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Mitochondrial uncoupling protein 2 in the central nervous system: neuromodulator and neuroprotector

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Abstract

Uncoupling proteins (UCPs) are localized in the inner membrane of the mitochondria in diverse tissues and decrease mitochondrial membrane potential. The first of these proteins, UCP1, was discovered in brown adipose tissue, where it has a well-described role in thermogenesis. The functional significance of other UCPs, including UCP2, is less well understood. Here we summarize the recent advancements on the role of UCP2 in the brain and portray this uncoupler as an important player in normal neuronal function as well as a key cell death-suppressing device. These previously unknown functions of UCPs offer new avenues not only for the better understanding of these proteins but also for the furthering of our knowledge on the central nervous system in healthy and disease states.

Keywords: Central nervous system; Neurons; Mitochondria; Uncoupling proteins; Neurotransmission; Neurodegeneration

1. UCPs

UCPs encoded by nuclear DNA are located in the inner membrane of the mitochondria, and their primary function is thought to be to leak hydrogen protons from the intermembrane space to the matrix of the mitochondria [1–6]. In the individual mitochondrion, these proteins, through this process (see Fig. 1), may deprive the driving force of ATP synthase from catalyzing ATP synthesis, dissipate energy in the form of heat, diminish the production of superoxides, and decrease the likelihood of calcium entry to the mitochondrial matrix [7–12]. UCP1, the most well-characterized UCP, is expressed solely in brown adipose tissue and is responsible for thermogenesis in small rodents [1,9]. Because brown adipose tissue is virtually insignificant for the normal primate, including human physiology, little attention has been paid until recently to this mechanism with regard to other tissues. In the last few years, however, several other members of the UCP family have been discovered and found to promote partial uncoupling of oxidation from phosphorylation *in vitro*. These proteins include UCP2, UCP3, UCP4, and BMCP1 [2–6]. The five putative UCPs differ greatly in tissue distribution and regulation and may have distinct physiological roles. While UCP1 and UCP3 are expressed only in peripheral tissues (UCP1 only in brown adipose tissue and UCP3 solely in skeletal muscle and the heart in humans) and UCP4 and BMCP1 are predominantly expressed in the central nervous system [5,6], UCP2 is expressed in muscle, adipose tissue, spleen, and the central nervous system [2,13–15]. It is of significance to note, however, that UCP4 and BMCP1 have only 30% similarity to UCP1 in amino acid sequence [5,6]. In addition, these proteins were not proven to be mitochondrial uncouplers either *in vivo* or *in vitro* in knockout animals. Because artificial insertion of proteins into the inner mitochondrial membrane can elevate uncoupling even though the protein is *ab ovo* a mitochondrial uncoupler [16], the question as to whether UCP4 and BMCP1 are natural mitochondrial UCPs remains to be proven.

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Abbreviations: BMCP1, brain mitochondrial carrier protein 1; UCP, uncoupling protein.

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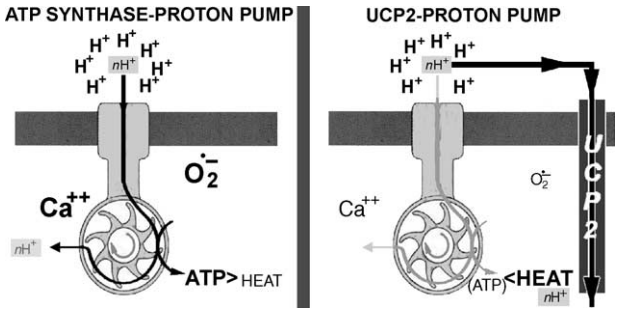

Fig. 1. Schematic illustration of functioning ATP synthase on the left and the potential effects of UCP2 on the right. The proton gradient drives ATP synthase and the production of ATP. If that proton gradient is decreased due to the activity of UCP2, ATP production is decreased, energy is dissipated in the form of heat (thermogenesis), superoxide ($O_2^{\cdot-}$) production is decreased, and calcium efflux is increased. However, despite decreased ATP production by individual mitochondria, overall the neurons will have more ATP available, because uncoupling supports mitochondrial proliferation.

2. UCP2 in the brain

In the brain, UCP2 is expressed predominantly in neuronal populations of subcortical regions that are involved in the central regulation of autonomic, endocrine, and metabolic processes [13–15]. While UCP2 mRNA was found to be absent from the human brain, it was detected at low levels in the mouse central nervous system [2]. In that study by Fleury *et al.* [2], human brain samples were analyzed from commercially available tissue blots, raising the possibility that sampling error, together with a site-specific expression of UCP2, may have contributed to the negative results. To test for the cross-species existence of UCP2 and to reveal whether UCP2 mRNA actually underlies the production of UCP2 in the central nervous system, we carried out several experiments [14,15].

We demonstrated that brain UCP2 is present in the inner membranes of mitochondria in neuronal profiles of brain regions that are known to regulate autonomic, metabolic, and endocrine processes in both rodents and primates [14,15]. These regions included key brain stem and hypothalamic nuclei. We then hypothesized that if UCP2 in neuronal circuits is a functional uncoupler in a manner similar to what was found in a yeast model [2], the proton leak of mitochondria in UCP2-containing brain regions should be increased. Indeed, we found that the mitochondrial respiratory control ratio (RCR) in rat extracts from regions with abundant UCP2 expression (hypothalamus) was significantly higher than that measured in regions that lack UCP2 expression (the striatum-lateral thalamus region). The presence of decreased mitochondrial energy coupling efficiency (increased proton leak) in UCP2-containing brain regions supported our hypothesis that a thermogenic mechanism is intrinsic to distinct neuronal pathways. To test this further, brain tissue temperature in the face of steady core body temperature was determined at several dorso-ventral and medio-lateral locations in rats, and it was found that UCP2-containing brain regions have a significantly higher local temperature when compared to other sites or to the core body temperature. The observation of a dorso-ventral temperature gradient was not novel. However, our studies showed for the first time that this increasing dorso-ventral temperature gradient does not follow a linear pattern and that the interruption of the linear pattern coincides with the appearance of UCP2 mRNA and protein in the lower diencephalon [14]. These studies also showed that brain sites other than those containing UCP2, such as the striatum and thalamus, exhibit a significant mitochondrial proton leak, which is consistent with the subsequent discovery of other putative brain uncouplers, UCP4 and BMCP1 [5,6].

3. Effect of UCPs on neuronal function

Regardless of the type of mitochondrial uncoupler present in neurons, the fact that neuronal mitochondria can be uncoupled by these proteins raised several intriguing possibilities regarding their impact on the central nervous system (Fig. 1).

3.1. Thermogenesis

In relation to neuronal functions, one of the most exciting and provocative aspects of controlled mitochondrial uncoupling by UCPs is the potential to affect the temperature in the microenvironment of presynaptic terminals, and hence to provide a basis for temperature as a neuromodulator [14]. There has been a great debate regarding the thermogenic capacity of UCPs other than that of UCP1. However, this debate is focusing on thermogenesis as it pertains to core body temperature rather then energy dissipation in the form of heat at the mitochondrial level. The distinction between these is critical. For example, the failure to do that led to the false conclusion that UCP2 and 3 are not thermogenic, because UCP2 and 3 do not appear to contribute to the generation of core body temperature [8,12]. When we propose thermogenic functions to UCP2 in the brain (let it be a mandatory by-product of their other functions such as antioxidants, see below), we simply address it in relation to the microenvironment of synapses and not to core body temperature. Thereby, when we consider that (a) UCPs are expressed in neuronal mitochondria, frequently accumulated in axon terminals in close proximity to synaptic vesicles and synaptic membranes, and (b) activation of UCPs leads to heat generation, it is only reasonable to conclude that this change in presynaptic temperature will have an impact on synaptic transmission as temperature affects all biological mechanisms. The regional and temporal specificity of this mechanism may be determined by the selective brain distribution of different UCPs and their availability for activating substances such as circulating free fatty acids and cofactors such as coenzyme Q.

3.2. ATP

UCPs dissociate oxidation from phosphorylation and dissipate energy in the form of heat. By this, UCPs will decrease mitochondrial ATP production. The outcome of this will clearly affect cellular activity. Indeed, observations on *UCP2* knockout animals revealed increased pancreatic ATP and ADP levels, which were temporarily associated with increased insulin secretion by pancreatic β cells [12]. Intriguingly, however, in the brain (our unpublished observation) as well as in the muscle [17], induction of neuronal mitochondrial uncoupling by UCP2 and UCP3, respectively, elevated levels of ATP and ADP. It is also likely that, in these areas, increased mitochondrial uncoupling suppresses ATP production per the mitochondria. But, in the brain (our unpublished observation) as well in adipose tissue [18], UCPs induce mitochondrial proliferation, which, in turn, will provide higher levels of ATP and ADP for a given cell. That UCPs could participate in mitochondriogenesis was already eluded to when a cold-activated transcriptional factor, PGC-1, was studied [19]. Whether UCPs are downstream or upstream in PGC-1-induced mitochondrial proliferation needs to be resolved.

3.3. Calcium

The mitochondrion is a major site of calcium storage in cells. Calcium influx or efflux in the mitochondria is dependent upon the inner mitochondrial membrane potential [11,20–22]. A significant drop in mitochondrial membrane potential underlies the release of calcium from the mitochondria, while elevation of membrane potential enhances influx. Because UCP2 regulates mitochondrial membrane potential, it is then reasonable to suggest that it will have an influence on establishing the set point for calcium transport. If activation of UCP2 causes not only the membrane potential to drop significantly, but also thermogenic uncoupling, calcium would also be released from the mitochondria. This, in turn, could enhance calcium-dependent presynaptic mechanisms. In addition, in the case of glutamate excitotoxicity, when there is a rapid elevation of cytosolic calcium due to the opening of ionotropic glutamate receptors at the perikaryal membrane, UCP2-induced lowering of mitochondrial membrane potential could limit the overloading of mitochondria with calcium, and hence decrease the potential for apoptotic events.

3.4. Superoxide

One of the functions of mitochondrial UCPs is their ability to reduce free radical production [7,8]. In *UCP2* knockout animals, increased free radical production by monocytes has been attributed to strengthening the innate immune system and preventing *Toxoplasma gondii*-induced lethality [8]. On the other hand, in UCP2 overexpressing animals, lipid peroxidation (a consequence of free radical action) is suppressed in the brain (our unpublished observation). Intriguingly, superoxides themselves have been shown to induce the expression of UCPs, including UCP2 [23], and to participate in the induction of proton transport by UCP1-3 [24,25]. This aspect of UCP function further strengthens the proposition that UCPs act, at least in part, as antioxidants, and, thus, may participate in neuroprotection.

In relation to brain functions, the effect of UCP2 will probably involve all of the aforementioned possibilities, but most likely to a various extent. For example, during degenerative processes, if UCP2 was expressed prior to the initiation of cellular stress (which can be achieved either in transgenic animals or by repetitive small subclinical stressors before a large insult), it is likely that increased mitochondria and ATP levels together with decreased free radical production will diminish neuronal loss. Regarding neurodegeneration (and any cellular degeneration in the periphery as well), it is very likely that functioning UCP2 provides preconditioning for cells to better withstand stress. In support of that, we found an inverse relationship between UCP2 expression levels and activation of an apoptotic signal, caspase-3, during acute brain injury [26]. Because most of the neurodegenerative disorders involve free radical production, it is very reasonable to propose that UCP2 induction will be part of the etiology of all of these disorders, including epilepsy, Parkinson's disease, Alzheimer's disease, as well as hypoxia and stroke. Thus, it is likely that if UCP2 activity can be enhanced in the initial phase of these disorders, neuronal loss could be diminished. In a similar vein, if UCP2 is active during critical developmental periods, its activity level may determine the adult cell number in different tissue types. In addition, the ability of developing neurons to respond to different stimuli may also be regulated by UCP2 via regulation of ATP, calcium homeostasis, and mitochondrial metabolism in general.

Because UCP2 is constitutively expressed in certain brain areas even when neurodegeneration is not eminent, such as the spinal cord and basal brain structures [13–15,27], it is anticipated that this mitochondrial uncoupler plays a role in normal neuronal functions as well. For example, we found that animals that express different levels of UCP2 respond to sensory cues differently: using *UCP2* overexpressing and knockout animals, we observed a negative correlation in ethanol-sensitized mice between *UCP2* expression level and the time spent on the hot plate, suggesting that UCP2 lowers the threshold for pain sensation [28]. Pain and temperature perception are mediated by primary sensory afferents of the spinal cord that express UCP2 [27]; thus it may be that neurotransmission within these pathways is affected by UCP2 via the mechanisms described above (temperature, ATP, and calcium homeostasis).

4. Regulation of UCP2

To date, limited information is available on the regulation of UCP2 mRNA expression and translation, as well as protein function, in the brain. UCP2 acting as a protonophore, similar to UCP1, requires fatty acids and is nucleotide-dependent [2,23–25,29,30]. *In vitro* and *in vivo* data that are available on peripheral UCP2 expression show varying levels of UCP2 regulation by different hormones, including leptin [31–33] and thyroid hormone [33,34]. It appears, however, that the regulation of UCP2 by these hormones is tissue-specific and most likely involves indirect mechanisms of action. Transcriptional regulation of UCP2 is further complicated by the robust promoter polymorphism of the *UCP2* gene [35].

Other biologically active substances were also shown to affect transcription, translation, and/or activity of UCP2. These include retinoic acid [36,37], lipopolysaccharides [38], coenzyme Q [29,30], and superoxides [24,25]. In fact, recently, *in vitro* evidence emerged to suggest the critical involvement of coenzyme Q [29,30] and superoxides [24,25] in the activation of UCP2 as an uncoupler in peripheral tissues. After the revelation that superoxides regulate UCP2 transcriptionally and posttranslationally [23], Klingenberg and his colleagues [29,30] showed that the functionality of UCP2 as a mitochondrial uncoupler requires coenzyme Q as a mandatory cofactor. Subsequently, through a chain of sophisticated, state-of-the-art *in vitro* experiments, Brand and his colleagues [24] came to the conclusion that it is superoxide from within the matrix of the mitochondria that is quintessential for the uncoupling activity of UCP2. Whether these findings apply *in vivo*, and whether tissue specificity and other endogenous activating substances will emerge, will be determined in future experiments.

Our results on UCP2 induction in the brain support the proposition that superoxides are the main controllers of UCP2 transcription: first, we have found that UCP2 mRNA expression is present in brain areas with the highest lipid peroxidation levels (our unpublished data). Subsequently, we demonstrated that acute brain injury, which is likely to result in increased free radical production, induces expression of UCP2 mRNA in areas of the brain where normally UCP2 is not expressed, such as the entorhinal cortex [26]. In fact, it is very likely that most of the neurodegenerative disorders that are associated with free radical production will involve UCP2. In this regard, we are currently studying the involvement of UCP2 in epilepsy, Parkinson's disease, hypoxia, and experimental allergic encephalomyelitis.

5. Synopsis

There is much to be done to decipher the full array of actions of UCPs in the functioning brain. However, from the early signs it is clear that these novel mitochondrial proteins are readily present in the nervous system and will offer an entirely unique approach to both the normal and diseased central nervous system. One of the current challenges and obstacles of UCP research is the lack of a broad understanding of what endogenous substances activate UCPs and, perhaps more importantly, what pharmacological compounds could selectively activate different UCPs. The availability of these compounds will be quintessential to an in-depth analysis of the functionality of these proteins. Until then, however, data must be collected *in vitro* and *in vivo* and cross-checked with each other continuously in order to decipher a meaningful understanding of the functionality of these proteins.

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References

[1] Bouillaud F, Ricquier D, Thibault J, Weissenbach J. Molecular approach to thermogenesis in brown adipose tissue: cDNA cloning of the mitochondrial uncoupling protein. Proc Natl Acad Sci USA 1985;82:445–8.
[2] Fleury C, Neverova M, Collins S, Raimbault S, Champigny O, Levi-Meyrueis C, Bouillard F, Seldin MF, Surwit RS, Ricquier D, Warden CH. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. Nat Genet 1997;15:269–72.
[3] Boss O, Samec S, Paoloni-Giacobino A, Rossier C, Dulloo A, Seydoux J, Muzzin P, Giacobino JP. Uncoupling protein-3: a new member of the mitochondrial carrier family with tissue-specific expression. FEBS Lett 1997;408:39–42.
[4] Vidal-Puig A, Solanes G, Grujic D, Flier JS, Lowell BB. UCP3: an uncoupling protein homologue expressed preferentially and abundantly in skeletal muscle and brown adipose tissue. Biochem Biophys Res Commun 1997;235:79–82.
[5] Mao W, Yu XX, Zhong A, Li W, Brush J, Sherwood SW, Adams SH, Pan G. UCP4, a novel brain-specific mitochondrial protein that reduces membrane potential in mammalian cells. FEBS Lett 1999;443:326–30.
[6] Sanchis D, Fleury C, Chomiki N, Goubern M, Huang Q, Neverova M, Gregoire F, Easlick J, Raimbault S, Levi-Meyrueis C, Miroux B, Collins S, Seldin M, Richard D, Warden C, Bouilland F, Ricquier D. BMCP1, a novel mitochondrial carrier with high expression in the central nervous system of humans and rodents, and respiration uncoupling activity in recombinant yeast. J Biol Chem 1998;273:34611–5.
[7] Negre-Salvayre A, Hirtz C, Carrera G, Cazenave R, Troly M, Salvayre R, Penicaud L, Casteilla L. A role for uncoupling protein-2 as a regulator of mitochondrial hydrogen peroxide generation. FASEB J 1997;11:809–15.
[8] Arsenijevic D, Onuma H, Pecqueur C, Raimbault S, Manning BS, Miroux B, Couplan E, Alves-Guerra MC, Goubern M, Surwit R, Bouillaud F, Richard D, Collins S, Ricquier D. Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production. Nat Genet 2000;26:435–9.
[9] Nicholls DG, Locke RM. Thermogenic mechanism in brown fat. Physiol Rev 1984;64:1–64.

[10] Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. Nature 2000;404:652–60.
[11] Nicholls DG, Ward MW. Mitochondrial membrane potential and neuronal glutamate excitotoxicity: mortality and millivolts. Trends Neurosci 2000;23:166–74.
[12] Zhang CY, Baffy G, Perret P, Krauss S, Peroni O, Grujic D, Hagen T, Vidal-Puig AJ, Boss O, Kim YB, Zheng XX, Wheeler MB, Shulman GI, Chan CB, Lowell BB. Uncoupling protein regulates insulin secretion and is a major link between obesity β cell dysfunction and type 2 diabetes. Cell 2001;105:745–55.
[13] Richard D, Rivest R, Huang Q, Bouillaud F, Sanchis D, Champigny O, Ricquier D. Distribution of the uncoupling protein 2 mRNA in the mouse brain. J Comp Neurol 1998;397:549–60.
[14] Horvath TL, Warden CH, Hajos M, Lombardi A, Goglia F, Diano S. Brain uncoupling protein 2: uncoupled neuronal mitochondria predict thermal synapses in homeostatic centers. J Neurosci 1999;19:10417–27.
[15] Diano S, Urbanski HF, Horvath B, Bechmann I, Kagiya A, Nemeth G, Naftolin F, Warden CH, Horvath TL. Mitochondrial uncoupling protein 2 (UCP2) in the non-human primate brain and pituitary. Endocrinology 2000;141:4226–38.
[16] Stuart JA, Brindle KM, Harper JA, Brand MD. Mitochondrial proton leak and the uncoupling proteins. J Bioenerg Biomembr 1999;31:517–25.
[17] Garcia-Martinez C, Sibille B, Solanes G, Darimont C, Mace K, Villarroya F, Gomez-Foix AM. Overexpression of UCP3 in cultured human muscle lowers mitochondrial membrane potential, raises ATP/ADP ratio, and favors fatty acid vs. glucose oxidation. FASEB J 2001;15:2033–5.
[18] Rossmeisl M, Barbatelli G, Flachs P, Brauner P, Zingaretti MC, Marelli M, Janovska P, Horakova M, Syrovy I, Cinti S, Kopecky J. Expression of the uncoupling protein 1 from the *aP2* gene promoter stimulates mitochondrial biogenesis in unilocular adipocytes *in vivo*. Eur J Biochem 2002;269:19–28.
[19] Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, Troy A, Cinti S, Lowell B, Scarpulla RC, Spiegelman BM. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell 1999;98:115–24.
[20] Budd SL, Nicholls DG. Mitochondrial calcium regulation and acute glutamate excitotoxicity in cultured cerebellar granule cells. J Neurochem 1996;67:667–79.
[21] Castilho RF, Hansson O, Ward MW, Budd SL, Nicholls DG. Mitochondrial control of acute glutamate excitotoxicity in cultured cerebellar granule cells. J Neurosci 1998;18:10277–86.
[22] Castilho RF, Ward MW, Nicholls DG. Oxidative stress, mitochondrial function, and acute glutamate excitotoxicity in cultured cerebellar granule cells. J Neurochem 1999;72:1394–401.
[23] Pecqueur C, Alves-Guerra MC, Gelly C, Lévi-Meyrueis C, Couplan E, Collins S, Ricquier D, Bouillaud F, Miroux B. Uncoupling protein 2, *in vivo* distribution, induction upon oxidative stress, and evidence for translational regulation. J Biol Chem 2001;276:8705–12.
[24] Echtay KS, Murphy MP, Smith RA, Talbot DA, Brand MD. Superoxide activates mitochondrial uncoupling protein 2 from the matrix side: studies using targeted antioxidants. J Biol Chem 2002;277:47129–35.
[25] Echtay KS, Roussel D, St-Pierre J, Jekabsons MB, Cadenas S, Stuart JA, Harper JA, Roebuck SJ, Morrison A, Pickering S, Clapham JC, Brand MD. Superoxide activates mitochondrial uncoupling proteins. Nature 2002;415:96–9.
[26] Bechmann I, Diano S, Warden CH, Bartfai T, Nitsch R, Horvath TL. Brain mitochondrial uncoupling protein 2 (UCP2): protective stress signal in neuronal injury. Biochem Pharmacol 2002;64:363–7.
[27] Horvath B, Spies C, Warden CH, Diano S, Horvath TL. Uncoupling protein 2 in primary pain and temperature afferents of the spinal cord. Brain Res 2002;955:260–3.
[28] Horvath B, Spies C, Horvath G, Kox WJ, Miyamoto S, Barry S, Warden CH, Bechmann I, Diano S, Heemskerk J, Horvath TL. Uncoupling protein 2 (UCP2) lowers alcohol sensitivity and pain threshold. Biochem Pharmacol 2002;64:369–74.
[29] Echtay KS, Winkler E, Klingenberg M. Coenzyme Q is an obligatory cofactor for uncoupling protein function. Nature 2000;408:609–13.
[30] Echtay KS, Winkler E, Frischmuth K, Klingenberg M. Uncoupling proteins 2 and 3 are highly active H^+ transporters and highly nucleotide sensitive when activated by coenzyme Q (ubiquinone). Proc Natl Acad Sci USA 2001;98:1416–21.
[31] Gong DW, He Y, Karas M, Reitman M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, β3-adrenergic agonists, and leptin. J Biol Chem 1997;272:24129–32.
[32] Liu Q, Bai C, Chen F, Wang R, MacDonald T, Gu M, Zhang Q, Morsy MA, Caskey CT. Uncoupling protein-3: a muscle-specific gene upregulated by leptin in *ob/ob* mice. Gene 1998;207:1–7.
[33] Zhou YT, Shimabukuro M, Koyama K, Lee Y, Wang MY, Trieu F, Newgard CB, Unger RH. Induction by leptin of uncoupling protein-2 and enzymes of fatty acid oxidation. Proc Natl Acad Sci USA 1997;94:6386–90.
[34] Masaki T, Yoshimatsu H, Kakuma T, Hidaka S, Kurokawa M, Sakata T. Enhanced expression of uncoupling protein 2 gene in rat white adipose tissue and skeletal muscle following chronic treatment with thyroid hormone. FEBS Lett 1997;418:323–6.
[35] Esterbauer H, Schneitler C, Oberkofler H, Ebenbichler C, Paulweber B, Sandhofer F, Ladurner G, Hell E, Strosberg AD, Patsch JR, Krempler F, Patsch W. A common polymorphism in the promoter of UCP2 is associated with decreased risk of obesity in middle-aged humans. Nat Genet 2001;28:178–83.
[36] Carmona MC, Valmaseda A, Iglesias R, Mampel T, Viñas O, Giralt M, Villarroya F. 9-*cis*-Retinoic acid induces the expression of the uncoupling protein-2 gene in brown adipocytes. FEBS Lett 1998;441:447–50.
[37] Rial E, Gonzalez-Barroso M, Fleury C, Iturrizaga S, Sanchis D, Jimenez-Jimenez J, Ricquier D, Goubern M, Bouillaud F. Retinoids activate proton transport by the uncoupling proteins UCP1 and UCP2. EMBO J 1999;18:5827–33.
[38] Cortez-Pinto H, Yang SQ, Lin HZ, Costa S, Hwang CS, Lane MD, Bagby G, Diehl AM. Bacterial lipopolysaccharide induces uncoupling protein-2 expression in hepatocytes by a tumor necrosis factor-α-dependent mechanism. Biochem Biophys Res Commun 1998;251:313–9.