

At the Cutting Edge

# Functional neuroanatomy of thyroid hormone feedback in the human hypothalamus and pituitary gland

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## Abstract

A major change in thyroid setpoint regulation occurs in various clinical conditions such as critical illness and psychiatric disorders. As a first step towards identifying determinants of these setpoint changes, we have studied the distribution and expression of thyroid hormone receptor (TR) isoforms, type 2 and type 3 deiodinase (D2 and D3), and the thyroid hormone transporter monocarboxylate transporter 8 (MCT8) in the human hypothalamus and anterior pituitary. Although the post-mortem specimens used for these studies originated from patients who had died from many different pathologies, the anatomical distribution of these proteins was similar in all patients. D2 enzyme activity was detectable in the infundibular nucleus/median eminence (IFN/ME) region coinciding with local D2 immunoreactivity in glial cells. Additional D2 immunostaining was present in tanycytes lining the third ventricle. Thyrotropin-releasing hormone (TRH) containing neurons in the paraventricular nucleus (PVN) expressed MCT8, TRs as well as D3. These findings suggest that the prohormone thyroxine (T4) is taken up in hypothalamic glial cells that convert T4 into the biologically active triiodothyronine (T3) via the enzyme D2, and that T3 is subsequently transported to TRH producing neurons in the PVN. In these neurons, T3 may either bind to TRs or be metabolized into inactive iodothyronines by D3. By inference, local changes in thyroid hormone metabolism resulting from altered hypothalamic deiodinase or MCT8 expression may underlie the decrease in TRH mRNA reported earlier in the PVN of patients with critical illness and depression. In the anterior pituitary, D2 and MCT8 immunoreactivity occurred exclusively in folliculostellate (FS) cells. Both TR and D3 immunoreactivity was observed in gonadotropes and to a lesser extent in thyrotropes and other hormone producing cell types. Based upon these neuroanatomical findings, we propose a novel model for central thyroid hormone feedback in humans, with a pivotal role for hypothalamic glial cells and pituitary FS cells in processing and activation of T4. Production and action of T3 appear to occur in separate cell types of the human hypothalamus and anterior pituitary.

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**Keywords:** TRH; TSH; Thyroid hormone; Deiodinase; Hypothalamus; Pituitary; PVN; Critical illness

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## 1. Introduction

In the 1970s and 1980s, immunocytochemical studies in rat hypothalamus demonstrated thyrotropin-releasing hormone (TRH) neurons in a number of hypothalamic nuclei for the first time and a key role for TRH neurons in the paraventricular nucleus of the hypothalamus (PVN) in the neuroendocrine regulation of thyroid hormone was gradually revealed. Elegant studies in rats showed an inverse relationship between serum thyroid hormone levels and TRHmRNA expression in the PVN during experimentally induced hypo- and hyperthyroidism (Segerson et al., 1987) confirming a pivotal role for these neurons in this classical endocrine negative feedback loop. The rat PVN consists of magnocellular neurons containing, e.g., vasopressin and oxytocin in its lateral portions, and of a parvocellular part in its more medial portions. TRH neurons in the medial and periventricular parvocellular subdivisions of the PVN project to the median eminence, which explains observations in experimental models of hypothyroidism showing increased TRHmRNA only in these subdivisions of the PVN (for review see Lechan and Fekete, 2006). These so-called hypophysiotropic TRH neurons project to the median eminence and terminate in its external zone, where TRH is released into the portal capillaries for transport to the anterior pituitary and regulation of TSH release. Hypophysiotropic TRH neurons in the PVN receive monosynaptic projections from leptin-responsive neurons in the arcuate nucleus (ARC) containing either alpha-melanocyte stimulating hormone ( $\alpha$ -MSH) and cocaine and amphetamine regulated transcript (CART), or neuropeptide Y (NPY) and agouti-related protein (AGRP). These projections play a key role in the leptin-mediated resetting of the thyroid axis during food deprivation resulting in reduced TRHmRNA expression in the PVN, which contributes to lower serum concentrations of thyroid hormone in the rat (for review see Lechan and Fekete, 2006).

So far, relatively little attention has been paid to central thyroid hormone feedback in man. Here we review a number of recent studies on the functional neuroanatomy of thyroid hormone feedback in the human hypothalamus and anterior pituitary.

## 2. TRH neurons in the human hypothalamus

In the 1990s it became clear that TRH containing neurons and fibers are present throughout the human hypothalamus, including some TRH neurons in the hypothalamic grey. Immunocytochemical studies reported many spindle-shaped and spheric multipolar parvocellular TRH neurons in the dorsocaudal portion of the human PVN, with only a small number of magnocellular neurons expressing TRH. Both the suprachiasmatic nucleus (SCN), which is the circadian pacemaker of the brain acting as a biological clock, and the sexually dimorphic nucleus (SDN) of the human hypothalamus contain a small number of bipolar TRH cells (Fliers et al., 1994). The exact efferent projections of hypothalamic TRH containing neurons in the human brain are unknown, but dense TRH fiber networks, e.g., in the tuberomammillary nucleus (TMN) and perifornical area, suggest an important role for non-hypophysiotropic TRH neurons in the human

brain. The distribution of TRH neurons shown by immunocytochemistry was confirmed by a subsequent study using mRNA in situ hybridization (Guldenaar et al., 1996) reporting numerous TRHmRNA containing cells in the medial region of the dorsocaudal portion of the PVN. In addition to the PVN and SCN, TRH mRNA labelled neurons appeared to be present in the perifornical area.

## 3. Hypothalamic thyroid hormone receptor (TR) expression

The thyroid hormone receptor isoforms  $\alpha 1$ ,  $\alpha 2$ ,  $\beta 1$ , and  $\beta 2$  are expressed in a large number of rat brain areas, including the hypothalamus. Prominent TR expression was reported in the PVN, the ARC and median eminence of the adult rat, notably of TR $\beta 2$  (Bradley et al., 1989; Cook et al., 1992; Lechan et al., 1994). An important role for TR $\beta 2$  in thyroid hormone negative feedback on TRH neurons in the PVN was suggested by studies in TR isoform-specific knockout mice (Abel et al., 2001), although TRH neurons in the rat PVN express all four TR isoforms (Lechan et al., 1994). Using a set of polyclonal antisera raised against the specific isoforms of TR, we studied the distribution of TR isoform expression in the human hypothalamus (Alkemade et al., 2005a). Although TRs have been assumed to be largely confined to the nuclear compartment, we found predominantly cytoplasmic localization of TR staining. Earlier in vitro studies (Hager et al., 2000) had shown that TRs may shuttle rapidly between the nuclear and cytoplasmic compartment. Such translocation of TR may be ligand-dependent (Zhu et al., 1998) and require protein interactions with various cofactors (Baumann et al., 2001). Cytoplasmic localization, in addition to nuclear localization, appears to be a general phenomenon in the human brain for steroid hormone receptors (Hager et al., 2000; Kruijver et al., 2002; Maruvada et al., 2003). Thus, given the extensive specificity tests performed with our TR antisera including negative Western blots in TR isoform-specific knockout mice, an artefact seems unlikely as an explanation for the observed cytoplasmic TR staining.

Both parvocellular and magnocellular neurons in the human PVN expressed the four TR isoforms studied. In addition, magnocellular neurons in the SON showed TR immunoreactivity. Since this neuronal population contains mainly vasopressin in the human hypothalamus (Fliers et al., 1985), this may represent an anatomical substrate for interactions between thyroid hormone status and osmoregulation (e.g., Skowsky and Kikuchi, 1978). Most prominent TR staining was present in the infundibular nucleus (IFN), which is the human homologue of the rat ARC. In an attempt to identify TR expressing neurons in the IFN we performed combined immunocytochemistry for TRs and in situ hybridization for NPY and POMC mRNA as candidate neurons for colocalization on the basis of earlier observations in the rat (Legradi and Lechan, 1998). Only sparse colocalization was observed, suggesting that neurons other than those expressing NPY and POMC are involved in thyroid hormone feedback in the IFN. Combined TR immunostaining with TRHmRNA in situ hybridization showed that a proportion of TRHmRNA expressing neurons in the human PVN express TRs (Alkemade et al.,

2005b). In contrast to the rat, the human SCN appeared to contain no TR expressing neurons, which may reflect a difference in expression levels, or an interspecies difference.

#### 4. Hypothalamic type 2 and type 3 deiodinase and monocarboxylate transporter 8 (MCT8) expression

Although the thyroid gland mainly secretes thyroxine (T<sub>4</sub>), most thyroid hormone actions are mediated via binding of the biologically more active thyroid hormone triiodothyronine (T<sub>3</sub>) to its receptor. The biologic activity of thyroid hormone in target cells is, therefore, determined in part by the intracellular concentration of T<sub>3</sub> which depends on the activity of the iodothyronine deiodinases. In the brain, type 2 deiodinase (D2) is responsible for deiodination of T<sub>4</sub> into T<sub>3</sub>, whereas type 3 deiodinase (D3) inactivates thyroid hormone by converting T<sub>3</sub> into the biologically inactive diiodothyronine (T<sub>2</sub>) and T<sub>4</sub> into reverse T<sub>3</sub> (rT<sub>3</sub>) (for review see Bianco et al., 2002). Interestingly, the administration of the endotoxin lipopolysaccharide (LPS), which has been used as a model for acute infection, selectively increases the activity of D2 in the mediobasal hypothalamus of rats and mice (Fekete et al., 2004; Boelen et al., 2004). Thus, mediobasal hypothalamus-specific and D2-mediated thyrotoxicosis may suppress the hypothalamus-pituitary-thyroid (HPT) axis by inhibition of hypophysiotropic TRH neurons, thereby contributing to the phenomenon of central down-regulation of the HPT axis associated with infection.

We have recently reported the expression and distribution of D2 and D3 in the human hypothalamus. D2 and D3 enzyme activities are detectable in pituitary and hypothalamic tissue samples obtained post-mortem (Alkemade et al., 2005b). Prominent D2 immunoreactivity is present in cells throughout the ependymal layer of the third ventricle, in glial cells within the infundibular nucleus/median eminence (IFN/ME) region and in blood vessel walls. In addition to glial staining, the IFN shows occasional weak neuronal staining. The distribution pattern of D2 immunostaining is generally in agreement with studies in rats where electron microscopy studies have identified D2 immunoreactive cells as astrocytes, including tanycytes (Diano et al., 2003; Tu et al., 1997). Tanycytes are cells lining the third ventricle establishing contacts with blood vessels of the ME, and they have been proposed to be involved in providing T<sub>3</sub> to the CNS following T<sub>4</sub> uptake from the cerebrospinal fluid (CSF) (Tu et al., 1997). D2 expression in rats was reported to be confined to the ventral part of the lining of the third ventricle, but is extended over the entire height of the lining of the third ventricle in the human hypothalamus. The distribution of hypothalamic D3 expression clearly differs from that of D2, showing intensely staining neurons in the IFN, PVN and SON. Less intense neuronal D3 staining is present in the suprachiasmatic nucleus, tuberolateral nucleus (NTL), tuberomammillary nucleus around the mammillary bodies and – sporadically – in the perifornical area. In contrast to D2, D3 is expressed exclusively in neurons showing a strong distribution overlap with TR, suggesting that D3 is expressed in T<sub>3</sub>-responsive neurons.

MCT8 has recently been identified as a thyroid hormone transporter with a crucial role in thyroid hormone metabolism

in the CNS, providing cells expressing deiodinases with thyroid hormone (Friesema et al., 2003; Heuer et al., 2005). The functional importance of MCT8 is evident from observations in patients with severe psychomotor retardation who carry mutations or deletions in the MCT8 gene (Friesema et al., 2004). Additional transporters capable of thyroid hormone transport have been identified. For example, the organic anion transporter OATP1C1 has a high affinity for T<sub>4</sub> and may be critical for transport of T<sub>4</sub> over the blood-brain-barrier (BBB) in view of its expression in capillaries throughout the brain (for review see Jansen et al., 2005).

We studied the expression of MCT8 in the human hypothalamus by immunocytochemistry and found heavily stained neurons in the PVN, SON and IFN (Alkemade et al., 2005b). Surprisingly, the perifornical area and LHA express MCT8 most prominently (Fig. 1). In the rat, D2 activity was reported in the LHA (Peeters et al., 2001), but in the human LHA no D2 and only sporadic D3 expression was observed. The LHA in the rat is innervated by leptin sensitive neurons from the ARC and is implicated in the regulation of food intake and body weight (Elias et al., 2001; Peeters et al., 2001; Sakurai et al., 1998). The presence of dense TRH fiber networks in the human perifornical area (Fliers et al., 1994) in combination with marked MCT8 and sparse D3 immunoreactivity (Alkemade et al., 2005a) suggests a neuroanatomical basis for effects of thyroid hormone on feeding behavior in humans as well. Using vimentin and NeuN as markers for tanycytes and neurons, respectively, the expression of D2 by glial cells and of D3 by neurons was confirmed, whereas MCT8 was present in both cell types (Alkemade et al., 2005b).

#### 5. Models for thyroid hormone feedback in the human hypothalamus

The classical scheme for feedback of thyroid hormone on TRH neurons of the PVN has focused on direct effects of thyroid hormone on TRH neurons. Indeed, unilateral stereotaxic implants of T<sub>3</sub> within the anterior hypothalamus was reported to induce a marked reduction of proTRHmRNA in the PVN of rats (Dyess et al., 1988). Based on above-mentioned morphological studies in human PVN, T<sub>4</sub> might indeed be taken up locally within the PVN from the circulation by astrocytes. This process would require active T<sub>4</sub> transport, e.g., by the organic anion transporter OATP1C1 which has been proposed to serve as a high affinity T<sub>4</sub> transporter in the human brain. In the rat, OATP1C1 is localized in brain capillaries and may be particularly important for transport of T<sub>4</sub> across the blood-brain-barrier (see Jansen et al., 2005). Following uptake, T<sub>4</sub> may then be converted to T<sub>3</sub> by D2 in astrocytes and subsequently transported to TRH neurons by MCT8 (Fig. 2(A)). Co-expression of D3, MCT8 and TRs with TRH in the PVN certainly supports the existence of this route for thyroid hormone feedback action in the human hypothalamus.

Feedback following thyroid hormone uptake from the CSF represents an alternative possibility (Fig. 2(B)). This route has been proposed earlier by other investigators based on neuroanatomical studies in rats (Diano et al., 2003; Guadano-Ferraz



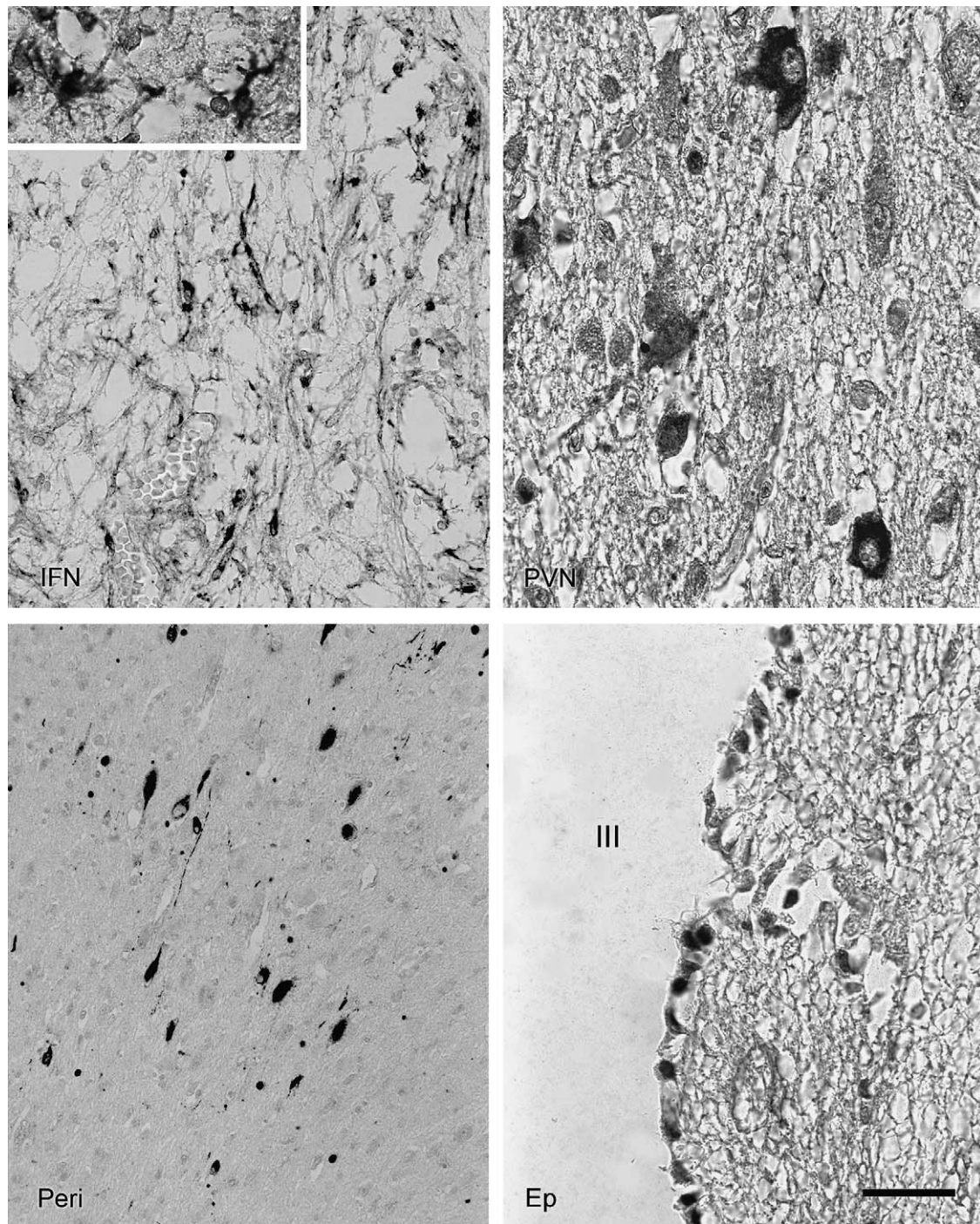


Fig. 1. MCT8 immunoreactivity in the IFN, PVN, perifornical area (Peri), and the ependymal layer of the third ventricle (Ep). The inset shows a high-power magnification of MCT8 expression in the IF of the same section. MCT8 is prominent in both glial cells and neurons. Scale bar, 100  $\mu$ m (IFN and Peri) and 25  $\mu$ m (PVN, Ep, and inset). Reproduced with permission from [Alkemade et al. \(2005b\)](#).

[et al., 1997](#); [Lechan and Fekete, 2004](#); [Tu et al., 1997](#)). In this model, thyroid hormone is taken up from the CSF in the third ventricle and transported by tanycytes to neurons in the arcuate nucleus that project to TRH cells in the PVN. T3 action in IFN neurons may alter firing pattern, thereby affecting TRH gene expression in PVN neurons via monosynaptic pathways demonstrated earlier by neuroanatomical tracing studies in the rat. Alternatively, T3 may be transported from the IFN to TRH

neurons in the PVN by anterograde axonal transport as proposed in the locus coeruleus by [Gordon et al. \(1999\)](#). Our observations in the human hypothalamus support uptake from the CSF at the level of the IFN as a possible route for thyroid hormone feedback on TRH neurons on the basis of immunostaining of D2 expressing glial cells along the lining of the third ventricle, and MCT8, TR and D3 expression by neurons in the IFN. In addition, uptake of T4 from the third ventricle at the level of the PVN

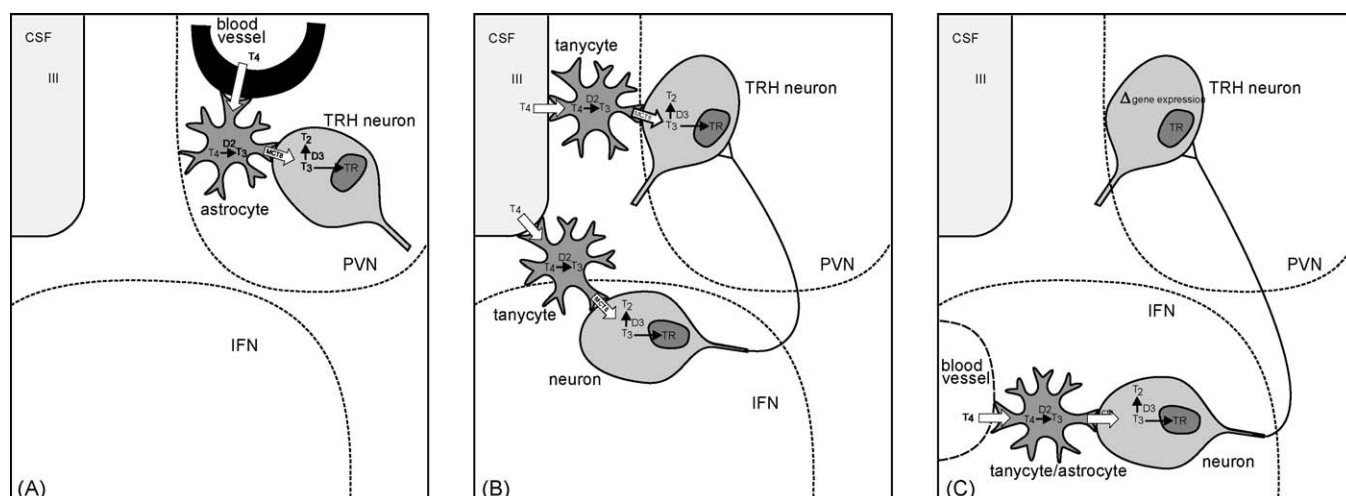


Fig. 2. Scheme of three proposed routes for thyroid hormone feedback on TRH neurons in the human PVN. Local thyroid hormone uptake from the vascular compartment within the PVN (A); thyroid hormone uptake from the CSF in the third ventricle followed by transport to TRH neurons in the PVN or IFN neurons projecting to TRH neurons in the PVN (B); and thyroid hormone sensing in the IFN of the mediobasal hypothalamus by neurons projecting to TRH neurons in the PVN (C). (A) T4 is taken up locally from the vascular compartment within the PVN by astrocytes expressing D2. In these astrocytes T4 is converted to T3 and transported to TRH neurons by MCT8. In the TRH neuron, T3 may bind to the TR and exert a negative feedback on TRH gene expression. T3 can be inactivated by D3 present in the TRH neuron. (B) T4 is taken up from the CSF by tanycytes expressing D2. In these cells T4 is converted to T3 and subsequently transported by MCT8 to TRH neurons of the PVN or to neurons in the IFN. T3 may bind to TRs expressed in these neurons and may (subsequently) be degraded by D3. TR binding in the PVN can alter TRH gene expression directly. In addition, TR binding in the IFN may result in altered firing of neurons projecting to TRH neurons in the PVN. Alternatively, T3 may travel from IFN neurons to TRH neurons in the PVN through axonal transport. (C) D2 expressing astrocytes or tanycytes sense T4 in the IFN/ME area, in which the BBB is absent and these cells convert T4 into T3. T3 is transported by MCT8 to IFN neurons. T3 may bind locally to the TR, altering gene expression of IFN neurons, or may be inactivated by D3. T3 may thus result in altered firing pattern of IFN neurons projecting to TRH neurons in the PVN. Alternatively, T3 may travel to TRH neurons in the PVN through axonal transport. Reproduced with permission from [Alkemade et al. \(2005b\)](#).

followed by transport to TRH cells in the PVN appears to be a possibility in view of D2-positive glial cells along the ependyma of the third ventricle in close approximation of the PVN.

Finally, thyroid hormone may have direct access from the circulation to the IFN in view of the absence of the BBB in this part of the mediobasal hypothalamus ([Fig. 2\(C\)](#)). That cells in the ARC sense circulating thyroid hormone concentrations is supported by increased D2 activity and mRNA in the ARC/ME after induction of hypothyroidism in rats ([Riskind et al., 1987; Tu et al., 1997](#)). In addition, TR $\beta$ 2 is predominantly expressed in rat ARC neurons that may be able to sense T3 produced by glial cells expressing D2. NPY, POMC and AGRP containing neurons from the ARC project to TRH neurons in the PVN ([Legradi and Lechan, 1998; Legradi and Lechan, 1999](#)). The finding of D2 in the human IFN in conjunction with earlier observation of TR $\beta$ 2 expression in the same area ([Alkemade et al., 2005a](#)) is suggestive of a similar pathway in the human hypothalamus. If indeed thyroid hormone may act via the vascular compartment-IFN-PVN route in the human hypothalamus remains, however, hypothetical.

In view of the importance of both the integrity of MCT8-mediated thyroid hormone transport and the balance between local D2 and D3 activity for the bioavailability of T3, local changes in thyroid hormone metabolism resulting from altered hypothalamic deiodinase or MCT8 expression may underlie alterations in HPT axis setpoint regulation as can be observed in various clinical conditions such as protracted critical illness and depression. If indeed altered hypothalamic deiodinase and MCT8 expression are among the determinants of decreased TRH

mRNA reported earlier in the PVN of patients with glucocorticoid treatment, critical illness and major depression ([Fliers et al., 1997; Alkemade et al., 2003; Alkemade et al., 2005c](#)) remains to be seen at this stage (cf [Fliers et al., 2006](#)).

## 6. Thyroid hormone feedback in human pituitary

A number of studies have reported that type II deiodinase (D2) in the human pituitary converts T4 into T3, while type III deiodinase (D3) converts T4 and T3 into inactive metabolites (for review see [Bianco et al., 2002](#)). Type I deiodinase activity is expressed ([Baur et al., 2002](#)) but does not appear to play a major role in thyroid hormone feedback in the human anterior pituitary ([Tannahill et al., 2002](#)) whereas expression of TRs in the human pituitary has been reported ([Yen et al., 1992](#)). We have recently studied cell types expressing deiodinases, TR isoforms and MCT8 in the human anterior pituitary ([Alkemade et al., 2006](#)) and found, surprisingly, prominent D2 and MCT8 immunoreactivity exclusively in folliculostellate (FS) cells. TR and D3 immunoreactivity was present in the cytoplasm of granular cells with FSH immunoreactivity, while D3 showed sporadic co-expression with TSH. Both TR $\alpha$ 2 and TR $\beta$ 2 showed clear colocalization with TSH. Earlier studies in rat anterior pituitary cell fractions and tumor cells reported D2 expression in hormone producing cells (e.g., [Koenig and Watson, 1984; Kim et al., 1998](#)). In addition, a recent study in rats has convincingly shown D2 mRNA expression in thyrotrophs ([Christoffolete et al., 2006](#)). The difference in D2 expressing cell types between human and rat anterior pituitary suggests an interspecies differ-



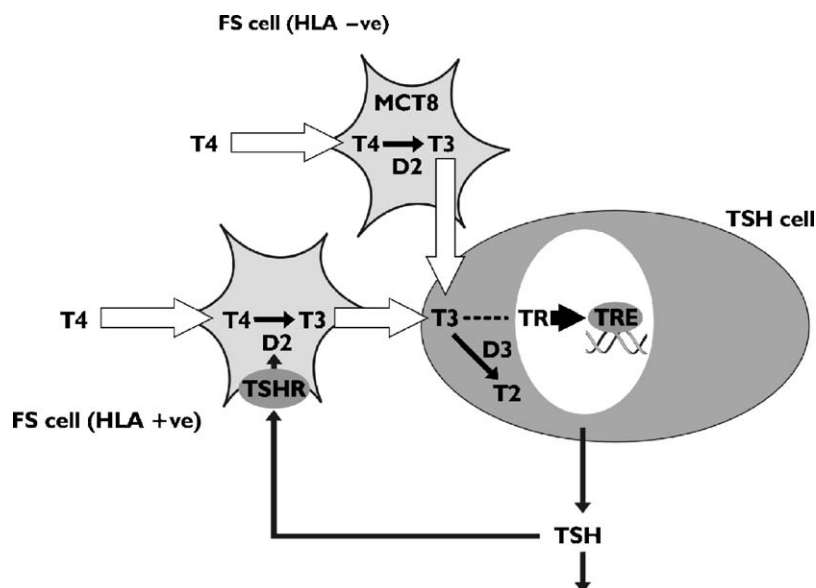


Fig. 3. Proposed model for thyroid hormone action on hormone-secreting cells of the anterior pituitary: T4 is taken up by FS cells (FS cells) and is converted by type II deiodinase (D2) into T3 in HLA + ve or –ve FS cells. TSH can stimulate D2 expression via binding to the TSH receptor (TSHR) in HLA + ve cells. T3 is subsequently transported to hormone-secreting cells that coexpress thyroid hormone receptor isoforms (TRs). T3 can bind to the TR and alter gene expression, or may be degraded locally by D3. The role of MCT8 is unclear at present. MCT8 may be involved in T4 transport into, or in T3 release from HLA–ve cells. Reproduced with permission from [Alkemada et al. \(2006\)](#).

ence, although at this time fatal illness in the patients studied cannot be completely ruled out as a potential confounding factor for the anatomical distribution of D2 expression observed in human specimens. A species difference in the functional anatomy of thyroid hormone feedback at the level of the anterior pituitary is further supported by expression differences in D1 (expressed in rats, but very limited expression in humans) and D3 (expressed in human, but not in rat anterior pituitary).

It is intriguing that both D2 and MCT8 immunoreactivity were observed in FS cells, since these cells have long cytoplasmic processes between endocrine cells and are able to modulate anterior pituitary hormone secretion ([Baes et al., 1987](#); [Allaerts and Denef, 1989](#); [Allaerts et al., 1990](#)). We found that HLA, a determinant of major histocompatibility complex (MHC)-class II which is expressed in a subset of FS cells, colocalized with D2 immunoreactivity. These results strongly suggest that a subset of FS cells produce T3 from T4 and may be capable of transporting T3 to other cells expressing TR isoforms. MCT8 and a subset of D2 expressing FS cells did not co-express HLA. In addition to D2, yet another key enzyme for endocrine feedback in the anterior pituitary is expressed by FS cells in the anterior pituitary, i.e., 11- $\beta$ -hydroxysteroid dehydrogenase (11- $\beta$ HSD) type 1 ([Korbonits et al., 2001](#)). This enzyme converts cortisone to the biologically active glucocorticoid cortisol. Thus, FS cells may be important for the regulation of local bioactive hormone concentrations in multiple endocrine axes.

We propose a novel neuroanatomical route for thyroid hormone feedback action on hormone-secreting cells of the human anterior pituitary. In this model, the FS cell is central in local hypophyseal T3 production (Fig. 3). The expression of the TSH receptor reported earlier in MHC-class II cells ([Prummel et al., 2000](#)) and the increase in D2 activity that has been observed

in TSH producing tumors ([Baur et al., 2002](#)) suggests that D2 expression in the anterior pituitary can be influenced directly by TSH.

The absence of D2 from cell types that express thyroid hormone receptors indicates that production and action of T3 in the human pituitary gland occurs in separate cell types, very similar to models for thyroid hormone feedback in the hypothalamus discussed above. Both thyroid hormone receptor isoforms and D3 expression appear to be present in hormone-secreting cells of the anterior pituitary. The overlap between TR isoform and D3 expression suggests that thyroid hormone action and degradation may occur in the same hormone-secreting cells, while T4 conversion to T3 occurs in a subset of FS cells of the anterior pituitary that may be stimulated by TSH via TSH-R binding. This fits very well with the ultrashort feedback loop regulation of TSH as proposed by [Prummel et al. \(2000\)](#). The subtype of FS cells expressing MCT8 remains to be identified. The absence of distribution overlap between MCT8 and deiodinases or TRs suggests that yet another thyroid hormone transporter may be involved in providing hormone-secreting cells of the anterior pituitary with T3. The affinity of MCT8 for T3 as a substrate is higher than for T4 ([Friesema et al., 2003](#)), but no data have been published on the role of MCT8 in thyroid hormone efflux. In view of the involvement of other members of the MCT family in substrate efflux a similar role for MCT8 in FS cells is an interesting possibility, which will require further investigation.

## 7. Conclusion

The distribution and expression of thyroid hormone receptor isoforms, type 2 and type 3 deiodinase (D2 and D3), and the thy-

roid hormone transporter monocarboxylate transporter 8 have recently been reported in the human hypothalamus and anterior pituitary. The observations suggest that the prohormone T4 is taken up in hypothalamic glial cells that convert T4 into the biologically active T3, which is subsequently transported to TRH producing neurons in the PVN. In these neurons, T3 may bind to TRs and/or may be degraded into inactive iodothyronines. Similarly, FS cells in the anterior pituitary are proposed to be pivotal in thyroid hormone activation and transport, whereas hormone producing cells express TRs (thyroid hormone action) and D3 (thyroid hormone degradation). Thus, production and action of T3 appear to occur in separate sets of cells in the human hypothalamus and anterior pituitary. This model for central thyroid hormone feedback in the human HPT axis is speculative and awaits confirmation in future studies.

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