MERCURY, INSULIN RESISTANCE AND IMPAIRED BETA-CELL FUNCTION

Several studies have shown a connection between mercury exposure and insulin resistance or type 2 diabetes. In Japan, patients with minamata disease (organic mercury poisoning) were found to have an increased incidence of diabetes[1] but even among patients without minamata disease Japanese diabetics were found to have significantly higher total hair mercury than non-diabetics[2]. Chang et al[3] investigated 1449 non-diabetics exposed to both dioxins and mercury and found that insulin resistance increased with blood mercury ($b = 0.01$, $P < 0.001$) and dioxins, with those with higher blood mercury being at a significantly increased risk for insulin resistance ($P(trend) < 0.001$). The joint highest tertile of serum dioxins and blood mercury was associated with elevated HOMA-IR at 11 times the odds of the joint lowest tertile.

Similarly, *in vitro* studies showed that mercury dose-dependently decreased the function and viability of pancreatic beta-cells, impaired insulin secretion and induced apoptosis through cytotoxicity. It also disrupted the mitochondrial membrane potential, impaired enzyme release and depleted intracellular ATP levels. The mechanism was probably through increased oxidative stress-induced increase in phosphoinositide 3-kinase (PI3K) signalling and its downstream effector Akt phosphorylation. Concentrations of glutathione and total protein thiols and the activity of glutathione peroxidase and superoxide dismutase are higher in those exposed to mercury, while N-acetylcysteine could reverse the cellular and mitochondrial dysfunction in beta cells and prevent inhibition of insulin secretion and Akt phosphorylation but not increased PI3K activity. [4,5,6] Mercuric chloride increased glucose influx into pancreatic cells, which negated the effect of insulin[7], while it caused a rapid and sustained depolarisation of resting membrane potential and increased intracellular free calcium ion concentration in islet cells[8]. Calcium ions are intimately involved in the induction by mercury of insulin release separate from the action of glucose in obese hyperglycaemic mouse islet cells; removal of the calcium inhibited insulin release. Mercury inhibited glucose transport as well as glucose oxidation in these islet cells.[9]

Studies of adipose tissue show that mercury alters glucose metabolism. It stimulates a 1.8-fold increase in glucose transport, which corresponds with an increase in GLUT 1 glucose transporters and phosphorylation of p38 kinase, both of which are indicative of a stress response, which can contribute to the induction of insulin resistance in adipocytes[10]. Exposure to mercury resulted in glucose utilisation of up to 20 times higher compared to cells not exposed to mercury and inhibition of lipolysis both in the basal state and when stimulated by ACTH[11]. Mercury also significantly decreased PPARgamma expression and exposure during cell differentiation increased basal glucose uptake in a dose-dependent manner and decreased insulin-induced uptake in some adipocyte cell lines, while decreasing GLUT 4 in others. Exposure had no effect on phosphorylation of ERK1/2, although it increased JNK phosphorylation in certain cell lines. These results indicate that mercury exposure can inhibit the differentiation of fibroblasts into adipocytes as well as influence signalling events and the subsequent metabolic activity of differentiated adipocytes.[12] It had previously been found that mercury, cadmium and zinc (all Group IIb metals) stimulated transport activity and cAMP phsophodiesterase in adipocytes, in the same manner and to the same extent as insulin, which indicated that these metals mimic insulin action by a post-receptor/kinase mechanism[13].

Other studies show that when used to induce renal failure in animals, mercury mediates the deposition of unusual cytoplasmic accumulation of glycogen within the distal tubular epithelium, which appears to contribute to the protection of distal tubular cells against

mercury-induced injury[14]. Finally, mercury was shown to induce fatty liver disease, as indicated by elevated ALT[15].

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