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NICOTINE AND TYPE 2 DIABETES

J. L. Borowitz and G. E. Isom

Neurotoxicology Laboratory

Department of Medicinal Chemistry and Molecular Pharmacology

College of Pharmacy

Purdue Univesity

West Lafayette, IN 47906

There are nearly 20 million type 2 diabetics in the USA. This common disease is characterized by a gradual decline in pancreatic insulin secretion and worsening hyperglycemia. There are many good drugs for treating type 2 diabetes but normal blood glucose levels are difficult to maintain. Hyperglycemia is especially detrimental since high glucose non-enzymatically cross links blood vessel proteins throughout the body, thickens vascular lumina and interferes with endothelial function. Any kind of peripheral vascular problem would be accentuated by hyperglycemia.

Type 2 diabetes is often part of the “metabolic syndrome” characterized by obesity, hypertension, high blood lipids and resistance to insulin. The metabolic syndrome affects about 25 % of the population and is increasing worldwide with the increase in obesity.

The hypertension and high blood lipids which often occur with diabetes, further stress vessels in the presence of hyperglycemia. These disease states combined with coronary heart disease, give rise to much morbidity and mortality and are leading causes of death in industrialized nations.

Since fetal development is so rapid, it is not surprising that chemicals can damage the fetus. Because type 2 diabetes may begin in utero, it is important to understand processes involved in formation of the endocrine pancreas. Endocrine cells arise from pancreatic progenitor cells during embryogenesis. These progenitor cells receive many signals, some mitogenic and some for differentiation (Dhawan et al 2007). Progenitor cells persist throughout embryogenesis, but in the early postnatal period, high rates of beta cell proliferation cause a large increase in endocrine cells. Although beta cell mass expansion is slow in adults, pregnancy or obesity can cause hyperplasia and increased insulin synthesis/secretion (Dhawan et al 2007). Existence of progenitor cells in the adult pancreas is controversial but Xu et al (2008) report that progenitor cells can be activated in injured adult mouse pancreas and are located in the ductal lining. They show expression of neurogenin-3, the earliest islet cell transcription factor, in the injured pancreas. Thus not only are fetal tissues at risk but beta cell proliferation, in the early postnatal period and perhaps in later periods also, may be sensitive to chemical damage.

Despite the known vulnerability of fetal cells, still chemical exposure and damage occurs. About 15-20 % of all women smoke during pregnancy (Andres and Day, 2000). Epidemiological studies show a relationship between smoking and hypertension, type 2 diabetes and obesity in the adult offspring of smoking mothers (Montgomery and Ekbom

2002; von et al 2002; Wideroe et al 2003). Such deliberate use of toxic substances which cause damage to developing humans places a large financial burden on our medical care program.

Nicotine replacement therapy is recommended to pregnant women in Canada as a safe aid for breaking the smoking habit. Yet Holloway et al (2005) report that rats exposed to nicotine during gestation and lactation (PND21) show apoptosis of insulin secreting cells. Increased postnatal weight with adiposity was also noted during the first 26 weeks of age. Both at 7 and 26 weeks these nicotine-exposed animals show abnormal glucose tolerance. Holloway et al (2005) concluded that fetal and neonatal exposure to nicotine in amounts comparable to those of human exposure causes a syndrome in rats similar to human type 2 diabetes.

Bruin et al (2007) found that beta cell mass is decreased by about 25 % following nicotine exposure either in utero or after both fetal and neonatal exposure. However those animals not exposed during lactation recover beta cell mass by 26 weeks whereas those exposed both in utero and during lactation do not. It appears that nicotine can destroy those cells responsible for beta cell regeneration if it is present both during pregnancy and lactation. Elevated and prolonged blood glucose was also seen in response to an oral glucose challenge at 26 weeks but only in offspring exposed to nicotine for the entire fetal and neonatal period. Thus two different cell processes may be affected by nicotine. One, beta cell proliferation and the other, beta cell apoptosis. Nicotine must be given for a longer period of time in order to affect cell proliferation.

In the paper highlighted in the present issue, Bruin et al (2008) further extended the studies of Holloway et al (2005) and elucidated some mechanisms by which nicotine

increased beta cell apoptosis. Number of mitochondria decreased about 13 % in beta cells from nicotine-exposed subjects and the remaining mitochondria were swollen so that they were about 50 % larger than in saline controls and most likely dysfunctional. Changes in proteins regulating apoptotic cell death were also noted. Bcl-2 decreased in cytoplasm and allowed Bax to attach to mitochondria. Bax opened the mitochondrial permeability transition pore to release cytochrome c into the cytosol. Cytochrome c formed an apoptosome and activated caspase 3, the executioner protease responsible for the apoptotic changes and cell death. Bruin et al (2008) concluded that nicotine exposure during pregancy and lactation increased beta cell apoptosis in the offspring by the mitochondrial pathway.

Nicotine-induced apoptosis of beta cells may be mediated through nicotinic receptors. Yoshikawa et al (2005) demonstrated specific binding of [3H] nicotine to beta cells and showed that nicotine inhibits glucose- as well as tolbutamide-induced insulin release from isolated rat and human islets. However nicotine given iv actually releases insulin in mice if the effect of adrenal epinephrine is eliminated by adrenalectomy (Karlsson and Ahren 1998). Ganglionic actions may overcome any direct effect of nicotine on pancreatic beta cells.

Nicotine need not act on surface nicotinic receptors. It is lipid soluble enough to penetrate into cells. Being an alkaloid, it is basic and would tend to collect in the relatively acidic intracellular environment. Also intracellular organelles like endoplasmic reticulum or secretory granules have a pH of about 4 so nicotine would concentrate further inside these compartments. It is not surprising that nicotine inhibits release of insulin from isolated islets.

Bcl-2 protein decreased in beta cells of nicotine exposed pancreas to initiate the process of apoptosis. Since Bcl-2 is a redox-sensitive factor (Voehringer and Meyn 2000), it appears that prolonged treatment with nicotine causes oxidative stress. How this occurs and whether nicotinic receptors are involved is not known. The mitochondrial changes are subsequent to changes in Bcl-2 protein and therefore are probably not a direct action of nicotine on mitochondria.

The vascular endothelium is a primary site for pathological changes in type 2 diabetes both in islets themselves and throughout the rest of the body. In fact islets may be more sensitive than other tissues to changes in vascular endothelium. Not only do islets have 5 times more capillaries but the endothelial lining shows 10 times more fenestrations than acinar tissue. Furthermore, the endothelium can affect adult beta cell function, promote beta cell proliferation, produce vasoactive and angiogenic substances and growth factors. The islet microendothelium also fine tunes blood glucose control (Zanone et al 2008). Vasoconstrictors like nicotine and angiotensin II probably have more important effects on circulation to beta cells than to other cells of the body. Macfarlane et al (2008) state that many clinical studies show drugs which block angiotensin II reduce the incidence of diabetes and may do so, in part, by improving islet function.

Once nicotine-induced damage to beta cells begins and type 2 diabetes develops, other mechanisms come into play. High glucose itself causes oxidative stress in beta cells (Robertson et al 2007) and leads to progressive loss of function. High blood lipids also cause a loss of beta cell function (Hull et al 2005). Associated deterioration of the

vascular endothelium with reduced vascular flexibility in type 2 diabetes results in increased

pulse pressure and pulse wave velocity and also shear stress (Cameron and Cruickshank

2007). Impaired nitric oxide production is part of vascular stiffening (Soucy et al 2006) and

type 2 diabetics lack the powerful vasodilating action of nitric oxide so that deterioration of

tissue perfusion occurs throughout the body. Continued exposure to the vasoconstrictor

nicotine would further exacerbate the problem. To counteract blood vessel stiffening, Sharma

(2007) suggests that drugs which block phosphodiesterase be used so that accumulation of

cyclic GMP would occur in endothelial cells releasing nitric oxide to promote profound

vasodilation. These nitric oxide generators may relieve endothelial dysfunction in type 2

diabetes.

Much effort and money has been spent developing drugs for treatment of type 2 diabetes. The sufonylureas have been used for about 50 years and the meglitinides are even more effective and actually enhance glucose-induced insulin release. They also have a shorter duration of action and cause less hypoglycemia. Metformin is even better and causes no hypoglycemia or obesity and reduces stroke and heart attacks in these patients. Many of these antidiabetic drugs give rise to obesity and the elevated blood lipids may explain why beta cell function deteriorates when these drugs are used. The significance

of the highlighted paper is that it provides mechanistic data on the adverse effects of nicotine

on the developing pancreas and suggests that another way to approach the type 2 diabetes problem would be to avoid exposure of the fetus and neonate to nicotine.

As alcohol has some specifity for brain cells (corpus callosum, cerebellum and frontal cortex) in fetal alcohol syndrome (FAS), so nicotine appears to have a specificity for beta cells of the pancreas. It was thought that the incidence of FAS was about 0.1 % of the population but now we know the incidence is 1 %. It is the number one cause of mental retardation in the USA and yet is 100 % preventable. The severe form of FAS with nasal hypoplasia, droopy eyelids and poor coordination, is rare but more subtle changes occur at lower doses. Even when no physical abnormalities are apparent behavioral changes can occur. Some FAS patients may have a normal IQ but at the same time may have impaired ability to relate to other people and are not able to use their intelligence. Similarly, low doses of nicotine during pregnancy and lactation may cause more subtle changes in pancreatic beta cell function and glycemic control.

Publications by Holloway et al (2005) and Bruin et al (2007, 2008) have highlighted the fact that nicotine destroys insulin secreting cells in the pancreas and these authors have exposed a major clinical toxicology problem. Beta cells of the pancreas are susceptible to the toxic action of nicotine both during gestation and in the neonatal period. Dysglycemia occurs in the offspring of nicotine-treated rats when they are challenged with glucose as young adults. These animals appear to have a form of type 2 diabetes. Nicotine in any form should be avoided during pregnancy and lactation.

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