Current Neuropharmacology, 2022, *20*, 662-674

REVIEW ARTICLE

Uncoupling Protein 2 as a Pathogenic Determinant and Therapeutic Target in Cardiovascular and Metabolic Diseases

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ARTICLE HISTORY

Received: February 04, 2021
Revised: March 10, 2021
Accepted: April 16, 2021

DOI:
10.2174/1570159X19666210421094204

Abstract: Uncoupling protein 2 (UCP2) is a mitochondrial protein that acts as an anion carrier. It is involved in the regulation of several processes, including mitochondrial membrane potential, generation of reactive oxygen species within the inner mitochondrial membrane and calcium homeostasis. UCP2 expression can be regulated at different levels: genetic (gene variants), transcriptional [by peroxisome proliferator-activated receptors (PPARs) and microRNAs], and post-translational. Experimental evidence indicates that activation of UCP2 expression through the AMPK/PPAR-α axis exerts a protective effect toward renal damage and stroke occurrence in an animal model of ischemic stroke (IS) associated with hypertension. UCP2 plays a key role in heart diseases (myocardial infarction and cardiac hypertrophy) and metabolic disorders (obesity and diabetes). In humans, UCP2 genetic variants (-866G/A and Ala55Val) associate with an increased risk of type 2 diabetes mellitus and IS development. Over the last few years, many agents that modulate UCP2 expression have been identified. Some of them are natural compounds of plant origin, such as Brassica oleracea, curcumin, berberine and resveratrol. Other molecules, currently used in clinical practice, include anti-diabetic (gliptin) and chemotherapeutic (doxorubicin and taxol) drugs. This evidence highlights the relevant role of UCP2 for the treatment of a wide range of diseases, which affect the national health systems of Western countries. We will review current knowledge on the physiological and pathological implications of UCP2 with particular regard to cardiovascular and metabolic disorders and will focus on the available therapeutic approaches affecting UCP2 level for the treatment of human diseases.

Keywords: UCP2, stroke, cardiovascular disease, diabetes, obesity, therapeutics.

1. INTRODUCTION

The uncoupling proteins (UCPs) family includes four components [1, 2]. UCP1, or thermogenin, was the first member of the family to be discovered in hibernators and small rodents, where UCP1 is highly expressed in the mitochondria of brown adipose tissue (BAT). Herein, UCP1 plays a physiological role in body temperature regulation by fat storage and mobilization control [3, 4]. UCP1 knock-out mice are unable to regulate the body temperature [5]. The other components of UCPs family (UCP2-UCP5) were characterized later on [6, 7]. UCP2 is ubiquitously expressed. UCP3 is more expressed in the skeletal muscle. UCP4 and UCP5 are present in the brain. The different tissue expression of UCPs reflects different functions. In fact, whereas UCP1 acts as a thermogenesis regulator in the BAT of vertebrates [8], UCP2 uncouples the proton flux and the ATP (adenosine triphosphate) synthesis and converts the energy generated in this process into heat instead of ATP. Moreover, the UCP2-UCP5 members of the family have a physiological role as reactive oxygen species (ROS) scavengers and regulators of ATP-dependent processes, including secretion [7, 9]. Interestingly, UCP2 and UCP3 knockout mice show increased ROS production [10]. This evidence has important implications for human health. In fact, it is known that high concentrations of ROS contribute to the development of several diseases [10]. As a matter of fact, evidence obtained in both animal models and humans demonstrates that UCPs are

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1875-6190/22 $65.00+.00

involved in the pathogenesis of metabolic, neurodegenerative and cardiovascular diseases. High levels of UCP2 exert a protective effect in atherosclerosis [11], heart diseases [myocardial ischemia/reperfusion (I/R) injury] [11] and ischemic stroke (IS) [12]. Consistently, a reduced expression of UCP2 correlates with increased renal and cerebrovascular damage in the stroke-prone spontaneously hypertensive rat (SHRSP) model [13, 14]. On the other hand, increased UCP2 expression inhibits insulin secretion from pancreatic β-cells and favors the development of type 2 diabetes mellitus (T2DM).

In this review, we describe the main physiological and pathological implications of UCP2 with a focus on its involvement in major cardiovascular and metabolic disorders, based on both experimental and human evidence. Furthermore, we discuss the therapeutic implications of UCP2 and the compounds available for the clinical use affecting UCP2 level.

2. PHYSIOLOGICAL FUNCTIONS OF UCP2

The sequence of human UCP2 is very similar to that of rat and mouse (99% and 95% of homology, respectively) [15]. The strong conservation of the gene sequence between the different species indicates that this protein exerts an important physiological role in all organisms. Transcription and translation, as well as UCP2 activity, may be controlled by many stimuli such as free fatty acids (FFA), retinoic acid, lipopolysaccharides, superoxide anion and hormones, including leptin and thyroid hormones [16, 17]. The main physiological role of UCP2 is related to the control of mitochondrial ROS production [9, 18]. Additional evidence shows that UCP2 plays an important role in the process of oxidative phosphorylation, in the regulation of ATP synthesis, in the maintenance of redox potential membrane, in the control of calcium homeostasis, cell apoptosis, and death [17, 19].

2.1. Oxidative Phosphorylation, ATP Synthesis and ROS Production

Oxidative phosphorylation is a complex process that, by a series of chemical reactions, generates highly energetic molecules of ATP. This process takes place within the inner mitochondrial membrane through the electron transport chain (ETC) made by five enzymatic complexes (labeled I to V) (Fig. **1**). During this process, a flow of electrons is generated by electron transporters starting from NADH (Complex I) or $FADH_2$ (Complex II). The Complex III (cytochrome oxidoreductase) and the Complex IV (cytochrome c oxidase) also pump protons through the membrane in the intermembranes space. The electrochemical gradient, together with the return of protons across the inner membrane, activates the last enzyme of the chain, the ATP synthase (Complex V). The latter produces ATP through the reaction $ADP + P_i + 3H^+ \rightleftharpoons ATP+H_2O$. The amount of ATP molecules generated from glucose catabolism varies across species and is related to various cellular processes. Under physiological conditions, when the energy demand of the cells is low, UCP2 dissociates the oxidation of different substrates (NADH, coenzyme Q, cytochrome c) from ADP phosphorylation. It consequently reduces the ATP synthesis and the electrochemical membrane potential (ΔΨ) [20]. UCP2, by decreasing ΔΨ, protects the cells from ROS damage and death. The energy generated in this process is dissipated in the form of heat [21]. As a consequence of the reduced ATP synthesis by UCP2, pancreatic β-cells from UCP2 knockout mice show an increased ATP, ATP/ADP ratio and insulin secretion, the latter due to the blockade of ATP-sensitive channels and the opening of the voltage-dependent Ca^{2+} channel involved in insulin secretion [22-24].

Mitochondria are the major source of ROS (mainly superoxide or hydrogen peroxide) in the aerobic cells [25]. They are generated at several sites of ETC, although the two main sites are Complex I (on the matrix side) and Complex III (on both the intermembrane and the matrix side) (Fig. **1**) [9]. At physiological concentration, ROS act as signaling factors, whereas high levels exert detrimental effects. Superoxide anion (O_2^-) is a dangerous element that rapidly interacts with the lipid component of the cell membrane, causing lipid peroxidation, protein and DNA damage. ROS level is kept under the control of few antioxidant systems such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR). ROS level is also influenced by ΔΨ [17] and is modulated by UCP2 activity [18]. UCP2, by subtracting electrons from ETC, reduces superoxide formation and limits the cell damage. Animal models lacking UCP2 show higher ROS level. Conversely, overexpression of UCP2 exerts a protective function against the oxidative stress damage [18, 26].

2.2. Calcium Regulation

The calcium ion (Ca^{2+}) is an important intracellular messenger, which acts as a regulator of cellular processes including the neurotransmitters release from neurons and the contraction of all muscle cell types. In addition, it is a fundamental cofactor of many enzymes. Ca^{2+} is also important for maintaining the difference in potential across membranes of excitable cells. Mitochondria and the endoplasmic reticulum sequester Ca^{2+} to ensure that homeostasis is maintained [27]. Cytosolic Ca^{2+} level is directly related to ΔΨ. Since UCP2 is involved in the regulation of ΔΨ, it can influence the calcium dynamic. In normal conditions, ΔΨ equals 30mV. However, this value can undergo small changes and it can alter important cellular functions in the presence of increased UCP2 level [28]. A drastic reduction of Ca^{2+} can influence cell signaling. On the other hand, a massive flow of Ca^{2+} in the cytosol can increase neuronal excitotoxicity, as it happens following IS or in neurodegenerative diseases [29, 30]. An excess of Ca^{2+} can induce apoptosis and necrosis [31].

2.3. Regulation of Cell Apoptosis and Death

The mitochondrion and some of the mitochondrial proteins play a key role in the control of apoptosis and cell death. Several studies demonstrated that UCP2 regulates mitochondrial apoptotic signaling. A recent study performed in a cerebral ischemia/reperfusion (I/R) mouse model demonstrated that UCP2 deletion exacerbated cell apoptosis [32]. Conversely, in the middle cerebral artery occlusion (MCAO) rat model, UCP2 inhibits cell death linked to mitochondrial dysfunction by inducing depolarization of the mitochondrial inner membrane, subsequent Ca^{2+} intake and ROS reduction [17, 33]. On the other hand, overexpression

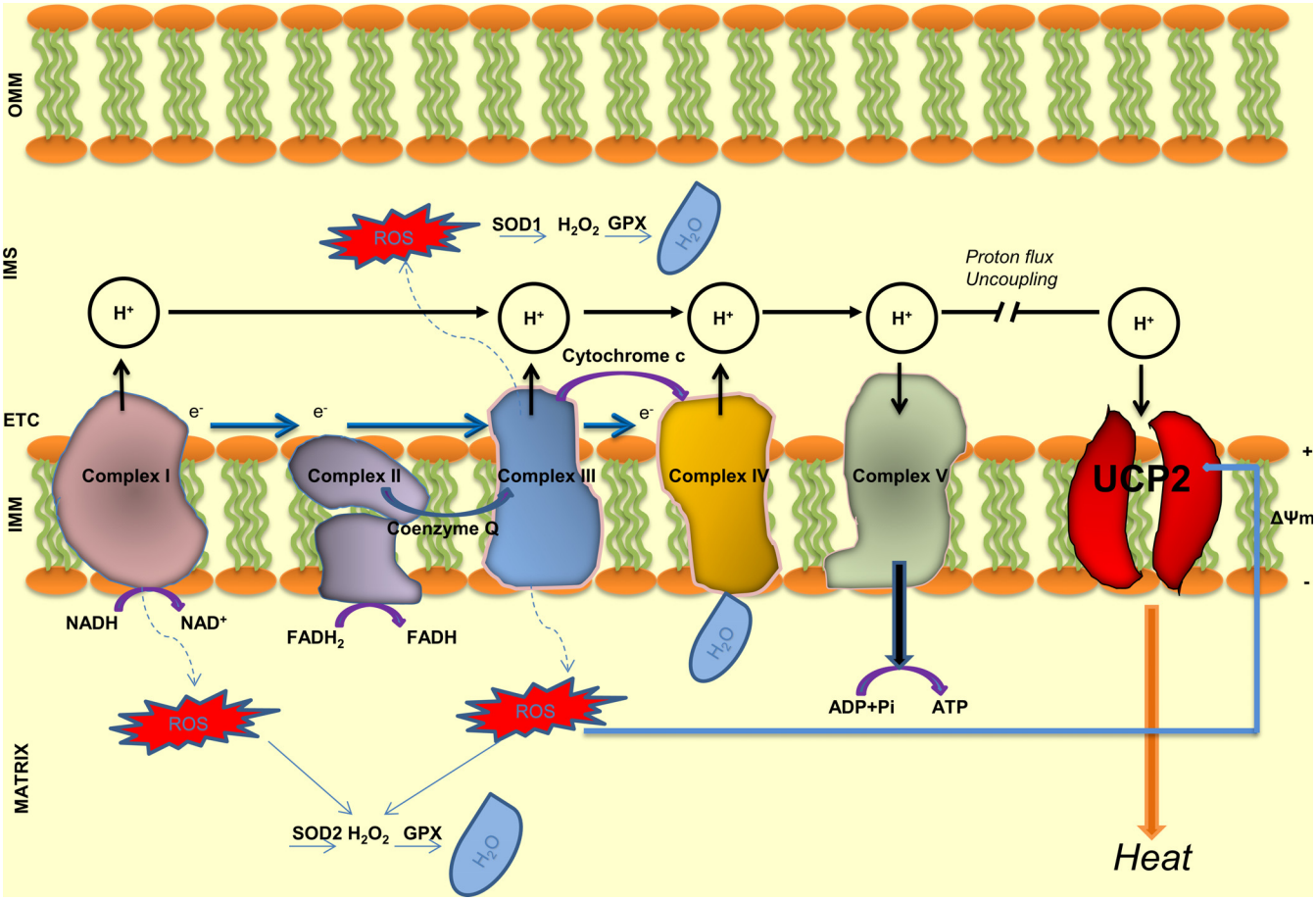

Fig. (1). Schematic representation of electron transport chain (ETC), mitochondrial enzymatic complexes and UCP2 functions. During the respiratory process, the energy generated from the oxidation of various substrates including glucose, is conserved in reduced molecules such as NADH (nicotinamide adenine dinucleotide) and $FADH_2$ (flavin adenine dinucleotide). Electron transporters and protonic pumps create a negative membrane potential and a proton-motive force across the inner mitochondrial membrane which activate the last enzyme of the chain, the ATP synthase. The latter, by the reaction between ADP (adenosine diphosphate) and inorganic phosphate (Pi) generates ATP (adenosine triphosphate**)**. When the energy requirement of the cell is reduced, protons can return into the mitochondrial matrix across the UCP2 protein with reduction of ATP synthesis and heat release. ROS generated during the respiratory process are first reduced at H_2O_2 and then at H_2O from several antioxidant enzymes such as SOD1 (superoxide dismutase 1), SOD2 (superoxide dismutase 2) and GPx (glutathione peroxidase). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

of UCP2 inhibits mitochondrial death pathway in primary cultures of neonatal rat cardiac ventricular myocytes [34].

3. IMPLICATIONS OF UCP2 IN PRE-CLINICAL MODELS AND HUMAN DISEASES

UCP2 is implicated in a wide range of physiological and pathological conditions including aging [35] obesity [36], inflammation [26], cerebral and myocardial ischemia [14, 37], hyperinsulinemia [36, 38]. With regard to aging, we reported an age-related decrease of UCP2 expression in the brain, heart and kidneys of the SHRSP model, likely involved into the higher predisposition to the hypertensive organ damage development of this strain [39]. Ren *et al*. also highlighted the relationship between UCP2, aging and cardiac dysfunction. UCP2 level decreased with advanced aging along with abnormal autophagy, mitophagy, and mitochondrial integrity. UCP2 level was lower in isolated cardiomyocytes from old mice compared to young ones [40, 41]. Moreover, aging was reported to suppress mitochondrial proteins, including UCP2, with a more pronounced effect in the aged mitochondrial aldehyde dehydrogenase (ALDH2) deleted mouse hearts [42]. This evidence clearly implies that increased ROS level, along with decreased UCP2 activity, contribute to the aging process.

3.1. UCP2 and IS

IS is the most common form of stroke and it results from cerebral blood vessel occlusion by an embolus or a thrombus. The initial event is followed by depolarization of neuronal membrane, ion imbalance, such as K^+ and Ca^{2+}, and a massive release of glutamate from the presynaptic vesicles into the extracellular space. Higher Ca^{2+} level increases both ROS production and caspase activation causing degradation of membrane phospholipids, structural proteins and nucleic acids. An increase of glutamate level, instead, contributes to excitotoxic neuronal death through overstimulation of glu-

tamate receptors. All these events contribute to amplify cellular damage [43-45].

The upregulation of UCP2 exerted a neuroprotective role in the MCAO mouse and rat models, mainly due to its ability to keep low the depolarization level of the mitochondrial inner membrane (approximately 10 mV). As a consequence, the ROS production, the calcium uptake and the induction of cell death-inducing factors (caspases and other apoptosis mediators) decreased [30]. Conversely, low UCP2 expression induced a membrane hyperpolarization with an increase of ΔΨ and consequent ROS accumulation [26, 33].

We previously demonstrated that both cerebral and renal expression of UCP2 were downregulated in the SHRSP model when fed with a stroke permissive high-sodium/low potassium diet (Japanese-style diet, JD), as compared to the stroke-resistant strain (SHRSR). In this experimental condition, we found that UCP2 downregulation was induced by an upregulation of the microRNA-503 [37]. The treatment of JD-fed SHRSP with a Brassica oleracea (BO) sprout extract or with fenofibrate, a drug used to treat abnormal blood lipid levels, significantly decreased brain expression of mir-503, rescued UCP2 expression and consequently reduced ischemic brain damage [37, 46, 47]. Interestingly, the epigenetic control of UCP2 plays a role also in the kidney of JD-fed SHRSP, where renal damage precedes stroke events. In fact, we demonstrated that renal UCP2 expression was regulated by microRNA-34a and microRNA-24 [48] (Table **1**).

Several studies showed that the antioxidant activity of UCP2 was mediated by the peroxisome expression of many genes. In particular, PPAR-α activation by fenofibrate, BO juice and curcumin administration exerted a protective role toward stroke and renal damage in JD-fed SHRSP [49, 50]. Activation of PPAR-γ can also modulate UCP2 expression in different tissues [51]. At the brain level, several PPAR-γ agonists, including troglitazone, an antidiabetic drug that

Table 1. Pathological implications of UCP2 in animal models.

Animal Model	UCP2 Modulation	Cellular Effects	Phenotypes	Refs.
Stroke				
MCAO mouse	downregulation	↑membrane hyperpolarization ↑ΔΨ ↑ROS	Ischemic stroke	[26]
JD-fed SHRSP	downregulation	↑ROS ↑inflammation	Ischemic stroke	[38, 48]
Heart diseases				
I/R rat model	downregulation	↑ROS ↑cell death ↓autophagy	Cardiac ischemia	[34, 61]
Wistar rat running on a treadmill	downregulation	↑extracellular matrix remodeling genes ↑cytoskeletal genes ↑protein synthesis genes ↑inflammatory genes	Compensated cardiac hypertrophy	[62]
Wistar rat with ligation of left anterior coronary artery	upregulation	↑cytoskeleton/extracellular matrix organization genes ↑cell death/apoptosis genes ↑cell growth/proliferation genes ↓β-oxidation of fatty acids genes	Decompensated cardiac hypertrophy	[62, 63]
ET(A) receptor cardiac-specific knockout mice exposed to cold stress	upregulation	↑oxidative stress ↑apoptosis ↑autophagy	Cold stress-induced cardiac hypertrophy	[64, 65]
Obesity, diabetes, metabolic syndrome				
UCP2 knockout mice	downregulation	↑insulin secretion	Obesity	[23]
UCP2 obese mice	upregulation	β-cell dysfunction ↓insulin secretion	Diabetes	[23]
MS rat model treated with natural compounds	upregulation	↑PPAR-α ↓oxidative stress	↓dyslipidemia ↓blood pressure level ↓insulin resistance ↓obesity risk	[89, 91]

Abbreviations: MCAO=middle cerebral artery occlusion; SHRSP=stroke-prone spontaneously hypertensive rat; JD=Japanese diet; (ΔΨ)=membrane electrical potential; I/R=ischemia/reperfusion; PPAR-α=type α-peroxisome proliferator-activated receptor.

improves insulin resistance in peripheral tissues, led to an increase of UCP2 level, improved the *in vitro* motoneurons survival [52] and the outcome following cerebral ischemia [53, 54]. This evidence confirmed that PPARs play a fundamental role in modulating the beneficial effects of UCP2 [46].

The role of UCP2 has also been investigated in relation to stroke in humans. UCP2 and UCP5 expression was analyzed in brain ischemic lesions where they appeared significantly elevated as compared to the intact area. The upregulation of both UCPs was considered as an adaptive response of neuronal cells to the ischemic insult [55].

In recent years, some human studies identified different single nucleotide polymorphisms (SNPs) within *UCP2* in relation to stroke occurrence. The -866G>A (rs659366) is a functional SNP located within the promoter region of *UCP2*, probably at the level of one or more transcriptional factors binding sites [56]. The A allele variant at -866 position is associated with increased *UCP2* expression. Many studies demonstrated that the G allele is associated with lower *UCP2* expression and higher ROS accumulation [57]. This gene variant was related to an increased risk of IS in Chinese women with T2DM in a 4-year prospective study [58, 59]. In a recent study, the relationship between this SNP and the functional prognosis was investigated in patients with embolic IS after early recanalization. Patients carrying the AA genotype showed a better functional outcome compared to patients harboring the AG or GG genotypes. This result suggests that the AA genotype acts as an independent marker of favorable prognosis in IS patients after recanalization of proximal MCAO [60] (Table **2**).

3.2. UCP2 and Heart Diseases

UCP2 is constitutively expressed in the heart of humans and rodents and its expression level depends on the plasma FFA concentration. The overexpression of UCP2 by adenoviral construct in primary cultures of neonatal rat cardiomyocytes protected them from the damage related to increased oxidative stress [34]. During myocardial infarction (MI), the same detrimental processes occurring in IS, such as increased oxidative stress and cell death, are detected. Wu *et al*. demonstrated that UCP2 protects the heart from myocardial I/R injury *via* induction of mitophagy, the selective form of autophagy for mitochondria. In fact, in preconditioning myocardial I/R performed in rats, UCP2 was upregulated in association with an increase of microtubule-associated protein-light chain 3 (LC3) and a decrease of p62, two markers of autophagy, indicating a strong activation of this process. In addition, mitochondrial dysfunction and cardiomyocytes death were reduced. By contrast, the protective effect of UCP2 in cardiomyocytes was abolished by mdivi-1, a specific inhibitor of dynamin 1-like, resulting in the inhibition of mitochondrial fission-induced autophagy [61].

UCP2 expression is differently modulated in cardiac hypertrophy. In this regard, Strøm *et al*. reported that Wistar rats subjected to running on a treadmill developed physiological adaptive hypertrophy with an increase of left and right ventricular mass, as compared to sedentary rats. Furthermore, gene expression profiling analysis of total RNA from hearts revealed that UCP2 was downregulated in this experimental context since ATP demand increased during exercise. In contrast, UCP2 was upregulated in the pathological or maladaptive hypertrophy resulting from MI induced by ligating the left coronary artery [62]. This evidence suggests that the downregulation of UCP2 acts as an adaptive response in compensated hypertrophy, whereas its upregulation is associated with the detrimental effects in maladaptive hypertrophy [62, 63]. Cardiac hypertrophy may also be induced in experimental animal models by exposure to low temperatures (4°C) along with increased cellular oxidative stress, apoptosis and autophagy. In this experimental condition, UCP2 is upregulated as a likely consequence of its role in thermogenesis regulation in specific conditions [64, 65] (Table **1**).

UCP2 is also upregulated in animal models of cardiomyopathy induced by chronic β-adrenergic receptor stimulation. In fact, UCP2 upregulation may be partially reverted by β-adrenergic receptor blockade or by angiotensin converting enzyme inhibition [66, 67]. In addition, UCP2 deleted mice exposed to pulmonary arterial banding appeared significantly protected against pressure overload-induced right heart failure as compared to UCP2 wild type mice [68].

In humans, the -866 AA and GA genotypes are associated with reduced survival and higher levels of myeloperoxidase post-MI in diabetic patients [69]. This SNP is associated with coronary artery disease also in young South African Indians [70]. Of interest, the 45 bp insertion/deletion within exon 8 of *UCP2* was related to heart rate variability and high blood pressure level in Japanese men [71] (Table **2**).

3.3. UCP2 in Thermogenesis, Obesity, T2DM and Metabolic Syndrome

Soon after its discovery, UCP2 was mainly interpreted as a thermogenic protein involved in the regulation of energy expenditure and obesity [10]. In fact, FFA increases the expression of UCP2 skeletal muscle mRNA, implying that UCP2 is somehow involved in fatty acid metabolism. Later on, it was understood that, differently from UCP1, UCP2 is not normally thermogenic and can be involved in this process only under specific conditions [10, 64, 65].

Obesity and T2DM are two strictly related pathological conditions and their prevalence is increasing worldwide [72]. UCP2 is involved in the development of obesity as well as of diabetes. Zhang *et al*. demonstrated that UCP2 acts as a negative regulator of insulin secretion playing a key role in the determination of pancreatic β-cell dysfunction and consequently in the development of obesity and diabetes in experimental conditions [23] (Table **1**). Consistently, when UCP2 expression was suppressed by microRNA-15a in mouse pancreatic β-cells, an increase in insulin secretion was observed [73]. UCP2 is downregulated in the streptozotocin (STZ)-induced diabetic mouse model. This model develops cardiomyopathy, a drastic reduction of mitochondrial $\Delta\Psi$ and an increase of cell death. The overexpression of ALDH2 in STZ-induced diabetic mice exerted beneficial effects on cardiac structure and function, mitochondrial function and cell survival. UCP2 levels were preserved in STZ-ALDH2 transgenic mice as compared to STZ mice [42, 74].

The correlation between the -866G/A SNP and a greater risk of developing diabetes in the presence of obesity has been established in humans [75]. The wild-type G allele of the -866G/A SNP was associated with reduced *UCP2* mRNA expression in adipose tissue, reduced transcriptional activity *in vitro* and increased risk of obesity *in vivo*. Kempler *et al*. showed that the pancreatic transcription factor paired box protein (PAX6) preferentially binds and activates the *UCP2* promoter in the presence of the wild-type G allele in the insulinoma cells (INS1-E) derived from rat pancreatic β-cells. In the same study, the correlation between *UCP2* genotypes and the pancreatic β-cells function was analyzed in 39 non-diabetic obese patients. Subjects carrying the G allele displayed a greater disposition index, the product of insulin sensitivity (SI) and acute insulin response (AIR) to glucose, as compared to subjects carrying the A allele variant. In addition, obese subjects with and without T2DM and the different *UCP2* genotypes were compared. This analysis revealed that the G allele was associated with a twofold reduction of T2DM risk in obese subjects compared to carrier of the A allele variant. Additional case/control and meta-analysis studies confirmed the relationship between -866G/A, obesity and T2DM in several human populations such as Finnish [76], Iranian [77], Spanish [78] and Danish [79] populations. The wild type G allele within the *UCP2* promoter, although frequently encountered in obese subjects, protected them from T2DM development [80] (Table **2**). A more recent meta-analysis confirmed that -866G/A SNP is significantly associated with T2DM especially in Asian populations [81].

Yang *et al*. observed that -866G/A SNP, in association with the Trp64Arg mutation of the β3-adrenergic receptor gene, was related to the therapeutic efficacy of rosiglitazone, an anti-diabetic drug, in Chinese T2DM patients [82].

Finally, the Ala55Val SNP (rs660339), a missense variant located within the exon 4 of *UCP2* (where there is a change of C to T in the position 164 of the transcript), is commonly associated with higher risk of obesity and higher incidence of T2DM [83] (Table **2**). On the other hand, additional studies reported that this SNP was associated with an increased insulin secretion in European-American women [84] and with a reduced risk of T2DM in Asian Indians [85].

The presence of obesity at the abdominal level is one of the four conditions needed to diagnose metabolic syndrome (MS), along with high blood glucose, high serum triglycerides and low serum high-density lipoprotein (HDL) levels [86]. Patients with MS show a 2-fold higher risk of developing cardiovascular events, such as MI and IS, and of developing T2DM compared to subjects without MS [87]. In the MS rat model (Mets), UCP2 expression is increased in the liver, where it acts as an adaptive mechanism of protection toward obesity-related oxidative stress [88]. In this model, the administration of both resveratrol and quercetin leads to increased UCP2 and PPAR-α expression in the abdominal white adipose tissue, and it improves metabolic parameters such as dyslipidemia, central adiposity and insulin resistance [89]. Recently, Wei D *et al*. demonstrated that a treatment with Shexiang Baoxin Pill (SBP) (containing a mixture composed of seven raw medicinal materials including Radix ginseng and Venenum bufonis) in the MS rat model exerted a protective therapeutic effect against this disorder, probably due to the interaction of anti-inflammatory and antioxidant mechanisms which are able to improve lipid metabolism and

Table 2. Main *UCP2* SNPs and their pathological implications in human diseases.

SNP	Molecular Effects	Clinical Phenotypes	Refs.
-866G>A SNP			
A allele	⬆UCP2 ⬇ROS		[80]
G allele	⬇UCP2 ⬆ROS		[57]
GG genotype	⬆plasmatic hs-CRP	⬇T2DM in obesity	[57, 80]
GA genotype	⬆ myeloperoxidase level	CAD (reduced post-MI survival in T2DM) ⬆Obesity and metabolic abnormalities in NAFLD patients	[69, 70] [92]
AA genotype	⬆ myeloperoxidase level	Associated with better functional outcome in IS patients after recanalization of proximal MCAO CAD (reduced post-MI survival in T2DM)	[60] [69, 70]
45 bp Ins/Del			
I/I genotype		Heart rate variability ⬆blood pressure	[71]
D/D genotype	⬆adiponectin level ⬇leptin ⬇TNFα ⬇IL-6 levels after exercise training	Obesity, MS	[93]
Ala55Val SNP C>T			
C allele carriers		⬆Obesity, ⬆T2DM	[83]

Abbreviations legend: SNP=single nucleotide polymorphism; hs-CRP= high-sensitivity-CRP, CAD=coronary artery disease; T2DM=type 2 diabetes mellitus; NAFLD= non-alcoholic fatty liver disease; MS= metabolic syndrome.

protect mitochondrial function. In particular, the authors demonstrated that the expression level of UCP2 increased in several tissues of MS rats, especially in the heart, after SBP treatment. Conversely, the expression level of cytochrome b, the main subunit of mitochondrial complex III, was downregulated in the liver, heart, skeletal muscle and adipose tissue of MS rats. The expression of ATPase (mitochondrial Complex V) appeared to be upregulated after treatment with SBP for 12 weeks [90, 91] (Table **1**).

Recently, the association of some components of MS with the -866G/A SNP has been observed in patients with non-alcoholic fatty liver disease (NAFLD). In a case/control study involving 75 patients with NAFLD and 76 healthy individuals, subjects carrying the GA genotype had higher values of central obesity indices and metabolic abnormalities compared with healthy individuals [92].

The 45 bp insertion/deletion (I/D) within the 3'-untranslated region (UTR) of *UCP2* was studied in relation to some MS markers such as adiponectin, leptin, tumor necrosis factor-α (TNFα), and interleukin-6 (IL-6) levels. In a study performed in post-menopausal obese women, subjects carrying the DD genotype, but not those carrying the ID genotype, showed an increased level of adiponectin whereas leptin, TNFα, and IL-6 levels were significantly decreased after exercise training [93] (Table **2**). The mechanism underlying this phenomenon remains obscure.

4. PHARMACOLOGICAL MODULATION OF UCP2

As discussed above, UCP2 expression can be regulated at multiple levels [94]. In addition, the UCP2 biological effects are tissue specific (Fig. **1**). Any therapeutic approach targeting UCP2 should take into account the type of target tissue [17]. Much of the therapeutic potential of UCP2 depends on its antioxidant and anti-inflammatory properties [53, 54], which make UCP2 an attractive therapeutic tool in many diseases, including heart and brain diseases, and inflammatory disorders [17].

Several available drugs affect UCP2 expression levels, although we cannot precisely state if they directly target UCP2. Among them, the dipeptidyl peptidase-4 (DPP-4) inhibitors or gliptins, a class of oral anti-diabetic drugs, are able to restore endothelial function in hypertension by reducing oxidative stress [95]. In particular, chronic sitagliptin administration attenuated endothelium-dependent contraction (EDC) and reduced ROS level by the upregulation of Glucagon-like Peptide-1 (GLP-1)/5-adenosine monophosphate-activated protein kinase (AMPK)/UCP2 pathway and the downregulation of cyclooxygenase-2 (COX-2) expression in renal arteries from spontaneously hypertensive rats (SHR) and angiotensin II (Ang II)-infused mouse aorta. Conversely, sitagliptin did not affect EDC in Ang II-infused UCP2-KO mice. In addition, the beneficial effects of sitagliptin on endothelial function were inhibited by genipin, a UCP2 inhibitor, in renal arteries of SHR, confirming the relevance of UCP2 in this context.

Consistently, UCP2 overexpression, obtained by an adenoviral construct, improved the vascular function in the same experimental rat model. The administration of exendin-4 (Ex-4), a GPL-1 agonist, also improved renal vascular function in renal arteries of both SHR and hypertensive patients through UCP2 level increase with a parallel decrease of COX2 and ROS levels [96, 97].

Other anti-diabetic molecules, such as metformin and berberine, modulate UCP2 level. Metformin, the most common anti-diabetic drug, acts by AMPK upregulation. In fact, AMPK inhibition by compound C prevented the UCP2 increase [98]. Berberine, an isoquinolone alkaloid extracted from plants and used in traditional Chinese medicine, shows anti-diabetic and anti-atherogenic properties, improves dyslipidemia and endothelial function, and reduces the incidence of cardiovascular diseases. Berberine significantly increases UCP2 mRNA and protein level in an AMPK-dependent manner both *in vitro* and in a mouse model of atherosclerosis [99].

Previous studies have shown that PPAR agonists are able to modulate the UCP2 expression level. These drugs are a group of structurally diverse compounds that bind and activate PPAR receptors. Some of them, the thiazolidinediones (TZD), also known as glitazones, are potent PPAR-γ agonists [100], commonly used in the clinical practice for the treatment of diabetes and MS with beneficial effects. These drugs cause a marked reduction of FFA plasmatic level and inhibit lipolysis in T2DM patients. Plasmatic FFA reduction, in turn, leads to fat mobilization from the muscle and the liver and improves insulin sensitivity in these organs [101]. Glitazones also contribute to lower blood pressure level and improve lipid metabolism by increasing HDL cholesterol level and by reducing triglycerides level [102, 103]. Several studies revealed that the TZD administration, mainly rosiglitazone, induced a rapid increase of UCP2 both in mouse and human adipocyte cell lines [104, 105] as compared to control cells. Its effect appeared to be mediated by PPAR-γ [104, 106]. In addition, administration of rosiglitazone in Sprague-Dawley rats reduced mitochondrial hydrogen peroxide level in rostral ventrolateral medulla, a region that contains the sympathetic premotor neurons for the maintenance of vasomotor tone and of systemic arterial pressure. Rosiglitazone can exert a protective effect against oxidative stress-associated neurogenic hypertension through UCP2 upregulation and ROS reduction [107].

Additional pre-clinical and *in vitro* studies analyzed the effect of pioglitazone, a well-known PPAR-γ agonist, toward oxidative stress in the rat brain [97]. It was demonstrated that this drug, through PPAR-γ activation and UCP2 upregulation, attenuated oxidative stress in cerebral arteries of aging rats. They also showed that one-month oral administration of pioglitazone improved endothelium-dependent relaxation by increasing both eNOS phosphorylation and nitric oxide (NO) availability. PPAR-γ appears as a promising target for the treatment of diabetes and age-related cerebrovascular dysfunction.

No side effects dependent on UCP2 upregulation have been so far reported with the available compounds, although it is known that NO, a mediator of UCP2, may contribute to exacerbate neuronal cell dysfunction and diminish cell survival after brain injury [108]. Exaggerate NO production is also associated with acute pancreatitis in rats [109] and liver damage in mice [110].

Interestingly, some chemotherapeutic drugs, such as doxorubicin (DOX) and taxol, used for the treatment of different types of cancers, downregulate UCP2 expression by activation of c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinase (MAPK)/extracellular-signal-regulated kinase (ERK) signaling, with consequent ROS accumulation and increase of apoptosis in melanoma cells [111]. UCP2 downregulation and consequent ROS accumulation have also been associated with severe cardiotoxicity in both animal models and cardiomyocytes treated with DOX. Interestingly, administration of melatonin counteracted the cardiac toxic effects of DOX by improvement of mitochondrial damage and upregulation of UCP2 [112].

Apart from the above mentioned drugs, UCP2 expression can be modulated by nutraceuticals as documented in the SHRSP model [13, 37] and in humans [13]. Pagliaro *et al*. described the beneficial effects exerted in the cardiovascular system by different natural compounds such as BO, curcumin, resveratrol and berberine. These natural compounds of plant origin, through the activation of both AMPK and silent mating type information regulation-1 (SIRT-1), upregulate PPARs (mainly PPAR-α and PPAR-γ) leading to UCP2 increase, reduction of ROS level and of inflammation, improvement of brain ischemic injury and decrease of stroke occurrence [113]. The beneficial effects of BO in humans were tested in a small clinical trial in which broccoli extract pills and fresh broccoli were administered simultaneously for 7 days to healthy subjects. At the end of the study, a significant reduction of both total and LDL cholesterol, along with a decrease of urinary 8-isoprostanes and other markers of oxidative stress, was observed [114]. The administration of broccoli juice for 12 weeks in 32 men with hypercholesterolemia significantly reduced plasma LDL cholesterol and increased both HDL cholesterol and GPx activity, thus lowering cardiovascular disease risk [115]. Interestingly, treatment with resveratrol, known for its beneficial effects on diabetes progression, oxidative stress and lipid metabolism, exerts a protective effect towards diabetic cardiomyopathy induced by STZ in a UCP2 dependent manner [116]. In fact, resveratrol administration significantly increased UCP2 expression, reduced ROS level and increased the manganese superoxide dismutase level. Conversely, UCP2 inhibition by siRNA hinders the cardioprotective effects of resveratrol on ROS production and apoptosis level in high glucose-treated cardiomyocytes [117].

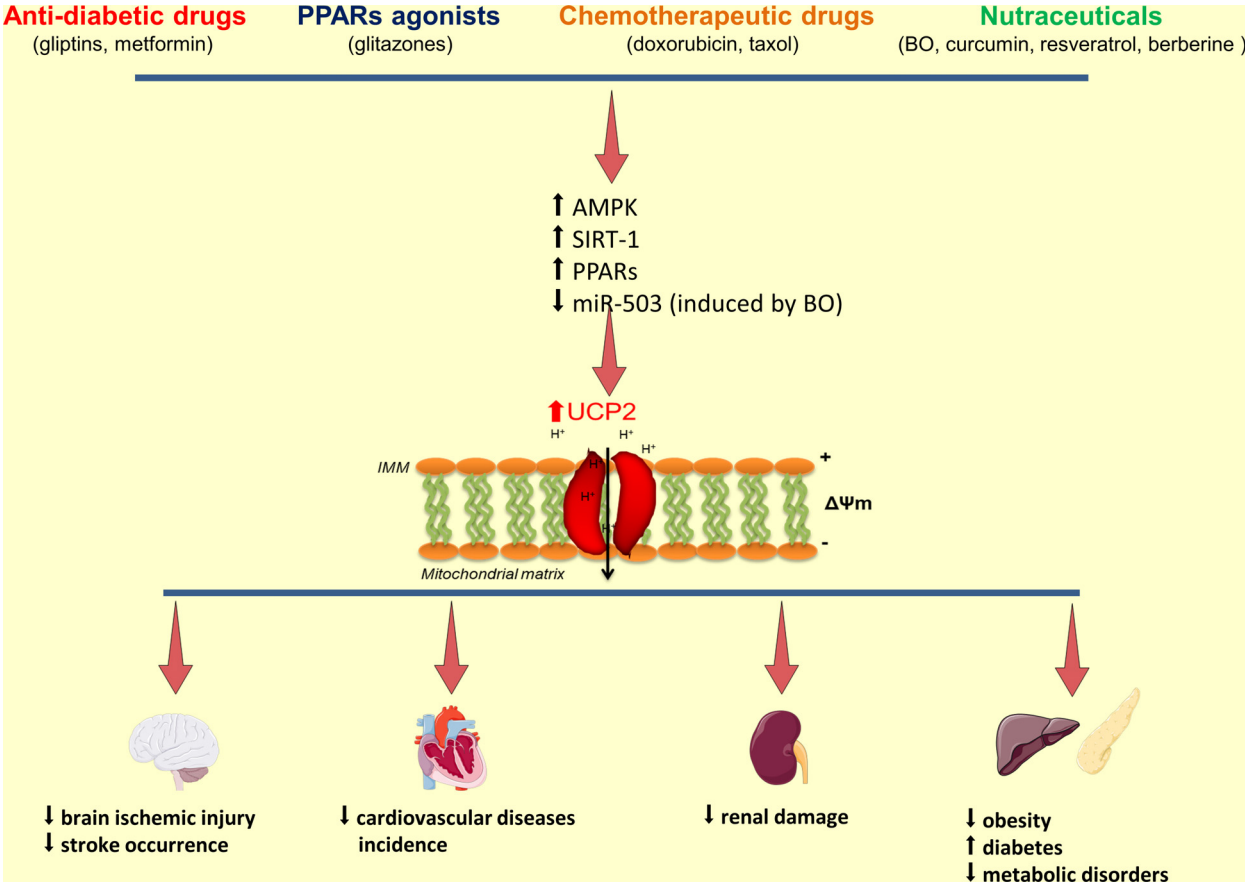

Fig. (2). UCP2 gene/protein expression modulation in relation to cardiovascular and metabolic diseases. Schematic representation of the modulation of UCP2 gene and protein expression by known agents. Both nutraceuticals and drugs can upregulate UCP2 level mainly through the AMPK/SIRT-1/PPARs pathway. Of interest, the epigenetic regulation can also be involved, as shown upon BO extract administration (see text). Increased UCP2 levels induce membrane mitochondrial depolarization, decreased ROS production, reduced cell death and inflammatory responses. Consequently, the occurrence of cardiovascular and metabolic diseases is significantly affected. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CONCLUSION

The physiological role of UCP2 appears complex and it still needs to be fully dissected out. UCP2 expression and functions are tissue specific. Most of the beneficial properties of UCP2 depend on its role as ROS scavenger. UCP2 is also involved in the regulation of ΔΨ, ATP synthesis, calcium level and cell death.

UCP2 upregulation attenuates mitochondrial ROS production, consequently the cellular oxidative damage, and exerts protective effects in several organs. On the other hand, UCP2 inhibition protects from hyperglycemia and diabetes through the control of insulin secretion in the pancreatic β-cells.

Therefore, UCP2 behaves as a critical determinant of many human disorders such as atherosclerosis, ischemic heart disease, neurodegenerative diseases, including IS, and diabetes. Current evidence suggests that UCP2 modulation may represent a suitable tool for the treatment of several human diseases (Fig. **2**).

Further experimental studies will allow improving our understanding of the molecular pathways involved in UCP2 activation. Human studies may reveal important new insights on the pathogenic role of UCP2 gene variants. The new knowledge could facilitate the identification of novel pharmacological strategies that, by controlling the expression of UCP2, can reduce the occurrence and progression of diseases in which UCP2 plays a fundamental role. In this latter regard, additional investigations are necessary to identify the exact relationship between molecular mechanisms, cellular effects and clinical consequences, along with potential caveats, upon pharmacological stimulation of UCP2.

AUTHORS' CONTRIBUTIONS

Conceptualization: [RS, SR]; Writing- original draft preparation: [RS]; Writing - review and editing: [RS, MF, SR]; Literature search: [RS, MC, FB, SM]; Critical revision: [CB, FF, SR]. All authors read and approved the final version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by a grant from the Italian Ministry of Health.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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