Thyroid

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This year, publications under the heading 'thyroid' revealed some amazing surprises. 50 years after its discovery and purification [1], and 30 years after the first description of TSH deficiency, TSH was rediscovered to play a crucial new role in transformation of light signals into photoperiodicity. However, the species in which this fundamental function was described, the Japanese quail, is not very close to us, but the beauty of such an unexpected completely new discovery brought this paper into the *Yearbook* chapter. Another fascinating paper, with the highest impact of the year, disclosed another fundamental new disease mechanism in thyroid function, e.g. the loss of iodine due to a defect in iodine recycling by iodine deiodinase/dehalogenase gene deficiency. Although the existence of this enzyme has been postulated for decades, it was only recently that systematic cloning of thyroid-expressed genes led to its identification, and this year the first patients were diagnosed to suffer from congenital hypothyroidism due to iodine loss. Besides these two highlight papers of the year, several interesting and clinically useful communications appeared and again it seemed that they run in clusters as they did last year [2] on themes like the 'Role of thyroid hormone in metabolism', 'The diagnosis of elevated TSH', 'Refinement of the MCT8 deficiency syndrome' and 'New indications for T₃'. In this last group of publications, this year's most literary editorial was written in response to a report about a benefit of T₃ treatment in heart disease entitled 'Thyroid hormones treatment to mend a broken heart'.

Mechanism of the year: TSH, periodicity and quails

Thyrotrophin in the pars tuberalis triggers photoperiodic response

Nakao N, Ono H, Yamamura T, Anraku T, Takagi T, Higashi K, Yasuo S, Katou Y, Kageyama S, Uno Y, Kasukawa T, Iigo M, Sharp PJ, Iwasawa A, Suzuki Y, Sugano S, Niimi T, Mizutani M, Namikawa T, Ebihara S, Ueda HR, Yoshimura T
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Background: Molecular mechanisms regulating animal seasonal breeding in response to changing photoperiod are not well understood. Rapid induction of gene expression of thyroid-hormone-activating enzyme (type 2 deiodinase, DIO2) in the mediobasal hypothalamus of the Japanese quail (*Coturnix japonica*) is the earliest event yet recorded in the photoperiodic signal transduction pathway.

Methods: The authors performed gene expression profiling of hypothalamic genes in long vs. short day-light exposure of Japanese quail.

Results: They identified cascades of gene expression in the quail mediobasal hypothalamus associated with the initiation of photoinduced secretion of luteinizing hormone. Two waves of gene expression were found. The first was initiated about 14 h after dawn of the first long day and included increased thyrotrophin (TSH) β -subunit expression in the pars tuberalis; the second occurred approximately 4 h later and included increased expression of DIO2. Intracerebroventricular (ICV) administration of TSH to short-day quail stimulated gonadal growth and expression of DIO2 which was shown to be mediated through a TSH receptor-cyclic AMP (cAMP) signaling pathway.

Conclusion(s): Increased TSH in the pars tuberalis therefore seems to trigger long-day photoinduced seasonal breeding.

Quails have been investigated as a model for photoperiodic mechanisms because they react sharply and robustly to changes in day length. When Japanese quails are transferred from short to long days, plasma LH increases as early as at the end of the first long day. Continuous exposure to long days leads to enlargement of gonads and reproduction. Based on this on-off model, the Japanese team has dissected over several years and in high-impact papers the signaling pathway that triggers LH secretion stimulated by long daylight. They clearly show that the GnRH drive is regulated by a

Fig. 1. New concept of TSH triggered gonadotrophin release in Quails as induced by daylight perception. Based on expression profiling in a long-day/ short-day paradigm, the authors dissected a new role of TSH in photoperiodic response of reproduction. The length of the day sunlight is transformed into a TSH signal in the pars tuberalis where TSH-beta subunit is expressed only during long days but not during short days (winter paradigm). The alpha-subunit of glycoprotein hormones is expressed every day periodically. By co-expression of both subunits within the same neurons a functional TSH is built 14 hours after dawn of the first long day. TSH binds in a paracrine manner to the TSH receptor in ependymal cells of the mediobasal hypothalamus. TSH receptor activation signaling induces a further cascade including activation of T4 to T3 by local deiodinase 2 to finally allow secretion of LH and FSH. Within this pathway the information of environment –springtime- is synchronized with the endocrine regulation of reproduction via a TSH-TSH receptor-signaling cascade to increase the likelihood of survival of the offspring.

paracrine TSH-TSH-R signaling activation at the border of hypothalamus and pituitary, e.g. in the mediobasal hypothalamus where the TSH-R is expressed and in the pars tuberalis of the pituitary where in response to light the TSH β -gene is expressed and forms with the daily cyclic abundant α -glycoprotein subunit TSH (fig.1, 2). Obviously in quails and other species with photoperiodicity, this pathway adapts seasonal changes with reproductive behavior, but it remains a mystery why Nature uses the otherwise established TSH-TSH-R signaling for that adaptation. Moreover, how the light signal itself is transferred to the pars tuberalis to induce TSH β -expression remains to be established. When we fall in love the next time when ‘feeling’ the longer warm days in May, we will wonder whether our human behavior is related to these new findings. However, there seems to be a long debate regarding the seasonality of human reproduction and this seems likely, at least for some individuals [3]. Based on the findings by Nakao et al. and given a conservation of the TSH effect of periodicity in humans, patients with TSH β -gene mutations [4] will not be seasonally photoperiodic. Hopefully they will still sense the beauty of longer days coming in spring.

Gene defect of the year: mutations in the iodotyrosine deiodinase gene and hypothyroidism

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Background: DEHAL1 has been identified as the gene encoding iodotyrosine deiodinase in the thyroid, where it controls the reuse of iodide for thyroid hormone synthesis.

Fig. 2. Biochemical pathway of thyroid hormone activation, deactivation and Iodine rescue. Thyroxine is secreted from the thyroid as a precursor of the biological active hormone T_3 . Activation of T_4 into T_3 is reached by deiodination via deiodinase-1 and -2. Deiodination via deiodinase-3 at the inner ring leads to inactive reverse (r) T_3 , which serves as a detoxification mechanism in conditions of hyperthyroidism. Further processing by cleavage of T_3 and rT_3 leads to the diiodinated and monoiodinated iodotyrosine rings (DIT, MIT). To keep the iodine of DIT and MIT within the process of T_4 production, a specialized enzyme cleaves iodine out of DIT and MIT- the recently discovered Iodotyrosine deiodinase/dehalogenase, DEHAL1.

Study Design: The authors screened patients with hypothyroidism who had features suggestive of an iodotyrosine deiodinase defect for mutations in DEHAL1.

Results: Two missense mutations and a deletion of three base pairs were identified in 4 patients from three unrelated families; all the patients had a dramatic reduction of in vitro activity of iodotyrosine deiodinase. Patients had severe goitrous hypothyroidism, which was evident in infancy and childhood. Two patients had cognitive deficits due to late diagnosis and treatment.

Conclusion(s): Mutations in DEHAL1 led to a deficiency in iodotyrosine deiodinase in these patients. Because infants with DEHAL1 defects may have normal thyroid function at birth, they may be missed by neonatal screening programs for congenital hypothyroidism.

Why was iodine introduced in evolution as an ingredient of thyroid hormones? It could have been easier to build a hormone based on two tyrosine rings itself without iodine as a substitute. So many children worldwide suffer from iodine-deficiency-induced cretinism in areas where iodine supplementation is not established. However, this paper of the year has shown that even in areas with sufficient iodine – either geographically or due to supplementation – some children still suffer from a newly identified form of iodine deficiency. Because iodine is so essential for thyroid hormone production and is so rare in nature, a mechanism has evolved to retain iodine within the circulation to recycle it after thyroid hormone breakdown. Iodine is usually removed by deiodinases from T_4 to gain the functional active hormone T_3 or the inactive form rT_3 and from T_3 itself to generate the equally

inactive T₂. But what will happen with iodine at the next steps of processing when the tyrosine rings will be separated? The resulting diiodinated (DIT) and monoiodinated (MIT) iodotyrosine rings would be eliminated via the kidney and iodine would be lost for further synthesis. To keep these iodine molecules within the body a specialized enzyme cleaves the DIT and MIT molecules to preserve the valuable iodine: the iodotyrosine deiodinase, DEHAL1. This enzyme was partially characterized decades ago but only a systematic screen for thyroid-expressed genes led to its complete description [5]. In the case of DEHAL1 deficiency, the bound iodine in DIT and MIT is lost and an 'endogenous' iodine deficiency despite sufficient iodine supply from the environment results, which can also lead to severe hypothyroidism as depicted in the 4 patients presented by the authors. The phenotype of the affected patients varied from early-onset severe congenital hypothyroidism and goiter to a late-onset form at an age of 8 years. Since DIT and MIT cannot be measured easily in urine or serum and DEHAL1 deficiency cannot be diagnosed simply on clinical grounds, all patients with primary congenital hypothyroidism with goiter are potentially affected and should undergo mutation screening that will resolve the true incidence of this new hereditary variant of congenital hypothyroidism.

Clinical concepts: T₃ for treatment of hypothyroidism? Triiodothyronine levels in athyreotic individuals during levothyroxine therapy

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Background: Thyroidal production of triiodothyronine (T₃) is absent in athyreotic patients, leading to the suggestion that T₃ deficiency may be unavoidable during levothyroxine (LT₄) therapy. However, trials evaluating therapy with combined LT₄ and T₃ have failed to demonstrate any consistent advantage of combination therapy. The authors aimed to determine whether T₃ levels in patients treated with LT₄ therapy were truly lower than in the same patients with native thyroid function.

Methods: A prospective study conducted in 50 euthyroid study participants aged 18–65 years who were scheduled for total thyroidectomy for goiter, benign disease, suspected thyroid cancer, or known thyroid cancer. Following thyroidectomy, patients were prescribed LT₄. Patients with benign thyroid disease and thyroid cancer were treated to achieve a normal and suppressed serum thyroid-stimulating hormone (TSH) level, respectively. The LT₄ dose was adjusted as necessary postoperatively to achieve the desired TSH goal. T₄, T₃, and TSH levels were measured twice preoperatively and twice postoperatively.

Results: By the end of the study, there were no significant decreases in T₃ concentrations in patients receiving LT₄ therapy compared with their prethyroidectomy T₃ levels (mean 127.2 ng/dl; 95% confidence interval [CI], 119.5–134.9 vs. 129.3 ng/dl; 95% CI 121.9–136.7 ng/dl; *p* = 0.64). However, free T₄ concentrations were significantly higher in patients treated with LT₄ therapy (mean 1.41 ng/dl; 95% CI 1.33–1.49 ng/dl) compared with their native free T₄ levels (1.05 ng/dl; 95% CI 1.00–1.10 ng/dl; *p* < 0.001). Serum TSH values of 4.5 mIU/l or less were achieved in 94% of patients by the end of the study. The T₃ concentrations were lower in the subgroup of patients whose therapy had not resulted in a TSH level of 4.5 mIU/l or less (*p* < 0.001).

Conclusion(s): The study revealed that normal T₃ levels were achieved with traditional LT₄ therapy alone in patients who had undergone near-total or total thyroidectomy, which suggests that T₃ administration is not necessary to maintain serum T₃ values at their endogenous prethyroidectomy levels.

Approximately 20% of circulating T₃ derives from deiodination within the thyroid gland itself; the remaining part is produced in other tissues, mostly the liver. In athyreotic patients, either due to thyroidectomy or as a result of thyroid dysgenesis in congenital hypothyroidism, substitution with L-thyroxine alone might therefore result in lower T₃ levels due to the lack of thyroid deiodination. Despite this, almost all studies have shown that L-thyroxine substitution leads to T₃ levels within the normal range and that no measurable parameter of hypothyroidism remains disturbed under monotherapy with L-thyroxine. However, some studies which compared T₄ alone versus T₄-T₃ combination therapy found a preference of the patients for the combination therapy which led to the idea that some subtle deficiencies in 'well-being' can result from individual partial T₃ deficiency but that the methods to estimate those changes are not sensitive enough.

In this new study the authors had the chance to measure T_3 in the same patients before and after thyroidectomy, under LT_4 monotherapy. Thereby the intraindividual T_3 changes could be monitored. After one point of dose adjustment, all patients reached a normal TSH level and under this condition T_3 was identical to the preoperative situation. This part of the result suggests that normal TSH is directly correlated with the intraindividual normal set-point of T_3 and that monotherapy with LT_4 is sufficient to reach this T_3 level even without thyroid deiodination. However, the normal TSH and T_3 levels are accompanied by a slightly higher ft_4 level – still in the normal range – which implicate that a higher level of T_4 substrate is necessary to reach normal T_3 levels by deiodination without the thyroid gland in place. In conclusion, it seems finally and for ever (?) proven that LT_4 alone is enough to reach *individually* normal T_3 levels. This data raises the concern that the higher ft_4 levels necessary to reach these T_3 levels might cause in some tissues – or regions of the brain – a state of partial hyperthyroidism and that these effects could be the reason for less ‘well-being’ and preference of a combination therapy, at least in some patients. Obviously further studies are necessary to address this question because every year about 100,000 patients lose their thyroid gland worldwide due to thyroidectomy and are dependent on an optimized thyroid hormone substitution.

Thyroid hormone replacement for central hypothyroidism: a randomized controlled trial comparing two doses of thyroxine (T_4) with a combination of T_4 and triiodothyronine

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Background: The dosage of T_4 in central hypothyroidism is primarily guided by the free serum T_4 level (ft_4). However, the optimum ft_4 range is ill defined, and subtle hypothyroidism might be missed using this approach. The aim of the study was to investigate the effects of a body weight (BW)-adapted T_4 treatment, alone or in combination with T_3 , on metabolism, well-being, and cognitive function in comparison to a regimen leading to normal ft_4 .

Design: This was a placebo-controlled trial (double-blind, crossover). A total of 29 patients (age 52 ± 2 years; females/males, 8/21) with hypopituitarism, including TSH deficiency, participated in the study. Three regimens were compared (5 weeks each): ‘EMPIRICAL- T_4 ’, empirical T_4 dosage ($1 \pm 0.05 \mu\text{g/kg BW}$) leading to normal ft_4 ; BW-ADAPTED- T_4 ($1.6 \mu\text{g/kg BW } T_4$), and ‘BW-ADAPTED- T_3T_4 ’, BW-adapted combination of T_3 and T_4 (ratio of 1:10).

Results: BW-ADAPTED- T_4 administration increased mean ft_4 concentrations to the upper limit of the normal range (peak levels). Compared with EMPIRICAL- T_4 , BW ADAPTED- T_4 treatment resulted in a lower body mass index (29.0 ± 0.7 vs. $29.5 \pm 0.7 \text{ kg/m}^2$; $p < 0.03$), lower total cholesterol (198 ± 9 vs. $226 \pm 7 \text{ mg/dl}$; $p < 0.01$), and lower low-density lipoprotein (LDL) cholesterol (116 ± 5 vs. $135 \pm 7 \text{ mg/dl}$; $p < 0.01$). BW-ADAPTED- T_3T_4 treatment was associated with additional beneficial effects on ankle reflex time and working memory but resulted in supraphysiological free serum T_3 (ft_3) levels.

Conclusion(s): Using a dose of $1.6 \mu\text{g/kg BW}$ improved markers commonly associated with central hypothyroidism. This suggests that T_4 dosage based on BW and aiming at ft_4 in the upper reference range is superior to titration of T_4 aiming at middle normal ft_4 concentrations in those patients.

While it seems easy to substitute patients with primary hypothyroidism – maybe not so, as discussed in the last section – this is far more difficult in patients with central hypothyroidism. Because TSH, the biomarker for individual normal T_3 level, is disrupted, the physician has no sensitive tool to optimize the LT_4 dose. The normal range of ft_4 and T_3 is wide and the only practical aim is in most centers to achieve an ft_4 level in the middle of the normal range. But this clearly does not meet in all patients the individual demand. The new study by Slawik et al. is the first randomized study comparing different treatment strategies in central hypothyroidism. Due to their results, it seems better to aim for an ft_4 in the upper normal range to improve the measurable markers of thyroid status and this can be achieved with a dose of $1.6 \mu\text{g/kg}$ body weight. Combination of T_4 with T_3 significantly improved the measured markers even more but the higher ft_3 levels in these patients are of concern that in the long term, the combination therapy would result in cardiovascular side effects. In central hypothyroidism it now seems reasonable that more is better, but still we should avoid too much.

Acute effects of triiodothyronine (T₃) replacement therapy in patients with chronic heart failure and low-T₃ syndrome: a randomized, placebo-controlled study

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J Clin Endocrinol Metab 2008;93:1351–1358

Background: Low-T₃ syndrome is a predictor of poor outcome in patients with cardiac dysfunction. The study aimed to assess the short-term effects of synthetic L-T₃ replacement therapy in patients with low-T₃ syndrome and ischemic or non-ischemic dilated cardiomyopathy (DC).

Design: A total of 20 clinically stable patients with ischemic (n = 12) or non-ischemic (n = 8) DC were enrolled. There were 10 patients (average age 72 years, range 66–77, median 25–75th percentile) who underwent a 3-day synthetic L-T₃ infusion (study group); the other 10 patients (average age 68 years, range 64–71) underwent placebo infusion (control group) (initial dose: 20 µg/m² body surface per day).

Results: After T₃ administration, free T₃ concentrations increased until reaching a plateau at 24–48 h without side effects. Heart rate decreased significantly after T₃ infusion (63, 60–66 vs. 69, 60–76 beats per minute; p = 0.008). Plasma noradrenaline, N-terminal pro-B-type natriuretic peptide and aldosterone significantly decreased after T₃ administration. The neurohormonal profile did not change after placebo infusion in the control group. After synthetic L-T₃ administration, left-ventricular end-diastolic volume (142, 132–161 vs. 133, 114–158 ml/m² body surface; p = 0.02) and stroke volume (40, 34–44 vs. 35, 28–39 ml/m² body surface; p = 0.01) increased, whereas external and intracardiac workload did not change.

Conclusion(s): In DC patients, short-term synthetic L-T₃ replacement therapy significantly improved neuroendocrine profile and ventricular performance. These data encourage further controlled trials with more patients and longer periods of synthetic L-T₃ administration.

In children and adults undergoing cardiac surgery with cardiopulmonary bypass and in patients after uncomplicated acute myocardial infarction, a predictable fall in serum T₃ occurs. Moreover, low T₃ has been documented in patients with heart failure and particularly in dilated cardiomyopathy where it is an independent predictor of poor outcome. The central question for all these conditions of heart failure is whether low T₃ might protect the heart from further harm or whether it promotes worsening of heart failure. The present study suggests that at least in patients with dilated cardiomyopathy and within a treatment schedule of 3 days, T₃ administration improves rather than worsens cardiac function. In the optimistic editorial 'Thyroid hormone treatment to mend a broken heart', Klein and Danzi [6] comment that the study 'proves the concept that altered thyroid hormone metabolism plays a pathogenetic role in progression of cardiac disease states'. Based on these data, further studies should be performed and should include children with heart failure.

New perspectives: treatment of obesity by activating the thyroid axis

Fasting induces profound changes in the hypothalamus-pituitary-thyroid (HPT) axis. The molecular mechanisms underlying this resetting of HPT axis regulation in the framework of caloric deprivation are still incompletely understood. Several studies have shown that weight loss induces a dramatic downregulation of thyrotropin-releasing hormone (TRH) gene expression in hypophysiotropic paraventricular nucleus (PVN) neurons. The subsequent decrease in serum thyroid hormone concentrations results to some extent from diminished thyroïdal secretion of thyroid hormones, especially in rodents. Decreased T₄ and mainly T₃ contribute to the downregulation of T₃-responsive genes such as liver D1. The overall result of these complex HPT axis changes in various tissues during fasting is downregulation of the HPT axis, which is assumed to represent an energy-saving mechanism, instrumental in times of food shortage. However, the relative contributions of these complex determinants remain to be defined in more detail. Especially the question, if restoration of reduced thyroid hormone levels after fasting by partial substitution with L-thyroxine might overcome the tendency to regain weight remains an open important issue. Nevertheless, these changes argue for a central role of the HPT axis in weight regulation and especially in weight maintenance.

Two studies published over the last year were selected for this *Yearbook* chapter dealing with these issues (see also the paper by Lomenick JP, El-Sayyid M, Smith WJ: Effect of levo-thyroxine treatment on weight and body mass index in children with acquired hypothyroidism. *J Pediatr* 2008;152:96–100, discussed in the Obesity Chapter of the *Yearbook*).

Low replacement doses of thyroxine during food restriction restores type 1 deiodinase activity in rats and promotes body protein loss

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J Endocrinol 2008;198:119–125

Background: During food restriction, decreased basal metabolic rate secondary to reduced serum thyroid hormones levels contributes to weight loss resistance. Thyroxine (T_4) or 3,3- or 3,3',5-triiodothyronine (T_3) administration during caloric restriction produce deleterious side effects, however the administration of physiological doses of T_4 during food restriction has never been evaluated.

Methods: The effects of low replacement doses of T_4 in Wistar rats submitted to 40% food restriction were analyzed.

Results: 30 days of food restriction led to significantly reduced liver type 1 deiodinase activity, serum TSH, leptin, T_4 , T_3 , metabolic rate and body mass. The significant reduction in hepatic deiodinase activity found during food restriction was normalized in a dose-dependent manner by T_4 replacement, showing that decreased deiodinase 1 (D1) activity is secondary to decreased serum thyroid hormone levels during caloric restriction. The lowest replacement dose of T_4 did not normalize resting metabolic rate (RMR), but was able to potentiate the effects of food restriction on fat carcass loss and did not spare body protein. The highest dose of T_4 produced a normalization of daily oxygen consumption and determined a significant reduction in both carcass fat and protein content.

Conclusion(s): The results show that serum T_4 normalization during food restriction restores serum T_3 and liver D1 activity, while body protein is not spared.

The background for this study is the principal treatment strategy to maintain a reduced body weight by substituting the relative deficiency of thyroid hormone induced by weight loss. Initiation of weight loss seems to be extremely difficult with either pharmacological strategy, but the maintenance of reduced weight in lifestyle intervention programs seems to be equally reasonable. In this perspective one might expect that the restoration of a reduced thyroid hormone tone after weight loss can lead to more sustained weight reduction because the counter-regulatory reduction of metabolic rate can be overcome by the readjusted thyroid hormone level. Although one might expect that such a treatment strategy will not have side effects – because thyroid hormone deficiency is restored – the experience of substituting the low T_3 syndrome in critically ill patients suggests that readjusting a low T_3 can possibly be harmful [7]. Overall the data of the above study suggest that the low T_3 in weight-losing animals does not only counter-regulate the weight loss, but also seems to protect against additional loss of proteins. Thus, decreased serum T_4 during caloric restriction corresponds to a protective mechanism to avoid body protein loss, highlighting the importance of other strategies to reduce body mass without lean mass loss.

The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans

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Background: Atherosclerotic cardiovascular disease is a major problem despite the availability of drugs that influence major risk factors. New treatments are needed, and there is growing interest in therapies that may have multiple actions. Thyroid hormone modulates several cardiovascular risk factors and

delays atherosclerosis progression in humans. However, use of thyroid hormone is limited by side effects, especially in the heart. To overcome this limitation, pharmacologically selective thyromimetics that mimic metabolic effects of thyroid hormone and bypass side effects are under development. In animal models, such thyromimetics have been shown to stimulate cholesterol elimination through LDL and HDL pathways, and decrease body weight without eliciting side effects.

Methods: Studies were undertaken on a selective thyromimetic [KB2115; (3-[[3,5-dibromo-4-[4-hydroxy-3-(1-methylethyl)-phenoxy]-phenyl]-amino]-3-oxopropanoic acid)] in humans.

Results: In moderately overweight and hypercholesterolemic subjects, KB2115 was found to be safe and well tolerated and elicited up to a 40% lowering of total and LDL cholesterol after 14 days of treatment. Bile acid synthesis was stimulated without evidence of increased cholesterol production, indicating that KB2115 induced net cholesterol excretion. KB2115 did not provoke detectable effects on the heart, suggesting that the pharmacological selectivity observed in animal models translates to humans.

Conclusion(s): Selective thyromimetics deserve further study as agents to treat dyslipidemia and other risk factors for atherosclerosis.

As outlined above, thyroid hormones' action on metabolic parameters is accompanied by a large range of effects which can be deleterious when trying to treat obesity just by giving L-thyroxine. To circumvent these numerous side effects, companies have tried to develop compounds that mimic the metabolic effect of T_3 but do not act as agonists in most other physiological pathways. One such compound has now proven to be efficient and safe in a phase 1 clinical trial as presented here. This gives hope that those compounds will find a place in a tailored endocrine treatment strategy to overcome obesity, at least in part.

Improving diagnostic strategy: central congenital hypothyroidism and elevated TSH

Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism

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Background: The current debate regarding whether to decrease the upper limit for the TSH reference range to 2.5 $\mu\text{IU/ml}$ has a considerable potential impact on the diagnosis and treatment of subclinical hypothyroidism worldwide. The authors intended to report the TSH distribution in a population with no evidence of thyroid disease, including a normal thyroid ultrasound.

Design: A 1,861 individuals' subset of the general population 'Hanford Thyroid Disease Study' cohort was used to examine the TSH distribution in a population having no evidence of thyroid disease, seronegative thyroid autoantibodies, no history of thyroid medications, and a normal thyroid ultrasound. The shape of the TSH distribution was compared with the gaussian and log-normal distributions. The Hanford Thyroid Disease Study participants were measured for TSH by ELISA and also underwent thyroid peroxidase antibody measurements.

Results: The TSH distribution in the normal reference group 3 (NRG-3) with no evidence of thyroid disease, including no positive antibodies and normal thyroid ultrasound, was right skewed and followed an approximate log-normal distribution. The best estimates of the 97.5th percentile, the percentage $>2.5 \mu\text{IU/ml}$, and the percentage $>3.0 \mu\text{IU/ml}$ for TSH by third-generation immunochemiluminometric assay are 4.1 $\mu\text{IU/ml}$, 20 and 10.2%, respectively.

Conclusion(s): These results indicate that the TSH reference range should be narrowed and support a value of approximately 4.0 as the upper reference limit.

The difficulties in making a diagnosis of hypothyroidism appeared with normative values for TSH. It has been recognized for a long time that TSH values are not normally distributed but show a 'shoulder' on the higher range around 2–4 $\mu\text{U/ml}$. In addition, higher TSH values were shown to correlate with higher incidence rates of autoimmune thyroid disease later in life. Therefore, large efforts were undertaken to re-estimate normal TSH values in preselected populations which are devoid of individuals with thyroid autoantibodies, thyroid nodules or a history of thyroid disease. As a consequence, a new limit of normal TSH level of approximately 2.5 has been proposed. Here, Hamilton et al. use a large well-defined, preselected population to investigate TSH values. The authors confirm that TSH is not normally distributed, but rather follows a log-normal distribution. Calculating from this log-normal value, a 97.5th percentile value for TSH of 4.1 $\mu\text{U/ml}$ was determined, exactly the level that was estimated from non-preselected populations before. We learn that life can sometimes be easier if we stick to traditional habits and we should keep in mind that human biology makes no difference between a TSH of 4.0 or 4.2 but clearly between 4 and 40.

Role of the thyrotropin-releasing hormone stimulation test in diagnosis of congenital central hypothyroidism in infants

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Background: In the case of congenital hypothyroidism of central origin (CH-C), the majority of patients have multiple pituitary hormone deficiencies (MPHD). This condition poses an additional threat to postnatal central nervous system development, primarily on account of neuroglycopenia due to ACTH/cortisol deficiency with or without additional GH deficiency. Therefore, in CH-C, rapid diagnosis is even more urgent than in congenital hypothyroidism of thyroïdal origin. However, due to a defect in TSH secretion, diagnosis of central hypothyroidism in newborns remains an unsolved clinical task.

Methods: To assess the pituitary response to intravenous administration of TRH (TRH test) the authors evaluated a TRH test in a cohort of infants with neonatal congenital hypothyroidism screening results indicative of CH-C. Results were analyzed within the framework of investigations of the anatomical and functional integrity of the hypothalamo-hypophyseal system. The study was a Dutch nationwide prospective study (1994–1996). 10 male and 5 female infants with CH-C, detected by neonatal screening, and 6 infants with false-positive screening results, non-thyroidal illness, or transient hypothyroidism, were included in the study.

Results: Three patterns of TSH response were defined: normal (type 1), deficient increase (type 2), and delayed and/or excessive response (type 3). All patients with type 3 TSH responses to TRH had MPHD, and the majority (67%) of patients with type 2 responses had isolated TSH deficiency.

Conclusion(s): The TRH test can be used to diagnose TSH deficiency in young infants. Abnormal TRH test results, especially a type 3 response, urge immediate assessment of integral hypothalamic-pituitary function because the majority of patients have MPHD.

In countries where screening includes T_4 and TSH, central hypothyroidism can be diagnosed and reveals an incidence of 1/16,000. Confirmation diagnosis in those cases can be difficult because TSH can be inadequately low but also inadequately high in defects of TSH regulation rather than production. The Dutch group that performs screening based on T_4 and TSH now presents elegant normative values for TSH responses to TRH test and built thereby the ground for a better diagnostic approach for central hypothyroidism in infants. They compare the TSH response curves rather than the absolute response of TSH in a long TRH test of 180 min. The two different pathological responses (termed group 2 and group 3) represent the formerly labeled 'pituitary/secondary' and 'hypothalamic/tertiary' responses, respectively. The strength of the data is the long follow-up and confirmation of the diagnosis after several years and the correlation with MRI abnormalities. It appears that the defined profiles are sensitive and specific to diagnose TSH regulation defects and most likely further studies will show if those 'Dutch curving data' can be confirmed in other cohorts.

MCT8 mutation analysis and identification of the first female with Allan-Herndon-Dudley syndrome due to loss of MCT8 expression

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Background: Mutations in the thyroid monocarboxylate transporter 8 gene (MCT8/SLC16A2) have been reported to result in X-linked mental retardation (XLMR) in patients with clinical features of the Allan-Herndon-Dudley syndrome (AHDS). Mutation frequency in XLMR patients without thyroid hormone abnormalities is unknown.

Design: The authors performed MCT8 mutation analysis including 13 XLMR families with lod scores >2.0 , 401 male MR sibships and 47 sporadic male patients with AHDS-like clinical features.

Results: One nonsense mutation (c.629insA) and two missense changes (c.1A>T and c.1673G>A) were identified. Consistent with previous reports on MCT8 missense changes, the patient with c.1673G>A showed an elevated serum T_3 level. The c.1A>T change in another patient affects a putative translation start codon, but the same change was present in his healthy brother. In addition, normal serum T_3 levels were present, suggesting that the c.1A>T (NM_006517) variation is not responsible for the mental retardation phenotype but indicates that MCT8 translation likely starts with a methionine at position 75. Moreover, a de novo translocation t(X;9)(q13.2;p24) was characterized in a female patient with full-blown AHDS clinical features including elevated serum T_3 levels. The MCT8 gene was disrupted at the X-breakpoint. A complete loss of MCT8 expression was observed in a fibroblast cell line derived from this patient because of unfavorable non-random X-inactivation.

Conclusion(s): Taken together, these data indicate that MCT8 mutations are not common in non-AHDS mental retardation patients, yet they support that elevated serum T_3 levels can be indicative for AHDS and that AHDS clinical features can be present in female MCT8 mutation carriers whenever there is unfavorable non-random X-inactivation.

Genotype-phenotype relationship in patients with mutations in thyroid hormone transporter MCT8

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Background: Loss-of-function mutations in thyroid hormone transporter monocarboxylate transporter 8 (MCT8) lead to severe X-linked psychomotor retardation and elevated serum T_3 levels. Most patients, for example those with mutations V235M, S448X, insI189, or delF230, cannot stand, walk, or speak. Patients with mutations L434W, L568P, and S194F, however, walk independently and/or develop some dysarthric speech.

Methods: The authors studied the relationship between mutation and phenotype by transfection of JEG3 and COS1 cells with wild-type or mutant MCT8. Expression and function of the transporter were studied by analyzing T_3 and T_4 uptake, T_3 metabolism (by cotransfected type 3 deiodinase), Western blotting, affinity labeling with N-bromoacetyl- T_3 , immunocytochemistry, and quantitative RT-PCR. Wild-type MCT8 increased T_3 uptake and metabolism about 5-fold compared with empty vector controls.

Results: Mutants V235M, S448X, insI189, and delF230 did not significantly increase transport. However, S194F, L568P, and L434W showed about 20, 23, and 37% of wild-type activity. RT-PCR did not show significant differences in mRNA expression between wild-type and mutant MCT8. Immunocytochemistry detected the non-functional mutants V235M, insI189, and delF230 mostly in the cytoplasm, whereas mutants with residual function were expressed at the plasma membrane. Mutants S194F and L434W showed high protein expression but low affinity for N-bromoacetyl- T_3 ; L568P was detected in low amounts but showed relatively high affinity.

Conclusion(s): Mutations in MCT8 cause loss of function through reduced protein expression, impaired trafficking to the plasma membrane, or reduced substrate affinity. Mutants L434W, L568P, and S194F showed significant residual transport capacity, which may underlie the more advanced psychomotor development observed in patients with these mutations.

Together these two reports on mutations in the MCT8 gene refine the clinical spectrum of this new syndrome. The first paper by Frints et al. clearly demonstrates that the abnormalities of circulating thyroid hormones described in the founder patients (high T_3 and low T_4) seem to represent a sine qua non observation to make the diagnosis of the disease. A large number of patients with X-linked mental retardation were screened for mutations and only 2 were affected – both with high T_3 . Until this report the question remained open whether a larger number of mentally retarded patients might be MCT8-deficient; now it is obvious that screening for MCT8 defects can be focused on those few patients with mental retardation associated with high T_3 . In the other paper the identified mutations were re-evaluated in terms of functional relevance and the authors found some hints for a genotype-phenotype correlation. Some mutations cause only partial functional deficiency and are more likely related with the less severe 'Allan-Herndon-Dudley syndrome' variant of the disease compared to the dramatic form with almost no motor development.

Effective cellular uptake and efflux of thyroid hormone by human monocarboxylate transporter 10

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Background: Cellular entry of thyroid hormone is mediated by plasma membrane transporters, among others a T-type (aromatic) amino acid transporter. Monocarboxylate transporter 10 (MCT10) has been reported to transport aromatic amino acids but not iodothyronines. Within the MCT family, MCT10 is most homologous to MCT8, which is a very important iodothyronine transporter but does not transport amino acids.

Design: In view of this paradox, the authors decided to reinvestigate the possible transport of thyroid hormone by human (h) MCT10 in comparison with hMCT8.

Results: Transfection of COS1 cells with hMCT10 cDNA resulted in: (1) the production of an approximately 55-kDa protein located to the plasma membrane as shown by immunoblotting and confocal microscopy; (2) a strong increase in the affinity labeling of intracellular type I deiodinase by N-bromoacetyl-[125 I] T_3 ; (3) a marked stimulation of cellular T_4 and, particularly, T_3 uptake; (4) a significant inhibition of T_3 uptake by phenylalanine, tyrosine, and tryptophan of 12.5, 22.2, and 51.4%, respectively, and (5) a marked increase in the intracellular deiodination of T_4 and T_3 by different deiodinases. Cotransfection studies using the cytosolic thyroid hormone-binding protein μ -crystallin (CRYM) indicated that hMCT10 facilitates both cellular uptake and efflux of T_4 and T_3 . In the absence of CRYM, hMCT10 and hMCT8 increased T_3 uptake after 5 min incubation up to 4.0- and 1.9-fold, and in the presence of CRYM up to 6.9- and 5.8-fold, respectively. hMCT10 was less active toward T_4 than hMCT8.

Conclusion(s): These findings establish that hMCT10 is at least as active a thyroid hormone transporter as hMCT8, and that both transporters facilitate iodothyronine uptake as well as efflux.

One unsolved question in MCT8 deficiency is the cellular pathology of the defect. It remains unknown which neurons and at what time in development – embryonic, fetal or postnatal – are affected by the MCT8 mutation. Obviously the alteration in T_3 and T_4 ratios in all patients identified so far suggest the involvement of thyroid hormone metabolism. But whether this alteration is a cause of the neurological phenotype or only one independent result of MCT8 mutation is questionable. Still the clinical picture does not correlate with classical signs of fetal or neonatal hypo- or hyperthyroidism and one may speculate that a very early defect of transport of maternal T_4 to the developing brain of the embryo in a brain region-specific manner might cause the particular symptoms. However, no morphological defect has been diagnosed in MRI so far and unfortunately MCT8 knockout mice strains do not show the human neurological phenotype. The paper by Friesema et al. adds another piece to this puzzling picture as they re-evaluated the thyroid hormone transportation

capacity of another MCT family member, MCT10, which was initially reported not to be a T₄ transport molecule. Now the authors show that MCT10 transports T₃ at least as well as MCT8. Only the very detailed expression studies of MCT8 and MCT10 during human embryonic and fetal development will give the framework for new hypotheses on how an inactivation of MCT8 might interfere with particular neurons during brain development. Those neurons which exclusively express MCT8 will be most vulnerable for mutations in contrast to neurons with expression of MCT8 and MCT10 together.

Two important negative results in the field of thyroid autoimmunity

Association scan of 14,500 non-synonymous SNPs in four diseases identifies autoimmunity variants

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Background: Major gene variants associated with autoimmune diseases are still rare. Genome-wide association studies are increasingly available and might reveal non-hypothesis-driven new genes involved in autoimmune responses.

Methods: The authors genotyped 14,436 non-synonymous SNPs (nsSNPs) and 897 major histocompatibility complex (MHC) tag SNPs from 1,000 independent cases of ankylosing spondylitis (AS), autoimmune thyroid disease (AITD), multiple sclerosis (MS) and breast cancer (BC) and compared these data against a common control dataset derived from 1,500 randomly selected healthy British individuals.

Results: The authors report initial association and independent replication in a North American sample of two new loci related to ankylosing spondylitis, ARTS1 and IL23R, and confirmation of the previously reported association of AITD with TSHR and FCRL3.

Conclusion(s): These findings, enabled in part by increased statistical power resulting from the expansion of the control reference group to include individuals from the other disease groups, suggest that IL23R may be a common susceptibility factor for the major ‘seronegative’ diseases but not AITD. No new major susceptibility gene variant for AITD was identified. Although twin studies clearly argue for strong genetic influence on the manifestation of thyroid autoimmune disease, it does not seem possible so far to resolve the genetics behind that epidemiological observation. This new and comprehensive association study including 14,500 nsSNPs did not reveal new SNPs relevant for thyroid autoimmune disease. The clear and frustrating conclusion is that such genetic variants with major impact on thyroid autoimmune disease do not exist and that a large set of minor subtle variants might cause the genetic risk for thyroid autoimmune disease rather than few really significant genes. It remains questionable whether the search for such minor variants makes sense although they might indicate pathways relevant to pathogenesis.

No immunological benefit of selenium in consecutive patients with autoimmune thyroiditis

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Background: Recently it has been demonstrated that after selenium (Se) supplementation in autoimmune thyroiditis (AIT) patients, there was a significant decrease of thyroid peroxidase (TPO) autoantibody (TPOAb) levels. The aim of this study was to evaluate the immunological benefit of Se administration in unselected AIT patients and thus address the question whether Se administration should generally be recommended for AIT patients.

Methods: 36 consecutive AIT patients (aged 19–85 years) were included. In addition to their levothyroxine (LT₄) treatment, 18 patients received 200 µg (2.53 µmol) sodium selenite per day orally for 3 months,

whereas 18 patients received placebo. All patients had measurement of thyroid hormones, thyrotropin (TSH), autoantibodies (thyroglobulin antibodies [TgAb] and TPOAb), Se levels, and intracellular cytokine detection in CD4+ and CD8+ T cells of peripheral blood mononuclear cells (PBMC) by flow cytometry before and after Se or placebo administration.

Results: No significant difference in the TPOAb levels was found after Se administration (524 ± 452 vs. 505 ± 464 IU/ml; $p > 0.05$). Furthermore, no significant differences in the CD4+ or CD8+ cytokine pattern (IFN- γ , IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, TNF- α , TNF- β) was observed.

Conclusion(s): The data suggest that Se administration in AIT patients may not induce significant immunological changes, either in terms of cytokine production patterns of peripheral T lymphocytes or of TPOAb levels. AIT patients with moderate disease activity (in terms of TPOAb and cytokine production patterns) may not (equally) benefit as patients with high disease activity.

Since the first report of Gärtner et al., that proposed a beneficial effect of selenium substitution in the course of thyroid autoimmune disease, selenium as treatment for Hashimoto's disease has been proposed as a clinical practice also in children. However, so far only two small further studies have shown few benefits in terms of antibody titer reduction under selenium. Up to now, no large placebo-controlled long-term studies with thyroid function rather than antibody concentration as the outcome have been performed, especially in children. The study by Karanikas et al. needs attention because the authors report for the first time the absence of effect of selenium substitution in patients with Hashimoto's thyroiditis. Again the study cohort is small with only 18 patients in each arm but it is a clear hint that selenium should not be recommended until valuable data of large studies have shown a benefit in terms of improvement of thyroid function during a longer course of thyroid autoimmune disease. Especially the data that too much selenium might increase the risk for diabetes as reported last year from the best controlled 7-year follow-up study of selenium supplementation [8] raise the concern that the already increased risk of diabetes in patients with Hashimoto's disease might further rise under selenium supplementation.

New pieces in a mystic puzzle: epidemiology of congenital hypothyroidism

High risk of congenital hypothyroidism in multiple pregnancies

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Background: In Italy, the surveillance of congenital hypothyroidism (CH) is performed by the Italian National Registry of Infants with CH (INRICH). Up to now, about 3,600 infants with CH are recorded in the INRICH, and a high number of twins are included. The objective was to estimate the risk of CH in multiple and single deliveries and to compare neonatal features of CH twins with twins from the general population.

Design: The Italian population of CH infants recorded in the INRICH from 1989 to 2000 was investigated.

Results: A more than 3-fold higher frequency of twins was found in the CH population than in the general population, and for the first time, it was possible to estimate the CH incidence in multiple (10.1 in 10,000) and single deliveries (3.2 in 10,000 live births). Significantly higher frequencies of in situ gland as well as lower TSH mean level at screening were found in twin than in singleton CH babies. The concordance rate for permanent CH was very low (4.3%) and due to only three concordant couples. However, a high recurrence risk for CH was estimated in siblings of affected babies recorded in the INRICH, including twins considered as siblings.

Conclusion(s): The authors conclude that the high CH incidence observed in twins is worthy of interest for the high number of induced pregnancies in Italy as well as in other Western countries. Moreover, they speculate that the low concordance rate for CH among twins together with a high recurrence risk for

the disease among siblings indicates that environmental risk factors may act as a trigger on a susceptible genetic background in the etiology of the disease.

Random variability in congenital hypothyroidism from thyroid dysgenesis over 16 years in Québec

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Background: Research on the etiology of congenital hypothyroidism from thyroid dysgenesis (CHTD) (comprising mostly ectopy and agenesis) over the past decade has focused on genetic mechanisms. However, the possibility that environmental factors might be involved has been raised by studies showing a seasonal variability of the incidence of CHTD. The objective of this study was to assess the variability in incidence of CHTD in the province of Quebec, Canada.

Methods: The Quebec provincial newborn screening database was analyzed from January 1990 to December 2005. Only cases of permanent congenital hypothyroidism with thyroid ectopy or agenesis on scintigraphy were analyzed.

Results: During the study period, 1,303,341 children were screened, and 424 cases of permanent congenital hypothyroidism were diagnosed, giving an overall incidence of 1:3,074. Of these, 306 had CHTD (overall incidence 1:4,259) from either ectopy ($n = 231$) or agenesis ($n = 75$). Over the 16 years of the study, this incidence remained stable ($p = 0.57$), and no significant variability in monthly incidence was found ($p = 0.87$).

Conclusion(s): The incidence of CHTD did not vary over the observation period, and its monthly variation was random. Therefore, environmental factors do not appear to play a significant role in the etiology of CHTD.

In contrast to the conclusions of the Italian authors, we believe that the main message of the data from the Italian CH registry is not in favor of environmental risk factors in congenital hypothyroidism. The surprising low concordance rate in twins (80 twins were described!) argues for the opposite. Both twins live in almost the same 'maternal' environment, more equal than every experimental setting can provide, and despite this identical environment they are discordant. Although this is a painful finding in terms of developing pathogenetic concepts for CH, we have to consider this high discordance as what it is. Environmental factors would lead to some clusters or endemics where so ever a pollutant is enriched in the world. But this has not been found so far. The paper by the Canadian group adds another negative epidemiological finding of CH, e.g. that seasonal differences do not seem to exist. They conclude that it cannot be an environmental factor that causes CH. It seems to be a mechanism that manifests by chance during very early life of an embryo after twins divide and with a very local effect only in small region of one twin space in the uterus of $<1\text{ mm}^2$. Whatever it is, it acts constantly over time in terms of 15 years' follow-up and in terms of seasons of the year as the Canadian group show. What is it?

Are the small human-like fossils found on Flores human endemic cretins?

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Background: Fossils from Liang Bua (LB) on Flores, Indonesia, including a nearly complete skeleton (LB1) dated to 18 kyr BP, were assigned to a new species, *Homo floresiensis*. The authors hypothesize that these individuals are myxoedematous endemic (ME) cretins, part of an inland population of (mostly unaffected) *Homo sapiens*.

Methods: Reinvestigation of the LB1 skeleton.

Results: The authors show that the fossils display many signs of congenital hypothyroidism, including enlarged pituitary fossa, and that distinctive primitive features of LB1 such as the double-rooted lower premolar and the primitive wrist morphology are consistent with the hypothesis. The authors find that

the null hypothesis (that LB1 is not a cretin) is rejected by the pituitary fossa size of LB1, and by multivariate analyses of cranial measures.

Conclusion(s): The authors argue that critical environmental factors were potentially present on Flores, how remains of cretins but not of unaffected individuals could be preserved in caves, and that extant oral traditions may provide a record of cretinism.

Since the first discovery in 1994 by Brown et al. [9], the skeleton from Flores of very early human species triggered a large debate if these bones represent the remnants of an own homo species '*Homo floresiensis*'. The actual paper brings this debate now into the field of thyroid pediatric endocrinology since they claim that the signs within the bones of LB1 and mainly the enlarged pituitary fossa are diagnostic for congenital hypothyroidism. Unfortunately, newborn screening programs were established only 30 years ago and not already in the late Pleistocene. If so, we could easily prove the hypothesis of the authors of this intriguing however speculative paper. Maybe some rests of DNA pieces as recently extracted from the *Homo neanderthalensis* – which will result in sequencing of the genome of this species – will be found also from the LB1 skeleton and might help to make a genetic diagnosis of e.g. TPO mutation in LB1. However, the question if a separate human new species as proposed for the Flores skeleton has existed is magic and will stimulate also in future many hypotheses and our fantasies.

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