

Thyroid Hormone Action and Brain Development

Noriyuki Koibuchi and William W. Chin

Thyroid hormone (TH) plays a crucial role in brain development. Developing rodent cerebellum might be an excellent model for studying the molecular mechanisms of TH action in the brain because perinatal hypothyroidism greatly affects its ontogeny. Although the TH-regulated genes that play crucial roles in cerebellar development have not yet been fully characterized, recent studies have provided novel insights into TH action in brain development.

The thyroid hormones (3,5,3'-L-triiodothyronine, T_3 ; 3,5,3'5'-L-tetraiodothyronine, T_4 ; TH) play crucial roles in the growth and differentiation of many organs, including the central nervous system (reviewed in Refs 1,2). Deficiency of TH during the perinatal period results in severe mental and physical retardation, known as cretinism in humans.

TH exerts its major effect by binding to the nuclear TH receptor (TR). TR is bound to specific DNA sequences known as TH-response elements (TREs), composed of two half-site core motifs (AGGTCA), with specific nucleotide spacing and orientation. TR also interacts with retinoid X receptors (RXRs) to form heterodimers, which, in turn, bind to several coregulators such as corepressors and coactivators. The liganded TR-RXR-coregulator complex ultimately determines nuclear TH action (reviewed in Ref. 3).

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T_3 , the most potent TH, is mostly produced locally in the brain by 5'-deiodination from T_4 , which enters the developing brain more readily than T_3 (Ref. 4). Type II iodothyronine 5'-deiodinase (D2), which is abundant in the brain⁵, is largely responsible for the conversion of T_4 to T_3 at this site⁶. In hypothyroidism, D2 activity is upregulated, probably to protect the brain from TH deficiency⁷. D2 is mainly found in astrocytes, suggesting that T_4 is taken up from capillaries by astrocytes, deiodinated to T_3 , and transferred to neurons with direct cell-to-cell contact for interaction with TR (Ref. 8). Although the gene encoding TR is highly expressed in many brain regions during development⁹, the target genes of TH that play crucial roles in brain development are not yet well defined.

• Developing Rodent Cerebellum as a Model System to Study TH Action in the Brain

Brain development in the rodent occurs early, relative to humans. For example, the rat brain at birth is at the same stage as the human brain at five to six months of gestation, and the rat brain at ten days of postnatal age is equivalent to the human brain at birth¹. The development

of the cerebellum occurs at a later stage of brain development. Thus, neuronal development of the rodent cerebellum is largely postnatal¹⁰, and perinatal hypothyroidism dramatically affects cerebellar development (reviewed in Refs 11,12) (Fig. 1). Each subset of neurons in the cerebellar cortex is readily identified histologically and its circuitry is relatively simple compared with other brain structures. Furthermore, TRs are expressed in all cerebellar neuron types^{9,13}. Therefore, the developing rodent cerebellum might be an excellent model system to study TH action in the brain.

In the cerebellum, various anatomical alterations induced by perinatal hypothyroidism have been well documented. These include: reduction of growth and branching of dendritic arborization of Purkinje cells^{11,14,15}; reduction of synaptogenesis between Purkinje cells and granule cell axons^{15,16}; delayed proliferation and migration of granule cells¹⁷; delayed myelination¹⁸; and changes in synaptic connection among cerebellar neurons and afferent neuronal fibers¹⁹. These abnormalities cannot be avoided unless TH is replaced within two weeks of birth¹⁴. Figure 2 summarizes these changes in the hypothyroid cerebellum.

• Current Progress in our Understanding of the Molecular Mechanisms of TH Action in Cerebellar Development*

As mentioned above, TH exerts its effect largely by binding to nuclear TR, a ligand-regulated transcription factor. At present, the expression of many

*In this review, we have used gene names following established gene nomenclature guidelines (reviewed in Refs 20,21): gene names are italicized and begin with an upper case letter followed by lower case letters; gene products are printed in non-italicized upper case.

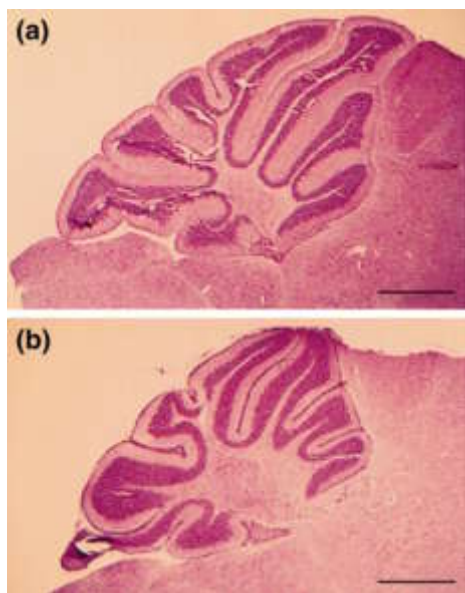


Figure 1. Photomicrographs showing the effect of perinatal hypothyroidism on cerebellar development. Sagittal cerebellar sections (at the level of the vermis) are shown of (a) a euthyroid mouse and (b) a hypothyroid mouse at postnatal day 15. Scale bars = 0.85 mm.

genes is known to be altered in perinatal hypothyroid cerebellum^{22–29}. Each gene has a distinct ‘critical period’, a limited time interval during which TH can affect its expression. The timing and duration of such periods vary among TH-responsive genes but, in most cases, occur within the first two weeks of postnatal life. After this time interval, the expression of these genes achieves the same level as that of the euthyroid animal, despite morphological alterations, although some of these genes are known to be regulated directly by TR (Refs 29–31). Although many TH-regulated genes are known, the direct TH target genes that are crucial for normal development are not well clarified. However, several genes that may play key roles in TH-mediated cerebellar development have been identified. Furthermore, recent studies have shown the involvement of several transcription factors that might regulate TR-mediated transcription in cerebellar neurons. The production of some of these transcription factors is regulated, in turn, by TH.

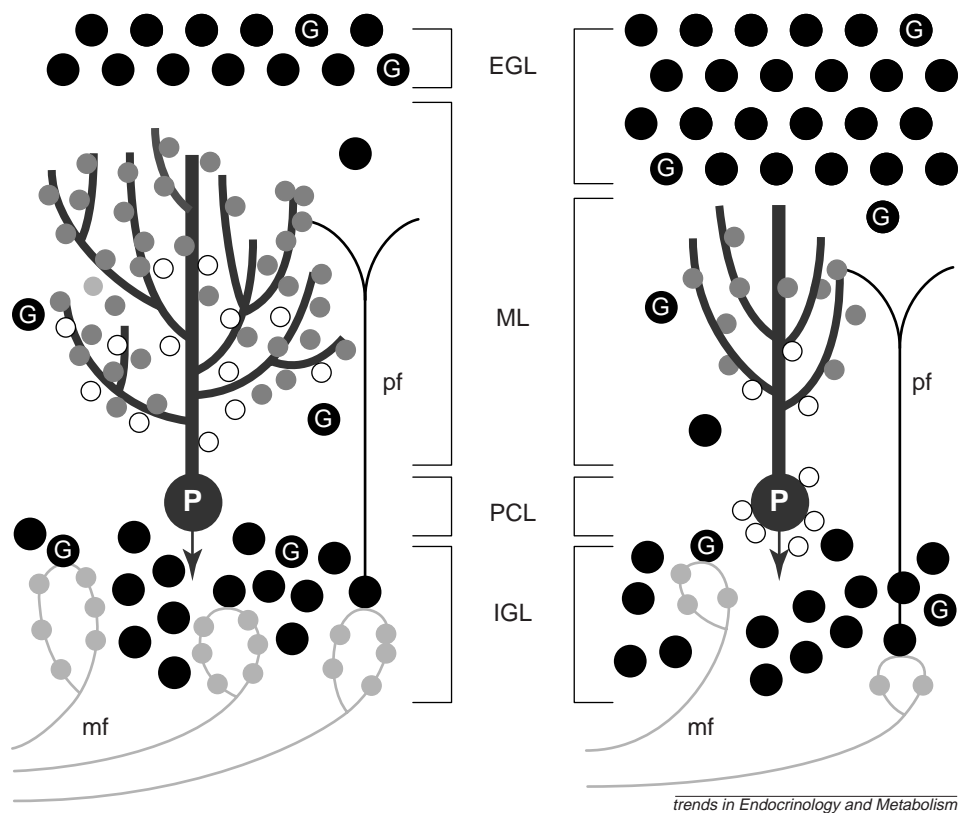
TH Target Genes in Cerebellar Development

There are several genes known to be regulated directly by TH in the cerebellum at

the transcriptional level. Among such genes whose function is established, the gene encoding myelin basic protein (MBP; encoded by *Mbp*) is the best studied³⁰. Delayed myelination induced by perinatal hypothyroidism is an established abnormality seen in the hypothyroid brain²⁰. *Mbp* is expressed in oligodendrocytes and regulates myelination of neurons. The changes in expression of *Mbp* in the oligodendrocyte might effect changes in myelination in altered TH states. However, this regulation cannot fully explain abnormal brain development seen in the hypothyroid animal.

Current studies have raised the possibility that neurotrophins, such as brain-derived neurotrophic factor (BDNF; encoded by *Bdnf*) and neurotrophin 3 (NT-3; encoded by *Nt3*), might be

regulated directly by TH. These factors belong to a group of proteins that also include nerve growth factor and NT-4/5, which play crucial roles in neuronal differentiation, neurite growth and synaptogenesis (reviewed in Ref. 32). In the hypothyroid rat, Purkinje cell dendrite arborization and synaptogenesis between Purkinje and granule cells are suppressed, events associated with decreased levels of *Nt3* and *Bdnf* mRNA (Refs 12,23,33,34) (Fig. 3). Replacing NT-3 or BDNF, in part, prevents hypothyroidism-induced abnormal cerebellar development²³. Furthermore, *Bdnf*-knockout mice show delayed migration of granule cells and decreased arborization of Purkinje cell dendrites³⁵, which are also seen in hypothyroid animals. These results indicate that BDNF and NT-3 might



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Figure 2. Schematic diagram showing the effect of perinatal hypothyroidism on neurogenesis and differentiation in the cerebellar cortex. In the hypothyroid cerebellum, disappearance of the EGL is retarded as a result of delayed proliferation and migration of granule cells (black circles, also shown as ‘G’) to the IGL. In the ML, the arborization of the Purkinje cell (P) dendrite is decreased. Synaptic connections between Purkinje cell dendrites and parallel fibers (pf) from granule cells (pale grey circles on the Purkinje cell dendrite) are also decreased. Synaptic connections between Purkinje cells and climbing fibers are shown by black, open circles. Note that the disappearance of axosomatic synapses between climbing fibers and Purkinje cells is retarded in the hypothyroid animal. Also note that synaptic connections between mossy fibers (mf) and granule cells (shown by pale grey circles on the mf) are decreased. Abbreviations: EGL, external granule cell layer; IGL, internal granule cell layer; ML, molecular layer; PCL, Purkinje cell layer.

play an essential role in TH-mediated cerebellar development. TREs within the promoter regions of their genes have not yet been identified. However, these genes contain multiple transcription start sites linked with different promoters, and their expression is regulated by TH in a promoter-specific manner^{34,36}.

Recently, reelin (encoded by *Reln*), which plays a crucial role in neuronal migration and lamination (reviewed in Ref. 37), has been shown to be under TH control²⁸. *Reln* is exclusively expressed in granule cells during cerebellar development. The level of *Reln* mRNA is decreased by hypothyroidism at an earlier stage of cerebellar development [embryonic day (E) 18, postnatal day (P) 0]. During the migratory period of the granule cell (P5–P15), *Reln* expression is still under the control of TH. These results indicate that the abnormal neuronal migration seen in the hypothyroid animal might be mediated in part by the change in *Reln* expression. Whether *Reln* is under direct control of TH is not known. Interestingly, BDNF regulates *Reln* expression³⁸. Therefore, changes in *Reln* expression seen in the hypothyroid cerebellum may be exerted, in part, through changes in *Bdnf* gene expression.

Another TH-regulated gene that might be crucial for cerebellar development is that encoding neural cell adhesion molecule (N-CAM; encoded by *Ncam*)²⁵. N-CAM plays an important role in controlling cell–cell interactions that affect neuronal migration, differentiation and synaptogenesis (reviewed in Ref. 39), events altered by perinatal hypothyroidism. The expression of *Ncam* is upregulated in the hypothyroid animal. A TR-binding site was identified in its intron, suggesting that the *Ncam* gene is directly regulated by TH. Because N-CAM plays a particularly important role in cellular migration by controlling the intensity of neuron–glia interactions³⁹, changes in N-CAM levels in perinatal hypothyroidism might alter the rate of neuronal migration.

Involvement of Transcription Factors in TR-mediated Cerebellar Development

We have recently shown that a retinoic acid receptor-related orphan nuclear

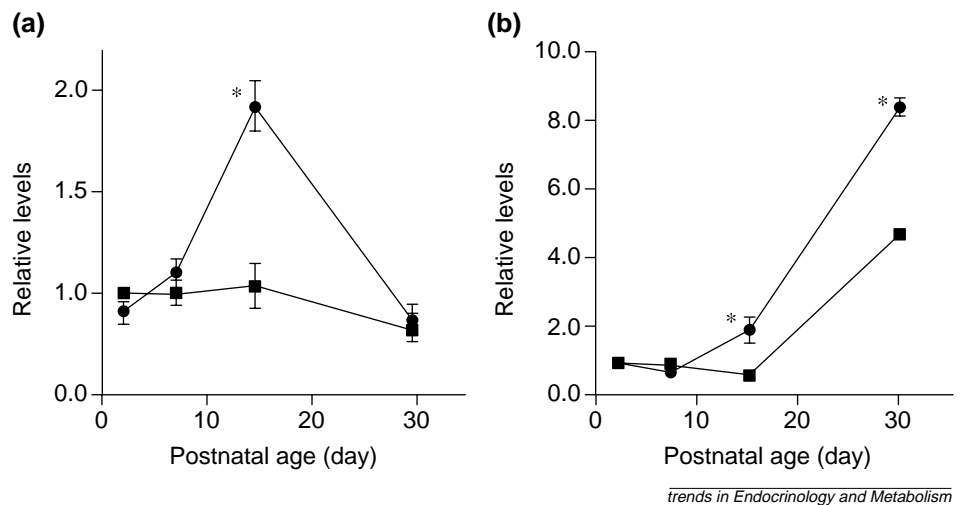


Figure 3. Effect of daily T₄ replacement on (a) *Nr3* and (b) *Bdnf* mRNA (encoding neurotrophin 3 and brain-derived neurotrophic factor, respectively) content in the hypothyroid newborn rat cerebellum (reproduced, with permission, from Refs 12,34, ©The Endocrine Society). Mothers of the pups received 0.05% propylthiouracil (PTU) in their drinking water. T₄ (2 µg 100 g⁻¹ body weight) was injected subcutaneously every day. *p < 0.01 compared with the hypothyroid rat. Key: closed squares, hypothyroid rats; closed circles, T₄-replaced rats.

receptor (RORα), a member of the steroid hormone nuclear receptor superfamily, might be involved in TH-mediated cerebellar development^{27,40}. A mutant mouse, called *staggerer*, in

which the *Rora* gene is disrupted⁴¹, exhibits morphological and neurological abnormalities of the cerebellum similar to those seen in the hypothyroid animals⁴², in the face of normal blood

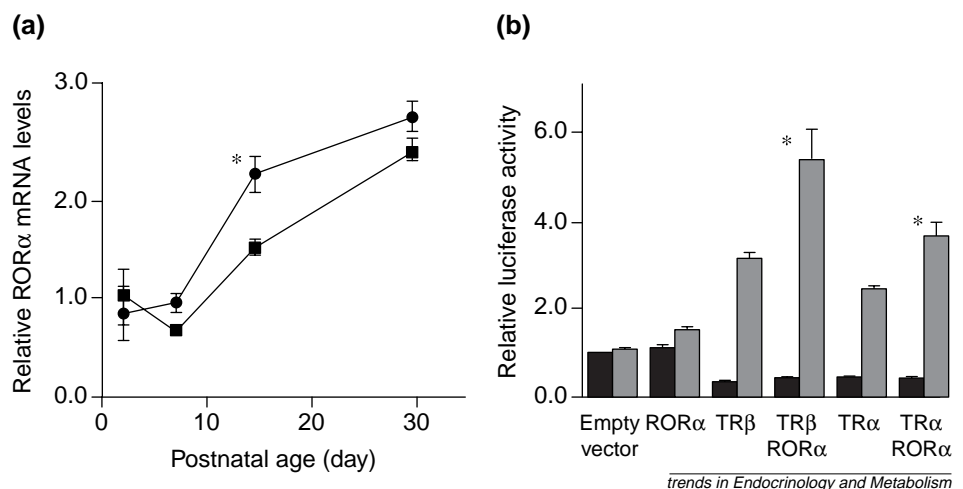
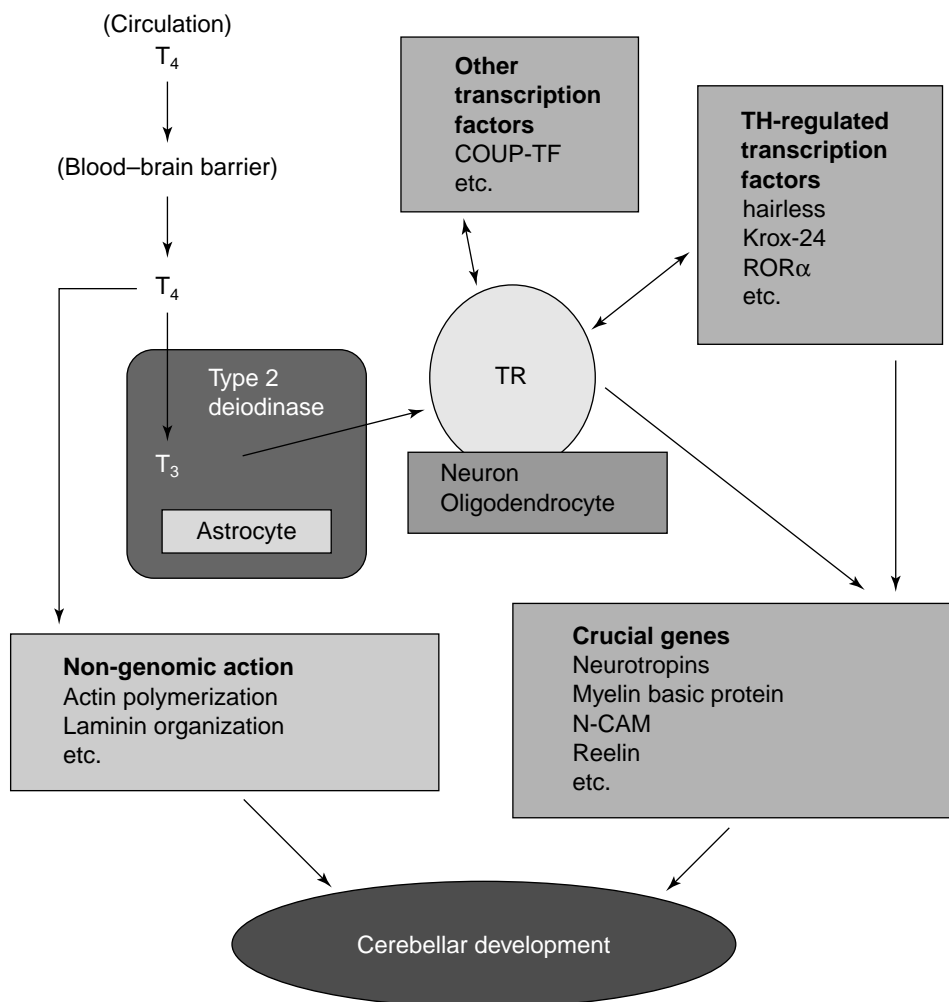


Figure 4. (a) Effect of daily T₄ replacement on *Rora* mRNA [encoding retinoic acid receptor-related orphan nuclear receptor (ROR)] content in the hypothyroid newborn rat cerebellum (reproduced, with permission, from Ref. 27, ©The Endocrine Society). Mothers of the pups received 0.05% propylthiouracil (PTU) in their drinking water. T₄ (2 µg 100 g⁻¹ body weight) was injected subcutaneously every day. *p < 0.01 compared with the hypothyroid rat at postnatal day 15 (closed squares, hypothyroid rats; closed circles, T₄-replaced rats). (b) Interaction of thyroid hormone receptor (TR) and RORα1 on the TR-response element (TRE) (reproduced, with permission, from Ref. 40, ©The Endocrine Society). DNA encoding TR and/or RORα1 was co-transfected into CV-1 cells along with a reporter plasmid containing DNA encoding a TRE coupled with the luciferase reporter gene, and cultured with (hatched bars) or without (solid bars) T₃. Luciferase activity in the cell extract was measured. Unliganded TRα1 and TRβ1 repressed basal transcription. In the presence of T₃, liganded TRs enhanced transcriptional activity above basal levels. Addition of RORα1 further augmented the *trans*-activation by T₃ but basal repression was unaffected. *p < 0.01 compared with TR-transfected and T₃-treated group.



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Figure 5. Diagram showing potential factors involved in thyroid hormone (TH) action in cerebellar development. Abbreviations: COUP-TF, chicken ovalbumin upstream promoter-transcription factor; N-CAM, neural cell adhesion molecule; ROR α , retinoic acid receptor-related orphan nuclear receptor; TR, TH receptor.

TH levels⁴³. *Rora* transcripts are highly expressed in the brain, especially in the Purkinje cell. Although the thyroid function of these mutant mice appears normal, the expression of a TH-regulated gene (*Pcp2*) is diminished⁴¹. *Pcp2* is expressed in the Purkinje cell but its function is unknown. Therefore, we hypothesized that either TH might regulate *Rora* gene expression, which then controls genes crucial for normal cerebellar development, and/or conversely ROR α modulates TR action. As shown in Fig. 4a, daily T₄ treatment significantly accelerated the increase in cerebellar *Rora* gene expression compared with that of the hypothyroid rat²⁷. Cerebellar *Pcp2* gene expression was also increased by T₄ administration. These

results suggest that TH might exert its effect, at least in part, by regulating the *Rora* gene, which might then regulate the expression of other genes essential for normal Purkinje cell development. Furthermore, ROR α augments the effect of liganded TR on various TREs, without affecting basal repression by unliganded TR (Ref. 40) (Fig. 4b). Although further studies are required to identify genes regulated by ROR α or TR-ROR α complexes, ROR α might play a key role in the full expression of TH action in cerebellar development.

Another orphan nuclear receptor, chicken ovalbumin upstream promoter-transcription factor (COUP-TF), a known transcriptional repressor, which is found in high amounts in fetal and

early neonatal cerebellum, decreases TR-mediated *trans*-activation⁴⁴. During the prenatal period when the *Couptf* gene is highly expressed in the Purkinje cell, TH-regulated gene expression is relatively unresponsive to TH (Ref. 45), indicating that this factor might control, in part, the responsiveness of TH-responsive genes to TH by modulating TR action during brain development.

There are other transcription factors whose functions in cerebellar development are not known but might also modulate TH-mediated cerebellar development. Thompson and Bottcher⁴⁶ have shown that *hairless* (*hr*), a gene that is expressed in perinatal cerebellum and is directly regulated by TR (Ref. 26), encodes a protein that interacts with TR to limit *trans*-activation by TR. On the other hand, *Krox24* (also known as *Ngf1a* or *Egr1*), an immediate-early gene encoding a zinc finger transcription factor playing an important role in cellular mitosis, has recently been reported to be under the direct control of TH (Ref. 29). The transcription of this gene is regulated by TH on P2 but not P6. However, no difference in the mitotic activity of the granule cell at the two time points was seen, so that the role of *Krox24* in TH-mediated cerebellar development is still unclarified.

• Concluding Remarks

Figure 5 summarizes the possible interactions mediating TH action in cerebellar development. Although we have focused mainly on the genomic action of TH, non-genomic actions of TH, such as actin polymerization and extracellular organization of laminin, might also play important roles in cerebellar development, in particular, neuronal migration^{47,48}. T₄ is converted to T₃ by type II 5'-deiodinase in astrocytes. Then T₃ is transferred to neurons to associate with nuclear TR to regulate gene expression. TH might, in part, exert its effect by directly regulating genes that encode peptides crucial for cerebellar development such as MBP, N-CAM, neurotrophins and reelin. On the other hand, TH might regulate the expression of genes encoding other transcription factors, which might, in

turn, regulate crucial genes. Such TH-regulated transcription factors might also interact with TR to modulate its action. Examples of such genes are *hr*, *Krox24* and *Rora*. In addition, there are other transcription factors that might not be regulated by TH but are developmentally regulated to modulate TR action, such as COUP-TF. However, these are not likely to be the only factors mediating TH action in cerebellar development. Clearly, additional factors must be involved in this process. Many studies to identify such crucial genes are currently under way.

There are still several issues that remain to be clarified. For example, recent experiments using TR-knockout mice have shown that they have a normal neuronal phenotype, without apparent abnormal brain development compared with perinatal hypothyroid animals (reviewed in Ref. 49). Why is there no apparent altered brain phenotype in these mice? To address this question, brain-specific inhibition of TH action using tissue-specific gene knockout might be necessary. Another important question to be investigated concerns the molecular mechanisms generating the critical period of TH action in the brain. What makes such genes responsive to TH only during a limited amount of time during development? Because multiple factors are involved in TR-mediated transcription, multiple *in vivo* and *in vitro* approaches are probably required to address this difficult issue.

Studies of the molecular mechanisms of TH action in cerebellar development will provide useful information for our further understanding of the role(s) of TH in cerebellar development. Because the rodent cerebellum is a useful model for such studies, it might provide new insights that will have clinical relevance to cretinism and infantile hypothyroidism.

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Current Therapy for Acromegaly

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Acromegaly is a disabling disease that is associated with reduced life expectancy. Lowering growth hormone (GH) concentrations rapidly improves patient wellbeing. Recent data also indicate that GH concentrations <2.5 $\mu\text{g l}^{-1}$ are associated with improved mortality, providing a therapeutic goal in the majority of patients. In most cases, initial therapy should be surgical via the transsphenoidal route and conducted by an experienced operator. In such centres of excellence, ~60 out of every 100 acromegalic patients should be 'cured' (GH <2.5 $\mu\text{g l}^{-1}$) by surgery alone. Effective medical therapies have been introduced in the form of long-acting somatostatin analogues – octreotide and lanreotide – and depot preparations of these drugs result in lowering of GH to <2.5 $\mu\text{g l}^{-1}$ and normalization of IGF-I concentrations in 55–65% of cases. Preliminary results are also emerging on Pegvisomant, a genetically engineered GH receptor antagonist, which is clinically and biochemically very effective. It is likely that this drug will be licensed for use in patients with acromegaly in the near future. These effective medical therapies will undoubtedly raise the issue of their use as primary therapy for acromegaly but at present they should be used as an adjunct to surgery and/or radiotherapy.

The primary aims of therapy for patients with acromegaly should be to remove symptoms, reduce tumour bulk, prevent regrowth of the tumour and improve long-term outcome. The symptoms

of the disease are frequently disabling and include lethargy, sweating, headaches, arthralgia and paraesthesiae. The disease can cause diabetes mellitus and hypertension, and patients have a two to threefold increase in mortality as a result of cardiovascular disease, respiratory disease and malignancy (notably colonic and breast cancer)¹. Although surgery and/or radiotherapy have been used to achieve these therapeutic aims

for many years, there have been several recent advances in the treatment of acromegaly. First, there is now evidence that effective lowering of growth hormone (GH) levels to <2.5 $\mu\text{g l}^{-1}$ improves mortality, providing a therapeutic goal that should be aimed for in all patients. Second, surgical techniques have improved so that surgical 'cure' rates in excess of 50% can now be anticipated. Third, effective medical treatments are now in place, and these are so beneficial in some patients that their use as primary therapy has been raised. Endocrinologists play a crucial and pivotal role in the management of patients with acromegaly and should therefore be aware of these new advances. Furthermore, the appropriate coordination of local resources and referral patterns can in themselves improve therapeutic outcome.

• Lowering GH Improves Mortality

Although symptomatic improvement occurs rapidly with lowering of GH levels, the absence of any long-term outcome data focused attention on the definition and achievement of cure in patients with acromegaly. Over the past 20 years, and based on scanty data, this cure value became more stringent, falling from values of 10 $\mu\text{g l}^{-1}$ to 5 $\mu\text{g l}^{-1}$ and most recently, to 2.5 $\mu\text{g l}^{-1}$. How to measure the GH–insulin-like growth factor (IGF)-I axis in defining cure has also been open to debate, with discussions on the merits of random GH, fasting GH, mean or nadir values across a glucose tolerance test, day profiles, stimulated values following thyrotrophin-releasing hormone (TRH) or

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