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A review study on Uncoupling Proteins UCP2 and UCP3 and their potential role to disorders

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Abstract

UCP2 and UCP3 (uncoupling proteins 2 and 3) are mitochondrial proteins; have been identified as homologues to uncoupling protein 1 that may control the energy lavishing in the synthesis of ATP. The UCP2 has been expressed widely in the different organs of body; respect to it, the UCP3 has been expressed only in muscles attached to skeleton and very less in BAT. They are important in diminishing the production of mitochondria in ROS, insulin regulation, indeed thermogenesis and obesity. Uncoupling proteins 2 and 3 may not effectuate the thermogenesis of whole body in mammals; in place they have variety of physiological role in the adjustment of fatty acid redox capacity in fasting and starving, protection from imbalance of free radicals and other harmful effects inside the body through neutralization. Although many scholars have devoted their efforts to demonstrate the mechanism of UCP2 and UCP3, little information is available about their physiological role. The possible data acquired about UCP2 and UCP3 is comprised in present review.

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Introduction

Energy is the basic requirement of cells for several life processes, and inside the cell mitochondria are the major cite of energy. The production of mitochondria, adenosine triphosphate (ATP) is perceived by the association of redox reaction and addition of one phosphate of adenosine diphosphate (ADP), process termed as phosphorylation. Although these reactions have not been observed as coupled processes, because of transporter family present inside the mitochondria. This transporter's family is renowned as the uncoupling proteins UCPs (Nicholls and Rial, 1984).

The uncoupling proteins (UCPs) are the members concern to the carrier proteins family; which is commonly found in theinterior membranes of mitochondria (Fisler *et al.,* 2006). UCPs have been classified into six distinct groups (UCP1, UCP2, UCP3, UCP4, BMCP1/UCP5 and plant UCP). Their presence in different animal species has been summarized in table 1 (Ledesma *et al.,* 2002). These proteins take account of energy transfer and have been reported in varied species of animals and plants, according to physiological evidences UCPs are also found on fungi and protozoa (Jarmuszkiewicz *et al.*, 1999). UCP1 was revealed in 1978 (Nicholls *et al.,* 1978) and molecularly cloned in 1988 (Bouillaud *et al.,* 1988). In 1997, the uncoupling protein 2 had been cloned (Fleury *et al.,* 1997; Gimeno *et al.,* 1997), afterwards uncoupling protein 3 had been cloned (Boss *et al.,* 1997; Vidal-Puig *et al.,* 1997; Gong *et al.,* 1997). According to Krauss, there are five homologues of uncoupling proteins, (UCP1–UCP5) expressed in mammals (Krauss *et al.,* 2005). UCP2 and UCP3 are closely twin to one another on the basis of amino acid sequence (Krauss *et al.,* 2005) and both possess resembling sequence with UCP1 (Azzu *et al.,* 2010), the reason they are said to be the homologous to UCP1, while UCP4 and UCP5 have different sequence as compared to uncoupling proteins (UCP1, UCP2 and UCP3).

The objective of this partial review is to compile all the available information about the structure, expression and functions of UCP2 and UCP3 and their possibly found role to disorders in human.

***Table 1.** Shows the presence of UCPs in different animal species.

Group	Protein	Species	Common name	Accession number
UCP1	*Bt*UCP1	*Bos taurus*	Cow	P10861
	*Cf*UCP1	*Canis familiaris*	Dog	Q9GMZ1
	*Hs*UCP1	*Homo sapiens*	Human	P25874
	*Rm*UCP1	*Macaca mulatta*	Rhesus macaque	Q9N1E0
	*Ma*UCP1	*Mesocricetus auratus*	Syrian hamster	P04575
	*Mm*UCP1	*Mus musculus*	Mouse	P12242
	*Oc*UCP1	*Oryctolagus cuniculus*	Rabbit	P14271
	*Ps*UCP1	*Phodopus sungorus*	Siberian hamster	Q9ER18
	*Rn*UCP1	*Rattus norvegicus*	Rat	P04633
UCP2	*Bt*UCP2	*Bos taurus*	Cow	Q9XSE1
	*Br*UCP2	*Brachydanio rerio*	Zebrafish	Q9W720
	*Cf*UCP2	*Canis familiaris*	Dog	Q9N2J1
	*Cc*UCP2	*Cyprinus carpio*	Common carp	Q9W725
	*Hs*UCP2	*Homo sapiens*	Human	P55851
	*Rm*UCP2	*Macaca mulatta*	Rhesus macaque	AF202130
	*Mm*UCP2	*Mus musculus*	Mouse	P70406
	*Ps*UCP2	*Phodopus sungorus*	Siberian hamster	Q9ER17
	*Rn*UCP2	*Rattus norvegicus*	Rat	P56500
	*Ss*UCP2	*Sus scrofa*	Pig	O97562
UCP3	*Bt*UCP3	*Bos taurus*	Cow	O77792
	*Cf*UCP3	*Canis familiaris*	Dog	Q9N2I9
	*Em*UCP3	*Eupetomena macroura*	Hummingbird	Q98T90
	*Gg*UCP3	*Gallus gallus*	Chicken	Q9DDT7
	*Hs*UCP3	*Homo sapiens*	Human	P55916
	*Mm*UCP3	*Macaca mulatta*	Rhesus macaque	Q9N1D8
	*Mg*UCP3	*Meleagris gallopavo*	Common turkey	Q90X50
	*Mm*UCP3	*Mus musculus*	Mouse	P56501
	*Ps*UCP3	*Phodopus sungorus*	Siberianhamster	Q9ER16

Group	Protein	Species	Common name	Accession number
	*Rn*UCP3	*Rattus norvegicus*	Rat	P56499
	*Ss*UCP3	*Sus scrofa*	Pig	O97649
UCP4	*Hs*UCP4	*Homo sapiens*	Human	O95847
	*Rn*UCP4	*Rattus norvegicus*	Rat	Q9EPH6
BMCP1	*Hs*BMCP1	*Homo sapiens*	Human	O95258
	MmBMCP1	*Mus musculus*	Mouse	Q9Z2B2
	RnBMCP1	*Rattus norvegicus*	Rat	Q9JMH0
Plant UCP	*At*UCP1	*Arabidopsis thaliana*	Mouse-ear cress	O65623
	*At*UCP2	*Arabidopsis thaliana*	Mouse-ear cress	Q9ZWG1
	*Le*UCP	*Lycopersicom esculentum*	Tomato	AF472619
	*Os*UCP1	*Oryza sativa*	Rice	Q9AVG2
	*Os*UCP2	*Oryza sativa*	Rice	Q9AVG1
	*St*UCP	*Solanum tuberosum*	Potato	O24391
	*Sr*UCP	*Symploca rpusrenifolius*	Cabbage	Q9MBE7
	*Ta*UCP	*Triticum aestivum*	Wheat	Q9FXQ5
	*Zm*UCP	*Zea mays*	Maize	AF461732

*Table 1. has been adopted from (Ledesma *et al.,* 2002). https://doi.org/10.1186/gb-2002-3-12-reviews3015.

Structural features of UCPs

The uncoupling proteins are intrinsic mitochondrial proteins having molecular mass around to 31kDa-34kDa. The mass of brain mitochondrial carrier protein 1 (BMCP1) and uncoupling proteins 4(UCP4) is 3638 kDa, considered as the larger proteins. Uncoupling proteins are considered as the basic proteins having isoelectric points around them. Their structure is a tripartite; having two hydrophobic parts exact to trans-membrane α-helices in each repeat. The lipid bilayer is crossed six times by polypeptide chain, and the amino carboxyl terminals extend beyond the inner membrane space of mitochondria (Fig. 1). (Azzu *et al.,* 2010). In each repeat the two helices are linked through a hydrophilic hoop and are deployed on matrix of the protein. Two similar subunits materialize the functional unit that is a dimer. For other carrier proteins it has been revealed that functionally capable unit is offered by two monomers are linked covalently in tandem (Freake and Hedley, 1998).

The amino terminal cleavable sequence has not been found in UCPs to fuse into mitochondria. The targeting signal in UCP1 is positive charge of first matrix loop and is collaborated with a receptor protein (hTom20) lies on the outer mitochondrial complex. There are two other binding sites of UCP1 for hTom20, in tripartite structure the second domain and central matrix loop, although second matrix is difficult to target and insert into the inner membrane.

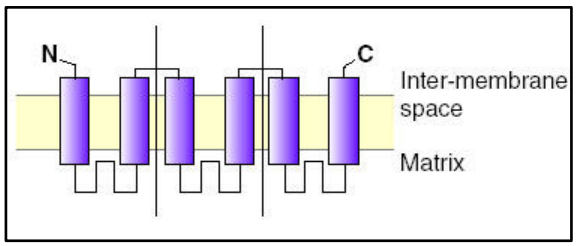

Fig.1. Tripartite structure of uncoupling proteins (Ledesma*et al.*, 2002).

Uncoupling proteins 2&3

Uncoupling proteins 2 & 3 are the resembling proteins to UCP1 according to amino acid sequence. By sequencing, UCP2 and UCP3 are 59% and 57% identical with UCP1 respectively and both are 73% homogenous to one another (Table 2). With respect to other carrier proteins; sequence identity of UCP2 and UCP3 is much different (Borecký *et al.,* 2001). As being the homologous of UCP1, UCP2 and UCP3 express resembling biochemical properties; they should be responsible in proton leak and regulation through purine nucleotides and fatty acids (Krauss *et al.,* 2005).

Table 2. Shows the comparison of the sequence identity of the uncoupling proteins.

Proteins^	Accession Number	%* Identity	Residues of Overlap
UCP1	P25874	100%	307
UCP2	P55851	59%	300
UCP3	P55916	57%	311
UCP4	O95847	30%	294
BMCP1 (UCP5)	O95258	33%	282

Proteins^ belong to human. %* amino acid identity had been identified by local similarity program SIM. (Krausss *et al.,* 2005).

Observed expression of UCP2 and UCP3

UCP2 has been widely expressed in mammalians, mainly notified in central nervous system, intestine, lungs, spleen, kidney, uterus and immune cells (Pecqueur *et al.,* 2001). It's wide expression had let it to involve in vital life processes mainly directive for the products of reactive oxygen species ROS (Andrews *et al.,* 2008), mechanism of feeding (Andrews *et al.,* 2008), insulin regulation (Azzu *et al.,* 2008), immune system and several diseases; i.e. atherosclerosis (Brand *et al.,* 2005), cancer (Derdak *et al.,* 2008), diabetes mellitus (Azzu *et al.,* 2008; Affourtit *et al.,* 2008) and the injury in neurons (Clapham *et al.,* 2000). UCP3 has been expressed only in the muscles attached to skeleton and very little in heart and BAT (Fig. 2.) (Ricquier *et al.,* 2000). Skeletal muscle is the principal mass of the body and it contributes vital role in thermogenesis and metabolic rate (Clapham *et al.,* 2000). The presence of UCP3 in skeletal muscles; make it the only responsible candidate for thermogenesis. The UCP3 is highly modulated in skeletal muscles during fasting and starving when the energy conservation is highly required for metabolism (Affourtit *et al.,* 2008).

The uncoupling proteins are suggested to be the power reducing device in ROS production (Affourtit *et al.,* 2008) mainly in FA oxidation. UCP3 has a great role of exporting mechanism in FA oxidation (Ricquier *et al.,* 2000), taking out of lipid hydro peroxides (Ricquier *et al.,* 2000).

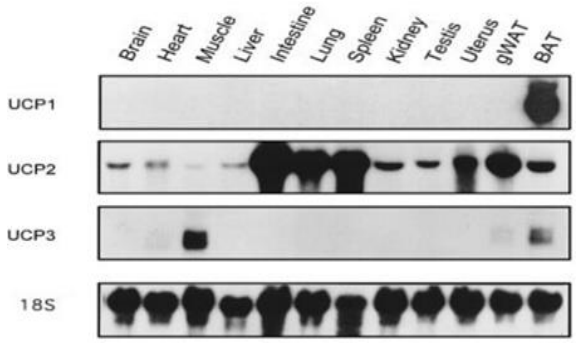

Fig. 2. Expression of different uncoupling mRNAs in mouse tissues has been spotted in this Fig. 20µg of RNA from each tissue and 10µg from BAT had been loaded. 18S RNA had been loaded for control (Ricquier *et al.,* 2000).

Potential role of UCP2 and UCP3 in human disease

UCP2 and the levels of oxygen

In resting condition, very less energy is utilized and ADP for phosphorylating respiration is also decreased. This condition may increase the oxygen and itsreluctant inside the cell (Nilsson *et al.,* 1996). The formation of ROS (reactive oxygen species) is supported by this condition; for instance inside the cell oxidative compensation is caused by superoxide anion, hydrogen peroxide and hydroxyl radicals. Due to lack of ADP, phosphorylating respiration fails to maintain the low levels of oxygen and reactive oxygen species then non phosphorylating respiration is responsible (Nilsson *et al.,* 1996). Inhibitor GDP from non-parenchymal cells of liver or from brown adipose tissues with the combination of UCP1, express the UCP2 mRNA to mitochondrial fraction, which raise the H_2O_2 products and membrane potential of mitochondria . UCP2 is very less in hepatocytes of mitochondria; make GDP ineffective (Nègre-Salvayre *et al.,* 1997). Inhibited UCP2 activity by GDP is responsible for the initiative of several cell processes; i.e. apoptosis or inflammation, oxidative damage (Nègre-Salvayre *et al.,* 1997).

UCP2 and insulin secretion

Mitochondria are required to insulin secretion for the maintenance of glucose level (Soejima *et al.,* 1996), are responsible candidate to increase the ratio of ATP/ADP within the cell (Nilsson *et al.,* 1996). The expression of UCP2 has been found in the pancreatic islets (Zhou *et al.,* 1997), ATP level and insulin secretion for the glucose induction might be decreased. Insulin response to glucose has been decreased by leptin (Koyama *et al.,* 1997), has been found to increase the expression of UCP2 mRNA in the pancreatic islets (Zhou *et al.,* 1997). It has been observed that an increased level of UCP2 can decrease the insulin secretion. Disturbance of insulin secretion are habitually coupled with hyperlipidemia and extended triglyceride substance in pancreatic islets of obese diabetic rodents (Zhou *et al.,* 1997), (Shimabukuro *et al.,* 1997). It can be hypothesized that expression of UCP2 has been enhanced by the increased levels of free fatty acids in pancreatic islet cells, and in results insulin secretion has been

impaired (Boss *et al.,* 1998). Peroxisome proliferators-activated receptor gamma (PPAR-γ or PPARG) is responsible to mediate the effects of free fatty acids on the expression of UCP2 since the increased level of UCP2 mRNA has been shown by troglitazone proliferators-activated receptor (Shimabukuro *et al.,* 1997).

UCP2 and UCP3 are the candidate genes for weight regulation

It has been hypothesized that uncoupling protein 2 and 3 are the responsible genes to be involved in energy indulgence and weight regulation. They possess a vital role in the progress of obesity and diabetes mellitus by certain mutations in their genetic sequences. Bouchard reported a suggestive association between markers of the edges in the environs of the UCP2 as well metabolic rate during resting condition in the population of Canada (Bouchard *et al.*, 1997), while no important linkage had been found with BMI or obesity in type 2 diabetic patients of Northern European (Elbein *et al.,* 1997). UCP2 shows A/V55 (a very common amino acid polymorphism), had not used in pathologic process for obesity or insulin in Danish heritage (Urhammer *et al.,* 1997). The UCP2 and UCP3 have been observed on same region, 11q13 between the D11S916 and D11S911 or D11S3966 (Solanes *et al.,* 1997; Boss *et al.,* 1998; Gong *et al.,* 1997). It has been observed the complete linkage among noted markers and resting metabolic rate might be because of certain mutation in the UCP2, UCP3 and their surrounding area (Bouchard *et al.*, 1997). The gratitude of polymorphic sequencing discussion may lead to very determinant linkage and certain functional role. During feeding and food consumption, expression of UCP3 in the skeletal muscles may avert the productivity of food and be responsible in lose weight and avoid regaining it. This maintenance therefore stops the brutal cycle, termed as phenomenon of 'yo-yo' (Boss *et al.,* 1998). Thus, uncoupling proteins 2 and 3 have been considered as the responsible genes for obesity in human.

Conclusion

Many scientists have devoted their research on uncoupling proteins, from their studies it is concluded that UCP2 and UCP3 are the homologues of UCP1, involved in uncoupling of ATP and ADP produced by mitochondrial respiration, consumption of energy as heat and affecting the energy metabolism efficiency.

Expression of UCP2 is extensively in various tissues, including white adipose tissues, uterus, immune system cells and others, has been reported as the candidate to effect the ROS production, regulate the ATP ratio and insulin secretion from pancreatic cells. Contrary UCP3 is expressed strictly to the skeletal muscles and is responsible for energy metabolism during fasting and starving. Moreover both UCP2 and UCP3 have been suggested to regulate the energy metabolism, insulin secretion and weight regulation; thus UCP2 and UCP3 are the target research for pharmetics to cure the obesity and diabetes.

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