Uncoupling protein 2 in the brain: distribution and function
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Abstract
Uncoupling protein 2 (UCP2) mRNA is expressed in a panoply of tissues, including the brain, where it is widely distributed. In the mouse brain, it is expressed in the hypothalamus (suprachiasmatic, paraventricular, dorsomedial, ventromedial and arcuate nuclei), the thalamus (submedius nucleus) and the brain-stem (dorsal motor nucleus of the vagus nerve). In the rat brain, it is also expressed in the hippocampus. The presence of UCP2 mRNA in neurons expressing corticotropin-releasing factor and arginine-vasopressin suggests a role for UCP2 in the control of neuroendocrine and behavioural functions. We have recently demonstrated that UCP2-deficient mice can resist the lethal effect of toxoplasmosis through an enhanced production of reactive oxygen species (ROS) from the macrophages. This finding provides evidence that UCP2 can be part of a mechanism preventing ROS production. UCP2 could therefore be involved in protecting the brain against oxidative stress. The involvement of UCP2 in neuroprotection is also consistent with the recent observation that kainic acid, which promotes Ca²⁺ uptake in the glutamate-activated neurons in the hippocampal CA1 field, can induce the UCP2 gene in the activated CA1 cells. The role of UCP2 in neuroprotection warrants further investigation.

Introduction
Uncoupling protein 2 (UCP2) is a member of the mitochondrial carrier superfamily with a predicted homology of sequence of 59% with UCP1 [1]. In contrast with the other UCPs, such as UCP1, which is uniquely expressed in brown adipose tissue (BAT), or UCP3, which is found in BAT and muscle, UCP2 is expressed in a large number of tissues. Although this specificity does not determine the exact function of UCP2, it nonetheless suggests that UCP2 can fulfill more general functions than UCP1 and UCP3. The role of UCP2 has yet to be fully delineated, even though two recent studies carried out in UCP2−/− mice have suggested that this protein could be involved in the production of reactive oxygen species (ROS) [2], as well as in the control of insulin secretion [3]. In contrast with what was first anticipated, UCP2 does not seem to be a major effector of thermoregulatory processes, but the possibility that this protein can be involved in obesity remains factual [4].

Another characteristic feature of UCP2 is that it is expressed in the brain [1], where the distribution of UCP2 mRNA is wide, but specific to certain areas [5]. The focus of this mini-review is to discuss the potential functions of UCP2 in the brain in the light of its distribution, uncoupling activity and role in the control of ROS production.

Uncoupling proteins
Mainly on the basis of studies addressing the function of UCP1 [6], UCPs have been described as mitochondrial inner membrane proteins capable of dissipating the proton electrochemical gradient (ΔψH⁺) that builds up across the inner mitochondrial membrane and drives the ATP synthase pathway (Figure 1) [6]. This uncoupling process is susceptible to decreases in ATP synthesis and generation of significant amounts of heat, as is the case of BAT, which serves as an efficient thermogenic effector in small mammals [7].

UCPs have also been demonstrated to be involved in ROS production [2], which seems to be facilitated in totally coupled mitochondria [8,9]. In fact, the increase in ΔψH⁺, which occurs when a mitochondrion is in respiration state 4 (that is, when ATP levels are high and the availability of ADP is low), would slow down the electron flow through the respiratory chain. This would facilitate the transfer of electrons from ubiquinone radicals to O₂ and subsequently promote the formation of superoxide radicals (O₂⁻). The total coupling of mitochondria could also enhance the
The potential function of uncoupling protein 2 (UCP2), similar to the other UCPs, is to dissipate the proton electrochemical gradient (Δψm) that builds up across the inner mitochondrial membrane and drives the ATP-synthase pathway. This uncoupling process is susceptible to the reducing of ATP synthesis and the prevention of the transfer of electrons from ubisemiquinone radicals to O2 and, subsequently, the formation of reactive oxygen species, such as superoxide radicals (O2•−).

Up until now, no less than three mammalian UCPs, referred to as UCP1, UCP2 and UCP3, have been cloned and identified as members of the UCP subfamily [12–14]. Other UCPs, cloned in plants [15] and birds [16], are also part of this family. Furthermore, two other mitochondrial proteins with uncoupling activities have recently been discovered, and designated UCP4 [17] and BMCP1 [18,19].

**Brain distribution of UCP2 mRNA**

One striking feature of the UCP2 gene is that it is expressed to a significant level in the brain [5]. Studies conducted in the mouse, as well as in the rat (Figure 2), have demonstrated that UCP2 mRNA is found in large amounts in the hypothalamus, the limbic system and in the brainstem. In the rat, as well as in the mouse [5], the hypothalamic expression of UCP2 is abundant in the suprachiasmatic, paraventricular, dorsomedial, ventromedial nucleus and arcuate nuclei. In both species, the expression of UCP2 is marked in the dorsal motor nucleus of the vagus nerve. In the mouse, UCP2 mRNA is abundantly expressed in the cerebellum, but hardly so in the hippocampus. The cerebellar expression is not seen in the rat, which, however, exhibits a strong expression of UCP2 in the hippocampus (Figure 2). The reasons for differences between strains in the expression of UCP2 are still obscure.

There is now evidence that expression is largely neuronal [5,20]. The chemical identity of the neurons expressing UCP2 mRNA has yet to be fully determined. Nonetheless, it is clear that neurons expressing corticotropin-releasing factor (CRF) in the parvocellular division of the paraventricular hypothalamic nucleus and arginine-
The expression of UCP2 mRNA in the rat brain

The film autoradiograms represent coronal rat brain sections that were hybridized with an antisense riboprobe complementary to the rat UCP2 mRNA. Regions expressing UCP2 mRNA are emphasized. '10', dorsal motor nucleus of the vagus nerve; AP, area postrema; ARH, arcuate hypothalamic nucleus; BLA, basolateral amygdaloid nucleus; CA1, Ammon's horn 1 field of the hippocampus; CA3, Ammon's horn 3 field of the hippocampus; DMH, dorso medial hypothalamic nucleus; LV, lateral ventricle; PVN, paraventricular hypothalamic nucleus; SCH, suprachiasmatic nucleus; SON, supraoptic nucleus; VMH, ventromedial hypothalamic nucleus.

Figure 2

Brain distribution and function of UCP2 in the brain

The brain distribution, as well as the cellular localization, of UCP2 mRNA in the brain supports...
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Neurons expressing CRF in the paraventricular hypothalamic nucleus (PVN) and arginine-vasopressin in the supraoptic nucleus (SON) express UCP2 mRNA. CRH and AVP neurons were first immunostained and hybridized with an antisense riboprobe complementary to the rat UCP2 mRNA. Doubly labelled cells are indicated by arrows. Magnification, x 20 (left panels) and x 100 (right panels). 3V, third ventricle.

a role for UCP2 in energy balance regulation, neuroendocrine and autonomic functions.

In the hypothalamus, UCP2 mRNA is found in at least four structures, playing a very important role in the control of food intake and energy expenditure. UCP2 mRNA is indeed expressed in the paraventricular, dorsomedial, ventromedial and arcuate nuclei [21]. In the arcuate nuclei, UCP2 mRNA has been found in neurons containing neuropeptide Y and agouti-related protein (A. Dunn-Meynel, B. Levin and D. Richard, unpublished results), which are undeniably two of the most important neuropeptides involved in the regulation of energy balance in laboratory rodents [22]. The putative role of UCP2 in the control of food intake and thermogenesis needs, however, to be ascertained. Factors such as obesity, leptin treatment and food deprivation do not apparently alter the expression of UCP2 in the brain (D. Richard, unpublished results). In addition, the UCP2−/− mouse does not appear to exhibit major changes in terms of energy balance regulation [2]. However, it has been demonstrated recently that this mutant has an increased ability to secrete insulin [3], which suggests that UCP2 might play some role in energy metabolism.

The expression of UCP2 mRNA in CRF and AVP cells raises the possibility that UCP2 is involved in neuroendocrine functions. CRF is expressed abundantly in the parvocellular division of the paraventricular nucleus, from which CRF neurons project to the median eminence to control the activity of the pituitary-adrenal axis. It is noteworthy that CRF neurons other than those from the paraventricular nucleus do not express UCP2 mRNA (D. Richard, unpublished results), indicating that UCP2 could play a role in neuroendocrine neurons specifically. UCP2 is also expressed in AVP neurons, whose role in the control the hydric balance has been credited for years. A role for UCP2 in neuroendocrine secretions appears feasible in the light of the recent demonstration of the involvement of UCP2 in insulin secretion [3]. Because it has the ability to control ATP levels, UCP2 has been assumed to influence β-cell glucose sensing. By controlling
of the vagus nerve, form the dorsal vagal complex, of the CRF and AVP neurons; the use of inhibitors of ATP synthesis has been reported to lower significantly the rates of basal and potassium-induced CRF release in a hypothalamic superfusion system [23].

One of the brain nuclei that express the most UCP2 is the dorsal motor nucleus of the vagus nerve, suggesting a role for UCP2 in the activity of the parasympathetic nervous system. In addition, the UCP2 transcript is found in the nucleus of the solitary tract and the area postrema. These two nuclei, together with the dorsal motor nucleus of the vagus nerve, form the dorsal vagal complex, a role for which in integrated visceral functions appears irrefutable [24].

**UCP2 and neuroprotection**

Given the apparent importance of UCP2 in the control of ROS production [2, 9], it seems reasonable to hypothesize that UCP2 is a part of a system limiting the neurodegenerative processes associated with oxidative stress. Even though the deficiency in UCP2 mRNA has been reported to have beneficial effect in the resistance to infection by promoting macrophagic microbicidal activity [2], the fact remains that ROS production, when it is sustained, has detrimental effects on cells. The marked expression of UCP2 in macrophages during infection probably occurs as a means to protect surrounding cells against ROS. Not many studies to date have addressed the role of UCP2 in neurodegenerative processes attributable to oxidative stress, but it seems clear that brain injuries cause the infiltration of phagocytic cells abundantly expressing UCP2 (S. Clavel and D. Richard, unpublished work). In the case of brain injuries, microglial cells are also observed to express UCP2 mRNA (S. Clavel, D. Arsenijevic and D. Richard, unpublished work). As yet, it is unclear as to whether UCP2 protects neurons that constitutively express it.

In addition to protecting neurons by preventing the production of ROS, UCP2 could also contribute to neuroprotection via at least one supplementary mechanism, which is still speculative. The fact that UCP2 can reduce the mitochondrial ∆µH⁺ supports that this protein could participate in the Ca²⁺-buffering capacity of the mitochondria, which seems in large part mediated by the mitochondrial ∆µH⁺ [25]. There is now a consensus that mitochondria play a vital role in buffering the cytosolic calcium overload in stimulated neurons. In mammalian neurons exposed to glutamate, a cellular Ca²⁺ overload is capable of initiating either necrotic or apoptotic pathways leading to cell death. UCP2, by lowering the mitochondrial ∆µH⁺, could limit the Ca²⁺-buffering capacity of the mitochondrial in order to protect cells against the detrimental effect of an overload of Ca²⁺. That UCP2 can be involved in protecting cells overloaded by Ca²⁺ is consistent with the recently observed increase in UCP2 expression in the CA (Ammon's horn)-1 field of the hippocampus in mice subjected to an acute intra-peritoneal injection of kainic acid (S. Clavel and D. Richard, unpublished work). The CA1 field, which does not constitutively express UCP2 mRNA in the mouse, undergoes a strong activation following treatment with kainic acid [26].

**Conclusion**

UCP2 is a unique UCP. It is expressed in an impressive array of tissues, including the brain, where the distribution of its mRNA is widespread, although specific to certain nuclei. The brain distribution and localization of UCP2 mRNA in CRF and AVP neurons suggest a role for UCP2 in energy balance regulation, as well as in neuroendocrine and autonomic functions. A role of UCP2 in the neuroendocrine functions is supported by the recent demonstration that UCP2 can be a regulator of ATP-dependent hormonal secretions [3]. Recent studies [2, 9] have suggested that UCP2 can negatively control ROS production, raising the possibility that brain UCP2 can protect neurons against oxidative stresses. A role for UCP2 in neuroprotection is supported further by the recent observation that kainic acid, which promotes Ca²⁺ uptake in the glutamate-activated neurons in the hippocampus, can induce UCP2 expression in the activated CAI cells. The protective role of UCPs against excitotoxicity lends itself to an interesting avenue of research in the light of the mitochondrial ∆µH⁺-dependent Ca²⁺-buffering capacity of the mitochondrion [25].

**References**


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