REVIEW

Thyroid hormone and astrocyte morphogenesis

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Abstract

Astrocyte cells clearly play a role in neural development, but nowadays their total action is seen as a far wider one. Recent findings consider them as stem cells, involved in the control of most facets of functional neural networks. Astrocytes play a central role in thyroid hormone metabolism in the brain, being the principal transporters of thyroxine from the blood, responsible for its conversion to 3,5,3'-triiodothyronine and hence supplying the neural tissues with the biologically active form of the hormone. Specific thyroid hormone transporters play an essential

role in this regulatory system. The presence of thyroid hormone receptors has been demonstrated in cultured astrocytes. Furthermore, thyroid hormone regulates several aspects of astrocyte differentiation and maturation, including the production of extracellular matrix proteins and growth factors, and thus controls neuronal growth and neuritogenesis. Therefore, astrocytes are currently suggested as important mediators of thyroid hormone in neuronal development.

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Introduction

Astrocytes, beyond their role as supportive glial cells

Astrocytes make up 20 to 50% of the volume of most brain areas and correspond to a heterogeneous class of cells that have many different roles. Glial fibrillary acidic protein (GFAP) is the classical marker used to identify differentiated astrocytes (Eng *et al.* 2000). The level of GFAP expression, however, can vary greatly from one cell to another, between different species, as well as under different conditions. Glutamine synthetase, the enzyme that catalyzes the conversion of glutamate into glutamine, is another protein that has been found to be specifically associated with astrocytes (Norenberg & Martinez-Hernandez 1979) and it is used to characterize the phenotype of differentiated glial cells (Loo *et al.* 1995). Specialized forms of astrocytes include Bergmann cells in the cerebellar cortex, Muller cells in the retina, pituicytes in the neurohypophysis, and tanycytes that line the walls of the third ventricle (Garcia-Segura *et al.* 1996a, Fields & Stevens-Graham 2002).

Astrocytes play a constitutive role in the formation of the blood–brain barrier (Janzer & Raff 1987), representing the major glycogen depots of the brain (Cataldo & Broadwell 1986) and supporting immune defence by producing various immunoactive cytokines (Benveniste 1992).

Classically, astrocytes are responsible for the regulation of neuronal metabolism and activity, regulating glucose supply, extracellular ion concentrations, cerebral blood flow, and neurotransmitter levels, in addition to the secretion of neuroactive substances. Astrocytes produce most of the extracellular matrix components in the central nervous system (CNS), including fibronectin and laminin (Liesi *et al.* 1986, 1995). Moreover, astrocytes exert an important role during development, modulating neuronal differentiation and guiding neuronal migration and axon growth (Garcia-Segura *et al.* 1996b, Fields & Stevens-Graham 2002). This classical functional range of astrocytes is now complemented with the emerging data that they retain stem cell characteristics (Song *et al.* 2002, Steindler & Laywell 2003), in addition to regulating synapse formation and synaptic transmission (Auld & Robitaille 2003, Newman 2003). For instance, astrocytes may express voltage-gated ion channels and neurotransmitter receptors that are co-activated at synapses and then participate in removing potentially toxic excitatory amino acids from synapses by high-affinity transporters. Dysregulation of these and other putative astrocyte functions has been variously implicated in the pathogenesis of numerous developmental, genetic, idiopathic, and acquired neurodegenerative diseases (Auld & Robitaille 2003, Nedergaard *et al.* 2003, Bachoo *et al.* 2004).

Astrocytes are mediators of thyroid hormone metabolism in the brain

The importance of thyroid hormone for normal brain development is well documented. Hypothyroidism during the early stages of the development of the CNS produces severe mental retardation in both animals and humans. Thyroid hormone deficiency during the fetal and neonatal periods leads to abnormal neuronal maturation, neurite outgrowth, synapse formation, neuroglial cell development, and subsequent myelination. Clinical observations describe the cerebral consequences of congenital hypothyroidism: cretinism. Neurological cretinism in its fully developed form is characterized by profound mental retardation, deaf-mutism, and spastic diplegia (Porterfield & Hendrich 1993, Konig & Moura Neto 2002).

Although small amounts of 3,5,3'-triiodothyronine (T3) are produced directly by the thyroid gland, more than 80% of this form of the hormone in the brain derives from the local conversion of thyroxine (T4) (Crantz *et al.* 1982, Courtin *et al.* 1986), catalyzed by a cAMP-inducible membrane-bound enzyme, the type II iodothyronine 5'-deiodinase (D2) (Courtin *et al.* 1988, Leonard 1988). D2 has been characterized as a selenoprotein (Pallud *et al.* 1997). Moreover, the 29-kDa substrate-binding subunit (p29) of the native D2 has been cloned and characterized (Leonard *et al.* 2000).

In the brain, D2 is predominantly expressed in astrocytes and tanycytes. Tanycytes are specialized glial cells that line the third ventricle and extend their processes to the adjacent hypothalamus and the median eminence (Guadano-Ferraz *et al.* 1997, 1999, Bernal 1999, 2005). A general mechanism concerning T3 distribution in the brain has been proposed in which T4 is captured by these cells from the blood-brain or blood-cerebrospinal fluid (CSF) barriers and converted into T3 for neuronal use. Neurons express type III deiodinase (D3) that degrades T3 to its inactive metabolite diiodothyronine (T2) (Bernal 2005, Santisteban & Bernal 2005).

In order to reach the intracellular targets, thyroid hormone must cross the plasma membrane. However, the hypothesis of passive thyroid hormone diffusion through the plasma membrane has been questioned by the identification of several thyroid hormone transporters (Hennemann *et al.* 2001, Abe *et al.* 2002). Recently, the organic anion-transport polypeptide Oatp14 was reported to be predominantly expressed in the brain, especially in the brain capillaries and choroid plexus, and this suggests involvement in the uptake of T4 from the blood to the CNS (Sugiyama *et al.* 2003). In addition, the monocarboxylate anion transporter (MCT8) was functionally characterized as a very active and specific thyroid hormone transporter (Friesema *et al.* 2003). MCT8 was observed to be highly expressed in choroid plexus and olfactory bulb, cerebral cortex, hippocampus and amygdala. Since, MCT8 was found to be predominant

in neurons, it was suggested that it plays a decisive role in the transport of T3 into them (Heuer *et al.* 2005). The physiological relevance of MCT8 transporter has recently been established. Mutations in the MCT8 gene have been described in the X-linked psychomotor retardation syndrome (Allan-Herndon-Dudley syndrome). The patients exhibit increased serum T3 and severe neurological defects (Dumitrescu *et al.* 2004, Friesema *et al.* 2004, Maranduba *et al.* 2005, Schwartz *et al.* 2005). Mutations in this gene have also been found in the X-linked paroxysmal dyskinesia (Brockmann *et al.* 2005). Thus, a model for thyroid hormone transport in the brain has been proposed in which Oatp transports T4 from the blood to the CNS. In the astrocytes and tanycytes, T4 is converted into T3 that enters into the neurons through MCT8, where it is degraded by D3. This model suggests an interplay between astrocytes and neurons in T3 homeostasis (Bernal 2005, Heuer *et al.* 2005).

In addition to cAMP (Courtin *et al.* 1988b, Leonard 1988), astrocytic D2 has been demonstrated to be strongly induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) that activates protein kinase (PK) C – in a glucocorticoid-dependent manner (Courtin *et al.* 1989) – and acidic fibroblast growth factor (aFGF) (Courtin *et al.* 1990). Thyroid-stimulating hormone, through a cAMP independent pathway, also induces D2 activity in astrocytes (Saunier *et al.* 1993). In addition, it has been suggested that astrocytic D2 activity is regulated by tyrosine phosphorylation (Mori *et al.* 1996).

Astrocyte D2 is a very short-lived enzyme, dynamically regulated by both T4 and 3,3',5'-triiodothyronine (rT3), but not T3. T4 down-regulates the levels of D2 in astrocytes in a process that involves the enzyme's internalization (Leonard *et al.* 1990, Siegrist-Kaiser *et al.* 1990). Myosin 5a is responsible for the binding of primary endosomes to the microfilaments, promoting actin-based endocytosis of D2 (Stachelek *et al.* 2000, 2001). T4 accelerates the rate of D2 inactivation by sequestering the p29 subunit in the endosomal pool (Farwell *et al.* 1996). It has recently been demonstrated that the D2 inactivation is mediated by selective ubiquitination and proteasomal degradation, a process in which target proteins are marked for degradation by conjugation to ubiquitin and subsequently recognized and degraded by the proteasome. D2 ubiquitination is accelerated by T4 catalysis and thus maintains local T3 homeostasis. Reversible ubiquitination rescues D2 from irreversible proteolysis and regulates the supply of active thyroid hormone in D2-expressing cells (Bianco *et al.* 2002, Bianco 2004, Bianco & Larsen 2005). In addition, the physiological role of D2 has been examined in a mouse strain that completely lacks D2 activity (D2 knockout, D2KO). Cultured astrocytes from these animals present no D2 activity, either after treatment with forskolin or after treatment with TPA. D2KO mice have no gross physiological behavioral abnormalities, reproduce normally, and present only a mild growth retardation

(Schneider *et al.* 2001). However, these animals exhibit the auditory phenotype similar to that caused by systemic hypothyroidism of thyroid hormone receptor deletion (Ng *et al.* 2004). Since the inactivation of D2 activity does not produce a syndrome as severe as that observed in the congenitally hypothyroid mice, it is suggested that D2 is not essential for all thyroid hormone-dependent developmental processes in the mouse CNS (Galton 2005). It has also been shown that D2 is up-regulated in hypothyroid cells and its activity increases when T3 levels are low, ensuring stable levels of brain T3 concentration despite fluctuations in T4 production (Bernal 1999, Anderson 2001). In addition, D2 is up-regulated in rat astrocytes after traumatic brain injury (Zou *et al.* 1998) or ischemic stroke (Margaill *et al.* 2005), suggesting a potential role for T3 action in the adult brain's response to injury and recovery.

Astrocytes also express D3, a selenoprotein that is responsible for the degradation of thyroid hormone in the brain (Courtin *et al.* 1986, Ramage *et al.* 1996). The opposing activities of D2 and D3 are believed to maintain brain T3 levels (Santini *et al.* 2001). In astrocytes, D3 is induced by multiple pathways, including cAMP, TPA, FGF, thyroid hormones and retinoic acid (Courtin *et al.* 1991, Esfandiari *et al.* 1994a). The effects of TPA and FGF on astrocytic D3 induction is mediated by the activation of the MEK/Erk signaling cascade (Pallud *et al.* 1999).

In contrast, astrocytes seem not to contain type I deiodinase (D1), the enzyme that converts the inactive rT3 to T2. Moreover, the production of sulfates (3,3'T2 sulfate, T2-S, and 3'T1 sulfate, T1-S), but not glucuroconjugates, by T3-treated astrocytes in culture has been demonstrated. T2-S is a major T3 metabolite produced by these cells (Esfandiari *et al.* 1994b).

Astrocytes express thyroid hormone receptors

The major thyroid hormone effects are mediated by transcriptional regulation of target genes. Thyroid hormone regulation of gene transcription is a complex process, mediated by multiple thyroid hormone receptors (TRs) and encoded on separate genes. The formation of ligand-bound TR complexes specifically interact with thyroid hormone-response elements located in regulatory regions of target genes, and is a necessary first step for their activation or suppression. These receptors are members of the superfamily that includes the steroid hormones, vitamin D, and retinoid acid receptors. Two genes coding T3 receptors have been identified and classified into alpha (TR α) and beta (TR β) subtypes, located on human chromosomes 17 and 3 respectively. They are the cellular homologs of the viral oncogene product v-erbA (Puymirat 1992, Forrest *et al.* 2002, Konig & Moura Neto 2002).

The presence of T3 receptors in astrocytes has been controversial, possibly due to the utilization of different technical conditions. Some studies have reported detecting

T3 binding sites in astrocytes (Kolodny *et al.* 1985). T3 receptor immunoreactivity has been found in protoplasmic and fibrous cells (Luo *et al.* 1989), and the isoforms TR α 1 and TR α 2 have been identified in fetal cultured astrocytes (Leonard *et al.* 1994). Moreover, the expression of TR α 1, TR α 2 and TR β 1 has been found in type 1 astrocytes from newborn rat brains. In these experiments, the levels of β 1 mRNA increased after T3 treatment, without changing TR α 1 and TR α 2 mRNA expression or T3 binding capacity (Lebel *et al.* 1993). Also using cultures from newborn rat brains, Carlson and co-workers (1996) detected the isoforms TR β 1, TR β 2, TR α 1 and TR α 2 in type 2 astrocytes, but found only the β 2 form in type 1 cells. Despite the marked differences in the profile of the TR isoform expression, the two astrocyte populations exhibited similar binding capacities. Recently, studies of slices from mutant mice showed that TR α 1 deficiency yields a severely altered pattern of astrocyte maturation in the cerebellum, which becomes normalized after the induction of hypothyroidism. These studies surprisingly suggest that liganded TR α 1 has a positive effect on astrocyte differentiation whereas liganded TR β 1 has an opposing effect and they indicate that normal astrocyte maturation requires a specific balance of TR β 1 and TR α 1 activity (Morte *et al.* 2004).

Thyroid hormone promotes astrocyte differentiation

It is known that during brain development, astrocytes are target cells for thyroid hormones (Clos & Legrand 1973, Patel *et al.* 1989, Gould *et al.* 1990). *In vivo*, neonatal hypothyroidism results in an increased number of astrocytes and Bergmann glia in the rat cerebellum and hyperthyroidism produces the opposite effect (Clos & Legrand 1973). *In vitro*, thyroid hormone has been reported to affect astrocyte morphology, GFAP organization and glutamine synthetase activity and expression (Aizenman & de Vellis 1987, Gavaret *et al.* 1991, Trentin & Moura Neto 1995, Trentin *et al.* 1995, 2003, Lima *et al.* 1997, Calloni *et al.* 2001) in addition to the regulation of protein phosphorylation (Ruel *et al.* 1986) and glucose transporter (Roeder *et al.* 1985, 1988, Ruel & Dussault 1985). In astrocytes, thyroid hormone is also involved in the regulation of extracellular matrix organization, growth factor secretion, and cell proliferation (Trentin & Moura Neto 1995, Trentin *et al.* 1995, 1998, 2001, 2003, Lima *et al.* 1997, Farwell & Dubord-Tomasetti 1999b, Martinez & Gomes 2002). It has also been suggested that thyroid hormone is involved in K⁺ buffering of the developing brain by regulating astrocyte NaKATPase expression (Banerjee & Chaudhury 2001). Moreover, the increased secretory phospholipase A2 (sPLA2) activity observed in primary cultures of newborn cerebral hemisphere astrocytes is partially reversed by thyroid hormone

addition, showing another contribution of thyroid hormone to brain homeostasis mediated by astrocytes (Thomas *et al.* 2000).

Thyroid hormone and astrocyte morphology

Astrocytes undergo changes in morphology, both during normal brain development (Fedoroff 1986) and during various pathological conditions (Duffy *et al.* 1980, Eng & Ghirnikar 1994). Extrinsic factors, including growth factors (Miller *et al.* 1995), neurotransmitters (Abe & Saito 1998), hormones (Aizenman & de Vellis 1987, Trentin & Moura Neto 1995, Trentin *et al.* 1995), transcriptional regulators (Gotz *et al.* 1998), cyclic-AMP derivatives (Lim *et al.* 1973) and phorbol esters (Mobley *et al.* 1986) have been suggested to regulate astrocyte morphology, leading to differentiation and maturation of these cells. The morphological differentiation of astrocytes induced by thyroid hormone has been explained on the basis of alterations in cytoskeleton. *In vitro*, T3 transforms flat polygonal astrocytes into process-bearing cells, accompanied by re-organization of GFAP filaments and protein synthesis (Aizenman & de Vellis 1987, Gavaret *et al.* 1991, Trentin *et al.* 1995). It has also been suggested that the effect of thyroid hormone on astrocyte morphological maturation is linked with the expression and phosphorylation of vimentin variants (Paul *et al.* 1999) as well as actin biogenesis and polymerization (Siegrist-Kaiser *et al.* 1990, Paul *et al.* 1996). In addition, thyroid hormone regulates the transition from radial glia to mature astrocytes, and from vimentin-positive to GFAP-positive cells in the basal forebrain and hippocampus (Gould *et al.* 1990, Martinez-Galan *et al.* 1997a). Neonatal thyroid hormone deficiency reduces GFAP concentration, promoting the delay in vimentin-GFAP transition in the cerebellum and hippocampus (Faivre-Sarrailh *et al.* 1991). Moreover, the effect of thyroid hormone on astrocyte maturation occurs during early development when maternal thyroid status regulates the expression of GFAP in the fetal brain (Sampson *et al.* 2000). Indeed, radial glia of fetal hypothyroid hippocampus have been shown to contain reduced amounts of GFAP, although the proportion of immature nestin-expressing fibers is not altered (Martinez-Galan *et al.* 1997), suggesting delayed maturation of glial cells.

In previous studies we have demonstrated, by the *in vitro* approach, that thyroid hormone induces morphological alterations in astrocytes from cerebral hemispheres and mesencephalon of newborn rats. These cells progressively change from a protoplasmatic to a process-bearing morphology. Fetal astrocytes also undergo similar morphological differentiation (Trentin *et al.* 1995, Lima *et al.* 1997). In addition, astrocytes from hypothyroid rats are more sensitive to T3 treatment than the control cells, displaying the process-bearing morphology earlier, possibly due to the up-regulation of thyroid hormone receptors (Trentin *et al.* 1995). The effect of thyroid

hormone on astrocyte morphological differentiation is suggested to be mediated by the synthesis and secretion of growth factor, because conditioned medium from T3-treated astrocytes presents similar results (Trentin *et al.* 1995, 1998, Lima *et al.* 1997). This factor presents a molecular weight lower than 8 kDa, which suggests insulin-like growth factor-I (IGF-I) (Trentin *et al.* 1998). Indeed, T3 has been implicated in the regulation of IGF-I production *in vivo* in both humans and animals (Fagin *et al.* 1989). Moreover, it has been demonstrated that β -adrenergic receptors can contribute to the thyroid hormone's morphological differentiation and maturation of cerebral astrocytes (Gharami & Das 2000), possibly associated with the sustained induction of mitogen-activated protein kinase (MAPK) (extracellular signal-regulated kinase; ERK) activity (Gharami & Das 2004). In fact, we have recently shown that congenital hypothyroidism alters the phosphorylation of ERK 1/2 and p38^{MAPK} kinases, but not of Jun N-terminal kinase, in the hippocampus *in vivo* (Calloni *et al.* 2005).

Thyroid hormone and astrocyte proliferation

Cerebellar astrocytes from newborn animals do not undergo morphological differentiation in response to T3 treatment, but proliferate instead (Trentin *et al.* 1995). Astrocytes cultured from 10-day-old cerebellum, however, display a stellate morphology after the same treatment (Lima *et al.* 1997), suggesting that the effects of thyroid hormone depend on the developmental state of the astrocyte. The cerebellar astrocyte's proliferation induced by T3 is mediated by the autocrine secretion of growth factors (Trentin *et al.* 1995, 1998, Lima *et al.* 1997). Our results revealed that T3 induces cerebellar astrocytes and the C6 glioma cell line to secrete a combination of growth factors, among which are acidic and basic fibroblast growth factor (aFGF and bFGF respectively), tumor necrosis factor- β (TNF β) and interleukin-3, which autocrinally promote cell proliferation. bFGF seems to be the principal growth factor (Trentin *et al.* 2001). Interestingly, the mitogenic effect of bFGF secreted by T3-treated C6 glioma cells is observed only after hyaluronidase digestion, suggesting that the growth factor is captured by proteoglycans and/or hyaluronic acid in the extracellular space, possibly representing a bFGF reservoir (Trentin *et al.* 2001).

Thyroid hormone and astrocyte extracellular matrix

Recently, we have shown that the bFGF secreted by cerebellar astrocytes after thyroid hormone stimulation, in addition to the proliferative effect, affects the extracellular matrix composition. T3-treated astrocytes display an increased amount of both laminin and fibronectin. These extracellular matrix proteins change their organization from a punctate to a fibrillar pattern, an effect which can

Figure 1 Model for the effect of thyroid hormone on neuronal development mediated by astrocytes. Thyroid hormone induces cerebellar astrocyte secretion of growth factors, such as basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), which autocrinally promote astrocyte proliferation, adhesion, and extracellular matrix (ECM) production and organization. The triiodothyronine (T3) action on astrocyte metabolism indirectly influences neuronal development. The growth factors secreted by astrocytes may also induce neuronal growth via the paracrine pathway. Adapted with permission from Trentin *et al.* (2003).

be reversed by neutralizing anti-bFGF antibodies (Trentin *et al.* 2003). Flat and spread astrocyte morphology has been observed, as well as increased attachment to the substratum (Trentin & Moura Neto 1995, Trentin *et al.* 2003). Moreover, epidermal growth factor (EGF) is secreted by cerebellar astrocytes after T3 stimulation, and it autocrinally regulates the extracellular matrix production in these cells through MAPK/phosphatidylinositol 3-kinase pathways (Martinez & Gomes 2002, 2005). In addition, T4 dynamically regulates integrin clustering and focal contact formation via modulation of micro-filament organization in astrocytes (Farwell *et al.* 1995). These affect the extracellular organization of laminin and thus control astrocyte attachment (Farwell & Dubord-Tomasetti 1999b).

Astrocytes are mediators of thyroid hormone in neuronal development

During brain development, thyroid hormone exerts significant influence on neuronal development. It has been

implicated in the survival, proliferation, migration, and also arborization and expression of specific phenotypic markers of neurons (Heisenberg *et al.* 1992, Muller *et al.* 1995, Gomes *et al.* 2001, König & Moura Neto 2002). Thyroid hormone is directly involved in the development of granule neurons by affecting the survival and differentiation of these cells (Heisenberg *et al.* 1992), in addition to preventing their apoptosis (Muller *et al.* 1995). Besides this direct effect of thyroid hormone on granular neuron development, an indirect mechanism mediated by astrocytes has been proposed (Gomes *et al.* 1999, Martinez & Gomes 2002, Trentin *et al.* 2003). Indeed, growth factor(s), secreted by astrocytes in response to T3 treatment induce(s) cerebellar granule cell proliferation. Such a growth factor has been identified as EGF, which, through the PKA pathway, promotes neuronal proliferation (Gomes *et al.* 1999, Martinez & Gomes 2005).

Moreover, thyroid hormone has been demonstrated to regulate the expression of extracellular matrix and adhesion molecules that are important for neuronal migration and development, such as tenascin-C (Alvarez-Dolado *et al.* 1998), Neural-cell adhesion molecule (N-CAM)

(Iglesias *et al.* 1996), reelin and dab1 (Alvarez-Dolado *et al.* 1999), L1 (Alvarez-Dolado *et al.* 2000), TAG-1 (Alvarez-Dolado *et al.* 2001), laminin and fibronectin (Trentin & Moura Neto 1995, Farwell & Dubord-Tomasetti 1999b, Calloni *et al.* 2001, Martinez & Gomes 2002, Trentin *et al.* 2003). *In vitro*, thyroid hormone down-regulates the expression of tenascin-C in glioma cell lines, whereas *in vivo*, hypothyroidism increases both RNA and protein levels of this extracellular matrix molecule in specific areas of the rat brain, including Bergmann glia of the cerebellum, in early post-natal life (Alvarez-Dolado *et al.* 1998). In addition, thyroid hormone regulates the expression of laminin in the developing rat cerebellum (Farwell & Dubord-Tomasetti 1999a), and of fibronectin in the midbrain but not in the cerebral hemispheres of newborn rats (Calloni *et al.* 2001).

Thyroid hormone regulates astrocyte morphogenesis to promote neuronal development

Consistent with the suggested indirect role of thyroid hormone in neuronal development via astrocytes, we verified that cerebellar neurons co-cultured on T3-treated astrocytes are more numerous and display longer neurites than those cultivated on control cells. This effect is related to the altered expression of extracellular matrix proteins induced by thyroid hormone and mediated by bFGF that stimulates, in astrocytes, the production and re-organization of laminin and fibronectin from a punctate to a fibrillar pattern (Trentin *et al.* 2003). In fact, laminin and fibronectin organized in a fibrillar pattern have been demonstrated to promote neurite outgrowth (Garcia-Abreu *et al.* 1995). Moreover, the EGF secreted after T3 stimulation has also been demonstrated to indirectly promote neurite outgrowth by the regulation of astrocyte extracellular matrix production involving MAPK/phosphatidylinositol 3-kinase pathways (Martinez & Gomes 2002). Indeed, a model for the effect of thyroid hormone on granular neuronal development mediated by astrocytes might be proposed in which T3 induces the astrocyte secretion of growth factors, such as bFGF and EGF, which autocrinally affects several astrocytic characteristics such as morphology, proliferation, adhesion and extracellular matrix production and organization, and thus influences neuronal development. These growth factors may directly influence neuronal growth and neurogenesis by themselves (Fig. 1).

Future directions

Classically, neurons and oligodendrocytes are studied as target cells for thyroid hormone. However, astrocytes are now viewed as important brain mediators of this morphogenetic hormone. Recent reports have demonstrated the action of thyroid hormone in adult neurogenesis in the

subventricular zone (Lemkine *et al.* 2005) and in the hippocampus (Desouza *et al.* 2005), and also in hippocampal neurogenesis during development (Uchida *et al.* 2005). Considering the emerging roles of astrocytes, such as their stem cell properties and involvement in synapse transmission, we might therefore predict that novel and important functions of this cell type concerning thyroid hormone actions on brain development will be revealed in the near future.

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