Not Only Levothyroxine

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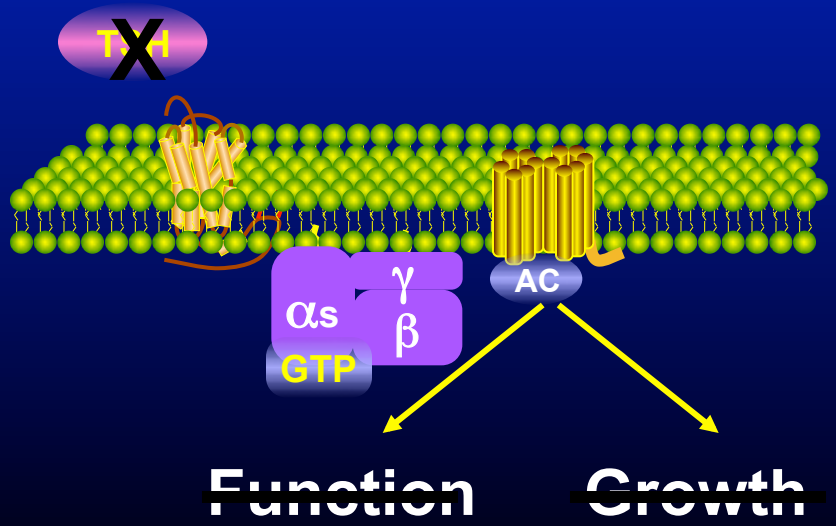
Overview

- Therapeutic goals in the treatment of multinodular goiter
- The peripheral metabolism of thyroid hormone in the maintenance of T3 levels
- Pharmacoequivalency studies on liothyronine vs. levothyroxine
- Metabolic effects of liothyronine only therapy
- Pharmacokinetics of liothyronine
- Alternative therapeutic approaches
- Conclusions

Therapeutic goals in the treatment of multinodular goiter

- **Block/regression of the growth of thyroid nodules**
  - **Inhibition of TSH trophic action**
  - **Euthyroid state**



Background

- The substitution/suppressive levothyroxine (L-T4) therapy is based on the peripheral conversion of (exogenous) T4 in T3 → metabolic effects
- A “target” TSH is the stated therapeutic goal
- …On the assumption that a euthyroid (minimal thyrotoxic) state in the pituitary equates to a generalized state of euthyroidism

T3 Production *in vivo*

Physiologic states:

T3 produced and secreted by the thyroid
T3 derived from the intrathyroid conversion of T4 (D1, D2)
T3 derived from the peripheral conversion
- **D1 (liver, kidney)**
- **D2 (skeletal muscle, pituitary, CNS, BAT)**

Catabolism of T4 (D3) - excretion

Replacement therapy:

T3 entirely derived from peripheral conversion
- **D1 (liver, kidney)**
- **D2 (skeletal muscle, pituitary, CNS, BAT)**

Catabolism of T4 (D3) - excretion

Pharmacokinetics of Levothyroxine and Liothyronine

Levothyroxine (LT4):

- **Half life**
  - **Seven days**
- **Administration**
  - **Daily**
- **Therapeutic Target**
  - **TSH**

Liothyronine (LT3):

- **Half life**
  - **6-26 hours**
- **Administration**
  - **Mostly daily**
- **Therapeutic Target**
  - **TSH?**
  - **Euthyroid state?**

Therapeutic use of liothyronine

unresolved questions

- **Therapeutic use of LT3**
  - Combination therapy LT3/LT4
  - Preparation for Nuclear Medicine procedures
- **Administration**
  - Dosage
  - Frequency
- **Pharmacokinetics (PK) non well characterized**
  - Previous studies performed in healthy volunteers
  - Supraphysiologic dosing
  - Indirect measurements (^{125}I/ ^{131}I T3)

Experimental protocols

- **Characterization of the metabolic effects of LT3 therapy**
- **Characterization of LT3 PK**
  - In thyroidectomized patients
  - In the absence of exogenous T4
  - Using therapeutic LT3 dosage
- **Experimental model**
  - Patients affected by thyroid cancer undergoing therapy withdrawal in preparation for Nuclear Medicine procedures

Peripheral metabolism of thyroid hormone

An agnostic approach

Background

- **Hypothyroid patients on replacement treatment depend entirely on the peripheral conversion of the pro-hormone T4 in T3**
- **"Experimental model" for the *in vivo* study of the physiologic role of peripheral conversion**

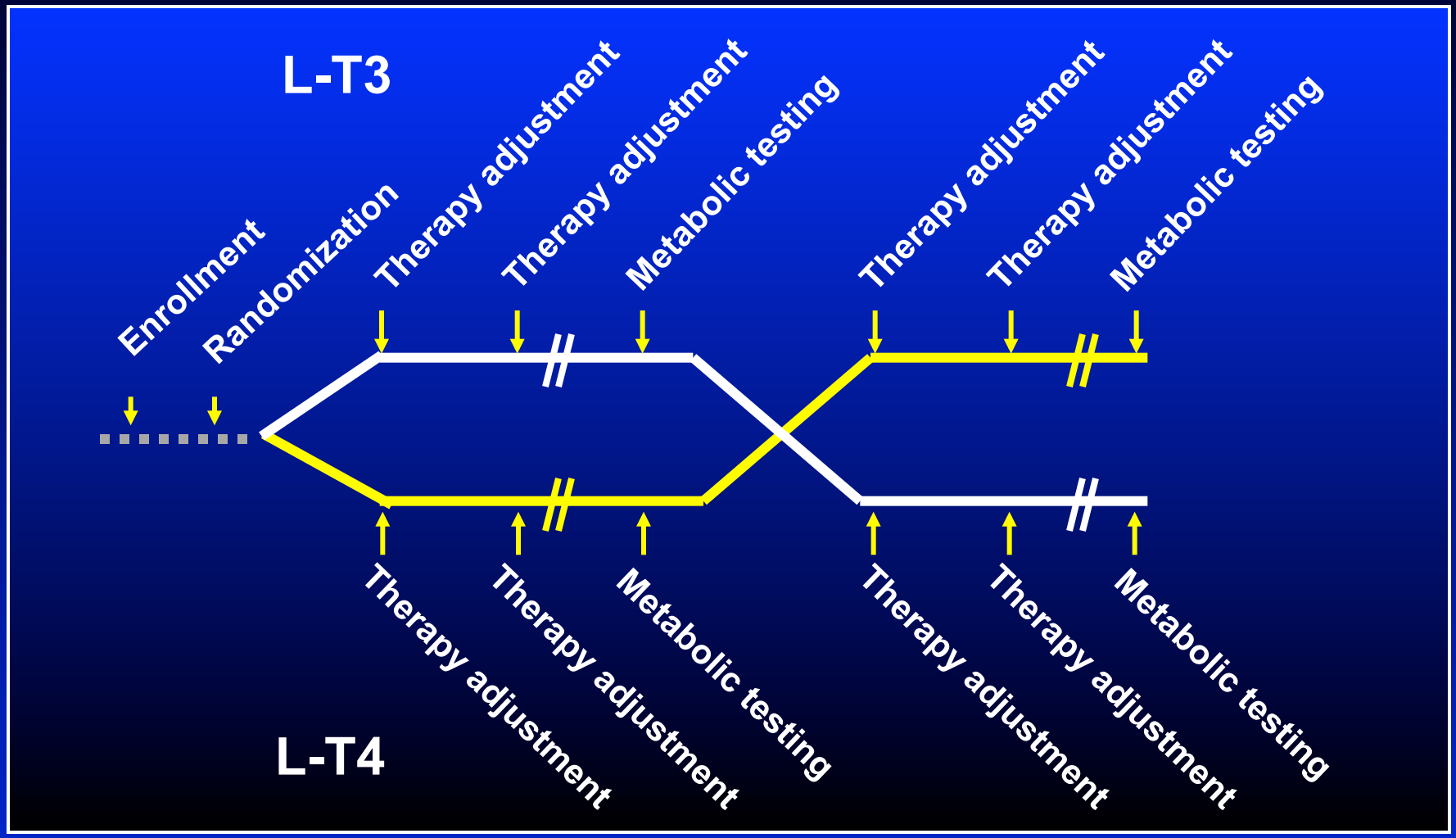
Experimental concept

- **Bypass of the peripheral conversion step while maintaining del a state of pituitary euthyroidism**

Aim of the study

- **Systematic characterization of the metabolic effects of replacement therapy**

Study design



Therapy adjustment intervals: 10-14 days; TSH goal ≥ 0.5 ≤ 1.5 mU/L

Results

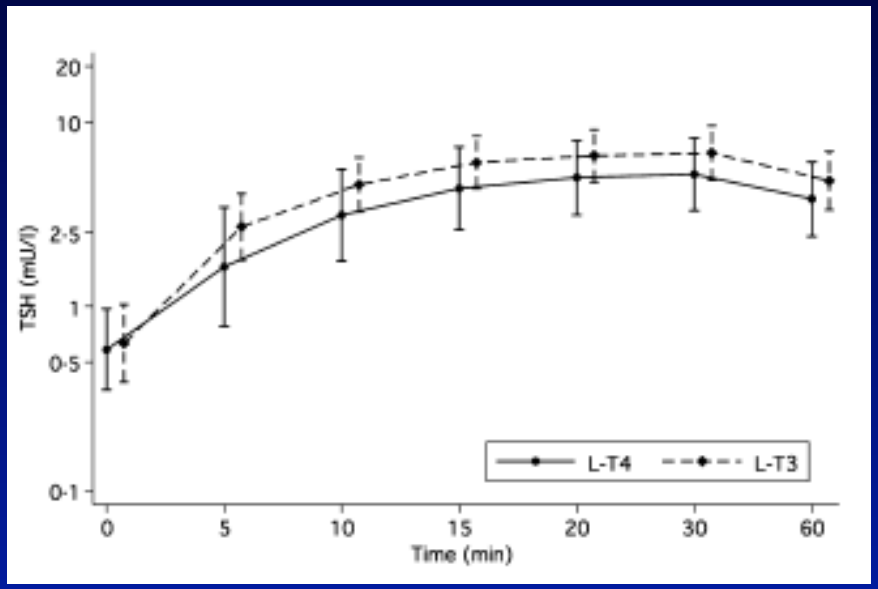
Study participants

- 13 females, 1 male
- Age 49.2±8.0 years
- 12 post-thyroidectomy, 1 post-RAI, 1 AITD
  - 3 FDTC, 1 MTC, 8 multinodular goiter
- LT4 111.8±34.0 mcg/day
  - 1.59±0.28 mcg/Kg
- LT3 40.1±9.8 mcg/day
  - 0.57±0.28 mcg/Kg

Results

Thyroid hormone, Pituitary-thyroid axis

	LT4	LT3	*p*
TSH (mU/L) ± SD 0.4-4.0	1.21 0.62	1.48 0.77	0.293
T3 (ng/dL) ± SD 90-215			
fT4 (ng/dL) ± SD 0.8-1.5			



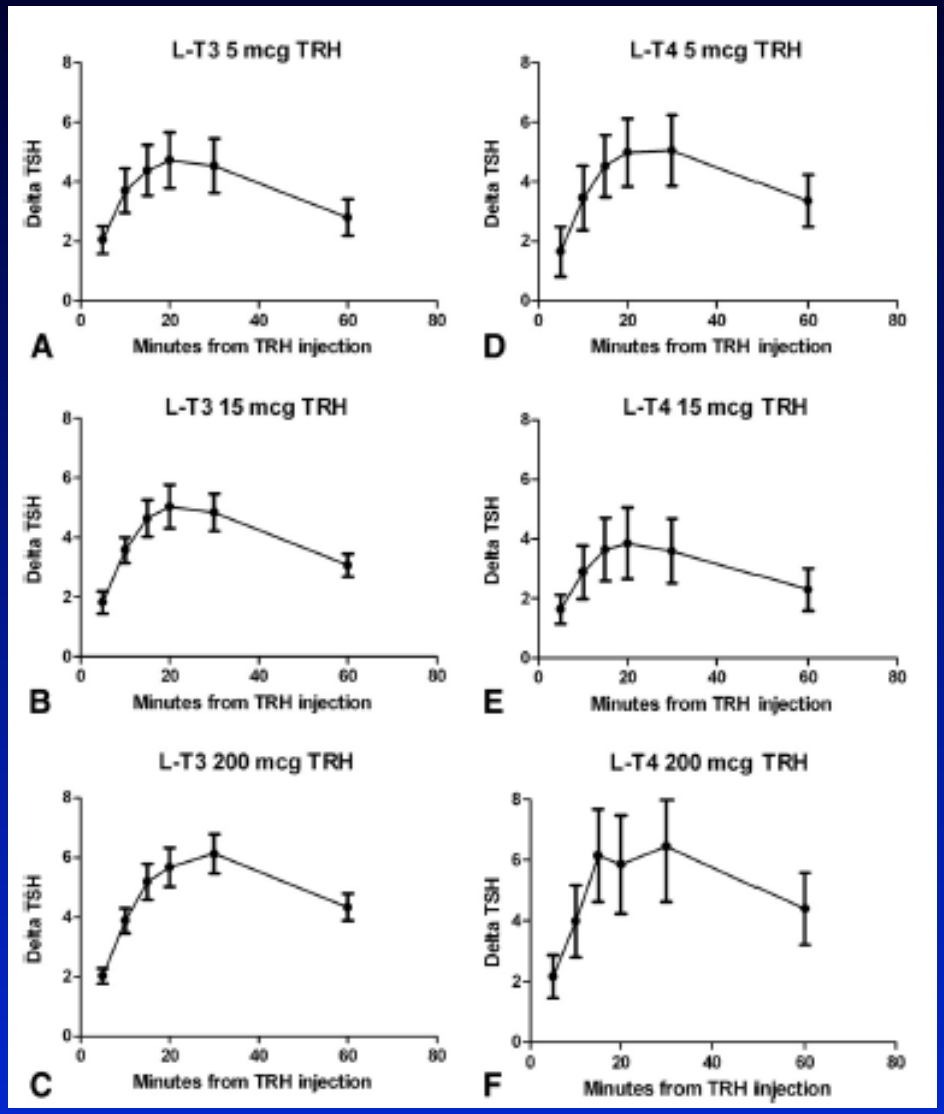
AUC 0-60 after 200 mcg TRH

- **LT3: 281.4 ± 113.6 mU*min /L**
- **LT4: 282.5 ± 165.6 mU*min /L**

Clin Endocrinol 2010;72(5):709-15.

Results

Thyroid hormone, Pituitary-thyroid axis

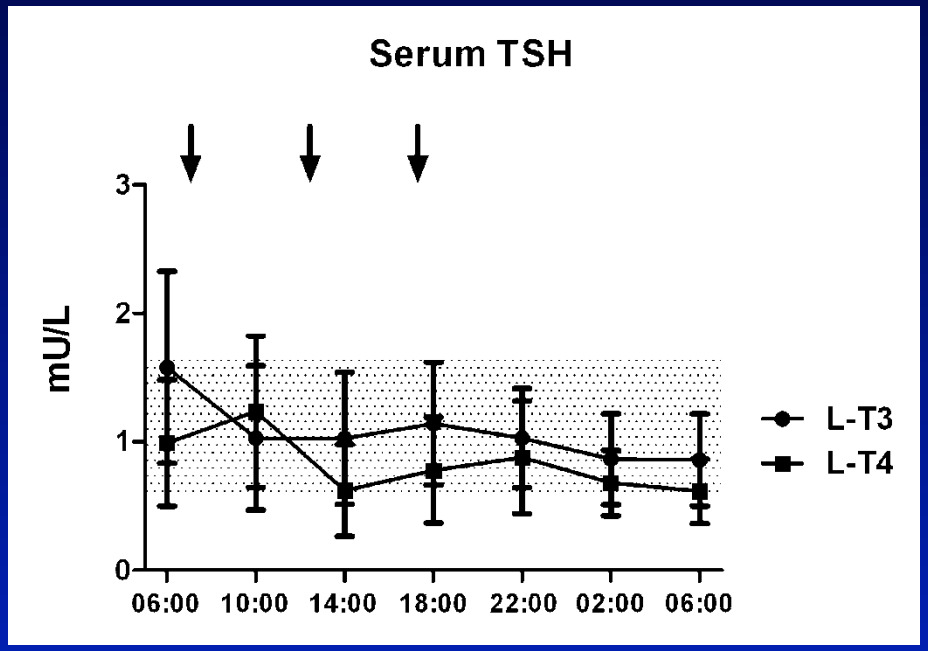


Yavuz *et al*. J Clin Endocrinol Metab. 2013

Results

Thyroid hormone, Pituitary-thyroid axis

	L-T4	L-T3	*p*
TSH (mU/L) ± SD 0.4-4.0	1.3 0.79	1.4 0.79	0.674
T3 (ng/dL) ± SD 90-215	92.9 19.0	172.0 88.2	0.003
fT4 (ng/dL) ± SD 0.8-1.5	1.57 0.3	<0.3	<0.0001



J Clin Endocrinol Metab. 2011;96(11):3466-74.

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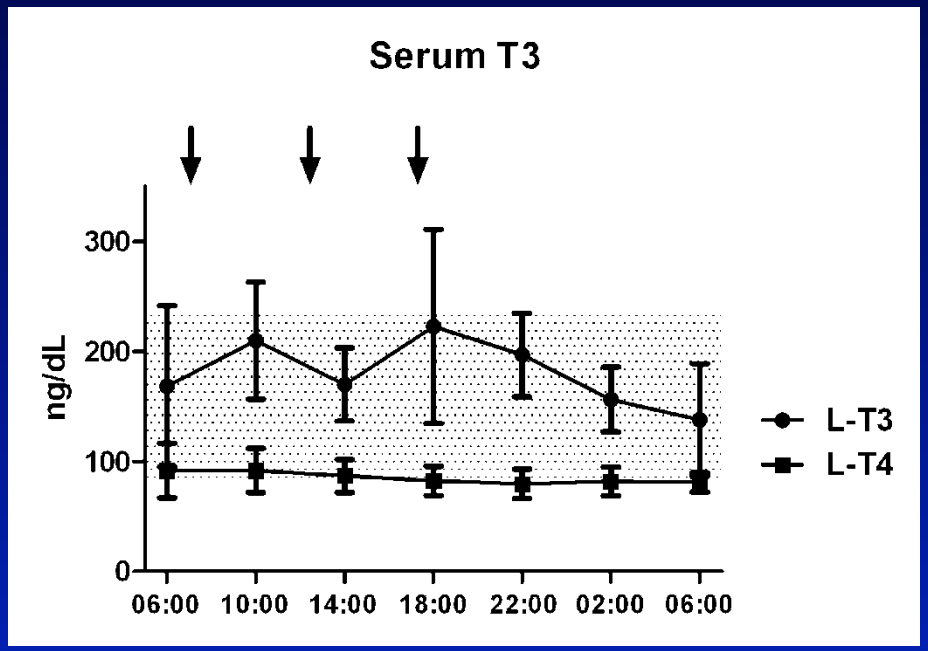


J Clin Endocrinol Metab. 2011;96(11):3466-74.

Results

Lipids Metabolism

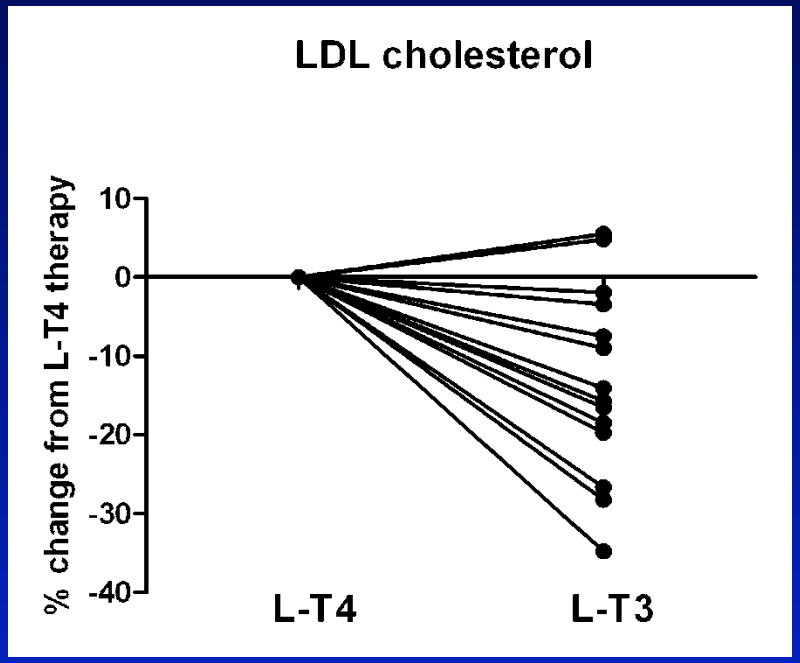
	LT4	LT3	*p*
Cholesterol (mg/dL) ± SD			
HDL (mg/dL) ± SD			
LDL (mg/dL) ± SD			
Triglycerides (mg/dL) ± SD			

J Clin Endocrinol Metab. 2011;96(11):3466-74.

Results

Lipids Metabolism

	LT4	LT3	*p*
Cholesterol (mg/dL) ± SD	195.9 25.9	173.9 27.7	0.002
HDL (mg/dL) ± SD	63.0 15.0	57.5 11.7	0.07
LDL (mg/dL) ± SD	122.6 25.2	106.2 27.7	0.002
Triglycerides (mg/dL) ± SD	78.2 30.8	78.8 28.6	0.937



J Clin Endocrinol Metab. 2011;96(11):3466-74.

Results

Energy and glucose metabolism, hepatic synthesis

	LT4	LT3	*p*
REE (Kcal/24H) SD	1201 ±281.5	1177 ±322.6	0.717
Glucose disposal ($mg/Kg*min^{-1}$) SD	7.3 ±2.7	7.4 ±4.4	0.889
HOMA SD	1.3 ±1.1	1.4 ±0.8	0.604
SHBG (nmol/L) SD			

Results

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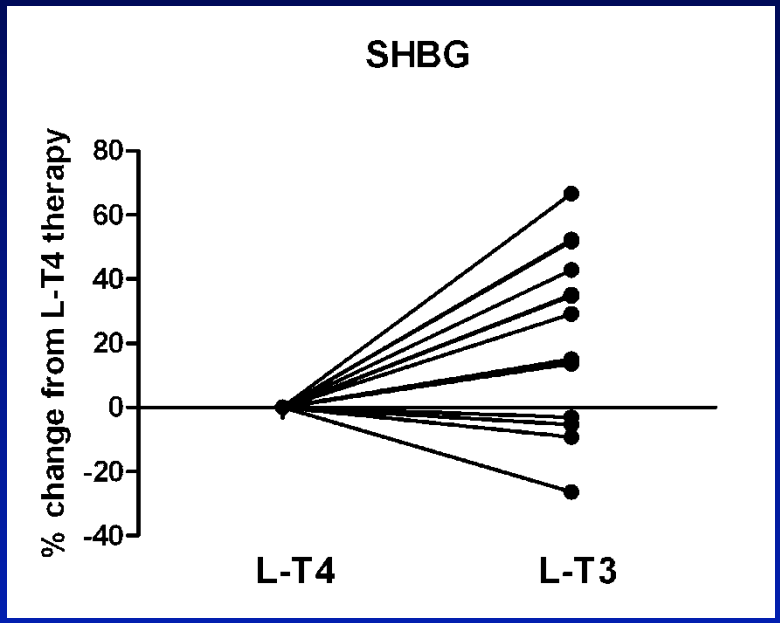
Glucose disposal ($mg/Kg*min^{-1}$) SD	7.3 ±2.7	7.4 ±4.4	0.889
HOMA SD	1.3 ±1.1	1.4 ±0.8	0.604
SHBG (nmol/L) SD	49.9 ±22.6	58.4 ±26.8	0.04



Results
Physiologic parameters

	LT4	LT3	*p*
SBP (mmHg) ± SD	113.4 10.0	119.3 10.6	0.122
DBP (mmHg) ± SD	68.2 7.3	73.1 9.9	0.08
HR (BPM) ± SD	65.0 8.1	68.21 7.3	0.20
Weight (Kg) ± SD			

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Results
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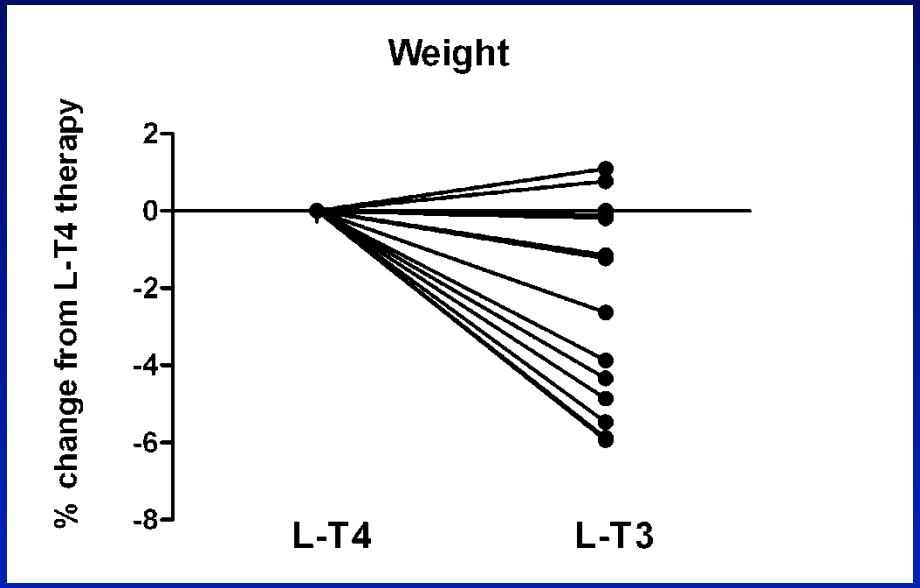
	LT4	LT3	*p*
SBP (mmHg) ± SD	113.4 10.0	119.3 10.6	0.122
DBP (mmHg) ± SD	68.2 7.3	73.1 9.9	0.08
HR (BPM) ± SD	65.0 8.1	68.21 7.3	0.20
Weight (Kg) ± SD	70.7 12.5	68.9 11.9	0.004



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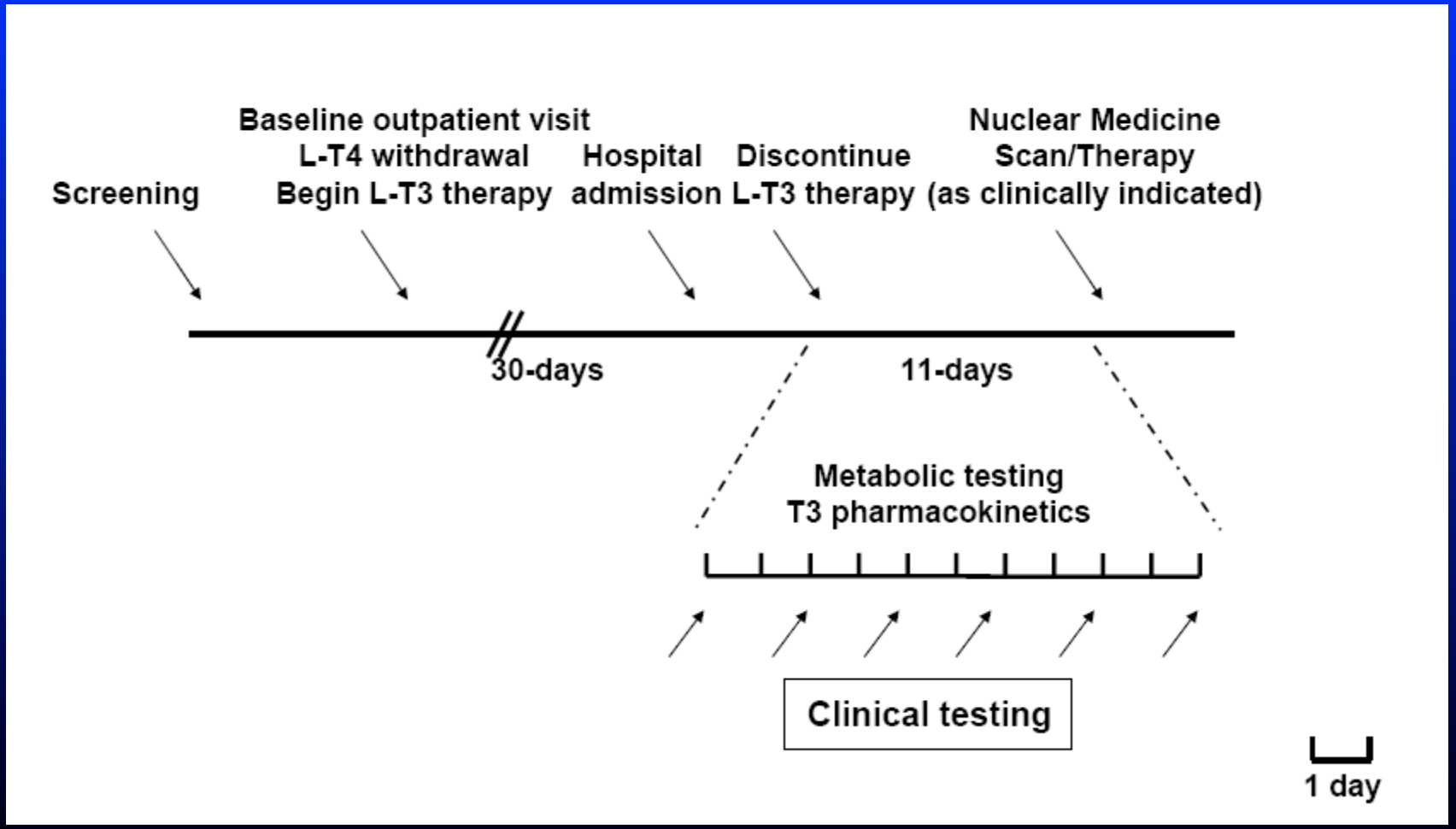
Peripheral metabolism of thyroid hormone
Summary

- The LT3 replacement therapy as compared to LT4 generates a differential response in
  - Lipid metabolism
  - Weight
  - Hepatic synthesis
- In the absence of significant changes in quality of life or cardiovascular parameters

Pharmacokinetics of LT3

- Thyroid cancer patients with clinical indication for therapy withdrawal
- Suppressed TSH at baseline
- One month substitution of LT4 for LT3 at 3:1 (mcg/mcg) dosage and thrice daily administration
- Last dose and terminal elimination PK
- Serial measurement of T3 levels

Study design



ClinicalTrials.gov Identifier:NCT01441154

Patients

Ten patients (6 males) age 49.5±16.6 years

Diagnosis 1.4±1.6 years

Papillary thyroid cancer

3 Treatment of metastases

1 Total body scan

6 Primary ablation

LT3 e LT4 -dosing-

	LT4	LT3 (24 h)	LT3 (AM)
mcg	170.0±48.3	55.6±13.4	19.0±5.8
mcg/kg	2.2±0.3	0.7±0.1	0.29±0.03

Thyroid function tests

Parameters	LT4	LT3	P
TSH (04-4.0 mcIU/ml)	0.08±0.17	0.03±0.03	0.32
T3 (90-215 ng/dl)			
fT4 (0.8-1.5 ng/dl)			

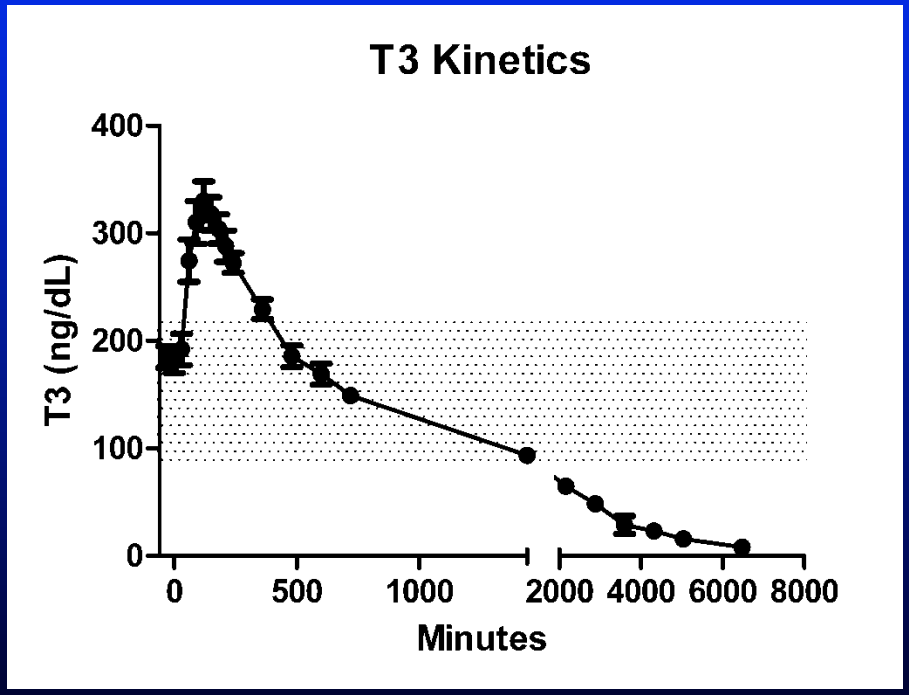
Thyroid function tests

Parameters	LT4	LT3	P
TSH (04-4.0 mcIU/ml)	0.08±0.17	0.03±0.03	0.32
T3 (90-215 ng/dl)	122.8±25.0	184.9±32.2	<0.001
fT4 (0.8-1.5 ng/dl)			

Thyroid function tests

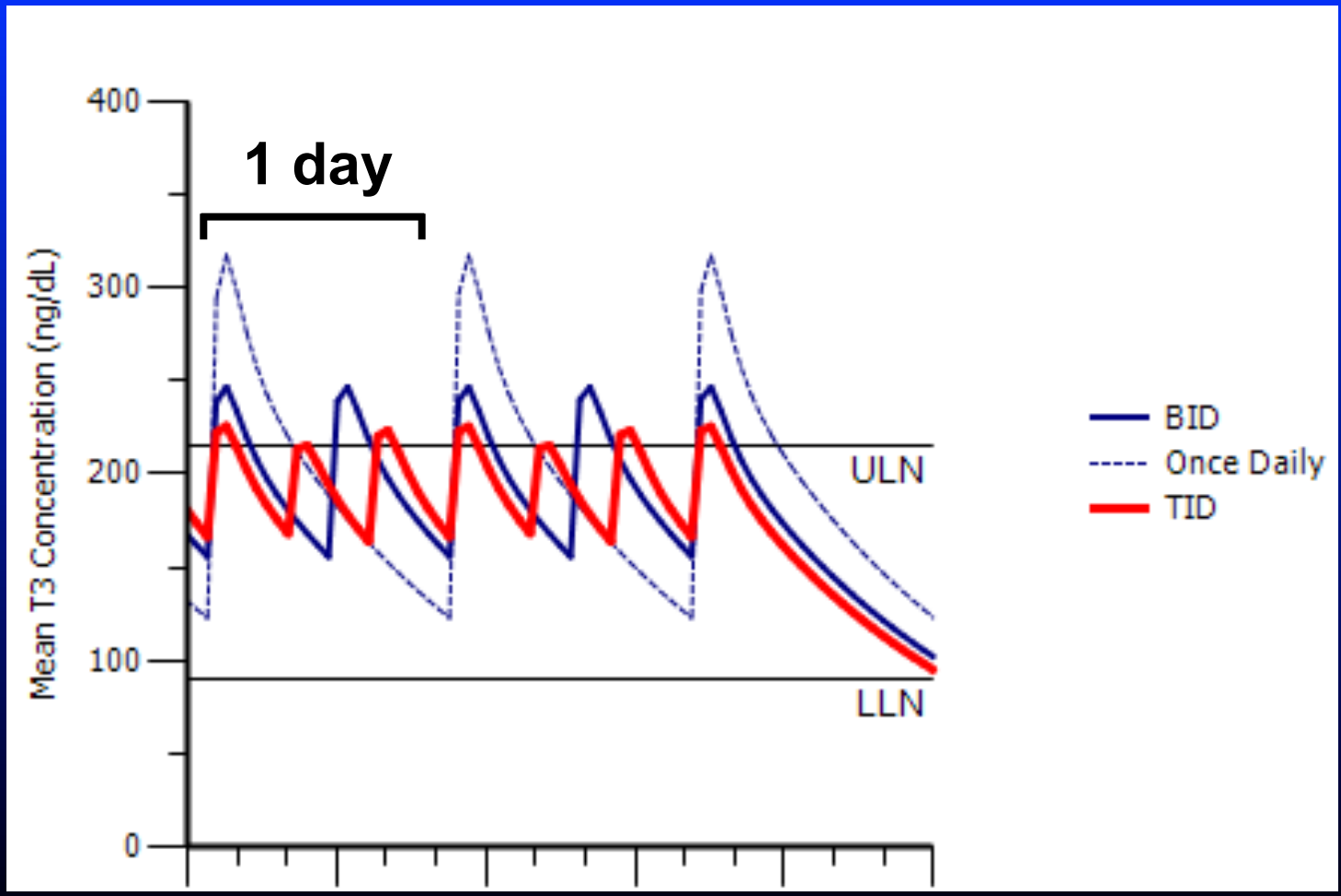
Parameters	LT4	LT3	P
TSH (04-4.0 mcIU/ml)	0.08±0.17	0.03±0.03	0.32
T3 (90-215 ng/dl)	122.8±25.0	184.9±32.2	<0.001
fT4 (0.8-1.5 ng/dl)	1.5±0.2	0.2±0.1	<0.001

PK and terminal elimination



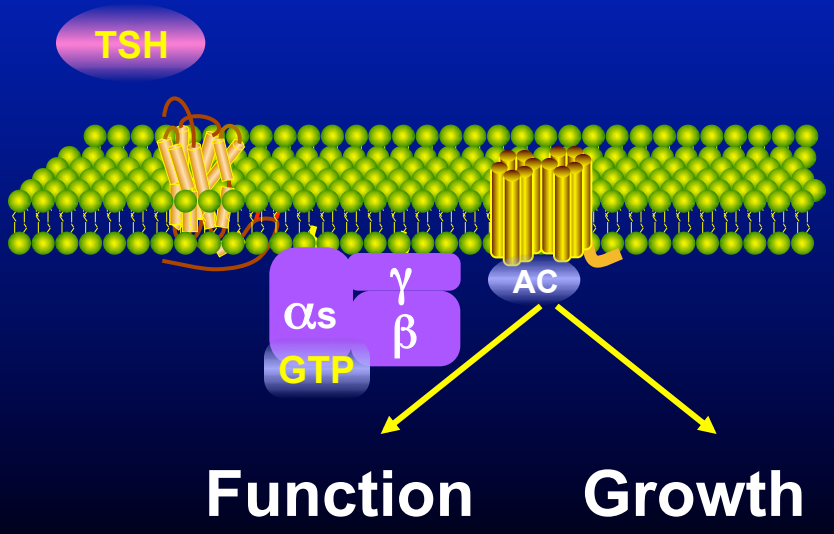
Cmax (ng/dl)	341.2±74.1
Tmax (hour)	1.75±0.29
Apparent half-life (hour)	27.0±12.0
Distribution half-life (hour)	3.30±2.36
Elimination half-life (hour)	44.54±41.29

LT3 pharmacologic models

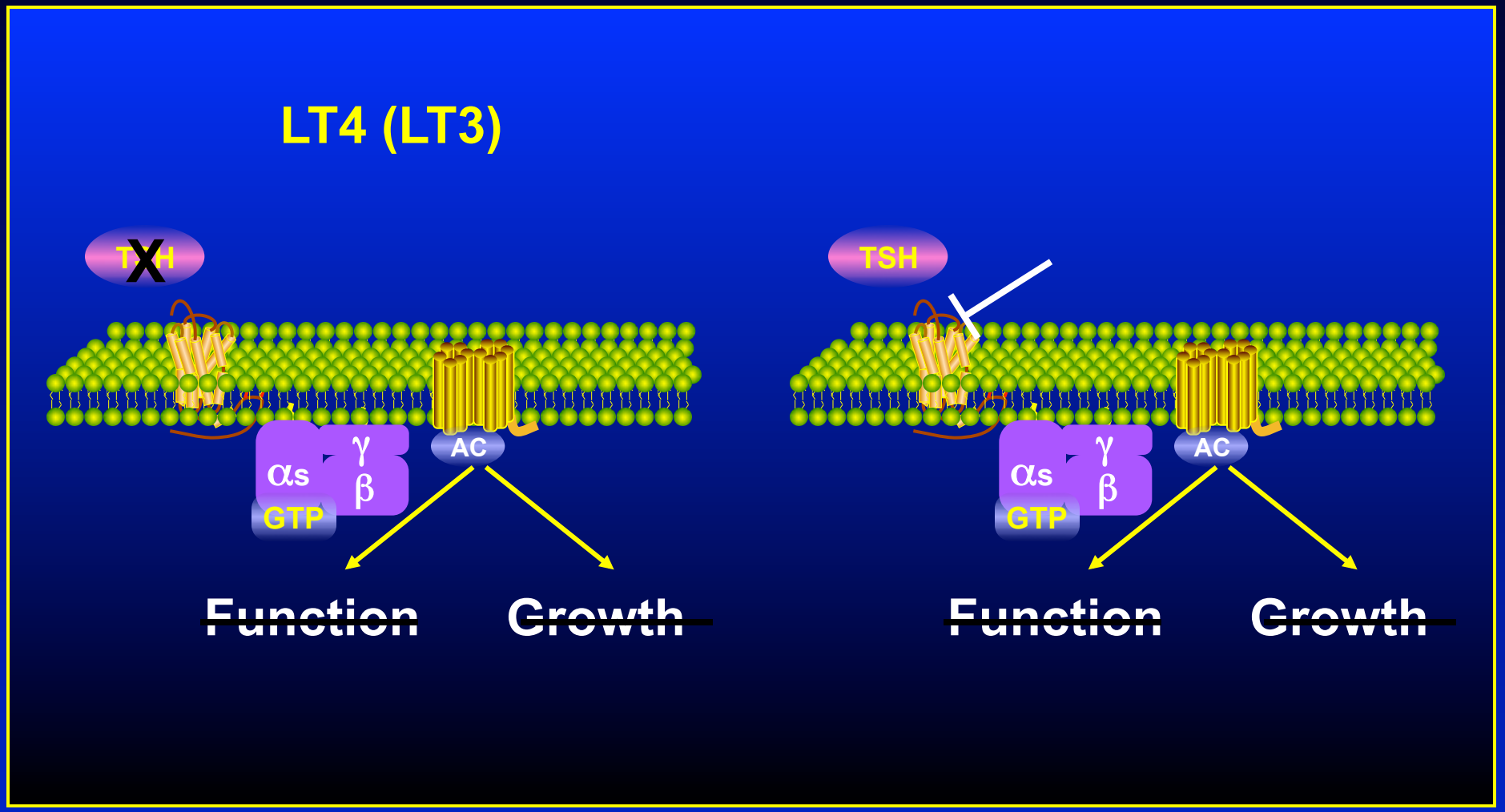


Alternative strategies

- **Major drawbacks of the suppressive therapy**
  - **Side/off-target effects**
    - **Arrhythmia**
    - **Bone mass loss**
    - **Elderly population**

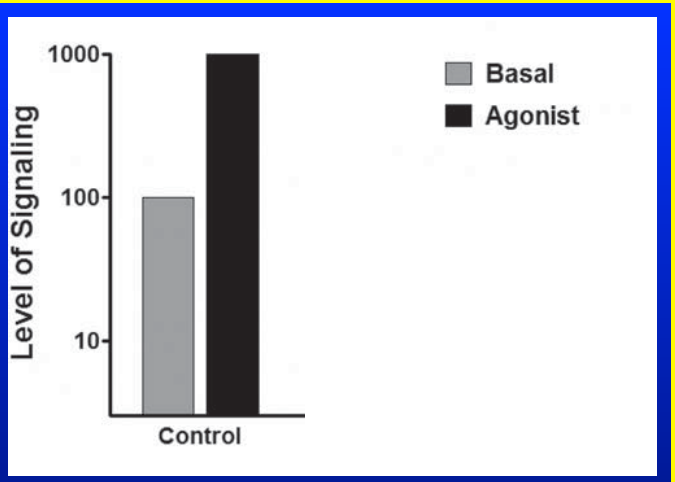


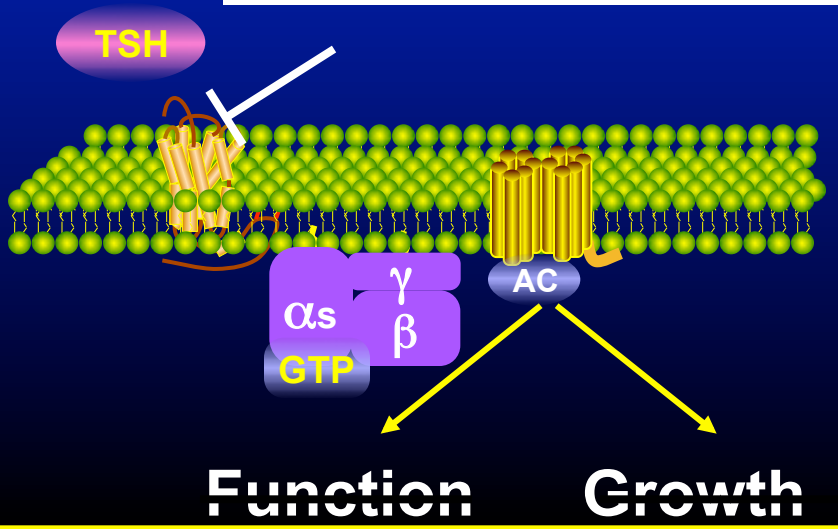
Alternative strategies



Alternative strategies

- The TSH receptor has a basal activity independent from the presence of ligand
- Inhibitors: compounds able to inhibit the hormonal action
- “Inverse agonists”: compounds able to suppress the receptor’s action below the basal activity





J Clin Endocrinol Metab, December 2012, 97(12):4287–4292

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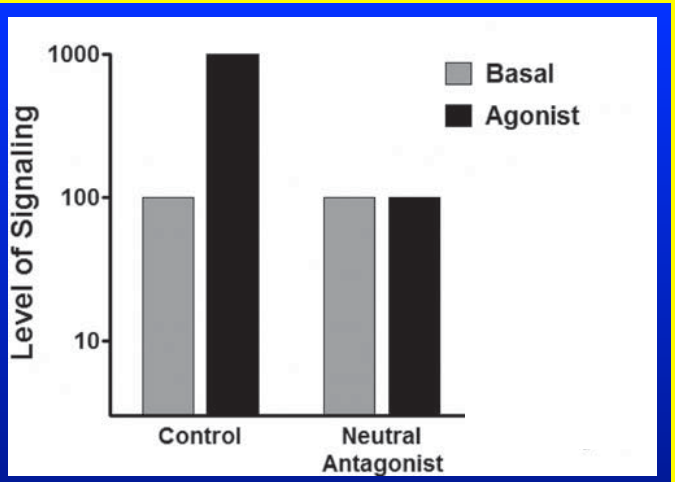

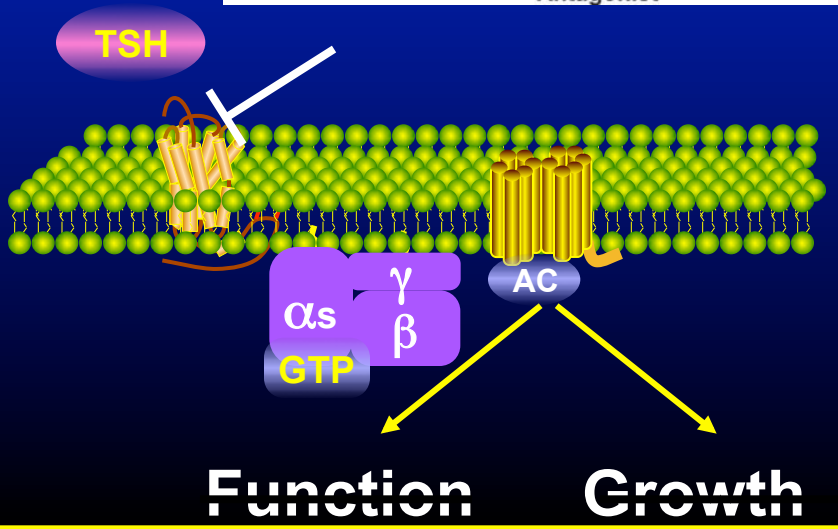

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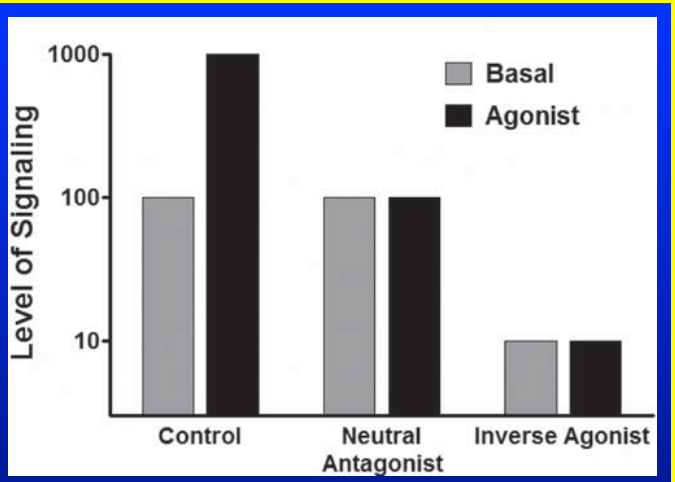

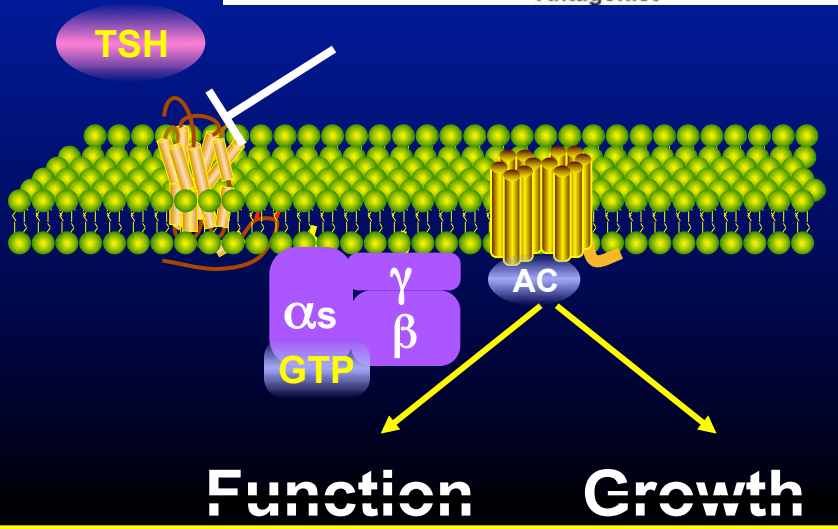

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Alternative strategies

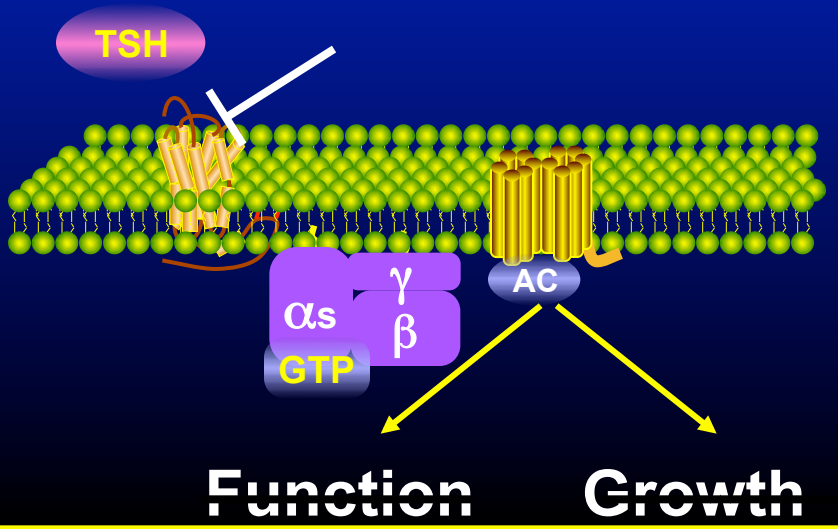
ORIGINAL ARTICLE

Endocrine Research

A New Small-Molecule Antagonist Inhibits Graves' Disease Antibody Activation of the TSH Receptor

Susanne Neumann, Elena Eliseeva, Joshua G. McCoy, Giorgio Napolitano, Cesidio Giuliani, Fabrizio Monaco, Wenwei Huang, and Marvin C. Gershengorn

- Inhibition of receptor activity
- Replacement therapy
- Effective even in the presence of stimulating antibodies
- Potential use in:
  - Differentiated thyroid cancer
  - Graves'
  - Ophthalmopathy/dermopathy



J Clin Endocrinol Metab, February 2011, 96(2):548–554

Conclusion

- The LT3 therapy at a correct dosage and multiple daily administration provides adequate suppression with T3 within normal limits
- The PK of LT3 is a two-component (fast distribution, and slow elimination)
- The administration in single of twice-daily regimens would result in prolonged over- and under-dosage (relative to T3 serum levels)
- Long-term studies are necessary to characterize the metabolic effects of LT3 and LT3/LT4 combination therapy
- Alternative therapies aimed to the direct inhibition of the TSH action might result superior to the standard suppression therapy

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- Charlotte Werner
- Maya Peltsverger
- Metabolic Unit staff
- Department of Laboratory Medicine

Acknowledgments

Our patients!

Questions?