Uncoupling proteins as a therapeutic target to protect the diabetic heart

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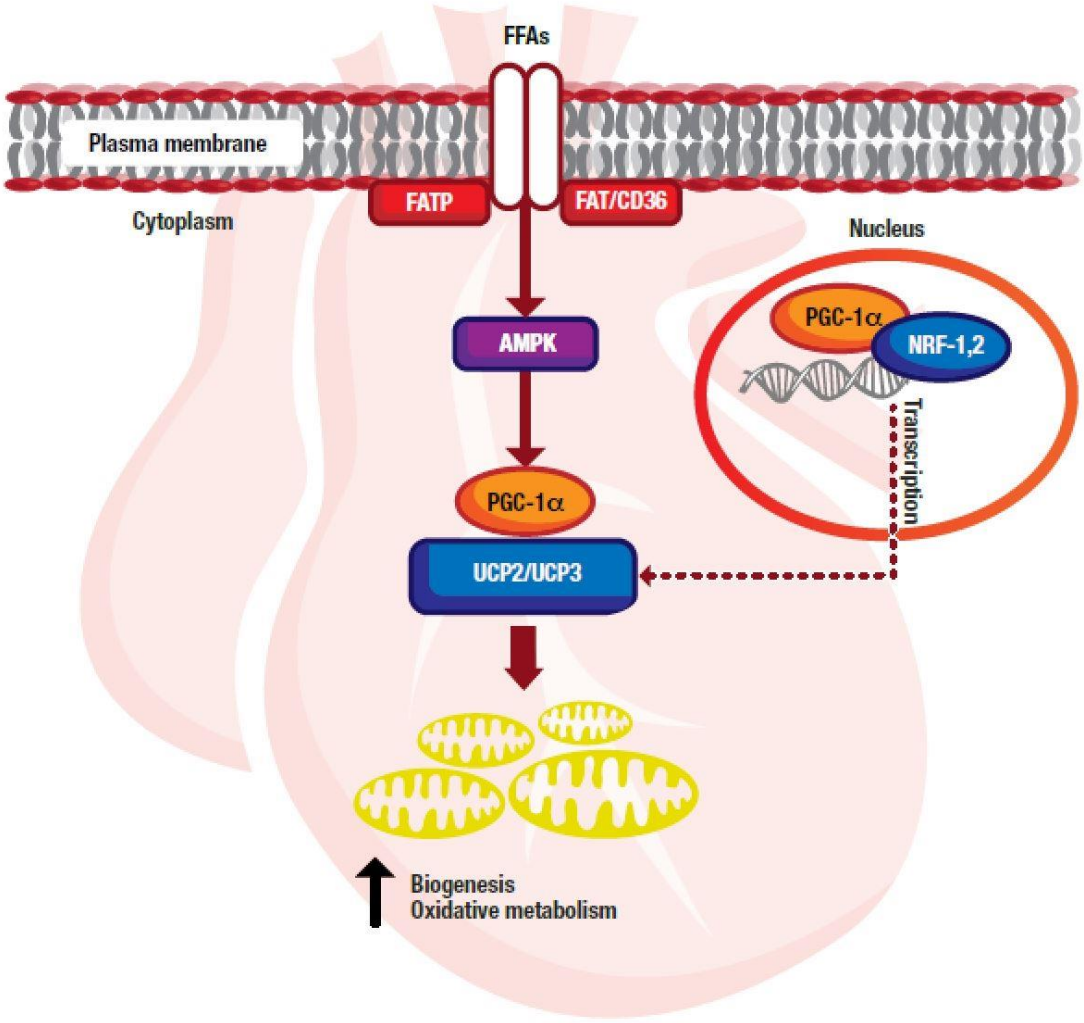
Abstract

Myocardial remodeling and dysfunction caused by accelerated oxidative damage is a widely reported phenomenon within a diabetic state. Altered myocardial substrate preference appears to be the major cause of enhanced oxidative stress-mediated cell injury within a diabetic heart. During this process, exacerbated free fatty acid flux causes an abnormal increase in mitochondrial membrane potential leading to the overproduction of free radical species and subsequent cell damage. Uncoupling proteins (UCPs) are expressed within the myocardium and can protect against free radical damage by modulating mitochondrial respiration, leading to reduced production of reactive oxygen species. Moreover, transgenic animals lacking UCPs have been shown to be more susceptible to oxidative damage and display reduced cardiac function when compared to wild type animals. This suggests that tight regulation of UCPs is necessary for normal cardiac function and in the prevention of diabetes-induced oxidative damage. This review aims to enhance our understanding of the pathophysiological mechanisms relating to the role of UCPs in a diabetic heart, and further discuss known pharmacological compounds and hormones that can protect a diabetic heart through the modulation of UCPs.

Key words: diabetes mellitus; cardiomyopathy; oxidative stress; uncoupling proteins.

Graphical abstract



Abbreviations

ACC: acetyl-CoA carboxylase, ACE: angiotensin-converting enzyme, AICAR: 5-aminoimidazole-4-carboxamide ribonucleotide, ALDH2: aldehyde dehydrogenase 2, AMPK: 5' AMP-activated protein kinase, ATP: adenosine triphosphate, Bax: Bcl-2-like protein 4, BNIP3: Bcl-2 interacting protein 3, DCM: diabetic cardiomyopathy, eNOS: endothelial nitric oxide synthase, FFA: free fatty acid, GDP: guanosine diphosphate, GLP-1: glucagon-like peptide-1, GLUT4: glucose transporter 4, , HAECs: human aortic endothelial cells, HO-1; heme oxygenase 1, HOMA-IR: homeostatic model assessment-insulin resistance, IR: ischemia-reperfusion, JAK: Janus kinase, MAPK: mitogen-activated protein kinase, MeSH: medical subject heading, mPTP: mitochondrial permeability transition pore, MST1: macrophage-stimulating protein 1, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, NRF2: nuclear factor (erythroid-derived 2)-like 2, OLETF: Otsuka Long–Evans Tokushima Fatty, PDK: pyruvate dehydrogenase kinase, PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PKC: protein kinase C, PPAR: peroxisome proliferator-activated receptor, SNRK: SNF-related serine/threonine-protein kinase, SIRT: NAD-dependent deacetylase sirtuin, SREBP-1: sterol regulatory element-binding protein 1, STAT: signal transducer and activator of transcription.

1. Introduction

Rubler and co-workers described diabetic cardiomyopathy (DCM) for the first time about four decades ago [1]. It is now well received that patients with diabetes mellitus are at an increased risk of heart failure even after adjusting for traditional risk factors such as coronary artery disease and hypertension, when compared to their non-diabetic counterparts [2]. Diabetic patients display increased left ventricular wall thickness that is usually accompanied by abnormalities in cardiac function, such as diastolic dysfunction [3]. A recent population based study demonstrated that this condition is prevalent in 16.9% of diabetic patients, while diastolic dysfunction as an independent abnormality was present in 54% of these diabetic patients [4]. Although data on global prevalence of diabetes is limited, its rapid rise [5] may exacerbate the incidence of DCM, leading to an increasing toll of cardiovascular-related deaths in diabetic patients. Currently, due to its asymptomatic nature, imaging modalities such as the echocardiography are considered the gold standard for the early detection of DCM as reviewed by Lorenzo-Almorós and colleagues [6]. However, most of these imaging techniques are not available in resource poor settings such as those in developing countries, including Africa, where cardiomyopathies have been among the leading cause of death in adults [7, 8]. Thus, attention has been focused on identifying pathophysiological mechanisms that are implicated in diabetes-induced cardiovascular damage, especially those occurring independent of coronary artery disease and hypertension. This is not only important for identifying early detection markers, but also crucial for the discovery of novel therapeutic targets to protect a diabetic heart.

Recent literature has focused on the role of altered mitochondrial function as a pathological link between diabetes and myocardial dysfunction [9-11]. Mitochondria are understood to be the main source of cardiac energy through mechanisms that primarily involve oxidative phosphorylation. Irregularities in mitochondrial respiratory function as a result of hyperglycemia, hyperlipidemia and insulin resistance have been associated with altered energy metabolism, generation of oxidative stress and subsequent myocardial apoptosis [9-11]. Interestingly, uncoupling proteins (UCPs), which belong to the group of mitochondrial anion carriers expressed in the mitochondrial inner membrane, are being explored for their role in modulating diabetes associated complications, including regulation of cardiac energy metabolism and oxidative stress. Furthermore, recent reviews by Liu et al., [12], Pierelli et al., [13], and Souza et al. [14] have highlighted the importance of these proteins, particularly the role of UCP2 in modulating complications associated with diabetes mellitus and heart failure. Although evidence provided by these studies highlights the overall

importance of UCPs, available data on the effect of these proteins on a diabetic heart has not been critically reviewed. Notably, experimental studies reporting on mitochondrial uncoupling and the involvement of UCPs in experimental models of obesity and diabetes have increased [15-20]. Thus, in addition to systematically discussing available literature on the cardioprotective role of UCPs in diabetes-oxidative stress injury, we review pharmacological compounds and hormones that protect the myocardium against diabetes associated complications, possibly through the modulation of UCPs. Since UCPs are highly expressed in the mitochondria, which is the main site of oxidative phosphorylation, a brief overview on the impact of diabetic hyperglycemia on mitochondrial function and subsequent generation of oxidative stress will also be provided.

2. Altered substrate metabolism and mitochondrial dysfunction in a diabetic heart

Currently, it is understood that pathophysiological mechanisms involved in diabetes-induced cardiac injury are multifactorial, with abnormalities in cardiac energy metabolism being a major factor implicated in this process. In a previous review, Bugger and Abel [21], as well as other investigators [22, 23], have discussed and demonstrated how altered myocardial substrate metabolism through impaired glucose and fatty acid (FFA) metabolism could contribute to cardiac dysfunction (Fig. 1). For example, in perfused hearts from type 2 diabetic (*db/db*) mice, contractile dysfunction indicators such as reduced cardiac output and cardiac power were linked with depressed rate of glucose oxidation and abnormally upregulated rate of FFA utilization [22]. In a similar mouse model, we have recently demonstrated that age-dependent development of left ventricular wall thickness was associated with elevated serum lipid levels [24]. This may suggest that there was increased intramyocardial lipid storage in these animals, although this phenomenon needed further assessment. Nonetheless, enhanced myocardial lipid accumulation has already been demonstrated in diabetic patients compared to their nondiabetic counterparts [25-27].

Lipids are the main source of energy in the myocardium. The decrease of lipid utilization and the increase of glucose assimilation have been linked to improved myocardial function in type 2 diabetic rats [28-30]. However, their aberrant uptake and utilization is associated with increased activity of the mitochondrial electron transport chain, as well as enhanced intramyocardial lipid storage. Excessive availability of lipid intermediates such as ceramides and diacylglycerol are known to activate protein kinase C (PKC) [31, 32]. In addition to promoting atherosclerosis [33],

activation of PKC in a diabetic heart has been associated with impaired insulin signaling, activation of advanced glycation end products, fibrosis and myocardial apoptosis [34]. Mitochondria are the main site of myocardial lipid oxidation and compelling evidence have been presented on the correlation between enhanced FFA flux, respiratory uncoupling, reduced ATP production, and accelerated generation of oxidative stress [16, 21, 35]. Using *db/db* mice, Boudina et al. [16] demonstrated that impaired oxidative phosphorylation was parallel to elevated mitochondrial reactive oxygen species (ROS) generation and lipid peroxidation that resulted in reduced cardiac function. Cortassa et al. [35] recently presented similar findings showing that exposing heart mitochondria isolated from streptozotocin (STZ)-induced diabetic pigs, to high palmitate conditions led to respiratory uncoupling and excess production of ROS. Although the levels of UCPs were not assessed or significantly affected in these studies [16, 35], mitochondrial uncoupling was reduced through guanosine diphosphate (GDP), which was thought to be a specific inhibitor for UCPs. However, GDP may also act on uncoupling activity of the adenine nucleotide translocase [36]. UCPs may play an important role in mitochondrial uncoupling and modulation of ROS in the diabetic heart but the molecular function of UCP2 and UCP3 is not finally settled.

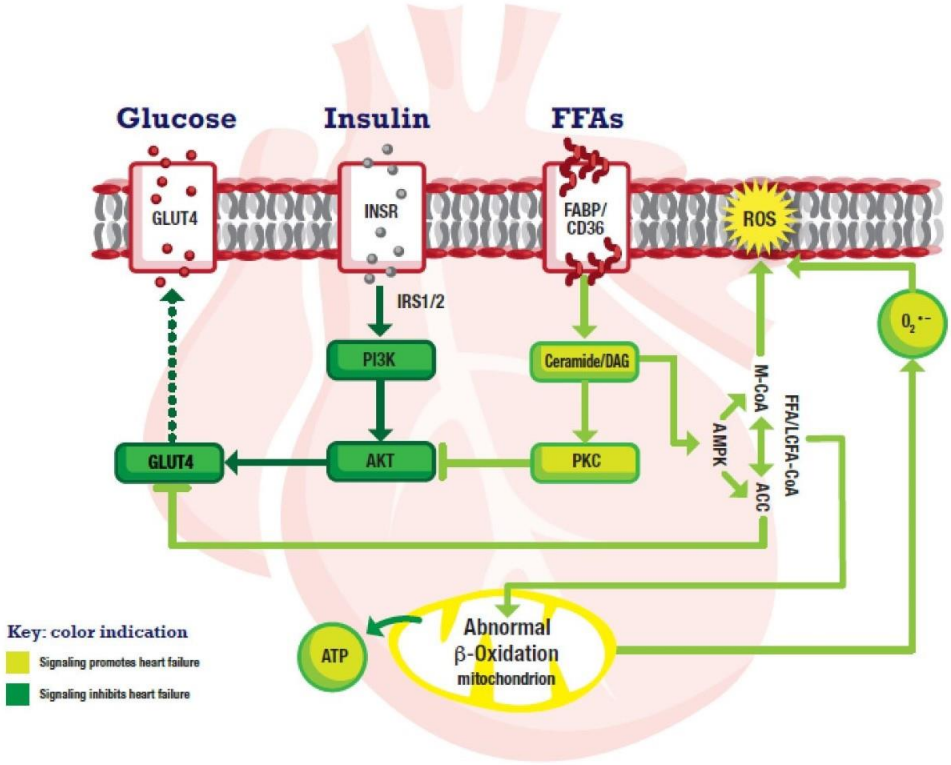


Figure 1. Impaired myocardial substrate metabolism is a prominent sign of diabetic cardiomyopathy. Enhanced free fatty acids (FFAs), through abnormal activation of β-oxidation are responsible for excessive production of reactive oxygen species (ROS) that lead to damage to cell membrane (lipid peroxidation). Alternatively, enhanced FFAs are also implicated in excessive storage of ceramide/diacyl glycerol (DAG) that activates protein kinase C (PKC) that subsequently impair insulin signaling leading to the inhibition of glucose uptake. Activation of 5' AMP-activated protein kinase (AMPK) remains an important enzyme in the modulation of FFA metabolism and has been linked with regulation of ROS. ACC: Acetyl-CoA carboxylase; AKT: protein kinase B; ATP: adenosine triphosphate; CD36: cluster of differentiation 36; FABP: fatty acid binding protein; GLUT4: glucose transporter 4; INSR: insulin receptor; IRS1/2: insulin receptor substrate 1 or 2; M-CoA: Malonyl-CoA; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase.

3. Mitochondrial dysfunction and oxidative stress-induced myocardial injury in a diabetic state

The production of ROS is necessary for maintaining physiological signaling, however its excessive and sustained generation can cause oxidative stress and lead to deleterious effects in cells [37]. Various subcellular compartments can generate ROS, but mitochondria are generally considered one of the primary sources of ROS production in cardiac cells [38]. In a diabetic state, the increased delivery of reducing equivalents through FFA oxidation due to altered substrate metabolism can impair competence of the electron transport chain resulting in enhanced ROS generation [21]. Given that a diabetic heart exhibits diminished ROS scavenging capabilities [39], the arising oxidative stress is usually involved in various signaling pathways that lead to accelerated myocardial damage. For instance, in hearts harvested from diabetic mice or cardiomyocytes exposed to hyperglycemic conditions, increased oxidative stress has been directly linked with cardiac remodeling and apoptosis, through up-regulated expression of pro-apoptotic proteins such as Bcl-2-like protein 4 (Bax) and tumor protein p53 [40-43]. Taken together, these studies provide evidence that abnormal elevated mitochondrial membrane potential is the vital factor involved in oxidative stress-induced cardiac injury, mainly by causing mitochondrial permeability transition pore (mPTP) opening. Available evidence demonstrates that mPTP opening is favored during elevated ROS conditions and can lead to oxidation of protein thiols such as glutathione that are essential in protecting against oxidative stress, leading to enhanced cell apoptosis [44].

4. Evidence on the role of UCPs in the diabetic heart

The functional role of UCPs has become of major interest in the fields of thermogenesis, obesity and diabetes [12, 45]. Increasing evidence shows that UCPs can participate in mitochondrial-inducible proton-leak, and thereby ameliorate raised membrane potential, leading to reduced oxidative stress-induced myocardial damage [13, 46]. However, the molecular mechanisms of UCP2 and UCP3 function remain elusive. It has been suggested that they dissipate increased electrochemical gradients, by mitochondrial proton leak activity [47, 48], while others propose a metabolite transport function of UCP2 and UCP3 [49, 50]. Thus far, the argument persists to whether UCPs are beneficial or detrimental, principally in the diabetic heart as induction of oxygen wastage through complex mechanisms can lead to reduced cardiac efficiency. This concept was developed in a study by Murray and co-workers where they showed that raised plasma FFA concentrations were correlated to increased UCP2 and UCP3 levels in patients undergoing coronary artery bypass graft surgery, and this was inversely proportional to cardiac glucose transporter (GLUT) 4 protein expression [15]. The initial proposal was that enhanced expression of UCPs was directly induced by peroxisome proliferator activated receptors (PPARs) as a result of raised FFA levels and this was subsequent to reduced mitochondrial proton gradient deprived of ATP generation, which is usually observed in failing hearts. However, while PPARs, especially PPARγ and PPARα are broadly accepted as regulators of cardiac UCPs in conditions of altered metabolism [51, 52], it has become apparent that other additional mechanisms can influence the expression of these transporter proteins in heart failure. For example, in a study by Rines and co-workers it emerged that enhanced UCP3 expression was linked with increased glucose and palmitate oxidation, as well as reduced mitochondrial efficiency in mice [19]. However, overexpressing AMP-activated protein kinase (AMPK)-related protein Snf1-related kinase (SNRK), a serine/threonine kinase, was able to ameliorate these effects including reducing UCP3 expression and oxygen consumption, leading to improved heart function. From these findings, it is apparent that although enhanced mitochondrial uncoupling can be useful as an adaptive response, sustained activation of mitochondrial uncoupling could cause cardiac dysfunction in conditions of impaired metabolism. In any case, the oxidative damage has been observed in UCP2 knockout models [53, 54]. Since a diabetic heart displays an abnormally increased activity of the electron transport chain that is linked with excess ROS production and disproportional generation of ATP [16, 21], reducing ROS by physiological mechanisms appears to be essential during the pathogenesis of diabetes-induced cardiac damage. Thus, it is likely that regulation of UCPs may represent a vital mechanism by which cardiomyocytes adapt to diabetes associated characteristic features, such as increased FFA flux that results in oxidative stress-induced cell damage.

Studies reporting on the impact of UCPs on diabetes-linked complications have increased over the past years (Table 1). However, these studies have not been systematically reviewed to provide a comprehensive picture on the potential role of UCPs in the diabetic heart. Therefore, a systematic search on the association between UCPs and a diabetic heart was conducted through the use of major search engines and databases such as PubMed/Medline, EMBASE, Cochrane Library Databases and Google Scholar, and this was done by modifying an already published protocol [55]. The search was conducted from inception until end of March 2018, grey literature such as abstract proceedings and pre-prints were also included. There were no language restrictions implemented, while review articles were screened for primary findings. Medical subject heading (MeSH) terms such as uncoupling proteins, diabetes mellitus, oxidative stress, and cardiovascular disease, including corresponding synonyms and associated terms for each item were used. Studies reporting on the aberrant expression of UCPs in heart failure in the absence of diabetes were also included. The search results revealed approximately "1023" articles linking UCPs to heart failure as well as diabetes associated compilations. However, only "50" studies were specific to cardiac complications in the presence or absence of diabetes, and are represented in Table 1.

Data presented from the included studies show that various experimental models, including in vitro, ex vivo and in vivo, have been used to investigate the role of UCPs in diabetes associated complications (Table 1). Although these models cannot reproduce traits of human pathophysiology, many have remained relevant for studying complications associated with the development of DCM. Previously, state of the art reviews summarizing information, including strengths and weaknesses of current experimental models such as Zucker rats, as well as *db/db*, *ob/ob* and Akita mice relevant to the development of DCM have been provided [56, 57]. Although disadvantages are acknowledged, each model can provide specific advantages in terms of exploring diabetes associated cardiac complications, which include functional, structural and metabolic abnormalities. Similarly, data from studies included in this review show that various in vitro, ex vivo and in vivo methods were used to understand the role of UCPs in diabetes-induced altered mitochondrial energetics and myocardial dysfunction (Table 1).

UCP paralogues (UCP1, UCP2 and UCP3) are differentially distributed in mammalian tissues (Fig. 2). To date, five mitochondrial anion carriers have been annotated as UCP paralogues but only UCP1, UCP2 and UCP3 qualify as UCP family members based on phylogeny. Thus far, the expression of UCP3 in the liver has only been shown to occur in situations of enhanced hepatic FFA catabolism, such as during treatment with fibrates alone or in combination with

high-fat feeding [58, 59]. Whereas UCP1 to UCP3 mRNA expression has been identified in the heart, but only UCP2 and UCP3 protein levels are confirmed in the heart [43, 50, 60, 61]. In fact, a few studies have supported the role of UCP3 in promoting FFA oxidation in myocytes, with facilitation of fatty acid oxidation suspected to be involved in reduction ROS production [62, 63]. Hidaka and colleagues showed that upregulated UCP3 expression was solely associated with elevated FFA levels in STZ-induced diabetic rats and was effectively corrected by swimming and insulin therapy, leading to reduced production of ROS [64]. Interestingly, among the UCPs investigated, more than 50% of included studies reported on the role of UCP3 in diabetes associated abnormalities [10, 11, 15-20, 65-82]. This may be related to diabetes being a hot topic, but does not necessarily entail a causal relationship between diabetes and UCP3. Evidence for the role of UCP3 in modulating FFA metabolism, as well as increased production of ROS and cardiac efficiency has been reported through either STZ-induced diabetes, transgenetic models, cultured cells, or biopsies from diabetic patients. Briefly, these experimental models demonstrated that increased expression of UCP3 is linked with altered cardiac metabolism through abnormally upregulated FFA metabolism, enhanced mitochondrial oxygen consumption, production of ROS, and reduced cardiac remodeling (Table 1). As depicted in Fig. 3 and proposed elsewhere [83], UCP3 may play an adaptive response in a diabetic heart in response to an increased flux of FFAs, exporting FFAs anions out of the mitochondrial matrix, leading improved β-oxidation and reduced ROS. For example, UCP3 knockout mouse hearts have been shown to be more prone to ROS damage, also displaying poorer recovery of left ventricular function when compared to wild type hearts during ischemia-reperfusion [84]. In another study, these results are confirmed where it is demonstrated genetic deletion of UCP3 causes abnormally increased ROS which exacerbates apoptotic cell death in the ischemic heart leading to heart failure [85].

The initial evidence provided by Young and colleagues [18], revealed that PPAR-α is vital for regulating the expression of UCP3, showing that increased availability of FFAs was associated with upregulated expression of UCP3. The protein levels of UCP3 were severely depleted in PPAR-α null mice. This is of interest, since PPAR-α regulates FFA metabolism, and its abnormal expression is linked with altered mitochondrial structure and metabolic function in a diabetic heart [52]. Furthermore, upregulation of PPAR-α, together with peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) has been linked with improved mitochondrial oxidative capacity [52]. As listed in Table 1, other studies have confirmed that regulation of PPAR-α, PGC-1α and UCP3 expression is important for the control of mitochondrial ROS generation, and improvement of mitochondrial oxygen

consumption and cardiac function. Improved cardiac function comes with improved mitochondrial respiration, thus the whole association has some obstacles that need to be resolved.

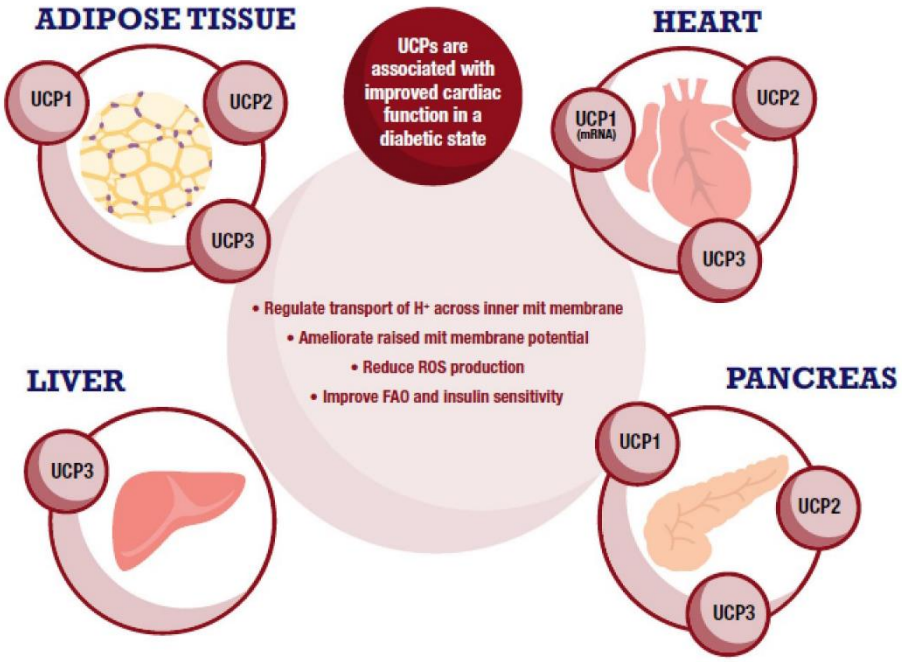


Figure 2. Uncoupling proteins (UCPs) are distributed differentially in mammalian tissue and are important in the amelioration of diabetes associated complications. To date, five mitochondrial (mit) anion carriers have been annotated as UCP paralogues but only UCP1, UCP2 and UCP3 qualify as UCP family members based on phylogeny. The expression of UCP3 in the liver has only been shown to occur in situations of enhanced hepatic free fatty acid oxidation (FAO), such as during treatment with fibrates alone or in combination with high-fat feeding. Whereas UCP1 to UCP3 mRNA expression was found in the heart but only UCP2 and UCP3 protein levels are confirmed in the heart. Although current data is inconclusive, expression of UCPs is associated with improved free fatty acid oxidation and the amelioration of excess production of reactive oxygen species (ROS).

In included studies (Table 1), UCP2 was the second most studied UCP in association with diabetes-induced cardiac injury (Table 1). While reports on UCP2 are increasing, its role in the diabetic heart remains controversial [13, 46, 86, 87]. This has prompted increased investigation on its role in aging, obesity and most importantly, in diabetes-induced myocardial injury. A widely proposed effect of UCP2 in a diabetic heart has been to abolish abnormally increased

mitochondrial ROS, better utilization of FFA substrate, and protection against oxidative stress resulting in improved cardiac function [54, 88-94]. Moreover, hearts of diabetic patients with a polymorphism in the UCP2 gene (G-866A) display enhanced oxidative stress and low antioxidant status when compared to control counterparts, further leading to poorer survival rates [95-98]. Several mechanisms have been proposed to be involved in the regulation of UCP2. In addition to modulating aldehyde dehydrogenase 2 (ALDH2) and PGC-1α [61, 99], the cardioprotective effect of UCP2 extends to increasing endothelial nitric oxide synthase (eNOS), an important enzyme in vasodilation, and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)- induced myocardial injury [53, 86, 87, 100]. Furthermore, activation of AMPK, an important enzyme in the modulation of FFA metabolism, has been linked with enhanced expression of UCP2 and subsequent reduction of ROS in human umbilical vein endothelial cells (HUVECs) and H9c2 cardiomyocytes exposed to hyperglycemic conditions [101].

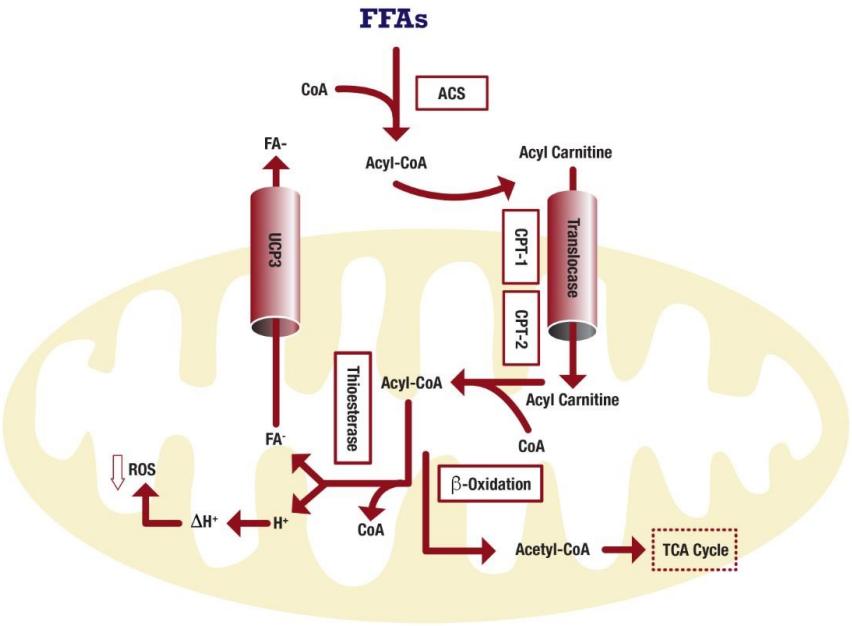


Figure 3. The proposed mechanism of uncoupling protein 3 (UCP3), involving modulation of increased free fatty acids (FFAs) in the mitochondrial to reduce excessive generation of reactive oxygen species (ROS), leading improved β-oxidation and myocardial function. ACS: Acetyl-CoA synthetase; CPT-1/2: carnitine palmitoyltransferase 1 or 2.

Consistent with UCP2 expression, in addition to ameliorating oxidative stress by increasing antioxidant capacity [53, 102], UCP1 can protect the myocardium by enhancing mitochondrial biogenesis through the upregulation of PPAR-α and PGC-1α [78]. However, these findings do not comprehensively solidify the role of UCP1 in the heart, with additional evidence necessary to better inform on the role of this anion carrier in the heart. Interestingly, recent evidence shows that UCP1 expression is enhanced in human epicardial adipose tissue and is negatively correlated with oxidative stress [103]. This further necessitates additional experiments to establish the mechanism associated with reduced oxidative stress in the myocardium and epicardial tissue of diabetic patients.

5. UCP activators and their protective potential against diabetes-induced myocardial injury

The use of antidiabetic therapies such as metformin and insulin has been efficient in minimizing diabetes associated complications [5, 104, 105]. However, there is a growing number of cardiovascular related deaths in diabetic patients [2, 5]. Mitochondria have been an ideal target by various therapies to prevent against oxidative stress-induced tissue injury (Table 2). Therefore, the abundance of mitochondria in the myocardium makes it an ideal target investigate potential mechanisms involved in diabetes-induced cardiovascular injury, including UCPs. A systematic search of literature reporting on the role UCPs in diabetic associated complications, studies reporting on substances, either pharmacological or natural, that activates UCP to protect a diabetic heart were also identified and summarized in Table 2. A brief description of each activator, and its role in modulating UCPs within a diabetic heart is provided below. Some of the discussed molecules and extracts include antioxidant biofactor, aspalathin, ghrelin, glibenclamide, losartan and ramiprilat, melatonin, metformin and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), pioglitazone, resveratrol, rosiglitazone, and sitagliptin and exendin-4 (Fig. 4).

6. Antioxidant biofactor protects a diabetic heart and upregulates UCP2 expression

Antioxidant biofactor is a phenol-rich processed grain product that is commercially available and made from different extracts, including citron, germ extracts, green leaf extract, green tea, malted rice, sesame, soybean, rice bran, tear grass and wheat [106]. This extract contains a variety of essential trace elements and antioxidants [95]. In a review by Minamiyama and colleagues [107], the authors highlighted the beneficial effects of this extract which includes

protecting against oxidative stress-induced renal, intestinal or liver damage, as well as aging related complications. To date, minimal information is available on the effect of antioxidant biofactor on diabetes associated complications. However, Minamiyama and colleagues have demonstrated that this extract protected the hearts and aortas of type 2 diabetic Otsuka Long–Evans Tokushima Fatty (OLETF) rats by reducing mitochondrial ROS via increasing aortic endothelial nitric oxide synthase and upregulating UCP2 expression [108].

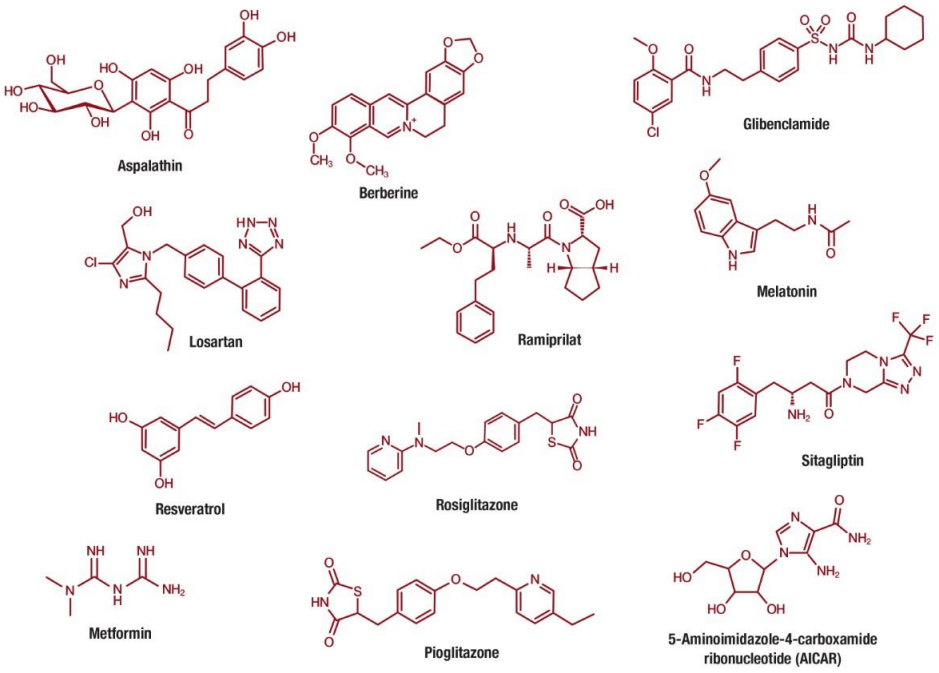


Figure 4. Chemical structures of some of the pharmacological compounds and hormones that can potentially modulate uncoupling proteins to protect a diabetic heart.

7. Aspalathin protects a diabetic heart and upregulates UCP1 and UCP2 expression

Aspalathin (PubChem CID: 11282394) is a *C*-dihydrochalcone, abundantly found in rooibos [109], that has been extensively explored for its metabolic benefits [110]. Although considered to have a low bioavailability [111, 112], our group and others have demonstrated that this dihydrochalcone can ameliorate metabolic disease associated complications such as insulin resistance, inflammation and oxidative stress, as reviewed by Johnson et al. [113].

Although a causal relationship was not clearly established, we have also shown that aspalathin can protect cardiomyocytes exposed to hyperglycemic conditions against altered myocardial substrate metabolism, increased mitochondrial membrane potential and subsequent apoptosis, in part by upregulating UCP2 expression in H9c2 cells [40]. A similar model of cultured cardiomyocytes exposed to hyperglycemia further showed that aspalathin upregulated UCP1 expression in association with modulation other genes involved in antioxidant response and inflammation such as super oxide dismutase 1/2 and interleukin 1/6, respectively [114]. Although UCP1 was not tested, the upregulated expression of UCP2 was associated with the enhanced expression of antioxidant response element, nuclear factor (erythroid-derived 2)-like 2 (NRF2) in hearts of *db/db* mice [115]. Other studies have shown that NRF2 promotes survival by enhancing the expression of UCPs under conditions of oxidative stress in the heart and other tissues [116, 117]. However, the major limitation on the role of aspalathin on UCPs include lack of studies reporting on protein expression levels after treatment with this compound, as well as functional studies assessing the result of inhibiting or overexpressing these proteins.

8. Berberine protects a diabetic heart and upregulates UCP2 expression

Berberine (PubChem CID: 2353) is an isoquinoline alkaloid that is abundantly found in several plants including *Coptis chinensis*, *Coptis trifolia*, and *Berberis vulgaris*, and has been extensively studied for its diverse pharmacological effects [118-120]. Although the poor oral bioavailability of this alkaloid poses a major challenge [121], accumulative evidence shows that it reduces diabetes linked complications. In type 2 diabetic patients, administration of berberine was more effective in reducing fasting plasma insulin, insulin resistance, and lowering raised lipid profiles in comparison to metformin [122]. In addition to downregulating the expression of genes involved in lipogenesis, experimental data shows that berberine can exerts effect through activation of AMPK [123]. In a study that investigated the interaction of berberine with mitochondria, it was shown that it is selectively accumulated in the mitochondria, followed by inhibition of cell proliferation, mitochondrial fragmentation and depolarization, oxidative stress, and reduced ATP production [124]. These results suggest that this compound can target the mitochondria and induce apoptosis in a specific immortal cell line, in this case K1735-M2 mouse melanoma cells. However, in association with the heart, this alkaloid can ameliorate the development of atherosclerosis associated with high fat feeding through promoting mitochondrial biogenesis and upregulating UCP2 expression [125].

9. Ghrelin protects a diabetic heart and upregulates UCP2 expression

Ghrelin, also known as lenomorelin, is a peptide hormone that is released by the gastrointestinal tract and plays a major role in nutrient sensing and regulation of appetite [126]. Upon release, ghrelin is known to induce its action through binding to growth hormone secretagogue receptors which are expressed in various tissues including the heart [127]. This hormone has been subjected to increasing research due to its potential modulatory effect of diabetes and metabolic syndrome associated complications [126]. Ghrelin is elevated during caloric restriction and fat depletion. Ghrelin administration has been correlated with increased mitochondrial oxidative enzyme activities independent of changes in expression of fat metabolism genes and phosphorylation of AMPK in rat skeletal muscle [128]. Further, it has been shown that obliteration of ghrelin averts the development of obesity associated with aging by modulating food intake and energy expenditure in mice [129]. These effects were linked with amelioration of reduced phosphorylation of AMPK and downstream mediators in muscle, and enhanced muscle endurance. In HUVECs, treatment with ghrelin attenuated the oxidized low-density lipoprotein (oxLDL)-induced inflammatory response and oxidative stress, in association with upregulated UCP2 expression [130].

10. Glibenclamide protects a diabetic heart and reduces raised UCP3 expression

Glibenclamide (PubChem CID: 3488), also known as glyburide, is a glucose lowering drug that belongs to sulfonylureas class of drugs [131]. It is established that these drugs bind and block ATP-sensitive potassium channels, prompting an increase in insulin release from the beta cells of the pancreas. Although glibenclamide has displayed slightly inferior effect than both insulin and metformin in lowering raised blood glucose levels in some diabetic patients [132], controversial data has been reported on the role of this compound on a diabetic heart. Glibenclamide blocks sarcolemma ATP-dependent potassium channels prompting a prolonged entry of calcium ions (Ca^{2+}) in the myocardium causing cardiac dysfunction [133]. Furthermore, it has also been reported that this sulfonylurea affects mitochondrial bioenergetics by permeabilizing the inner mitochondrial membrane to Cl^- without significant changes on membrane permeabilization to H^+ in rat liver [134]. Recently, in a βV59M mouse model of diabetes, it was

demonstrated that glibenclamide reversed enhanced pyruvate dehydrogenase kinase 4 and UCP3 expression resulting in improved cardiac metabolism and function [135].

11. Losartan and ramiprilat protect a diabetic heart and reduce enhanced UCP2 expression

Losartan (PubChem CID: 3961) and ramiprilat (PubChem CID: 5464096) are accomplished angiotensin-converting enzyme (ACE) inhibitors that are used to lower raised blood pressure [136, 137]. Although associated with adverse effects in some patients, especially pregnant women [138], losartan is well tolerated and effective at reducing blood pressure and left ventricular mass in hypertensive patients [139]. On the other hand, Lonn et al. [140] has also reviewed literature showing that in addition to maintaining glucose homeostasis, ramipril can prevent atherosclerosis progression, and plaque stabilization as well as improve on myocardial structure and function. Interestingly, the combinational use of losartan and ramipril has been shown to suppress ischemia-reperfusion injury through reducing enhanced UCP2 expression in a rat model [141]. These findings are consistent with results of another ACE inhibitor, perindopril, showing that it suppresses UCP2 mRNA expression concomitant to improving systolic and diastolic blood pressure in an aortic regurgitation rat model [142]. However, such data needs to be confirmed at protein level and in other models and human subjects.

12. Melatonin protects a diabetic heart and upregulates UCP2

Melatonin, also known as *N*-acetyl-5-methoxy tryptamine, is a hormone that is produced by both mammals and plants and plays a major role in protecting against oxidative stress [143]. Melatonin in mammals is produced by the pineal gland and is involved in a wide-array of functions, including the control of circadian rhythms such as sleep-wake timing, blood pressure, and seasonal reproduction [143]. Its established physiological effect feature ameliorating free radical-induced cell damage [144], while it also has protective properties against diabetes associated cardiovascular complications have been reported [145, 146]. In an STZ-induced diabetic rat model and high glucose exposed H9c2 cardiomyocytes, melatonin preserved cardiac function and ablated oxidative damage in part through modulating NRF2-heme oxygenase 1 (HO-1) and mitogen-activated protein kinase (MAPK) signaling pathways [145]. Whereas in a mouse model of DCM, melatonin prevented cardiac remodeling and dysfunction via upregulation of autophagy,

restriction of apoptosis, and modulating mitochondrial integrity and biogenesis through macrophage-stimulating protein 1 (MST1)/ NAD-dependent deacetylase sirtuin-3 (SIRT3) signaling [146]. This hormone has been further shown to play vital role in protecting against changes in cellular morphology, mitochondrial membrane potential loss, mitochondrial Ca^{2+} overload, mPTP, and subsequent elevated ROS generation and ATP reduction through upregulation of UCP2 [147].

13. Metformin and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) protect a diabetic heart and reduce UCP1 and UCP2 expression

Metformin (PubChem CID: 4091) is an established blood glucose lowering therapy for type 2 diabetics, while AICAR (PubChem CID: 46780289) s an analog of adenosine monophosphate (AMP) [148, 149]. Both metformin and AICAR are established activators of AMPK [150]. By activating AMPK, these compounds can modulate β-oxidation and exert beneficial effects to the myocardium by regulating substrate metabolism and autophagy [151, 152]. It is currently known that mitochondrial autophagy, a process that selectively removes dysfunctional or damaged mitochondria, is the most important type of mitochondrial quality control [153]. In hearts of STZ-induced diabetic mice and high glucose exposed HUVECs, both metformin and AICAR can target the mitochondria to reduce elevated ROS and through AMPK-dependent upregulation of UCP2 [101]. Indeed, metformin in particular can target both UCP1 and UCP2 to inhibit mitochondrial ROS and the modulation of AMPK as demonstrated in bovine aortic endothelial cells [154].

14. Pioglitazone protects a diabetic heart and increases UCP2 expression

Pioglitazone (PubChem CID: 4829) is an antidiabetic drug belonging to a class of thiazolidinedione. These drugs are known to activate PPARγ, and thus promote organ lipid storage in muscle, adipose and liver tissues, leading to reduced circulating FFA levels [155]. Although considered beneficial in ameliorating impaired glucose tolerance, the use of pioglitazone has been associated with significant weight gain and edema [156]. The use of this thiazolidinedione has also been linked development of congestive heart failure and pulmonary edema in a patient with preserved ejection fraction [157]. However, contradictory information exists on the beneficial effects of pioglitazone in patients with a

high risk or history of cardiovascular disease [158]. It has already been established that this thiazolidinedione can attenuate renal fibrosis by targeting the mitochondria, ameliorating altered mitochondrial membrane potential, and inhibiting elevated ROS and apoptosis, leading to improved kidney function [159]. In isolated heart tissue from mouse hearts, increased expression of UCP2 was linked with chronic PPARγ stimulation through dietary supplementation of pioglitazone, leading to slight mitochondrial membrane depolarization and enhanced superoxide dismutase levels [160].

15. Resveratrol protects a diabetic heart and upregulates UCP1, UCP2 and UCP3 expression

Resveratrol (PubChem CID: 445154) is a natural phenol, classified under stilbenoids, that occurs in several food sources, including red wine, skin of grapes, blueberries, raspberries, and mulberries [161]. The pharmacokinetic profile of resveratrol shows that after oral ingestion, its conjugates can be detected in plasma and urine of subjects, and has been associate with various therapeutic effects [162]. It is well established that resveratrol can act on various tissues to induce diverse effects related to the amelioration of diabetes and metabolic syndrome [163]. Resveratrol possess strong antioxidant properties, and is known to be a major target for mitochondrial proteins such SIRT1 and PGC-1α [163]. In addition to modulating FFA oxidation, activation of AMPK and SIRT1 is linked with enhanced mitochondrial biogenesis via PGC-1α [119]. Interestingly, resveratrol can also target the regulation of UCP1, UCP2 and UCP3 to improve heart function in hearts of diabetic and nondiabetic rodents [164-166].

16. Rosiglitazone protects a diabetic heart and upregulates UCP1 expression

Rosiglitazone (PubChem CID: 77999) is another antidiabetic drug that belongs to the class of thiazolidinedione [167]. Although possess accomplished hypoglycemic potential, rosiglitazone has been associated with increased risk of myocardial infarction, heart failure, and all-cause mortality in diabetic patients when compared with pioglitazone [168]. In a mouse model, rosiglitazone induced cardiotoxicity via a PPARγ-independent mechanism involving oxidative stress-induced mitochondrial dysfunction [169]. However, data showing that rosiglitazone does not cause ischemic cardiovascular events among patients with type 2 diabetes and established coronary artery disease has also been presented [170]. It has been demonstrated that rosiglitazone-induced mitochondrial biogenesis is independent of

PGC-1α, but that this transcriptional cofactor is necessary for the expression of brown adipose tissue-related genes such as UCP1 [171]. Similarly, in obese Zucker rats, rosiglitazone promoted the browning of the epicardial adipose tissue through regulation of UCP1, PGC-1α, NADH dehydrogenase 1 and cytochrome oxidase [172].

17. Sitagliptin and exendin-4

Sitagliptin (PubChem CID: 4369359) is a dipeptidyl peptidase-4 (DPP-4) inhibitor, while exendin-4 (PubChem CID: 56927919) is a glucagon-like peptide-1 (GLP-1) receptor agonist [173, 174]. The mechanism of action for both drugs is based on enhancing insulin secretion by the pancreatic beta cells, resulting in reduced blood glucose levels. Both drugs are widely used in combination with other blood glucose lowering drugs such as metformin [175, 176]. While limited studies report on the effect of exendin-4 on diabetic patients at risk of heart failure, the use of sitagliptin has been associated with increased risk of myocardial infarction in type 2 diabetics on dialysis or with pre-existing heart failure [177, 178]. However, experimental data shows that both sitagliptin and exendin-4 can protect the myocardium against diabetes-induced damage and improve cardiac function [179, 180]. Some of the implicated mechanisms include down-regulation of the Janus kinase (JAK)/ signal transducer and activator of transcription protein (STAT) signaling pathway, which is one of the major pathways involved in inflammation induced tissue injury. Furthermore, more data showed that these drugs can prevent hypertension-related vascular events by upregulating UCP2 expression in rodents [181].

18. Conclusion remarks

Evidence reporting on the involvement of UCPs in diabetes-induced myocardial injury has significantly increased over the years. Available evidence shows that UCP3 is the most studied among the UCPs in the diabetic heart, especially in relation to the modulation of FFA flux and amelioration of oxidative stress. Similarly, transgenic models as well as human studies consisting of diabetic patients with a polymorphism in the UCP2 gene (G-866A) have proposed an importance of this UCP in maintaining enhanced antioxidant status and survival. Although this review highlights a controversy regarding the function of UCP2 and UCP3, modulation of their expression appears to be interesting as target in ameliorating oxidative stress-induced cardiac injury within a diabetic state. Moreover, although

activation of AMPK, NRF2, PPAR-α, and PGC-1α has been linked with the activity of UCPs and improved mitochondrial biogenesis, the complete mechanisms implicated in the regulation of these proteins have to be resolved first. Similarly, although compounds and hormones summarized in this review demonstrate an association with improved cardiac function, we do not know whether these drugs stimulate UCP2/3 to protect the heart, or whether they are just consequences of other drug functions. Therefore, further studies are needed to provide a comprehensive understanding of their therapeutic properties relevant to targeting these UCPs to improve heart function in a diabetic state.

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Conflict of interest

The authors declare no conflict of interest.

Table 1. Evidence reporting on the role and regulation of cardiac uncoupling proteins in presence and absence of diabetes associated complications.

Author and year	Experimental model	Role of uncoupling proteins
Hidaka et al., 1999 [64]	Hearts of male Zucker fatty rats and streptozotocin (STZ)-induced diabetic male Wistar rats	Uncoupling protein 3 (UCP3) was upregulated, while no effect with UCP2 in STZ-injected rats. UCP3 levels were not affected in Zucker rats
Boehm et al., 2001 [17]	Hyperthyroid male Wistar rat hearts perfused with palmitate	Increased UCP2 and UCP3 was associated with improved myocardial efficiency
Young et al., 2001 [18]	High-fat feeding and STZ-induced diabetic male Sprague-Dawley rats Peroxisome proliferator-activated receptor alpha null (PPARα$^{-/-}$) male mice	The expression of UCP2 and UCP3, together with PPARα was reduced when cardiac workload was either increased (pressure overload by aortic constriction) or decreased (mechanical unloading by heterotopic transplantation) in rats The level of cardiac UCP3 but not UCP2 expression was severely reduced in PPARα$^{-/-}$ mice when compared to wild-type mice
Razeghi et al., 2002 [65]	Left ventricular tissue from diabetic patients with non-ischemic heart failure	Reduced UPC3 levels were associated with altered cardiac substrate metabolism and down-regulated glucose transporter 4 (GLUT4) expression
Young et al., 2002 [66]	Hearts of STZ-induced diabetic male Wistar rats	Increased UCP3 levels were linked enhanced myosin heavy chain beta, pyruvate dehydrogenase kinase (PDK) expression, as well as altered circadian patterns
Abu-Elheiga et al., 2003 [67]	Hearts of acetyl-CoA carboxylase ACC2 (ACC2$^{-/-}$) mice fed high-fat/high-carbohydrate diets	UCP2 and UCP3 levels were higher in the mutant mice when compared to the wild type. This was correlated with fatty acid oxidation
Hoerter et al., 2004 [102]	Transgenic male U13 mice (with abundant UCP1 expression levels in heart mitochondria) subjected to ischemia	UCP1 expression did not alter the sensitivity to ischemia, but significantly improved functional recovery on reperfusion and makers for oxidative stress, glutathione and aconitase
Dhamrait et al., 2004 [95]	Plasma samples from diabetic men	A common functional variant in the UCP2 gene was associated with both increased oxidative stress and cardiovascular disease risk

Murray et al., 2004 [15]	Blood samples from 39 patients undergoing coronary artery bypass graft surgery	Raised plasma free fatty acid concentrations correlated with increased levels of cardiac UCP2 and UCP3
Lee et al., 2005 [100]	Human aortic endothelial cells (HAECs)	UCP2 overexpression led to increase in endothelial nitric oxide synthase (eNOS) and reduction in endothelin-1 levels. UCP2 further inhibited reactive oxygen species (ROS) production, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and apoptosis resulting in improved vascular relaxation
Murray et al., 2005 [68]	Hearts of STZ-induced diabetic PPARα$^{-/-}$ male mice, and type 2 diabetic (*db/db*) male mice	UCP2 and UCP3 were significantly lower in the PPARα$^{-/-}$ mouse than in the wild type. *Db/db* mice presented higher UCP2 and UCP3 levels compared to controls. Furthermore, not UCP3, but UCP2 levels were modulated via PPARα-dependent and -independent mechanisms
Gerber et al., 2006 [69]	Hearts of STZ-induced diabetic male Wistar rats	Increased UCP3 was associated with enhanced fatty acid oxidation
Bodyak et al., 2007 [86]	Hearts of female Dahl Salt Sensitive (DSS) rats and primary cultured adult cardiomyocytes from female Sprague-Dawley rats	UCP2 increased sensitivity to hypoxia-re-oxygenation leading to the accumulation of pro-death protein Bc-l2 interacting protein 3 (BNIP3)
Ihnat et al., 2007 [88]	Human umbilical vein endothelial cells (HUVECs) exposed to high glucose	Overexpression of UCP2, together with oxypurinol, apocynin and the poly(ADP-ribose) polymerase inhibitor PJ34 ablated the elevated levels of ROS
Boudina, 2007 [16]	In male *db/db* mice	Downregulated UCP2 and UCP3 expression was linked to increased oxygen consumption, mitochondrial ROS generation, and reduced cardiac function
King et al., 2007 [70]	Hearts of STZ-induced diabetic male Wistar rats	Increased UCP3 corresponded to enhanced mitochondrial respiration and mitochondrial thioesterase I via PPARα modulation
Minamiyama et al., 2007 [89]	Heart and aorta of male type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats	Increased UCP2 corresponded with enhanced mitochondrial ROS production and it was reversed through caloric restriction
Bo et al., 2008 [90]	Hearts of male Sprague-Dawley rats subjected to endurance training	UCP2 was upregulated during prolonged exercise, and was linked with reduced mitochondrial membrane potential and ROS production

Bugger et al., 2008 [10]	Hearts of male type 1 diabetic Akita mice	Upregulated UCP3 expression did not correlate with oxidative stress or reduced cardiac efficiency
Carley et al., 2008 [71]	Perfused hearts of *db/db* mice	Although UCP3 content remained unchanged, free fatty acid uptake and oxidation was increased
El-Osta et al., 2008 [53]	HAECs exposed to high glucose and male UCP2 heterozygous knockout ($UCP2^{+/-}$) mice	Overexpression of UCP1 and UCP2 reduced levels of transcription factor p65 and NF-κB
Herlein et al., 2008 [72]	Hearts of STZ-induced diabetic male Sprague Dawley rats	Increased UCP3 expression was associated with oxidative stress
Moukdar et al., 2008 [91]	Heart and aorta of female C57BL/6J mice lacking UCP2 ($UCP2^{-/-}$) on an atherogenic diet	Endothelial dysfunction was correlated with reduced endothelial nitric oxide synthase, an increased vascular cell adhesion molecule-1 expression and ROS. This was consistent to impaired antioxidant capacity response, as well as enhanced aortic macrophage infiltration and atherosclerotic lesions
Stephens et al., 2008 [96]	Blood plasma of diabetic patients exposed to smoking	Diabetic patients with polymorphism in UCP2 gene (G-866A) were associated with increased oxidative stress and low antioxidant status compared to control counterparts
Palmer et al., 2009 [97]	Blood plasma of diabetic patients following myocardial infarction	Patients with polymorphisms in UCP2 gene (G-866A) were associated with poorer survival and higher myeloperoxidase levels than their nondiabetic control counterparts
Dabkowski et al., 2010 [11]	Hearts of male *db/db* mice	Increased UCP3 expression was associated with altered mitochondrial morphology and oxidative damage
Cole et al., 2011 [73]	Hearts of male Wistar rats fed a high fat diet	Upregulated UCP3 expression was associated with increased free fatty acid oxidation, oxygen consumption, and reduced cardiac efficiency
Bugger et al., 2012 [182]	STZ-induced diabetic male mice with cardiomyocyte-restricted deletion of insulin receptors (CIRKO)	Increased UCP3 expression was associated with altered myocardial metabolism, increased oxygen consumption and ROS, while cardiac efficiency was reduced
Koziel et al., 2012 [92]	HUVECs exposed to high glucose	Increased UCP2 activity was associated with enhanced oxidation of palmitoylcarnitine and glycerol-3-phosphate and reduced oxidation of pyruvate

Yang et al., 2012 [74]	Hearts of male *db/db* mice	Upregulation of acyl-coA thioesterase 1 was associated with reduced ROS, as well as repressed PPARα/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and UCP3
Zhang et al., 2012 [61]	Hearts of STZ-induced diabetic male FVB and aldehyde dehydrogenase 2 (ALDH2) transgenic mice	ALDH2 was associated with improved cardiac function through the regulation of PGC1α and UCP2
Harmancey et al., 2013 [75]	Hearts of male Sprague-Dawley rats fed high sucrose diet and L6 myocytes subjected to ischemia	High sucrose diet exposure was associated with reduced UCP3 levels and cardiac dysfunction
Lehtoranta et al., 2013 [76]	Hearts of STZ-induced female Sprague-Dawley rats	Upregulated UCP2 and UCP3 expression was associated with enhanced apoptosis and cardiac remodeling
Mansor et al., 2013 [77]	Hearts of high fat diet and STZ-induced diabetic male Wistar rats	Increased UCP3 and pyruvate dehydrogenase kinase 4 expression was associated with reduced glucose transporter 4 levels
Gargiulo et al., 2014 [82]	Cardiac ^{18}F-fluorodeoxyglucose (FDG) uptake was performed in male UCP3 knockout (UCP3$^{-/-}$) mice one week after induction of myocardial infarction	Myocardial infarction caused an increased left ventricular volume. Furthermore, infarction led to increased FDG uptake. While UCP3 deficiency caused a metabolic shift that favored glycolytic metabolism and increased FDG uptake in remote areas
Kukat et al., 2014 [93]	Male and female UCP2-deficient (UCP2$^{-/-}$) mice and mitochondrial DNA (mtDNA) mutator mice	Upregulation of UCP2 was not associated with altered proton leak kinetics or ROS production. High UCP2 levels were linked with better utilization of fatty acid oxidation and longer lifespan
Liepinsh et al., 2014 [78]	Hearts of male Goto–Kakizaki rats and Wistar rats	Reduced expression of PPARα and PGC1α corresponded with lower levels of UCP1 and UCP3 in the fed state compared to fasted state
Ma et al., 2014 [54]	UCP2 knockout (UCP2$^{-/-}$) mice and wild-type littermates fed a normal salt or a high salt diet	UCP2$^{-/-}$ mice receiving high-salt diet developed severe cardiovascular and renal remodeling that was associated with increased oxidative stress, upregulations of matrix metalloproteinase-2/-3/-9 and downregulation of TIMP metallopeptidase inhibitor 1
Zhang et al., 2014 [99]	Male young (4–5 months) and old (26–28 months) ALDH2 transgenic mice	Aging promoted O_2^- release, and mitochondrial injury, which was exacerbated in ALDH2 transgenic mice

Banke et al., 2015 [79]	Perfused hearts of male *db/db* mice	Increased UCP3 expression was associated with inefficient citric acid cycle flux during post ischemia
Da Silva et al., 1985 [183]	STZ-induced diabetic male Wistar rats	Swimming and insulin therapy ameliorated increased mitochondrial permeability transition pore (mPTP) opening, UCP2 expression, and ROS
Holley et al., 2015 [87]	Swine that underwent revascularized hibernating myocardium after coronary artery bypass grafting (CABG)	During dobutamine infusion, revascularized hibernating myocardium demonstrated lower blood flows and reduced wall thickening compared with remote regions. Furthermore, revascularized hibernating myocardium had lower respiratory control indices with persistently increased UCP2 content
Ji et al., 2015 [94]	Male C57BL/6J mice were subjected to pressure overload by using transverse aortic constriction	TAC induced left ventricular hypertrophy, reduced ATP concentration, and increased ROS levels, apoptosis and fibrosis markers. However, inhibition of UCP2 prevented against these complications.
	Parallel set of experiments was also conducted in male UCP2$^{-/-}$ mice	Furthermore, hypertrophy and associated changes induced by TAC in UCP2$^{-/-}$ mice were much less pronounced than in WT mice.
Harmancey et al., 2015 [81]	Male C57BL/6J mice and cultured L6 myocytes exposed to hyperinsulinemia conditions	Exposure to hyperinsulinemia was associated with a decrease in UCP3 in the myocardium. The decrease in UCP3 was mirrored by increased expression and maturation of sterol regulatory element-binding protein 1 (SREBP-1).
Dhamrait et al., 2016 [80]	Serum of healthy young UK men and Scandinavian diabetic patients	Angiotensin-converting enzyme (ACE) activity was significantly higher amongst UCP3-55C (rather than T) and UCP2 I (rather than D) allele carriers
	HUVECs	Inhibition of UCP2 was associated with increased ACE activity in vitro
Chechi et al., 2017 [103]	Human epicardial adipose tissue and primary adipocytes from male and female lean, overweight and obese individuals	Epicardial adipose tissue exhibits consistent presence of UCP1 in conjunction with the expression of majority of known beige markers. Furthermore, this tissue shows upregulation of UCP1 and its uncoupling respiration upon stimulation
Lee et al., 2017 [98]	Genomic DNA from diabetic patients (male and female) withUCP2 exon 8 insertion/deletion polymorphism	Cardiac dysfunction through ECG-derived QRS duration was linked with UCP2 polymorphism in these patients

Pan et al., 2017 [20]	Serum samples of human subjects (majority were females) with insulin resistance as determined through homeostatic model assessment-insulin resistance (HOMA-IR)	UCP1, UCP2 and UCP3 were associated with differences in HOMA-IR. Multiple logistic regression analysis indicated that low UCP1 was an independent determinant for high HOMA-IR.
Rines et al., 2017 [19]	Male and female mice overexpressing SNF-related serine/threonine-protein kinase (SNRK) and SNRK knockout mice	Overexpression of SNRK was associated with decreased UCP3, mitochondrial uncoupling, as well as glucose and palmitate metabolism and oxygen consumption, but maintained power and function. Conversely, SNRK knockout mice have increased glucose and palmitate oxidation and UCP3. SNRK further reduced infarct size after ischemia/reperfusion and decreased cardiac cell death in a UCP3-dependent manner.

Table 2. Known modulators of uncoupling proteins to protect the myocardium against diabetes associated complications.

Treatment compound	Experimental model	Role of UCPs	Refs
Antioxidant biofactor	Otsuka Long-Evans Tokushima Fatty (OLETF) rats	Reduced reactive oxygen species by upregulating uncoupling protein (UCP) 2 expression	[108]
Aspalathin	High glucose exposed H9c2 cells	Prevented high-glucose induced oxidative damage by reducing elevated levels of UCP1 and UCP2 expression	[40, 114]
	Type 2 diabetic (*db/db*) mice and high glucose exposed H9c2 cells	Prevented hyperglycemia-associated damage by reducing elevated levels of UCP2 expression	[115]
Berberine	ApoE ($ApoE^{-/-}$) mice fed Western diet and cultured human umbilical vein endothelial cells	Reduced aortic lesions and oxidative stress, while significantly increasing UCP2 levels	[125]
Ghrelin	Human umbilical vein endothelial cells	Inhibited oxidized low-density lipoprotein-induced inflammatory response by upregulating UCP2	[130]
Glibenclamide	βV59M mouse of diabetes	Improved euglycemia, cardiac metabolism and function by restoring increased pyruvate dehydrogenase kinase 4 and UCP3 levels	[135]
Losartan and ramiprilat	Rats subjected to ischemia-reperfusion (IR)	UCP2 protein but not mRNA level was increased in the ischemic area of the left ventricle (LV). Following acute myocardial IR, UCP2 protein levels were increased in the ischemic area of the LV but not in RV, suggesting the local effect of ischemia on UCP2 expression. IR-induced overexpression of UCP2 was suppressed by ramiprilat and losartan	[141]
Melatonin	UCP2-knockout mice and cardiomyocytes exposed to lipopolysaccharide	Upregulated UCP2 expression and protected the cells from the changes in morphology, mitochondrial membrane potential loss, mitochondrial Ca^{2+} overload, the opening of mitochondrial permeability transition pore, and subsequent increased ROS generation as well as ATP reduction	[147]
Metformin and 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)	STZ-induced diabetic mice and human umbilical vein endothelial cells exposed to high glucose	Reduced both $O_2^{\cdot-}$ and prostacyclin synthase nitration through 5' AMP-activated protein kinase (AMPK)-dependent upregulation of UCP2	[101]

Metformin	Bovine aortic endothelial cells	Overexpression of UCP1 and UCP2 inhibited mitochondrial production of ROS and abolished metformin-enhanced phosphorylation of both ACC and AMPK	[154]
Pioglitazone	Wild-type (WT) and UCP2 knockout (KO) mice	Chronic PPARγ stimulation leads to depolarization of the inner membrane and reduced superoxide of isolated heart mitochondria, which was critically dependent on increased expression of UCP2. Thus, UCP2 expression affords resistance to brief anoxia-reoxygenation	[160]
Resveratrol	High-fat diet combined with STZ-induced diabetic rats and high glucose exposed H9c2 cells	Alleviated diabetic cardiomyopathy by improving mitochondrial function through upregulation of UCP2	[164]
	Hypothermic preserved rat hearts	Improved cardiac function by reducing overexpression of UCP2	[165]
	Nondiabetic rats	Improved cardiac function and oxidative metabolism through increasing UCP1 and UCP3 expression	[166]
Rosiglitazone	Zucker rats	Increased browning of the epicardial adipose tissue UCP1, PGC-1α, NADH dehydrogenase 1 and cytochrome oxidase	[172]
Sitagliptin and exendin-4	Hypertensive rats, as well as C57BL/6 and UCP2 knockout mouse aortae	Prevented hypertension-related vascular events by upregulating UCP2 expression	[181]

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