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Heavy metals, islet function and diabetes development

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It has long been beleived that heavy metals possess many adverse health effects. Uncontrolled industrialization has released heavy metal pollution in the world. Heavy metal pollutants damage organ functions and disrupt physiological homeostasis. Diabetes mellitus is growing in prevalence worldwide. Several studies have indicated that the deficiency and efficiency of some essential trace metals may play a role in the islet function and development of diabetes mellitus. Some toxic metals have also been shown to be elevated in biological samples of diabetes mellitus patients. In the present work, we review the important roles of heavy metals in islet function and diabetes development in which the in vitro, in vivo or human evidences are associated with exposure to zinc, arsenic, cadmium, mercury and nickel. Through this work, we summarize the evidence which suggests that some heavy metals may play an important role in diabetes mellitus as environmental risk factors.

Introduction

Diabetes mellitus is growing in prevalence worldwide and is becoming a serious threat to human health. Uncontrolled industrialization has resulted in a very wide segment of the human population being exposed to agents that have the potential to cause or exacerbate diseases. According to the report from the Centers for Disease Control and Prevention (CDC), there is a 49% increase in prevalence of diabetes in Americans during 1991 to 2000. Diabetic population now is about 150 million globally and the World Health Organization (WHO) predicts it will double by 2025.[1] Thus, more attention is needed to investigate and prevent the possible factors which may induce hyperglycemia or diabetes. Diabetes mellitus is a metabolic disorder, which is characterized by fasting hyperglycemia, deficient insulin secretion or insulin receptor insensitivity. Diabetes has several types. Several studies have suggested that active oxygen is an important participant in the destruction of the pancreatic β-cells, which, in turn, leads to type I or insulin-dependent diabetes mellitus.[2,3] The selective destruction of islet β-cell has been considered to be related to the autoimmune effects of humoral, cellular and defective immune regulation.[4,5] Type II diabetes may be due to either reduced insulin secretion and/or insulin resistance.[6] The reactive oxygen species (ROS) have been demonstrated to promote the progression of islet cells dysfunction.[7] Because of anti-oxidative defense systems in pancreatic islet cells are weakness, islet cells are highly sensitivity to oxidative stress.[8] In type I diabetes, there have been suggested that various pro-inflammatory cytokines, such as interleukin (IL)-1, IL-1β and tumor necrosis factor α (TNFα), interferon (IFN) γ and ROS, such as superoxide radicals, hydrogen peroxide and nitric oxide, play the important role in islet β-cell destruction.[8-10] Previous study has also indicated that nitric oxide is involved in the IL-1β-induced inhibition of insulin secretion in islet β-cells.[11] NFκB signaling has been shown to be a key switch of cytokine-induced β-cell dysfunction and death.[10] The linking of oxidative stress and type I diabetes could be found in the expression levels of antioxidant enzymes. Overexpression of antioxidant enzymes, such as superoxide dismutase (Mn-SOD) and cytosolic SOD (Cu/Zn-SOD), inhibited the cytokine- and ROS-induced damage in islet β-cells.[2,9,12-16] On the other hand, pancreatic β-cell dysfunction and insulin resistance are the hallmark of type II diabetes. In type II diabetes, oxidative stress has been found to decrease the insulin gene promoter activity and insulin mRNA expression in islet β-cells under hyperglycemia condition.[9,17-24] Antioxidants, such as N-acetyl-L-cysteine, vitamin C and vitamin E, have been shown to enhance the PDX-1 expression in the nuclei of islet, preserve the insulin secretion ability and insulin mRNA level, and decrease the glucose intolerance in type II diabetic C57BL/KsJ-db/db mice.[9,22] These findings suggest that oxidative stress contributes to the pancreatic islet β-cell destruction or dysfunction in type 1 or type 2 diabetes, respectively.

Heavy metals have been known to possess many adverse health effects; still, heavy metal pollution continues, and is even increasing in some parts of the world, in particular in less developed countries.[25] Due to the uncontrolled industrialization, it has caused

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many kinds of the heavy metals accumulation in our organ tissue and inducing chronic toxicities. The studies that compared the levels of essential trace elements in biological samples of patients who have diabetes mellitus type 2, with those of nondiabetic control subjects, have suggested that deficiency and accumulation of some essential trace metals may play a role in the development of diabetes mellitus.[26,27] However, some toxic metals have been analyzed that the mean concentrations of these heavy metals were significantly higher in scalp hair samples of smoker and non-smoker diabetic patients as compared to control subjects, suggesting that toxic metals may play a role in the development of diabetes mellitus.[28] In the present work, we review the important roles of heavy metals in islet function and diabetes development in which the in vitro, in vivo or human evidences are associated with exposure to zinc, arsenic, cadmium, mercury and nickel.

Zinc

Zinc (Zn) is an essential trace element and it is important for cellular processes like cell division and apoptosis. The role of Zn in the pancreas and diabetes based on rodent studies and experimental manipulations of Zn have been described.[29,30] Zn deficient has been linked to the diabetes mellitus in experimental and clinical studies.[31-33] In Zn deficiency rats, they were found that pancreatic zinc levels and serum insulin levels were significantly decreased, and glucose intolerance was increased. Zn supplementation has been shown to be effective for preventing or ameliorating diabetes in several rodent models of type 1 and type 2 diabetes.[29,30] The epidemiological evidences, associating diabetes with Zn deficiencies, have also indicated the effects of Zn and associated metallothionein (MT) on reducing diabetic complications associated with oxidative stress.[30] Moreover, it has been suggested that the Zn transporter ZnT-8 is a key protein for both zinc accumulation and regulation of insulin secretion in pancreatic β-cells.[34] Recently, several genome-wide association studies analyzing the genetic background of diabetes mellitus by genotyping SNPs have found that a nonsynonymous SNP in SLC30A8 (the gene of ZnT8), rs13266634, has frequently been shown to be associated with type 2 diabetes.[35] Taken together, these studies indicate that Zn may importantly maintain the pancreatic islet cell function and as a possible prevention of diabetes; however, more human intervention trials are needed regarding its use in the treatment of diabetes.

Arsenic

Arsenic (As) is a naturally occurring toxic metalloid. It could be found as inorganic and organic forms in the environment. Arsenic could be easily solubilized in ground water. Natural arsenic in ground water at concentrations above the drinking water standard of 10 μg/liter was not uncommon. Man-made sources of arsenic, such as mineral extraction and processing wastes, poultry and swine feed additives, pesticides and highly soluble arsenic trioxide stockpiles were also not uncommon and had caused the contamination of soil and ground water. An estimated 36 million people in the Bengal Delta, India are at risk from drinking arsenic-contaminated water. The occurrence of arsenic contamination in ground water in Taiwan had been recognized for several decades.[36] Many epidemiological studies have demonstrated that chronic exposure to arsenic in drinking water was associated with the increase in rates of various chronic diseases, including cancers, nervous system diseases, peripheral vascular disease (blackfoot disease (BFD), a peripheral artery disease) and endocrine dysfunction in the United States and other countries.[37-40] Therefore, the United States Environmental Protection Agency (U.S. EPA) recommended a reduction in the maximum contaminant level (MCL) from 50 μg/L to 10 μg/L for arsenic in public drinking water supplies. In Taiwan, the areas along the south-western coast were known to have arsenic contamination in drinking wells or underground water and the hyper-endemic occurrence of a peripheral vascular disease (blackfoot disease) in these area's villages.[39-43] In these areas, arsenic concentrations in drinking water were measured and ranged from 0.35 to 1.14 mg/L, with a median of 0.78 mg/L in the early 1960s.[41] Many studies have also indicated that it was a dose-response relationship between accumulative arsenic exposure and prevalence of diabetes mellitus in the villages of the south-western coast of Taiwan exposed to arsenic from drinking water (0.1–15 and >15 mg/L-year). The incidence of diabetes in these areas (the village exposed to arsenic) was two to five times higher as compared with those in the other non-endemic areas.[42,43] Moreover, similar findings have also been reported in Bangladesh and others.[28,44,45] Recent study has reported that after adjustment for biomarkers of seafood intake, total urine arsenic (median urine level, 7.1 μg/L) is associated with increased prevalence of type 2 diabetes. The authors suggested that low levels of exposure to inorganic arsenic in drinking water may play a role in diabetes prevalence.[46] From these findings, chronic exposure to arsenic is an important risk factor for induction of diabetes mellitus in an arsenic-contaminated environment.

Arsenic might be impairing glucose metabolism;[47] however, only few studies have evaluated that the impairment of insulin secretion in β-cells associated with environmental arsenic exposure in mammals.[48] On the other hand, many studies have indicated that arsenic could alter signaling transduction factors, including NFκB, p38 mitogen-activated protein kinase (MAPK), tumor necrosis factor-α (TNFα), phosphatidydylinositol-3-kinase (PI3K) and PI3K-dependent phosphorylation of protein kinase B (PKB/Akt), and affecting the insulin-stimulated glucose uptake (ISGU) in adipocytes or skeletal muscle cells, which may potentially link with insulin resistance.[49-52] PI3K signaling is a pivotal role in the metabolic actions of insulin and its activation regulates multiple signaling transductions. A PI3K-dependent signaling pathway has been demonstrated to exist in β-cells and that it might function to restrain glucose-induced insulin secretion from β-cells.[53] Increased PI3K-mediated PKB/Akt phosphorylation has been reported in β-cells exposed to high dose of arsenic.[54] The phosphorylation of PKB/Akt signaling was also one of the key steps in the activation of glucose transporter 4 (GLUT4) by insulin.[55] Thus, it has been suggested that the exposure to high dose of arsenic might mimic the action of insulin by phosphorylation of PKB/Akt-mediated GLUT4 expression in vitro. However, exposure to low dose of arsenic has been shown to inhibit ISGU in 3T3-L1 adipocytes; the phosphorylation of PKB/Akt was suppressed in exposed cells,

which was an important requirement for GLUT4 translocation to the cellular membrane in response to insulin.[51] Moreover, Paul et al.[56] have reported that the phosphorylation of PKB/Akt by 3-phosphoinositide dependent kinase 1 (PDK-1) activation was inhibited by treatment with low-dose of arsenic. It has been well known that arsenic has the ability to induce oxidative stress.[57-59] Several studies have also shown that ROS could regulate the activation of Akt signaling.[60,61] Thus, arsenic may, through the generation of oxidative stress to affect Akt-related signaling pathways, cause β-cell dysfunction and glucose metabolism/homeostasis disturbance. Recently, combination of humic acid and arsenic has been shown to increase ROS generation, decrease insulin secretion, and induce cell death in pancreatic β-cells.[62] Mukherjee and colleagues have also reported that arsenic induced oxidative damage in rat pancreatic tissues, which could be ameliorated by folic acid and vitamin B12.[63] Theses findings indicate that oxidative stress plays an important role in the arsenic-induced pancreatic β-cell damage.

Cadmium

Cadmium is a well-known useful heavy metal worldwide. It is a soft, silver-white metal, which is found naturally in air, water and soil. Used in nickel-cadmium rechargeable batteries and electroplating, cadmium was one of the most important notorious toxic heavy metals, which is widespread in industrial and environmental pollution. When cadmium is released to water, it is absorbed by plant or is uptaken by fish and other animals.[64,65] Cadmium is not physiologically or biochemically essential to an organism. Long-term exposure to cadmium results in kidney accumulation, which may induce proximal tubule damage and blockade calcium reabsorption. In addition, loss of bone calcium induced by long-term cadmium exposure results in bone injury consisting of a combination of osteomalacia and osteoporosis, which is called Itai-Itai disease.[66-70] Recently, there were many studies have shown that cadmium could accumulate in kidney, liver, lung and reproductive tissues in which the physiological functions were damaged.[69,71-73]

A previous study has shown that exposure of experimental animals to cadmium compounds (0.84 mg/kg) increased the blood glucose concentration.[74] A recent evaluation of cadmium concentration in biological samples of diabetes mellitus patients (type-2 age ranged 31–60) has shown that the mean concentrations of blood cadmium of male non-smoker and smoker diabetic patients were significantly higher (4.3–7.1 μg/L and 7.78–10.23 μg/L, respectively) than in their respective controls (3.13–5.31 μg/L and 4.02–6.68 μg/L).[28] An epidemiological investigation has also indicated that the increased blood glucose level and decreased serum insulin level were shown in cadmium-exposed workers in a smeltery as compared with the control subjects.[75] However, the detailed effects and mechanisms of cadmium on insulin secretion/utilization and blood glucose regulation are still unclear. Till now, there are only a few reports investigating the relationship between cadmium pollution and diabetes occurrence. Cadmium-induced cellular toxicity has been described in various targets including metalloenzymes interference, thiol protein alterations, energy metabolism inhibition, DNA and membrane structure/function alterations, and excessive oxidative damage.[68,69,76-78] Moreover, several studies have shown that cadmium-induced hyperglycemia was associated with increased lipid peroxidation, decreased insulin release, increased activation of gluconeogenic enzymes and impaired insulin receptor.[74,78-80] Cadmium has also been demonstrated to induce a dose-dependent reduction in GLUT4 protein and mRNA expressions in rat adipocytes. Also, cadmium has been shown to impair glucose tolerance in rats.[78] Other studies have indicated that cadmium exposure caused a metal accumulation, and induced degeneration, necrosis, and weak degranulation in the pancreatic β-cells.[81,82] Thus, cadmium exposure might cause diabetic symptoms through the induction of oxidative stress and disruption of islet β-cell function.

Mercury

Mercury (Hg) is a heavy metal that is widespread and persistent in the environment. Mercury has become an important concern in public health of modern time, because of growing evidence of its presence in some components of the human food chain. For example, fish consumption is beneficial to the prevention of cardiovascular diseases and Alzheimer disease; however, several reports have indicated that fish consumption was the major source of mercury exposure.[83-86] Mercury is present in three forms in the environment, including elemental or metallic mercury, inorganic mercury and organic mercury. The mercury compounds are generally used in dry-cell batteries, fluorescent bulbs, arc lamps, mirrors, and in the extraction of gold and silver from ores, thermometers, dental amalgam fillings and vaccine preserver.[87-91] Thimerosal (ethylmercurithiosalicylic acid) is a mercury-containing compound and a preservative for the vaccine and biological products for more than 70 years. Thimerosal dissociates as 49.5% ethylmercury by weight and thiosalicylic acid and may possess higher cytotoxicity on renal cells.[92] Thus, it must be noted that mercury is a common environmental pollutant, and imposes a rather high risk to our health.

In the Third National Report on Human Exposure to Environmental Chemicals published by the Centers for Disease Control and Prevention, the geometric mean blood mercury levels were 0.3 μg/L in children and 1.2 μg/L in women of childbearing age. Several studies, assessing populations who consume less than one fish meal per week, indicated that the average blood mercury level in adults was around 8 μg/L.[93-96] Latshaw et al.[86] further analyzed the blood mercury content in older urban residents, and found that persons in the highest quartile of fish consumption had median mercury levels 1.82 times above the levels in the lowest quartile, while those in the highest education category had median mercury levels 1.57 times higher than levels in the lowest category. Moreover, a study in workers exposed to mercury cadmium telluride layers has shown that mercury value was estimated at 1.60 ± 0.20 μg Hg/L in control and at 10.72 ± 1.34 μg Hg/L in phase I and 8.08 ± 1.15 μg Hg/L in phase II; an individual who met with a mercury accident showed 226 μg Hg/L of blood.[97] Another report also showed that daily intake of 1,100 μg/kg of mercury induced significantly adverse effect in nonhuman mammals.[98] The study of Nakagawa has shown that the total mercury concentrations in the hair of ordinary diseased people, including diabetes,

were from 2.08 to 36.5 ppm; those values were considerably higher than that of healthy people of the same age-groups.[99]

Organic or inorganic mercury compounds are well known to induce cellular damage in various cell types, such as renal cells,[92] astrocytes,[100] lymphoma cells,[101] human gingival fibroblast cells,[102] alveolar epithelial cells[103] and pancreatic islet β-cells.[104] Except for organic and inorganic forms of mercury toxicity, many studies focus on the vaccine preservative-thimerosal. The ethylmercury was the metabolite of thimerosal. According to previous studies, ethylmercury could be converted to the inorganic form of mercury to induce cell membrane damage and DNA breakage.[105] In primary cultures of mouse pancreatic islet cells, mercuric chloride altered the intracellular calcium homeostasis and insulin secretion.[106,107] A report has shown that Minamata disease patients, who suffered from organic mercury poisoning from 1986 to 1994 (mean age: 63 years), had significantly elevated urine glucose levels. The authors suggested that increased mercury level in Minamata disease may enhance an incidence in diabetes.[108]

The toxicity of mercury in islets is highly related to oxidative stress. It has been shown that 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, is significantly elevated in urine samples of people from mercury-contaminated areas.[109] The concentrations of glutathione (GSH) and total protein thiols and the activities of glutathione peroxidase and superoxide dismutase were higher in the mercury-exposed group than in the control group.[84,109] Our recent study has also shown that mercury is capable of affecting the islet β-cell function and survival through an oxidative stress pathway in vivo and in vitro.[104,110] Low-dose mercury induced mouse pancreatic islet β-cell dysfunction through a PI3K-activated or oxidative stress-triggered Akt pathway in cell culture and animal models.[110] Moreover, methylmercury could induce oxidative stress-triggered β-cell apoptosis and death.[104] Thus, these observations provide evidences to confirm the possibility that mercury is an environmental risk factor for diabetes.

Nickel

Nickel is one of the five ferromagnetic elements. It is a silver-white metal with a slight golden tingle that takes on a high polish. Nickel is often used to be as electroplating and alloy production, such as nickel-cadmium batteries.[111] Nickel is often found in combination with other element, for examples, sulphur, iron and arsenic. Thus, the nickel is widely present in soil, meteorities and emitted from volcanoes.[112-114] The range in surface water and groundwater of nickel levels was about 3 and 10 μg/L. Based on this average nickel concentration, a person took 2 L/day water would intake 4 to 8.6 μg/L nickel.[111] The nickel toxicity depends on the routes of exposure, such as oral and skin. Previous studies have shown that long term orally exposure of nickel, the kidney was the major organ of nickel accumulation; the order of nickel accumulation by different organs from larger to smaller is kidney, lungs, liver and heart.[111,115,116] Toxicity of nickel has been reported in many systems, manifested as diseases including pneumonitis, rhinitis, sinusitis, dermatitis, nasal cavity and lung cancer.[117]

To exposure of nickel caused free radicals production. Nickel has been shown to impair DNA repair-related enzymes through the production of ROS.[111,118] Other studies have also indicated that nickel increases DNA bases oxidation in vitro and lipid-peroxidation in vivo.[111,112,119] Several studies have demonstrated that nickel possesses the ability to induce hyperglycemia.[120-125] It has also been shown that nickel could increase hepatic glycolysis and pancreatic glucagon release, decrease peripheral utilization of glucose, and induce gluconeogenesis.[125] An in vivo study has also found that nickel could block the glucose homeostasis in rats, which caused hypoglucagonemia and hypoinsulinemia, leading to a drastic drop in the insulin/glucagon plasma ratio.[121] Some studies have demonstrated that nickel administration impairs islet function and increases plasma glucose level.[120,123] The antioxidant α-tocopherol appears to be beneficial for downregulation of nickel-induced hyperglycemia in rats.[125] It seems that nickel induces glucose deregulation through ROS pathway. Moreover, elevated inducible nitric oxide synthase (iNOS) and cyclic guanosine monophosphate (cGMP) have also been found to be involved in the nickel-induced hyperglycemia.[124] They found that a significant increase in iNOS protein expression in the pancreas was observed, which was associated with a significant elevation in cGMP levels in adrenals, brain and pancreas, possibly via the stimulation of cytosolic guanylate cyclase. However, there was a report showing that nickel chloride administration could prevent alloxan or streptozotocin-induced hyperglycemia, and suggested that this protective effect was related to the increase of Cu-Zn superoxide dismutase activity.[126] This contradictory observation leaves the relationship between nickel and diabetes still controversial, and would warrant further investigation into the etiological role of nickel in diabetes in the future.

Conclusions

Several studies have indicated that the deficiency and efficiency of some essential trace metals may play a role in the islet function and development of diabetes mellitus. Some toxic metals have also been shown to be elevated in biological samples of diabetes mellitus patients. In this work, we review the important roles of heavy metals in islet function and diabetes development in which the in vitro, in vivo or human evidences associated with exposure to zinc, arsenic, cadmium, mercury and nickel are discussed. Some toxic metals may disrupt glucose uptake and alter the related molecular mechanism in glucose regulation. The dosage, timing, duration, target and toxic process of toxic metal exposure associated with diabetes were mentioned. This work provides a way of thinking about the role of toxic metals/environmental factors in the blood glucose regulation and homeostasis. We summarize the experimental or human investigations of these toxic metals on diabetes in **Table 1**. Schematic representation of proposed intracellular signaling leading to toxic metals-induced islet β-cell dysfunction is shown in **Figure 1**.

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Table 1. Summary of experimental or human investigations of toxic metals on diabetes

Toxic metals	Study models	Targets	Results	Main references
Arsenic	Human	Epidemiologic investigation	↑ incidence of diabetes	27, 42–45
	In vivo	Rat pancreatic islet β-cells	↓ cell viability ↓ insulin secretion ↓ insulin mRNA	48
	In vitro	3T3-LI adipocytes	↓ phosphorylation of protein kinase B (PKB/Akt) ↓ insulin-responsive glucose transporter (GLUT4) ↓ insulin-stimulated glucose uptake	51
	In vitro	3T3-LI adipocytes	↓ phosphorylation of 3-phosphoinositide-dependent kinase-1 (PDK-1) ↓ putative PDK-2 ↓ PKB/Akt activity ↓ insulin-stimulated glucose uptake (ISGU)	56
Cadmium	Human	Epidemiologic investigation	↑ blood glucose level ↓ serum insulin level	75
	Human	Biological samples of type II diabetic patients	↑ blood cadmium of male diabetic patients	27
	In vivo	Rat blood samples	↑ plasma glucose concentration	74
	In vivo	Rat adipocytes	↓ GLUT4 expression	78
	In vivo	Rat blood samples	impaired glucose tolerance (IGT)	78
	In vivo	Monkey pancreatic islet β-cells	↓ insulin-positive areas in histomorphometrical examination ↑ glucagon-positive areas in histomorphometrical examination degeneration of islet B cells	81
	In vivo	Rat pancreatic islet cells	degeneration, necrosis and weak degranulation in the pancreatic islets	82
Mercury	Human	Hair samples	In pregnant population: >4.0 μg/gm	95
	Human	Blood samples	In children: 0.34 μg/L In women: 1.02 μg/L	96
	Human	Hair samples of diseased people, including diabetes	2.08 ppm to 36.5 ppm	99
	Human	Blood samples of an individual who met with a mercury accident	226 μg Hg/L	97
	Human	Human peripheral blood lymphocytes	Cell membrane damage and DNA breakage	105
	Human	Urine samples of Minamata disease patients	↑ urine glucose	108
	Human	Urine samples of mercury contamination area persons	↑ 8-OHdG concentration ↑ DNA oxidative stress damage	109
	In vivo	Mouse pancreatic islet cells	↓ intracellular calcium ↓ homeostasis insulin secretion	106, 107
	In vivo and in vitro	mouse pancreatic islet β cells and HIT-T15 cells	↑ PI3K-activated or oxidative stress-triggered Akt pathway ↑ β-cell apoptosis and death	104, 110
Nickel	In vivo	Rats samples	↑ hyperglycemia ↑ hepatic glycolysis ↓ pancreatic glucagon release ↓ peripheral utilization of glucose ↑ gluconeogenesis ↑ plasma glucose level ↑ inducible nitric oxide synthase (iNOS) and cGMP	120–124

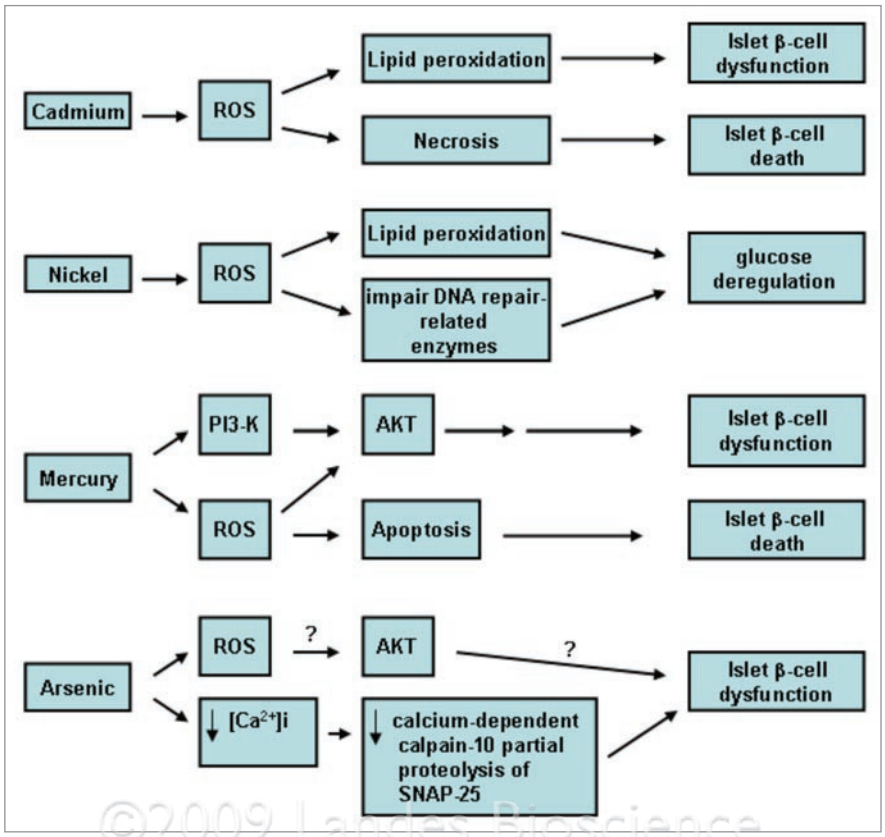

Figure 1. Schematic representation of proposed intracellular signaling leading to toxic metals (arsenic, cadmium, mercury and nickel)-induced islet β-cell dysfunction.

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