Mercury exposure triggers diabetes mellitus through a pancreatic beta cell endoplasmic reticulum stress mechanism

La exposición al mercurio desencadena la diabetes mellitus a través de un mecanismo de estrés del retículo endoplásmico de las células beta pancreáticas.

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Abstract

Mercury the source of free radicals,can trigger the activation of ER stress can cause beta cell pancreas injuries and result in diabetes mellitus. There have been many studies on mercury toxicity in various organs, but there are still few scientific studies that examine the pathomechanism of diabetes mellitus caused by mercury through the endoplasmic reticulum stress.This study was conducted to investigate the triggering of the endoplasmic reticulum stress pathway due to mercury exposure in beta cell pancreas injury resulting diabetes mellitus. Research using randomized true laboratory experiment method with post-test control group design. The number of samples used was 28 Wistar rats. The research group consisted of 2 groups, control group was given aquadest ad libitum, and intervention group was given water contaminated with mercury per oral once a day (15 kg/WB). The treatment period was 14 consecutive days and on the 15th day, blood samples were taken. ER stress marker was assessed by examining Ca2+ count, expression levels of GRP 78 and JNKp; beta cell injuries were assessed by examining fasting blood sugar. The collected data were analyzed by independent t-test with 95% confidence level; significant if p>0.05. 7373The study found that mercury exposure can trigger ER stress activation of pancreatic beta cells and cause impairment in their function in metabolising glucose, resulting in hyperglycaemia, which can lead to diabetes mellitus. Further research needs to be conducted to look for the involvement of higher-level cellular biomolecular mechanisms that could form the basis of specific therapies for mercury-induced diabetes mellitus.

Keywords: ER stress, Ca^{2+} intracelluar, GRP78, JNKp, Mercury, Beta cells pancreas

Resumen

El mercurio la fuente de radicales libres puede desencadenar la activación del estrés del retículo endoplásmico puede causar lesiones en las células beta del páncreas y la diabetes mellitus resultante. Se han realizado muchos estudios sobre la toxicidad del mercurio en diversos órganos, pero todavía hay pocos estudios científicos que examinen el patomecanismo de la diabetes mellitus causada por el mercurio a través del estrés del retículo endoplásmico. Este estudio se llevó a cabo para investigar la activación de la vía del estrés del retículo endoplásmico debido a la exposición al mercurio en la lesión de la célula beta del páncreas resultante de la diabetes mellitus. La investigación utilizó el método de experimento de laboratorio real aleatorizado con diseño de grupo de control posterior a la prueba. El número de muestras utilizadas fue de 28 ratas Wistar. El grupo de investigación consistió en 2 grupos, el grupo de control recibió aquadest ad libitum, y el grupo de intervención recibió agua contaminada con mercurio por vía oral una vez al día (15 kg/WB). El periodo de tratamiento fue de 14 días consecutivos y el día 15 se tomaron muestras de sangre. Se evaluó el marcador de estrés RE examinando el recuento de Ca2+, los niveles de expresión de GRP 78 y JNKp; las lesiones de las células beta se evaluaron examinando la glucemia en ayunas. Los datos recogidos se analizaron mediante una prueba t independiente con un nivel de confianza del 95%; significativa si p>0,05. El estudio reveló que la exposición al mercurio puede desencadenar la activación del estrés de retorno de las células beta pancreáticas y alterar su función de metabolización de la glucosa, lo que provoca hiperglucemia y, por consiguiente, diabetes mellitus. Es necesario seguir investigando para buscar la implicación de mecanismos biomoleculares celulares de nivel superior que podrían constituir la base de terapias específicas para la diabetes mellitus inducida por mercurio.

Palabras clave: Estrés de RE, Ión calcio, GRP78, JNKp, Mercurio, Células beta pancreáticas.

Introduction

Mercury has become a widespread pollutant that causes negative effects on humans, can accumulate, enlarge, and reach high levels in the ecological food chain, and people can consume it through food intake, especially fish and seafood and cause toxic effects[1–3]. Mercury is part of the group of heavy metals that has the highest toxicity in its class so that even at low concentrations it will cause toxicity to organs in the form of increased blood glucose levels, liver cell damage through increased transaminase enzymes, and increased MDA levels[4]. However, the level of toxicity exhibited by this compound depends on the number and length of time a living organism is exposed to it[5]. Mercury leads to significant changes in the biochemistry of cells. Mercury primarily binds to sulfhydryl groups and secondarily to amide, carboxyl, and phosphoryl groups, which interrupt cellular enzymes and protein systems throughout the body. Therefore, mercury can cause significant dysfunction of enzymes, membranes, transport mechanisms, and structural proteins[6]. Its effects are mainly associated with oxidative stress production of reactive oxygen species, depletion of glutathione (GSH), and alteration of protein synthesis[7].

Mercury causes pancreatic beta cell defects cause abnormalities in insulin secretion as the basis of diabetes pathophysiology is very closely related to apoptosis and necrosis through oxidative stress pathways[8,9]. This mechanism of cell death involves intrinsic pathways in the endoplasmic reticulum through the endoplasmic reticulum stress, which will activate apoptosis, necrosis and inflammatory signals[10,11]. The role of RE in pancreatic beta cells as intracellular Ca^{2+} stores not only regulates cytosolic Ca^{2+} signaling but also conforms newly synthesized protein folds. Changes in ER homeostasis such as intracellular Ca^{2+} depletion and defects in protein fold conformations are early events in the pathophysiology of many diseases. Loss of Ca^{2+} in the lumen causes defects in insulin secretion through the process of insulin exocytosis of cell membranes also aggravates the state of incorrect protein conformation. Biological systems already provide adaptive mechanisms for ER stress conditions that aim to restore ER function to normal or result in cell death[8,12,13]. Failure of the homeostatic mechanism of RE will trigger a decrease in intracellular Ca^{2+} will also trigger a disruption in protein conformation that will activate the *unfolded protein response* **(UPR) mechanism, which functions to restore normal ER function or eliminate damaged cells[10,14–16]. In diabetes mellitus, an increase in glucose is associated with an increase in the production of ROS , which leads to an increase in oxidative stress[17,18]. Inorganic mercury targets its action on pancreatic beta cells**

and causes dysfunction and apoptosis by several mechanisms such as alteration of Ca^{2+} homeostasis, activation of PI3K signaling pathway, MAPK, Akt, and ROS production[19,20].

There are still few studies that explain in depth the occurrence of ER stress triggered due to mercury exposure, which causes pancreatic beta cell defects through endoplasmic reticulum stress which will result in hyperglycemic conditions that will lead to diabetes mellitus. Therefore, it is very necessary to study to further explore this to find the pathophysiology of diabetes mellitus due to mercury exposure and it is hoped that this discovery will be one of the first step to find the right therapy based on the pathophysiology.

Materials and methods

The study was authorized by the local Health Research Ethics Committee of Faculty of Medicine and Health Science, Lambung Mangkurat University, South Kalimantan, Indonesia No: 042/KEPK-FKIK/EC/2024. Research using true laboratory experiment method with a random design complete with a post-test one group with control group design..

The study subjects consist of 28 male Wistar strain *Rattus Norvegicus* rats sourced from the Animal Laboratory of the Faculty of Medicine, Brawijaya University, East Java, Indonesia. The rats are aged 8 to 12 weeks, weigh between 200- 250 g. The expression of GRP78, JNKp, and Ca2+ measured using immunofluorescence examination with JNKp (MKK Ser271+Thr275 Antibody,PerCP-Cy7 Cobjugated, cat No. bs-3277R-Per-Cy, BIOSS®), GRP78 (GRP78 Polyclonal Antibody,Cy5.5 Conjugated-100, cat No bs-1219R-Cy 5.5, BIOSS®), dan Ca^{2+} (Fura-2,Pentapotassium salt, cell imperment 1 mg, cat No F1200, INVITROGEN®). The manufacturer's guidelines were meticulously adhered to during the testing procedure. The reagents, standard solutions, and samples were prepared and analyzed at room temperature.

Acclimatization stage

The Wistar strain *Rattus norvegicus* underwent a one-week acclimatization period in cages of 40 cm x 60 cm x 60 cm within a controlled animal laboratory, where the temperature was maintained at 20°C–22°C, humidity at 50%–60%, and a 12-hour light-dark cycle was implemented. Standard commercial rodent pellets and water were provided to the rats on an *ad libitum* basis. The study began with experimental rats being acclimatized for one week in separate cages to provide the same physical and psychological conditions. The rats received their normal diet, and daily behavioral and physical observations will be conducted to track any changes in each rat. The acclimatization stage ended on day eight. The exclusion criteria of this study was rats that die during the acclimatization phase and $HgCl_2$ induction process or look sick after 3 days induction.

Intervention and termination stage

The research procedure included establishing the requisite equipment and techniques, along with selecting research objects and subjects that met the inclusion requirements. Total of 28 male adult Wistar rats were randomly assigned to 2 groups. Research group was divided into 2 groups: the control group (ctrl) rats were given distilled water and the intervention group (Hg) were given water contaminated with $HgCl_2$ per oral once a day (15 kg/WB) for 14 days. The administration was carried via the oral route. Feed and water was given *ad libitium.*

Immunoflouresence examination procedure

Grow cells on sterile 12 mm glass coverslips placed in 24-well culture plates. Remove culture medium (step 2). Gently wash cells 3 times with ice-cold PBS for 5 minutes per wash. Fix cells by adding a volume of 1% formaldehyde in PBS equal to the original volume of culture medium. Incubate on ice for 5 minutes. Remove the fixative and wash as in Step 2. Permeabilize cells for 20 minutes on ice with permeabilization buffer. Prepare primary antibody appropriately diluted in antibody dilution buffer. React cells with primary antibody for 1 hour at room temperature. Wash as in Step 2. Prepare dilution of fluorescein-conjugated affinity-purified secondary antibody. React cells for 1 hour at room temperature with reagent. Alternatively, use a biotin-conjugated secondary antibody followed by a wash as in Step 2. Add fluorescein-conjugated diluted 1:200 in PBS buffer. React for 30 minutes at room temperature. Wash as in Step 2. Counterstain cells with bis-benzimide solution for 15 minutes at room temperature. Wash as in Step 2. Add aqueous mounting agent. Affix coverslips to slides. Allow coverslips to dry in the dark before viewing.

Statistical analysis

Data analysis using the Shapiro-Wilk test was implemented to determine normality, and Levene's test was implemented to determine homogenity. The data were normally distributed and homogeneous ($p > 0.05$). Statistical analyses were conducted using SPSS software version 25. All variables analysis (FGB level, GRP78, Ca^{2+}, and JNKp expressions) by the independent t test to compared between intervention and control group. The data was analyzed with t test independet with significant value $P<0.05$. The confidence level used in the study was 95%, and the significance level value $p < 0.05$.

Results

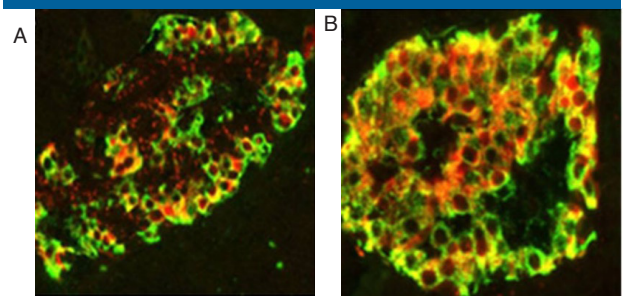
The table shows the results of the evaluation of variables measured by an independent t-test which is used to compare the results of the control group research to the treatment group.

Table 1. Effects of Mercury Exposure on FBG, GRP78, JNKp, and Ca^{2+} intracelullar

Variables	Control	Intervention (HgCl2)	P value
FBG (mg/dl)	90.00±10.43	129.07±10.455	0.005*
GRP78(intensitas/mm^2)	740.82±389.037	2234.30±21.14	0.000*
JNKp(intensitas/mm^2)	359.859±80.314	2319.01±1317.66	0.003*
Ca^{2+} (intensitas/mm^2)	2385.369±480.68	1088,796±127.74	0.004*

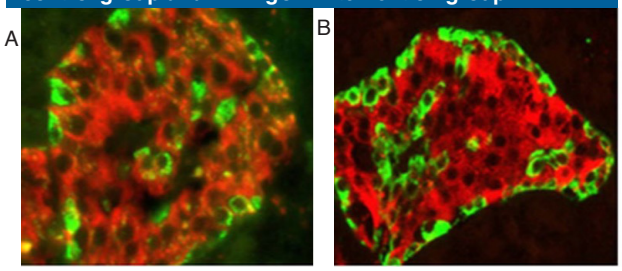
*$P < 0.05$ (significanty compared with the control group) ; independent t-tests

Figure 2. Immunoflorescence showed the expression of GRP 78 (red) and JNKp (yellow);



A = control group and B = HgCl2 intervention group

Figure 3.Immunoflorescence showed the expression of intracellular Ca2+ ions (green), counterstain (red) ; A = control group and B = HgCl2 intervention group



Discussion

Mercury acts on the active side of protein enzymes in the sufhydryl group of cysteine residues and bonds covalently to metals. The high affinity of mercury for the sulfhydryl group of the enzyme catalytic site is the main commonly known way of inactivating enzymes[6]. Mercury releases radical oxygen during decomposition and the release of ROS causes severe damage to the cell by activating the peroxidized lipid chain of the cell membrane. When mercury circulates in the body, disulfides will be produced which by strongly binding to other protein sulfide groups thereby changing protein structure and enzyme function. Mercury can affect gene expression, disregulate metabolism, and/or interfere with signal transduction, including phosphorylation of p38MAPK[5,10,20,21]. Associated with the incidence of diabetes, mercury targets its action on β pancreatic cells and causes dysfunction and apoptosis by several mechanisms such as alteration of Ca^{2+} homeostasis, activation of PI3K, Akt signaling pathway, and the production of ROS[22,23].

The endoplasmic reticulum is a vast intracellular organelle that provides a place for protein modification and folding. Disturbances in the ectral or intraluminal environment of RE can affect protein folding and processing and vice versa. The reduction of folding capacity and the accumulation of misfolded proteins within the ER activate a series of signaling pathways collectively known as the RE stress response or *unfolded protein response* (UPR). UPR acts to modulate the folding capacity and protein load in the ER to restore homeostasis. UPR signaling should act to improve survival and adaptation to RE stress, but it can also increase cell death in the event of excessive proteotoxic stimuli [24,25].

In this study, data were obtained that mercury exposure can trigger ER stress which results in the occurrence of UPR which can be seen from the increased expression of JNKp protein kinase and GRP78 protein conformational companion protein (Table 1 and Figure 2). The results of this study are in line with the research conducted by Placido Rojas-Francoa et al. which showed that HgCl2 activates PERK, ATF-4, ATF-6, and IRE1[26]. Likewise, research conducted by Wei Liu et al. found that methylmercury causes oxidative stress, apoptosis, increased expression of GRP78, GRP94, Xbp1, ATF4, ER kinase-eIF2a, inositol, and ATF6, as well as EBP and caspase-12 proteins[27]. The results of this study are in line with the theory of the occurrence of the UPR response, namely the UPR activation process encourages an increase in the expression of companion proteins (GRP 78, Chaperone, calsineurin, calreticulin/calnexin, GRP 94), an increase in protein catabolism through the degradation system associated with RE (ERAD) or imposing a

cell death response (macroautophagy) if protein damage is too severe. The presence of these companion proteins is to facilitate the conformation of synthesized proteins. In addition, there are 3 main sensor proteins involved in the detection of RE stress and activating UPR signals in the cytosol and other organelles, namely IRE1, PERK, and ATF6. UPR sensor proteins have their own peculiarities in the activation process. A sensor protein directly related to its activation by p38MAPK that can regulate UPR and cellular response to RE stress is IRE-1[28]. The IRE1 protein is activated by inflammatory conditions by activating the IRE1-JNKp-ASK axis through binding to the transcription factor TRAF2 (causing the production of inflammatory cytokines and increased immune cells). Other sensor proteins (PERK&ATF6) also contribute to inflammation by activating NF-κB through different mechanisms. Ultimately, if RE stress and UPR activation are chronic, it can lead to oxidative stress and ROS production which further exacerbates necrosis and leads to hyperglicemia[29–32].

Another role of RE is to maintain Ca2+ homeostasis by strictly regulating the storage and release of Ca2+ in the luminal RE to the cytosol. Calcium plays an important role in insulin secretion, acting as the main signaling molecule that triggers the release of insulin from pancreatic beta cells so that if there is a disturbance in its amount in the ER then it impacts the hyperglycemic event. Failure of the homeostatic mechanism of RE, for example, the occurrence of inhibition of SERCA channels, IP channels, and RyR channels will trigger a decrease in intracellular Ca2+.[16,33].

One of the objectives of the study was to find evidence that exposure to mercury can stimulate ER stress which has an impact on intracellular Ca2+ homeostasis disorders. In this study, the number of Ca2+ RE of pancreatic beta cells was lower in the intervention group compared to the control group (Table 1 and Figure 3). The results of the study of reducing the amount of Ca2+ are in line with previous studies that showed exposure to mercury HgCl2 targets its toxicity to the pancreatic organs by altering the intracellular homeostasis of Ca2+ in cells [10,34,35]. A decrease in the number of Ca2+ ions is related to the inhibition of the SERCA channel, IP channel, and RyR channel will trigger a decrease in intracellular Ca2+[16,33]. In addition, the occurrence of UPR and Ca2+ ion defects cause hyperglycemic through the activation of the UPR PERK1 main sensor protein which is related to Ca2+ homeostasis and the IRE1 protein which activates the IRE 1-JNKp-TRAF2 axis resulting in the disruption of pancreatic beta cell metabolism.[25,32].

Methylmercury toxicity can interfere with the development and function of pancreatic beta cells, resulting in an increase in blood sugar.[36] Based on the results of the study, it was found that there was a significant increase in the GDP of the intervention group compared to the control group (Table 1). In rats, there is a classification of GDP levels if a GDP level of >126 mg/dL (7.0 mmol/L) is considered a fasting glucose disorder/prediabetes, while a GDP level of > 135 mg/dL (7.5 mmol/L) indicates a condition of diabetes mellitus. Based on the results of GDP in the intervention group (GDP of the intervention group = 129 mg/dl) is included in the classification of fasting glucose disorders/prediabetes. These results are in line with the results of a study conducted by Faheem Maqbul et al. which found that administration of MeHg 2.5 mg, 5 mg and 10 mg for 4 weeks with a dose of 2.5 – 5 mg/kgBB peroral can lead to an increase in GDP levels (dose 2.5 mg; 117 ± 3.1mg/dL, dose 5 mg; 138.16 ± 6.2 and dose 10 mg; 149.5 ± 6.6) [37].The results of this study are also in line with the study of Chen et al. who found a marked increase in blood glucose levels after 2-4 weeks of exposure to low doses of mercury. Oral administration of HgCl2 at a dose of 250 ug/kgBB for 14 days also showed a significant effect on an increase in GDP levels of > 7.0 mmol/L (prediabetes) accompanied by the involvement of oxidative stress as an important regulator of glucose homeostasis during mercury chloride exposure. The study by Benloughmari Douae et al. found that in the group exposed to $HgCl_2$, rats were given 0.375 mg/kg/day of $HgCl_2$ orally for 45 consecutive days showing a significant improvement in fasting blood glucose levels compared to the control group ($p < 0.001$) [38].

Methylmercury can negatively impact the development and function of pancreatic beta cells, potentially leading to reduced insulin production and increased insulin resistance and leading to increased fasting blood sugar levels.[39,40] Hyperglycemic can also be induced by mercury due to beta cell RE stress, a study conducted by Placido Rojas-Francoa et al. showed that HgCl2 activates PERK, ATF-4, ATF-6, and IRE1 which are sensor proteins that activate UPR during ER stress.[26] Likewise, research conducted by Wei Liu et al. found that methylmercury causes oxidative stress, apoptosis, increased expression of GRP78, GRP94, Xbp1, ATF4, ER kinase-eIF2a, inositol, and ATF6, as well as EBP and caspase-12 proteins[27]. The results of the above study are in line with the results of this study, namely the presence of hyperglycemic events directly or indirectly related to the occurrence of RE stress known from the markers of RE stress (increased expression of GRP 78 and JNKp and decrease in the number of Ca2+ ions).

Conclusions

The study found that mercury exposure causes hyperglycemic due to EE stress of pancreatic beta cells characterized by depletion intracellular Ca2+ and increased JNKp dan GRP78. This found can make a new approach in understanding the pathophysiology of mercury-induced defects in pancreatic beta cells and opens up the opportunity to find the right diabetes mellitus therapy induced by mercur.y.

Conflict of interests . None

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