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A REVIEW ON HEALTH RISKS OF BISPHENOL A (BPA): IMPACTS ON LIVER FUNCTION AND METABOLIC REGULATION

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ABSTARCT

Bisphenol A (BPA) is a widely recognized endocrine-disrupting chemical found in numerous everyday products, including food containers, medical devices, and consumer goods. Despite its low concentrations in food, chronic exposure to BPA has been linked to a variety of adverse health effects, particularly on liver function and metabolic regulation. BPA's estrogenic, antiandrogenic, and oxidative properties interfere with hormone signaling, leading to disruptions in glucose homeostasis, insulin resistance, and lipid metabolism. The liver, a key organ in detoxification and metabolic regulation, is particularly vulnerable to BPA-induced toxicity. BPA exacerbates oxidative stress, inflammation, and mitochondrial dysfunction, contributing to conditions such as glucose intolerance, hyperinsulinemia, and hepatic inflammation. These effects are further compounded by the potential bioaccumulation of BPA and its ability to interfere with key cellular pathways regulating glucose and lipid metabolism. Moreover, concerns over BPA substitutes, such as bisphenol S (BPS) and bisphenol F (BPF), highlight the need for careful evaluation of their safety and endocrine-disrupting potential. This review underscores the pressing need for continued research into the long-term effects of BPA exposure and the development of safer alternatives to mitigate its health risks.

Keywords: BPA, Glucose Intolerance, Lipid Metabolism, Homeostatsis.

I. INTRODUCTION

Bisphenol A (BPA) is an organic synthetic chemical that is formulated as (CH3)2C(C6H4OH)2 with a molecular weight of 228 Da. With two hydroxyphenyl groups, it belongs to the class of bisphenols and derivatives of diphenylmethane. The Russian chemist Aleksandr P. Dianin created this chemical compound for the first time in 1891 by combining phenol and acetone with the aid of an acid catalyst. Scientists discovered in the 1950s that BPA reacted with phosgene (carbonyl chloride) to form polycarbonate, a clear, hard resin that was widely used in thermal paper, dental compounds, safety and medical devices, and food and drink packaging.

Because of its low volatility, BPA has a half-life of around 4.5 days in water and soil and less than a day in the air. In 2013, it held a 15 billion pound global market share, making it one of the major production chemicals in the synthetics industry. On the other hand, BPA is present in the air because it has attached itself to solid particulates in the atmosphere. They are a vital component of safety equipment such as motorcycle helmets, safety glasses, face guards, and bullet-resistant windows because they can withstand exposure to high temperatures, which allows them to be heated in microwave ovens, and they can withstand high-impact accidents. BPA prolongs the shelf life of food and beverage goods by being a component of epoxy resins in protective coatings, like those lining the inner sides of cans.

Because of their resilience, BPA plastics are used in dental sealants and fillers, incubators, artificial kidneys (hemodialyzers), heart-lung machines, and spectacles. Their light weight and optical clarity make them particularly helpful in these applications. A wide range of other items, such as paper receipts and compact disks, also include the chemical. Leaching out of plastic products is the main way that BPA becomes contaminated. Baby and beverage bottles, food cans, and even medical equipment like polycarbonate hemodialysis machines are among the many environmental, socioeconomic, and age-related variables that can contribute to BPA intake. Human health could be harmed by consuming these tainted foods and beverages, particularly the liver.

There are numerous ways that BPA can enter the body; they include by ingestion, vertical transmission (maternofetal), inhalation, and integumentary contact (skin and eye contact). During any stage of a product's life cycle—production, use, or disposal—BPA may be released into the environment, either directly or indirectly.

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BPA has been found in human placenta and maternal and fetal serum, and it can pass the placental barrier. Exposure to embryos during pregnancy increases the risk and complicates diagnosis because the problems take decades to manifest. Since hormones are involved in both organogenesis and embryo-fetal development at different stages, any disturbance in their function may have an impact on the proper development of an organism. It has also been discovered that BPA is present in umbilical cord blood, follicular fluid, placental tissue, and amniotic fluid in breast milk. Specifically, the presence of this EDC in breast milk, fetal serum, and mother serum may indicate a potential link between long-term BPA exposure during the fetal and neonatal period and long-term negative effects on the newborn.(Lim et al., 2022) BPA can therefore enter the tissues and bodily fluids of a developing human. Diets and sedentary lifestyles alone cannot explain the increased rate of obesity, so researchers have concentrated on BPA's obesogenic and/or diabetogenic effects.(2)

Through their effects on adipocyte, liver, pancreatic, and neuroendocrine metabolism, environmental EDCs can modify glucose homeostasis. Numerous research conducted in the past ten years have shown that BPA is harmful, even at low concentrations. Through the formation of reactive oxygen species (ROS), studies have demonstrated that BPA can harm the liver, kidney, brain, epididymal sperm in rodents, and other organs.

By connecting nuclear and membrane receptors like estrogen receptor α/β (ERα/β), androgen receptor (AR), G protein-coupled estrogen receptor (GPER)—also referred to as G protein-coupled receptor 30 (GPR30)—, insulin-like growth factor-1 receptor (IGF-1R), and estrogen-related receptor gamma (ERRγ), BPA most likely acts in an indirect manner, lowering the biological response associated with their activation by their physiological ligands. It is possible for this substance to directly utilize its effects by stimulating these receptors through BPA.

Reduced BPA concentrations have been demonstrated to disrupt the molecular signaling pathway that results in glucagon release by inhibiting intracellular calcium ion oscillations in α-cells in response to reduced blood glucose levels via a nongenomic method. Low concentrations of endocrine disruptors can alter insulin- and glucagon-secretory cells in the pancreas, upsetting pancreatic physiology and changing how glucose and fat metabolism are regulated. The fundamental processes comprise not only nongenomic but also traditional ER-mediated processes. To fully understand the possible connections to human health, more research is needed.

Interest in BPA substitutions and alternatives has increased as a result of the controversy surrounding the chemical. Producers have developed coatings and polymers free of bisphenol A (BPA), often containing bisphenol S (BPS) and bisphenol F (BPF). Nevertheless, recent studies suggest that these alternatives might have comparable endocrine-disrupting characteristics, casting doubt on their safety and suitability as BPA replacements The search for BPA alternatives has led to the development of other bisphenol equivalents, including bisphenol S (BPS), bisphenol F (BPF), and bisphenol B (BPB)

As alternatives to plastics containing BPA, manufacturers have also looked into non-bisphenol materials such polyethylene terephthalate (PET), polyethylene (PE), and polypropylene (PP) .Nonetheless, questions have been raised over these alternatives' possible effects on the environment and human health, highlighting the significance of thorough safety evaluation.

II. BPA EFFECT ON LIVER

The liver is the largest internal organ and is responsible for maintaining a constant blood glucose level, creating proteins, and detoxifying and metabolizing waste materials. Liver enzymes are essential for carrying out the aforementioned tasks because they accelerate chemical reactions. On the other hand, variations in the amount of liver enzymes may indicate a shift in the bile supply or liver damage. Human health, particularly the liver, may be harmed by consuming tainted foods and beverages. The liver is the main organ involved in the detoxification of a range of drugs and xenobiotics, and it plays a crucial role in the regulation of many physiological functions of the body. It therefore contributes significantly to the removal of ingested BPA.

III. BPA ROLE IN HEPATOTOXICITY

It was previously believed that when BPA (that is, the effective version) is ingested orally, the liver swiftly conjugates the chemical's unconjugated form, which is subsequently eliminated in the bile or urine. Nevertheless, BPA can be deconjugated by the β-glucuronidase enzyme, which is found in many organs, which may cause BPA to bioaccumulate in the body. As an endocrine disruptor, BPA is widely considered toxic to the body and is known to cause oxidative stress by negatively affecting vital organs.

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By interfering with insulin signal transduction and causing a deficiency in Akt phosphorylation, BPA may hinder the liver's ability to oxidize glucose, boosting glycolysis and encouraging the reduction of glycogen formation. Sub chronic exposure to BPA causes structural and functional alterations in the liver, including a markedly higher incidence of parenchymal deterioration and edema.

Animals exposed to BPA had glucose intolerance, hyperinsulinemia, and hyperglycemia after fasting. Male progeny of moms exposed to BPA later on had an obesity-related diabetes phenotype. This phenotype was similar to animals that weren't exposed to BPA but were fed a high-fat diet. By stimulating intracellular signals involving insulin receptor substrate (IRS) proteins and Akt signaling, glucose transporters, such as glucose transporter-4 (GLUT4), are able to absorb and use glucose. To regulate blood sugar levels, insulin increases muscle and adipocyte glucose uptake while blocking the liver's ability to produce glucose.

By triggering oxidative stress, encouraging mitochondrial apoptosis, and blocking the SIRT1/PGC-1α signaling pathway, BPA causes liver damage. Intestinal flora disruption and a decrease in SCFA levels—both linked to hepatoxicity—were further effects of BPA exposure.

One key sign of liver injury is oxidative stress, which is a result of a redox system imbalance. The primary causes of oxidative stress are an overabundance of free radicals, particularly reactive oxygen species (ROS), and a reduction in antioxidant defense, which both start and accelerate liver damage. Overproduction of reactive oxygen species (ROS) in the body can cause lipid buildup, DNA damage, and eventually cell death.

IV. BPA EFFECT ON GLUCOSE AND LIPIDS

BPA exposure may cause metabolic dysfunction that affects glucose homeostasis on multiple levels and has an impact on the main tissues in charge of preserving glucose homeostasis. With a decrease in glucose oxidation and an impairment in insulin signaling, BPA raises glucose production and decreases glycogen synthesis in the liver. Even though the buildup of fat in the liver is a benign process, lipotoxicity and hepatic inflammation arise when the liver's ability to detoxify is compromised. Furthermore, de novo lipogenesis (DNL), the process by which carbohydrates are transformed into fatty acids, increases in response to increased glucose and hyperinsulinemia and decreases levels of the anti-inflammatory cytokine adiponectin (ADP).

The expression of enzymes involved in several stages of lipid metabolism, such as fatty acid oxidation and uptake, triacylglycerol (TAG) synthesis, accumulation, and/or secretion, is coordinately regulated by a complex network of nuclear receptors in the liver (Nguyen et al., 2008). The ligand-inducible transcription factors known as Peroxisome Proliferator-Activated Receptors (PPARs) or α, β/δ, and γ isoforms are responsible for regulating the expression of genes related to lipid homeostasis. The effects of BPA have been studied at the cellular level in adipocytes, where high doses (20–30 μg mL−1) cause lipid accumulation, differentiation, and up-regulation of genes related to lipid metabolism.

Male mice's livers are badly damaged by BPA due to a variety of processes, including inflammation and oxidative stress. The complicated process of inflammation is mediated by free radicals generated by macrophages and proinflammatory cytokines. Superoxide anion and hydrogen peroxide are two examples of reactive oxygen species (ROS) that are produced by liver macrophages in response to hepatotoxicants. Proinflammatory cytokines themselves can cause oxidative stress, even while ROS can boost proinflammatory cytokines.

V. CONCLUSION

To summarize, Bisphenol A (BPA) is a widely used endocrine disruptor with serious implications for human health, notably liver function and metabolic regulation. BPA's ubiquitous presence in the environment, consumer products, and food supply offers continuous health concerns via several routes of exposure, including ingestion, skin contact, and vertical transfer during pregnancy. As a result of its oxidative, estrogenic, and antiandrogenic qualities, endocrine signaling pathways are disrupted, affecting lipid metabolism, insulin sensitivity, and glucose homeostasis. BPA-induced inflammation and oxidative stress in the liver are important contributors to hepatotoxicity, which includes altered lipid metabolism, hyperinsulinemia, and glucose intolerance. BPA's negative effects are further compounded by its capacity to bioaccumulate and interfere with mitochondrial function. Furthermore, BPA's ability to bioaccumulate and alter mitochondrial function amplifies its negative consequences. The intricacy of BPA's effects on metabolic pathways emphasizes the need for more investigation to completely understand its modes of action and long-term health effects. The investigation of

BPA equivalents such as bisphenol S (BPS) and bisphenol F (BPF) has highlighted concerns about their similar endocrine-disrupting qualities, emphasizing the need for ongoing scrutiny of alternatives. In the end, lowering BPA exposure and enhancing safety assessments of possible alternatives are essential actions in minimizing the related health hazards.

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