THE FUNCTION OF MELATONIN HORMONE IN THE REORGANIZATION OF THE IMPACT OF THE OXIDATIVE STRESS INDUCED BY BISPHENOL A IN HYPERLIPIDEMIA ALONG WITH DIABETES IN SERUM OF RATS

Haitham L. Abdulhadi1*, Banan R. Dabdoub2, Loay H. Ali1, Azza I Othman3, Mohamed A El-Missiry3

1Biology Department, College of Education for Pure Sciences, University of Anbar, Iraq
2Biology Department, College of Education for Pure Sciences, University of Mosul, Iraq
3Zoology Department, University of Mansoura, Egypt

*Corresponding author E-mail: hatemloay81@gmail.com (Abdulhadi)

ABSTRACT

Environmental pollution had been a reality of life for several centuries however it became a true drawback since the beginning of the commercial revolution. Environmental contaminants are shown to induce ROS generation in each intra- and animate thing areas of cells or people resulting in cell death and tissue injury. Chemicals that induce effects by uncomfortable endocrine systems or mimicking endocrine mediators are jointly delineated as endocrine disrupting compounds (EDCs).

Bisphenol A, (BPA) (2, 2-bis (4-hydroxyphenyl) propane) is one of the world's highest production volume compounds. It a phenolic compound and is wide utilized in the assembly of resins and polycarbonate plastics. Earlier, it's been shown that BPA induced oxidative stress in numerous tissues in human and rats. This study investigates the results of Bisphenol A pollution on Lipids profile, glucose level, antioxidants and therefore the potential pollution protection by melatonin in experimental. The rats received ten mg/kg of internal secretion pursued by 50 mg/kg of Bisphenol A 3 days per week for 6 incontestable increase triglycerides, total cholesterol, LDL and VLDL, illustrate important in cluster treated with BPA for three and 6 weeks cluster. These were related to the enlarged in lipid peroxidation and cut inhibitor glutathione, superoxide dismutase, enzyme activity and increase in malondialdehyde levels. The protection by internal secretion was determined in connection with the rejuvenation of all oxidative parameters within the blood serum, suggesting that internal secretion is employed for management of many diseases, like avoirdupois, diabetes, cancer, and immune and cardiac disorders. It will recapture ROS by its antioxidant qualities and raise antioxidant enzyme activities.

Keywords: Pollutants, endocrine disrupting chemical, oxidative stress, melatonin, diabetes, antioxidants, bisphenol A

How to cite this article: Abdulhadi HL, Dabdoub BR, et al (2020): The function of melatonin hormone in the reorganization of the impact of the oxidative stress induced by bisphenol A in hyperlipidemia along with diabetes in serum of rats, Ann Trop Med & Public Health; 23 (4): S481. DOI: http://doi.org/10.36295/ASRO.2020.23429

©Annals of Tropical Medicine & Public Health S481
INTRODUCTION

Environmental contaminants are shown to induce Reactive oxygen Species (ROS) generation at intervals every intra- and extracellular areas of cells or people resulting in tissue injury and necrobiosis \(^{(1)}\). Humans are usually principally and conjointly innocently exposed to BPA, and can be detected within the majority of people in several countries worldwide \(^{(2)}\). When BPA is truly consumed through food, it may be apace received from the digestive tract and might be detected in numerous body fluids, organs, furthermore as tissues \(^{(3, 4)}\).

EDCs, like dioxins, bisphenol A and pesticides, cause insulin resistance and convert β-cell operate in animal models. These EDCs are exist in human blood and might accumulate in and be discharged from adipocytes. Once binding to cellular receptors and alternative targets, EDCs either imitate or stop hormonal responses \(^{(5)}\). Moreover, epidemiological proof links BPA levels in excrement with metabolic disorders. These embody type-2 diabetes, ATP rapid insulinotropic action involving BPA cardiovascular diseases and insulin resistance \(^{(6)}\). Diabetes mellitus (DM) is represented as "a disorder of numerous etiology characterized by chronic hyperglycemia with disorder of carbohydrates, protein, and metabolic process ensuing from disturbances in insulin secretion, internal secretion action, or both" \(^{(7, 8)}\). The long run effects of diabetes mellitus carries with it gradual development of the particular complications of retinopathy beside potential blindness, nephropathy which can cause to renal failure, and/ or risk of foot ulcer amputation, Charcot joints, and options of involuntary pathology, as well as sexual dysfunction \(^{(9)}\) and Prolonged high blood glucose cause glucose absorption, that causes to changes within the form of the lenses of the eyes, leading to vision changes; suffered smart glucose manage typically returns the lens to its original form \(^{(10)}\). Melatonin (MLT) syntheses within the pineal gland are reviewed in important detail \(^{(11)}\). Melatonin, a derivative of a vital amino acid, L-tryptophan, synthesized in varied organs like the epiphysis, intestine, retina, bone marrow, cells and skin. Numerous attributes of melatonin distinguish it from a classic secretion like its direct, non-receptor-mediated radical scavenging activity. As melatonin may eaten in foodstuffs as well as vegetables, fruits, wheat, rice additionally to seasoned medicines, from the nutritional purpose of view, melatonin may additionally be categorized as a vitamin \(^{(12)}\). The cell membrane has the very best concentration of MLT followed by mitochondria, cytosol, and nucleus what is more, its inhibitor and preventative qualities against oxidative stress in many laboratory and clinical conditions with an oversized margin of error upon its management \(^{(13, 14)}\).

MATERIALS AND METHODS

Animal exposure

Male Sprague Dawley rats (8-week old, weight 200–220 g) were taken from the lab Animal Center, Mansoura University, Egypt. The animals were kept underneath normal laboratory (temperature 22 ± 2°C; humidity 500th -70%; and 12h (light) /12h (dark) period). Food and water were given ad libitum. All the trials were done according to protocols and global pointers for care and use of lab animals and maintained by the native trial.
committee. Once 2 weeks of acclimation, the rats were at random arranged into six teams. A standard control cluster (n = 6) failed to receive any treatment. Cluster 2 (n = 6) received ten mg/kg weight of internal secretion dissolved in traditional saline 3 days per week for 6 weeks. Cluster three and four (n = 6) was given BPA dissolved in vegetable oil at 50 mg/kg weight three days per week for three and half dozen weeks.

Cluster 5 and 6 (n = 6) took 10 mg/kg of melatonin pursued by 50 mg/kg of Bisphenol A 3 days by week for 6 weeks. The potions of melatonin and BPA were supported previous reports (15, 16).

Biochemical determinations

The insulin and glucose levels in serum were resolved exploitation kits provided by SpinreactAbcam (Cambridge, MA, USA) and (St.Spain), severally. The lipid profiles in blood serum, as well as total lipids, triglyceride, total cholesterol, low-intensity lipoprotein (LDL), high-density lipoprotein (HDL), and extremely low-density lipoproteins (VLDL), were performed in line with the manufacturer’s instructions (Spinreact, St., Spain). interleukin 1 beta (IL-1b) and tumor sphacelus factor alpha (TNF-α) were evaluated exploitation kits conferred by R&D Systems (Minneapolis, MN, USA) and bioscience (San Diego, CA, USA). Lipid peroxidation was assessed by crucial the number of malondialdehyde (MDA).

The superoxide dismutase (SOD) activities, catalase (CAT) activities and also the glutathione (GSH) concentration were examined exploitation kits provided by Biodiagnostic (Giza, Egypt). The protein concentrations were assayed as antecedently delineated (17).

Histopathological study

The pancreas was dissected out, fastened in 10% solution and embedded in paraffin. 4micrometre-thick paraffin sections were stained with haematoxylin and eosin.

Statistical analysis

The results obtained within the present work were evaluated by a technique examination of diversity pursued by Students Keul’s post hoc –Newman check. Information was conferred as mean + sd. statistical significance was thought of as p < 0.05.

RESULTS

The lipid profile, as well as total lipids, triglycerides, total cholesterol, LDL, and VLDL, illustrate important increase in cluster treated with Bisphenol A for 3 and 6 weeks cluster when put next with control (fig. 1). On alternative hand, the concurrent treatment with MLT+BPA for 3 and 6 weeks showed important protection and demonstrated a decrease when put next with BPA only treated teams. whereas HDL showed a significant decrease treated with BPA for 3 and 6 weeks cluster compared with control, and showed important protection and demonstrated increase with MLT+BPA for 3 and 6 weeks teams when put next with BPA only treated teams. The therapy with BPA fulfilled three times per week for 3 and 6 weeks important increases within the MDA levels of the BPA-administered cluster confront with the control and vehicle-treated groups (Fig. 2). The therapy with MLT and Bisphenol Aat the same time resulted in a very important decrease within the MDA levels
within the blood serum compared with the Bisphenol A - treated rats. In distinction, the GSH content in bodily fluid showed a considerably decreased within the BPA-treated rats compared with the control teams (Fig. 2).

The SOD and CAT activities considerably ablated within the BPA-treated teams. The decrease within the level of GSH and antioxidant enzymes was ameliorated within the MLT + BPA-treated teams compared with the BPA-treated cluster. Interestingly, MLT therapy alone produced in a very significant rise in SOD activity compared with the management rats (Fig. 2). Meantime, MLT treatment produced important raises within the CAT activity compared with the control cluster (Fig. 2). The blood serum glucose illustrates significant increase in cluster treated with BPA for 3 and 6 weeks cluster compared with control (Table 1). On different hand, the co-occurring treatment with MLT+BPA for 3 and 6 weeks showed protection and demonstrated significantly lowered blood serum glucose compared with BPA only treated teams. In distinction, a major decrease in insulin levels in cluster treated with Bisphenol A for 3 and 6 weeks cluster when put next with control, these rats had significantly higher insulin levels within the MLT + BPA-treated teams compared with the BPA-treated cluster. TNF-α, IL-1β and HOMA-IR was measured within the blood serum that showed significant increase in cluster treated with BPA for 6 weeks cluster only in TNF-α and for 3 and 6 weeks cluster in IL-1β and HOMA-IR. On different hand, the co-occurring treatment with MLT+BPA for three and six weeks showed significant protection and demonstrated a decrease compared with BPA only treated teams in TNF-α, IL-1β and HOMA-IR. Pancreas the islets of Langerhans were determined to be giant and regular in addition as their limits were known well. The islet cells of Langerhans were found to be in an exceedingly traditional histological appearance (Figure 3). The most important changes within the cluster with BPA were degenerative and necrotic changes within the islet cells of Langerhans. Significant cell loss was observed within the islets as well because the cellular order was disrupted, the islets were wasted and also the structure was deteriorated. Hydropic degeneration and degranulation were ascertained within the protoplasm of degenerative cells. Degenerative and necrotic changes were shaped in just many cells in (BPA- 6 weeks) treatment cluster (Figure 3). A major improvement was observed within the islet of Langerhans of rats in (BPA+ MLT) treatment group rats.
Fig. 1: Impact of MLT and Bisphenol A on total lipids, triglycerides, total cholesterol, LDL, HDL and VLDL, in serum of the control and vehicle-treated rat teams.

*Significant (P<0.05) as compared with control group.
#Significant (P<0.05) as compared with BPA 3 weeks group.
$Significant (P<0.05) as compared with BPA 6 weeks group.
Fig. 2: Impact of MLT and Bisphenol A on the levels of oxidative stress and antioxidants in serum in adult male rats.

* Significant (P<0.05) as compared with control group.

# Significant (P<0.05) as compared with BPA 3 weeks group.

$ Significant (P<0.05) as compared with BPA 6 weeks group.
Figure 3: (control) Normal histological view of pancreas in control group rats at 400X. (MLT): Pancreas section of a rat from MLT group showing a Normal histological view of pancreas. (BPA – 3 weeks): Section of pancreas from BPA treated group rats showing shrunken and distorted islets of Langerhans contained cells with degenerative and necrotic changes. (BPA- 6 weeks): Pancreas section of a rat from BPAGroup showing shrunken and distorted islet of Langerhans displaying cells with vacuolated cytoplasm. (BPA + MLT – 3 weeks) showing normal islet of Langerhans with numerous β-cells with mild necrosis. (BPA+ MLT – 6 weeks): shows the gradual increase in the restoration in the exocrine pancreatic tissue (acinar cells) and endocrine pancreatic tissue (Islets of Langerhans).

Table 1: Impact of MLT and Bisphenol A on the serum glucose (mg/dl) and insulin (pg/ml) levels and TNF-α levels and IL-1b expressed as pg/ml, the percentages of HOMA-IR and testosterone levels (ng/ml) in the different rat groups at the end of the experimental time.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MLT 3 weeks</th>
<th>Bisphenol A 3 weeks</th>
<th>Bisphenol A 6 weeks</th>
<th>BPA+MLT 3 weeks</th>
<th>BPA+MLT 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose mg/dL</td>
<td>83.86± 8.73</td>
<td>76.93± 10.55</td>
<td>198.0± 1.03*</td>
<td>390.5± 4.04*</td>
<td>73.11± 3.65#</td>
<td>92.54± 1.07$</td>
</tr>
<tr>
<td>Insulin pg/mL</td>
<td>99.63± 5.95</td>
<td>119.5± 9.42</td>
<td>79.44± 2.64*</td>
<td>54.88±10.25*</td>
<td>120.2± 9.01#</td>
<td>144.3±7.84*$</td>
</tr>
<tr>
<td>TNF-α</td>
<td>29.08± 28.13</td>
<td>30.46± 1.6</td>
<td>42.85± 2.08*</td>
<td>24.03±1.28*#</td>
<td>23.55±0.98*$</td>
<td></td>
</tr>
</tbody>
</table>
This study investigates the consequences of Bisphenol A (BPA) pollution on Lipids profile, glucose level, and antioxidants and also the possible protection by melatonin in experimental. Rats exposed to BPA (50 mg/kg, i.p.) for 5 weeks showed increased triglycerides, total cholesterol, LDL and vldl, illustrate vital in cluster treated with BPA for three and six weeks cluster in comparison with management (fig. 1). These changes were related to risen lipid peroxidation and reduced antioxidant glutathione and superoxide dismutase. The current investigation additionally increased to estimate the ability of melatonin within the protection against any renal consequences or results that might ensue from BPA \(^{(18)}\). The current study disclosed that BPA administration induced a state of oxidative stress within the heart of rats as evident from the rise in MDA levels and reduce in catalase activity at the two tested doses (10 and 25 mg/kg) once 6 weeks and also the decrease in GSH levels once the administration of the 2 doses of BPA the least bit tested time segments. Increased lipid peroxidation could indicate an increased oxygen free radical generation. BPA induces ROS production and significantly compromises mitochondrial operation \(^{(19, 20)}\). It is thought that melatonin could also be helpful within the management of many diseases, like depression, insomnia, obesity, diabetes, cancer, and immune and cardiac disorders. It will fail ROS by its antioxidant traits and rise antioxidant enzyme activities \(^{(20)}\). Oxidative stress is a disproportion between the assembly of reactive oxygen varieties and antioxidant defenses, inflicting oxidative damage \(^{(21)}\). The current study affirmed that BPA appearance not only increased the oxidant molecule nitric oxide (NO) nonetheless additionally decreased the antioxidant glutathione (GSH) and superoxide dismutase enzyme (SOD) within the kidney tissues. This imbalance managed to renal oxidative stress and, later, renal oxidative damage as proved by an increase lipid peroxidation index, the malondialdehyde (MDA) \(^{(18, 22)}\). Consistent with the present study, BPA has antecedently been shown each in vitro and in vivo to cause oxidative injury during a sort of cells and organs, such as the liver, testes, and pancreas. The relations between high blood serum BPA levels and raised oxidative stress markers have additionally been notified in hemodialysis sufferers using BPA-containing polysulfone dialyzers\(^{(18)}\). The protection by melatonin was recognized in association with the returns of all oxidative parameters (NO, GSH, SOD, and MDA) within the body tissues, proposing that melatonin exercised its renoprotection via antioxidant mechanism. This is often compatible with many publications showing the radical scavenging and inhibitor properties of melatonin.

<table>
<thead>
<tr>
<th></th>
<th>pg/mL</th>
<th>1.2</th>
<th>1.15</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>66.10±1.53</td>
<td>61.91±1.42</td>
<td>82.34±4.78*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>20.92±3.04</td>
<td>22.42±3.36</td>
<td>38.85±1.31*</td>
</tr>
</tbody>
</table>

* Significant (P<0.05) as compared with control group.

# Significant (P<0.05) as compared with BPA 3 weeks group.

$ Significant (P<0.05) as compared with BPA 6 weeks group.
It has been confirmed that melatonin decreases the activity of each constitutive and inducible nitric oxide synthase, the enzymes involved within the creation of the potentially toxic nitric oxide. Melatonin additionally excites the activity and mRNA expression of glutathione peroxidase and will raise the supply of glutathione, additionally to the will increase in alternative antioxidant enzyme activities \((18, 23)\). A recent study indicated that animals that greeted a pinealectomy showed weakened glucose tolerance, insulin impedance, and polygenic disease that were improved by treatment with melatonin. In the high-cholesterol diet rat sample, supplementation with melatonin may reduce plasma total cholesterol and liver cholesterol and triglyceride, and rise plasma high-density lipoprotein-cholesterol (HDL-C). In ZDF rats (Zucker diabetic fatty), supplementation with melatonin not only decreased elevated plasma leptin, insulin, and high blood glucose, however but also raised low levels of adiponectin. During STZ rat sample of streptozotocin-induced DM, supplementation with melatonin decreased abstinence blood glucose (FBG) and improved liver harm, and decreased the oxidative stress \((20)\). In past studies, melatonin administration decreased plasma triglyceride and cholesterol and increased plasma HDL-C level at 10–20 mg/kg in an extremely gene- or diet-induced overweight rat model and an STZ-induced diabetic rat sample. In the high-cholesterol diet rat sample, melatonin may lower plasma total cholesterol and liver cholesterol and triglyceride, and increase plasma HDL-C, that exerted similar impact as hypocholesterolemia agents, cholestryamine. The existing study explained that oral melatonin management may raise plasma HDL-C level and reduce triglyceride and cholesterol in each the plasma and liver of mice with NA/STZ-induced diabetes, which corresponded to previous studies. Melatonin may increase HDL-C level beside lower plasma cholesterol, that resulting in lower total cholesterol/HDL-C ratio \((20)\). Many studies rumored that increased MDA levels in diabetic forms were decreased by melatonin, although whether the glucose level was below or not. Throughout this study, melatonin reduced MDA levels within the liver and plasma. Though, SOD and GPx activities could increase, decrease or sojourn unchanged in diabetic forms. In some studies, melatonin failed to increase SOD or GPx activities but, different researchers reported that melatonin increased SOD or GPx activities. In this study, each hepatic SOD and GPx activities were lower in cluster D. melatonin administration increased liver SOD activity however not GPx activity \((20, 24-26)\).

**CONCLUSION**

Internal secretion is employed for management of many diseases, like avoirdupois, diabetes, cancer, and immune and cardiac disorders. It will recapture ROS by its antioxidant qualities and raise antioxidant enzyme activities.

**ETHICAL CLEARANCE**

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.
FUNDING: Self-funding

REFERENCES

12. Journal of pineal research, Melatonin: a hormone, a tissue factor, an antioxidant vitamin, a paracoid, and an autocoid, 2003,34 75-78.


