

T3 plus T4 Combination Therapy: Yes or No?

Antonio C. Bianco, MD, PhD
Division of Endocrinology and Metabolism
Rush University Medical Center
Chicago, IL

Contact: www.BiancoLab.org

Disclosures: Chief, Division of Endocrinology and Metabolism; Executive Vice-Chair, Department of Internal Medicine, Rush University Medical Center, President-Elect American Thyroid Association, Board of Scientific Counselors of the NIDDK-NIH, Bethesda MD, USA

A Patient's Email

Dear Dr. Bianco,

I know my body well enough to know when the thyroid is out of sorts.

I had a sense of being unwell this entire season.

Before my college classes start in the fall, I must get regulated.

I am the type of person, who never misses a day of work.

I believe this crisis is the result of a doctor taking me off of XXX and not giving me liothyronine.

He just gave me levothyroxine.....I cannot walk a straight line and am in a constant state of dizziness.

My vision is blurry and I feel like I have vertigo.

I have chronic insomnia and am extremely jumpy.

I cannot focus and worse of all cannot focus on reading.

My thyroid problems all started when XXX went off the market.

Since then I have had a 30 pound weight gain.

I cannot understand why all these new med cannot do the job of XXX.

I think this drug was taken off the market several times.....each time when I go back on it, I feel healthy and have the energy and alertness of a 20 year old.

Would you please give me both levothyroxine and T3?

Sincerely, KB

2/12 - KB is a 65 y.o. female that in 1973 was diagnosed with hypothyroidism.

Treated with XXX (desiccated porcine thyroid). However, ever since XXX came out of the market she was placed on levothyroxine and ***does not feel well***. She is gaining weight and has difficulty in focusing (she is a high school teacher).

Currently on 100mcg/day levothyroxine;
TSH = 2.75; FT4 = 1.6; T3 = 71

Recommendation:

Increase levothyroxine by ½ tablet/week
or
add to 5-10 mcg/day of liothyronine to the levothyroxine regimen?

Clinical Practice Guidelines for Hypothyroidism in Adults:

Jeffrey R. Garber, Rhoda H. Cobin, Hossein Gharib, James V. Hennessey, Irwin Klein, Jeffrey I. Mechanick, Rachel Pessah-Pollack, Peter A. Singer, and Kenneth A. Woeber

How should patients with hypothyroidism be treated and monitored?

RECOMMENDATION 22.1

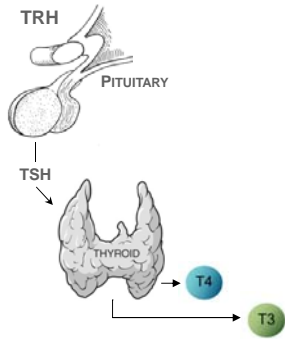
Patients with hypothyroidism should be treated with L-thyroxine monotherapy.
Grade A

RECOMMENDATION 22.2

The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism.
Grade B

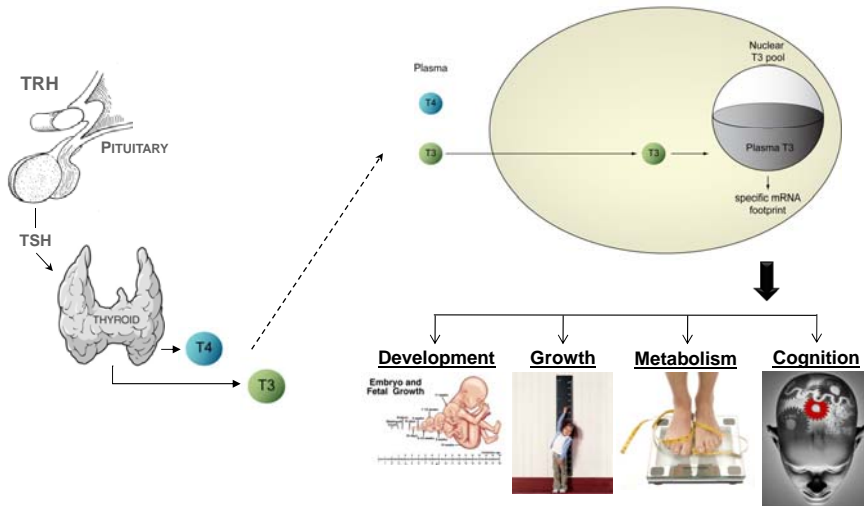
Recommendation 22.2 was downgraded to Grade B because of still-unresolved issues raised by studies that report that some patients prefer and some patient subgroups may benefit from a combination of L-thyroxine and L-triiodothyronine..

HYPOTHALAMUS-PITUITARY THYROID AXIS

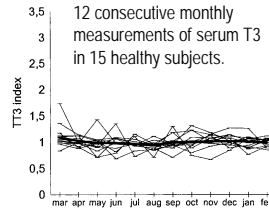
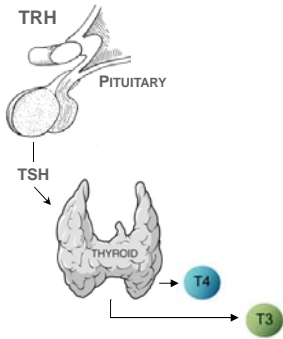


HYPOTHALAMUS-PITUITARY THYROID AXIS

DEIODINASE-CONTAINING TISSUES

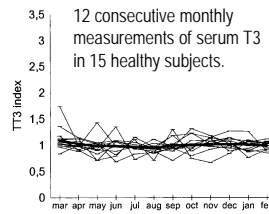
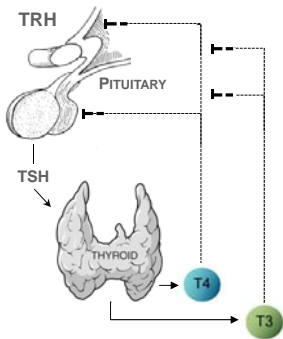


HYPOTHALAMUS-PITUITARY THYROID AXIS



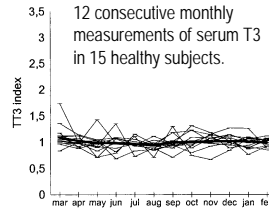
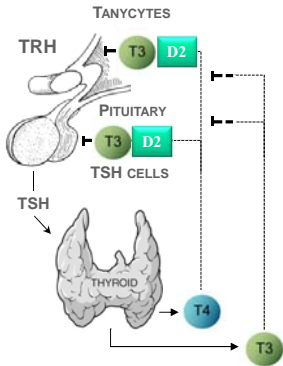
Andersen et al. *Thyroid*, 2003

HYPOTHALAMUS-PITUITARY THYROID AXIS



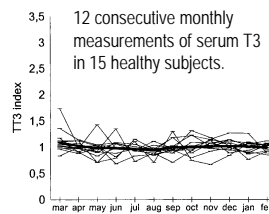
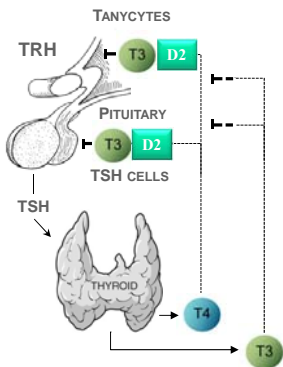
Andersen et al. *Thyroid*, 2003

HYPOTHALAMUS-PITUITARY THYROID AXIS



Andersen et al. Thyroid, 2003

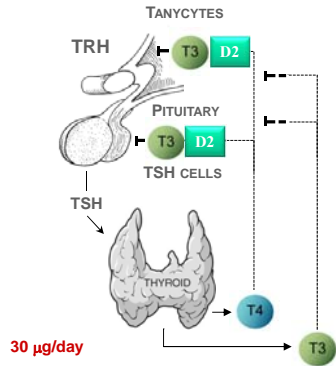
HYPOTHALAMUS-PITUITARY THYROID AXIS



Andersen et al. Thyroid, 2003

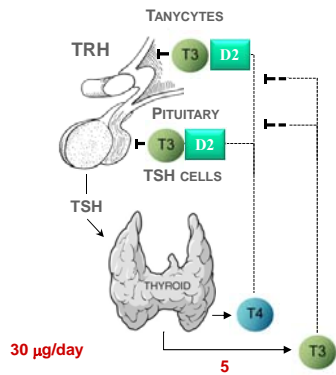
ACCE&ATA Guidelines: ...serum T3 measurement, whether total or free, has limited utility in hypothyroidism because levels are often normal due to hyperstimulation of the remaining functioning thyroid tissue by elevated TSH and to up-regulation of type 2 iodothyronine deiodinase.

HYPOTHALAMUS-PITUITARY THYROID AXIS



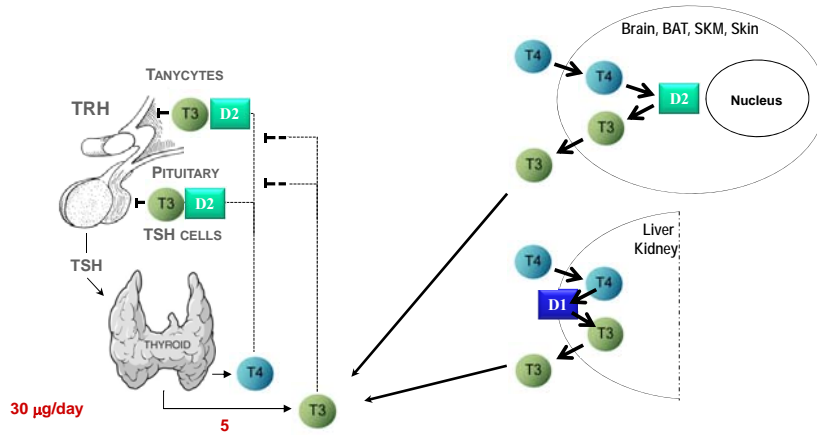
WHAT ARE THE SOURCES OF SERUM T3?

HYPOTHALAMUS-PITUITARY THYROID AXIS



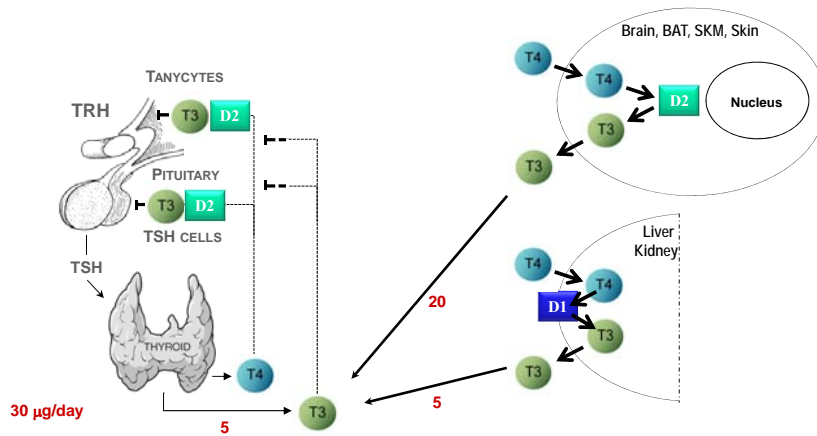
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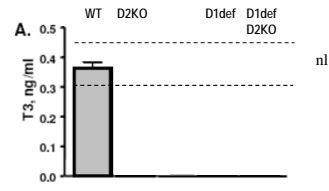
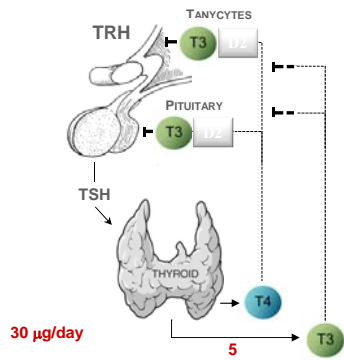
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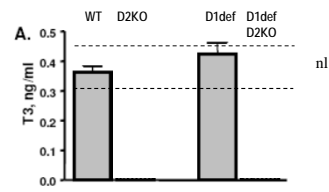
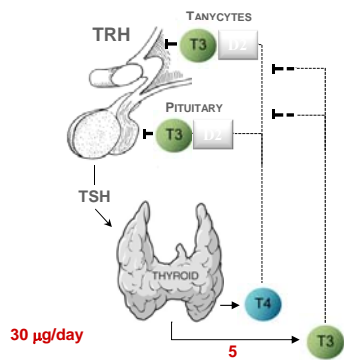
HYPOTHALAMUS-PITUITARY THYROID AXIS



Christoffolete et al, Endocrinology 2007

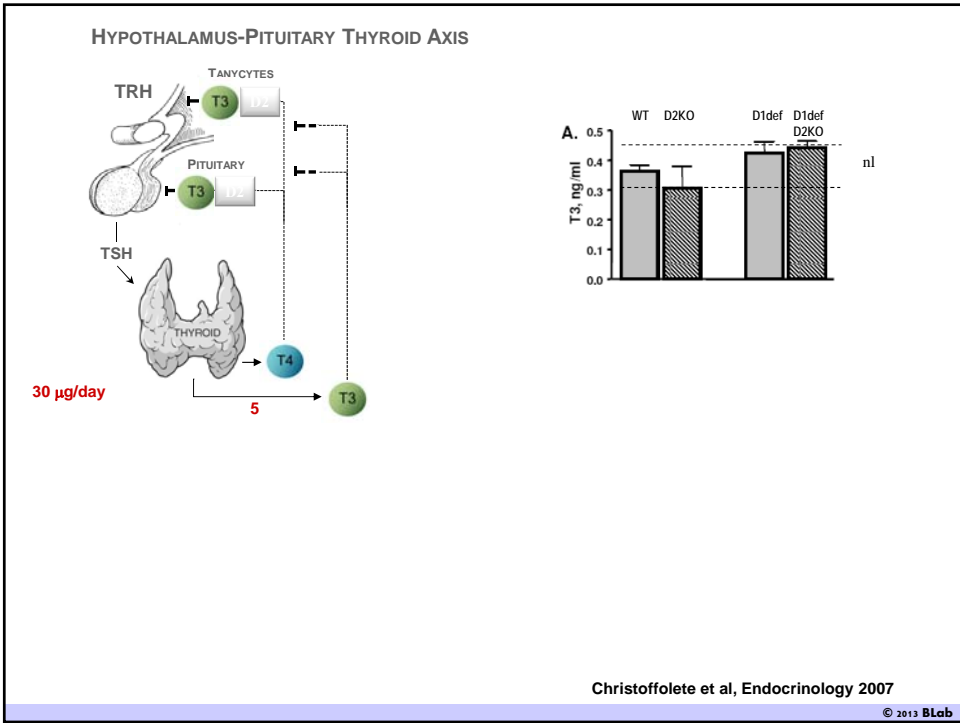
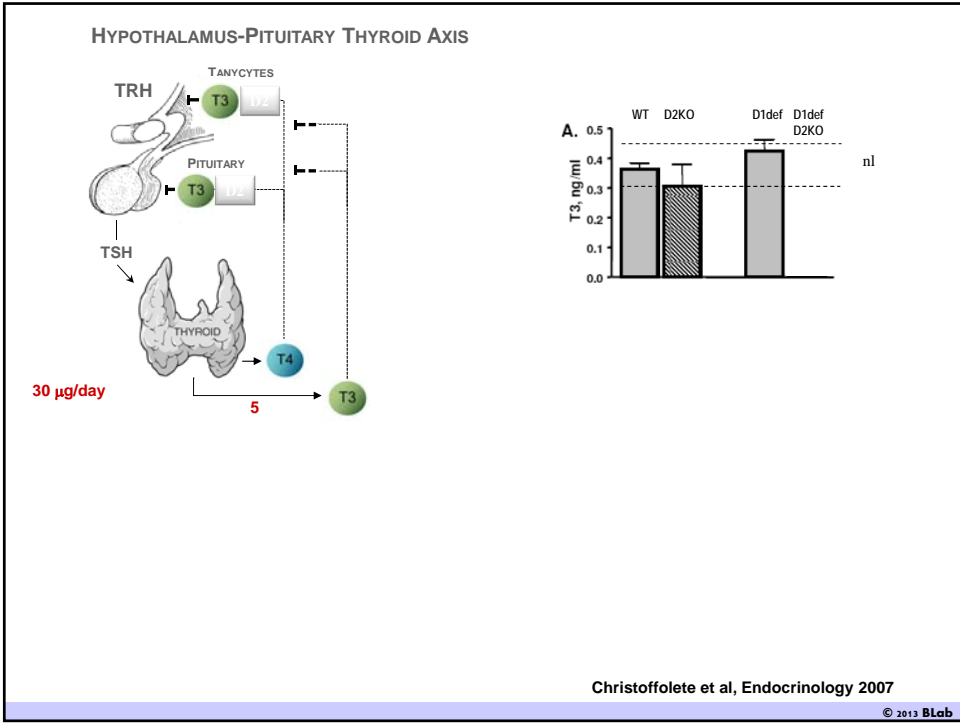
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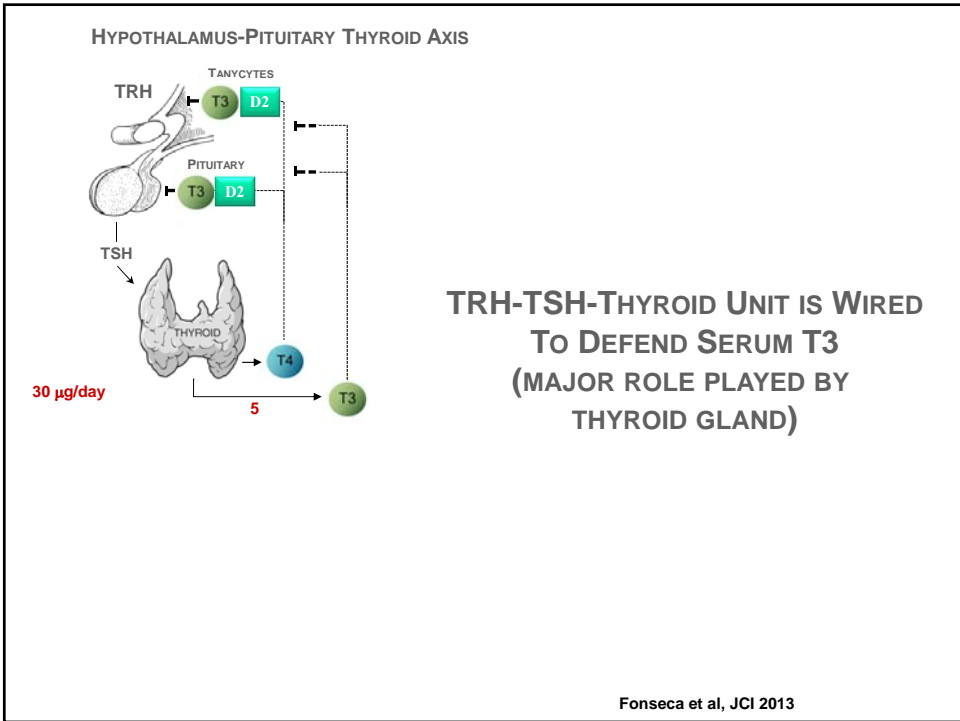
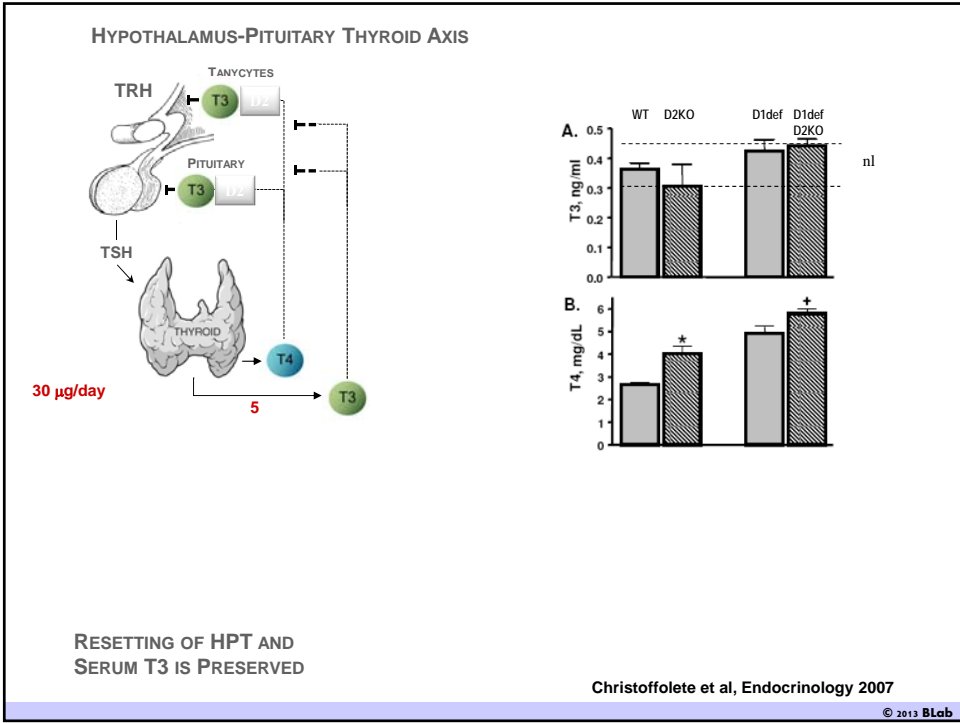
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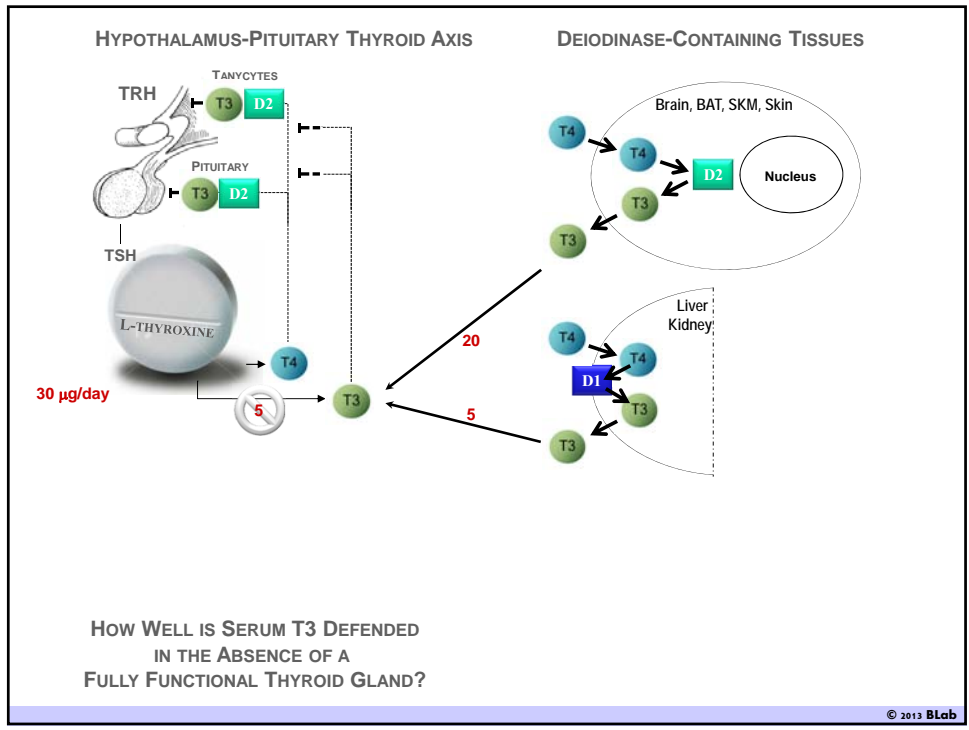
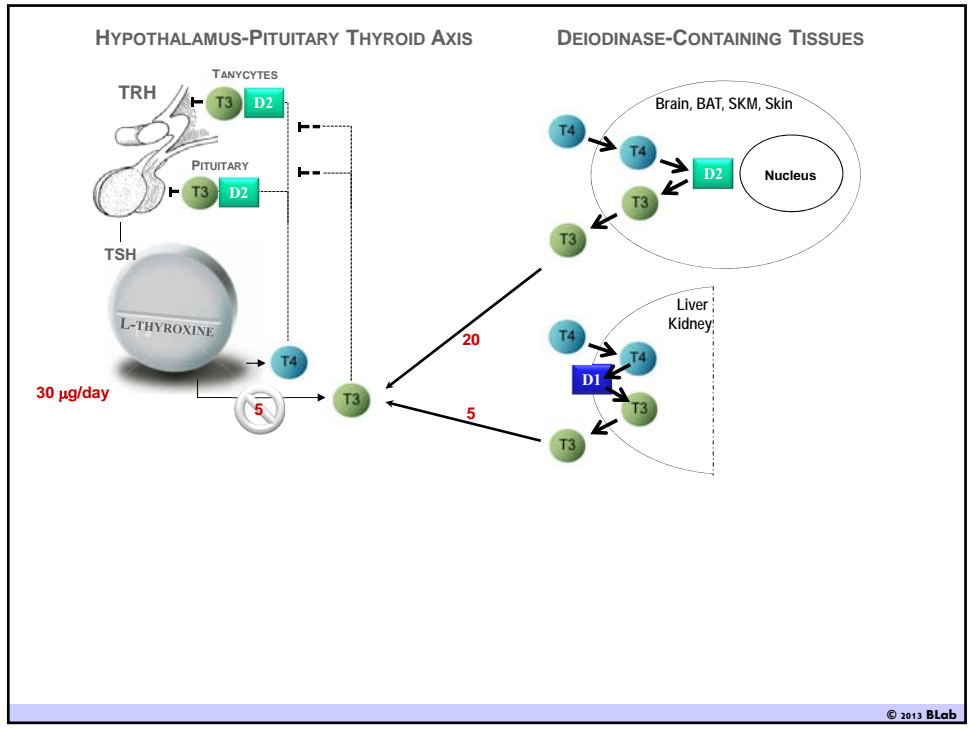


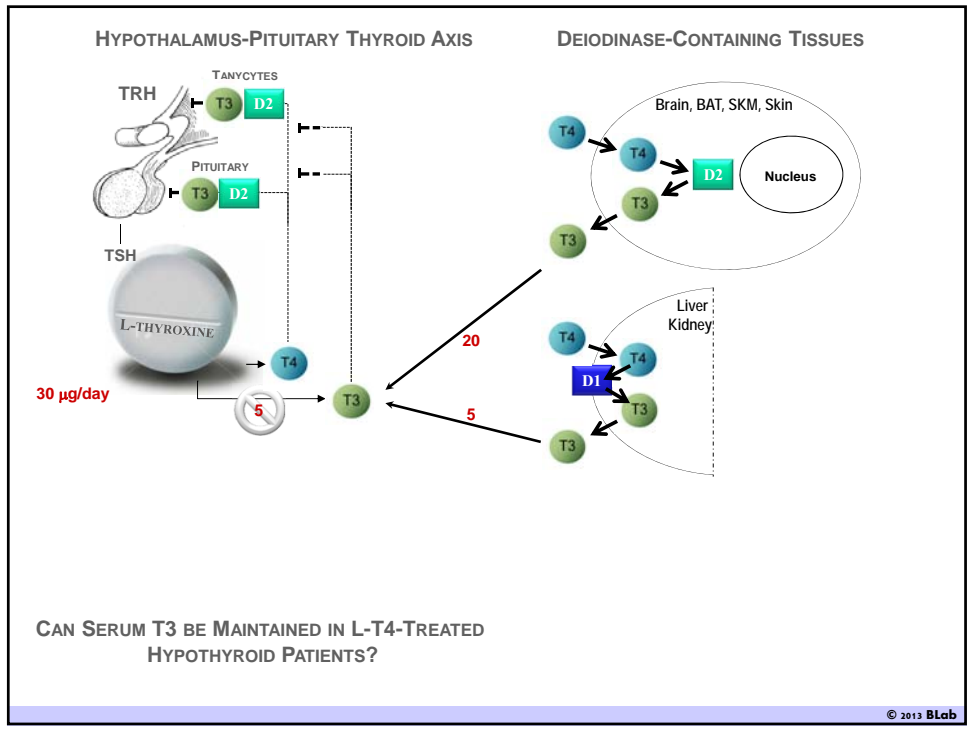
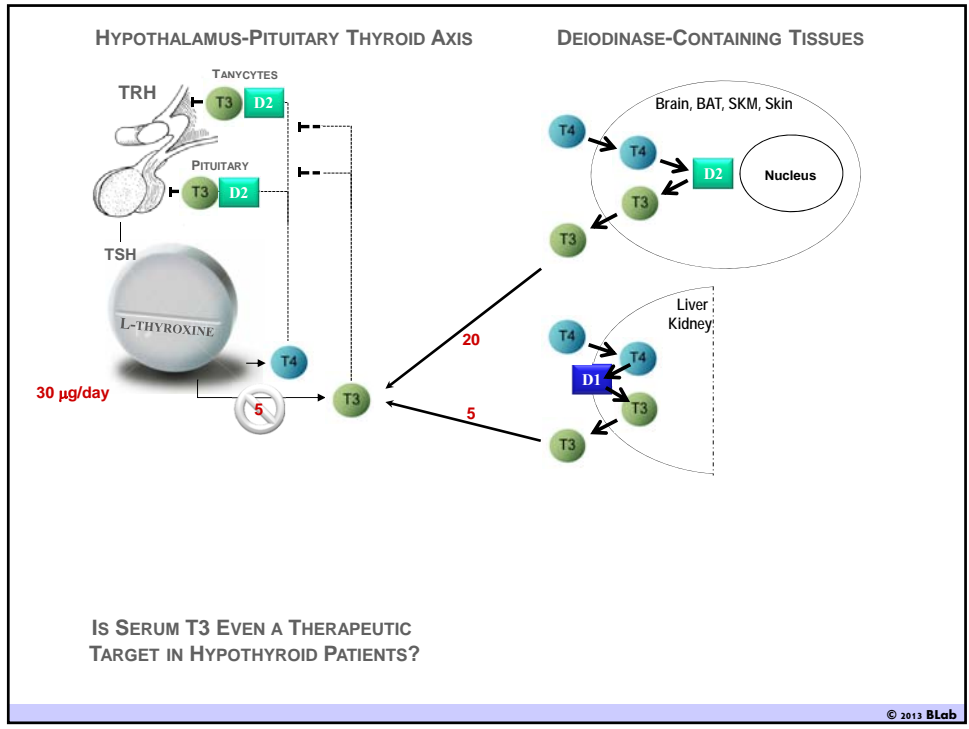
Christoffolete et al, Endocrinology 2007

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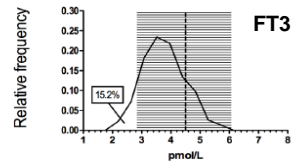
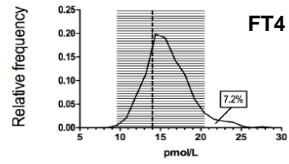
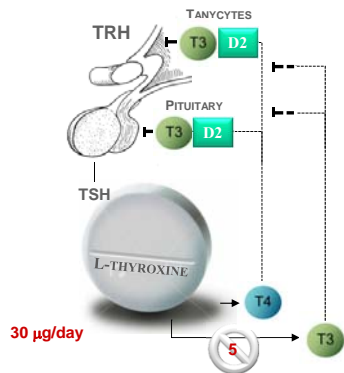






HYPOTHALAMUS-PITUITARY THYROID AXIS

Gullo et al ; 2011

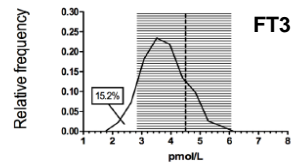
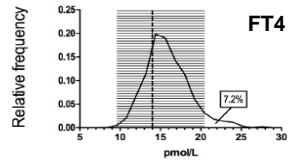
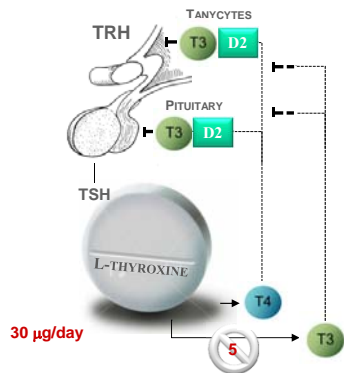


CAN SERUM T3 BE MAINTAINED IN L-T4-TREATED HYPOTHYROID PATIENTS?

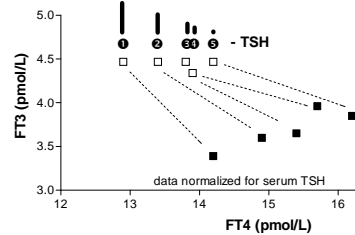
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HYPOTHALAMUS-PITUITARY THYROID AXIS

Gullo et al ; 2011



- Euthyroid controls (3875)
- Athyrotic on l-thyroxine (1811)



CAN SERUM T3 BE MAINTAINED IN L-T4-TREATED HYPOTHYROID PATIENTS?

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American Thyroid Association Guidelines (2014)

Guidelines for Treatment of Hypothyroidism

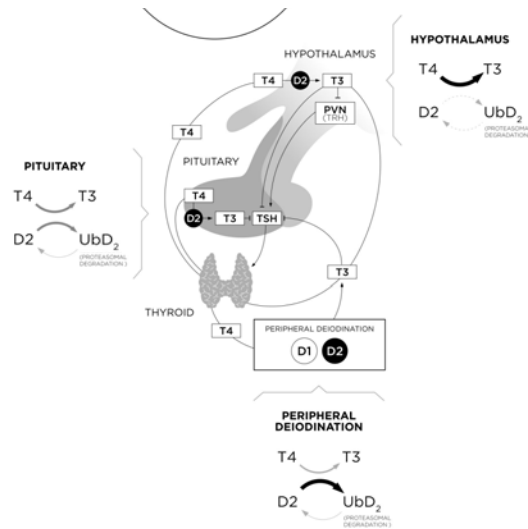
Jonklaas, J. & Bianco, A.C., Bauer, A.J., Burman, K.D., Cappola, A.R., Celi, F.S., Cooper, D.S., Kim, B.W., Peeters, R.P., Rosenthal, M.S., Sawka, A.M.

7b. Does levothyroxine therapy that returns the TSH levels of hypothyroid patients to the reference range also result in normalization of their T3 levels?

Summary statement

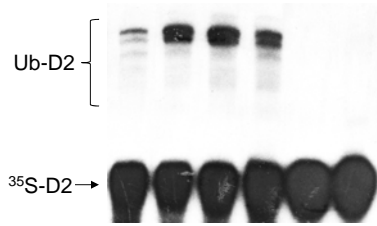
Patients with hypothyroidism treated with levothyroxine to achieve normal TSH values often have T3 concentrations that are at the lower end of the reference range, or even below the reference range. The clinical significance of this is unknown.

What is the mechanism?

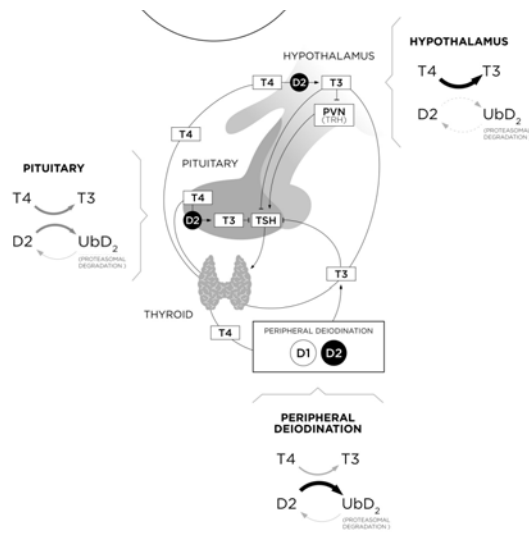


What is the mechanism?

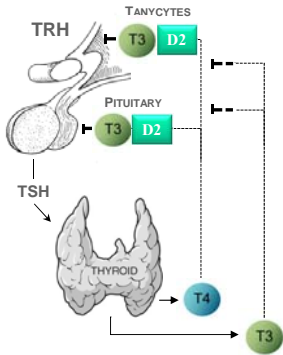
Hippocampus	-	-	-	+	-	-
Cerebral Cortex	-	-	+	-	-	+
Hypothalamus	+	+	-	-	-	-
ubiquitin	+	+	+	+	+	-
GST-WSB-1	-	+	-	-	-	-
GST	+	-	+	+	+	+



What is the mechanism?

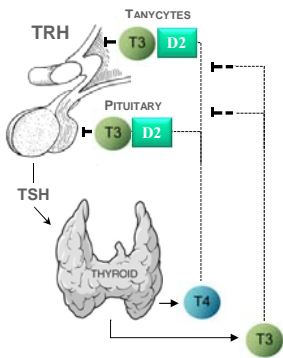


HYPOTHALAMUS-PITUITARY THYROID AXIS

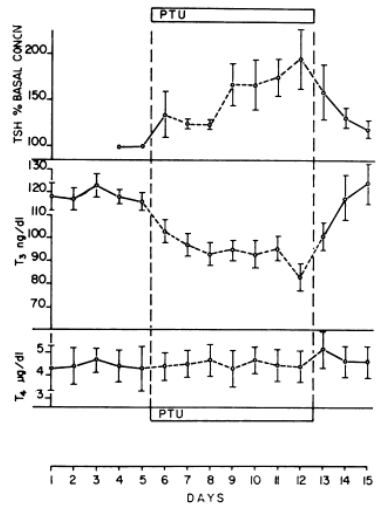


IS SUCH A SMALL DECREASE
IN SERUM T3 CLINICALLY RELEVANT?

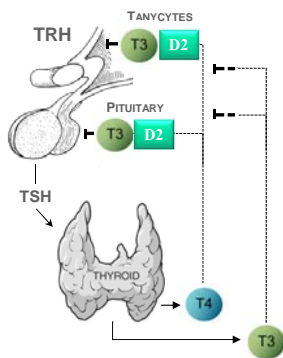
HYPOTHALAMUS-PITUITARY THYROID AXIS



IS SUCH A SMALL DECREASE
IN SERUM T3 CLINICALLY RELEVANT?



HYPOTHALAMUS-PITUITARY THYROID AXIS



IS SUCH A SMALL DECREASE
IN SERUM T3 CLINICALLY RELEVANT?

Methods

- Surgically Tx rats
- Implanted with LT4 or LT4+LT3 pellets
- Killed 7 weeks later

Results and Conclusions

- 1-Monotherapy results in normal serum TSH, higher serum T4 and lower serum T3
- 2-Monotherapy results in brain, liver and skeletal muscle hypothyroidism

Rationale for combination therapy with levothyroxine and liothyronine

1. Thyroidectomized patients on monotherapy with levothyroxine normalize serum FT4 and TSH but do not seem to normalize serum T3, maintaining a high serum T4/T3 ratio and in some cases serum T3 levels that are below the normal range.

However, with very few exceptions, most clinical trials failed to show any significant advantage/benefit of combination therapy vs. monotherapy.

American Thyroid Association Guidelines (2014)

Guidelines for Treatment of Hypothyroidism

Jonklaas, J. & Bianco, A.C., Bauer, A.J., Burman, K.D., Cappola, A.R., Celi, F.S., Cooper, D.S., Kim, B.W., Peeters, R.P., Rosenthal, M.S., Sawka, A.M.

13a. In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is the combination treatment including synthetic triiodothyronine and levothyroxine superior to the use of levothyroxine alone?

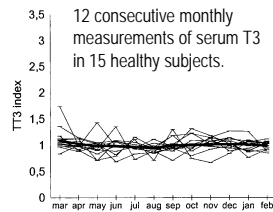
Recommendation:

There is no consistently strong evidence of superiority of combination therapy over monotherapy with levothyroxine. Therefore, we recommend against the routine use of combination treatment with levothyroxine and liothyronine as a form of thyroid replacement therapy in patients with primary hypothyroidism, based on conflicting results of benefits from randomized controlled trials comparing this therapy to levothyroxine therapy alone and a paucity of long-term outcome data.

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How good are the clinical trials?

Q: Does combination therapy with tablets of levothyroxine and liothyronine normalize plasma T3?



Andersen et al. *Thyroid*, 2003

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How good are the clinical trials?

Twenty-four hour hormone profiles of TSH, Free T3 and free T4 in hypothyroid patients on combined T3/T4 therapy.

Saravanan P, Siddique H, Simmons DJ, Greenwood R, Dayan CM.
Exp Clin Endocrinol Diabetes. 2007 Apr;115(4):261-7.

Methods

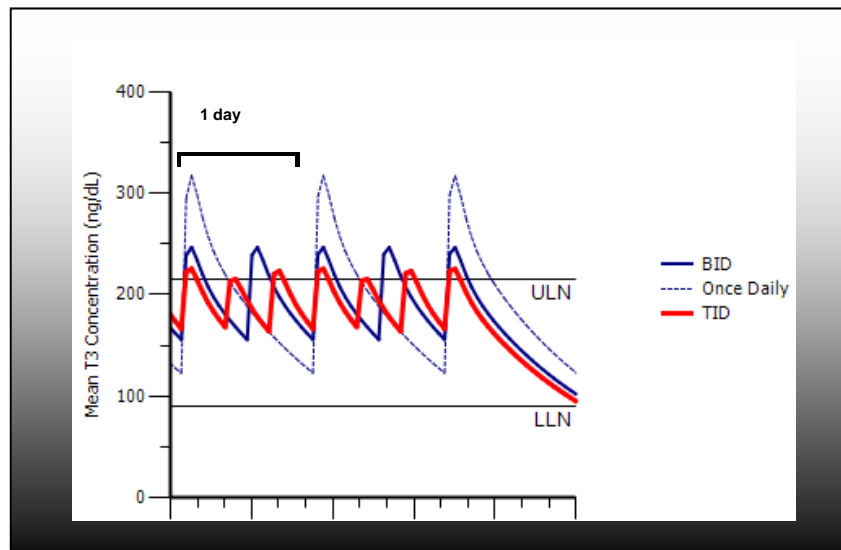
In this study, we have compared 24-hour profiles of thyroid stimulating hormone (TSH), free T4 (fT4) and free T3 (fT3) and cardiovascular parameters in 10 hypothyroid patients who had been on once daily combined T3/T4 therapy for more than 3 months with 10 patients on T4 alone.

Results and Conclusions

On T4 alone, a modest 16% rise in fT4 with no change in fT3 was seen in the first 4-hours post-dose. In contrast, on combined treatment, **fT3 levels showed a marked rise of 42% within the first 4-hours post-dose** (T3/T4:T4=6.24: 4.63 mU/L, $p<0.001$). Mean exposure to fT3 calculated by area under the curve (AUC) was higher (T3/T4:T4=1148:1062, $p<0.0001$) on T3. Our data suggests that despite chronic combined T3/T4 therapy, wide peak-to-trough variation in fT3 levels persists.

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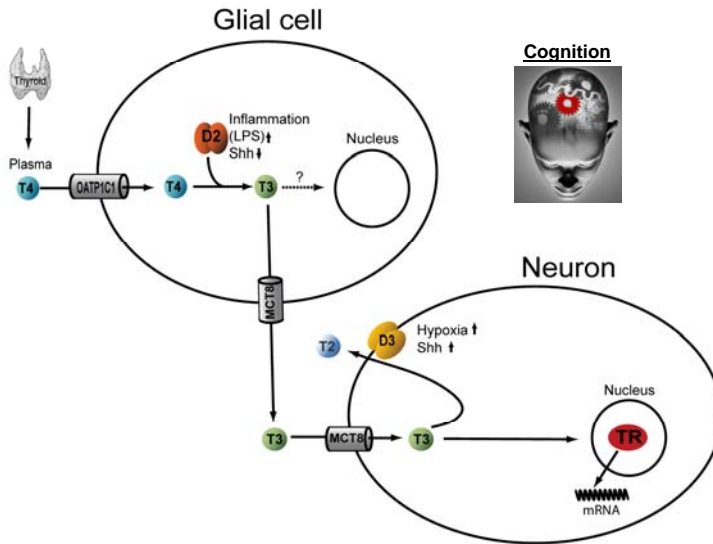
L-T3 administration modeling



Francesco Celi, NIH

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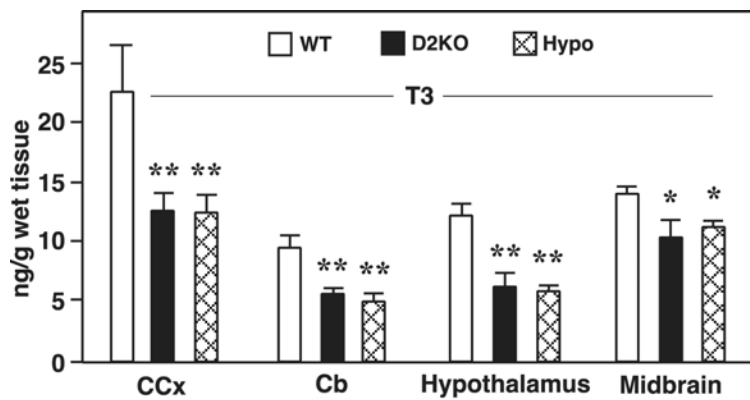
Neuron-Astrocyte Crosstalk



Juan Bernal, Ronald Lechan & Theo Visser

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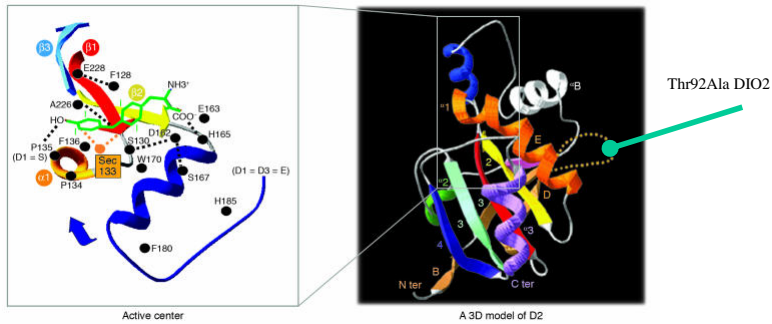
D2 KO MOUSE HAS BRAIN-SPECIFIC HYPOTHYROIDISM



Galton et al, Endocrinology, 2007

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Thr92AlaD2 polymorphism



Association Between a Novel Variant of the Human Type 2 Deiodinase Gene Thr92Ala and Insulin Resistance: Evidence of Interaction With the Trp64Arg Variant of the β -3-Adrenergic Receptor

Daniela Mentuccia, Laura Proietti-Pannunzi, Keith Tanner, Vincenzo Bacci, Toni I. Pollin, Eric T. Poehlman, Alan R. Shuldiner and Francesco S. Celi; *Diabetes* 2002 vol. 51 no. 3 880-883

Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: case-control study and meta-analysis. Dora, J.M., et al., *Eur J Endocrinol*, 2010

Case-control study with 1057 type II diabetes patients and 516 non-diabetic subjects indicated that the homozygosity for D2 Thr92Ala polymorphism is associated with increased risk for type II diabetes, a conclusion that was supported by a meta-analysis including 11,033 individuals.

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Thr92AlaD2 polymorphism

Table 1. Clinical features associated with the Thr92AlaD2 polymorphism

Association	Reference (first author)
Insulin resistance and increased BMI	Mentuccia [53]
Type 2 diabetes	Canani [54] Dora [55]
Mental retardation	Guo [56]
Hypertension	Gumieniak [57]
Osteoarthritis	Meulenbelt [58]
Bipolar disorder	He [59]
Clinical manifestations of thyrotoxic cardiomyopathy	Grineva [60]
Accelerated bone turnover	Heemstra [61]
Response to lung injury	Barca-Mayo [51] Ma [62]

Bianco & Casula, ETJ 2012

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Rationale for combination therapy with levothyroxine and liothyronine

1. Thyroidectomized patients on monotherapy with levothyroxine normalize serum FT4 and TSH but do not seem to normalize serum T3, maintaining a high serum T4/T3 ratio and in some cases serum T3 levels that are below the normal range.
2. Possible defects (e.g. genetic polymorphism) in the type 2 deiodinase, which contributes with half of the total T3 in the brain and brown adipose tissue, could result in tissue-specific hypothyroidism, explaining impaired cognition, body weight gain, etc.

However, with very few exceptions, most clinical trials failed to show any significant advantage/benefit of combination therapy vs. monotherapy.

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Thr92AlaD2 polymorphism

Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients.

*Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM
J Clin Endocrinol Metab 2009;94:1623-1629*

Methods:

Response to T₄/T₃ in 552 subjects on T₄ from the Weston Area T₄ T₃ Study (WATTS)

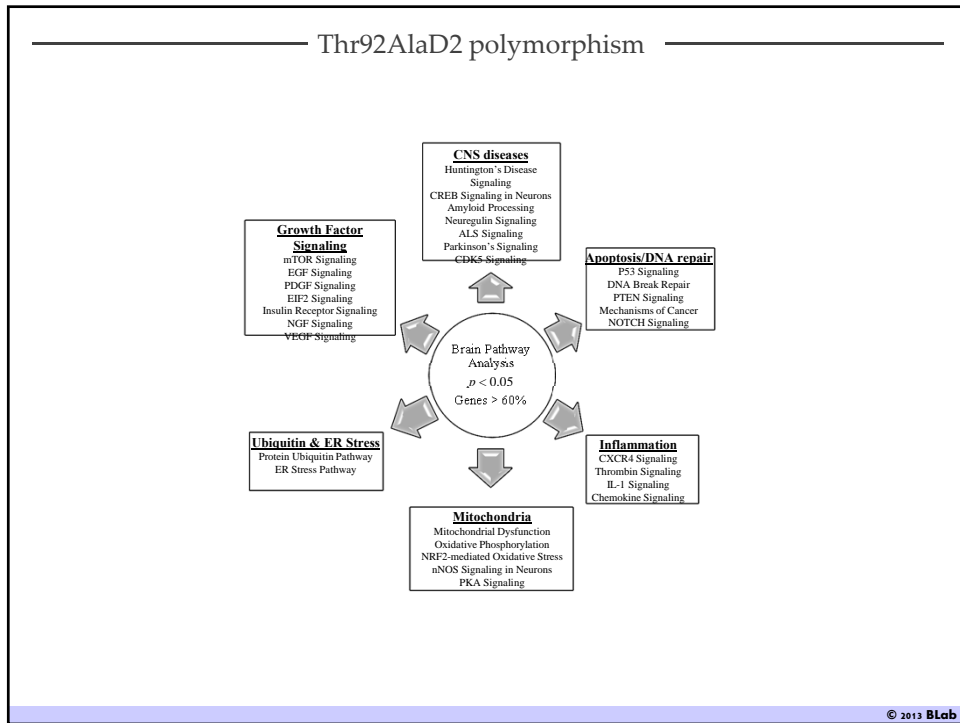
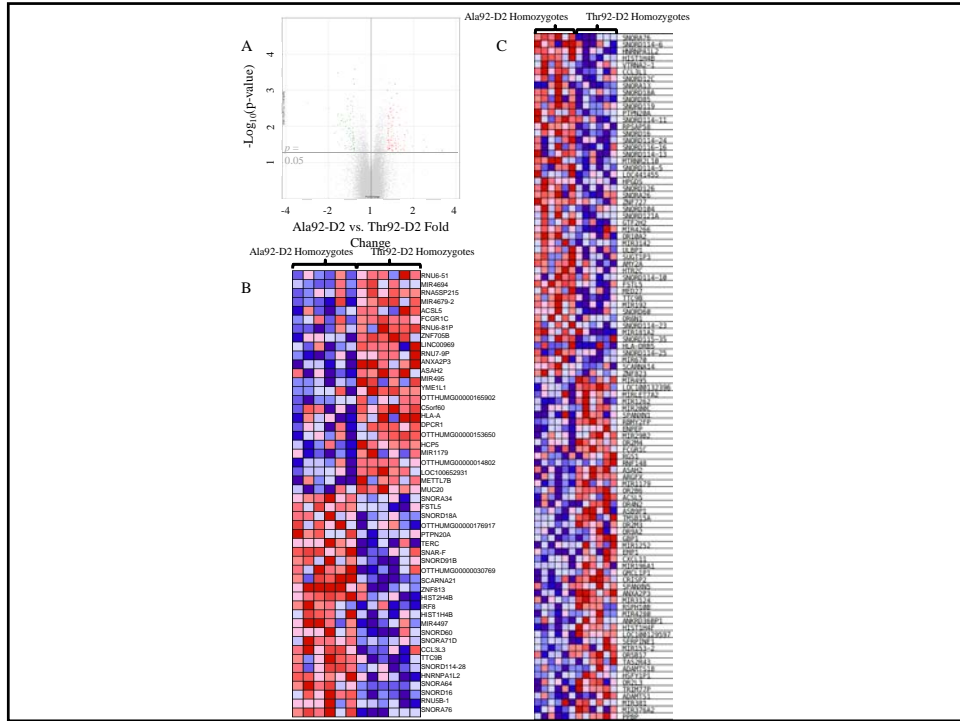
Original dose of levothyroxine minus 50ug and added 10ug of liothyronine

Primary outcome was improvement in psychological well-being assessed by the General Health Questionnaire 12 (GHQ-12), Thyroid Specific Questionnaire (TSQ).

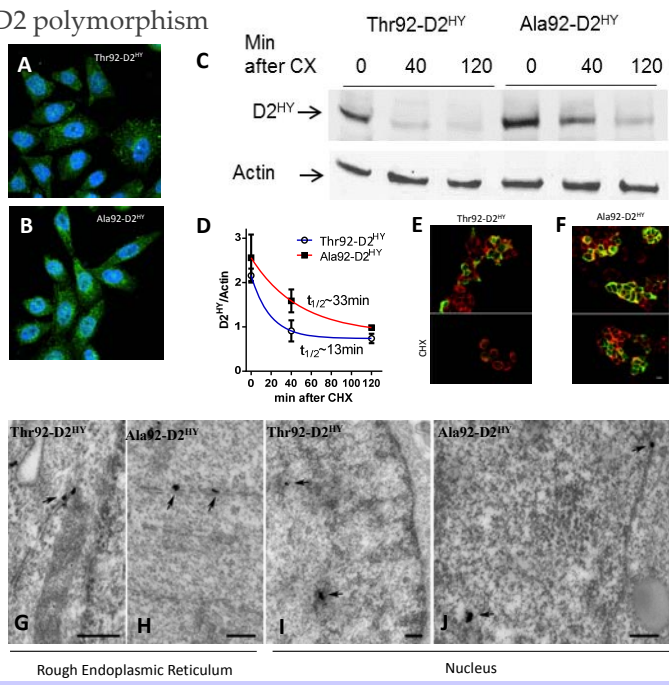
Results and Conclusions:

There was a statistically significant association between the DIO2 gene polymorphism and an improved outcome of the combination therapy vs. monotherapy for (i) general health, (ii) thyroid specific and (iii) satisfaction questioners.

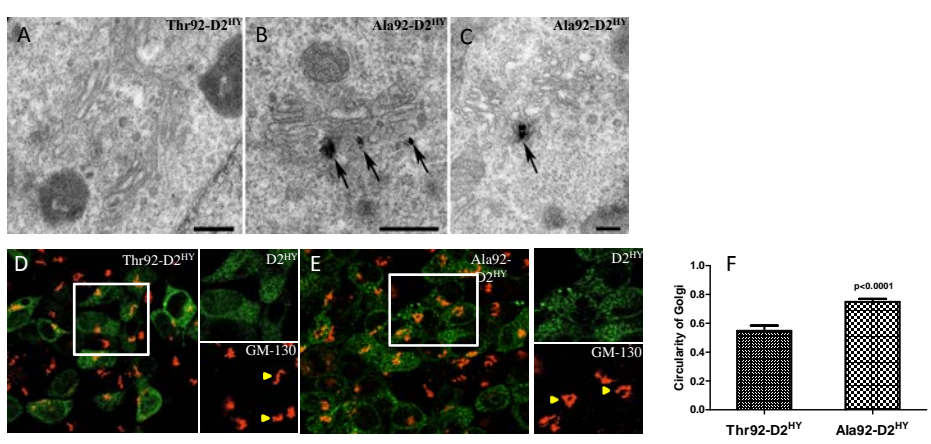
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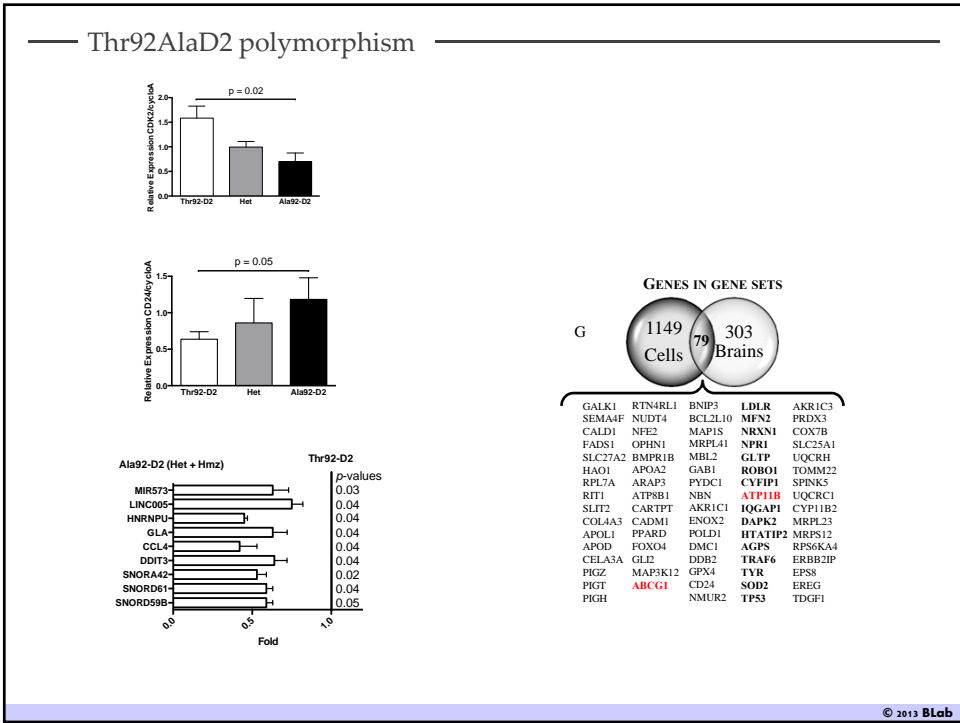
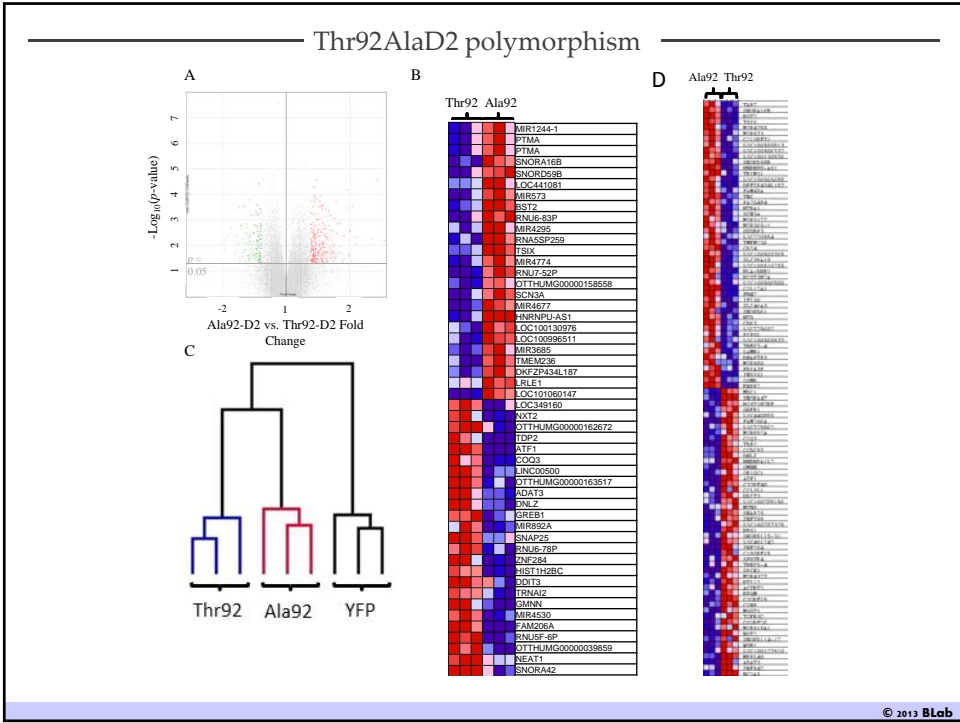


Thr92AlaD2 polymorphism



Thr92AlaD2 polymorphism





Conclusions

- The hypothalamus-pituitary-thyroid axis is wired to maintain serum T3. The thyroid gland plays a major role in this process.
- Limited data available indicate that serum T3 cannot be maintained/defended in the absence of a fully functional thyroid gland. More studies are needed to define whether normalization of serum T3 and/or serum T3/T4 ratio in hypothyroid patients is clinically relevant.
- There is a need to develop a new long-acting T3 delivery system in order to execute clinical trials testing combination vs. monotherapy; current L-T3 tablets are not suitable.
- Defects in the D2 pathway compromising T3 production could explain residual symptoms in hypothyroid patients that have normal serum TSH. The commonly observed Dio2 gene polymorphism Thr92Ala seems to have effects that are independent of T3 production; more studies are needed to define its clinical role.

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