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Glycaemic Control and Protection of the Vasculature from Glucose Toxicity

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1. Introduction

Diabetes, notably type 2 diabetes, is a major and prevalent health problem with a minimal current estimate of 250 million sufferers worldwide, a prediction of 366 million by 2030 and, based on the evidence of numerous reports, we can also anticipate an excessive morbidity and mortality rate in this population primarily as a result of cardiovascular disease (Kannel & McGee, 1979; Wild et al., 2004). As reflected by the data from the 1991 United Kingdom Prospective Diabetes Study, UKPDS, with 5102 subjects with type 2 diabetes, and the 1993 Diabetes Control and Complications Trial, DCCT, with 1441 type 1 diabetics, the established dogma for the best form of management for patients with diabetes is tight glycaemic control (DCCT 1993; UKPDS 1991, 1998). Such conclusions have been re-emphasised as reflected by a report by Standl and colleagues (2009) indicating that the incidence of cardiovascular events associated with diabetes is reduced by 10-15% per 1% reduction in absolute glycated haemoglobin, HBA_{1c}, levels. In addition, the Emerging Risk Factors Collaboration (ERFC) study, a collaborative meta-analysis of 102 prospective studies, made the observation that the pre-existence of diabetes enhanced the risk of vascular disease more than two fold (ERFC, 2010). Furthermore, the ERFC study of 820,900 participants also concluded that a 50-year-old with diabetes died approximately 6 years earlier than a person without diabetes and that diabetes was moderately associated (but not necessarily causality) with death from certain cancers such as liver, pancreas, bladder, breast, colorectal, lung and ovary as well as other causes including infectious diseases, degenerative disorders and others (ERFC, Seshasai et al 2011). Nonetheless, a 'glucocentric' approach to the treatment of diabetes was delivered a setback with the results, released in 2007, from the Action to Control Cardiovascular Risk in Diabetes, ACCORD study of 10,251 patients. The intensified glucose lowering arm of the ACCORD study with 5,128 patients targeted glycated haemoglobin, HBA_{1c}, of <6% was discontinued when it became apparent that such an intensive regimen resulted in a significantly higher all-cause risk of death of 22% and a 35% increase in cardiovascular mortality (Gerstein et al., ACCORD, 2008). In contrast, data from the Action in Diabetes and Vascular Disease, ADVANCE, that was released shortly after that from the ACCORD study provided no evidence of an increased mortality amongst the 11,140 high-risk patients who were randomly assigned to either standard or intensive glucose control (HbA_{1c} of 6.5 or less) in the study, but also reported a 10% reduction in combined micro- and macrovascular events (ADVANCE 2008). Similarly for the Investigators in the Veterans Affairs Diabetes Trial,

VADT, wherein 1791 military veterans were subjected to either an intensive or a standard therapy for glycaemic control no significant increase in mortality was noted, but there was no significant reduction in microvascular events excepting a reduction in the progression of albuminuria (Duckworth et al., 2009).

Although, initially, it appeared that no one particular subgroup in the ACCORD study had a particularly higher mortality, independent concerns have been raised concerning an elevated cardiovascular risk with some of the drugs used in these studies, for instance as reported in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes, RECORD, study (Goldfine 2008; Komajda 2010). New information also indicates that additional post-hoc subgroup analysis from the ACCORD trial may be helpful in the identification of sub-groups (Calles-Escandon, 2010). In addition, the meta analysis performed by the Collaborators on Trials of Lowering Glucose, CONTROL, on the data from the ACCORD, ADVANCE, UKPDS and the VDAT trials concluded that a more intensive glucose-lowering regimen did reduce, albeit modestly, major cardiovascular events in patients with type 2 diabetes, but increased major hypoglycaemic episodes (Turnbull et al., 2009). Issues over the make up of the patient groups versus the onset of diabetes have also been raised, as have questions over the benefits of intensive glycaemic control versus cholesterol and/or blood pressure lowering (ACCORD 2010a,b; Emanuele, 2010; Nilsson 2010; Yudkin & Richter, 2010). A 2009 meta analysis of 5 trials that addressed intensive control of glucose and cardiovascular outcomes indicated that intensive compared with standard glycaemic control did significantly reduce coronary events without an increased risk of death; however, population variability may be evident regarding the optimum mechanism, speed, and extent of reduction (Ray et al., 2009). Putting all of these data sets together and considering the conclusions from a number of meta-analysis and subgroup analysis that have been completed and reviewed one can conclude that the management of glycaemia remains central to the treatment of patients with diabetes and important for reducing cardiovascular disease risk, but individualised treatment is to be preferred (Mazzone, 2010). This conclusion is supported by the 2011 recommendations made by the American Association of Clinical Endocrinologists (AACE) (Handlesman et al., 2011). Nonetheless questions remain as to how to optimise the treatment protocols for the better protection of patients with diabetes from cardiovascular disease as well as stroke.

To summarize, although further analysis and potentially new studies are required what does remain clear is that the morbidity and mortality associated with diabetes predominantly reflect cardiovascular pathophysiological sequelae that result in a 2- to 4-fold increase in the incidence of coronary artery disease, a 10-fold increase in peripheral vascular diseases and a 3- to 4-fold increase mortality rate that, primarily, reflect a doubling of the risk of vascular disease (Grundy et al 2002; ERFC 2010).

2. Diabetes, cardiovascular disease and endothelial dysfunction

Changes in the function of the endothelium are argued to be early indicators of the onset of vascular disease including that associated with diabetes and, as an example, are apparent prior to the detection of atherosclerotic plaque development (McLenachan et al., 1990; Werns et al., 1989). Endothelial dysfunction is frequently defined as a reduced endothelium-dependent vasodilatation (EDV) response to either an endothelium-dependent vasodilator, such as acetylcholine or bradykinin, or to flow-mediated vasodilatation. This functional

definition of endothelial dysfunction is one that can be readily demonstrated using the methodology first described by Furchgott and Zawadzki in their 1980 in vitro study of endothelium-dependent relaxation to acetylcholine in rabbit aortae and has been extended to include wire and pressure myography studies in small arteries from animals as well as man. In humans, both non-invasive and invasive techniques have been applied to measure both vasodilator and flow-mediated vasodilatation and the data generated have advanced our understanding of the pathophysiology of coronary artery disease in humans (Anderson et al., 1995; Bohm et al., 2005). It is not just the vasodilatation response that is decreased or lost, but, in addition, an increased expression of adhesion molecules including the soluble adhesion molecules, sE-Selectin and sICAM-1, pro-inflammatory molecules, altered regulation of smooth muscle cell proliferation and the development of a procoagulatory state. Increased levels of the soluble adhesion molecules, sE-Selectin and sICAM-1, and also the endothelium-specific marker, soluble thrombomodulin have been determined by biomarkers for the risk and severity of diabetes-associated coronary artery disease and cardiovascular disease in general (Constans 2006; Thorand 2006). Thus, a revised and broader definition of 'endothelial dysfunction' is required and has been suggested by Triggle & Ding (2010):

"Endothelial dysfunction reflects a reduced (EDV) response to either an endothelium-dependent vasodilator, such as acetylcholine (or bradykinin), or to flow-mediated vasodilatation that is accompanied by elevated expression of adhesion molecules, enhanced vascular smooth muscle proliferation and the development of a hypercoagulatory state."

Endothelial dysfunction has been demonstrated in a number of studies to be both an early indicator of vascular disease and a predictor of a future cardiovascular event (see Esper et al., 2006). Furthermore, endothelial dysfunction in diabetes has been linked to hyperglycaemia- and hyperlipidaemia (hypertriglceridemia)-induced oxidative stress as demonstrated in both human and animal studies (Ceriello et al., 2002; Monnier et al., 2006; Triggle et al., 2005). Furthermore, high glucose induces both premature senescence and reduces total numbers of endothelial progenitor cells (EPCs) and thus impairs both repair and angiogenic processes (Balestrieri et al., 2008). Endothelial cells normally have a relatively long turnover rate that has been stated to be approximately three years, however, damage to the endothelium results in replacement by regenerated cells that may not have the same properties as normal endothelial cells (Brandes et al., 2005; Vanhoutte, 2010).

2.1 Hyperglycaemia and endothelial dysfunction

Elevated glucose levels acutely as well chronically affect vascular function. Acute effects include a rapid loss of flow-mediated EDV in humans with a pronounced delayed recovery in type 2 diabetes that most likely reflects a glucose-induced uncoupling of endothelial nitric oxide synthase (eNOS) secondarily to the oxidation of the key eNOS co-factor tetrahydrobiopterin (BH_4) (Ihlemann, 2003; Kawano et al, 1999; reviewed by Ding & Triggle, 2010). A key observation is the ratio BH_4 to BH_2 (oxidised product of BH_4) that is critical for eNOS function as BH_4 and BH_2 bind with equal affinity to eNOS and hyperglycaemia promotes BH_4 oxidation (Crabtree et al., 2008). Studies with the db/db leptin receptor mutant diabetic mouse also substantiate the important role of the BH_4/BH_2 ratio in endothelial function (Pannirselvam et al., 2002; 2003; 2006). Simply supplementing with BH_4 in the presence of hyperglycaemia may not improve eNOS function, or at best only acutely, as persistent hyperglycaemia will, via enhanced superoxide production, oxidise BH_4 to BH_2. Interestingly ascorbic acid, but not vitamin E, helps stabilize BH_4 and increases eNOS

activity of aortic endothelial cells from ApoE-deficient mice (d'Uscio et al., 2003) and also porcine endothelial cells (Huang et al., 2000).

Under hyperglycaemic conditions the glycolytic and oxidative phosphorylation pathways are overloaded and the result is the shunting of glucose and the intermediates of glucose metabolism, namely fructose 1,6 biphosphate and glyceraldehyde 3 phosphate, into pro-oxidative stress pathways such as hexosamine metabolism, sorbitol metabolism, protein kinase C activation, α-ketoaldehyde formation and methyglyoxol/advanced glycated end product (AGE) formation (Robertson, 2005). In addition, glucose in the physiological range of 4 to 10mM, following metabolism and protein kinase C activation, rapidly depresses voltage-gated potassium channel, Kv, currents in rat mesenteric myocytes and inhibits Kv channel modulation by endothelin-1 (Rainbow et al., 2006). Kv channels are key regulators of vascular tone (Knot and Nelson, 1995; Cole et al., 2005) and thus glucose-induced reduction of Kv channel activity would have profound effects on blood flow, glucose disposal and ultimately could contribute to the development of insulin resistance and hyperglycaemia-linked vascular disease (Straub and Nelson, 2006). Calcium homeostasis is also affected and exposure of primary endothelial cells for 24-72 hours to high glucose also alters Store-Operated Ca^{2+} Entry (SOCE) and has been associated with changes in expression of the Transient Receptor Potential Channel 1 (TRPC1) (Bishara and Ding, 2010). Comparable changes have been reported in the expression levels of TRPC1 and also another Store-Operated Ca^{2+} Channel protein, STIM1, in the coronary artery of of the Ossabaw pig model of diabetes (Edwards et al., 2010). An increase in expression levels of TRPC1 has also been associated with vascular disease and injury thus suggesting that alterations in SOCE may be closely associated with the development of vascular disease and thus, potentially, another target for therapeutic intervention (Kumar et al., 2006; van Breemen et. al., 2006).

2.2 Postprandial hyperglycaemia is an important risk factor

The importance of postprandial regulation of blood glucose as a determinant of the impact of hyperglycaemia on vascular function is receiving increasing attention (Ceriello 2005; Woerle et al., 2007; Aryangat & Gerich 2010) and another confounding influence seems to be that the impact of oscillating levels of glucose on endothelial function may be more damaging than sustained high glucose (Ceriello 2008a). Indeed, a high postprandial glucose 'spike' starting from a lower basal fasting glucose may be more damaging than that produced by the equivalent 'spike' level, but starting from a higher basal glucose simply because it is the extent of the change in glucose that determines the degree of endothelial dysfunction (Ceriello, 2008b). Data from the RIAD study (Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes) also indicated that the postprandial glucose 'spike' is a better predictor of carotid artery intima-media thickness (a measure of atherosclerosis) than fasting glucose or HbA1c (Hanefield et al., 2000; Temelkova-Kurtschiev et al., 2000). Thus, collectively these data indicate that reducing the extent of post-prandial excursions in blood glucose should reduce cardiovascular events.

2.3 Consequences of chronic hyperglycaemia

Chronic exposure to high glucose results in the non-enzymatic formation of AGEs, alters proteasome function, as well as produces epigenetic changes in histone methylation and demethylation that, secondary to glucose-induced elevated oxidative stress, result in

persistent gene activation that likely forms the basis for the development of 'hyperglycaemic memory' (Brasacchio et al., 2009; Cognali, 2008; Queisser et al., 2010; Vlassara & Palace, 2002). Hyperglycaemic memory is a serious consequence of a lack of adequate glycaemic control as, despite restoration of normoglycaemia, vascular disease continues to progress (reviewed by Triggle & Ding, 2010). Figure 1 summarizes the potential contributions of AGEs and epigenetic changes to the development of hyperglycaemic memory, pancreatic beta cell dysfunction and vascular disease:
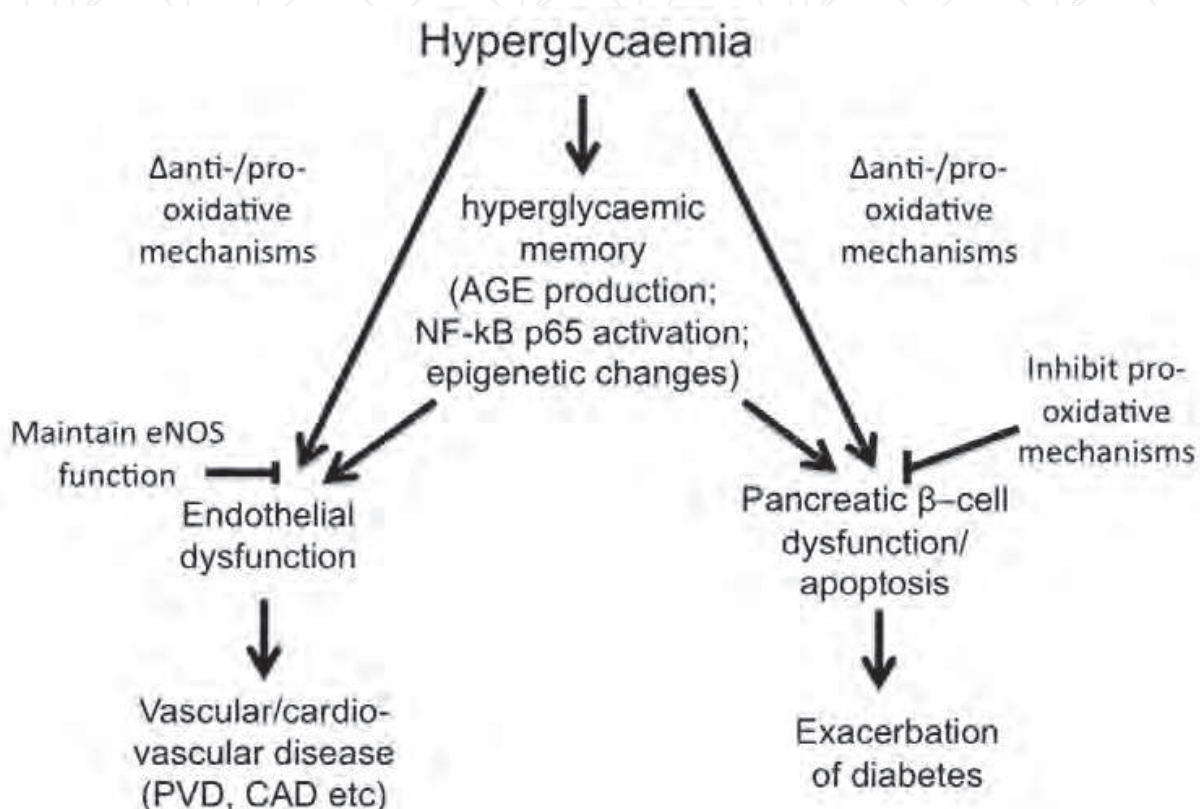

Fig. 1. Hyperglycaemia induces both endothelial and pancreatic β-cell dysfunction. The long-term sequelae of hyperglycaemia results in cardiovascular disease include peripheral vascular disease (PVD) and coronary artery disease (CAD).

If AGEs are important contributors to hyperglycaemic memory then arguably tight and aggressive glycaemic control should be translated into better protection against future cardiovascular events (Chalmers & Cooper, 2008). In addition, early treatment designed to reduce cellular reactive species, glycation and the build up of AGEs should minimize long-term diabetic complications (Ceriello, 2009). Glucose toxicity is also linked to pancreatic β-cell apoptosis that may involve several pathways including links to oxidative stress, endoplasmic (ER) stress, changes in the expression of the antiapoptotic protein Bcl-2 and epigenetic changes in the promoter for nuclear factor kappa B (NF-KB) subunit p65 (Eizirik et al., 2008; El-Osta et al., 2008; McKenzie et al., 2010; Robertson 2004).

2.4 Antioxidant therapy and diabetic vascular disease
Although many animal studies clearly indicate that oxidative stress results in endothelial dysfunction (see reviews by Ding & Triggle 2010; Triggle & Ding 2010) antioxidant therapy

in humans has been demonstrated to be ineffective in reducing mortality [MRC/BHF, 2002]. In the MRC/BHF randomised study 20,536 individuals with various prior cardiovascular disease morbidities were recruited into 69 hospitals and were treated with either a statin, antioxidant vitamin therapy (600 mg E, 250 mg C and 20 mg beta-carotene daily or a placebo). Nonetheless, protection of endothelial function as is evident by a reduction in oxidative stress as well as enhanced levels of the dimeric 'coupled' eNOS can be demonstrated by provision of the precursor of BH_4, sepiapterin, at least in endothelial cells in culture (Ding et al., 2007; Aljofan & Ding, 2010). The role of antioxidant dietary adjuncts and therapy in prevention and treatment remains a highly important clinical question and Dusting and Triggle (2005) argued that there is a need for re-thinking of the choice of antioxidants as well as better-designed studies. Thus, further studies of the benefits of antioxidants and, in the cellular setting, appropriately targeted antioxidants to the cellular source(s) of excessive free radical production are clearly justified. It is thus of value to reflect on the apparent benefits of the natural phenolic resveratrol on lifespan in a number of organisms, including yeast, worms, flies as well as mice on a high fat diet (see Baur et al. 2005). The cellular basis for the protective effect of compounds such as the polyphenol antioxidant, resveratrol, in diabetes may be linked to activation of AMP-activated protein kinase (AMPK) – the so-called metabolic master switch that has multiple targets facilitating, for instance, glucose uptake in muscle, fatty acid oxidation and inhibition of glucose production by the liver (Um et al., 2010).

Antioxidant enzyme levels are low in pancreatic β cells and chronic oxidative stress is thought to be a major contribution to β cell dysfunction in diabetes (Robertson, 2004; Tiedge et al., 1997). These data suggest that antioxidant therapy should benefit β cell function; however, the efficacy of the common antioxidants available either from dietary or supplement sources may simply not be high enough to have significant benefit (Robertson, 2004). Furthermore, with the exception of the PPAR-gamma agonists and incretin-mimetics that do have protective and/or trophic effects, direct beneficial effects of most anti-diabetic agents on β cells have not been clearly documented (Bonora 2008).

2.5 Endoplasmic Reticulum (ER) stress and diabetes

The ER plays a critical role in protein folding and sorting and stress will impair these functions resulting in the *'Unfolded Protein Response'*, or UPR, that, initially, despite an increase load on the protein folding machinery, helps to maintain homeostasis. Prolonged ER stress, which may include oxidative stress secondary to the contribution of molecular oxygen to disulphide bond formation, results in cell death via apoptosis and there is increasing evidence that ER stress plays an important role in the aetiology of many diseases including diabetes and atherosclerosis (Eizirik et al., 2008; Hosoi and Ozawa, 2010; Tabas 2010; Tu and Weissman 2004). It is also now recognised that UPR is regulated by a signal transduction pathway with three major components: 1/ inositol requiring 1 (IRE1); 2/ Protein kinase RNA-like ER kinase (PERK); 3/ Activating Transcription factor 6 (ATF6) that can all contribute to ER stress. As our knowledge on ER stress expands so do avenues for interventions that may slow the progression of a disease (Patil & Walker 2001; Eizirik et al., 2008).

Notably in response to obesity, post-prandial hyperglycaemia and the development of insulin resistance the insulin producing pancreatic β-cell is exposed to considerable stress as newly formed pro-insulin is directed to the ER for appropriate folding. ER stress in the

pancreatic β-cell results in progressive pancreatic β-cell dysfunction and death (Fonesca et al., 2009). The loss of pancreatic β-cell function is a key contributor to the later stages of type 2 diabetes and results in the requirement for insulin therapy. A key mediator of ER stress-induced apoptosis is the transcription factor CHOP (also known as GADD153), which under normal conditions has a low expression level, but levels increase with increasing ER stress (Eizirik et al., 1993; Oyadomari & Mori, 2004). Similarly the endothelial cell, just like the pancreatic β-cell, when exposed to hyperglycaemia responds with an increase in ER stress that seems to be secondary to mitochondria metabolism and superoxide generation (Sheikh-Ali et al., 2010a). Of additional interest and relevant to the protective role of resveratrol is that ER stress in endothelial cell is enhanced with the deletion of AMPKα2 and that certain antioxidants can reduce ER stress (Dong et al., 2010; Sheikh-Ali et al., 2010b).

3. What can we learn from other mammalian species?

The "thrifty" gene hypothesis ('Diabetes Mellitus: A "Thrifty" Genotype Rendered Detrimental by "Progress"?'), as originally proposed by Neel, argues that we are descended from hunter-gatherers who survived and evolved despite having to cope with an unpredictable availability of food and therefore survival was based on "selectivity" to store energy as fat (Neel, 1962). Europeans have maintained a comparatively lower prevalence of diabetes than most other populations and, perhaps, this can be related to the fact that Europeans have arguably been exposed to relatively stable food supply and "modern" technology for a comparatively longer period than other ethnic groups. However, support for this latter speculation is reduced by evidence that Australians and North Americans of European descent have significantly higher rates of diabetes than their European counterparts (Diamond 2003; Dunstan et al., 2002; Harris et al., 1998). Various explanations can be provided to explain such differences and whether we accept a "thrifty (like) gene", or a "drifty gene" hypothesis, or even the role(s) of environmental influences such as bacteria and viruses, continues to be debated (Diamond 2003: Prentice et al., 2008; Speakman, 2008; Zinn, 2010). Of relevance to the thrifty gene debate are data from studies of domesticated pigs and cattle that have been bred for countless centuries to store energy for future human consumption and yet do not, or only rarely, develop diabetes (Gerstein & Waltman 2006). These observations provide a basis for a tentative conclusion that it is possible to provide 'protection' against diet- and hyperglycaemia-induced vascular disease in mammals despite exposure to ample food supply and limited exercise and thus warrant further studies of the comparative physiology/genetics of these species (Venn-Watson et al., 2011). Nonetheless, as reflected in the Ossabaw pig colony on Ossabaw Island, (Georgia, USA) in as little as 500 years domestic pigs exposed to a feast and famine environment do become prone to the development of metabolic syndrome and diabetes when these feral pigs are provided the same diet as their domesticated cousins (Gerstein and Waltman, 2006; Whitfield 2003). Studies with Ossabaw pigs are providing insights into the pathophysiology of vascular disease associated with metabolic syndrome and diabetes (Edwards et al., 2010). The one-humped camel, *Camelus dromedaries*, is a desert animal that can withstand both a harsh climate and limited supplies of food and water, but, similar to the Ossabaw pig, when exposed to a high calorie diet develops signs of diabetes (Ali et al., 2006). On the other hand milk from *Camelus dromedaries* has been known through ethnomedical practice and recent clinical trials to lessen the insulin requirements of diabetics (Mohamad et al., 2009). Whether the anti-diabetic factor in camel milk, which might be insulin or an insulin-like factor, also

provides some protection to the camel when exposed to a high carbohydrate diet is unknown.

It is of interest to note that certain mammalian species, specifically the bottlenose dolphin, *Tursiops truncates*, can maintain high post-prandial glucose levels and a diabetic-like state that is probably essential for the dolphin to maintain adequate brain levels of glucose and yet not, apparently, truly develop diabetes (Venn-Watson & Ridgway, 2007). About 55 million years ago dolphins, pigs and ungulates shared a common ancestor that was a herbivore and the possible link between elevated blood glucose levels in dolphins may relate to the need to maintain adequate glucose levels for an enlarged brain size and function (Thewissen & Mador, 1999; Venn-Watson et al., 2007; 2011). Miller and Colagiuri (1994) have advanced the hypothesis that for Homo sapiens the low carbohydrate and high protein carnivorous diet that existed for about 2 million years up until the end of the last ice age disadvantaged the insulin-sensitive phenotype in favour of insulin resistance. Europeans have, on the other hand, been exposed to a long period of agricultural development and thus the selection process for insulin resistance was relaxed with the result that present-day Europeans are more resistant to type 2 diabetes than most other ethnic groups (Miller & Colagiuri, 1994).

The more generally held view is the present obesity/diabetes pandemic has resulted from a combination of greater food availability, reduced physical activity and genetic susceptibility. We should, however, be cautious about accepting this view without considering other influences (Zinn 2010). A hypothesis advanced by Klimentidis et al (2011) is based on the "Canary in the coal mine" analogy and notes that similar trends in body weight increase have been observed in some domesticated and non-domesticated mammals including feral rats trapped in urban Baltimore that showed a 5.7% increase in body weight per decade. The data presented by Klimentidis et al (2011) is suggestive of environmental influences such as endocrine-disrupters and infectious diseases that may have epigenetic effects on mammalian genomes. Nonetheless the close link between diet, a sedentary lifestyle, obesity and cardiovascular disease in humans is difficult to deny. Alternatively, or in addition, the "thrifty phenotype" hypothesis argues that poor foetal and infant nutrition that negatively affect growth result in permanent changes in glucose homeostasis that result in the development of the metabolic syndrome and type 2 diabetes (Hales and Barker, 2001). Calorie restriction on the other hand has been shown to increase longevity in rats and, more recently, studies in non-mammalian species that include yeast and invertebrate species, have linked longevity to the SIRT1, the mammalian homolog of Sir2 (silent information regulator 2 and originally termed MARI, Mating-Type Regulator-1). In *Saccharomyces*, *Caenorhabditis elegans* and *Drosophila* Sir2 mediates the effects of calorie restriction on life extension and therefore has been associated with the regulation of longevity (Dali-Youcef, et al., 2007). Collectively these data have led to the hypothesis that, in mammals, SIRT1, by virtue of the key role it plays in post-transcriptional regulation, is the central co-ordinator of metabolic regulation and insulin sensitivity and obesity (Holness et al., 2010). SIRT1 as a target for the treatment of metabolic diseases is discussed in more detail later in this chapter.

Regardless of the genetic basis for susceptibility to obesity and diabetes evidence for atherosclerotic changes linked to a high fat diet is clearly shown in human remains from several ancient societies including the mummies of Egyptian pharaohs, priests and other privileged members of the Egyptian society back to at least 1500 AD (David et al., 2010). These findings seem to parallel those in a society, such as the USA today, where the impact

of diet is clearly evident on the prevalence of obesity that from 1976--1980 to 2007--2008, increased from 15% to 34% among adults and from 5% to 17% among children and adolescents (Freedman et al., 2008). Perhaps *Homo sapiens*, unlike *Sus scrofa domesticus,* have not evolved, or adapted, sufficiently such that its cardiovascular system cannot withstand the abuse of a diabetogenic/atherogenic diet? The debate continues as to whether diabetes in *Homo sapiens* reflects a 'thrifty' genotype or simply a genetic drift – the 'drifty' gene hypothesis with, perphaps, the latter being supported by the Ossabaw pig example (Prentice et al., 2008; Speakman 2008)?

4. How to proceed?

The results from the ACCORD study questioned the benefits of an overly intensive glycaemic control regimen and yet data from animal studies as well the UKPDS & DCCT data indicate that hyperglycaemia is detrimental to vascular function and increases morbidity and mortality. Thus, the question arises: "Can we, in addition to pursuing a more modest reduction in blood glucose levels and HBA_{1c}, determine new approaches to protect the cardiovascular system against glucose toxicity?" In other words: "Are there new therapeutic approaches that can provide improved cardiovascular protection?" Most therapeutic interventions targeting cardiovascular disease modulate endothelial function indirectly via targeting the risk factors linked to endothelial dysfunction. Thus, for hypertension, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used and for dislipidemia the lipid-lowering statins. Many of these drugs have been reported to have pleiotropic effects that improve endothelial function and their actions have been reviewed (Dobarro et al., 2009). A number of the drugs that are used as anti-hypoglycaemic agents for the treatment of type 2 diabetes also have been reported to have direct and/or indirect effects to improve endothelial function.

4.1 Metformin

Metformin, a first-line and most widely prescribed drug for the treatment of type 2 diabetes, has has been demonstrated to not only correct hyperglycaemia but also to improve endothelial function in human subjects (Mather et al., 2001). Metformin also seems more effective in obese patients with the recent observation suggesting that metformin, a substrate for organic cation transporters, OCTs, and notably OCT1, reduces adipogenesis as a result of an increased action in adipocytes from obese patients that could be linked to an elevated expression of OCTs (Rotella et al., 2006; Moreno-Navarrete, 2011). The therapeutic efficacy of metformin thus makes it an ideal drug to study in terms of its cellular mode(s) of action and, in particular, although effective a high level of non-fatal gastrointestinal side effects can reduce patient compliance. Metformin, at least in part, mediates its' cellular action(s) via the activation of AMPK with the reported involvement of mitochondrial-derived reactive nitrogen species and the requirement of eNOS expression (Mather et al., 2001; Zhou et al., 2001; Zou et al., 2004). The ability of metformin to reduce hepatic glucose output has been credited to an action via the LKB1 (a serine/threonine kinase)-AMPK/SIRT1 pathways and inhibition of key glucogenic genes in the liver (Zhou et al., 2001; Shaw et al., 2005). The role of SIRT1 and GCN5 (a histone acetyltransferase), two regulators of gluconeogenic gene expression via the modulation of cAMP-response element binding protein (CREB), in the action of metformin are of particular interest because AMPK is known to activate SIRT1 which, via deacetylase of key targets, including LKB1, may mediate the beneficial effects of metformin (Canto et al., 2009;

Caton et al., 2011; Lan et al., 2008). As discussed later in this chapter SIRT1 is a key target of interest for the treatment of metabolic disorders.

AMPK-independent actions on hepatic gluconeogenesis and endothelial function have also been reported suggesting that the beneficial actions of metformin in type 2 diabetes result from effects on several targets including a protective action on complex I and the mitochondrial permeability transition pore (PTP) (Detaille et al., 2005; Foretz et al., 2011; Zhou et al 2001). Thus, conceivably, metformin has multiple actions on cell metabolism via AMPK, SIRT1 and GCN5.

4.2 The incretins

Recent advances in new medications for the treatment of type 2 diabetes include the introduction of modulators of the incretin pathway such as the glucagon-like peptide-1 (GLP-1), exenatide, and the dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, has increased the armamentarium for the treatment of type 2 diabetes with favourable clinical results (Chia and Egan, 2008; Hansen et al., 2009). Exenatide, however, is inconvenient to use as the drug requires sub-cutaneous administration and is also associated with a high frequency of nausea (>50%) and vomiting (17%), however, use is associated with improved β-cell function and weight loss (Chia & Egan, 2008). Sitagliptin is orally effective, weight neutral, well tolerated, but has been associated with a relatively high incidence of nasopharyngitis (6.4%) and headache (5.1%) (Amori et al., 2007). Incretin mimetics have not been shown to have direct vascular protective actions although the ability of GLP-1 to inhibit cytokine, lipid and glucose induced apoptosis of β-cells would infer that incretin mimetics should at least indirectly infer protection via improved β-cell function (Hvidberg et al., 1994).

4.3 Fibroblast Growth Factor 21 (FGF21)

The human genome encodes 22 members of the Fibroblast Growth Factor superfamily and Fibroblast Growth Factor 21 (FGF21) lacks mitogenic activity and is a high profile prospect and/or target as a novel therapeutic agent for the treatment of metabolic diseases by virtue of its ability to lower plasma glucose, triglycerides as well as improve insulin sensitivity (Kharitonenkov et al., 2005; Kharitonenkov and Shanafelt 2009; Kharitonenkov and Larsen 2011). FGF21 has been reported to enhance insulin-independent uptake via GLUT1 into adipocytes and skeletal muscle and dramatically reduce blood glucose levels in the ob/ob, leptin-resistant, diabetic mouse (Kharitonenkov et al., 2005; Mashili et al., 2011). Although the liver was assumed to be the source of FGF21, brown adipose tissue, skeletal muscle and, possibly, other tissues can also express FGF21 thus inferring hepatokine, adipokine and myokine functions (Hondares et al., 2011; Mashili et al., 2011). βKlotho, a type 1 transmembrane glycoprotein and a coreceptor for FGF21, is expressed in the mouse aorta suggesting that FGF21 may contribute to the regulation of blood vessel function (Fon Tracer et al., 2010). FGF21 expression is regulated by both PPAR alpha and gamma activation and preclinical assessment of FGF21 indicates a lack of any major side effects (Kharitonenkov and Shanafelt); Hondares et al., 2011). FGF21 has important endocrine-functions in the regulation of glucose and lipid homeostasis that include an increase in the expression of GLUT1 (Mashili et al., 2011; Berglund et al., 2009). Elevated plasma levels of FGF21 are seen in humans with type 2 diabetes and mouse models where "FGF21 resistance" is associated with a reduced response to the blood glucose and triglyceride lowering and insulin

sensitizing actions of FGF21 (Kharitonenkov et al., 2005; Berglund et al., 2009). To date there is a lack of any functional data on the effects of FGF21 on vascular function, but, via the ability of FGF21 to enhance insulin sensitivity and improve glucose disposal, FGF21 will indirectly protect the vasculature against glucose toxicity. Evidence indicating that FGF21 regulates metabolic homeostasis and enhances mitochondrial oxidative function in adipocytes via activation of AMPK and SIRT1 suggests that the effects of FGF21 should also be pursued in vascular tissue (Chau et al., 2010).

4.4 Sirtuins

The sirtuins are a seven-member family (SIRT1-7) of NAD$^+$-dependent protein deacetylases and ADP-ribosyltransferases associated with the regulation of a wide range of biological processes ranging from apoptosis, adipocyte and muscle differentiation, and energy expenditure to gluconeogenesis and, SIRT1 in particular, has been implicated as the central epigenetic controller of metabolism (Michan and Sinclair, 2007; Holness et al., 2010). SIRT1 gain of function in mice has been shown to increase insulin sensitivity in mice fed a high fat diet or backcrossed onto leptin resistant db/db diabetic mice (Banks et al., 2008). Overexpression of SIRT1 in the liver of diabetic and obese leptin deficient ob/ob mice reduces insulin resistance and reduces expression of X-box binding protein-1 (XBP-1), a key transcription factor that regulates ER stress (Li et al., 2011). Furthermore, treatment of EPCs with high glucose downregulated EPC numbers, reduced SIRT1 expression levels and increased expression levels of the acetylated Forkhead transcription factor, FoxO1 (Balestrieri et al., 2008).

SIRT1 has an ubiquitous distribution and exerts its effects on metabolism via deacetylation-mediated activation of the peroxisome proliferator-activated receptor-gamma (PPARγ) transcription co-activator, PGC-1α (Michan and Sinclair, 2007). PGC-1α increases fatty acid utilisation in muscle, whereas in the liver gluconeogenesis is regulated by SIRT1-mediated deacetylation and the subsequent nuclear retention of FoxO1. FoxO1 regulates the expression of gluconeogenic enzymes and the actions of FoxO1 are suppressed by insulin (Jackson et al., 2000). The transcriptional activity of FoxO1 is inhibited by SIRT1-mediated deacetylation (Yang et al., 2005). FoxO1 transcriptional activity is also regulated by XBP-1s, which, in addition to being involved in the upregulation of genes that reduce ER stress, promotes proteasome-mediated degradation of FoxO1 (Zhou et al., 2011).

SIRT1, PGC-1α, and FoxO1 are all targets for intensive investigation as potential additions to the armamentarium of drugs for the treatment of obesity, diabetes and cardiovascular disease (Alcain & Villalba, 2009; Borradaile & Pickering, 2009; Brandes, 2008; Lavu et al., 2008; Liang & Ward, 2006; Milne et al., 2007; Nagashima et al., 2010; Zhou et al., 2011). For instance, small molecule inhibitors of FoxO1 have been reported to have a hypoglycaemic effect in diabetic db/db mice (Nagashima et al., 2011; Tanaka et al., 2010). The oral hypoglycaemic agent, metformin, a first line choice for the treatment of type 2 diabetes, also has SIRT1, as previously discussed, as one of its potential targets (Caton et al., 2011; Lan et al., 2008). Interestingly, the polyphenol antioxidant resveratrol has also been associated with positive effects on longevity, activation of SIRT1, and beneficial effects on mice fed a high calorie diet (Bauer et al., 2006).

The overexpression of SIRT1 is cardioprotective and endothelium-specific overexpression of SIRT1 decreases atherosclerotic lesions in apoE null mice (Alcendor et al., 2007; Zhang et al., 2008). Of particular interest in the Zhang et al study (2008) was the observation that calorie

restriction increased whereas a high-fat diet decreased the expression of SIRT1; however, SIRT1 overexpression overcame high-fat induced endothelial dysfunction and enhanced the expression of eNOS. Furthermore, in a cell culture protocol, the overexpression of SIRT1 was protective against apoptosis (Zhang et al., 2008). The constitutively active serine/threonine protein kinase, LKB1, has been reported to be a binding partner and intracellular target for SIRT1 in porcine aortic endothelial cells and SIRT1-mediated deacetylation of LKB1 may be a key pathway for promoting proliferation and retarding endothelial senescence via limiting LKB1/AMPK activation as a result of proteasome-mediated degradation of LKB1 (Zu et al., 2010).
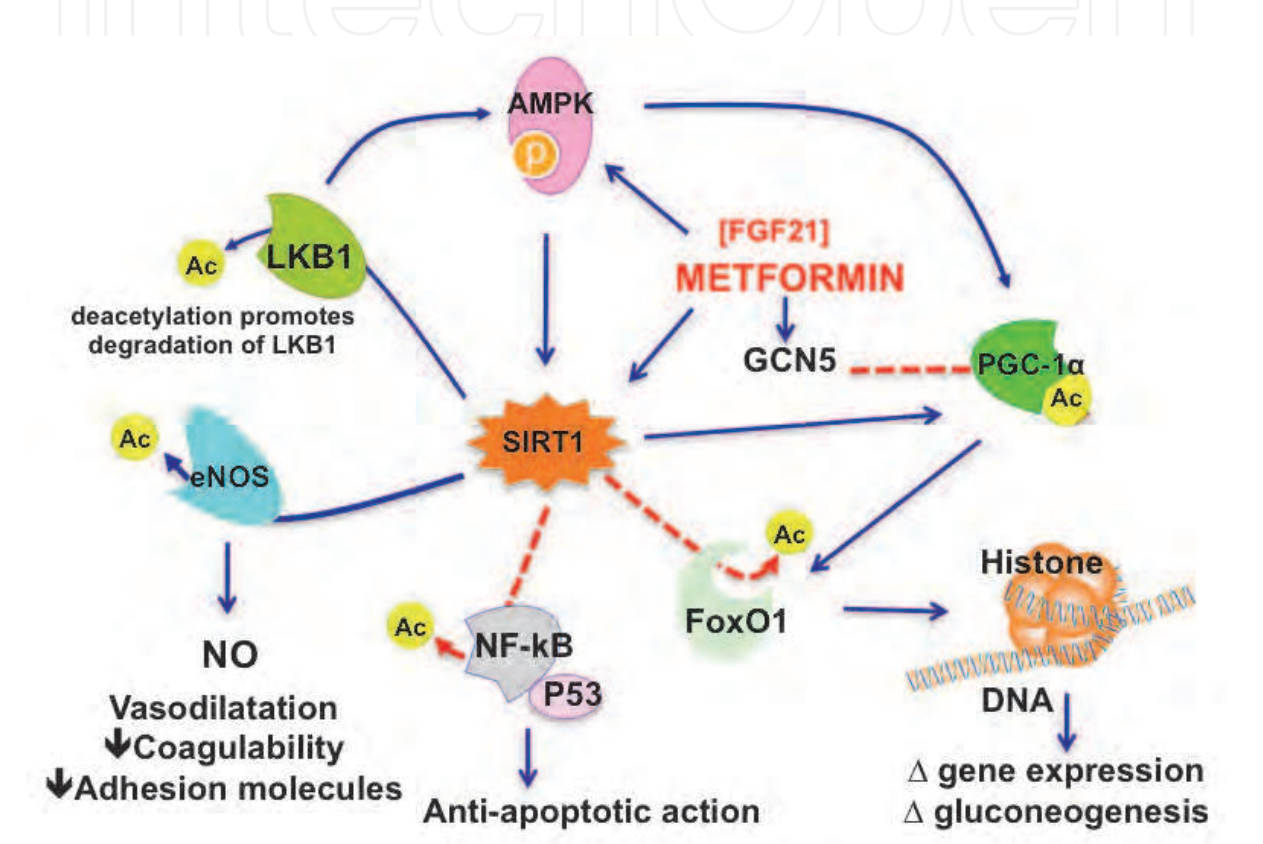
Fig. 2. Summarises the key cellular pathways that are involved with the effects of metformin and FGF21 on endothelial function and gluconeogenesis. SIRT1 can activate, as depicted by a solid blue arrow, a target via deacetylation (Ac), or inactivate via deacetylation (Ac) as depicted by a dotted red arrow. Thus, SIRT1 can via deacetylation, enhance eNOS activity, reduce apoptosis via inactivation of NF-kB and p53, reduce endothelial cell senescence via the acetyl transferase GCN5 deacetylation and subsequent degradation of LKB1 thus limiting phosphorylation-mediated AMPK activation, and also, in the liver, decrease, gluconeogenesis via deactylation of FoxO1. Metformin and FGF21 may have direct effects on both SIRT1 and AMPK and SIRT1 and metformin, via GCN5, can activate PGC-1α thus promoting fatty acid utilization.

Metformin, as already mentioned, is currently the most widely used oral hypoglycaemic agent and possesses insulin-sensitizing actions and also has proven endothelial protective actions in humans subjects with diet-treated type 2 diabetes (Mather et al., 2001). Mather et al (2001) measured blood flow responses to intraarterial administration of endothelium-

dependent (acetylcholine) versus endothelium-independent (sodium nitroprusside) and nitrate-independent (verapamil) vasodilators using forearm plethysmography. Subjects who received metformin demonstrated statistically significant improved responses to acetylcholine versus placebo, but not nitroprusside-stimulated or verapamil-stimulated blood flow. Several studies indicate that one of the targets for metformin is SIRT1, possibly in part also involving AMPK, with subsequent multiple target actions that include an inhibition of hepatic gluconeogenesis (Caton et al., 2010; Detaille et al., 2005; Foretz et al., 2011; Zhou et al., 2001). SIRT1 activation has also been shown to increase the generation of NO via the deacetylation of eNOS at lysines 496 and 506 (Mattagajasingh et al., 2007) thus providing a cellular basis for the improvement of acetylcholine-mediated forearm blood flow in human subjects with diabetes that was reported by Mather et al (2001). Thus, metformin provides us a valuable prototype drug to serve as a template for the development of new and possibly more specific drugs with fewer side effects that target the key cellular pathway(s).

5. Conclusion

Good glycaemic control remains an important target in the treatment of diabetes, however, new approaches to the treatment of diabetes, metabolic diseases and glucose toxicity that offer improved benefits over existing treatments are required. Studies of the beneficial effects of FGF21 on metabolism and, in particular, glucose utilization as well as elucidation of the metabolic and cell survival pathways regulated by SIRT1 and its cellular targets, such as FoxO1, appear to be worthy avenues for further study.

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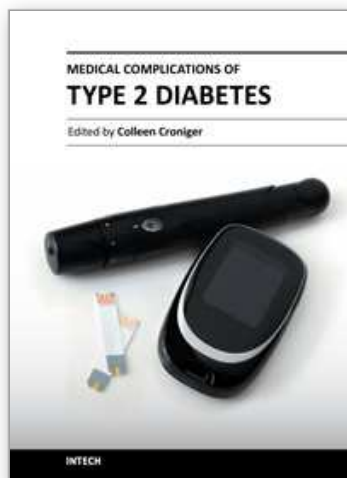
Medical Complications of Type 2 Diabetes
Edited by Dr. Colleen Croniger

Obesity and type 2 diabetes are increasing worldwide problems. In this book we reviewed insulin secretion in both healthy individuals and in patients with type 2 diabetes. Because of the risk associated with progression from insulin resistance to diabetes and cardiovascular complications increases along a continuum, we included several chapters on the damage of endothelial cells in type 2 diabetes and genetic influences on endothelial cell dysfunction. Cardiovascular complications occur at a much lower glucose levels, thus a review on the oral glucose tolerance test compared to other methods was included. The medical conditions associated with type 2 diabetes such as pancreatic cancer, sarcopenia and sleep disordered breathing with diabetes were also discussed. The book concludes with several chapters on the treatments for this disease offering us hope in prevention and successful alleviation of the co-morbidities associated with obesity and type 2 diabetes.

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