Bisphenol A (BPA) as a disruptor for molecular and cellular pathways, leading to type 2 diabetes.

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1. Introduction

Worldwide, around 537 million adults have diabetes, primarily type 2, and this figure is projected to reach 783 million by 2045. Additionally, roughly 352 million individuals have abnormal glucose tolerance or abnormal fasting glucose, with 5–10% potentially progressing to type 2 diabetes mellitus (T2DM) each year. The disorder has a complex origin, influenced by various factors such as high-calorie diets, sedentary lifestyle, excess lipid stored in the abdominal cavity, and different rare and typical genetic variations. Type 2 diabetes pathophysiology involves initial hyperinsulinemia, insulin resistance, and a subsequent decline in pancreatic β cell insulin production. The relationship between insulin resistance and the reduction of the function of beta cells plays a key role into to the complexity of T2DM (Ahmad et al., 2022).

In the 1990s, studies linked Bisphenol A (BPA), to glucose metabolism and type 2 diabetes (T2D). BPA, a common endocrine-disrupting chemical, is found in polycarbonate plastics, food can linings, epoxy resins, cash register, recycled paper, receipts, and CD/DVD coatings. Even with brief biological half-lives and brief bioaccumulation, continuous exposure occurs due to widespread product use, resulting in detectable BPA levels in over 90% of individuals (Alonso-Magdalena et al., 2006). BPA, structurally similar to natural 17β-oestradiol, operates through extranuclear estrogen receptors (ERβ and ERα). However, its precise cellular mechanisms remain unclear. Despite potential links between BPA and metabolic disorders, population-based studies on BPA and T2DM risk have yielded conflicting results (Dong et al., 2011). This literature review aims to comprehensively analyse the current research on cellular pathophysiology associated with type 2 diabetes and Bisphenol A, providing a critical evaluation of the existing knowledge and the gaps within the literature.

2. T2DM and BPA, from epidemiological links to pathological evidence

2.1 Normal regulation vs type 2 diabetes

2.1.1 Normal glucose regulation

The pancreas is a vital organ that plays a crucial role in the body, serving both exocrine and endocrine functions. Exocrine functions involve the production of digestive enzymes and hormones, while endocrine functions involve the regulation of metabolism through the releasing hormones (A. & J., 2002). Within the pancreas, there are groups of cells

referred to as Langerhans islets or pancreatic islets who are responsible for generating and releasing hormones such as insulin into the bloodstream. Within these islets, various types of cells exist, each with the responsibility of producing distinct hormones, such as β-cells, which specialize in the production of insulin (Rorsman & Braun, 2013).

Hormones in the pancreas have specific roles. Glucagon elevates glucose found in the blood, while insulin reduces it. Somatostatin hinders the action of both hormones, while PP regulates pancreatic secretion. Insulin-producing β-cells, comprising 65–80% of pancreatic cells, release hormones into the bloodstream in an endocrine manner. These hormones collectively maintain glucose homeostasis when triggered by external signals like stress or nutrient intake (A. & J., 2002). Post-meal, β-cells release insulin, facilitating glucose uptake by muscles and fat tissues, consequently reducing blood sugar. Insulin also supports glycogen, fat, and protein formation. Conversely, while asleep or between meals with low blood sugar, α-cells release glucagon, promoting liver glycogen breakdown and generating glucose (Galicia-Garcia et al., 2020).

These opponents interact within the islet–organ/tissues network, including the liver, brain, gut, muscle tissues and insulin-dependent adipose. This complex system involves signalling molecules like neuropeptides, hepatokines, enteroendocrine hormones, myokines (fibroblast growth factor-21 and IL-6), and adipokines (leptin and adiponectin). They primarily communicate through GPCR signalling pathways, like the cAMP cascade, PI3K, and MAPKK (Röder et al., 2016).

β-cells produce insulin from pre-proinsulin, undergoing modification in the endoplasmic reticulum and maturing into proinsulin. Proinsulin is then moved to the Golgi apparatus, where it transforms into insulin and C-peptide. Mature insulin is kept until released, primarily prompted by high glucose levels (Lustig et al., 1993). Other factors like fatty acids and amino acids can induce release as well. Glucose uptake via GLUT2 prompts catabolism, increasing ATP/ADP ratio. This closes potassium channels, triggering the depolarization of the membrane and Ca^{2+} entry. Increased intracellular Ca^{2+} prompts insulin-containing the fusion of granules with the membrane, causing insulin exocytosis 3. β-cells are well known to release ATP by exocytosing insulin granules when activated by glucose (Halban et al., 2014).

2.1.2 Pathophysiology of type 2 diabetes

Type 2 Diabetes (T2D), a common metabolic disorder, results from faulty insulin secretion by pancreatic β-cells and insulin-sensitive tissues not responding properly to insulin. As insulin plays a crucial role in glucose balance, disruptions in its synthesis, release, or detection can cause metabolic imbalances, contributing to the disease (Schwartz et al., 2016).

Organs implicated in the progression of T2DM include the pancreas (β-cells and α-cells), the liver, the kidneys, the skeletal muscle, the brain, the small intestine, and the adipose tissue (Fu et al., 2013). New findings indicate that issues with adipokines, immune function, gut microbiota , and inflammation may have a significant role in the underlying factors of the condition (Röder et al., 2016).

Traditional views link β-cell dysfunction to cell death. However, recent findings propose a complex interplay between molecular pathways in T2DM-related β-cell dysfunction and the environment. Excessive nutrition, common in obesity, favour hyperlipidemia and hyperglycemia, promoting insulin resistance (IR) and chronic inflammation. In this case, β-cells, varying in genetic susceptibility, face toxic pressures like inflammation, ER stress, and metabolic/oxidative stress, potentially jeopardizing pancreatic islet integrity (Kulkarni et al., 2022).

2.2 Lipids, insulin resistance and glycaemia

BPA functions as a xenoestrogen with phenolic properties in the environment, mimicking the effect of natural estrogen (See figure 1). Various studies have demonstrated that both BPA and E2 trigger a fast, dose-dependent alteration in insulin levels and the glycaemic response in adult mice (Soriano et al., 2012), (Adachi et al., 2005).

A study showcased that being briefly exposed to only one reduced dosage of E2 or BPA provokes a fast reduction in the escalation of glycaemia within the initial 30 minutes following the inaugural injection. This effect is attributed to increased plasma insulin. Moreover, prolonged contact with E2 or BPA at 100 and 10 (µg/kg/day) caused elevated insulin levels in β-cells, an outcome facilitated or mediated by the receptor of estrogen. Being exposed to an elevated bisphenol A dosage led to hyperinsulinemia, displaying plasma insulin levels that can be compared to those witnessed in the later stages of pregnancy. The mice treated with BPA and E2 both showed a 1.7- and 1.53-fold increase in the quantity of insulin found in the blood, respectively, all the while keeping their levels of glucose found in blood consistent. This pattern is indicative of the evolvement of insulin resistance (Alonso-Magdalena et al., 2006).

Similarly, experiments using mice showcased the hyperinsulinaemic impact of BPA, revealing that exposure to BPA for a duration of eight days led to basal insulin secretion suppression and heightened glucose-stimulated insulin secretion (GSIS). Notably, the influence of BPA on blood sugar levels and GSIS ceased entirely in islets from rodents without the ERα receptor, while remaining unaffected in islets from rodents without the ERβ receptor. This implies that bisphenol A enhances the insulin levels in the pancreas through a process that involves activating Erα. (Hagobian et al., 2020), (Ruzzin et al., 2010).

T2DM has been linked with an increased intake of fats. When rodents are subjected to a high-fat diet that includes various fat sources (monounsaturated, saturated fats, and polyunsaturated), it triggers pathological changes closely resembling the ones showed in patients with a (T2D)-like phenotype observed in humans such as insulin resistance (Stott & Marino, 2020), (Strissel et al., 2007), (Kalupahana et al., 2011).

Ding et al. investigated the prolonged impact of bisphenol A, which was 50 µg/kg/day, with a high fat diet. After 35 weeks, male rats treated with bisphenol A displayed significantly higher glucose levels than the untreated controls. Additionally, combining BPA with a high-fat diet caused a greater increase in glucose levels compared to a high-fat diet only. Furthermore, BPA-treated rats on a regular diet exhibited elevated insulin,

increased HOMA-IR, and reduced ISI in comparison to the control group. The sustained hyperglycemia, despite heightened insulin induced by BPA, suggests disturbed glucose homeostasis and insulin resistance (Ding et al., 2014).

Similarly, a study carried out by Marmugi and their colleagues, provided higher doses of bisphenol A to male mice aged 6 weeks for 32 weeks using water. Prolonged exposure triggered a rise, which was dose dependent, in the amount of plasma glucose. Moreover, mice given the highest dose exhibited markedly dysregulated glucose tolerance compared to controls. Notably, this research found no difference relevant in a significant way in plasma insulin levels between controls and rodents treated with bisphenol A (Marmugi et al., 2014). Moon and their colleagues presented another study that found that 12 weeks of fifty μg/kg/day bisphenol A exposure orally to mice on HFD induced insulin resistance and glucose intolerance (Moon et al., 2015). Consistent with the study carried out by Marmugi and colleagues, there was not a significant statistically rise observed in the insulin levels when fasting comparing the control group and the group treated with bisphenol A (Marmugi et al., 2014).

According to Ding et al., high-fat diet results in elevated total cholesterol levels and serum triglycerides evaluating the results from the diet that was standard; nevertheless, no notable distinction in fat characteristics was noted in the untreated groups and the BPA-treated patients (Ding et al., 2014). However, Marmugi and colleagues, illustrated an elevation in the total amount of cholesterol in mice in contact with bisphenol A, a phenomenon regulated by the increased expression of hepatic genes associated with de novo cholesterol biosynthesis (Moon et al., 2015).

The findings from Ding et al. indicate that both BPA and a high-fat diet result in elevated glucose levels. Notably, even mice exposed solely to BPA in a normal diet exhibited heightened insulin levels. Consequently, the lipid profile outcomes, plasma insulin levels and insulin resistance from the previous studies align, except for Marmugi et al., and Moon et al., study, where an increase in cholesterol and no insulin resistance was observed in both untreated and BPA-treated groups, in contrast to other studies that found no differences in lipid profiles. A thorough understanding is needed to gain a clearer insight into the complex interactions among lipid metabolism, plasma insulin resistance, and BPA exposure.

2.2.1 BPA and β-cells ion channels regulating glucose-stimulated insulin secretion (GSIS)

Recent research emphasizes BPA's influence on the ion channels of beta cells regulating glucose-stimulated insulin secretion. When fasting, low ATP:ADP ratio rises the ATP-sensitive potassium channels activity, hyperpolarizing β-cell membranes. Post-meal glucose uptake raises ATP:ADP ratio, generating oscillatory currents, alternating between depolarized and hyperpolarized phases, mediated by Ca^{2+} and Na+ channels. This alteration involves Ca2+ and Na+ channels, sparking action potentials and insulin release via Ca2+-activated K^{+} channels. The result is a rhythmic pattern of Ca^{2+} release. A study carried out by Martinez-Pinna and their colleagues, found that exposing beta

cells from rodents to bisphenol A disrupts their electrical activity (Martinez-Pinna et al., 2019).

Electrophysiological studies on BPA-exposed mice islets reveal reduced K^+ and Na+ channel activity. Analysis of gene expression reveals dysregulation of genes associated with sodium (Na+) and potassium (K+) channels, including KCNIP1, KCNMA1, KCNB2, and SCN9A. Notably, these influences were absent in beta cells from rodents without estrogen receptor β, insinuating that the BPA influence of Na+ and K+ currents relies on estrogen receptor β. Essentially, the amount of bisphenol A utilized in this trial matches the one present in non-rodent blood, and modifications in the expression or functioning of the ion channels of beta cell are linked with type 2 diabetes (Martinez-Pinna et al., 2019).

Alterations in the electrical motion of beta cells, induced by BPA, can play a key role in the abnormal secretion of insulin and development of diabetes. Oral BPA inhibits glucose-stimulated secretion of insulin in individuals with obesity in human studies, suggesting varied impacts on early and later insulin responses such as release of stored insulin and de novo synthesis (Martinez-Pinna et al., 2019). Murine studies support this, indicating BPA effects on insulin secretion depend on glucose presence, concentration, and involve Erα and ERβ (Villar-Pazos et al., 2017).

Soriano et al. showed that ERβ regulates KATP channel activity, the flow of Ca2+ and the release of insulin are impacted by doses of BPA that are environmentally relevant. BPA notably decreased KATP channel activity by nearly 50% in both mouse and human islets, enhancing insulin secretion and pulsatile Ca2+ release. The absence of these effects in ERβ−/− mice affirms that si induces alterations in insulin secretion through the mediation of ERβ. Considering the similar BPA concentration in serum to the study dose, additional research is needed to investigate the role of other estrogen receptors in β-cells. This is particularly important as unusual actions when connected to bisphenol A should be considered. Conducting more essential human β-cell studies is crucial, addressing potential distinctions between rodent and human physiology (Soriano et al., 2012).

2.3 B-cell morphology and BPA doses

BPA exhibits reduced estrogenic activity compared to other phenolic estrogen contaminants such as nonylphenol, octyphenol, and diethylstilbestrol (Laws, 2000). In a study by Lin et al., various doses of BPA were examined using cell culture. The findings strongly suggest that a 48-hour exposure to BPA has a dose-dependent impact on the function and viability of healthy beta cells. Additionally, it increases the rate of cellular death in INS-1 cells (Lin et al., 2013).

Bisphenol A (BPA) triggers apoptotic signaling in B-cells by upregulating the expression of the pro-apoptotic Bax protein and downregulating the expression of the anti-apoptotic Bcl-2 protein. Structural abnormalities in mitochondria of rat β-cells have been observed as a precursor to changes in glucose homeostasis after contact with 50 µg/kg/day of BPA. These findings suggest that perinatal contact to the previously mentioned dose of BPA (50 µg) disrupts normal glucose regulation in adult rat

descendants on a standard diet and predisposes them to metabolic challenges when on a high-fat diet. Importantly, the high-fat diet serves as a trigger that activates metabolic effects associated with BPA exposure (Wei et al., 2011).

Studies employing transmission electron microscopy (TEM) showed that 25 µg/L of bisphenol A leads to a high number of empty vesicles and a reduction in the number of insulin vesicles containing content (Song et al., 2012). Likewise, prolonged exposure to bisphenol A results in an elevated β-cell mass caused by the expansion of islets, a phenomenon exacerbated by a high-fat diet (Ding et al., 2014). Inconsistencies in results have been documented as well. Moon et al. did not find any alterations in the islet morphology of mice who were in contact with HFD and BPA when comparing the results to those receiving high fat diet alone. Under electron microscopy, there were no discernible variations in the quantity and structure of mitochondria, same as the insulin content within the cells (Moon et al., 2015). The variability in outcomes can, in part, be explained by variations in mice species, duration, age, route, and intensity of exposure. However, a more comprehensive analysis would be needed to give a clear understanding of these variabilities and the impact on the outcomes.

In a comparable investigation, Song et al. illustrated that when using rat islet cells at a level of 2.5 µg/L, BPA reduces the vitality of β-cells. Intriguingly, a comparable influence was noted at considerable higher concentrations of alternative estrogenic pollutants. This finding will be further discussed below. The size of β-cells got bigger when exposed to BPA levels between 25 and 2.5 µg/L but smaller in a 250 µg/L dose, probably because it harms the cells due to its cytotoxic effects at this higher level. It was seen that phenolic estrogen and E2 below 2.5 µg/l elevated insulin release and consequently, the amount of insulin was higher. In addition, this study demonstrated that bisphenol A and other phenolic estrogens trigger structural changes in beta cells. In BPA-treated islets, distinct changes were noted, including compromised function of mitochondrial cytochrome c oxidase, swelling of β-cell mitochondria associated with structural damage, and decreased levels of ATP in the cytosol (Song et al., 2012). These findings are in line with the idea explored by Alonso-Magdalena et al., indicating that the heightened release of insulin in response to glucose stimulation in islets treated with phenolic compounds may be a result of their elevated insulin levels (Alonso-Magdalena et al., 2006).

2.3.1 Interaction of BPA with human islet amyloid polypeptide (hIAPP)

Other mechanism linked with β-cell apoptosis and reduction in β-cell mass is the interaction of BPA with human islet amyloid polypeptide (hIAPP), which is a soluble polypeptide. It consists of 37 building blocks, produced by the β-cells and released alongside insulin. The role of hIAPP in β-cells is not entirely clear, and it's quite challenging to differentiate between its normal and potentially harmful effects (Westermark et al., 2011).

In normal functioning, it helps regulate blood sugar levels by supressing glucagon and insulin secretion, slowing down stomach emptying, and signaling the brain satiety. Additionally, hIAPP monomers have a natural tendency to misfold, creating structures

called β-sheet oligomers that join together in linear fibrils. These fibrils and oligomers then harm pancreatic β-cells by causing disruptions and permeabilization in their membranes (Brender et al., 2011). Extensive research has solidly established the link between type 2 diabetes and hIAPP, as evidenced by studies revealing the presence of IAPP aggregates in most of patients affected with diabetes. Furthermore, a geographical association has been observed, connecting IAPP deposits with the decline in the mass of beta cells. (Lorenzo et al., 1994).

IAPP clusters integrate into the membrane of beta cells, leading to the release of cellular contents and, with time, cell death. Importantly, experiments conducted in a laboratory setting using a cell line from rat insulinoma revealed that BPA influences the aggregation of hIAPP and the disruption of cell membranes in a manner that depends on the dosage. When the cell membrane allows more substances to pass through, calcium ions (Ca2+) get into the cell and cause the production of toxic reactive oxygen species (ROS). This happens when both hIAPP and BPA are present, not just bisphenol A alone, hinting they might work together (Sellin et al., 2010). A study carried out by Gong et al. indicates that bisphenol A could be important when developing type 2 diabetes mellitus by influencing the survival of β-cells. Normally, hIAPP tends to form harmful structures, but its interaction with inhibitors like insulin and zinc ions usually prevents this (Gong et al., 2013).

Certain authors have proposed a hypothesis suggesting the development of IAPP aggregates is a crucial factor in the progression from insulin resistance in an early stage to fully manifested type 2 diabetes. When the body compensates for insulin resistance with increased insulin production, more hIAPP is also produced, causing elevated endoplasmic reticulum stress. This heightened stress further contributes to the decline of β-cells, ultimately resulting in increased production of insulin and IAPP in the remaining β-cells (Costes et al., 2010), (Gong et al., 2013). Despite these insights into the potential role of IAPP aggregates in the progression of type 2 diabetes and the impact of insulin resistance, the mechanisms underlying their formation, the consequential effects on pancreatic β-cells, and the specific involvement of BPA in this process remain incompletely understood.

2.3.2 BPA doses relationship

BPA and other phenolic estrogen contaminants with reduced estrogenic activity, the correlation between insulin secretion and the doses exhibited an inverted U-shaped pattern, initially increasing and then decreasing (Song et al., 2012). These results are also in line with the outcomes reported by Wei et al., where exposure to BPA (50 µg/kg per day) during perinatal stages led to elevated insulin levels and impaired glucose regulation in the mice offspring. Notably, these effects were not evident at higher doses (Wei et al., 2011).

This finding suggests a dose response non-monotonic indicating that exposure to low doses of certain endocrine-disrupting chemicals (EDCs) may have a more pronounced effect on modifying β-cell function. However, there is no immediate explanation for this

phenomenon, hinting at the existence of two different mechanisms for low and high doses. Alternatively, the non-linear dose-response pattern seen with bisphenol A could be a result of its influence on the kinetics and specificity of receptors (Duan et al., 2018), (Wang et al., 2019).

The connection between BPA and metabolic outcomes is difficult to establish, given evidence from studies showing a non-linear dose-response curve.Numerous studies previously discussed in this literature review highlight negative outcomes at BPA levels considerably lower than the recommended intake per day established by the US Environmental Protection Agency (50 µg/kg–bw/day) and the old tolerable daily intake (TDI) from the European Food Safety Authority (EFSA) (4 µg/kg–bw/day).

In April 2023, EFSA reassessed the tolerable daily intake based on recent scientific evidence, replacing the earlier provisional level of 4 micrograms (4µg or 4 millionths of a gram) with a TDI of 0.2 nanograms (0.2ng or 0.2 billionths of a gram) per kilogram of body weight per day (kg/bw/day) (European Food Safety Authority, no date). This suggests that extremely high BPA doses may not fully capture the complete range of impact on the cells. Numerous studies have outlined negative impacts of bisphenol A at levels under the standard safe threshold. Additionally, xenoestrogens like bisphenol A can synergistically interact with the body's natural estrogen, implying that even reduced doses of BPA may be enough to interrupt specific endocrine functions (Vom Saal & Hughes, 2005).

A number of substances display a linear pattern, leading regulatory bodies to typically assume a linear relationship when determining the safe dosage range for a specific substance. Even in epidemiological studies, there's an assumption of a linear relationship between the risk of type 2 diabetes and BPA exposure, even if this might not accurately represent the actual dose–response relationship (Welshons et al., 2003).

Given that many endocrine-disrupting compounds (EDCs) exhibit a non-linear dose-response curve, the highest dose of an EDC may not be most impactful. Importance should be given to identifying the dose that produces the maximum abnormal effects on a particular pathway (Marmugi et al., 2014).

Considering the substantial evidence supporting a non-linear dose–response outcome for bisphenol A, additional analysis is essential to revaluate the accepted range of safe exposure like the EFSA implemented and additionally, to gain a deeper understanding of the molecular mechanisms driving such a response.

2.4 Impact of bisphenol A on other tissues

BPA exposure in animal studies alters feeding patterns and whole-body metabolism. It leads to changes in the melanocortin system, evidenced by reduced proopiomelanocortin expression and increased neuropeptide Y and leptin levels in the arcuate nucleus, impacting energy balance. BPA-treated mice, compared to controls, show reduced overall energy expenditure, spontaneous activity, and nocturnal food

intake, possibly influenced by BPA's estrogenic properties affecting the central nervous system and leptin and insulin levels (Batista et al., 2012).

Skeletal muscle, with its high metabolic demand and insulin sensitivity, represents a crucial role in the regulation of circulating glucose. Contact to doses of bisphenol A that are environmentally relevant doses of BPA can alter insulin-signaling pathways in muscle, impacting processes like insulin receptor signaling and glucose homeostasis. BPA-treated mice show a high regulation of insulin receptor substrate 1 (IRS1) in skeletal muscle, leading to impaired insulin-stimulated phosphorylation of the insulin receptor β subunit and reduced Akt phosphorylation. These alterations suggest the onset of insulin resistance in peripheral tissues, a pivotal characteristic of type 2 diabetes. Comparable findings in Akt phosphorylation were observed in investigations involving muscle cells from individuals diagnosed with T2DM. (Batista et al., 2012), (Hagobian et al., 2020).

BPA induces similar disruptions in insulin signaling in hepatocytes as seen in skeletal muscle. BPA exposure upregulates IRS1 in the liver, affecting lipid and glucose metabolism. Both acute and chronic BPA exposure reduce glucokinase activity under various glucose concentrations, contrary to estrogen's stimulatory effect. Prolonged contact with 500 μg/kg/day BPA increases glucokinase and pyruvate kinase enzymes (Bindhumol et al., 2003). BPA triggers oxidative stress in hepatocytes, decreasing antioxidant enzyme activities, and is associated with alterations in the activity of the liver, hepatocyte apoptosis, and DNA damage in animal studies (Kim et al., 2018), (Thoene et al., 2017). BPA also stimulates lipid accumulation in the liver, potentially contributing to non-alcoholic fatty liver disease, a common issue in type 2 diabetes mellitus (Shimpi et al., 2017).

Extended BPA exposure in adult mice for eight months significantly upregulates genes related to de novo lipogenesis, including encoding fatty acid synthase, THRSP, SDC1, PNPLA3, and SREBF1. This long-term BPA exposure also increases key enzymes in de novo cholesterol biosynthesis, such as HMG-CoA reductase. While hepatic cholesterol levels rise, there is not any alteration who is significant in cholesteryl esters and hepatic triglycerides (Fang et al., 2022). The increased expression of these genes aligns with hyperinsulinemia and metabolic deregulation observed in Marmugi et al., contradicting some findings suggesting a reduction in insulin secretion. However, this inconsistency can be attributed to the varied impact of BPA on the initial and final stages of insulin secretion (Marmugi et al., 2014).

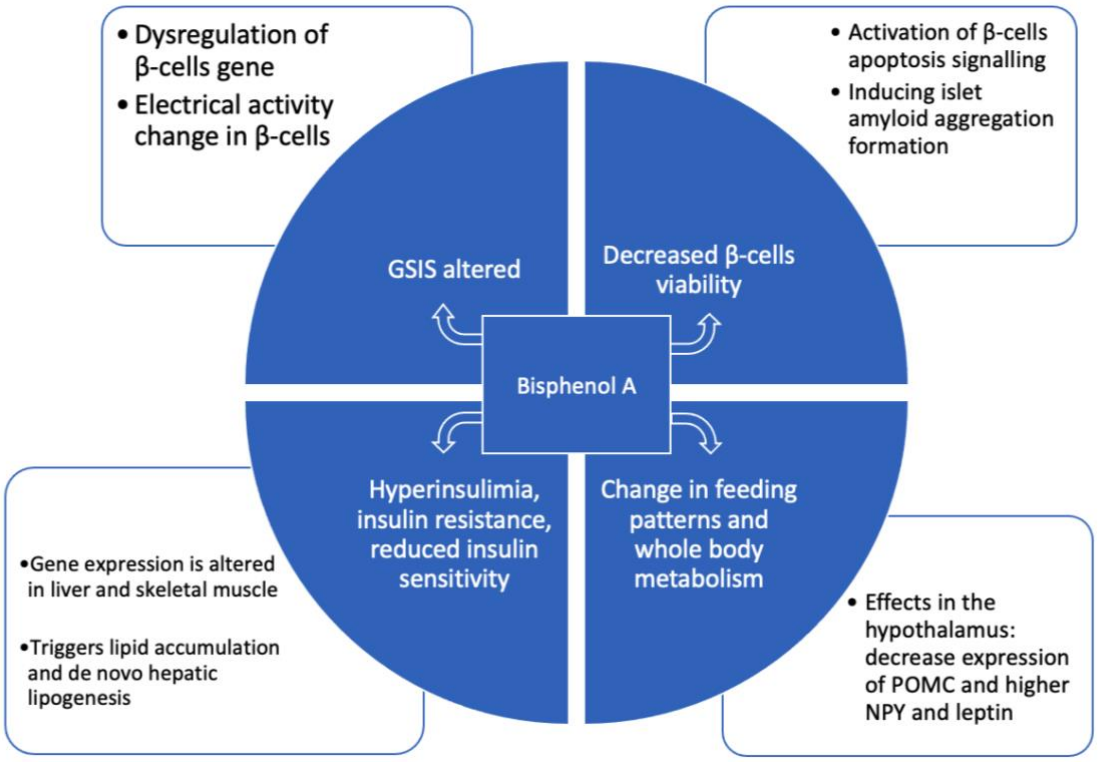

Figure 1: *a diagram summarizing how the main pathophysiological pathways affected by BPA in T2DM. BPA influences various tissues that control glucose balance in different ways. It may change the production of insulin in the pancreas, affecting both the early and late phases of glucose-stimulated insulin secretion. BPA also impacts insulin sensitivity in muscles and the liver, increases lipogenesis, decreases the release of adiponectin, and alters eating habits through various pathways in the brain.*

3. Conclusion

The extensive evidence shows how BPA, as a xenoestrogen, influences pathways related to T2DM development. It affects various tissues involved in glucose regulation, impacting pancreatic insulin release, β-cell gene expression, adipocytokine function, and insulin sensitivity in the liver and muscles. It influences various tissues, impacting pancreatic insulin release, beta cell gene expression, structure, electrical activity, and apoptosis. BPA also alters the function of adipocytokine, insulin sensitivity in the liver and muscles, stimulates lipogenesis, and influences central nervous system pathways regulating metabolism.

Despite conflicting population-based findings, limited follow-up studies, self-citation, the controversy around unconjugated BPA in blood, and distinctions within the human and rodent physiology, lessons from this research can guide prioritization of endocrine-disrupting chemicals (EDCs) in public health. Healthcare professionals should be mindful of the indirect impacts of bisphenol A on the risk of chronic diseases and human development, considering the complex factors contributing to disorders like T2DM.

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