Mercury: Its role in endoplasmic reticulum stress of pancreatic beta cells in the incident of diabetes mellitus

Mercurio: Su papel en el estrés del retículo endoplasmico de las células beta pancreáticas en el incidente de diabetes mellitus

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Abstract

Oxidative stress induced by mercury can cause an inflammatory state in cells that results in cell damage. Free radical formation and decreased antioxidant defences create an imbalance that contributes to the incidence of diabetes mellitus. Mercury as a free radical agent targets its action on pancreatic beta cells and causes defects in these cells resulting in abnormalities in insulin secretion as the pathophysiological basis of diabetes is closely related to apoptosis and necrosis through oxidative stress pathways. One of the components of pancreatic beta cells that mercury targets to cause defects is the endoplasmic reticulum. The role of endoplasmic reticulum in pancreatic beta cells as an intracellular calcium store not only regulates cytosolic calcium signalling but also the conformation of protein folds, so if there is a defect in endoplasmic reticulum homeostasis, known as endoplasmic reticulum stress, it is an early event in the pathophysiology of diabetes mellitus.

Keywords: Endoplasmic reticulum stress, Calcium cytosolic, Protein conformation; Mercury, Pancreatic beta cells

Resumen

El estrés oxidativo inducido por el mercurio puede provocar un estado inflamatorio en las células que da lugar a daños celulares. La formación de radicales libres y la disminución de las defensas antioxidantes crean un desequilibrio que contribuye a la incidencia de la diabetes mellitus. El mercurio, como agente de los radicales libres, dirige su acción a las células beta pancreáticas y provoca defectos en estas células que dan lugar a anomalías en la secreción de insulina, ya que la base fisiopatológica de la diabetes está estrechamente relacionada con la apoptosis y la necrosis a través de la vía del estrés oxidativo. Uno de los componentes de las células beta pancreáticas a los que se dirige el mercurio para causar defectos es el retículo endoplásmico. La función del retículo endoplásmico en las células beta pancreáticas como almacén intracelular de calcio no sólo regula la señalización citosólica de Ca2+, sino también la conformación de los pliegues proteicos, por lo que si se produce un defecto en la homeostasis del retículo endoplásmico, conocido como estrés del retículo endoplásmico, se trata de un acontecimiento temprano en la fisiopatología de la diabetes mellitus.

Palabra clave : Estrés del retículo endoplásmico, Citosólico calcio, Conformación de proteínas, Mercurio, Células beta pancreáticas

According to the International Diabetes Federation in 2022, 537 million adults are living with diabetes worldwide. This number is expected to increase to 643 million (1 in 9 adults) by 2030 and 784 million (1 in 8 adults) by 20451. Diabetes mellitus caused 6.7 million deaths in 2021. An estimated 44% of adults living with diabetes (240 million people) are undiagnosed. 541 million adults worldwide, or 1 in 10, have impaired glucose tolerance, putting them at high risk of developing type 2 diabetes. Based on WHO estimates an estimated 350 million people worldwide have diabetes and that the disease will be the 7th leading cause of death by 2030. The prevalence of diabetes is increasing worldwide, and has already reached 10-12% of the entire population in the world. According to recent studies, the global prevalence of diabetes mellitus increased to 8.5% in 2014 and is expected to increase from 422 to 642 million by 20402. In the last decade, the prevalence has increased rapidly due to several factors, including average age, hereditary influences, unhealthy diet, and lifestyle3. The increasing incidence of diabetes is also thought to be related to changes in lifestyle and other contributing factors, including exposure to environmental pollutants and industrial chemicals including heavy metal exposure. Several investigations have indicated a role for mercury in the related pathogenesis of dyslipidemia, hypertension, insulin resistance, and obesity[4-9].

Based on chemical and physical properties the order of toxicity of metals from the most toxic to humans is mercury ranks first followed by other heavy metals9. Mercury has become a widespread pollutant that causes negative effects on humans, can accumulate, magnify, and reach high levels in the ecological food chain, and people can consume it through food intake, especially fish and seafood, causing toxic effects10,11. The toxicity of mercury is related to its high affinity for sulfhydryl groups (-SH), forming stable complexes and causing several changes, such as structural changes in sulfhydryl enzymes and inactivation of their active sites12. Therefore, the binding of mercury to the -SH group of antioxidants, such as glutathione (GSH), reduces the neutralisation capacity of reactive species. The decrease in antioxidant defence coupled with the fact that mercury exposure can increase the levels of reactive species results in an imbalance in the pro-oxidant/antioxidant system, and produces a state of oxidative stress13.

Mercury targets its action on pancreatic beta cells and causes defects in these cells resulting in abnormalities in insulin secretion as the pathophysiological basis of diabetes is closely related to apoptosis and necrosis through oxidative stress pathways. This cell death mechanism involves instrinsic pathways in the mitochondria and endoplasmic reticulum (RE). In mitochondria, apoptosis activation occurs through the intrinsic mitochondria-dependent pathway, while in the RE through activation of endoplasmic reticulum stress that activates apoptotic and inflammatory signals13-15. The role of pancreatic beta cell REs as intracellular Ca2+ stores not only regulates cytosolic Ca2+ signalling but also protein folding conformation. Alterations in RE homeostasis such as intracellular Ca2+ depletion and defects in protein fold conformation are early events in the pathophysiology of many diseases. 15 Loss of Ca2+ in the lumen leads to defects in insulin secretion through the process of cell membrane insulin exocytosis also aggravates the situation of incorrect protein conformation. Biological systems already provide adaptive mechanisms to RE stress conditions that aim to restore RE function to normal or result in cell death when cell injury occurs. 15-18 A state of homoestasis in the RE must be maintained in order to maintain a continuous intracellular Ca2+ signalling environment. Sources of failure of the RE homeostatic mechanism, such as inhibition of SERCA and RyR channels, will trigger a decrease in intracellular Ca2+, as well as a disturbance in protein conformation that will activate the unfolded protein respone (UPR) mechanism to restore normal RE function or eliminate damaged cells. Activation of the UPR warning signal can activate signal pathways by p38 Mitogen- Activated Protein Kinases (MAPK), phosphatidylinositol 3-kinase (PI3K), JNK, Akt, and ROS production11,13,15,17,18.

There are still few references that explain in depth the mechanism of RE stress in pancreatic beta cells triggered by oxidative stress due to mercury exposure. This reference delves deeper and invites readers to understand how mercury can affect the work of pancreatic beta cells that will have an impact on hyperglycaemia as the basis of the basic pathophysiology of diabetes mellitus from a biomolecular point of view, especially the occurrence of endoplasmic reticulum stress in pancreatic beta cells on intracellular Ca2+ homestasis defects and protein conformation due to mercury exposure. If this pathomechanism can be well understood, the opportunity to find new and targeted alternative antidiabetic therapies is very likely to be researched and developed9.

Develompent

The Role of Oxidative Stress in the Incidence of Diabetes Mellitus

Diabetes mellitus is a chronic hyperglycaemic progressive disease associated with insulin resistance that causes defects in glucose metabolism that occur due to insulin resistance and pancreatic β-cell failure19-21. Pancreatic beta cell defects lead to abnormalities in insulin secretion as the pathophysiological basis of diabetes is closely related to apoptosis and necrosis through

oxidative stress pathways20,21. This cell death mechanism involves instrinsic pathways in the mitochondria and endoplasmic reticulum. In mitochondria, there is activation of apoptosis through the intrinsic mitochondria-dependent pathway while in RE through activation of endoplasmic reticulum stress that activates apoptotic and inflammatory signals. Oxidative stress has a key role in the pathophysiology of various diabetic complications through lipid peroxidation, DNA damage, and mitochondrial dysfunction 21.

Free radicals formed from mercury oxidative stress are hydrogen peroxide and hydroxyl radicals. These hyperactive elements have unpaired electrons in the outer layer of the molecule so they can bind to other biomolecules and modify them to oxidise proteins, lipids and nucleic acids and produce toxic by-products that cause tissue dysfunction22-25. They also alter the structure of biological molecules and even break them down. In diabetes mellitus elevated glucose is associated with increased production of mitochondrial reactive oxygen species (ROS), leading to increased oxidative stress26. Reactive oxygen species have been shown to activate various cellular stress response pathways, which can disrupt cellular signalling pathways. Inorganic mercury targets its action on pancreatic beta cells and causes dysfunction and apoptosis by several mechanisms such as alteration of Ca2+ homeostasis, activation of phosphatidylinositol 3-kinase (PI3K) signalling pathway, JNK, Akt, and ROS production26-28.

Free radicals play a central role in interactions involving inflammation, oxidative stress, and metabolic control. Sources of ROS include NADPH oxidase, dysfunctional eNOS, and xanthine oxidase. Excessive ROS production can feedback and contribute to the pathogenesis of insulin resistance and impaired insulin secretion. Oxidative stress leads to impaired glucose uptake decreasing insulin secretion from beta cells26. Oxidative stress is thought to increase the state of diabetes by affecting insulin signalling. The pathways used by ROS are through PKB/AKT (P13K), JNK/SAPK, p38 MAPK and NF-κB. Activation of JNK results in serine phosphorylation and inhibition of IRS(Insulin Receptor Substrate) 1 and 2. IRS1 and IRS2 are required for downstream signalling through additional serine/threonine kinases and their phosphorylation by JNK results in decreased insulin signalling and insulin stention20,21,29. The reduction in insulin resistance is thought to act through upregulation of PPAR-gamma activity30.

Unfolded Protein Respone (UPR) on the Endoplasmic Reticulum in Pancreatic Beta Cells

The endoplasmic reticulum is a perinuclear organelle that serves as a quality control system for protein conformation and intracellular Ca2+ homeostasis. The role of the RE on protein conformation begins after protein synthesis and translocation into the luminal RE. The protein folding mechanism begins once the formed protein is in the lumen of the RE, the synthesised protein must fold into a unique three-dimensional shape and undergo various post-translational modifications, including glycosylation and disulfide bond formation31. These processes are catalysed by a number of folding enzymes as well as chaperone proteins in the RE that are also components of protein quality control systems such as chaperones, glycosylation enzymes, oxidoreductases, ATPases, GRP 94 proteins, GRP78 (Hsp70 family member), and two proteolytic systems (ubiquitin-proteasome and lysosome-autophagy systems)28. A large number of chaperone proteins including calreticulin, calnexin, PDI, and GRP78/BiP bind unfolded or misfolded proteins via hydrophobic residues or improper hypoglycosylation. Calreticulin and calnexin bind polypeptide chains entering the RE lumen through glycosylated residues, while PDI mediates the formation of correct disulfide bonds. GRP78 undergoes a cycle of binding and unfolding of the unfolded protein until it is properly folded and hydrophobic residues are inaccessible. RE chaperone proteins such as calreticulin, GRP78 and GRP 94 require high Ca2+ RE for their activity by binding to their amino acid residues In addition, some RE chaperones also act as Ca2+ buffers. When the protein is folded and ready to be secreted, it is cotranslated through the translocon complex, where the signal sequence is removed by proteases when polypeptide translation is complete. The protein will be released by the chaperone and packaged for transport through the Golgi to its final destination (such as the plasma membrane or secreted) or move to the peroxisome32,33.

As the success rate of proper folding is still quite low (below 20%) in luminal RE, the unfolded protein forms that are not tolerated by the cell will be removed by a strict quality control system through a process called ER-associated degradation (ERAD). ER-associated degradation moves the unfolded proteins to the cytosol where they are ubiquitinated and degraded by the 26S proteasome)17. Stimulation of the UPR also involves the mechanism of abnormal GRP 78 binding of the unfolded protein The significant presence of the unfolded protein is thought to be the cause of RE stress that causes binding competition with the GRP 78 binding receptor and results in the activation of three sensors during GRP 78 dissociation that triggers the UPR33-35.

The amount of intracellular calcium must be maintained in a continuously normal environment. If there is a failure of this homeostatic mechanism, for example by inhibition of the calcium pump channel, it will trigger the UPR to re-establish normal RE function. There are factors that cause stress conditions of the RE that interfere with protein glycosylation, disulfide bond formation, protein overexpression, or mutations in proteins entering the RE. Cellular and environmental perturbations including gene mutations, prion transmission, viral infections, and ROS will increase RE stress17,36. Ensure protein folding capacity is balanced with demand, cells through the

RE constantly monitor the amount of misfolded proteins in the RE lumen and initiate corrective responses. When misfolded proteins in the RE accumulate above a critical threshold, this accumulation signals an incipient problem in protein folding and sets in motion a signal transduction pathway called the unfolded protein response(UPR) that tries to correct the situation. This type of proteostasis disturbance requires a reduction in protein synthetic load and an increase in the availability of RE chaperones particularly GRP 78. GRP 78 proteins associated with UPR transmembrane proteins (IRE1, PERK and ATF6) are released into the RE lumen to facilitate folding while activating these UPR proteins14,36.

The adaptive mechanisms initiated by the UPR involve the following17:

1. reduction in translation of misfolded proteins

2. enhancement of RE chaperone proteins to increase the folding capacity of REs

3. degradation of misfolded proteins through ER-assisted degradation

Unfolded Protein Response will activate by three sensor proteins in the transmembrane RE namely IRE1(inositol-requiring enzyme 1), PERK(PKR-like ER kinase), and ATF6 (activating transcription factor 6). Upon release of GRP78, both IRE1 and PERK will undergo trans-autophosphorylation to function whereas ATF6 moves to the Golgi undergoing intermembrane proteolysis by site 1 and 2 proteases and produces the transcription factor ATF617,35.

These three RE stress sensor proteins all contain RE-luminal domains that are believed to be able to directly or indirectly sense misfolded proteins. Recognition of misfolded proteins by Ser/Thr kinase PERK leads to phosphorylation and inactivation of eukaryotic initiation factor 2a (eIF2a), this leads to termination of translation by mRNA, thus preventing accumulation of newly synthesised proteins in the RE. Additionally the misfolding signal will activate the transcription factor ATF4, which increases the level of chaperones such as GRP78 and GRP94, and helps restore cellular redox homeostasis. Ire1 has endoribonuclease activity and Ser/Thr- kinase activity. Its endoribonuclease activity degrades many mRNAs to reduce the protein load on the RE. IRE 1 removes introns from the mRNA of XBP1 protein which plays a role as a transcription factor in the expression of several UPR and ERAD genes. The kinase activity of IRE1 is also involved in apoptotic signalling through ASK1 and JNK. JNK activates the proapoptotic protein Bim and inactivates the antiapoptotic protein Bcl-2. IRE1 also recruits caspase 12/caspase 4. Here are the detailed roles of UPR sensor proteins15,35:

1. The phosphorylated PERK protein will function if it activates eIF2a to autophosphorylate into eIF2a-P. eIF2a-P plays a role in recognising and protecting nominal proteins among the misfolded/unfolded proteins formed by increasing antioxidants (glutathione and NADPH), increasing chaperone proteins such as GRP78/BiP and GRP94 through the activation of ATF 4. In addition, eIF2a-P will inhibit the translational process by stopping mRNA translation thus preventing the accumulation of newly synthesised proteins in the RE.

2. IRE1 is involved in the UPR mechanism through:

a. Its endoribonuclease activity will destroy many mRNAs to reduce the protein load at the RE. The destruction of mRNAs by Ire1 by deleting the intron of X-box-binding protein 1 (XBP1). This transcriptase is involved in the expression of several UPR and ERAD genes.

b. IRE1 recruits caspase 12 which plays a role in apoptosis induced by RE stress

c Ire1 kinase activity is involved in proapoptotic mechanisms via:

- IRE 1- JNKp- ASK1 axis activated by TRAF 2 derived from p38MAPK activation.

- JNK activates the proapoptotic protein Bim and inactivates antiapoptotic protein Bcl-2.

- Activation of the inflammatory pathway through activation of NF-κB activated by TRAF2

- NF-κB inflammatory signals activate cytokines (IL 1, IL 8, IL 10, IL 6).

- The misfolded proteins are finally eliminated through proteins involved in the ERAD pathway, which is induced and controlled by the IRE1 -XBP1 and ATF6 pathways.

3. Transcription factor ATF6 is transported to the Golgi during RE stress. The p38MAPK protein activates ATF6 which is stimulated at the time of UPR. ATF6 stimulates RE UPR stress genes such as XBP1, GRP78. ATF6 is cytoprotective, which is mediated by RCAN1, an endogenous inhibitor of calcineurin. This enzyme dephosphorylates the proapoptotic protein Bad(Bcl-2 antagonist of cell death), inhibiting antiapoptotic such as Bcl-2 and Bcl-Xl.

4. The formation of CHOP protein comes from the induction of ATF4, ATF6, XBP1, IRE1-ASK1-JNK pathway will increase the activity of CHOP in post-transcription. CHOP is a protein involved in apoptosis induced by RE stress by decreasing the expression of antiapoptotic Bcl-2 and by inducing the expression of pro-apoptotic Bim and RE oxidase, thus making RE more oxidative and aggravating RE stress. Increasing CHOP levels will cause an increase in ROS in the RE so that some ROS are released into the mitochondria. The presence of ROS in the mitochondria will cause damage to the mitochondrial membrane

and result in the release of cytochrome c which induces the instrinsic apoptotic pathway signal which is part of the UPR proapoptotic mechanism.

Intracellular Ca2+ Homeostasis in the Endoplasmic Reticulum Pancreatic Beta Cell

Another role of the RE is to maintain Ca2+ homestasis by tightly regulating the storage and release of Ca2+ in the luminal RE to the cytosol. In pancreatic beta cells, Ca2+ triggers insulin secretion to maintain post-prandial blood glucose. Ca2+ regulation in the cytosol must be precise because it plays an important role in controlling cell functions such as proliferation, differentiation, secretion, contraction, metabolism, gene transcription and apoptosis (Chen et al, 2023). Decreased RE Ca2+ concentration is associated with RE stress and apoptosis and its regulation is governed by the balance between Ca2+ uptake via endoplasmic sarcoreticulum Ca2+-ATPases(SERCA pumps) and Ca2+ release by inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs). Both IP3Rs and RyRs both trigger Ca2+-induced Ca2+ release under certain conditions36. Specifically, their role in maintaining Ca2+ homestasis is required to trigger insulin exocytosis to the cell membrane. This situation is influenced by several factors34,36:

(1) Ca2+ channel pumps that can transport Ca2+ from the cytosol to the lumen, namely the IP3-IP3R channel.

(2) Ca2+ binding proteins in the lumen to store Ca2+ as a Ca2+ buffer such as calsequetrienand calnexsin, PDI, GRP78, GRP94

(3) Ca2+ channels for controlled release of luminal RE Ca2+ to the cytosol i.e. RyRs and SERCA channels

There are 3 RE intercellular Ca2+ pumps located at the RE membrane site which are SERCA pumps , RyRs and a pump at the cytosolic membrane which is the IP3-IP3R channel and as the main Ca2+ pump the RyR channel. The RyR channel plays an important role in RE stress-induced Ca2+ dysfunction and apoptosis. The release of Ca2+ from the RE during normal cytosolic Ca2+ signalling should not reduce RE Ca2+ unless there is a disruption in the membrane and luminal part of the RE that results in Ca2+ disruption. The disruption can originate from uncontrolled leakage of Ca2+ from the RE membrane to the cytosol resulting in increased Ca2+ concentration in the cytosol or Ca2+ depletion in the RE. Disruption of Ca2+ homestasis in the RE is caused by the following28,34:

1. Decreased ATP due to mitochondrial stress

2. Disruption of the Ca2+ pump in the ER (channels in the ER membrane and channels in the ER cytosol)

3. Disruption of synthesis and transport of Ca2+ binding protein as a buffer

Cytosolic calcium concentration must be carefully regulated because calcium controls important cell functions such as proliferation, differentiation, secretion, contraction, metabolism, movement, gene transcription, and apoptosis28,34.

Relationship between Disruption of Ca2+ Homeostasis and Protein Conformation Due to Endoplasmic Reticulum Stress

Disturbances in Ca2+ concentration in the form of abnormal decreases/depletions caused by disorders of calcium channels, calcium transporters, calcium pumps, and calcium-binding proteins can cause various pathological conditions including disorders of insulin secretion due to defects in insulin exocytosis and become the pathophysiology of diabetes mellitus14. Calcium depletion can also stimulate the occurrence of unfolded proteins due to defects in the conformation of protein formation because the process of protein synthesis really requires intracellular calcium concentration. The formation of unfolded protein will cause activation of the GRP78 protein by p38MAPK activation which worsens RE stress conditions. ER stress will be responded to by an adaptive mechanism in the form of UPR activation which aims to restore normal ER function or eliminate damaged cells. Under conditions of chronically reduced ER Ca2+ chaperone function is disrupted and unfolded proteins aggregate and act as a buffer for luminal GRP78. Upon RE stress, GRP78 and becomes activated, resulting in an adaptive response as well as a late response that promotes apoptosis under conditions of severe or sustained RE stress. IRE1 undergoes dimerization and activation of its kinase and endoribonuclease activities, thereby cleaving XBP1 mRNA and producing a potent transcriptional activator that induces the expression of genes involved in ERAD, ATF6 goes to the Golgi compartment, where it is proteolytically cleaved to produce a cytosolic fragment (p50) which migrates to the cell nucleus and activates transcription of UPR genes such as GRP78/BiP and CHOP. PERK autophosphorylates, and phosphorylates eIF2a, thereby suppressing activity and reducing the rate of translation initiation, while increasing the translation rate of ATF4, a powerful transcription factor that increases the expression of genes involved in antioxidant stress, amino acid metabolism, and protein release. During sustained ER stress or irreversible ER damage, the apoptotic pathway is activated. Ire1 phosphorylates JNK, leading to inhibition of Bcl-2 activity and Bim activation, and recruits, releases, and activates procaspases in the cytosol. Induction of CHOP via XBP1, ATF6, or ATF4, decreases survival-promoting Bcl-2 family members, increases death-promoting proteins (such as Bim) and ROS, and decreases glutathione levels to capture ROS. The presence of increased ROS will cause some of the ROS to be released into the mitochondria, causing damage to the mitochondrial membrane and leading to the release of cytochrome c.

This condition continues to disrupt the balance between Bcl-2 family members which promotes the activation of the intrinsic apoptotic pathway15,34.

Figure 1

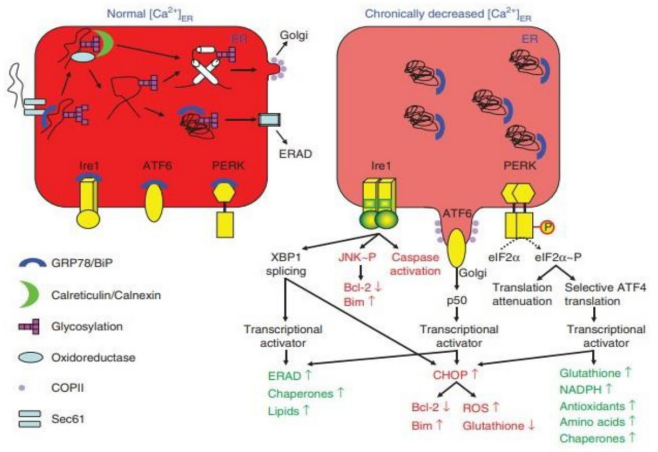

Figure 1. Relationship between Ca2+ and UPR (Unfolded Protein Response). In normal Ca2+ RE, the RE-stress sensor is facilitated and deactivated by GRP78/BiP. Protein delivery and quality control mechanisms work normally. The polypeptide is translocated via Sec61 and glycosylated. This transport is assisted by the molecular chaperone GRP78/BiP. Glucosidase then prepares glycoproteins to bind to ER binding proteins, namely calreticulin and calnexin, while oxidoreductase catalyzes the formation of disulfide bonds. Chaperones located in the ER facilitate proper folding of newly formed proteins and prevent protein clumping. Further deglucosidation releases binding ER proteins, and once the proteins are folded and processed properly, they leave the ER via protein-coated vesicles (COPII) for the secretory pathway. In contrast, misfolded proteins interact with various chaperones, including GRP78/BiP, and are removed from the ER via ERAD15.

The Role of Mercury as a Cause of Endoplasmic Reticulum Stress in Pancreatic Beta Cells

Mercury is in first place followed by other heavy metals (the order of toxicity of heavy metals is based on physical and chemical properties Hg2+ > Cd2+ >Ag2+ > Ni2+ > Pb2+ > As2+ > Cr2+ Sn2+ >Zn2+)9. Mercury has a high potential to interact through its active site on enzymes involved in glucose metabolism mediated by insulin. The action of mercury on the active site of enzymes containing sufhydryl groups from cysteine residues will bind covalently to metals. The high affinity of mercury for the sulfhydryl groups of enzyme catalytic sites is a commonly known primary motif in enzyme inactivation. Methylmercury releases oxygen radicals when decomposing and the release of ROS causes severe damage to cells by activating the lipid chain peroxidation of the cell membrane. When methylmercury flows in the body, disulfide is produced which binds strongly to other protein sulfide groups, thereby changing protein structure and enzyme function37,38.

Mercury is a heavy metal known for its toxicity in several forms. Inorganic Hg includes elemental or metallic mercury (Hg0) and mercury salts (Hg2++) or mercury (Hg++), while organic Hg includes compounds where Hg is bound to structures containing carbon atoms (ethyl, methyl, phenyl , and others). Related to diabetes, mercury targets its action on pancreatic β-cells and causes dysfunction and apoptosis by several mechanisms such as changes in Ca2+ homeostasis, activation of the phosphatidylinositol 3-kinase (PI3K) Akt signaling pathway, and production of reactive oxygen species (ROS)5,6. The toxicity of mercury is related to its high affinity for the sulfhydryl group (-SH), forming a stable complex and causing several changes, such as structural changes in the sulfhydryl enzyme and inactivation of its active site. binding of mercury to the -SH group of antioxidants, for example glutathione (GSH), reduces the neutralization capacity of reactive species. The reduction in antioxidant defenses coupled with the fact that exposure to mercury can increase levels of reactive species results in an imbalance in the pro-oxidant/antioxidant system, resulting in a state of oxidative stress5,38.

The mechanism of mercury-induced oxidative stress is demonstrated by observations via 8-hydroxy-2'-deoxyguanosine (8-OHdG); Biomarkers of oxidative DNA damage were significantly increased in urine samples of people from mercury-contaminated areas as well as glutathione (GSH) and total protein thiol concentrations and glutathione peroxidase and superoxide dismutase activities were higher in the mercury-exposed group. This process is due to mercury induction via the PI3K-activated Akt pathway or is triggered by oxidative stress. In addition, methyl mercury can induce apoptosis and cell death triggered by oxidative stress37. Another study found that MeHg (1-4 μM) significantly reduced insulin secretion and cell viability in pancreatic β cells. An increase in mitochondria-dependent apoptotic events was also observed, including a decrease in mitochondrial membrane potential and an increase in the proapoptotic (Bax, Bak, p53)/antiapoptotic (Bcl-2) mRNA ratio, cytochrome c release, caspase-3 activity, and caspase-3/activation. -7/-926. Exposure of RIN-m5F cells to MeHg (2 μM) also induced protein expression of signaling molecules associated with endoplasmic reticulum (ER) stress, including C/EBP homologous protein (CHOP), X-box binding protein (XBP-1), and caspase-12. MeHg can also trigger the activation of c-Jun N-terminal kinase (JNK) and NrF2 in RE stress39.

Another study found that oxidative stress caused by HgCl2 exposure activates the p38MAPK pathway through the formation of ROS. Studies show that environmental exposure to natural or synthetic chemicals, which can act as obesogens or diabetogens, may also be a factor in DM. In experiments using mice and fish, it

was found that HgCl2 changes intracellular Ca2+ homeostasis and reduces insulin secretion in pancreatic beta cells or islets. Mercury has been shown to induce toxic effects through the induction of oxidative stress leading to changes in cell function and ultimately resulting in cell death and pathological injury13,38,39. Research by Chen et al found that mercuric chloride (HgCl2) was able to reduce the insulin secretory function and viability of pancreatic beta cells and isolated rat pancreatic islets. HgCl2 significantly increased ROS generation in pancreatic islets. His research shows that HgCl2 has the ability to induce apoptosis related to mitochondria-dependent apoptotic signals including disruption of mitochondrial membrane potential, increased release of mitochondrial cytochrome c and activation of poly (ADP-ribose) polymerase (PARP) and caspase 340.

Conclusions

The endoplasmic reticulum in pancreatic beta cells as an intracellular Ca2+ store not only regulates cytosolic Ca2+ signals but also regulates the conformation of newly synthesized proteins. Alterations in ER homeostasis such as intracellular Ca 2+ depletion and defects in protein conformation are early events in the pathophysiology of many diseases. Oxidative stress due to exposure to mercury causes defects in the process of releasing intracellular Ca2+ signals in beta cells which is triggered by endoplasmic reticulum stress.

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