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Review

Molecular dissection of cellular response of pancreatic islet cells to Bisphenol-A (BPA): A comprehensive review

Oly Banerjee [a], Siddhartha Singh [a], Ishita Saha [b], Swagata Pal [c], Maitrayee Banerjee [d], Sudipta Kundu [e], Alak Kumar Syamal [f], Bithin Kumar Maji [a], Sandip Mukherjee [a,*]

[a] Department of Physiology, Serampore College, 9 William Carey Road, Hooghly 712201, India
[b] Department of Physiology, Medical College & Hospital, Kolkata 700073, India
[c] Department of Physiology, Raja Peary Mohan College, Hooghly, India
[d] Department of Physiology, Krishnagar Government College, Nadia-741101, West Bengal, India
[e] Department of Physiology, Kalka Dental College, Partapur By-Pass Road, UP, India
[f] Department of Physiology, Hooghly Mohsin College, Chinsurah, Hooghly, India

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ABSTRACT

Bisphenol A (BPA) is an endocrine disrupting chemical which poses great concern because of its high proportionate industrial production, omnipresent human exposure and budding toxic consequences in human. A plethora of previous studies has connected BPA to a variety of negative health outcomes and diabetes mellitus is among the first bencher. However, there is disagreement over the degree of toxic effects generated by low and high doses of BPA and critical period of exposure. Furthermore, the safe level of BPA determined by classical toxicological studies does not protect pancreatic islet cells from low dose effects of BPA. Thus, the extremities of toxic effects on pancreatic islets associated with BPA exposure are complicated and contentious. In this review, we highlighted different cellular and molecular pathways targeted by BPA to mediate its action on pancreatic islets with consideration of both low and high dose effects. Besides estrogen receptor α and β, BPA also uses non canonical membrane bound estrogen receptor and G-protein coupled estrogen receptor to confer its toxic effects. In doing so, BPA modulates ion channels, and transcription factors; causes aggregation of human islet amyloid polypeptide, endoplasmic reticulum and mitochondrial stress; and results in activation of NFκB in pancreatic β cells. BPA also renders a major shift in β to α cell ratio in islets causing deregulated glucagon secretion. Hence, understanding of various mechanisms of BPA action on the pancreatic islets will provide meaningful insights in recognizing the risk posed by exposure to low and high doses of BPA.

1. Introduction

The emergence of type 2 diabetes mellitus (T2DM) as global pandemic poses a major threat to human health in the 21st century. T2DM, which was once considered as the disease of the affluent "Western" countries of Europe and North America, has now spread to almost every part of the world. According to the latest report of the International Diabetes Federation (IDF, 2021), more than 537 million adults (20–79 years) worldwide as of 2021 are suffering from diabetes; which is likely to increase to 783 million by 2045 [1]. T2DM and its complications are majorly responsible behind the global load of disability and mortality. The number of people living with type 2 diabetes quadrupled between 1980 and 2014 globally [2]. It is assumed that within 2010 and 2030, the number of adults suffering from diabetes mellitus would increase up to 20% and 69% in developed countries and in developing countries respectively [3]. In continuation, Asia seems to be a major region with rapidly increasing T2DM epidemic. According to International Diabetes Federation Atlas (2021) [1], China and India are marked as the top two epicentres of the global epidemic of T2DM. While some contributing factors can be well-identified (e.g. sedentary lifestyles, diet, age and ethnicity), other diabetes-triggering risk factors are less studied or poorly acknowledged. These lesser studied risk factors include environmental exposures to diabetogenic toxicants [4].

Notably among the various environmental risk factors, significant number of evidence suggests that exposure to environmental endocrine disrupting chemicals (EDCs) might have a pivotal role in the onset of

* Corresponding author at: Department of Physiology, Serampore College, 9 William Carey Road, Serampore, Hooghly-712201, West Bengal, India.
E-mail address: sandip@seramporecollege.ac.in (S. Mukherjee).

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T2DM [5]. Bisphenol A (BPA) is one such environmental contaminant that has evoked great concern as a potential endocrine disrupting compound with diabetogenic outcome [6–7]. Many recent studies also have highlighted that BPA was a supplemental risk factor to be considered in the development of insulin resistance and T2DM [8–10]. In a *meta*-analysis, Huang et al. (2019) reported that both serum and urinary BPA levels showed a positive association with risk of T2DM [11]. Furthermore, experimental studies also reported that BPA might contribute to or aggravate the progression of T2DM [12,13]. It has been reported that BPA was associated with promptly growing number of metabolic disorders such as obesity and T2DM through genomic as well as nongenomic estrogen receptor–mediated pathways [6,14].

However, there are some discrepancies in epidemiological studies lacking consistent results regarding the link between BPA exposure and risk of developing T2DM. Reports of US National Health and Nutrition Examination Survey (2003–2004 and 2005–2008) revealed that likelihood of T2DM is positively associated with BPA concentration [6,15]. Furthermore, BPA can be denoted as a contributing factor for the development of T2DM [16,17]. On the other hand, according to the report of Duan et al. (2018), no significant association between elevated urinary BPA concentrations and an increased risk of T2DM was found [18]. Another report by Bi et al. (2016) demonstrated a negative association between exposure to BPA and the incident of T2DM among subgroup of older women with an average age of 60 years [7]. However, no causal relationship can be drawn between the risk of T2DM and urinary BPA levels as most of the above mentioned investigations were cross sectional in nature and thus reverse explanation might exist. Moreover, there is an ongoing debate among the scientific community regarding the concentration of EDCs required to produce biological effects in both humans and wildlife, because BPA being unstable in water undergoes biodegradation to a much lesser active compound [19]. This is the reason of the half-life being 2 days for BPA in rivers [19]. Despite this, traces of BPA can still be found in drinking water which affects cellular functions [20]. According to the US Food and Drug Administration and the European Food Safety Authority, human exposure to BPA is considered below safe exposure levels (from 50 to 4 μg/Kg weight/day) [21,22]. Contradictory to these reports, France has already banned the use of BPA in food packaging materials [23]. Additionally, plastic manufacturers all around the world have started selling ‘‘BPA-Free’’ plastic containers, and the scientific community is still hesitant to publish substantial statements regarding the risk imposed to human beings and wildlife health due to exposure to BPA. Only nanomolar concentrations of BPA may alter the normal functioning of α- and β-cells of the endocrine pancreas. Additionally, nongenomic activities as well as genomic pathways can also be affected by low concentrations of EDCs [24]..

The possible mechanisms of BPA action at low-doses have garnered attention from the scientific community which is another subject of significant debate. Indeed, BPA activates different mechanisms which include the involvement of nuclear receptors, orphan receptors (eg, aryl hydrocarbon receptor, AhR) and other noncanonical steroid hormone receptors [25]. But these underlying mechanisms are far from detailed illustration. Further, understanding of many mechanisms of BPA action on pancreatic islets could help us to critically explain underlying pathophysiology of insulin resistance as well as provide new insights of therapeutic intervention. In addition to focussing on different therapeutic interventions and exposure management policies to identify BPA-induced disease risk, understanding the molecular mechanism by which BPA alter glucose homeostasis should gather interest of the scientific community as well. The goal of the present review is to provide an insight into the several mechanisms of BPA action on pancreatic islets in order to analyze whether different mechanisms are at the root of the effect of low dose of BPA in altering glucose homeostasis.

2. Bisphenol A: An overview

4′4-isopropylidenediphenol, frequently known as BPA with a molecular weight of 228.29 g/mol and chemical structure of $C_{15}H_{16}O_2$, (Fig. 1) was first synthesized in the year 1891. Commercial production of BPA began in the early 1950 s, after epoxy resins were developed [26]. These epoxy resins are broadly used as protective coatings on different metal equipment such as food cans, piping, and dental sealants. In 1957, scientists discovered that polymerization of BPA with phosgene resulted in the formation of polycarbonate. The presence of BPA is ubiquitous in the environment because polycarbonate plastics manufactured from BPA have amazing physical and chemical properties, like good strength, hardness, resistance to acids and oils and thermal stability. Furthermore, BPA also acts as a stabilizer and as an antioxidant in the manufacture of polyvinyl chloride plastics. BPA is primarily released in the environment as BPA monomer which is formed following degradation of different polymers or during the industrial manufacture of polycarbonate plastics. Although the primary route of BPA for the human being is believed to be through digestive tract but BPA could easily enter organisms through the respiratory tract and skin as well [27]. In human beings, BPA could be detected in urine, blood, breast milk and other tissues [28–30]. Pharmacokinetic studies on BPA revealed that, following dietary intake, BPA was rapidly absorbed through the gastrointestinal tract and then transported to the liver where BPA conjugated with UDP-glucuronic acid to form BPA-glucuronide (BPA-gluc) [31]. Consequently, BPA and its metabolites being hydrophilic in nature were excreted into the bile and mostly, urine, with a half-life corresponding to less than six hours [32,33].

Based on a number of studies, the United States Environmental Protection Agency (EPA) selected a reference dose of 50 μg/kg bw/day for BPA. As a response to a precise risk assessment of BPA and its undesirable health outcome, the European Food Safety Authority (EFSA) reduced the tolerable daily intake (TDI) to 4 μg/kg bw/day from the 50 μg/kg bw/day in 2015 [22]. In spite of this evidence, there is a never ending argument with the chemical industry that is still sceptical about the burden of low doses of BPA. The European Commission’s Scientific Committee on Food (ECSCF, 2002) presented a tolerable daily intake (TDI) of 10 μg/kg/day. According to previous studies performed in the 1980 s, the U.S. Environmental Protection Agency (U.S. EPA) once established 50 μg/kg/day dose as the reference dose based on the lowest observed adverse effect level of 50 mg/kg/day [34].

3. Cellular and molecular mechanisms that connects BPA with pancreatic β-cell dysfunction and insulin resistance

3.1. Mechanism of BPA action mediating through estrogen receptors

Glucose homeostasis in blood is maintained by the release of hormones from different types of cells integrated in the islet of Langerhans, insulin being the most crucial hormone involved. Islets of Langerhans are composed of a heterogeneous population of insulin-releasing β cells (65–90%), glucagon-releasing α cells (15–20%), somatostatin-producing δ cells (3–10%), and pancreatic polypeptide producing (PP) cells (1%). The stimulus-secretion coupling of β cells has been studied the most of this population. While the endocrine pancreas might not be regarded as the classic estrogen target but the presence of estrogen

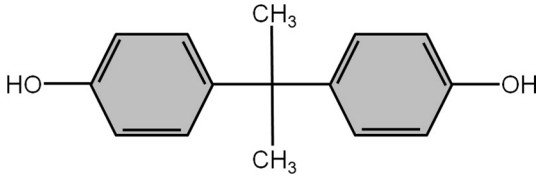

Fig. 1. Molecular structure of Bisphenol A (BPA).

receptors and the effects of 17β estradiol in some physiological aspects of the islet of Langerhans have been known to some degree [35]. Both the variants of estrogen receptors (ER) i.e. ER alpha (ERα) and beta (ERβ) - are present in the liver, pancreas, adipose tissues and muscle [36]. It was earlier reported that estrogens, when bound to ER at abnormal concentrations, can exert adverse effect on pancreatic islet cells (specifically for β cells) as well as on insulin-sensitive peripheral tissues and also may impair insulin secretion and insulin sensitivity to induce T2DM [37]. Although there is a consensus that estrogen plays a crucial role in maintaining blood glucose homeostasis, but reports could not reveal in which state it exerts a beneficial or deleterious effect. Earlier report has suggested that estrogen receptors, ERα and ERβ both played key role in blood glucose homeostasis and ERα being the main mediator [38].

One of the earlier studies has reported physiological concentrations of 17β estradiol to negatively regulate the $[Ca^{2+}]$i oscillatory pattern in α cells whereas it stimulated glucose-induced $[Ca^{2+}]$i oscillations in β cells, suggesting an opposite effect of 17β estradiol in α and β cells [39]. However, the differential effect of 17β estradiol exhibited in α and β cells can be a matter of debate. According to a previous report, physiological concentration of 17β estradiol in β cells resulted in a significant reduction in K_{ATP} channel activity in a reversible way [40]. This causes membrane depolarization and the subsequent opening of voltage-gated Ca^{2+} channels, potentiating glucose-induced $[Ca^{2+}]_i$ oscillations. In α cells, a similar mode of action may occur, where plasma membrane K_{ATP} channels have been identified [41]. The K_{ATP} channel performs similar function in both types of cells i.e. it depolarizes the membrane in response to an increase in extracellular glucose. The opposing impact could be explained by the fact that each type of cell has a different set of ion channels. In both α and β cells, 17β estradiol reduces K_{ATP} channel activity, depolarizing the plasma membrane in a similar manner to that of glucose. In β cells, depolarization stimulates the opening of voltage-gated Ca^{2+} channels, resulting in a $[Ca^{2+}]_i$ potentiation, while in α cells, depolarization inactivates membrane conductance, leading to abolishment of Ca^{2+} oscillations. In this way, 17β estradiol exerts opposite effect on Ca^{2+} signals through a common ion channel in α and β cells.

Previously, the role of many second messengers employed by estradiol to exert quick effects in other cell systems was investigated, and it was discovered that estrogen stimulation enhanced islet cGMP [42]. Moreover, in β cells the principal target protein of cGMP, cGMP-dependent protein kinase (PKG), was reported to be involved, as evidenced by reduction in the effects of estradiol in presence of PKG inhibitors [42]. Surprisingly, the second messenger implicated in α cells has also been identified as cGMP. Consequently, a common mode of action can cause opposite effects on $[Ca^{2+}]$i signals in both cell types. Estradiol's actions begin once it binds to estrogen receptors in the nucleus, plasma membrane, and cytoplasm [43]. ERs regulate gene transcription in the nucleus as transcription factors and both ERα and ERβ can also be found at the plasma membrane, where they activate alternative pathways in a rapid manner [44]. Furthermore, alternative pathways such as Src/Ras/extracellular signal-regulated kinase (ERK or alternatively MAPK) and PI3-kinase/Akt can rapidly be triggered by 17β estradiol upon binding to cytosolic ERs [45–47]. Estradiol can exert its function through other receptors in addition to classical ERs, either at the plasma membrane or in the cytosol. Earlier reports have suggested that 17β estradiol as well as xenoestrogens can operate via non-canonical membrane estrogen receptors (ncmERs) in the endocrine pancreas [43]. Furthermore, immunocytochemistry using multiple anti-ERα and anti-ERβ antibodies revealed that none of them possessed any structural similarity in the plasma membrane of islet cells [35]. The membrane estrogen receptor, on the other hand, appears to be an undefined receptor that binds adrenaline, noradrenaline, and dopamine but does not bind to antiestrogens or other steroids like estradiol [35,39]. The lack of interaction with particular ligands for these receptors indicates that this ncmER is unrelated to adrenergic or dopaminergic receptors. This evidence suggests the presence of a novel ncmER in the endocrine pancreas.

One of the pioneer findings on mechanism of BPA action carried out by Alonso-Magdalena et al. (2006) suggested that BPA exhibited its primary endocrine disrupting activity by interacting with classical and nonclassical ER and resulted in altered estrogen-responsive gene expression [48]. Administration of BPA to adult mice, at doses (50 μg/kg/day) about 1,000-fold less than the lowest observed adverse effect level established by the U.S. EPA was shown to impair blood glucose homeostasis in vivo [48]. According to that report, BPA was also able to increase plasma insulin level and thereby altered blood glucose level through a noncanonical estrogen pathway (Fig. 2). However, longer exposure of mice to BPA was seen to enhance β cell insulin content and this effect was mediated by classical estrogen receptors.

3.2. *Involvement of cAMP-response element binding protein (CREB) in the BPA mediated action on pancreatic β cells*

According to reports published between year 2000 and 2008, the mechanism for BPA action was based on its capacity to interact with classical ERs (ERα and ERβ), triggering estrogenic signals that modulate gene expression. However, the binding affinity of BPA to ER being 1000 to 10,000 times weaker than the ER natural ligand 17β estradiol (17β-E2) suggested BPA of possessing other mechanisms of action, which are not dependant on ER [49]. Previously, Quesada et al. (2002) demonstrated that similar doses of the endocrine disruptor BPA and the hormone 17β-E2 were shown to activate the transcription factor CREB via a non classical membrane estrogen receptor (ncmER) which further induced the transcriptional activation of CREB-responsive genes (Fig. 2) [24]. Activation of CREB caused closure of K_{ATP} channels responsible for the resting membrane potential which led to the depolarization of the plasma membrane potential. As a result of membrane depolarisation, L-type voltage-dependent calcium channels opened and increased $[Ca^{2+}]_i$ in pancreatic islets which further induced insulin secretion whereas, L-type calcium channel is the only type of voltage gated calcium channel to be present in mouse β-cells [50]. The affinity of BPA to classical ER, being very weak, always raises a debate about whether the

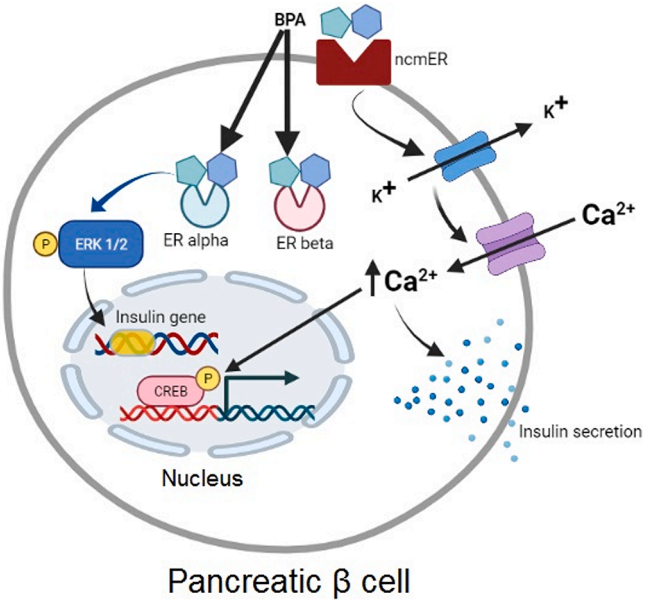

Fig. 2. BPA acts on pancreatic β cells through ERα, ERβ and ncmER involving CREB and ERK1/2. ERα: Estrogen receptor α; ERβ: Estrogen receptor β, ncmER: non classical membrane estrogen receptor; CREB: cyclic AMP response element binding protein; ERK: extracellular signal regulated kinase; up arrow (↑) indicates increase/up regulation; down arrow (↓) indicates decrease/down regulation. [Figure prepared with BioRender].

concentration of BPA generally present in the environment can result in any alteration of glucose homeostasis [51,52]. However, Quesada and co-workers (2002) demonstrated that BPA and 17β-E2 are equally capable of inducing the transcription factor CREB, even at concentrations as low as 10^{-9} M [24].

3.3. ERK1/2 – Another target of BPA for its action on pancreatic β cells

BPA exerts its estrogenic effects with same efficacy as E2 and the E2-mediated elevation of insulin biosynthesis was mimicked by BPA at similar doses of E2 and following the same mechanism [36,38,48] but, Nadal and co-workers (2004) speculated that similar efficacy exhibited by both BPA and E2 in insulin biosynthesis regulation was contradictory [53]. Previous study clearly reported BPA as "weak" estrogen for its low binding capability to both ERα and ERβ [54] and also for expressing comparatively lesser transcriptional activity mediating via the estrogen response element (ERE) binding receptors [55]. One possible justification could be that BPA might exert its effects via ERα through mechanisms apart from binding to ERE (Fig. 2). Additionally, researchers also revealed that activation of protein kinases can be triggered by nuclear ERα [46,56]. ERα agonist PPT [1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole] promptly enhanced the phosphorylation of ERK1/2 in pancreatic β cell cytoplasm [36]. On the other hand, phosphorylation of ERK1/2 was inhibited by MEK inhibitor PD98059 through abolishing the action of PPT, E2 and BPA on islet insulin content [36]. Also, Src inhibitor PP1 greatly abrogated the stimulatory effect of BPA on islet insulin content indicating that kinase Src might play a significant role. These findings clearly suggest that enhancement of insulin biosynthesis can be triggered by ERα mediated through ERK1/2. However, several earlier studies also demonstrated that estrogens and phytoestrogens may activate other mechanisms which did not involve ERα and ERβ to amplify insulin secretion rapidly, in vitro and in vivo [35,40,48,53,].

3.4. hIAPP aggregation: A possible link between BPA and T2DM

Misfolding of human islet amyloid polypeptide (hIAPP), a 37-residue peptide synthesized and released by the pancreatic β-cells, is a crucial factor behind T2DM [57,58]. hIAPP has significant susceptibility to misfold into toxic oligomers and linear fibrils in spite of possessing critical physiological functions that include regulation of key hormones and glycemic management [59]. Membrane permeabilization capacity of hIAPP oligomers and linear fibrils is responsible behind the cytotoxicity of hIAPP, which lead to apoptosis and eventually results in the development of diabetes [60,61]. An earlier study by Gong et al. (2013) revealed that addition of BPA enhanced the conversion of hIAPP from unordered structure to β structure and also resulted in hIAPP aggregation dose-dependently [62]. It was also revealed in their study that addition of BPA induced a hike in the cytotoxicity of hIAPP in INS-1 cells. Thus it can be suggested that BPA induced toxic hIAPP oligomers can distort the pancreatic β-cell membrane leading to permeabilization [62]. This observation is in consistency with earlier reports which demonstrated that BPA itself also impaired cellular physiology by activating the estrogen-receptor and other pathways related to apoptosis [63–65]. It was surprising to find out in the study that BPA and hIAPP aggravated cellular toxicity synergistically particularly at high molar ratios of BPA. To observe exclusively the membrane disruption ability of hIAPP, Gong and co-workers (2013) [62] also carried out dye leakage assays after addition of BPA because the hIAPP oligomers could bind and permeate membranes more accurately than monomers and are considered crucial for β-cell death [66]. Results of their study also revealed that in the hIAPP group, BPA significantly enhanced the capacity of hIAPP to impair membrane structure as indicated by serious dye leakage and it was increased in a dose-dependent manner following addition of BPA [62].

Additionally, hIAPP mediated increase in membrane permeability resulted in enhancement of intracellular calcium levels which altered mitochondrial function and eventually lead to increased reactive oxygen species (ROS) production [67]. This finding is in agreement with a previous report that has associated amyloid formation with generation of ROS [68]. The sharp rise in the ROS levels after addition of BPA in the hIAPP group indicated that BPA and hIAPP exhibited a synergystic effect on ROS production as BPA alone had limited effect on ROS levels. Since exposure to BPA is ubiquitous and unavoidable, it is legitimate to predict long term exposure to BPA may result in increased formation of hIAPP and β-cell apoptosis, and ultimately causing a greater risk of developing T2DM.

3.5. Impact of BPA on ion channels to regulate insulin secretion

Another possible mechanism of BPA action leading to altered glucose homeostasis might involve ion channels. It is intriguing to note that BPA might possess other mechanisms of action other than interacting with estrogen receptors that include the direct binding of BPA moieties to the ion channel pore. We believe that if a more illustrated report of the mode of BPA actions on ion channels at environmentally relevant doses can be presented, we will be able to bring mechanistic understanding into the proposed link between BPA exposure and impaired glucose homeostasis.

Pancreatic β cells play a critical role in regulating glucose homeostasis as they biosynthesise and release insulin, a key hormone involved in controlling blood glucose levels. These are the most abundant electrically excitable cells in the endocrine pancreas that play significant role in glucose homeostasis [69,70]. Pancreatic β cells, in response to glucose generate bursts of action potentials that are triggered by ion channels expressed in their membrane, which subsequently potentiate insulin release. Therefore, any change in the expression or activation of ion channels in β cells results in altered insulin secretion and glucose homeostasis. Pancreatic β cells possess a hyperpolarised membrane potential in the absence of stimulatory glucose concentrations because of high activity of the ATP-sensitive K^+ channel (K_{ATP} channel). A rise in the ATP/ADP ratio results in decreased K_{ATP} channel activity in response to glucose stimulation. As a result, membrane input resistance increases and, therefore, small depolarising currents alter membrane potential, producing bursts of electrical activity that changes between a hyperpolarised silent phase and a depolarised phase with action potentials [71]. An oscillatory pattern of intracellular Ca^{2+} concentration is induced as a consequence of the bursting pattern of electrical activity, leading to exocytosis of insulin-containing vesicles [72]. Gene–environment interactions cause type 2 diabetes in the long run and β cell activity is reported to be greatly affected by genetic modifications in the expression of voltage-activated channels that may further lead to the development of type 2 diabetes [73].

3.5.1. Action of BPA on K^+ channel

3.5.1.1. ATP-sensitive potassium (K_{ATP}) channel. ATP-sensitive potassium (K_{ATP}) channel is an important ion channel in pancreatic β cells. The cell membrane resting potential remains around −70 mV at low glucose concentrations with K_{ATP} channels mostly in the open state. However, increased ATP/ADP ratio leads to closure of K_{ATP} channels when glucose levels increase. This further causes depolarization of membrane up to −40 mV followed by opening of voltage-dependent Ca^{2+} channels and elevation of intracellular calcium concentration [71]. To counter balance the increased plasma glucose concentration, $[Ca^{2+}]i$ and cyclic AMP oscillatory pattern induce a pulsatile insulin secretion [74]. Previous study by Soriano et al. (2009) in mice demonstrated that 17β estradiol (100 pM-1 nM), in alliance with glucose, downregulated K_{ATP} channel activity via cGMP generation at physiological concentrations, and thereby elevating $[Ca^{2+}]i$ oscillations concentration-dependently [75]. This mechanism is responsible behind the induction of calcium signalling mediated insulin secretion. Nadal and co-workers (2000) demonstrated that the receptor which

potentiated this mechanism was situated outside the nucleus, and it was suggested to be different than the classical cytosolic estrogen receptors ERα and ERβ [35]. This non-canonical membrane estrogen receptor involved could be G-protein coupled estrogen receptor (GPER) which is also located in β cells [76]. It was already well documented that there were other compounds like BPA which could exert their effects in a non-genomic pattern without acting via classical estrogen receptors ERα and ERβ. This further points out that those compounds can also modify the activity of the K_{ATP} channel as well. In this way, some xenoestrogens or EDCs like BPA modulates ion channels in different cells by simulating the mechanisms of the natural hormone [13,77]. Soriano et al., (2009) also demonstrated that K_{ATP} channels in human and mice β cells can be modulated by 1 nM BPA which exhibited a rapid insulinotropic effect [75]. They also suggested that BPA could also trigger insulin release by rapidly reducing K_{ATP} channel activity at environmentally relevant doses (Fig. 3) [13].

3.5.1.2. Voltage-activated and calcium activated K^+ channels. The voltage-activated K^+ channels $K_v2.1$ (encoded by Kcnb1) and $K_v2.2$ (Kcnb2), along with $K_{Ca}1.1$ channel (Kcnma1), are considered to be the major contributors of the repolarisation phase of the action potential in pancreatic β cells [78,79]. Furthermore, K^+ channel-interacting protein 1 (encoded by Kcnip) seems to be crucial for glucose stimulated insulin secretion (GSIS) [80]. Nadal and co-workers (2004) found out that BPA administration altered the expression of these channel subunits and except for Kcnb1, mRNA expressions of Kcnb2, Kcnma1 and Kcnip1 were reduced post treatment both in vivo and ex vivo [53]. However, it was observed that in the islets of $Er\beta^{-/-}$ mice, BPA's effects on Kcnb2, Kcnip1 and Kcnma1 mRNA expression were abolished in islets indicating that BPA down regulated the expression of K^+ channel subunits and K^+ currents via ERβ (Fig. 3) [81].

3.5.2. Action of BPA on Na^+ channel

The most abundant Na^+ channel present in mouse β cells is the $Na_v1.7$ channel that contributes to roughly 85% of the Na^+ current and according to earlier reports this channel might be associated with insulin biosynthesis pathway [81,82]. One of the previous studies has shown BPA to amplify insulin content through an ERα/ERK pathway [36]. Furthermore, results of microarray analysis revealed that BPA administration down-regulated the expression of $Na_v1.7$ channel, encoded by Scn9a, mediating via ERβ (Fig. 3) [81]. However, BPA exposure could not alter the expression of another Na^+ channel $Na_v1.3$, encoded by Scn3a [81].

3.5.3. Action of BPA on Ca^+ channel

Earlier study revealed that in pancreatic islets, BPA resulted in down regulation of the voltage-activated Ca^{2+} channel $Ca_v2.3$ and also caused reduction in the R-type Ca^{2+} current in an ERβ-dependent pattern (Fig. 3) [83].

It has already been established that BPA impaired ion channel activity in excitable cells. This explanation is crucial to get an insight into the mechanism that demonstrates BPA mediated alterations in endocrine system as well as in other excitable cells in nervous and cardiovascular systems. It can be speculated that different studies demonstrate BPA to regulate the activity of several ion channels that play a key role on different endocrine, metabolic and neurological diseases. Nevertheless, more systematic mechanistic approach towards ion channel-mediated effects of BPA at environmentally relevant doses is still needed.

3.6. BPA mediated endoplasmic reticulum stress and/or mitochondrial dysfunction: Role in pancreatic β cell damage and insulin signalling

Folding, transport, and processing of nascent insulin by the endoplasmic reticulum and the generation of energy, in the form of adenosine triphosphate (ATP), by the mitochondria are required for the release of insulin from the β cell [84–86]. Earlier reports have already associated dysfunction of the normal activity of the endoplasmic reticulum and the mitochondrial electron transport chain with altered β cell functions and increased rate of β cell death [84,86]. Considering the previous reports that exposure to BPA resulted in endoplasmic reticulum stress and impaired mitochondrial functions in other tissues [87,88], Makaji and co-workers (2011) hypothesized that addition of BPA to pancreatic β cells would also result in endoplasmic reticulum stress and/or

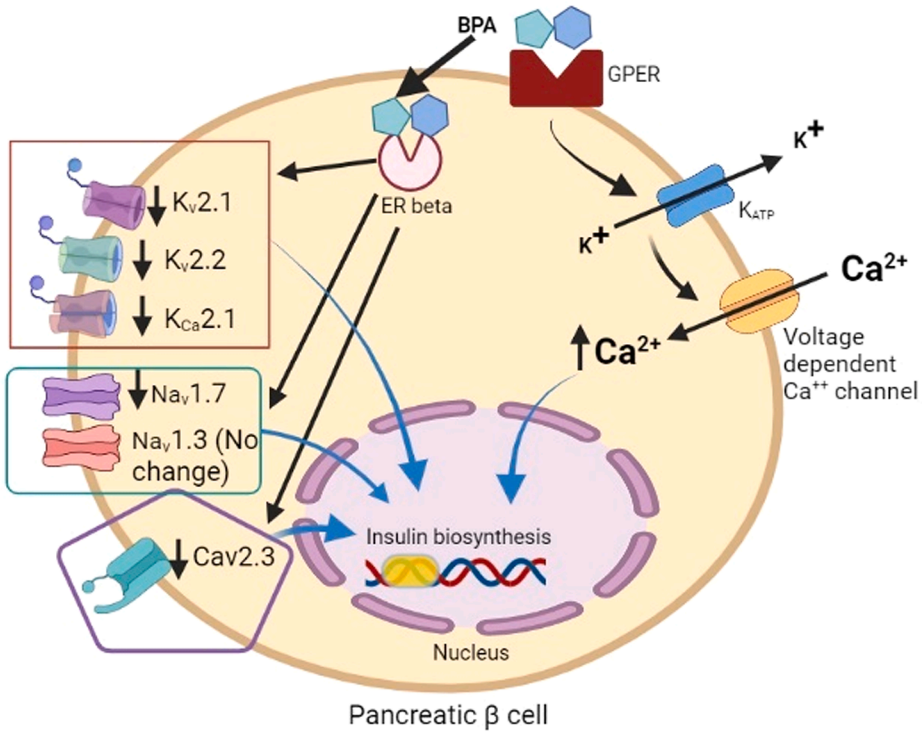

Fig. 3. Ion channels coordinate BPA action on insulin secretion. KATP: ATP-sensitive potassium channel; Kv2.1 and Kv2.2: Kv2 voltage-dependent potassium channels; $K_{Ca}1.1$: Calcium-activated potassium channel subunit alpha-1; $Na_v1.7$: Voltage-gated sodium ion channel subtype 1.7; $Na_v1.3$: Voltage-gated sodium ion channel subtype 1.3; $Ca_v2.3$: R-type (pharmacoresistant) voltage-gated Ca^{2+} channels; up arrow (↑) indicates increase/up regulation; down arrow (↓) indicates decrease/down regulation. [Figure prepared with BioRender].

mitochondrial dysfunction [89]. They observed no effect in mitochondrial electron transport chain (ETC) function of β TC-6 cells upon BPA administration for almost 48 h but BPA exposure managed to alter the components of the cellular response to endoplasmic reticulum stress. Considering the past report of BPA-induced elevation in the production of reactive oxygen species in other cells [87] and profound alteration of activities of enzymes involved in mitochondrial electron transport chain by oxidative stress [85], it was very surprising to find out that the effect of BPA had on mitochondrial activity was very less. However, a recent review by Kumar et al. (2010) has highlighted the fact that estrogenic compounds exert their effects on redox balance based upon the cell type and estrogen receptors involved in the cellular response [90]. In pancreatic β cells, estrogen induced insulin release emerges to be mediated via the noncanonical G-protein-coupled receptor GPR30 [91] whereas ERα mediates the estrogen-stimulated increases in insulin content [36]. Previous study revealed that insulin secretion was roughly 50-fold higher in the BPA exposed cells compared to unexposed cells [84]. One possible explanation behind this modification could be that secretory cells under chronic overstimulation secret proteins entering into the endoplasmic reticulum much rapidly than they can be folded, which results in cellular stress and more categorically endoplasmic reticulum stress [84]. Makaji and co-workers (2011) hypothesized that both cellular and endoplasmic reticulum stress, as consequence of hypersecretion of insulin in presence of BPA would induce certain chaperone proteins that include GRP78, GRP94 and HSP70 [89]. These proteins mitigate cellular and endoplasmic reticulum stress to maintain normal endoplasmic reticulum activity and provide protection from apoptosis [92,93]. Post 24 h of treatment with BPA, at a dose that deeply triggered insulin secretion, showed significant increase in the levels of HSP70 [89], which is further consistent with an in vivo study that reported increased pancreatic HSP70 expression in the presence of hyperinsulinemia [94]. In a study conducted on β TC-6 cells, it was reported that expressions of the endoplasmic reticulum chaperone proteins GRP78 and GRP94 were greatly reduced post 24 and 48 h of BPA treatment, respectively [89]. Therefore, it is important to note that longer exposure to BPA would result in endoplasmic reticulum stress-mediated β cell death; specifically as down regulation of GRP94 is not noticeable until post 48 h of treatment. Up regulation of GRP78 and GRP94 under conditions of ER stress, enhances protein-folding activity, reduces protein-aggregation, and therefore, inhibits further cell damage and death [95]. It can be speculated that in pancreatic β cells, decreased expression of both GRP78 and GRP94 can be associated with increased rate of apoptosis [96,97]. Additionally, previous report by Wang et al. (2009), revealed that in the NIT-1 insulinoma cell line, decreased expression of GRP78 was linked with both upregulation of CHOP/GADD153, which is the proapoptotic transcription factor triggered by apoptosis and endoplasmic reticulum stress (Fig. 4A) [97]. Thus, it is quite evident that BPA precisely regulates pancreatic β cell physiology and that BPA exposure to pancreatic β cells in vitro would lead to endoplasmic reticulum stress in the cells.

Previous reports revealed that mitochondria are key organelle for the maintenance of β-cell activity pairing glucose stimulus with insulin release and are main targets of BPA induced toxicity [98,99]. Furthermore, there exists a strong association of impairments in mitochondrial dynamics with onset and progression of T2DM and obesity [100]. Carchia and co-workers (2015) conducted a study to investigate the mechanisms of BPA mediated toxicity at environmentally relevant dose ($1 \times 10–9$ M) on cultured murine primary hepatocytes and primary pancreatic islets using a toxicogenomic approach [101]. Results of their study revealed disruption of mitochondrial function and its subsequent damage as a result of suppressed expression of genes involved in mitochondrial activity following BPA exposure. This further decreased glucose stimulated insulin secretion and resulted in increased rate of apoptosis. This finding is in line with the previous report that demonstrated BPA to disrupt mitochondrial structure and hinder mitochondrial function in pancreatic islets [102].

Further, in primary hepatocytes, no transcriptional effect was restored, whereas in islets only a few transcripts were prohibited [103]. The inhibited transcripts propose distinct mechanisms, by which BPA could regulate islet dysfunction and death. The reduced expression of transcripts associated with mitochondrial respiratory chain (Uqcrb and Ndufs4), as well as ATP6v1f, is linked to an altered oxidative phosphorylation [101]. This leads to impairment in glucose-stimulated ATP production, thereby, precisely hindering insulin secretion (Fig. 4B). Carchia and co-workers (2015) in their experiments also found that ATP1b1, a subunit of sodium/potassium-transporting ATPase, is also down regulated indicating that modifications in the Ca^{2+} and K^{+} homeostasis could also be responsible for islet damage (Fig. 4B) [101].

So, there are two possible complementary mechanisms exploring the mode of BPA toxicity focussed on mitochondria: elevation of oxidative

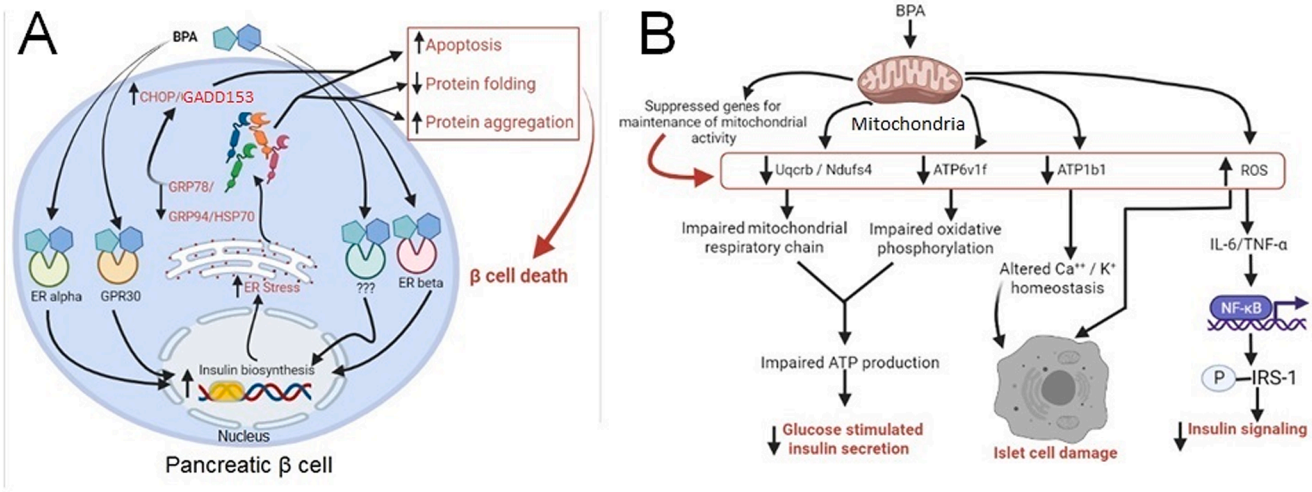

Fig. 4. Involvement of [A] endoplasmic reticulum stress and [B] mitochondrial stress in BPA mediated pancreatic β cell damage and altered insulin signalling. GPR30: G protein-coupled receptor 30; GRP78: Glucose-regulated protein 78; GRP94: Glucose-regulated protein 94, HSP70: Heat shock protein 70; CHOP: CCAAT-enhancer-binding protein homologous protein; GADD153: growth arrest- and DNA damage-inducible gene 153; Uqcrb: Ubiquinol cytochrome *c* reductase binding; Ndufs54: NADH dehydrogenase [ubiquinone] iron-sulfur protein 4; ATP6V1f: ATPase H^{+} transporting V1 subunit f; ATP1b1: ATPase Na^{+}/K^{+} transporting subunit beta 1; ROS: reactive oxygen species; IL-6: interleukin 6; TNF-α: Tumour Necrosis Factor α; NF-κB: Nuclear factor kappa beta; IRS-1: Insulin receptor substrate −1. Up arrow (↓) indicates increase/up regulation; down arrow (↑) indicates decrease/down regulation. [Figure prepared with BioRender].

damage and reduction of the ROS scavenging systems, inducing apoptosis. Their concurrent alteration was shown to magnify the toxicity of BPA. Whereas, BPA mediated endoplasmic reticulum stress in pancreatic islet cells was mostly relied on modulation of the chaperon proteins. However, in vivo study of BPA action on endoplasmic reticulum and mitochondrial stress and pancreatic β cell function is still lacking and warrants thorough investigation.

Insulin resistance (IR) precedes the development of T2DM by several years, making investigation of the cellular and molecular causes of IR an appealing area of research for new drugs and therapeutic strategies to treat or prevent the disease. Previous studies also demonstrated that altered ER physiology led to the promotion of mitochondrial dysfunction in metabolic disorders and prolonged ER stress dampens mitochondrial respiration, reduces cellular ATP levels and affects insulin signalling [104,105]. Additionally, recent data suggest that the protein kinase RNA-like ER kinase (PERK) signalling pathway of the unfolded protein response (UPR) regulates mitochondrial function during ER stress [106]. Considering the earlier report of BPA mediated ER stress and/or mitochondrial dysfunction [89], we hypothesized that BPA surely have inescapable impact on insulin signalling which needs experimental confirmation.

3.7. BPA mediated epigenetic deregulation in pancreatic β cell

One of the vital mechanisms responsible behind the disruptive endocrine characteristics of BPA is suggested to be the dysregulation of epigenetic machinery (Fig. 5). Recent epigenetic study revealed that the deleterious effects of environmental toxicants could possibly be exerted through the dysregulation of epigenomic elements [107]. The process of gene expression is regulated by epigenetic machinery that comprises of DNA methylation system, noncoding RNA and histone modifications [108]. MicroRNAs (miRNAs) are known to have significant roles in regulating homeostatic mechanisms by manipulating the cellular and tissue response to physiologic and pathologic stress. To maintain the insulin secretory activities in the pancreatic islets, the miRNA-mediated regulatory system plays critical role [109]. For example, miR-338 coordinates the expression of pancreatic master gene and duodenal homeobox 1 (Pdx1), production of ATP and glucose-stimulated insulin secretion in pancreatic islets [110]. The dysregulation of miRNAs may also find significance in some BPA-mediated disorders [111].

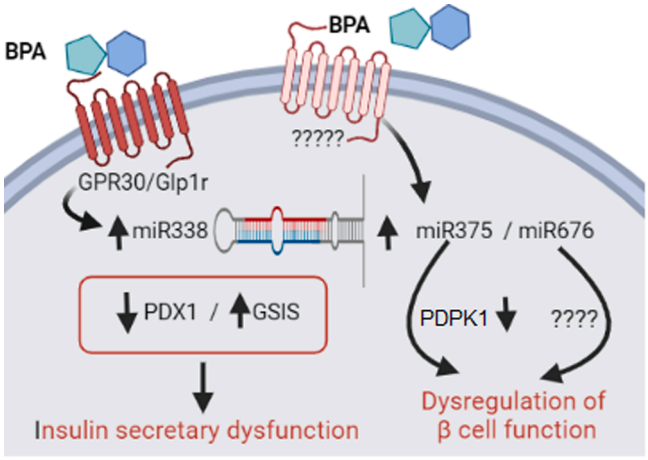

Fig. 5. Impact of BPA mediated epigenetic regulation on pancreatic β cell function and insulin secretion. GPR30: G protein-coupled receptor 30; Glp1r: Glucagon like peptide 1 receptor; miR338: microRNA 338; miR375: microRNA 375; miR676: microRNA 676; Pdx1: Pancreatic and duodenal homeobox 1; GSIS: Glucose stimulated insulin secretion; PDPK1: 3-phosphoinositide-dependent protein kinase 1. Up arrow (↑) indicates increase/up regulation; down arrow (↓) indicates decrease/down regulation. [Figure prepared with BioRender].

Although, there are many reports available regarding the underlying mechanisms of BPA mediated endocrine toxicity, but many questions still need detail clarification [112–114]. Rahmani and co-workers (2020), in their recent study revealed that BPA treatment resulted in significantly altered expression of 21 miRNAs in the rat pancreatic islets [115]. Earlier reports too suggested the regulatory role of some of these miRNAs in glucose homeostasis pathways [116,117]. BPA induced disruption that occurred in glucose tolerance might be related with the increased expression of miR-375 which is in line with previous reports that demonstrated miR-375 to be the most abundantly expressed miRNA in the pancreatic β cells of humans and that was significantly overexpressed in T2DM of both humans and animals [118,119]. Expression of PDPK1 (3-phosphoinositide-dependent protein kinase 1), an essential element of the PI3K pathway is also suppressed by miR-375 that results in the alteration of β-cell function and hyperglycemia [120]. A recent study reported that administration of BPA also resulted in remarkable overexpression of miR-676, miR-126a and miR-340-5p, among which miR-676 was the key miRNA, involved in glucose homeostasis pathway [115]. Compared to control mice, obese type 2 diabetic mouse model showed significantly over expressed miR-676 [121] and surprisingly, in prediabetic NOD mice, miR-676 also underwent a marked up regulation in pancreatic β-cells [122]. Furthermore, accumulation of lipid molecules as a consequence of fatty acid oxidation, could possibly be induced by the over expression of hepatic miR-676 that subsequently activates inflammatory pathways in fatty liver [123].

Rahmani and coworkers (2020) also investigated the status of DNA methylation in two of the key regulatory genes in pancreatic β cells of BPA treated rats, peroxisome proliferator- activated receptor gamma (PPARγ) and Pdx1 and found out that BPA administration could markedly perturb the DNA methylation pattern of both the genes [115]. BPA and its derivatives are known ligands of PPARγ that impair its physiological function as evidenced by a number of in vitro and in vivo studies [124,125]. PPARγ is known to be a key transcriptional regulator of many crucial pancreatic β-cell genes, including Glut2, Pdx1, and INS that play significant roles in glucose sensing, pancreatic development and glucose-stimulated insulin secretion [126]. Up regulation of PPARγ in isolated pancreatic β-cells induces intracellular calcium mobilization, insulin secretion, and β-cell gene expression [127]. On the other hand, Pdx1 is a critical β-cell-specific transcription factor that is significantly down regulated under diabetic conditions, and it's up regulation seems to hold an impressive therapeutic potential in glucose metabolism disorders [128].

The mechanism by which the islets of BPA-treated mice acclimatize to peripheral insulin resistance involves increase in β-cell mass, insulin biosynthesis and secretion, and production of ATP [110]. Decreased expression of Pdx1 in pancreatic β cells of streptozotocin-induced insulin deficient mice has been shown to be retrieved by a single dose of BPA [129]. Thus, activation of Pdx1 induced by early insulin resistance might have a contribution toward the compensatory escalation of insulin secretion in the islets of BPA-treated mice. Using in vitro models, Wei et al. (2017) reported the downregulation of miR-338 in primary mouse islets enhanced Pdx1 expression, insulin secretion, and ATP production post 4 h of BPA treatment, whereas 48 h of BPA exposure resulted in upregulation of miR-338 and subsequently led to reduction in Pdx1 expression and GSIS [110]. Moreover, the same study also suggested that G-protein-coupled estrogen receptor 1 (Gpr30) and glucagon-like peptide 1 receptor (Glp1r) were responsible behind the dysfunction of miR-33 in the process of BPA-mediated insulin secretory dysregulation and established Gpr30/Glp1r-miR-338-Pdx1 axis to be a crucial molecular pathway mediating the BPA-induced islet insulin secretory deregulation [110]. Nonetheless, further inspections are still necessary to illustrate the exact underlying mechanism of these regulations.

In parallel with reduced Pdx1 expression, maternal exposure to BPA (10 μg/kg bw/day) caused deacetylation of histones H3 and H4, as well as demethylation of histone 3 lysine 4 (H3K4) and methylation of

histone 3 lysine 9 (H3K9) at the promoter of Pdx1, with no significant changes in DNA methylation status [130]. However, to our knowledge, no other study has explored the impact of BPA on DNA methylation status of Pdx1 promoter in primary islet tissue during foetal development. Future research is in desperate need of documentation of long-term effects of BPA on DNA methylation of the promoter region of Pdx1 and the molecular interactions involved in this process. Moreover, through the male germ line, early life BPA exposure can cause generational transfer of glucose intolerance and β cell dysfunction in the offspring, which is linked to hypermethylation of insulin like growth factor 2 (Igf2) in the islets.

3.8. Effect of BPA on transcription factors involved in islet cell development and proliferation

According to emerging evidence, several transcription factors are involved in the action of BPA in general [130]. But, majority belongs to adipogenic transcription factors. Reports of BPA's effect on transcription factors involved in islet cell development and proliferation are very limited. The expression of Pdx1 in endodermal cells initiates the concert of a hierarchy of transcription factors that is represented by the development of pancreatic β cells [131]. Pdx1 plays a crucial role in pancreatic development and β-cell ontogeny during fetal development. In both human and animal models, genetic and acquired reductions in Pdx1 expression have been demonstrated to confirm the involvement of Pdx1 in pancreatic development, while according to other reports, overexpression of Pdx1 in pancreatic β cells has been shown to restore β cell mass and inhibit the onset of diabetes [132–134]. Chang and co-workers (2016) in their study revealed that fetal development of pancreatic β cell was impaired following perinatal exposure to BPA, as evidenced by a lower $PDX1^+$ cell fraction at gestation day (GD) 15.5, as well as decreased pancreatic β cell mass at birth. At GD 15.5, impairment in histone modification of the Pdx1 promoter towards an inactivated chromatin was identified in tandem with a decrease in the $PDX1^+$ cell percentage [130]. The same study also confirmed that perinatal period to be the most crucial phase for BPA exposure [130]. Pdx1 plays a key role in regulating cell lineage during pancreatic development and preserving the function of β cells in adulthood. Previous reports suggest that reduced expression of Pdx1 during development contributes to the reduction in pancreatic β cell mass caused by nutritional deficiencies during development [135,136]. Chang and co-workers (2016) also found that the expression of Pdx1 was significantly reduced following BPA exposure at birth which is in agreement with the reduction in pancreatic β cell mass [130]. Results also showed that at GD 15.5, Pdx1 and Ptf1a expression levels were considerably lower compared to that of control group. Genetic tracing experiments suggest that a pool of progenitor cells that express the transcription factors Pdx1 and Ptf1a, gives rise to both endocrine and exocrine cells of the pancreas [137,138]. These findings suggest that the impairment of pancreatic β cell development may be due to a reduction in $PDX1^+$ progenitor cells at an early developmental stage. Chang and co-workers (2016) further suggested that a reduction in $PDX1^+$ progenitor cells caused by BPA exposure could have long-term consequences for pancreatic cell β development and glucose homeostasis in adults [130]. Results of their study also revealed that BPA exposure resulted in minor alterations in glucose metabolism and insulin response in offspring at as early as 8 weeks, which progressed to insulin resistance by 20 weeks [130]. Although BPA exposure might have reduced pancreatic β cell mass by lowering the $PDX1^+$ progenitor cell pool at an early stage, more research is still needed to determine the exact mechanisms at work.

Furthermore, HNF1A (Hepatocyte Nuclear Factor-1α; also known as transcription factors 1, TCF-1) and HNF1B (Hepatocyte Nuclear Factor-1β; also known as transcription factors 2, TCF-2) are reported to regulate the growth and development of islet cells and play an essential role in controlling pancreatic organogenesis and differentiation [139]. Previously it was reported that loss of HNF1A resulted into higher expression of α-cell markers including glucagon and also decreased expression of PAX4, a critical transcription factor regulating β-cell development [140]. Faruggia et al., (2021) reported downregulation of Pdx1 and HNF1A in the BPA exposed pancreatic islets [141]. Thus, BPA induced Pdx1 and HNF1A deficiency would lead to impaired islet development and function.

3.9. Critical involvement of NF-κB (nuclear factor kappa light chain enhancer of activated B cells) pathway in the BPA mediated insulin resistance

Several mechanisms by far have been proposed to explain the effect of BPA on glucose intolerance in adult. Moon et al., (2015) observed the incidence of insulin resistance and glucose intolerance following long term BPA treatment in the postnatal and adult period in diet-induced obesity mouse model [142]. The down regulation of respiratory chain genes could induce the leakage of electrons triggering free radical deposition to which the reduced expression of the ROS scavenging transcripts (Sod2 and Gpx3) could contribute, leading to NF-κB activation [143]. NF-κB proteins can give rise to numerous homo- and heterodimers that can bind to identical DNA elements. The key mechanism responsible for the inhibition of NF-κB involves the interaction of NF-κB with the subunits of IκB protein. In response to specific signal, IκB is phosphorylated and degraded releasing NFκB for nuclear translocation and successive regulation of gene specific transcription [144]. Thus, collective processes in the control of NF-κB activity show that this transcription factor has a very complex and context-dependent function.

It can be suggested that BPA activates NF-κB pathway following elevation of intracellular ROS level in pancreatic β cells. Further, BPA mediated increase in ROS level leads to the activation of the NF-κB pathway in an IκB kinase (IKK) dependent way which is further established by the decrease in IkB-α cellular content in pancreatic islets treated with BPA [143] (Fig. 6). Moreover, inflammation is a critical causative factor that contributes to the progression of insulin resistance mediating via the IκB kinase-β (IKKβ) /NF-κB pathway in particular [142]. The c-Jun NH2-terminal kinase (JNK) and/or IKKβ pathways are known to be activated by increased production of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α). JNK and IKKβ are most common serine kinases that phosphorylate insulin receptor substrate 1(IRS-1) at serine residues, leading to down-regulation of insulin signalling [145,146]. This explanation resonates with the noticeable rise in the serum IL-6 and TNF-α levels following BPA administration. Earlier report also suggested that impairment in adiposity and/or the formations of adipocytokines, such as leptin, adiponectin, TNF-α and IL-6 also affected insulin signalling along with inflammation and/or oxidative stress [147]. Using in vivo mouse model, Moon and co-workers (2015) demonstrated that BPA downregulated Akt phosphorylation in skeletal muscle [142]. The authors also observed that in the liver, BPA downregulated insulin-induced tyrosine phosphorylation of the insulin receptor β subunit but the effect was not significant. These results are in agreement with a previous report which demonstrated that treatment with 100 μg/kg BPA for 8 days altered insulin-induced tyrosine phosphorylation of the insulin receptor β subunit and insulin-mediated Akt phosphorylation on the Thr308 residue in skeletal muscle of adult mice [12]. Another study by Kidani et al. (2010) reported that levels of Akt and phosphorylated Akt in 3 T3-L1 adipocytes were decreased by 46% and 29%, respectively following 24 h of treatment with BPA [148].

3.10. GSK3β: A causal factor of BPA induced insulin resistance and its crosstalk with NF-κB

Glycogen synthase kinase-3 (GSK3) has been enmeshed in the pathophysiology of several prevalent diseases, and diabetes of the focal condition. Insulin signalling can acutely inactivate GSK-3 by upregulating different substrates associated with the glucose uptake pathway

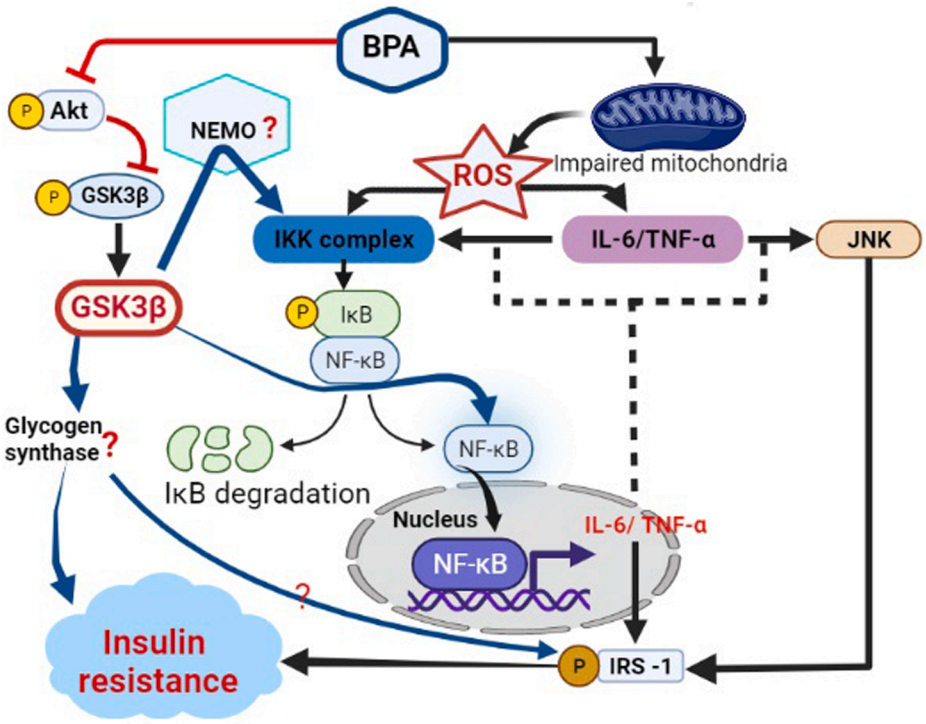

Fig. 6. Involvement of NF-κB and GSK-3β and their cross talk in BPA mediated insulin resistance. However, in-depth exploration of GSK-3β mediated NF-κB regulation in BPA-induced insulin resistance is still pending and it was marked by red question mark. ROS:reactive oxygen species, IKK: I kappa B kinase, GSK-3β: Glycogen synthase kinase 3 beta, IκB: I-kappa-B, NF-κB: nuclear factor kappa light chain enhancer of activated B cells, JNK-cJun N-terminal kinase, IL-6: Interleukin 6, TNF-α: Tumour Necrosis Factor alpha, NEMO: NFκB Essential Modulator. [Figure prepared with BioRender]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

namely PI3-kinase (Phosphoinositol-3-kinase) and IRS-1 (Insulin receptor substrate) and eventually through the activity of Akt that phosphorylates specific serine residues located on the enzyme [149]. IRS-1, another substrate of GSK-3 when phosphorylated on serine and threonine residues results in alteration of insulin signalling [150]. These observations suggest that activated GSK-3 negatively impacts insulin action on glycogen synthase, an enzyme which converts glucose to glycogen for storage and thereby alters glucose transport activity. Insulin, by binding to its receptor and upregulating the PI3K / Akt signaling pathway can lift the GSK-3-mediated inhibition on glycogen synthase.

BPA is known to upregulate GSK3β activity by downregulating GSK3β phosphorylation at Ser 9 leading to insulin resistance, because GSK3β, a serine kinase, originally considered as a crucial regulator of glycogen synthesis was negatively regulated by insulin (Fig. 6) [142]. Therefore, it can be suggested that drugs which have the ability to inhibit GSK-3 could mimic the action of insulin to convert glucose to glycogen, conquering insulin resistance. Previous report has already reported the increase in GSK3β activity by twofold in both basal and insulin-stimulated muscle in type 2 diabetes [151]. Additionally, insulin's action and glucose metabolism have been seen to be improved following GSK3β inhibition in human smooth muscle [151]. Eldar-Finkelman & Krebs (1997) have also shown GSK3β to directly phosphorylate IRS1 at serine332 in vitro and in vivo and impair insulin signalling [150]. Thus, GSK3β may play a contributory role in the development of BPA induced insulin resistance.

Additionally, several studies have suggested the role of GSK-3 in the regulation of different signalling mechanisms which include regulation of NF-κB1/p105 along with IKK activity that subsequently upregulate NF-κB but specific mechanism has remained inconclusive (Fig. 6) [152–154]. The adaptor protein NEMO was reported to be involved in IKK kinase activation and has been proven to be crucial for NF-κB pathways [152]. Medunjanin et al. (2016) hypothesized that NEMO has been a crucial connection in the transcriptional activity of GSK-3 and NF-κB [152]. Further, it has been demonstrated that p65 subunit of NF-κB to be the direct target of GSK-3 kinase activity as GSK3β regulates direct phosphorylation of NF-κB (p65) and affects DNA binding activity or dimerization resulting into alterations in the NF-κB-dependent gene reporter response. This direct phosphorylation of p65 by GSK-3 is supported by several studies [155,156]. Therefore, GSK-3β has a positive impact on NFκB activation which is completely different from its role in insulin and Wnt signalling pathways [157]. However, it is yet to uncover whether inhibitory Ser phorphorylation at NFκB signaling (like it is in insulin signalling) affects GSK-3β. Additionally, it has also been reported that GSK-3β expedites NF-κB function by mounting regulation at the extent of transcriptional system [158].

But, in-depth elaboration of this crosstalk in between GSK-3β and NF-κB in the context of BPA mediated insulin resistance and glucose intolerance is still pending. Thus, this review proposes further exploration of this pending issue to get insight into the potential mechanisms of crosstalk between GSK-3β and NF-κB in the development of BPA mediated insulin resistance.

3.11. Non monotonic effect of BPA on pancreatic β cell: Understanding of dose controversy

It is well established that BPA executes its effect on pancreatic β-cell insulin content and secretion by interacting with intracellular estrogen receptors ERα and ERβ.

Up-regulation of insulin gene expression in pancreatic β-cell is mediated by ERα upon BPA binding and thereby resulting into increased insulin content [36], whereas BPA binding to ERβ ensures K_{ATP} channels closure along with a consequent and timely elevation of insulin release [13]. It's worth noting that in case of BPA binding to ERβ, the relationship between BPA dose and effect follows a monotonic dose–response (MDR) pattern. While in the binding of BPA to ERα, the relationship between BPA dose and effect follows a non-monotonic dose–response (NMDR) pattern [36].

MDR curves show whether a relationship is linear or nonlinear, with positive or negative slopes [159]. NMDRs, on the other hand, appear when the slope of the curve changes direction at some point within the dose range investigated [159]. BPA increased the dispersion and decreased the amplitude of glucose-mediated action potentials in β-cells, according to a previous study [83]. Voltage-gated Ca^{2+} channels are

thought to be involved in the amplitude of action potentials in mouse β-cells [83]. As a result, a decrease in Ca^{2+} influx leads to the reduction in amplitude of the action potential. Notably, their findings revealed that the link between [Ca^{2+}] signalling (caused by depolarization due to high extracellular Ca^{2+}) and BPA was non-monotonic, i.e., low BPA doses (100 pM and 1 nM) were able to reduce Ca^{2+} signalling, whereas higher values (10 and 100 nM) had no effect [83]. It should be taken into consideration that 1 nM BPA is usually the serum BPA concentration of US population [159,160], while industry workers exposed to BPA showed higher serum concentration ranging from 10 to 100 nM [161].

Villar-Pazos et al. (2017) also suggested that dose of 100 nM and 1 μM BPA elicits Ca^{2+} currents involving ERα-dependent mechanism [83]. It has earlier been discussed that BPA targets cytoplasmic ERα to activate PI3K which is thought to be directly or indirectly responsible for the induction of Ca^{2+}currents [36]. The definite Ca^{2+}channel types controlled by BPA are still being investigated, but the whole Ca^{2+}current is expanded in response to 100 nM BPA via ERα- and PI3K-mediated counteractions of ERβ-mediated downregulation [83]. Furthermore, low concentrations of BPA (0.1 to 1 nM) transcriptionally down regulate gene expression of Cav2.3 (R-type calcium channel), resulting into reduction in whole Ca^{2+}current and increase in the extracellular K^{+}-induced Ca^{2+} entry [83]. However, both ERβ and ERα are involved in the dynamic actions of higher concentrations (100 nM-1 μM) of BPA. 100 nM BPA down regulates Cav2.3 gene expression via ERβ leading to decrease in the whole Ca^{2+}current, but ERα simultaneously heighten whole Ca^{2+}currents through a PI3K-dependent pathway. Both effects were observed to counteract each other [83].

Therefore, it can be speculated that NMDR curve is the outcome of at least two different mechanisms activated by low and high doses of BPA involving ERβ and ERα. The discovery of NMDR molecular processes should have a significant impact on toxicology since they indicate that dose and effect do not follow a predictable pattern. It's not necessarily safe to presume that EDCs that are toxic at large doses aren't as dangerous at smaller, more environmentally relevant doses. As a result, conventional regulatory toxicology principles such as potency and threshold of effects are difficult to apply to BPA and, most likely, other EDCs. In-depth exploration of different mechanisms behind the NMDR will help to develop new testing protocol for better understanding of the associated hazard and risk. Most importantly, NMDR relationships obtained with EDCs have important implications for risk assessment because safety at high doses does not ensure safety at low doses.

4. Action of BPA on pancreatic alpha cell: Cellular and molecular mechanisms

Although α-cells have great importance in insulin signalling but very little is known about the stimulus secretion coupling and its regulation by other neurotransmitters and hormones. This is possibly due to lack of α-cells that comprise only about 10–20% (in rodent) and about 30% (in human) of the total number of islet cells [70,114]. Activity of circulating hormone 17β-E2 was shown be to mimicked by BPA to abolish low-glucose–mediated [Ca^{2+}]i oscillations in pancreatic α-cells of whole islets [114]. It has earlier been reported that a nonclassical membrane estrogen receptor (ncmER) mediates the rapid nongenomic effects of estrogen in pancreatic α- and β-cells of intact islets [35,39]. This ncmER pharmacologically differs from classical ERs as it is not sensitive to anti-estrogens such as ICI182780 and tamoxifen [53]. Moreover, Alonso-Magdalena et al. (2005) reported the existence of a common binding site for both BPA and E2 in ncmER of immunocytochemically identified α-cells [114]. This binding site differs pharmacologically from classical ERs and binds to both BPA and E2 at equal doses of remarkably low concentrations (10^{-9} M). BPA is considered a weaker estrogen by researchers due to its much lesser potency than 17β-E2 in terms of interacting with classical ERs located in the cell interior [54]. This further indicates that BPA might mediate its action via receptors other than the classical ER in α-cells as well. Additionally,17β-E2 mediated regulation of [Ca^{2+}]$_i$ in α-cells occurs via ncmER by utilizing a cGMP/PKG-mediated pathway, which was earlier demonstrated by Alonso-Magdalena et al. (2005) for β cells as well [114].

Upstream of cyclic guanosine monophosphate (cGMP)/ protein kinase G (PKG), nitric oxide synthase (NOS) is activated, producing nitric oxide and activating a guanylyl cyclase (GC) that in turn increases cGMP levels [162]. Previous report demonstrated that the suppression of low glucose–induced [Ca2 +]i oscillations by E2 and BPA was reproduced by the NO donor sodium nitroprusside (SNP) [114]. Low-glucose–mediated [Ca^{2+}]$_i$ oscillations were not affected by E2 and BPA upon using the GC inhibitor. This clearly indicates that NOS regulates the activity of E2 and BPA which in turn produces NO and activates a GC. This further upregulates cGMP and results in downstream activation of PKG that will in turn block ion channels [114]. Therefore, it can be suggested that BPA imitates the actions of 17β-E2 via non canonical mechanisms other than the known classical mechanism that do not preferably involve classical ERs [163]. These classical and nonclassical ERs are speculated to be located in the cytosol and the plasma membrane that bring about the alternative effects [43]. Src/PI3-Kinase/Akt and Src/Ras/ERKs pathways are two crucial molecular pathways that ultimately up-regulate NOS along with other enzymes [164,165].

Whitehead et al. (2016) further reported that BPA caused an increase in the number of α-cells or area within the islets when administered prenatally [166]. On the other hand, no change was observed in the number or area of β-cells following BPA administration. This indicates a potential alteration in the α:β-cell ratio in islets following prenatal BPA treatment. Furthermore, increased α-cell number in their study was also associated with an increased glucagon expression at E18.5 (embryonic day 18.5), and this may hold accountable for the impaired glucagon secretion later in life. The same study also suggested that this increment in the number of α-cells as a consequence of prenatal BPA treatment may trigger the considerable β-cell proliferation period that usually appears between E19 (embryonic day 19) and E21 (embryonic day 21). This submission was further supported by another study which demonstrated prenatal BPA induced islet neogenesis of dysfunctional β-cells or low β-cell turnover in 3-month-old mice offspring [167].

Previous studies have revealed that paracrine interactions between α and β cells are necessary for normal pancreatic development and function [168,169]. Because of their pivotal and interrelated impact on glucose homeostasis, any alteration in both α- and β-cells exerts significant structural and functional implications in the fetal pancreas [168]. Also, Liu et al. (2013) reported that altered expression of glucagon and glucagon secretion in combination impacted paracrine interaction between α- and β-cells [167]. Thus it is plausible that increase in the number of α cells and decreased β cell turnover upon BPA treatment might have potential detrimental effect on β cell function and morphology later in life.

5. Conclusion

There is considerable evidence suggesting that BPA contributes to the onset and progression of type 2 diabetes. Different mechanisms are responsible behind these effects which involve binding of BPA to classical and non-classical estrogen receptors, modification in the synthesis or in the metabolism of hormone, modulating ion channels, interaction with other nuclear and nonnuclear receptors and epigenetic dysregulation. Moreover, hIAPP aggregation, ER stress and/or mitochondrial dysfunction, NF-κB activation and GSK3β upregulation are reported to be involved in executing BPA action on islet cells. Many of these mechanisms are seen to be triggered at BPA concentrations much below the concentration range in which detrimental effects are recognized by classical toxicology and produce nonmonotonic dose–response curves. Results highlighted in the review points out those low- and high-dose effects of BPA which are not consistent between physiological alterations. It is quite evident from the review that the safe level estimated for BPA by classical toxicological reports does not defend against low-

dose impairments. This further raises questions about the possible synergistic and additive effects of concurrent exposure to the large number of endocrine-disrupting compounds present in the environment. Accumulating all the reports, it is very challenging to determine at which concentrations and at which point of time BPA enhances the chances of the toxic effects. Therefore, efforts should be made to gather information about different mechanisms responsible behind the hazardous effects of BPA at low concentration. Till the time arrives, the execution of the precaution principle in use and industrial manufacture of BPA is crucial.

CRediT authorship contribution statement

Oly Banerjee: Writing – original draft, Writing – review & editing. **Siddhartha Singh:** Writing – review & editing. **Ishita Saha:** Writing – review & editing. **Swagata Pal:** Writing – review & editing. **Maitrayee Banerjee:** Data curation. **Sudipta Kundu:** Data curation. **Alak Kumar Syamal:** Supervision. **Bithin Kumar Maji:** Supervision. **Sandip Mukherjee:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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