs experimental; $^{a}p<0.05$, $^{b}p<0.01$ and $^{c}p<0.001$ BPS vs. Mel+BPS.

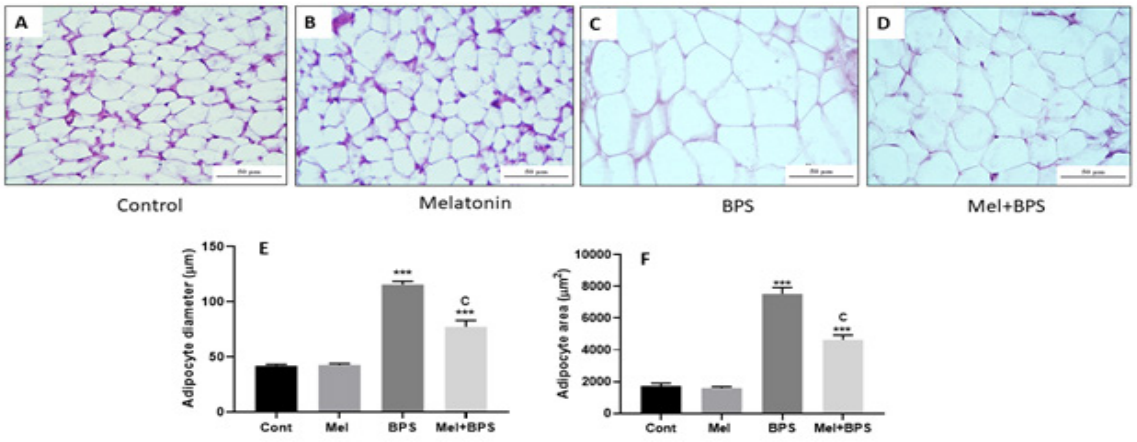


Figure 2. Effect of melatonin and BPS administration on histoarchitecture of white adipose tissue. Photomicrographs showing histology of adipose tissue in **(A)** control hamsters, **(B)** melatonin-treated hamsters, **(C)** BPS-only treated group, and **(D)** Melatonin+BPS group. **(E)** and **(F)** show adipocyte diameter and adipocyte area, respectively. Data are represented as mean ± ***SEM, w***here $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ control vs experimental; $^{a}p<0.05$, $^{b}p<0.01$ and $^{c}p<0.001$ BPS vs. Mel+BPS.

3.3 Effect on Ovarian Histology and BMP-15 Expression

Detrimental changes were observed in ovarian histoarchitecture, shown by a marked increase in the number of atretic follicles and a decrease in the number of growing and healthy follicles and corpora lutea in case of BPS-only treated hamsters in comparison to the control group. However, the BPS-induced impairment was ameliorated upon melatonin treatment with an increase

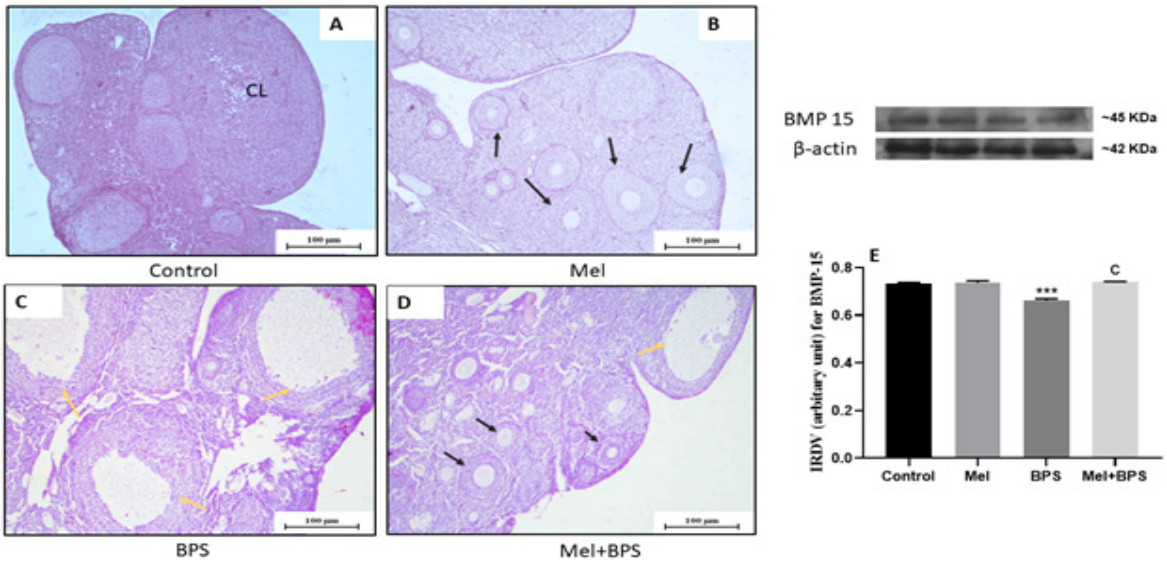


Figure 3. Effect of melatonin and BPS administration on ovarian histology and BMP-15 expression in **(A)** control group, **(B)** melatonin treated animals, **(C)** BPS-exposed hamsters, and **(D)** melatonin + BPS-treated group; **(E)** shows expression of ovarian BMP-15. Black arrows indicate growing follicles and yellow arrows denote atretic follicles; CL: corpus luteum. Data are represented as mean ±SEM, where $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ control vs experimental; $^{a}p<0.05$, $^{b}p<0.01$ and $^{c}p<0.001$ BPS vs. Mel+BPS.

in the number of healthy and growing follicles (Figure 3A-D). Furthermore, a significant ($p<0.001$) decrease in the expression of BMP-15 was reported in BPS-treated animals in comparison to the control group, whereas melatonin supplementation to the BPS-treated hamsters showed a significant ($p<0.001$) increase in the ovarian BMP-15 expression (Figure 3E).

4. Discussion

Bisphenols are widely used plasticisers in the production of polycarbonate plastics and epoxy resins. Due to their environmental persistence and bioaccumulative potential, they have been recognised as endocrine-disrupting chemicals (EDCs)[41]. Bisphenol S (BPS), which is an analogue of Bisphenol A, has been found to cause various deleterious effects influencing female reproductive health. According to various studies, BPS correlates with genotoxicity, influencing ovarian physiology, steroidogenesis, alterations in uterine functions and hormonal imbalance[5,42,43]. BPS also possesses estrogenic potential similar to BPA[7] and also possesses obesogenic effects[25]. Obesity, a major contribution for compromised female reproductive health, has been influenced by various lifestyle factors and exposure to various environmental pollutants[17]. It can also dysregulate ovarian function by increasing androgen production and suppressing the gonadotropins and impairing folliculogenesis and steroidogenesis[44,45].

Infertility is a universal health issue affecting millions of people worldwide, and female infertility is a major problem. Several factors appear to incite various abnormalities in females, including ovarian dysfunctions, uterine and cervical defects, and implantation failure, although approx. 25% of the cases remained unexplained[16,46]. Even if the aetiology remains unclear, exposure to various environmental factors may be a subsidy for the anomalies leading to female infertility[47,48]. These environmental toxins are acquired mainly by hampering normal metabolism and acting as EDCs (endocrine-disrupting chemicals)[49].

The findings of the present study indicated a significant elevation in body weight upon BPS treatment, while melatonin supplementation reversed the effect. Furthermore, a marked elevation in serum LDL (low-density lipoproteins), cholesterol level, and triglycerides, and a decrease in HDL (high-density lipoproteins) causes dyslipidemia in females. Dyslipidemia has been found to be associated with PCOS (polycystic ovarian syndrome) and hyperandrogenism, impairing ovarian functions[50,51]. Alterations in lipid profile also affect steroidogenesis, ovarian and uterine functions, reduced fertility, obesogenic effects, preeclampsia and prolonged time to pregnancy[22,52]. However, upon melatonin administration, the altered lipid profile was normalised.

BPS treatment leads to an increase in diameter and area of adipocytes, resulting in hypertrophy of the cells. Adipocyte expansion under metabolic stress is deleterious as it is susceptible to cause an inflammatory response, apoptosis and release of free fatty acids[26]. These responses are also found to be associated with ovarian defects such as PCOS, DOR (decline in ovarian reserve) and altered expression of steroidogenic enzymes[53]. Further, BPS plus melatonin co-treatment resulted in a reduction in adipocyte mass and hypertrophy. Melatonin promotes the basal lipolysis, activation of PGC1α, promoting mitochondrial biogenesis, decrease of lipid droplet size in white adipose tissue (WAT) and reduced adipocyte hypertrophy and hyperplasia[54].

Bisphenol has been found to be associated with impaired folliculogenesis, disruption of metabolic pathways and ovarian steroidogenic enzymes[11,23]. In this study, BPS exposure leads to a reduced number of healthy and growing follicles observed by the ovarian histoarchitecture, also an increase in the number of atretic follicles was seen in BPS-treated animals. BMP15, which is a member of the TGFβ family protein, is associated with various ovarian functions such as enhancing early folliculogenesis, preventing premature luteinisation, and supporting cumulus cell expansion[28]. Expression of BMP-15 was found to be declining in the BPS group. However, melatonin supplementation against BPS treatment overturned the effects. Hence, metabolic and reproductive anomalies caused by BPS exposure were found to be ameliorated by melatonin treatment.

In conclusion, we examined the adverse effects of BPS treatment on ovarian functions. Marked alterations in lipid profile resulting in dyslipidemia and hypertrophy of peri-gonadal adipose were documented, eventually compromising female reproductive health. Melatonin administration restored the BPS-induced abnormalities. These results indicate that melatonin could be a promising

therapeutic molecule against Bisphenol S-induced metabolic and reproductive abnormalities.

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6. References

1. Mukhopadhyay R, Prabhu NB, Kabekkodu SP, Rai PS. Review on bisphenol A and the risk of polycystic ovarian syndrome: An insight from endocrine and gene expression. Environ Sci Pollut Res. 2022; 29(22):32631-32650. https://doi.org/10.1007/s11356-022-19244-5 PMid:35199272 PMCid:PMC9072519
2. Kinch CD, Ibhazehiebo K, Jeong JH, Habibi HR, Kurrasch DM. Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish. Proc Nat Acad Sci. 2015; 112(5):1475–1480. https://doi.org/10.1073/pnas.1417731112 PMid:25583509 PMCid:PMC4321238
3. Roelofs MJE, Berg M van den, Bovee TFH, Piersma AH, Duursen MBM van. Structural bisphenol analogues differentially target steroidogenesis in murine MA-10 Leydig cells as well as the glucocorticoid receptor. Toxicology. 2015; 329:10–20 https://doi.org/10.1016/j.tox.2015.01.003 PMid:25576683
4. Thoene M, Dzika E, Gonkowski S, Wojtkiewicz J. Bisphenol S in food causes hormonal and obesogenic effects comparable to or worse than Bisphenol A: A literature review. Nutrients. 2020; 12(2):532. https://doi.org/10.3390/nu12020532 PMid:32092919 PMCid:PMC7071457
5. Liao C, Liu F, Guo Y, Moon HB, Nakata H, Wu Q, *et al*. Occurrence of eight Bisphenol analogues in indoor dust from the United States and several Asian countries: Implications for human exposure. Environ Sci Technol. 2012; 46(16):9138–9145. https://doi.org/10.1021/es302004w PMid:22784190
6. Nevoral J, Kolinko Y, Moravec J, Žalmanová T, Hošková K, *et al*. Long-term exposure to very low doses of bisphenol S affects female reproduction. Reproduction (Cambridge, England). 2018; 156(1):47–57. https://doi.org/10.1530/REP-18-0092 PMid:29748175
7. Silva JPA, Ramos JG, Campos MS, da Silva Lima D, de Azevedo Brito PV, Mendes EP, *et al*. Bisphenol-S promotes endocrine-disrupting effects similar to those promoted by bisphenol-A in the prostate of adult gerbils. Reprod Toxicol. 2019; 85:83–92. https://doi.org/10.1016/j.reprotox.2019.02.009 PMid:30822521
8. Yang O, Kim HL, Weon JI, Seo YR. Endocrine-disrupting Chemicals: Review of Toxicological Mechanisms Using Molecular Pathway Analysis. Journal of Cancer Prevention [Internet]. 2015 Mar 1; 20(1):12–24. https://doi.org/10.15430/JCP.2015.20.1.12 PMid:25853100 PMCid:PMC4384711
9. Beatriz A, Filipa Carreiró, Ramos F, Sanches-Silva A. The role of endocrine disruptors in female infertility. Mol Biol Rep. 2023; 50(8):7069-7088. https://doi.org/10.1007/s11033-023-08583-2 PMid:37402067 PMCid:PMC10374778
10. Hill CE, Sapouckey SA, Suvorov A, Vandenberg LN. Developmental exposures to Bisphenol S, a BPA replacement, alter estrogen-responsiveness of the female reproductive Tract: A pilot study. Cogent Med. 2017; 4(1):1317690. https://doi.org/10.1080/2331205X.2017.1317690 PMid:31231671
11. Pal S, Sahu A, Verma R, Haldar C. BPS-induced ovarian dysfunction: Protective actions of melatonin via modulation of SIRT-1/Nrf2/NFκB and IR/PI3K/pAkt/GLUT-4 expressions in adult golden hamster. J Pineal Res. 2023; 75(1):e12869. https://doi.org/10.1111/jpi.12869 PMid:37002642
12. Shi M, Whorton AE, Sekulovski N, MacLean JA, Hayashi K. Prenatal exposure to Bisphenol A, E, and S induces transgenerational effects on female reproductive functions in mice. Toxicol Sci. 2019; 170(2):320-329. https://doi.org/10.1093/toxsci/kfz124 PMid:31132128

13. Zhang MY, Tian Y, Yan ZH, Li WD, Zang CJ, *et al*. Maternal Bisphenol S exposure affects the reproductive capacity of F1 and F2 offspring in mice. Environ Poll. 2020; 267:115382. https://doi.org/10.1016/j.envpol.2020.115382 PMid:32866863

14. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Clinician's corner among US adults, 1999-2008. J Am Med Ass. 2013; 303(3):235-241. https://doi.org/10.1001/jama.2009.2014 PMid:20071471 PMCid:PMC12680873

15. Kelishadi R, Poursafa P, Jamshidi F. Role of environmental chemicals in obesity: a systematic review on the current evidence. J Environ Pub Heal. 2013; 2013:896789. https://doi.org/10.1155/2013/896789 PMid:23840234 PMCid:PMC3687513

16. Dağ ZÖ, Dilbaz B. Impact of obesity on infertility in women. J Turk German Gynecol Ass. 2015; 16(2):111-117. https://doi.org/10.5152/jtgga.2015.15232 PMid:26097395 PMCid:PMC4456969

17. Broughton DE, Moley KH. Obesity and female infertility: Potential mediators of obesity's impact. Fertil Steril. 2017; 107(4):840-847. https://doi.org/10.1016/j.fertnstert.2017.01.017 PMid:28292619

18. Zheng L, Yang L, Guo Z, Yao N, Zhang S, Pu P. Obesity and its impact on female reproductive health: Unraveling the connections. Front Endocrinol. 2024; 14:1326546. https://doi.org/10.3389/fendo.2023.1326546 PMid:38264286 PMCid:PMC10803652

19. Klop B, Elte J, Cabezas M. Dyslipidemia in obesity: Mechanisms and potential targets. Nutrients. 2013; 5(4):1218–1240. https://doi.org/10.3390/nu5041218 PMid:23584084 PMCid:PMC3705344

20. Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. Metabolism. 2019; 92(3):71-81. https://doi.org/10.1016/j.metabol.2018.11.005 PMid:30447223

21. Pugh SJ, Schisterman EF, Browne RW, Lynch AM, Mumford SL, *et al*. Preconception maternal lipoprotein levels in relation to fecundability. Human Reprod. 2017; 32(5):1055-1063. https://doi.org/10.1093/humrep/dex052 PMid:28333301 PMCid:PMC6075456

22. Zhu X, Hong X, Wu J, Zhao F, Wang W, *et al*. The association between circulating lipids and female infertility risk: A univariable and multivariable mendelian randomization analysis. Nutrients. 2023; 15(14):3130. https://doi.org/10.3390/nu15143130 PMid:37513548 PMCid:PMC10384410

23. Dalamaga M, Kounatidis, D., Tsilingiris, D., Vallianou NG, Karampela I, *et al*. The role of endocrine disruptors bisphenols and phthalates in obesity: Current evidence, perspectives and controveirses. Int J Mol Sci. 2024; 25(1):675. https://doi.org/10.3390/ijms25010675 PMid:38203845 PMCid:PMC10779569

24. Ahn YA, Baek H, Choi M, Park J, Son SJ, *et al*. Adipogenic effects of prenatal exposure to bisphenol S (BPS) in adult F1 male mice. Sci Total Environ. 2020; 728:138759. https://doi.org/10.1016/j.scitotenv.2020.138759 PMid:32403013

25. Meng Z, Wang D, Liu W, Li R, Yan S, *et al*. Perinatal exposure to Bisphenol S (BPS) promotes obesity development by interfering with lipid and glucose metabolism in male mouse offspring. 2019; 173:189–198. https://doi.org/10.1016/j.envres.2019.03.038 PMid:30921577

26. Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. Reproduction. 2015; 149(5):R219–R27. https://doi.org/10.1530/REP-14-0435 PMid:25628442

27. Varghese SV, Hall JM. Bisphenol A substitutes and obesity: A review of the epidemiology and pathophysiology. Front Endocrinol. 2023; 14:1155694. https://doi.org/10.3389/fendo.2023.1155694 PMid:37529602 PMCid:PMC10390214

28. Peng C, Clelland E, Tan Q. Potential role of bone morphogenetic protein-15 in zebrafish follicle development and oocyte maturation. Comparative Biochemistry and Physiology Part A Mol Integrat Physiol. 2008; 153(1):83–87. https://doi.org/10.1016/j.cbpa.2008.09.034 PMid:18951993

29. Persani L, Rossetti R, Di Pasquale E, Cacciatore C, Fabre S. 2014. The fundamental role of bone morphogenetic Protein 15 in ovarian function and its involvement in female fertility disorders. Human Reprod Upd. 2014; 20(6):869-883. https://doi.org/10.1093/humupd/dmu036 PMid:24980253

30. Sahni C, Kumar R, Kuma M, Dada R. Integral Role of BMP-15 in Premature Ovarian Insufficiency. Int J Heal Sci. 2022; 6(S6):3555-3564. https://doi.org/10.53730/ijhs.v6nS6.10189

31. Tarocco A, Caroccia N, Morciano G, Wieckowski MR, Ancora G, *et al*. Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care. Cell Death Dis.

2019; 10(4):1–12. https://doi.org/10.1038/s41419-019-1556-7 PMid:30962427 PMCid:PMC6453953

32. Shen M, Cao Y, Jiang Y, Wei Y, Liu H. Melatonin protects mouse granulosa cells against oxidative damage by inhibiting FOXO1-mediated autophagy: Implication of an antioxidation-independent mechanism. Redox Biol. 2018; 18:138–157. https://doi.org/10.1016/j.redox.2018.07.004 PMid:30014903 PMCid:PMC6068202
33. Ferlazzo N, Andolina G, Cannata A, Costanzo MG, Rizzo V, *et al.* Is melatonin the cornucopia of the 21st Century? Antioxidants. 2020; 9(11):1088. https://doi.org/10.3390/antiox9111088 PMid:33167396 PMCid:PMC7694322
34. Hansda SR, Haldar C. Uterine anomalies in cell proliferation, energy homeostasis and oxidative stress in PCOS hamsters, M. auratus: Therapeutic potentials of melatonin. Life Sci. 2021; 281:119755. https://doi.org/10.1016/j.lfs.2021.119755 PMid:34175318
35. Zheng B, Meng J, Zhu Y, Ding M, Zhang Y. Melatonin Enhances SIRT1 to ameliorate mitochondrial membrane damage by activating PDK1/Akt in granulosa cells of PCOS. J Ovarian Res. 2021; 14(1):1-13. https://doi.org/10.1186/s13048-021-00912-y PMid:34758863 PMCid:PMC8582167
36. Basini G, Grasselli F. Role of Melatonin in Ovarian Function. Animals [Internet]. 2024 Jan 1; 14(4):644. https://doi.org/10.3390/ani14040644 PMid:38396612 PMCid:PMC10885985
37. Pivonello C, Negri M, Patalano R, Amatrudo F, Montò T, *et al.* The role of melatonin in the molecular mechanisms underlying metaflammation and infections in obesity: A narrative review. Obesity Rev. 2021; 23(3). https://doi.org/10.1111/obr.13390 PMid:34861097 PMCid:PMC9285339
38. Ghafoor S, Abbasi MH, Khawar MB, Tayyeb A, Saleem T, Ashfaq I, Sheikh N. Bisphenol S Induced Dysregulations in Liver; Iron Regulatory Genes and Inflammatory Mediators in Male Wistar Rats. Environmental Science and Pollution Research. 2022; 29(55):83711-83722. https://doi.org/10.1007/s11356-022-21672-2 PMid:35771333 PMCid:PMC9997876
39. Escribano BM, Muñoz-Jurado A, Caballero-Villarraso J., Valdelvira ME., Giraldo AI, *et al.* Protective Effects of Melatonin on Changes Occurring in the Experimental Autoimmune Encephalomyelitis Model of Multiple Sclerosis. Mult Scler Relat Disord. 2022; 58:103520. Doi:10.1016/j.msard.2022.103520.
40. Ishtiaq A, Ali T, Bakhtiar A, Bibi R, Bibi K, *et al.* 2021. Melatonin Abated Bisphenol A–Induced Neurotoxicity via P53/PUMA/Drp-1 Signaling. Environ Sci Pollut Res Int. 28(14):17789–177801. Doi:10.1007/s11356-020-12129-5.
41. Shen J, Kang Q, Mao Y, Yuan M, Le F, *et al.* Urinary Bisphenol A concentration is correlated with poorer oocyte retrieval and embryo implantation outcomes in patients with tubal factor infertility undergoing *in vitro* fertilisation. Ecotoxicol Environment Safet. 2020; 187:109816. https://doi.org/10.1016/j.ecoenv.2019.109816 PMid:31648075
42. Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, *et al.* Bisphenol S in urine from the United States and seven Asian countries: Occurrence and human exposures. Environ Sci Technol. 2012; 46(12):6860–6866. https://doi.org/10.1021/es301334j PMid:22620267
43. Ziv-Gal A, Wang W, Zhou C, Flaws JA. The effects of in utero Bisphenol A exposure on reproductive capacity in several generations of mice. Toxicol Appl Pharmacol. 2015; 284(3):354-362. https://doi.org/10.1016/j.taap.2015.03.003 PMid:25771130 PMCid:PMC4410077
44. Rachoń D, Teede H. Ovarian function and obesity—Interrelationship, impact on women's reproductive lifespan and treatment options. Mol Cell Endocrinol. 2010; 316(2):172–179. https://doi.org/10.1016/j.mce.2009.09.026 PMid:19818376
45. Wei W, Zhang X, Zhou B, Ge B, Tian J, Chen J. Effects of female obesity on conception, pregnancy and the health of offspring. Front Endocrinol. 2022; 13:949228. https://doi.org/10.3389/fendo.2022.949228 PMid:36034428 PMCid:PMC9409626
46. Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. Reprod Biol Endocrinol. 2018; 16(1). https://doi.org/10.1186/s12958-018-0336-z PMid:29523133 PMCid:PMC5845358
47. Segal TR, Giudice LC. Before the beginning: Environmental exposures and reproductive and obstetrical outcomes. Fertil Steril. 2019; 112(4):613–621. https://doi.org/10.1016/j.fertnstert.2019.08.001 PMid:31561863
48. Zhang N, Zhao Y, Zhai L, Bai Y, Jia L. Urinary Bisphenol A and S are associated with diminished ovarian reserve in women from an infertility clinic in Northern China. Ecotoxicol Environ Safe. 2023; 256(April):114867. https://doi.org/10.1016/j.ecoenv.2023.114867 PMid:37027940

49. Kumar M, Sarma DK, Shubham S, Kumawat M, Verma V, Prakash A, *et al*. Environmental endocrine-disrupting chemical exposure: role in non-communicable diseases. Front Pub Heal. 2020; 8:1–28. https://doi.org/10.3389/fpubh.2020.553850 PMid:33072697 PMCid:PMC7541969

50. Guo F, Gong Z, Fernando T, Zhang L, Zhu X, Shi YL. The lipid profiles in different characteristics of women with PCOS and the interaction between dyslipidemia and metabolic disorder states: A retrospective study in Chinese population. Front Endocrinol. 2022; 13. https://doi.org/10.3389/fendo.2022.892125 PMid:35860700 PMCid:PMC9289193

51. Liu Z, Cong J, Liu X, Zhao H, Lai S, He S, *et al*. Dyslipidemia is negatively associated with the cumulative live-birth rate in patients without PCOS following IVF/ICSI. Front Physiol. 2021; 12. https://doi.org/10.3389/fphys.2021.713356 PMid:34483966 PMCid:PMC8414789

52. Bukhari SA, Zafar K, Rajoka MI, Ibrahim Z, Javed S, Sadiq R. Oxidative Stress-Induced DNA Damage and Homocysteine Accumulation May Be Involved in Ovarian Cancer Progression in Both Young and Old Patients. Turk J Med Sci. 2016; 46(3):583-589. https://doi.org/10.3906/sag-1406-17 PMid:27513230

53. Felmerer G, Stylianaki A, Hägerling R, Wang A, Ströbel P, *et al*. Adipose tissue hypertrophy, an aberrant biochemical profile and distinct gene expression in lipedema. J Surg Res. 2020; 253:294–303. https://doi.org/10.1016/j.jss.2020.03.055 PMid:32407981 PMCid:PMC9560129

54. Xu Z, You W, Liu J, Wang Y, Shan T. Elucidating the regulatory role of melatonin in brown, white, and beige adipocytes. Adv Nutrit. 2020; 11(2):447-460. https://doi.org/10.1093/advances/nmz070 PMid:31355852 PMCid:PMC7442421

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