Thyroid

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Again in the last 12 months a number of more than 3,000 references were published under the search heading 'thyroid'. Most of the papers are related to thyroid malignancies, a topic which has not seen a relevant pediatric contribution this year. The two papers with the highest impact factors and relevance to pediatric endocrinology deal with iodine and with interrelation of thyroid function and regulation of metabolism. Iodine got its share from a publication in the New England Journal of Medicine showing the possibly harmful effect of iodine overdose resulting in a pro-immunogenic effect. The *Cell* paper on metabolism and thyroid function was provided by the NURSA consortium which went out to analyze the expression of the known 49 nuclear receptors. As part of this 'mega-project', the researchers identified that most of the nuclear receptors are expressed in a coordinated and timely synchronized fashion referred to as 'megagenic entity' influencing metabolism. The thyroid hormone receptors α and β are members of this entity and are expressed in several tissues with daytime rhythmicity. These data may explain daily differences in thyroid hormone function despite the fact that circulating thyroid hormone remains constant around the clock.

Thyroid function around the clock: rhythmicity in the thyroid axis

Nuclear receptor expression links the circadian clock to metabolism

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Background: As sensors for fat-soluble hormones and dietary lipids, oscillations in nuclear receptor expression in key metabolic tissues may contribute to circadian entrainment of nutrient and energy metabolism.

Methods: Survey of the diurnal expression profiles of all 49 mouse nuclear receptors in white and brown adipose tissue, liver, and skeletal muscle.

Result: Of the 45 nuclear receptors expressed, 25 are in a rhythmic cycle and 3 exhibit a single transient pulse of expression 4 h into the light cycle. While thyroid hormones are generally constant, they found that TR α and TR β dramatically cycle, suggesting that fundamental concepts such as 'basal metabolism' may need to be revisited.

Conclusion: The dynamic but coordinated changes in nuclear receptor expression, along with their key target genes, offer a logical explanation for the known cyclic behavior of lipid and glucose metabolism and suggest novel roles for endocrine and orphan receptors in coupling the peripheral circadian clock to divergent metabolic outputs.

Day-cycle rhythmicity of physiological functions is rendered by a sophisticated molecular clockwork which has a pendulum, so to say, of transcription factor activation and inactivation with a 24-hour phase (fig. 1). This molecular clock, which was discovered in *Drosophila* mutants and was shown to equally function in mice, is synchronized in the suprachiasmatic nucleus via light sensed in specialized melanopsin-positive ganglion cells of the retina. However, how the synchronized suprachiasmatic nucleus clock signals its day cycle to the several clocks of the different organs and tissues is still unknown. The cycling activation and inactivation of transcription factors lead to downstream target gene regulation dependent on the respective cell populations where the local clockworks tick. The present paper of Yang et al. describes for the first time the rhythmicity of the complete range of nuclear receptor genes in metabolic tissues of mice, e.g. white and brown adipose tissue, liver and muscle. All nuclear receptor genes which were identified as being expressed in a day-cycle-dependent way can be seen as targets of the molecular clockwork factors. Among them the authors found the

Fig. 1. Coordination of circadian timing of thyroid hormone receptor expression in metabolic tissues. Sunlight activation of melanopsin-positive retinal ganglion cells (1) which form a retinohypothalamic tract that projects to the suprachiasmatic nucleus (SCN) (2). Within SCN neurons a molecular clock mechanism of positive and negative feed-back loops (3) leads to a rhythmic expression of KEY transcription factors like the clock-gene, *bmal1* gene and *per1/2* gene products with a 24-hour cycle. Sunlight synchronizes the cycle with the day-night cycle via the retinohypothalamic tract (4). The information of the synchronized central clock mechanism is transferred to peripheral tissue with an unknown mechanism with the consequence of day-night cycle synchronized expression of target genes. By that mechanism, thyroid hormone receptors α and β are tissue-specific differentially expressed (6). The non-rhythmic secreted free T_4 exerts its effect on the metabolic tissues in a rhythmic function via the partially rhythmic expression of the two different thyroid hormone receptors (7).

thyroid hormone receptors α and β ; both were rhythmic in white adipose tissue, α rhythmic in brown adipose tissue and liver while none of them are rhythmic in muscle. Since it has been shown that the free thyroid hormone is constantly present in serum all over a day cycle without fluctuation – most likely due to the long half-life of thyroid hormones – it was so far puzzling how thyroid effects are day-cycle-dependent, especially metabolic activity. The study of Yang et al. now explains this daytime-specific effect of thyroid hormone by the rhythmic expression of the receptors. However, one might argue that the long biological half-life of thyroid hormones for even several days as initiated via the classical nuclear signal transduction of thyroid hormone receptors is not compatible with a 24-hour rhythmicity. This well-taken argument is losing strength since the following paper published in *PNAS* this year further underlines the non-classical, non-nuclear receptor and rapid responses of thyroid hormone receptors.

Rapid signaling at the plasma membrane by a nuclear receptor for thyroid hormone

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Proc Natl Acad Sci USA 2006;103:5197–5201

Background: Many nuclear hormones have physiological effects that are too rapid to be explained by changes in gene expression and are often attributed to unidentified or novel G-protein-coupled receptors. Thyroid hormone is essential for normal human brain development, but the molecular mechanisms responsible for its effects remain to be identified.

Result: The authors present direct molecular evidence for potassium channel stimulation in a rat pituitary cell line (GH₄C₁) by a nuclear receptor for thyroid hormone, TR β , acting rapidly at the plasma membrane through phosphatidylinositol 3-kinase (PI₃K) to slow the deactivation of KCNH₂ channels already in the membrane. Signaling was disrupted by heterologous expression of TR β receptors with mutations in the ligand-binding domain that are associated with neurological disorders in humans, but not by mutations that disrupt DNA binding. More importantly, PI₃K-dependent signaling was reconstituted in cell-free patches of membrane from CHO cells by heterologous expression of human KCNH₂ channels and TR β , but not TR α , receptors.

Conclusion: TR β signaling through PI₃K provides a molecular explanation for the essential role of thyroid hormone in human brain development and adult lipid metabolism.

As mentioned above, this paper resolves the enigma of the rapid and transient effects of thyroid hormones on their receptors and of the need for a rhythmic expression of the thyroid hormone nuclear receptors. Because the biological half-life of the gene regulation function of the TRs is so long, it would make no sense that the TRs are expressed in a day-cycle-specific rhythm. But the rapid function via the cell membrane rather than via the nucleus creates a perfectly fitting picture of cycling thyroid hormone function: while the thyroid hormone levels themselves are constant (see next paper), the receptors are cycling and the rapid signal transduction pathways of the TRs at least give short-lasting cycling biological responses on metabolic functions.

Effects of evening versus morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients

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Background: Standard drug information resources recommend that L-thyroxine be taken half an hour before breakfast on an empty stomach, to prevent interference of its intestinal uptake by food or medication. Cases were observed in which TSH levels improved markedly after changing the administration time of L-thyroxine to the late evening. Therefore, 12 female patients were studied on two occasions: on a stable regimen of morning thyroxine administration and 2 months after switching to night-time thyroxine using the same dose. On each occasion, patients were admitted for 24 h and serial blood samples were obtained.

Result: A significant difference in TSH and thyroid hormones was found after switching to bedtime administration of L-thyroxine. 24-hour average serum values amounted to (mean $\pm$ SD, morning vs. bedtime ingestion): TSH, 5.1 ± 0.9 vs. 1.2 ± 0.3 mU/l ($p < 0.01$); FT₄, 16.7 ± 1.0 vs. 19.3 ± 0.7 pmol/l ($p < 0.01$); T₃, 1.5 ± 0.05 vs. 1.6 ± 0.1 nmol/l ($p < 0.01$). There was no significant change in T₄, rT₃, albumin and TBG serum levels, nor in the T₃/rT₃ ratio. The relative amplitude and time of the nocturnal TSH surge remained intact.

Conclusion: L-Thyroxine taken at bedtime by patients with primary hypothyroidism is associated with higher thyroid hormone concentrations and lower TSH concentrations compared to the same L-thyroxine dose taken in the morning. At the same time, the circadian TSH rhythm stays intact. The findings are best explained by a better gastrointestinal uptake of L-thyroxine during the night.

While searching for a better treatment in patients with unsatisfying TSH levels despite high LT_4 doses, the authors tested the hypothesis that resorption of ingested LT_4 at night-time might be better than at day-time. And surprisingly they could show that taking LT_4 at night increases FT_4 and decreases TSH. Including several other LT_4 kinetic parameters they could show that the differences in 24-hour total T_4 levels are secondary to changes in the binding proteins TBG and albumin and that FT_4 remains impressively stable over 24 h. This paper has important practical implications for millions of patients worldwide who are told to take their thyroid hormone half an hour before breakfast and who may – if the data are confirmed – sleep half an hour longer and take their tablets in the evening. In addition, these data nicely show the daily rhythmicity of TSH, T_4 and FT_4 . While TSH levels increase at night-time without change in FT_4 – most likely due to a lower biological activity of night-time TSH hypoglycosylation – total T_4 decreases over night parallel to the lower binding proteins TBG and albumin at night-time. The authors explain the lower night-time protein concentrations by postural changes with lower levels in supine positions. However, the changes in TSH bioactivity cannot be easily explained and might represent the effect of the molecular 24-hour clockwork within pituitary thyrotropic cells.

Linking eating and heating: new complex interrelations of the thyroid axis and metabolism

A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T_3 and UCP2

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Cell Metab 2007;5:21–33

Background: The active thyroid hormone, triiodothyronine (T_3), regulates mitochondrial uncoupling protein activity and related thermogenesis in peripheral tissues. Type 2 deiodinase (DII), an enzyme that catalyzes active thyroid hormone production, and mitochondrial uncoupling protein-2 (UCP2) are also present in the hypothalamic arcuate nucleus, where their interaction and physiological significance have not been explored.

Result: The authors report that DII-producing glial cells are in direct apposition to neurons coexpressing neuropeptide Y (NPY), agouti-related protein (AgRP), and UCP2. Fasting increased DII activity and local thyroid hormone production in the arcuate nucleus in parallel with increased GDP-regulated UCP2-dependent mitochondrial uncoupling. Fasting-induced T_3 -mediated UCP2 activation resulted in mitochondrial proliferation in NPY/AgRP neurons, an event that was critical for increased excitability of these orexigenic neurons and consequent rebound feeding following food deprivation.

Conclusion: These results reveal a physiological role for a thyroid-hormone-regulated mitochondrial uncoupling in hypothalamic neuronal networks.

In the periphery, thyroid hormone exerts its influence on increased metabolic rate by an increase of the mitochondrial uncoupling protein activity, which leads to increased thermogenesis. This pathway of T_3 -UCP2-mitochondria activation was surprisingly found also within the hypothalamus (fig. 2). Within arcuate nucleus glial cells, serum T_4 is transformed into the receptor-active T_3 by deiodinase 2. T_3 is subsequently transferred to the neighboring neuronal cells expressing NPY where UCP2-dependent mitochondrial activation leads to increased neuronal activity of the orexigenic, weight-increasing NPY cells. It seems that nature likes winning teams and the same efficient T_3 signal pathway known in the periphery is surprisingly used in the central nervous system too, however with an opposing effect. While the T_3 -UCP2-mitochondria pathway in the periphery increases caloric use by increasing thermogenesis, the central T_3 -UCP2-mitochondria pathway leads to stimulation of the NPY orexigenic pathway with the consequence of an increase of caloric intake. Maybe the simultaneous activation of burning calories and increasing calories by peripheral and central T_3 function respectively represent a wise counterbalancing system to avoid a too strong oscillation and to maintain energy homeostasis.

Fig. 2. Reciprocal activation of UCP2-mitochondrial activation by T_4 . Increased fat tissue leads to increased leptin levels (1, 2). As recently shown, leptin activates the thyroid axis via TRH neurons in the nucleus paraventricularis (3, 4). Increased thyroid function (5) leads to stimulation of energy expenditure via UCP2 in muscle tissue (6) with the result of counteracting decrease of fat tissue (7). At the same time, increased T_4 activates in the hypothalamus the new pathway of UCP2-related activation of NPY neurons (8) which in turn leads to more food intake (9) and as a subsequent response increased fat tissue (10).

The role of intracerebroventricular administration of leptin in the stimulation of prothyrotropin releasing hormone neurons in the hypothalamic paraventricular nucleus

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Background: The authors have previously shown that leptin regulates proTRH in the paraventricular nucleus (PVN) of the hypothalamus through two pathways. The first one acts directly on proTRH neurons, and the second one (indirectly) acts through the melanocortin system (arcuate nucleus). However, it is unknown whether the direct or the indirect pathways of leptin action on proTRH neurons occurs on separated or on the same subsets of neurons within the PVN region.

Result: In this study they used immunostaining for the phosphorylated signal transducer and activator of transcription-3 to localize direct leptin signaling, and the phosphorylated cAMP response element binding protein to localize indirect signaling on proTRH neurons in animals intracerebroventricularly injected with leptin. They were able to identify two subsets of neuronal populations responsive to leptin, which are distributed in different regions within the PVN. proTRH neurons directly responsive to leptin were located mainly in the medial and posterior part of the PVN, and they were not primarily related to the hypothalamic pituitary thyroid axis. Whereas proTRH neurons indirectly responsive (through α -MSH) to leptin were located mainly in the anterior, medial, and periventricular part of the PVN, and related to the hypothalamic pituitary thyroid axis. In addition, α -MSH showed to affect the processing of proTRH and upregulated the prohormone convertase 1/3.

Conclusion: Together they show evidence supporting the hypothesis that in the PVN there are subpopulations of proTRH neurons responding to leptin, which is dependent upon the way leptin reaches its primary target(s) in the hypothalamus. These findings are critical to a better understanding of leptin-mediated actions on energy expenditure.

In contrast to the last paper that describes an effect of T_3 on metabolism, this paper confirms and describes in more detail the reciprocal effect of leptin itself on the thyroid axis. In leptin deficiency a mild form of central hypothyroidism has been described and in subsequent studies a direct stimulatory effect of leptin on the thyroid axis by activating the TRH gene was discovered. The leptin-stimulated proTRH gene expression leads to increased TSH and thyroid hormone levels. This central activation of thyroid function in times of increased leptin seems to represent one orexigenic counteractivity of the neuroendocrine feedback loop to maintain a set point of body weight. Interestingly, the authors could now show that two different neuron populations of the PVN are activated by leptin – one via the arcuate nucleus and α -MSH leading to activation of proTRH and prohormone convertase 1/3 – and the second by direct binding of leptin to the PVN. It remains unsolved which neuronal responses are targeted by this direct leptin binding to the PVN. However, these robust experimental data are in agreement with the observations described in the following paper in obese children who tend to have mildly elevated TSH and T_3 levels. These changes in the thyroid axis are more likely the consequence of a normal regulatory response than the indication of hypothyroidism causing obesity as discussed in the next paper.

Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids

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Background: The objective of this study was to examine whether hyperthyrotropinemia is a cause or a consequence of obesity. The study was designed as a cross-sectional comparison between obese and lean children and includes a 1-year follow-up study. The study was set in a primary care facility. There were 246 obese and 71 lean children. A 1-year intervention program was based on exercise, behavior therapy, and nutrition education. The main outcome measures were TSH, free T_3 (FT_3), free T_4 (FT_4), high-density lipoprotein, low-density lipoprotein, and total cholesterol at baseline and 1 year later.

Results: TSH ($p = 0.009$) and FT_3 ($p = 0.003$) concentrations were significantly higher in obese children than in normal weight children, whereas there was no difference in FT_4 levels ($p = 0.804$). Lipids did not correlate significantly to thyroid hormones in cross-sectional and longitudinal analyses. FT_3 , FT_4 , and lipids did not differ significantly in the 43 (17%) children with TSH levels above the normal range from the children with TSH levels within the normal range. Substantial weight loss in 49 obese children led to a significant reduction of TSH ($p = 0.035$) and FT_3 ($p = 0.036$). The 197 obese children without substantial weight loss demonstrated no significant changes of thyroid hormones.

Conclusion: Because FT_3 and TSH were moderately increased in obese children and weight loss led to a reduction, the elevation of these hormones seems to be rather a consequence of obesity than a cause of obesity. Because FT_3 and TSH were both increased in obesity and thyroid hormones were not associated with lipid levels, the authors propose that there is no need for thyroxine treatment in this situation.

This paper, dealing with the clinical impact of the link between central weight regulation and thyroid function, is extremely useful to argue against a thyroxine treatment in obese children with elevated TSH. Most physicians tend to treat obese children with moderately elevated TSH despite normal T_4 and T_3 ; the parents are convinced that the 'gland' is responsible for obesity. However, the data available so far about the interrelation of central leptin function and proTRH expression were very suggestive that the elevated TSH in obese children is the consequence and not the cause of obesity. The authors could demonstrate that the elevated TSH normalize after weight reduction efforts which proves the consequence concept rather the cause concept. We have now at least one citable paper to argue against the widespread use of LT_4 in obese children. Less eating and more moving remain as the only options. The topic of euthyroid TSH elevation as touched in this paper becomes increasingly

relevant based on the discussion of the normal upper limit of TSH. One informative review about this discussion appeared in 2006 and is included in the following section.

To treat or not to treat: a European statement on the upper limit of normal TSH values

Is there a need to redefine the upper normal limit of TSH?

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Background: Mild forms of hypothyroidism – subclinical hypothyroidism – have recently been discussed as being a risk factor for the development of overt thyroid dysfunction and for a number of clinical disorders. The diagnosis critically depends on the definition of the upper normal limit of serum TSH as, by definition, free thyroxine serum concentrations are normal. Cut-off levels of 4–5 mU TSH/l have been conventionally used to diagnose an elevated TSH serum concentration. Recent data from large population studies have suggested a much lower TSH cut-off with an upper limit of 2.0–2.5 mU/l, but application of strict criteria for inclusion of subjects from the general population studies aiming at assessing TSH reference intervals (no personal or family history of thyroid disease, no thyroid antibodies and a normal thyroid on ultrasonography) did not result in an unequivocal upper limit of normal TSH at 2.0–2.5 mU/l.

Result: When summarizing the available evidence for lowered upper TSH cut-off values and their potential therapeutic implications, there is presently insufficient justification to lower the upper normal limit of TSH and, for practical purposes, it is still recommended to maintain the TSH reference interval of 0.4–4.0 mU/l.

Conclusion: Classifying subjects with a TSH value between 2 and 4 mU/l as abnormal, as well as intervening with thyroxine treatment in such subjects, is probably doing more harm than good.

This review discusses the questionable indication to treat patients with 'borderline' TSH in the range of 2–4 mU/l as it is increasingly propagated from different groups in the USA. The main message is that most likely treatment of these patients will result in a large number of borderline hyperthyroid patients with suppressed TSH. This iatrogenic condition is more harmful than the borderline hypothyroid condition as a large number of studies suggest, especially in older patients with heart disease. Since we are faced with an increasing demand of treating children with borderline elevated TSH (see previous paper on obese children) the cited references and the argumentation of the paper are also relevant for pediatric endocrinologists. Even more in children, borderline TSH might represent a variant and not a disease and a lifelong treatment with LT_4 will most likely be even more harmful compared to adults.

New mechanisms: a pathfinder function of cervical arteries for the developing thyroid gland

Arteries define the position of the thyroid gland during its developmental relocation

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Development 2006;133:3797–3804

Background: During vertebrate development, the thyroid gland undergoes a unique relocation from its site of induction to a distant species-specific position in the cervical mesenchyme.

Results: The authors have analyzed thyroid morphogenesis in wild-type and mutant zebrafish and mice, and find that localization of growing thyroid tissue along the anteroposterior axis in zebrafish is linked

to the development of the ventral aorta. In grafting experiments, ectopic vascular cells influence the localization of thyroid tissue cell non-autonomously, showing that vessels provide guidance cues in zebrafish thyroid morphogenesis. In mouse thyroid development, the midline primordium bifurcates and two lobes relocate cranially along the bilateral pair of carotid arteries. In hedgehog-deficient mice, thyroid tissue always develops along the ectopically and asymmetrically positioned carotid arteries, suggesting that, in mice (as in zebrafish), co-developing major arteries define the position of the thyroid.

Conclusion: The similarity between zebrafish and mouse mutant phenotypes further indicates that thyroid relocation involves two morphogenetic phases, and that variation in the second phase accounts for species-specific differences in thyroid morphology. Moreover, the involvement of vessels in thyroid relocation sheds new light on the interpretation of congenital thyroid defects in humans.

The 22q11 deletion syndrome candidate gene *Tbx1* determines thyroid size and positioning

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Background: Thyroid dysgenesis is the major cause of congenital hypothyroidism in humans. The underlying molecular mechanism is in most cases unknown, but the frequent co-incidence of cardiac anomalies suggests that the thyroid morphogenetic process may depend on proper cardiovascular development. The T-box transcription factor TBX1, which is the most probable gene for the 22q11 deletion syndrome (22q11DS/DiGeorge syndrome/velo-cardio-facial syndrome), has emerged as a central player in the coordinated formation of organs and tissues derived from the pharyngeal apparatus and the adjacent secondary heart field from which the cardiac outflow tract derives.

Results: The authors show that *Tbx1* impacts greatly on the developing thyroid gland, although it cannot be detected in the thyroid primordium at any embryonic stage. Specifically, in *Tbx1*^{-/-} mice, the downward translocation of *Titf1/Nkx2.1*-expressing thyroid progenitor cells is much delayed. In late mutant embryos, the thyroid fails to form symmetric lobes but persists as a single mass approximately one-fourth of the normal size. The hypoplastic gland mostly attains a unilateral position resembling thyroid hemiagenesis. The data further suggest that failure of the thyroid primordium to re-establish contact with the aortic sac is a key abnormality preventing normal growth of the midline anlage along the third pharyngeal arch arteries. In normal development, this interaction may be facilitated by *Tbx1*-expressing mesenchyme filling the gap between the pharyngeal endoderm and the detached thyroid primordium.

Conclusion: The findings indicate that *Tbx1* regulates intermediate steps of thyroid development by a non-cell-autonomous mechanism. Thyroid dysgenesis related to *Tbx1* inactivation may explain an overrepresentation of hypothyroidism occurring in patients with the 22q11DS.

Most children with congenital hypothyroidism are affected by a developmental defect of the thyroid gland, summarized as thyroid dysgenesis. In the last 10 years we have become familiar with several genes identified as key transcription factors during early steps of thyroid development, e.g. *TITF1/NKX2.1*, *FOXE1/TF2* and *PAX8*, which all act in a cell-autonomous way. These two new papers describe a mechanism how the developing thyroid gland is guided through the complex pharyngeal field to reach its proper position in anterior neck which is far away from the origin of the thyroid primordium in the pharyngeal endoderm. In the first paper the zebrafish was instructive as a model for thyroid development where cervical arteries could be identified in several genetic models to be responsible for the relocation of thyroid follicles in the fish head region. Based on these fish data, a detailed description of the three-dimensional orientation of the developing mouse thyroid revealed a complex co-development of the gland with the cervical arteries, mainly the aortic arch during a first phase of caudal migration and in later stages during cranial relocation with the carotid arteries. Disturbed artery development in a sonic hedgehog-deficient mouse model confirmed a causal link between cervical artery and thyroid development.

The second paper focused on the observation that in the 22q11 deletion syndrome, aortic arch malformations are associated with some thyroid alterations in up to 20% of patients. Reinvestigation of the Tbx1 knockout mouse, which resembles most of the 22q11 deletion human phenotypes, revealed a constant asymmetric hypoplastic thyroid defect. The authors concluded that the thyroid defect most likely is a consequence of the surrounding field defect because Tbx1 is not expressed in the developing thyroid itself and further speculated that the cervical arteries might attract the thyroid bud by soluble growth factors.

Together these papers open the search for additional external growth factors in the developing pharyngeal field which are similarly relevant for normal thyroid development as the cell-autonomously acting so far known transcription factors. Signal molecules sent out by the arteries to stimulate and position the gland seem to be attractive candidates in this view. This brings us to some clinically relevant papers about congenital hypothyroidism summarized in the next section.

How to manage congenital hypothyroidism: a US consensus and a European innovation

Update of newborn screening and therapy for congenital hypothyroidism

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Pediatrics 2006;117:2290–2303

Unrecognized congenital hypothyroidism leads to mental retardation. Newborn screening and thyroid therapy started within 2 weeks of age can normalize cognitive development. The primary thyroid-stimulating hormone screening has become standard in many parts of the world. However, newborn thyroid screening is not yet universal in some countries. An initial dosage of 10–15 $\mu\text{g/kg}$ L-thyroxine is recommended. The goals of thyroid hormone therapy should be to maintain frequent evaluations of total thyroxine or free thyroxine in the upper half of the reference range during the first 3 years of life and to normalize the serum thyroid-stimulating hormone concentration to ensure optimal thyroid hormone dosage and compliance. Improvements in screening and therapy have led to improved developmental outcomes in adults with congenital hypothyroidism who are now in their 20s and 30s. Thyroid hormone regimens used today are more aggressive in targeting early correction of thyroid-stimulating hormone than were those used 20 or even 10 years ago. Thus, newborn infants with congenital hypothyroidism today may have an even better intellectual and neurologic prognosis. Efforts are ongoing to establish the optimal therapy that leads to maximum potential for normal development for infants with congenital hypothyroidism. Remaining controversy centers on infants whose abnormality in neonatal thyroid function is transient or mild and on optimal care of very low birth weight or preterm infants. Of note, thyroid-stimulating hormone is not elevated in central hypothyroidism. An algorithm is proposed for diagnosis and management. Physicians must not relinquish their clinical judgment and experience in the face of normal newborn thyroid test results. Hypothyroidism can be acquired after the newborn screening. When clinical symptoms and signs suggest hypothyroidism, regardless of newborn screening results, serum free thyroxine and thyroid-stimulating hormone determinations should be performed.

Recombinant human TSH in the diagnosis of congenital hypothyroidism

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Background: The modern approach to congenital hypothyroidism requires a definitive diagnosis of the underlying mechanisms; this can be achieved within the first weeks of life. When uncertainty persists, treatment is commenced, and the definitive diagnosis of congenital hypothyroidism is deferred to the age of 3 years. The interruption of thyroid replacement treatment is perceived as risky by parents and

physicians. The aim of this pilot study was to test the possibility of a definitive diagnosis during thyroid replacement treatment, utilizing stimulation of thyroid tissue by rhTSH.

Results: Eight patients, 3 boys and 5 girls, aged 5–15 years, mean 9.5 ± 3.7 years, with congenital hypothyroidism who had been diagnosed by the neonatal screening program and a verified diagnosis between 3 and 4 years of age were re-evaluated while on thyroid replacement therapy. Patients received i.m. 0.6 mg/m^2 rhTSH (Thyrogen, Genzyme) on 2 consecutive days. rhTSH pharmacokinetics, $C_{\max}$, $t_{1/2}$ and AUC in children were different as compared to adults. In the patients with intact TSH receptors, FT_4 levels decreased after the first and the second injection of rhTSH ($p = 0.0137$, $p = 0.0149$). All 8 children showed identical scintigraphy after rhTSH administration, as compared to thyroid replacement withdrawal.

Conclusions: The use of rhTSH is effective for definitive diagnosis of congenital hypothyroidism during thyroid replacement treatment and no safety issues were encountered.

Almost 30 years after the initiation of newborn screening for congenital hypothyroidism in the USA, this paper summarizes the actual diagnostics and treatment consensus of the American Academies involved in the treatment of patients with congenital hypothyroidism. The consensus is quite openly formulated when dealing with the controversial topics of thyroid imaging at diagnosis, treatment of hyperthyrotropinemia and the LT_4 dose, and the authors leave it to the decision of individual physicians. However, the more conservative US habits in imaging studies might not find an equal European counterpart, because the statement that scintigraphy is more recommended than ultrasound because an ectopic gland might be overseen is not outcome relevant in the view of adequate higher doses and does need to be performed in every child. Also the question of LT_4 dose, which was traditionally lower in the USA compared with Europe, is slowly moving towards higher doses and the authors now recommend $10\text{--}15 \mu\text{g/kg}$, but state that the 'higher' dose of $50 \mu\text{g}$ will make an evaluation of cognitive outcome important to recognize overtreatment. In a normal-weight newborn of ca. 3.5 kg , $50 \mu\text{g}$ LT_4 corresponds with $15 \mu\text{g/kg}$ and with the recommendations made. Moreover, since the US market only offers LT_4 tablets and no LT_4 solution, the only practical alternatives are 50 or $37.5 \mu\text{g}$ and the latter dose was shown to be less efficient to reach normal IQ according to the two prospective ongoing studies [1]. Statistically significant differences of 5 IQ points with 37 vs. $50 \mu\text{g}$ might have a lifelong impact in the affected child and the future debate in this field will clearly focus on such minor differences in dose recommendations. The second paper approaches a new diagnostic procedure in thyroid imaging in congenital hypothyroidism adopted from post-surgery cancer treatments in adolescents. The authors suggest avoiding the withdrawal of LT_4 treatment in the confirmatory phase of diagnosis after at least 2 years of treatment by stimulation thyroid function with exogenous recombinant TSH rather than endogenous TSH. They show in 8 patients a reliable scintigraphy image under this regimen. However, in most cases nowadays of 'the modern approach to congenital hypothyroidism', the withdrawal will be mainly indicated in those children with normal-appearing thyroid tissue in ultrasound at birth and only mild hypothyroidism to exclude a transient form of congenital hypothyroidism. The recombinant TSH approach will not help to exclude a mild hypothyroidism with a normal gland in place, since for this diagnosis the endogenous increase of TSH is the key diagnostic feature and not the image of the gland.

The syndrome of the year . . .

Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism

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Background: The authors recently described a new neonatal diabetes syndrome associated with congenital hypothyroidism, congenital glaucoma, hepatic fibrosis and polycystic kidneys.

Results: Now they show that this syndrome results from mutations in GLIS3, encoding GLI-similar 3, a recently identified transcription factor. In the original family, they identified a frameshift mutation predicted

to result in a truncated protein. In two other families with an incomplete syndrome, they found that affected individuals harbor deletions affecting the 11 or 12 5'-most exons of the gene. The absence of a major transcript in the pancreas and thyroid (deletions from both families) and an eye-specific transcript (deletion from one family), together with residual expression of some GLIS3 transcripts, seems to explain the incomplete clinical manifestations in these individuals. GLIS3 is expressed in the pancreas from early developmental stages, with greater expression in β cells than in other pancreatic tissues.

Conclusion: These results demonstrate a major role for GLIS3 in the development of pancreatic β cells and the thyroid, eye, liver and kidney.

Careful clinical observations in one consanguineous family defined this new syndrome with the two endocrine features of congenital diabetes and hypothyroidism and the lack of appearance of two further informative consanguineous families opened the way to identify the molecular basis for this disease with only 3 familial cases. Two large deletions with a likely effect on the GLIS3 gene expression and one intragenic insertion mutation were enough to identify GLIS3 as the gene involved. The spectrum of the syndrome can vary and the different deletions might differentially affect the expression in different tissues, which demonstrate a very nice example of a molecular mechanism for a variable phenotype in a monogenic disease. The thyroid phenotype was described in the first clinical description of the syndrome by the same authors [2] and it seems that at least in 1 patient a normally located gland was shown by ultrasound while TSH was elevated with a low FT₄ and elevated thyroglobulin, suggesting a functional rather than a developmental thyroid defect. It will be of great interest to learn more about the role of GLIS3 for normal thyroid function, especially the target genes of this transcription factor.

Iodine around the world

Sodium/iodide symporter (NIS) gene expression is the limiting step for the onset of thyroid function in the human fetus

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Background: Terminal differentiation of the human thyroid is characterized by the onset of follicle formation and thyroid hormone synthesis at 11 gestational weeks (GW). This study aimed to investigate the ontogeny of thyroglobulin (Tg), thyroid peroxidase (TPO), sodium/iodide symporter (NIS), pendrin (PDS), dual oxidase 2 (DUOX2), thyroid-stimulating hormone receptor (TSHR), and thyroid transcription factor 1 (TTF1), forkhead box E1 (FOXE1), and paired box gene 8 (PAX8) in the developing human thyroid. Thyroid tissues from human embryos and fetuses (7–33 GW; n = 45) were analyzed by quantitative PCR to monitor mRNA expression for each gene and by immunohistochemistry to determine the cellular distribution of TTF1, TSHR, Tg, TPO, NIS, and the onset of T₄ production.

Results: TTF1, FOXE1, PAX8, TSHR, and DUOX2 were stably expressed from 7 to 33 GW. Tg, TPO, and PDS expression was detectable as early as 7 GW and was correlated with gestational age (all $p < 0.01$), and the slope of the regression line was significantly different before and after the onset of T₄ synthesis at 11 GW (all $p < 0.01$). NIS expression appeared last and showed the highest fit by the broken-line regression model of all genes (correlation age $p < 0.0001$, broken-line regression $p < 0.0001$). Immunohistochemical studies detected TTF1, TSHR, and Tg in unpolarized thyrocytes before follicle formation. T₄ and NIS labeling were only found in developing follicles from 11 GW onwards.

Conclusion: These results imply a key role of NIS for the onset of human thyroid function.

The extraordinary role of iodine for the synthesis of thyroid hormone has been known for a long time. Now it seems that also during development the supply of the already built thyroid follicles with iodine

is the key step of onset of thyroid function during embryogenesis. This ethically sensible study in human fetuses demonstrates that all other genes necessary for thyroid hormone production are already expressed but that just in the moment when thyroid hormone secretion begins expression of the iodine symporter, NIS is initiated. For future studies these data give much food to think about because now the question needs to be answered how this orchestrated expression pattern of the functionally relevant genes in thyroid development is regulated, especially which transcription factor might be the critical specific one to initiate the expression of NIS at that later time point when all other factors which are known so far are already expressed but are obviously not yet sufficient to induce NIS expression.

Assessment of iodine status using dried blood spot thyroglobulin: development of reference material and establishment of an international reference range in iodine-sufficient children

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Background: Thyroglobulin (Tg) may be a valuable indicator of improving thyroid function in children after salt iodization. A recently developed Tg assay for use on dried whole blood spots (DBS) makes sampling practical, even in remote areas. The study aim was to develop a reference standard for DBS-Tg, establish an international reference range for DBS-Tg in iodine-sufficient children, and test the standardized DBS-Tg assay in an intervention trial. Serum Tg reference material of the European Community Bureau of Reference (CRM-457) was adapted for DBS and its stability tested over 1 year. DBS-Tg was determined in an international sample of 5- to 14-year-old children (n = 700) who were euthyroid, anti-Tg antibody-negative, and residing in areas of long-term iodine sufficiency. In a 10-month trial in iodine-deficient children, DBS-Tg and other indicators of iodine status were measured before and after introduction of iodized salt.

Results: Stability of the CRM-457 Tg reference standard on DBS over 1 year of storage at –20 and –50°C was acceptable. In the international sample of children, the third and 97th percentiles of DBS-Tg were 4 and 40 µg/l, respectively. In the intervention, before introduction of iodized salt, median DBS-Tg was 49 µg/l, and more than two-thirds of children had DBS-Tg values >40 µg/l. After 5 and 10 months of iodized salt use, median DBS-Tg decreased to 13 and 8 µg/l, respectively, and only 7 and 3% of children, respectively, had values >40 µg/l. DBS-Tg correlated well at baseline and 5 months with urinary iodine and thyroid volume.

Conclusion: The availability of reference material and an international reference range facilitates the use of DBS-Tg for monitoring of iodine nutrition in school-age children.

A brief summary of the findings would be helpful. This methodological paper opens new perspectives for the general feasibility of iodine measurement based on screening filter paper. The implementation of newborn screening makes it very attractive to measure additional parameters in the blood spots with the chance to generate population-based data of a variety of parameters – although this is of some ethical concern too. This paper started with the general proof that Tg levels mirror iodine status in schoolchildren as measured in DBS on filter paper and supplied us with the reference ranges for Tg in this material. They also showed that Tg is stable in DBS after 1 year of storage at –20°C. Measurement of Tg in screening blood samples might have additional indications in the differential diagnosis of positive screening results, e.g. to discriminate iodine exposure, dysgenesis and dysmorphogenesis.

Selenium and goiter prevalence in borderline iodine sufficiency

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Background: Selenium (Se) is required for the biosynthesis of selenocysteine-containing proteins. Several selenoenzymes, e.g. glutathione peroxidases and thioredoxin reductases, are expressed in the thyroid.

Selenoenzymes of the deiodinase family regulate the levels of thyroid hormones. For clinical investigators, it is difficult to determine the role of Se in the etiology of (nodular) goiter, because there are considerable variations of Se concentrations in different populations as reflected by dietary habits, bioavailability of Se compounds, and racial differences. Moreover, most previous clinical trials which investigated the influence of Se on thyroid volume harbored a bias due to the coexistence of severe iodine deficiency in the study populations. Therefore, the authors investigated the influence of Se on thyroid volume in an area with borderline iodine sufficiency.

Methods: The authors investigated randomly selected probands for urinary iodine and creatinine excretion in spot urine samples and determined the prevalence of goiter and thyroid nodules by high-resolution ultrasonography as well as urinary Se excretion in probands with goiter and matched probands without goiter.

Results: The mean urinary Se excretion and urinary iodine rates of all 172 probands were 24 $\mu\text{g Se/l}$ or 27 $\mu\text{g Se/g creatinine}$ and 96 $\mu\text{g iodine/l}$ or 113 $\mu\text{g iodine/g creatinine}$ indicating borderline Se (20–200 $\mu\text{g/l}$) and iodine (100–200 $\mu\text{g/l}$) sufficiency of the study population. Probands with goiter ($n = 89$) showed significantly higher urinary Se levels than probands with normal thyroid volume ($n = 83$; $p < 0.05$). Urinary Se rates were not influenced by present smoking or pregnancy.

Conclusion: Urinary Se is not an independent risk factor for the development of goiter. The higher urinary Se in probands with goiter in comparison with probands with normal thyroid volume is most likely a coincidence. Se does not significantly influence thyroid volume in borderline iodine sufficiency because the iodine status is most likely the more important determinant.

There is a hype of the role of Se in several aspects of human physiology and pathology. However, this paper, at least for the thyroid, brings it down to reality. The authors searched for a role of Se deficiency as an additional factor for the development of goiter in a borderline iodine-sufficient area. In contrast to the expectation, urinary Se excretion was higher in patients with goiter compared with normal thyroid individuals, suggesting that Se deficiency is not the key factor in the pathogenesis of thyroid enlargement. It seems that the good old trace element iodine is by far the more relevant element in terms of goiter development.

Effect of iodine intake on thyroid diseases in China

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Background: Iodine is an essential component of thyroid hormones; either low or high intake may lead to thyroid disease. The authors observed an increase in the prevalence of overt hypothyroidism, subclinical hypothyroidism, and autoimmune thyroiditis with increasing iodine intake in China in cohorts from three regions with different levels of iodine intake: mildly deficient (median urinary iodine excretion, 84 $\mu\text{g/l}$), more than adequate (median, 243 $\mu\text{g/l}$), and excessive (median, 651 $\mu\text{g/l}$). Participants were enrolled in a study in 1999, and during the 5-year follow-up through 2004, the effect of regional differences in iodine intake on the incidence of thyroid disease was examined. Of the 3,761 unselected subjects who were enrolled at baseline, 3,018 (80.2%) participated in this follow-up study. Levels of thyroid hormones and thyroid autoantibodies in serum, and iodine in urine, were measured and B-mode ultrasonography of the thyroid was performed at baseline and follow-up.

Results: Among subjects with mildly deficient iodine intake, those with more than adequate intake, and those with excessive intake, the cumulative incidence of overt hypothyroidism was 0.2, 0.5, and 0.3%, respectively; that of subclinical hypothyroidism, 0.2, 2.6, and 2.9%, respectively, and that of autoimmune thyroiditis, 0.2, 1.0, and 1.3%, respectively. Among subjects with euthyroidism and antithyroid antibodies at baseline, the 5-year incidence of elevated serum thyrotropin levels was greater among those with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake. A baseline serum thyrotropin level of 1.0–1.9 mIU/l was associated with the lowest subsequent incidence of abnormal thyroid function.

Conclusion: More than adequate or excessive iodine intake may lead to hypothyroidism and autoimmune thyroiditis.

This impressive and highest impact factor clinical paper in the thyroid field this year unambiguously demonstrates that too much iodine might be harmful for the wellbeing of the thyroid. By comparing three different areas in northeast China with three different iodine intake habits as mildly deficient, more than adequate and excessive (it remains unclear why a whole region ingested very high amounts of iodine in drinking water), the authors compared alterations of thyroid function. The prospective observation of more than 3,500 individuals enabled the authors to show that too much iodine causes a status of subclinical hypothyroidism as well as thyroid autoimmune phenomena. However, the incidences increased from mild deficiency to more than adequate and excessive iodine from 0.2 to 2.6 and 2.9 for subclinical hypothyroidism and from 0.2 to 1.0 and 1.3 for autoimmunity. Compared to the hazard resulting from iodine deficiency, these numbers are more reason to reassure rather than to be concerned. Compared with these incidences, the ten times higher rates of goiter development in severe iodine deficiency and the negative impact of maternal iodine deficiency for the mental outcome of the offspring seems to be much more dangerous. Nevertheless, care should be taken to prevent overdosing a population with iodine. However, providing an individualized iodine supplementation program fitting personal needs is not a feasible task worldwide.

At the end (of the chapter) but probably not the end (of the problem) – course and treatment of Hashimoto's thyroiditis in childhood

The natural history of euthyroid Hashimoto's thyroiditis in children

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Background: The natural history of Hashimoto's thyroiditis (HT) in children and factors predictive of thyroid dysfunction have not been described in many studies so far. The authors evaluated 160 children (43 males and 117 females, mean age 9.10 ± 3.6 years, with HT and normal (group 0; 105 patients) or slightly elevated (group 1; 55 patients) serum thyroid-stimulating hormone (TSH) concentrations. The patients were assessed at presentation and then followed for at least 5 years if they remained euthyroid or if their TSH did not rise twofold over the upper normal limit.

Results: At baseline, age, sex, thyroid volume, free thyroxine, free triiodothyronine, thyroid peroxidase antibody (TPOab), and thyroglobulin antibody (TGab) serum concentrations were similar in the two groups. During follow-up, 68 patients of group 0 remained euthyroid, and 10 patients moved from group 0 to group 1. In 27 patients, TSH rose twofold above the upper normal limit (group 2), and 9 of these patients developed overt hypothyroidism. Sixteen patients of group 1 ended up in group 0, 16 remained in group 1, and 23 moved to group 2. A comparison of the data of the patients who maintained or improved their thyroid status with those of the patients whose thyroid function deteriorated revealed significantly increased TGab levels and thyroid volume at presentation in the latter group. However, none of these parameters alone or in combination were of any help in predicting the course of the disease in a single patient.

Conclusion: The presence of goiter and elevated TGab at presentation, together with progressive increase in both TPOab and TSH, may be predictive factors for the future development of hypothyroidism. At 5 years of follow-up, more than 50% of the patients remained or became euthyroid.

Hashimoto's disease is the most frequent thyroid disease in childhood with little reliable prospective data. Therefore, these two retrospective studies are included in this chapter. Taken together, this retrospective 5-year follow-up study confirms the course of the disease in patients with positive thyroid antibodies with resolution in a few patients and deterioration in a large number. The well-organized Italian pediatric endocrinologists have brought together 20 centers to collect data from more than 150 patients. However, the data calls for a prospective study to clarify if thyroxin treatment will improve thyroid function in the long term. However, most patients in this study have an additional condition including diabetes, celiac disease or Turner syndrome and the conclusion might not apply to other patient groups with Hashimoto's thyroiditis.

L-Thyroxine in euthyroid autoimmune thyroiditis and type 1 diabetes: a randomized, controlled trial

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Background: Patients with type 1 diabetes (T1D) have an increased risk of autoimmune thyroiditis (AIT). The authors determined whether LT₄ treatment prevents the clinical manifestation of AIT in euthyroid subjects with T1D in a prospective, randomized, open, controlled clinical trial in six tertiary care centers for pediatric endocrinology and diabetes including 611 children and adolescents with T1D.

Results: 89 individuals (14.5%) were identified with positive thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), or both. Of these, 30 patients (age 13.3 ± 2.1 years) met the inclusion criteria and were randomized to receive LT₄ (16 patients) or no treatment (14 patients). Intervention: LT₄ (1.3 µg/kg daily) was given for 24 months in the treatment group, followed by an additional observation period of 6 months in both groups. Thyroid gland volume (as determined by ultrasound), serum levels of thyrotropin, thyroid hormones, TPOAb, and TgAb were assessed every 6 months for 30 months. Mean thyroid volume decreased in the treatment group after 24 months (-0.60 standard deviation score, SDS) and increased in the observation group ($+1.11$ SDS, $p = 0.0218$). Serum thyrotropin, FT₄, TPOAb, and TgAb levels were not significantly different in both groups during the entire study period. Hypothyroidism developed in 3 individuals treated with LT₄ and in 4 untreated patients (conversion rate, 9.3% per year).

Conclusions: In this study in euthyroid patients with AIT and T1D, LT₄ treatment reduced thyroid volume but had no effect on thyroid function and serum autoantibody levels.

The authors tried to search for an effect of LT₄ treatment in euthyroid patients affected with DM1 and Hashimoto's thyroiditis. Within an unfortunately small group of 30 patients they performed a randomized prospective study with a follow-up of 30 months. No significant change of the thyroid function parameters after the treatment period was found between the treated and non-treated groups. However, although a few patients per group were included and the study concerned patients with Hashimoto's thyroiditis and diabetes, this study is important because it tries to resolve the important question of thyroid hormone treatment in euthyroid Hashimoto's thyroiditis. In this patient population, treatment with thyroid hormone did not improve thyroid function after 24 months. Obviously, further studies with longer treatment durations, more patients in various age groups and with isolated Hashimoto's thyroiditis are needed. Given the widespread use of thyroid hormones in euthyroid Hashimoto's thyroiditis, these preliminary results stress the need for these studies.

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