Welcome to Thyroid Deficiency and Beyond.
This are slides from the talk I presented to the Residents and Students at the Brooklyn Hospital on August 13.
It contains some of the commentary while audio narration is in production.
I hope you find the evidence compelling.

Thyroxine Deficiency in Pregnancy and Beyond?

Timothy Bilash MD MS FACOG

Obstetrics and Gynecology Resident Teaching Presentation
The Brooklyn Hospital
August 13, 2019

American College of Obstetricians and Gynecologists elected Fellow 1995
Board Certification, Obstetrics and Gynecology 1993

Residency, Obstetrics and Gynecology, Albany Medical Center NY (4 yr)
Chief Administrative Resident Senior Year
Myron Gordon MD, John Goldkrand MD, Donald Swartz MD

MD Medical School, University of Illinois Urbana-Champaign IL (4yr)
Daniel Bloomfield MD, Richard Gumport PhD, IC Gunsales PhD

MS Graduate Physics, University of Illinois Urbana Champaign IL (2 yr)
Membrane Fluidity Fluorescence Polarization Research Assistant
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Senior Technical Associate, Bell Telephone Laboratory Murray Hill NJ (4 yr)
Membrane Biophysics Small Angle X-Ray Scattering
James Stamatoff PhD, Peter Eisenberger PhD, William Brinkman PhD,
Linda Powers PhD, Y Ching MS

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Electron Micrograph Digital Image Processing Programming
Joachim Frank, PhD

BS Physics cum laude, University at Albany NY (4 yr)
Minor: Mathematics, Chemistry
Teaching, Class Lab and Research Assistant Physics
Defects in Semiconductors, Ion Implantation, Electron Paramagnetic Resonance
James Corbett PhD, Luther Andrews PhD, Akira Inomata PhD,
Young Hoon Lee PhD, David Peak PhD

X-Ray Diffraction Intensities of a Smectic-*A* Liquid Crystal

J. Stamatoff, P. E. Cladis, D. Guillon, M. C. Cross, T. Bilash, and P. Finn
Bell Laboratories, Murray Hill, New Jersey 07974

(Received 20 April 1979; revised manuscript received 3 January 1980)

Higher-order diffraction from the smectic-*A* liquid-crystalline phase of cyanooctylbiphenyl (COB) has been measured. The dominant short-range disorder, described by the relative intensities, is in agreement with our estimate of the smectic order parameter based on McMillan's mean-field theory.

Compartmental Analysis Approach to Fluorescence Anisotropy: Perylene in Viscous Solvents

David W. Piston, Timothy Bilash, and Enrico Gratton*

Department of Physics, Laboratory for Fluorescence Dynamics, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801 *(Received: September 6, 1988; In Final Form: November 22, 1988)*

The Journal of Physical Chemistry, 1989, 93, 3963

•HEALTHCARE REPORTS•

California Universal Health Care Workbook (www.CaSinglePayerInfo.com FEB 18)
Medicine is Changing / WBDN Radio 760 AM, Tampa, FL (FEB 96)
Changes to Medical Education 1940-85: the Federal Role, Urbana, IL (MAY 87)

THE PROPORTIONAL HAZARD MODEL IN RANDOMIZED STUDIES - STATISTICAL INSIGHTS INTO THE WOMEN'S HEALTH INITIATIVE STUDIES (2002-2017) USING REGRESSION ANALYSIS OF MORTALITY.

Timothy D. Bilash, M.D., M.S., F.A.C.O.G

Biophysical Society Annual Meeting
March 2-6, 2019

Thyroxine Deficiency in Pregnancy

Timothy Bilash MD MS OBG

Northern Inyo Hospital, Bishop, CA
October 20, 2006 1:30 PM

sponsible for a share of the costs and it could influence their decisions to get expensive testing.

The same is true of lab tests. Neither Quest Diagnostics nor LabCorp provides cost information in the books we receive for ordering their tests. Consequently, I have absolutely no idea what many of them cost. One of the key concepts we hear about is medical transparency, yet to effectively accomplish this, doctors and the public need to be provided with data on the actual costs of imaging studies, lab tests, and other medical procedures.

I would be very interested if Dr. Dami[illegible] or anyone else has any ideas on how to contact the insurance companies, state Medicaid offices, or the CMS to facilitate a national effort at publicizing this cost information.

Kenneth E. Kochmann, M.D.
Baltimore

What Is Normal, Really?

Dr. Rhoda H. Cobin's editorial ("What Is Normal Thyroid Function, Really?" Guest Editorial, Aug. 15, 2008, p. 9) prompts me to write. I have diagnosed and treated hundreds of patients, particularly in pregnancy, when they demonstrate classic signs of hypothyroid disease or medical problems and have lower than expected thyroxine levels. I offer the following observations:

▶ Little attention is paid to the functional differences in thyroid assays from different companies, especially in distinguishing abnormal low values. Thyroid assays have not been standardized for pregnancy and at the very least need to be adjusted by gestational age.

▶ Multiple studies have indicated that increased rates of preterm labor, diabetes, macrosomia, placental abruption, weight gain, fatigue, and other complications are associated with low thyroid states.

▶ In my experience, thyroid-stimulating hormone (TSH) does not correlate with these clinical effects, and is useful only when outside the mid-normal range or above. Studies which obtain only the pituitary TSH do not accurately reflect thyroid function at the cellular level, only pituitary response. TSH likely identifies immune thyroiditis/primary hypothyroidism. It is clear that if one wishes to look one can find a much larger group of patients with "extrathyroidal" disease. I call this "subnormal hypothyroidism" (symptomatic, low free T_4, normal TSH).

▶ Free T_4 (FT_4) seems to correlate with this clinical response. Although some researchers advocate using the total T_4 in pregnancy, for example, and say that the FT_4 only reflects total T_4, I have found the FT_4 is very useful in delineating patients who improve with thyroxine supplementation.

▶ I suspect that at less than 20 weeks, FT_4 is essential for both maternal and fetal health, turbocharged by human chorionic gonadotropin. FT_4 would be a sensitive indicator for both gravida and fetus. Deficiency in FT_4 at this stage is devastating to the fetus if left untreated.

▶ After 20 weeks, total T_4 might be a more sensitive indicator than FT_4 for the fetus, since the action of D3-deiodinase to release iodine to the fetus depends on thyroxine-binding globulin–bound T_4, which is approximated by total T_4 in pregnancy.

This process is not a steady-state equilibrium, but a dynamic rate reaction. FT_4 would still be an important indicator for maternal health after 20 weeks, as the gravida's thyroid function depends on FT_4, not iodine level. The consequences of T_4 vs. FT_4 deficiency may vary with gestational age and whether one looks at the fetus or the gravida.

What is the downside of treating these pregnant patients with small doses of thyroxine? There are many theoretical and physiologic reasons, and also studies which support this idea. None indicate harm to the fetus or gravida from treatment during pregnancy, especially if FT_4 levels are kept within the "normal" nonpregnant range.

Timothy D. Bilash, M.D.
Del Mar, Calif.

"Raise the reimbursement rate?! Don't be misled by the Santa outfit."

Research Summit
& Spring Symposium
of the American Thyroid Association

RESEARCH SUMMIT
Thyroid Hormone in Pregnancy and Development

&

SPRING SYMPOSIUM
Thyroid Dysfunction and Pregnancy: Miscarriage, Preterm Delivery and Decreased IQ

April 16–17, 2009
The Madison
Washington, DC

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

BOSTON UNIVERSITY

www.thyroid.org

14th ITC
PARIS 2010

14th International
Thyroid Congress

September 11th - 16th, 2010
Palais des Congrès, Paris, France

Paris, September 16th, 2010

POSTER PRESENTATION CERTIFICATE

We hereby certify that:

Timothy Bilash

has presented the poster N° **P-0546**

Title :

THYROID STIMULATING HORMONE (TSH) AND FREE THYROXINE LEVELS (FT4) IN PREGNANT FEMALES >25 WEEKS GESTATION AND NON-PREGNANT FEMALES WHO HAVE CLINICAL PROBLEMS AND HYPOTHYROID SYMPTOMS: EVIDENCE SUPPORTING POOR CORRELATION BETWEEN TSH AND FT4

on the occasion of the :

14th International Thyroid Congress
which has been held at the
Palais des Congrès, Paris, France
September 11th to 16th, 2010

Thyroxine Deficiency in Pregnancy and Beyond?

Timothy Bilash MD MS FACOG

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August 13, 2019

HIDING IN PLAIN SIGHT ?

Physiol Rev 94: 355–382, 2014
doi:10.1152/physrev.00030.2013

THYROID HORMONE REGULATION OF METABOLISM

1) Thyroid Hormone Receptors exist as distinct **sub-types**, and function differently in different tissues.

Rashmi Mullur, Yan-Yun Liu, and Gregory A. Brent

Department of Medicine, VA Greater Los Angeles Healthcare System, Departments of Medicine and Physiology, David Geffen School of Medicine at UCLA, Los Angeles, California

Mullur R, Liu Y-Y, Brent GA. Thyroid Hormone Regulation of Metabolism. *Physiol Rev* 94: 355–382, 2014; doi:10.1152/physrev.00030.2013.—Thyroid hormone (TH) is required for normal development as well as regulating metabolism in the adult. The thyroid hormone receptor (TR) isoforms, α and β, are differentially expressed in tissues and have distinct roles in TH signaling. Local activation of thyroxine (T_4), to the active form, triiodothyronine (T_3), by 5′-deiodinase type 2 (D2) is a key mechanism of TH regulation of metabolism. D2 is expressed in the hypothalamus, white fat, brown adipose tissue (BAT), and skeletal muscle and is required for adaptive thermogenesis. The thyroid gland is regulated by thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). In addition to TRH/TSH regulation by TH feedback, there is central modulation by nutritional signals, such as leptin, as well as peptides regulating appetite. The nutrient status of the cell provides feedback on TH signaling pathways through epigentic modification of histones. Integration of TH signaling with the adrenergic nervous system occurs peripherally, in liver, white fat, and BAT, but also centrally, in the hypothalamus. TR regulates cholesterol and carbohydrate metabolism through direct actions on gene expression as well as cross-talk with other nuclear receptors, including peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways. TH modulates hepatic insulin sensitivity, especially important for the suppression of hepatic gluconeogenesis. The role of TH in regulating metabolic pathways has led to several new therapeutic targets for metabolic disorders. Understanding the mechanisms and interactions of the various TH signaling pathways in metabolism will improve our likelihood of identifying effective and selective targets

Physiol Rev 94: 355–382, 2014
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THYROID HORMONE REGULATION OF METABOLISM

2) Surprisingly, Nutrition modulates underlying Central Thyroid Regulation within the Hypothalamus. **Epigenetic** (rather than purely inherited Genetic) modification of **Histones** (the Protein complexes integrated with DNA in the Nucleus), is a mechanism that Centrally modulates Peripheral Andrenergic Nerves.

Rashmi Mullur, Yan-Yun Liu, and

Department of Medicine, VA Greater Los Angeles Healthcare System, Departments of Medicine and Physiology, David Geffen School of Medicine at UCLA, Los Angeles, California

Mullur R, Liu Y-Y, Brent GA. Thyroid Hormone Regulation of Metabolism. *Physiol Rev* 94: 355–382, 2014; doi:10.1152/physrev.00030.2013.—Thyroid hormone (TH) is required for normal development as well as regulating metabolism in the adult. The thyroid hormone receptor (TR) isoforms, α and β, are differentially expressed in tissues and have distinct roles in TH signaling. Local activation of thyroxine (T_4), to the active form, triiodothyronine (T_3), by 5′-deiodinase type 2 (D2) is a key mechanism of TH regulation of metabolism. D2 is expressed in the hypothalamus, white fat, brown adipose tissue (BAT), and skeletal muscle and is required for adaptive thermogenesis. The thyroid gland is regulated by thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). In addition to TRH/TSH regulation by TH feedback, there is central modulation by nutritional signals, such as leptin, as well as peptides regulating appetite. The nutrient status of the cell provides feedback on TH signaling pathways through epigentic modification of histones. Integration of TH signaling with the adrenergic nervous system occurs peripherally, in liver, white fat, and BAT, but also centrally, in the hypothalamus. TR regulates cholesterol and carbohydrate metabolism through direct actions on gene expression as well as cross-talk with other nuclear receptors, including peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways. TH modulates hepatic insulin sensitivity, especially important for the suppression of hepatic gluconeogenesis. The role of TH in regulating metabolic pathways has led to several new therapeutic targets for metabolic disorders. Understanding the mechanisms and interactions of the various TH signaling pathways in metabolism will improve our likelihood of identifying effective and selective targets

Physiol Rev 94: 355–382, 2014
doi:10.1152/physrev.00030.2013

THYROID HORMONE REGULATION OF METABOLISM

3) Thyroid Receptors regulate **cholesterol** and **carbohydrate** metabolism

Rashmi Mullur, Yan-Yun Liu, and Gregory A. Brent

Department of Medicine, VA Greater Los Angeles Healthcare System, Departments of Medicine and Physiology, David Geffen School of Medicine at UCLA, Los Angeles, California

Mullur R, Liu Y-Y, Brent GA. Thyroid Hormone Regulation of Metabolism. *Physiol Rev* 94: 355–382, 2014; doi:10.1152/physrev.00030.2013.—Thyroid hormone (TH) is required for normal development as well as regulating metabolism in the adult. The thyroid hormone receptor (TR) isoforms, α and β, are differentially expressed in tissues and have distinct roles in TH signaling. Local activation of thyroxine (T_4), to the active form, triiodothyronine (T_3), by 5′-deiodinase type 2 (D2) is a key mechanism of TH regulation of metabolism. D2 is expressed in the hypothalamus, white fat, brown adipose tissue (BAT), and skeletal muscle and is required for adaptive thermogenesis. The thyroid gland is regulated by thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). In addition to TRH/TSH regulation by TH feedback, there is central modulation by nutritional signals, such as leptin, as well as peptides regulating appetite. The nutrient status of the cell provides feedback on TH signaling pathways through epigentic modification of histones. Integration of TH signaling with the adrenergic nervous system occurs peripherally, in liver, white fat, and BAT, but also centrally, in the hypothalamus. TR regulates cholesterol and carbohydrate metabolism through direct actions on gene expression as well as cross talk with other nuclear receptors, including peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways. TH modulates hepatic insulin sensitivity, especially important for the suppression of hepatic gluconeogenesis. The role of TH in regulating metabolic pathways has led to several new therapeutic targets for metabolic disorders. Understanding the mechanisms and interactions of the various TH signaling pathways in metabolism will improve our likelihood of identifying effective and selective targets

Physiol Rev 94: 355–382, 2014
doi:10.1152/physrev.00030.2013

THYROID HORMONE REGULATION OF METABOLISM

4) There is **cross-talk** between Endocrine Receptors in the Nucelus of Cells, rather than only singular functioning

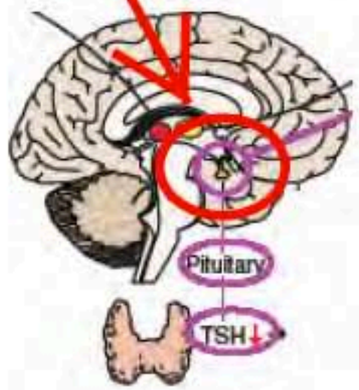
Rashmi Mullur, Yan-Yun Liu, and Gregory A. Brent

Department of Medicine, VA Greater Los Angeles Healthcare System, Departments of Medicine and Physiology, David Geffen School of Medicine at UCLA, Los Angeles, California

Mullur R, Liu Y-Y, Brent GA. Thyroid Hormone Regulation of Metabolism. *Physiol Rev* 94: 355–382, 2014; doi:10.1152/physrev.00030.2013.—Thyroid hormone (TH) is required for normal development as well as regulating metabolism in the adult. The thyroid hormone receptor (TR) isoforms, α and β, are differentially expressed in tissues and have distinct roles in TH signaling. Local activation of thyroxine (T_4), to the active form, triiodothyronine (T_3), by 5′-deiodinase type 2 (D2) is a key mechanism of TH regulation of metabolism. D2 is expressed in the hypothalamus, white fat, brown adipose tissue (BAT), and skeletal muscle and is required for adaptive thermogenesis. The thyroid gland is regulated by thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). In addition to TRH/TSH regulation by TH feedback, there is central modulation by nutritional signals, such as leptin, as well as peptides regulating appetite. The nutrient status of the cell provides feedback on TH signaling pathways through epigentic modification of histones. Integration of TH signaling with the adrenergic nervous system occurs peripherally, in liver, white fat, and BAT, but also centrally, in the hypothalamus. TR regulates cholesterol and carbohydrate metabolism through direct actions on gene expression as well as cross-talk with other nuclear receptors, including peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways. TH modulates hepatic insulin sensitivity, especially important for the suppression of hepatic gluconeogenesis. The role of TH in regulating metabolic pathways has led to several new therapeutic targets for metabolic disorders. Understanding the mechanisms and interactions of the various TH signaling pathways in metabolism will improve our likelihood of identifying effective and selective targets

Dogma: "Thyroid is TSH from Pituitary"

There is a long standing impenetrable Dogma:
that the Pituitary Hormone TSH measures Thyroid Function.



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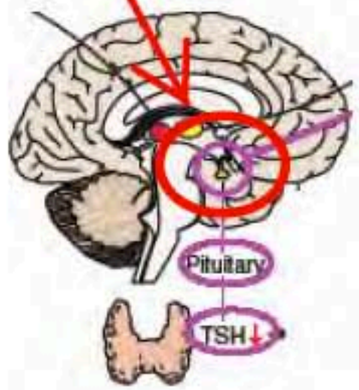
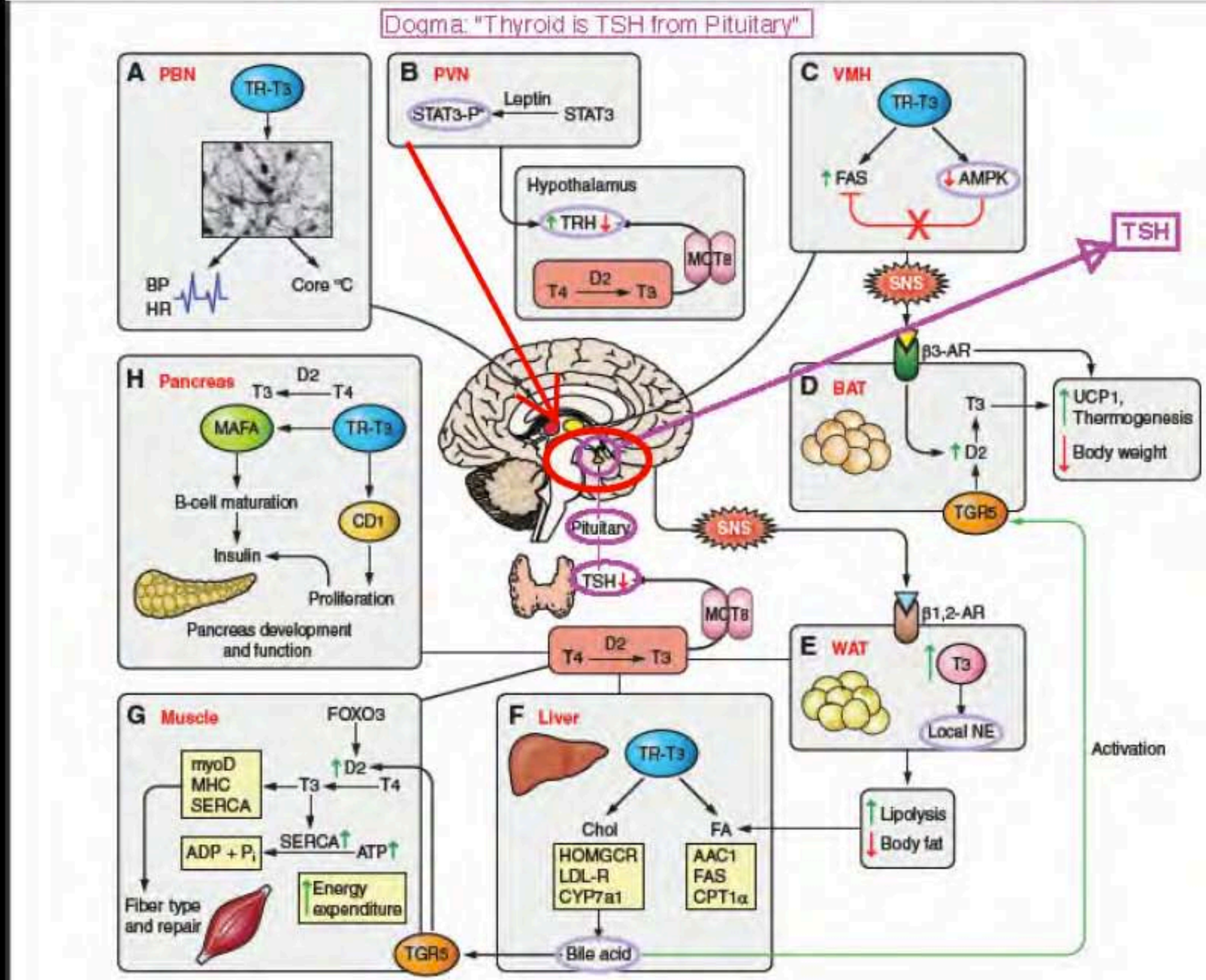
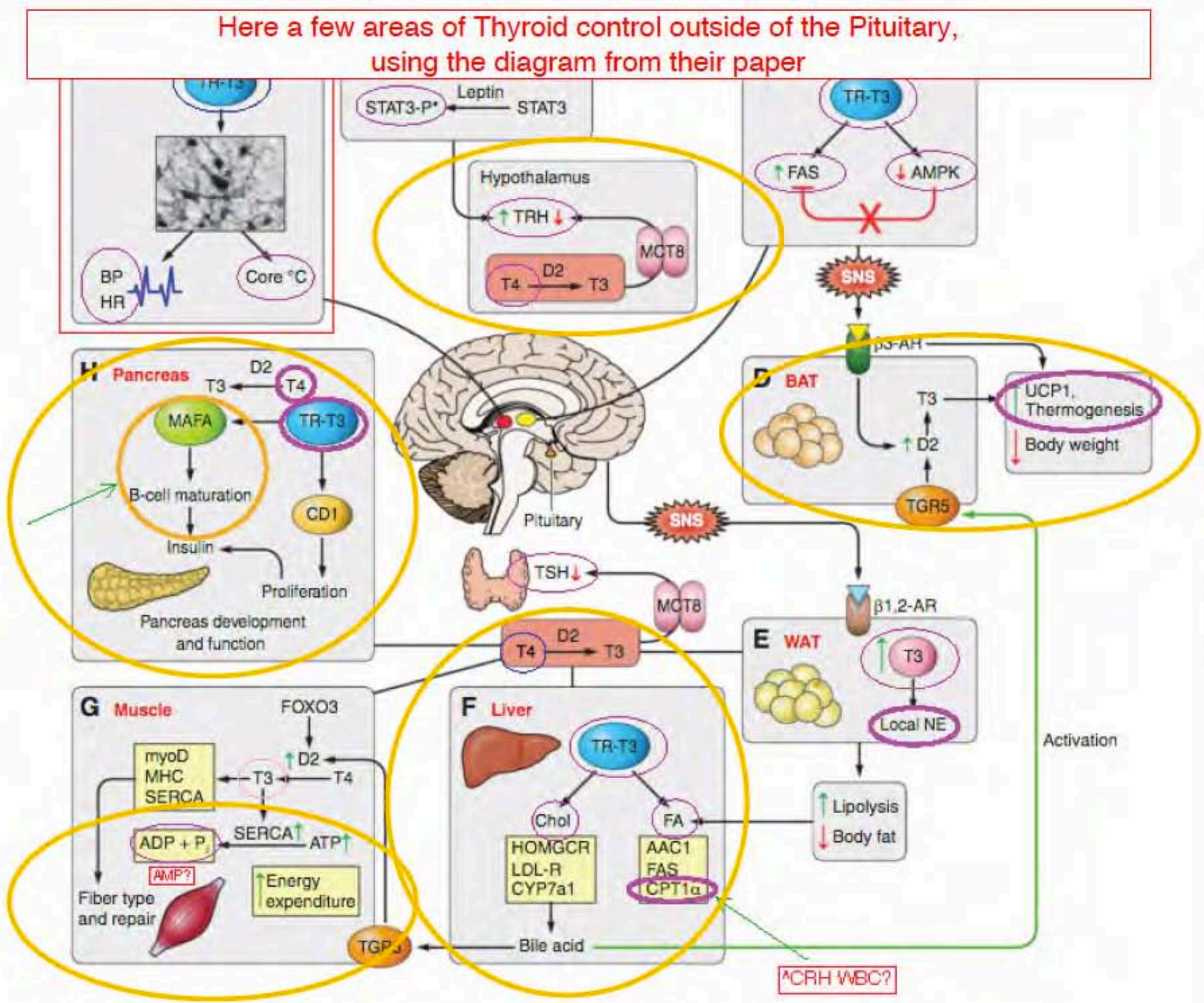


REALLY?

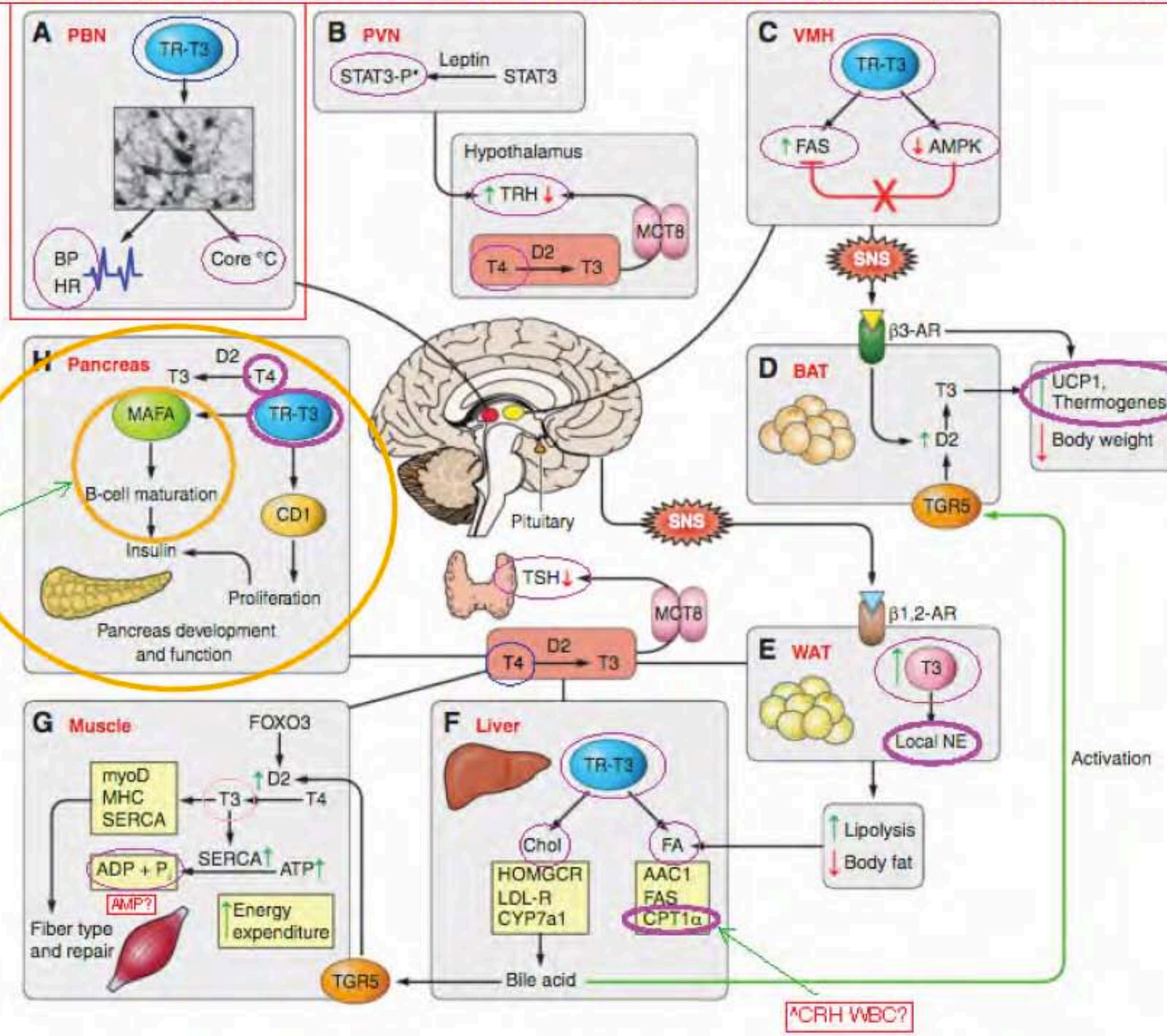
There is a whole world of Thyroid Function Beyond the Pituitary



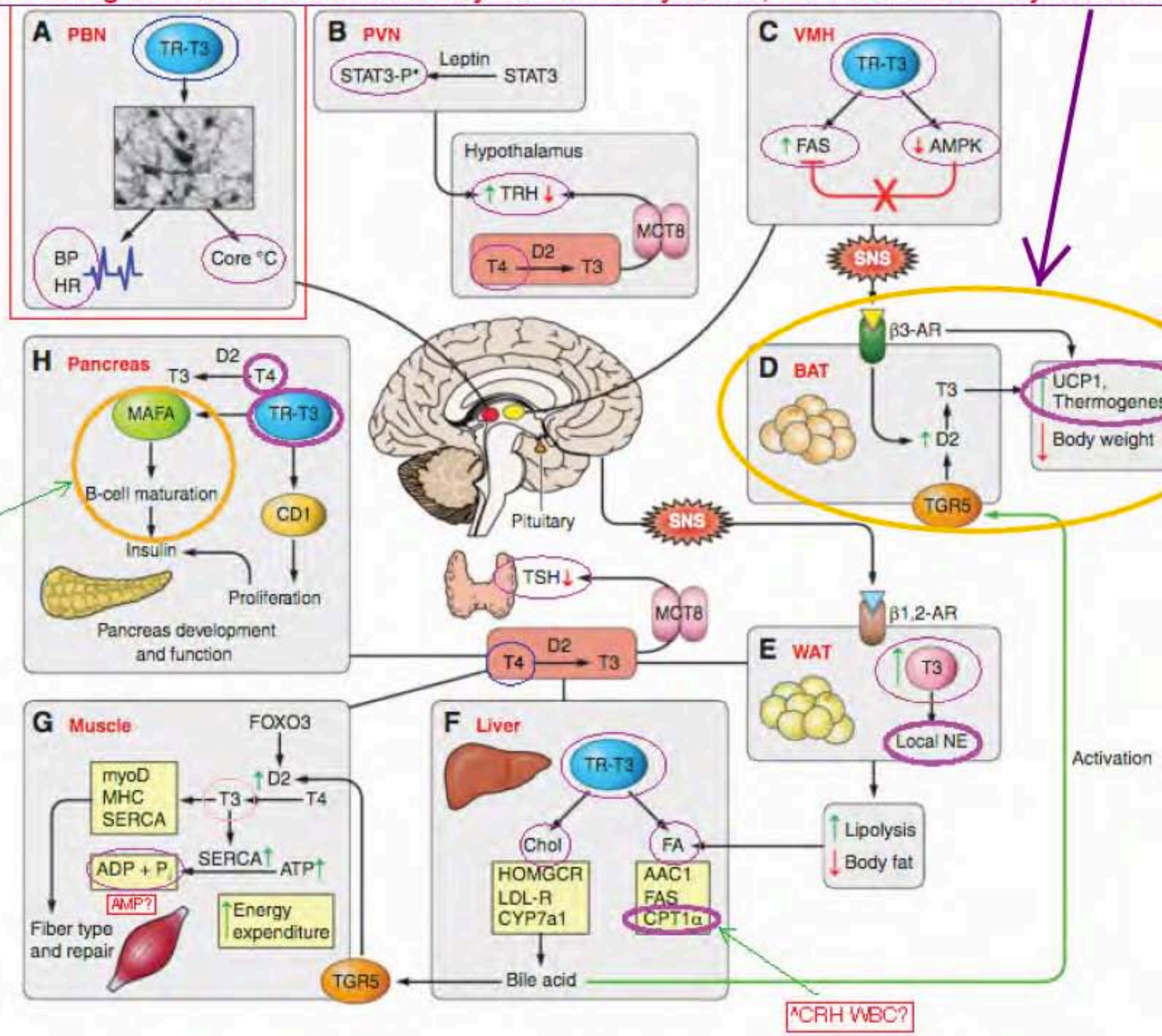
Here a few areas of Thyroid control outside of the Pituitary,
using the diagram from their paper



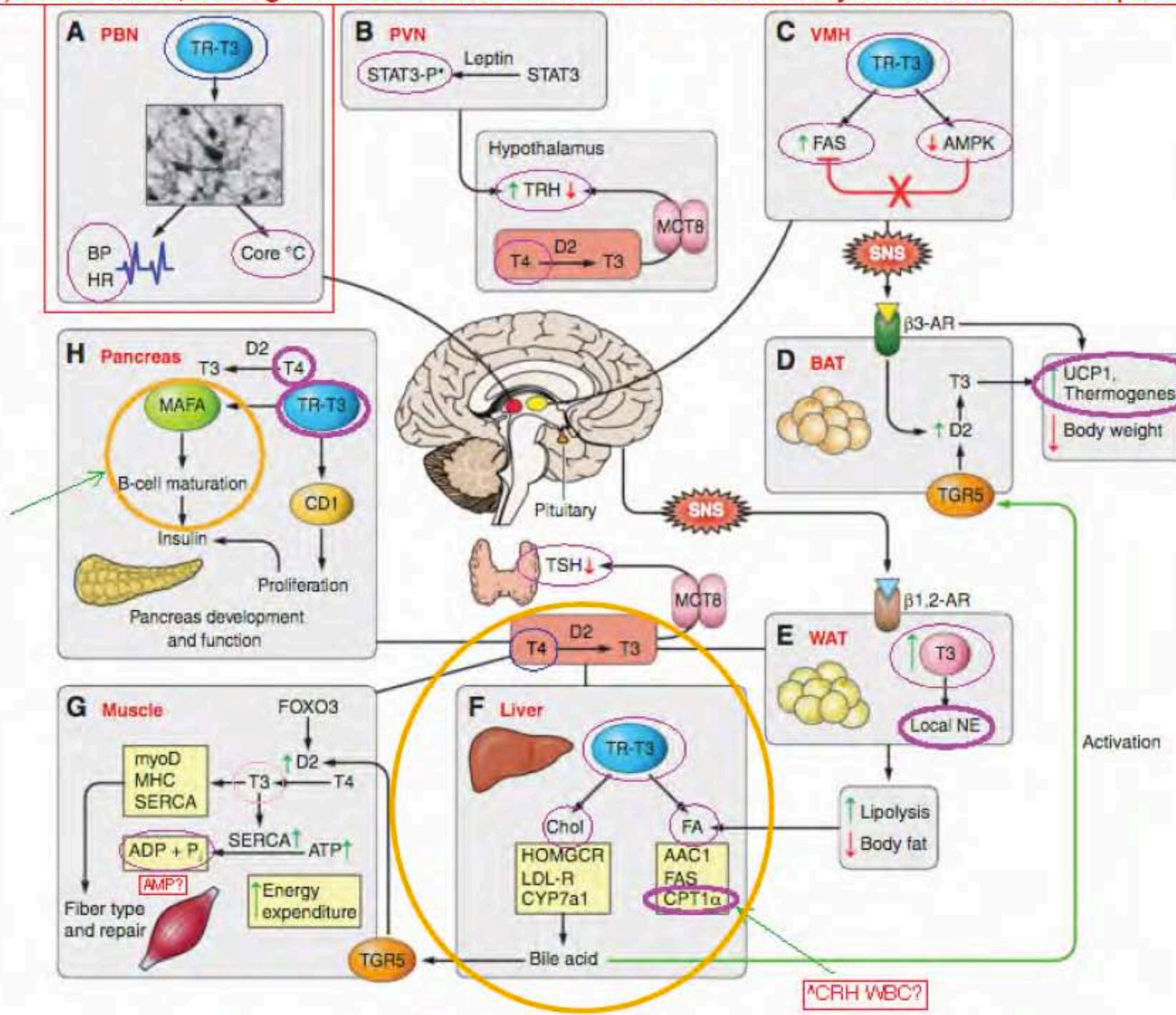
1) In the **Pancreas**, T4 Thyroxine stimulates Insulin production. Any cell that utilizes glucose requires adequate Thyroid hormone.



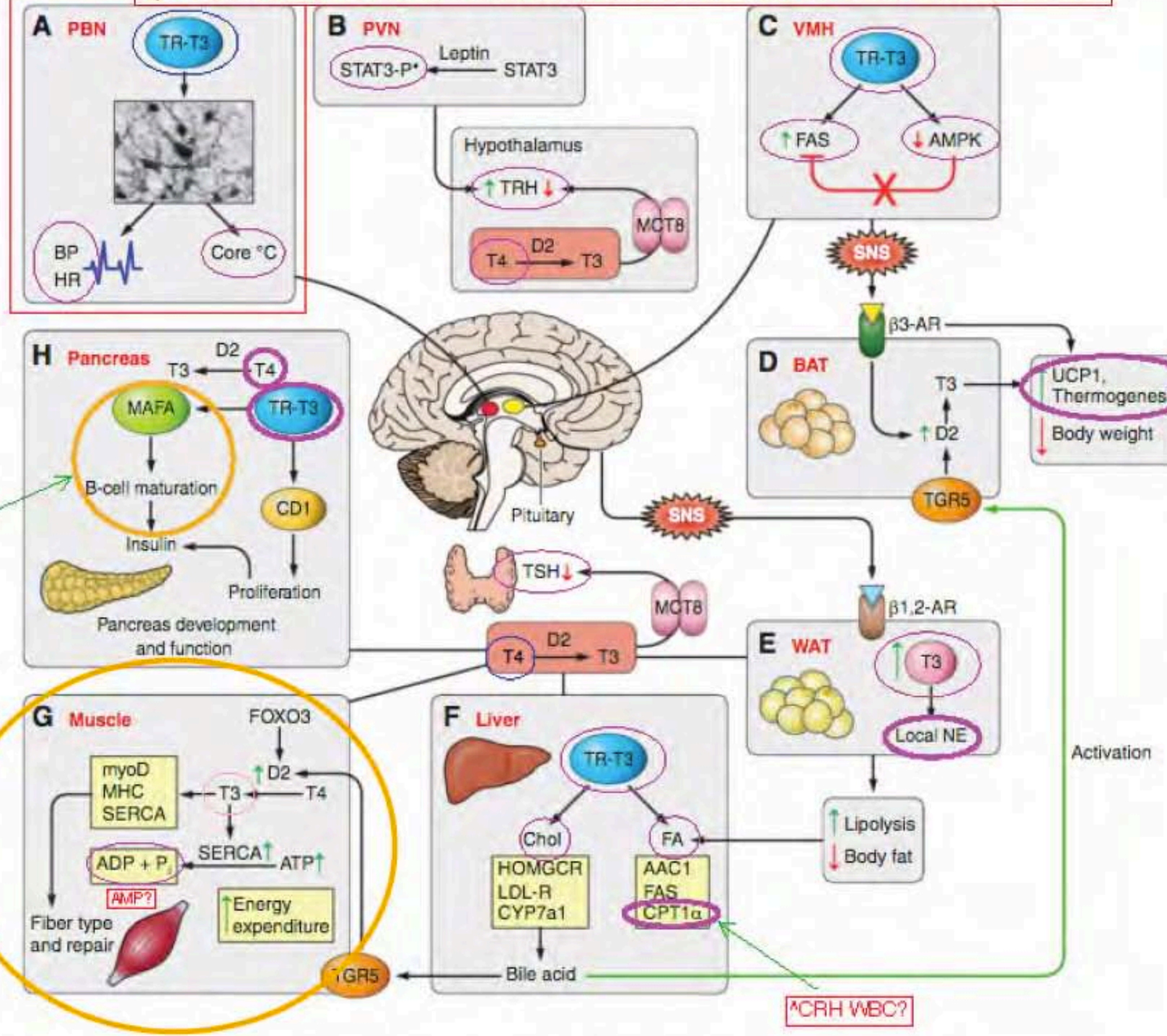
2) Burning Brown Fat is stimulated by T3 Triiodothyronine, the most active Thyroid form

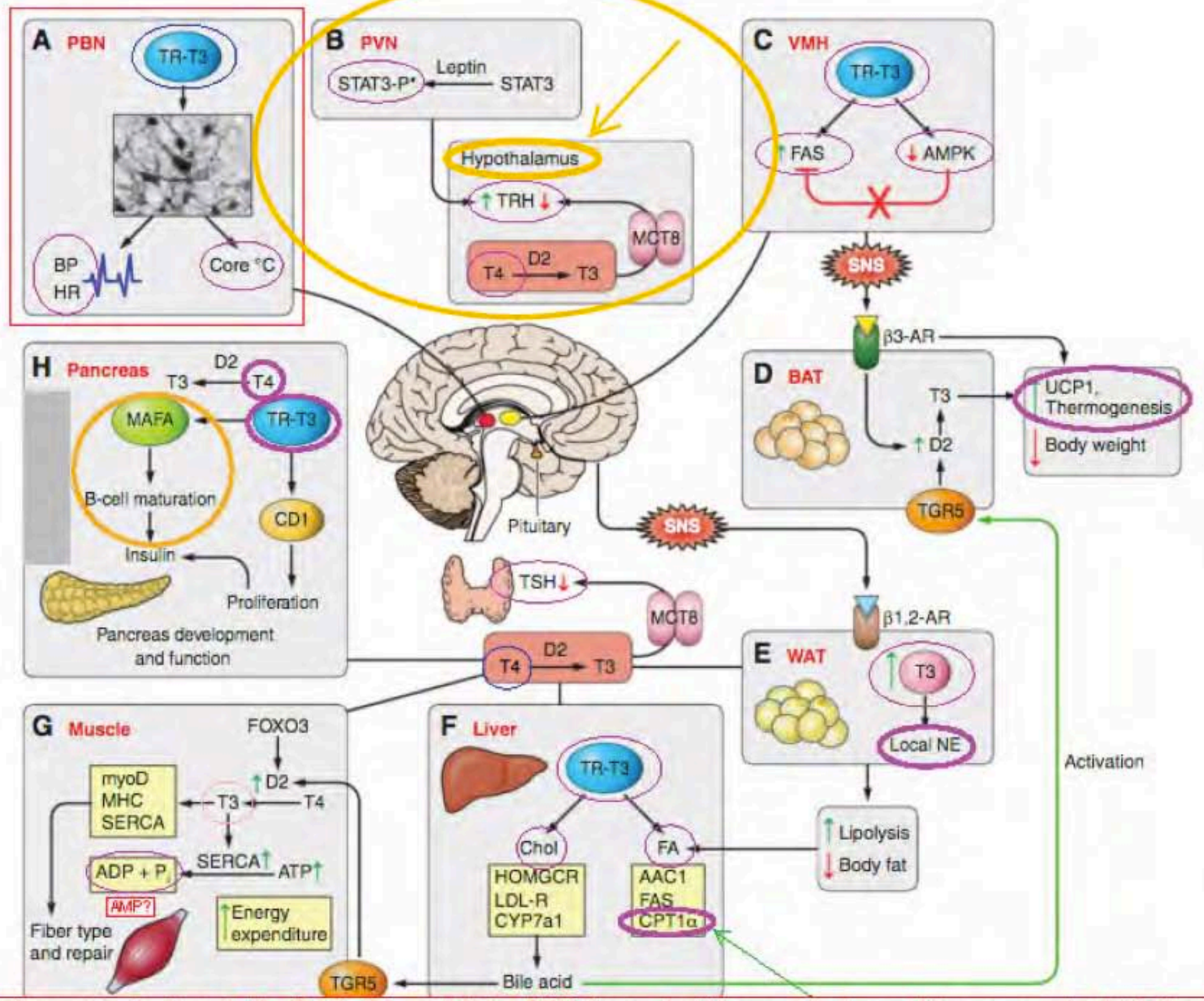


3) In the **Liver**, T3 regulates cholesterol and bile acids necessary for nutritional absorption.



4) In **Muscle**, T4 converted to T3 stimulates muscle mass and function.





5) Most surprisingly, deep **in the Brain, T3 modulates TRH**, the control Hormone that cannot be measured outside the bc released by the Hypothalamus to the Pituitary. It is central to TSH and Thyroid levels.

The take away is this: **Thyroid Hormones are the primary modulator of Glucose metabolism**.

Any cell that is dependent on **Glucose** requires Thyroid.

A discussion of Thyroid Physiology is in order. The 2006 introductory talk I gave on Thyroid in Pregnancy is available at my website. It covers more of the basics about the Thyroid.

THYROID PHYSIOLOGY

THYROID PHYSIOLOGY

Pituitary, Thyroid, and Parathyroid Pharmacology

Gail T. Galasko, in Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017

From Pituitary, Thyroid and Parathroid Pharmacology
Gail T. Galasko in Phamacology and THerpautics for Dentists

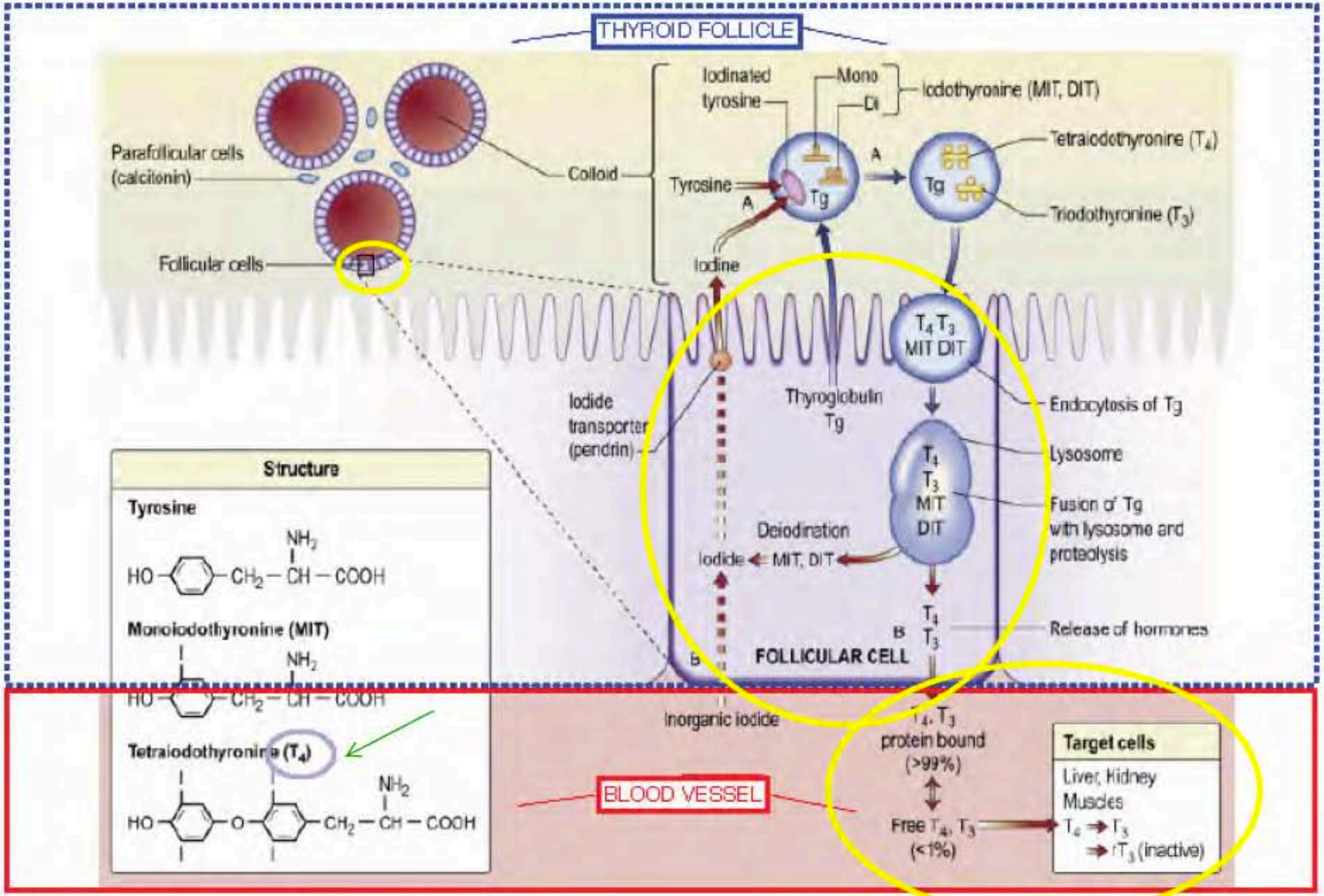


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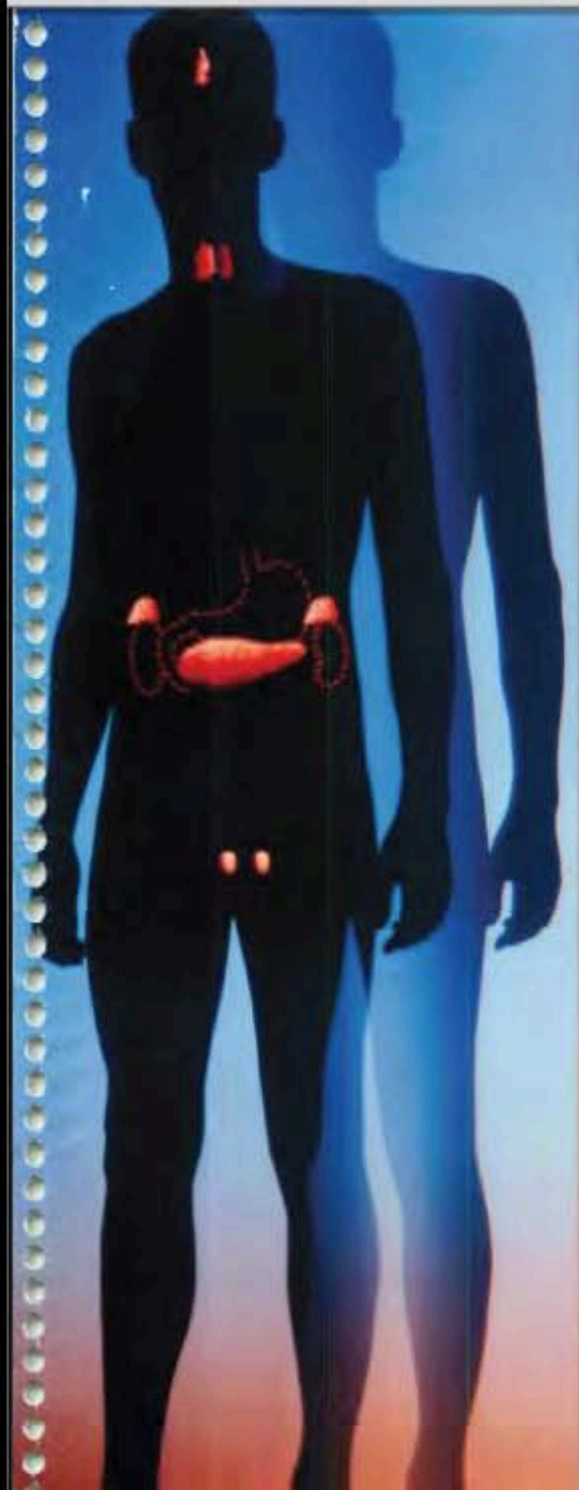
FIG 29-3. Synthesis of thyroid hormones. The sites of action of the thioamides are shown. See text for details. Shown are A, sites of inhibition by propylthiouracil and other



The New Endocrinology: New Applications of Current Research for Integrative Solutions

Book 1

American Academy of Environmental Medicine

Oregon Convention Center
Portland, Oregon

The American Academy of Environmental Medicine

Presents

The New Endocrinology:

New Applications of Current Research for Integrative Solutions

Alan B. McDaniel, M.D

November 16—17, 2011

Reprints available to purchase through:
The American Academy of Environmental Medicine
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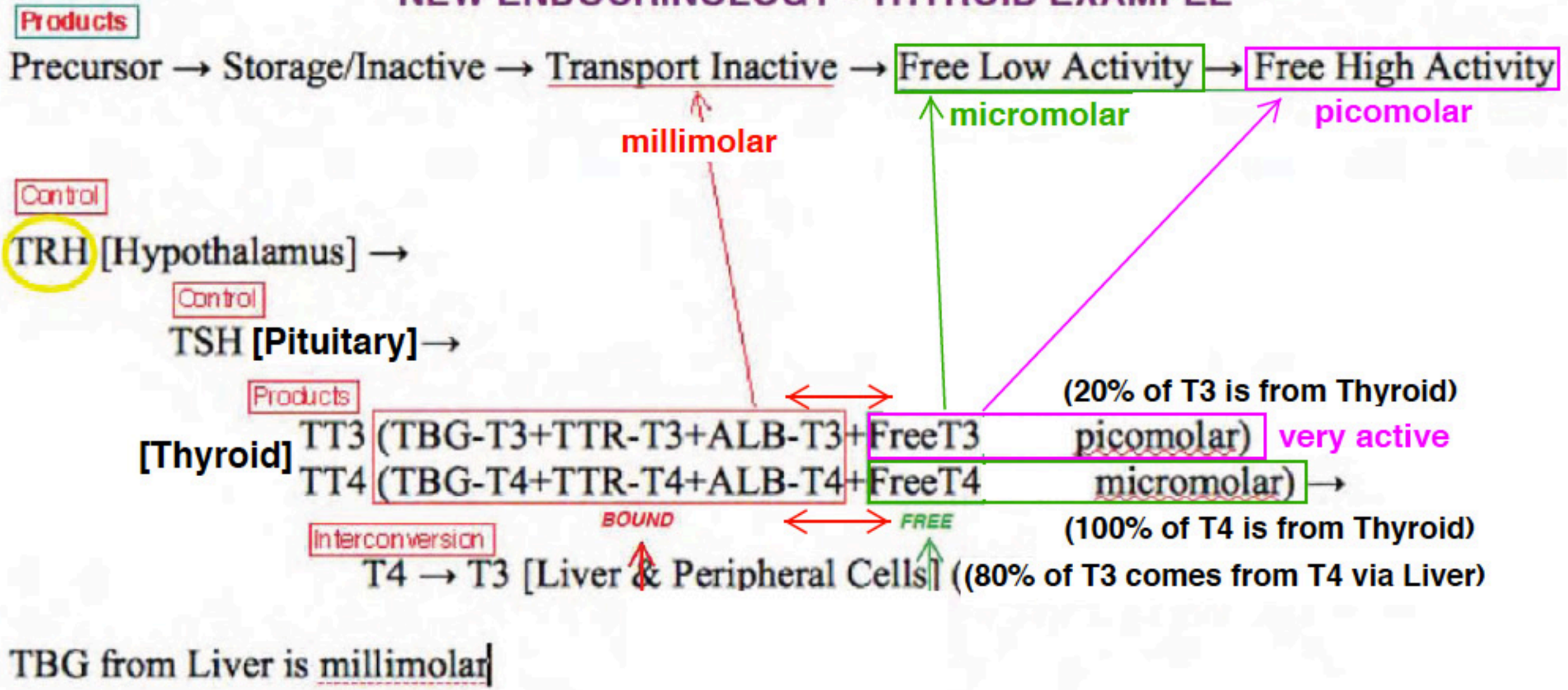
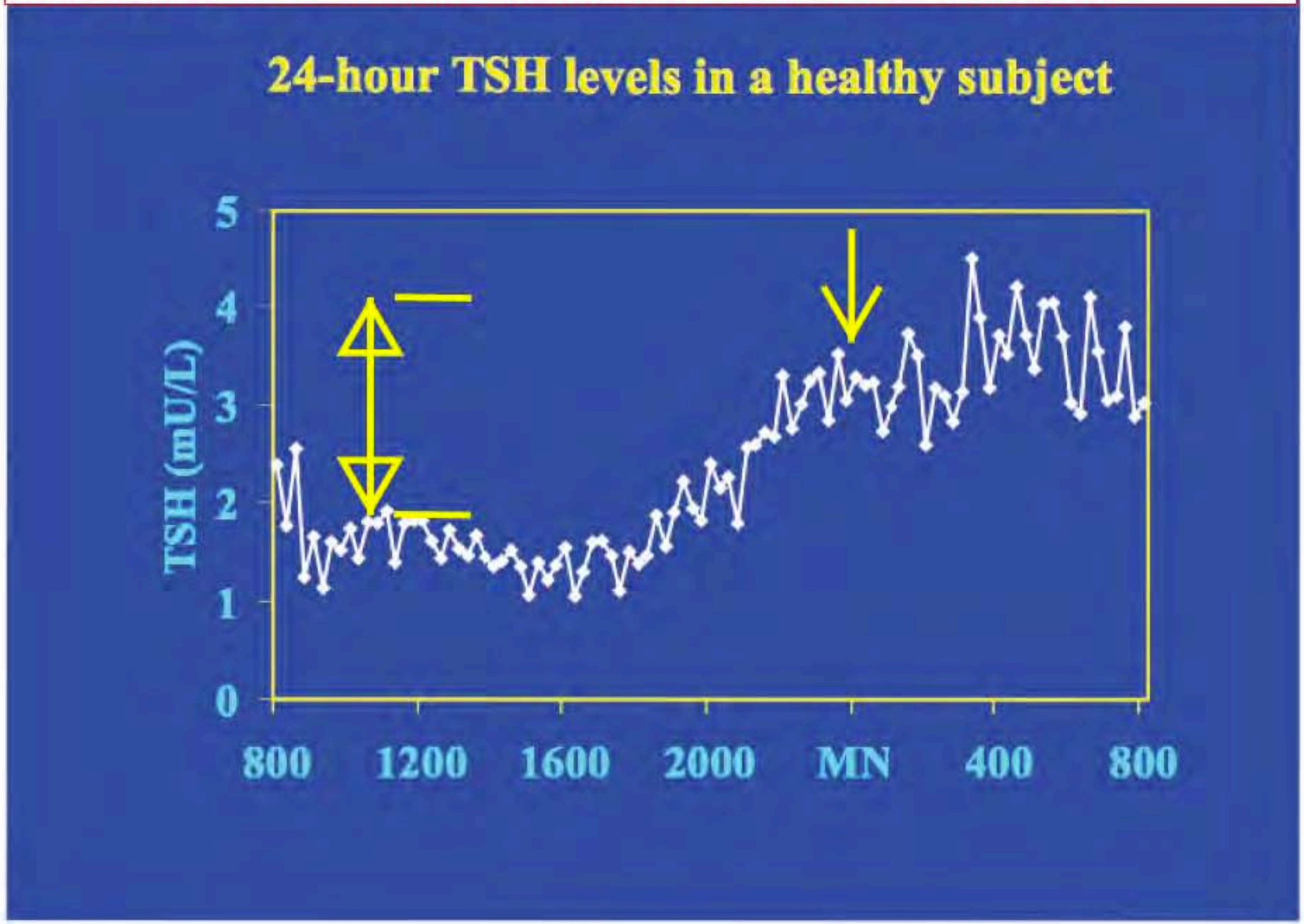
NEW ENDOCRINOLOGY - THYROID EXAMPLE



TBG from Liver is millimolar

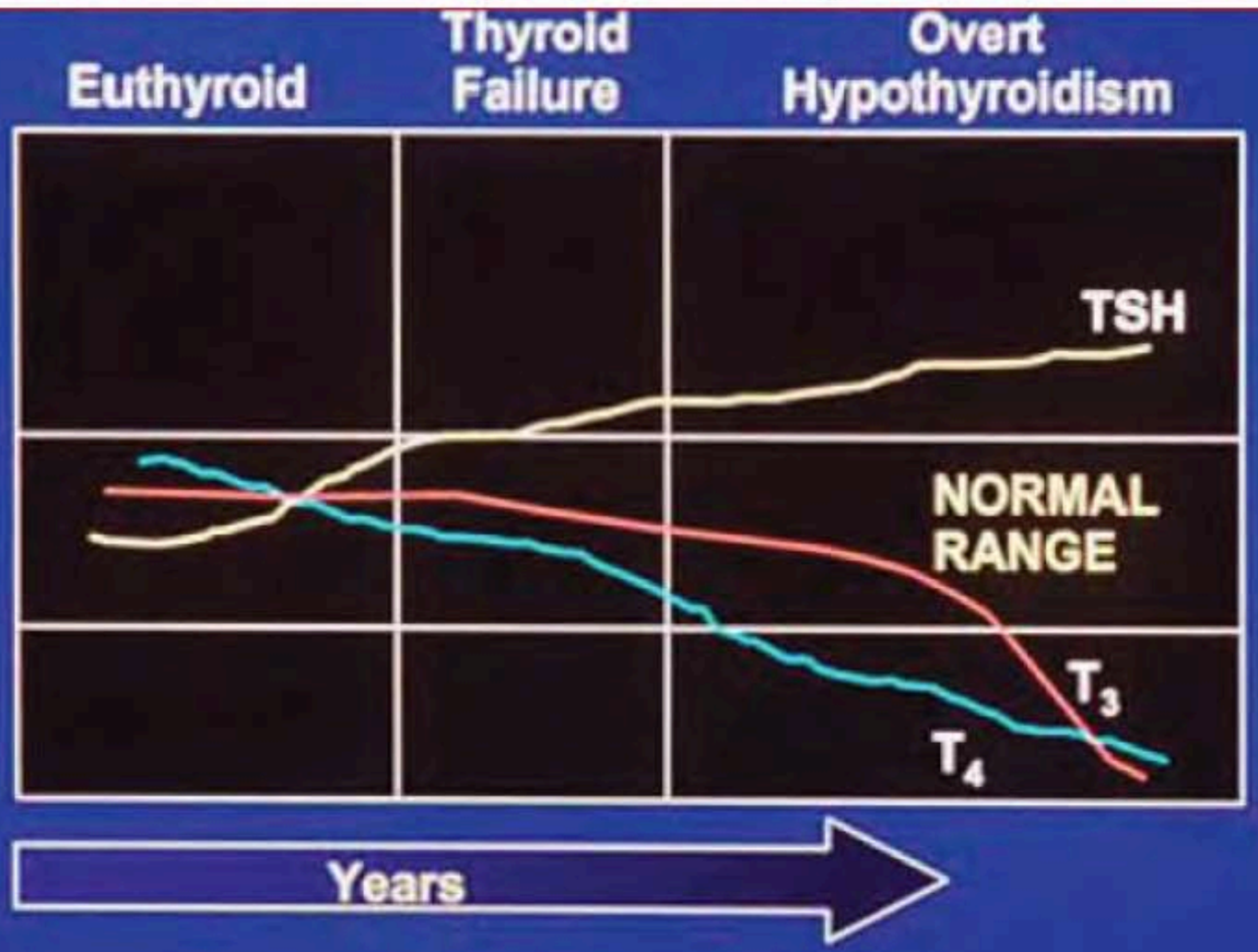
WHY IS THYROID PROBLEMATIC ?

For starters, the lab often measured, Serum TSH from the Pituitary gland, is not constant but varies. Its secretion is pulsatile to begin with, and also diurnal with a tendency to peak around midnite. It can vary by 1-2 units, shown here for a healthy male, while the normal range has been considered 1-5 units for a usual level of 2 mU/L.



Progression of Mild Thyroid Failure

The most common form of Thyroid failure, Hashimoto's Thyroiditis, often has a slow, insidious onset over years. This means that levels of T4 and T3 are not just normal or abnormal, but slowly drift lower non-linearly BEFORE TSH ever elevates into the extreme Hypothyroid state with High TSH and low T3 lower than low T4.



dapted from Ayala AR, Wartofsky L. *The Endocrinologist.* 1997; 7:44.

T4/T3 Ratios from Montoglou 2004

		T3/T4**	T4/T3	T4/T3 norm*	
Euthyroid (Eu)	(TSH<3.5)	15.89	0.0629	1.00	
Hypothyroid (Hypo)	(TSH>15)	24.12	0.0415	**0.66**	(Lo T4)
Hypothyroid Rx		13.42	0.0745	**1.18**	(NL T4 & NL T3)
Hyperthyroid (Hyper)	(TSH<.09)	19.57	0.0511	0.81	(Hi T4 or Hi T3)
Subacute Thyroiditis		15.16	0.0660	1.05	
Graves Hyperthyroid		>19		<0.84	
Thyroiditis		>16		<1.05	

Hypothyroid patients have low T4/T3, but when Hyperthyroid patients have low T4/T3 also!

**T3 in ng/dl and T4 in µg/dl
*T4/T3 norm = (T4/T3)/(T4/T3Eu)

It is not just the levels, but the ratio of the levels that indentifies Thyroid dysfunction.

In a paper by Montoglou, the ratios of Total T4 to Total T3 are shown to transition from Euthyroid to Hypothyroidism.

1) Hypothyroid is characterized by an excess of T3 to T4 (low ratio)
2) Thyroiditis and Graves have inverse ratios to each other.
3) Adequately treated patients need higher than normal T4 to T3.

THYROID LABS

Reference range for thyrotropin

Post hoc assessment

The Larisch Group in Germany in one recent paper focused on this problem for Thyrotropin TSH.

R. Larisch[1]; A. Giacobino[1]; W. Eckl[1]; H.-G. Wahl[2]; J. E. M. Midgley[3]; R. Hoermann[1]

[1]Klinik für Nuklearmedizin, Klinikum Lüdenscheid, Germany; [2]Institut für Laboratoriumsmedizin, Klinikum Lüdenscheid, Germany; [3]North Lakes Clinical, Ilkley, UK

Keywords

TSH, reference range, thyroid hormones

Summary

Setting the reference range for thyrotropin (TSH) remains a matter of ongoing controversy. Patients, methods: We used an indirect method to determine the TSH reference range post hoc in a large sample. A total of 399 well characterised subjects showing no evidence of thyroid dysfunction were selected for definition of the TSH reference limits according to the method of Katayev et al.. To this end, the cumulative frequency was plotted against the individual logarithmic TSH values. Reference limits were calculated by extrapolating the middle linear part of the regression line to obtain the cut-offs for the 95% confidence interval. We also examined biological variation in a sample of 65 subjects with repeat measurements to establish reference change values (RCVs). Results: Based on these, the reference interval obtained by the novel technique was in close agreement with the conventionally established limits, but differed significantly from earlier recommendations. Discussion: Following unverified recommendations could result in a portion of patients with subclinical thyroid dysfunctions being missed, an important consideration in a setting with a high prevalence of thyroid autonomy. Conclusion: Indirect post hoc verification of reference intervals from a large retrospective sample is a modern approach that gives plausible results. The method seems particularly useful to assess the adequacy and performance of reference limits reported or established by others in a particular setting. The present data should encourage re-evaluation of reference systems on a broader scale.

Schlüsselwörter

TSH, Referenzbereich, Schilddrüsenhormone

Zusammenfassung

Die vorliegende Arbeit befasst sich mit dem Referenzbereich des Thyreotropins (TSH). Patienten, Methoden: Mit der indirekten Methode von Katayev et al. wurde der Referenzbereich von TSH post hoc in einer Gruppe von insgesamt 399 gut untersuchten Personen ohne klinisch fassbare Zeichen einer Schilddrüsendysfunktion erhoben. Dafür wurde die kumulierte Häufigkeit gegen die logarithmierten TSH-Werte aufgetragen. Der mittlere, lineare Bereich, der dem 95%-Konfidenzintervall der Regressionsgerade entsprach, war der Referenzbereich. Zudem wurde die biologische Variabilität der Referenzwerte in einer Gruppe von 65 Personen mit Mehrfachmessungen bestimmt. Ergebnisse: Der so bestimmte Referenzbereich stimmte gut mit aktuellen, konventionell erhobenen Referenzdaten überein. Allerdings ergaben sich signifikante Unterschiede zu früheren Empfehlungen. Diskussion, Schlussfolgerung: Die indirekte Post-hoc-Bestimmung des TSH-Referenzbereichs aus einer retrospektiven Stichprobe ist ein moderner Ansatz, der plausible

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Thyrotropin-Referenzbereich
Post-hoc-Festsetzung
Nuklearmedizin 2015;54:-
http://dx.doi.org/10.3413/Nukmed-0671-14-06
received: June 6, 2014

current selection

The TSH for a population gives a spread that is wider than the spread for an individual, in fact twice the individual. That is, the combined variation for the Lab Range may go from 0.5 to 2.2 MIU/L [GREEN line], but for an individual it is 0.8 to 1.3 [RED line].

The population range does not identify the abnormal individual, because it falls wholly inside the population envelope [BLUE line].

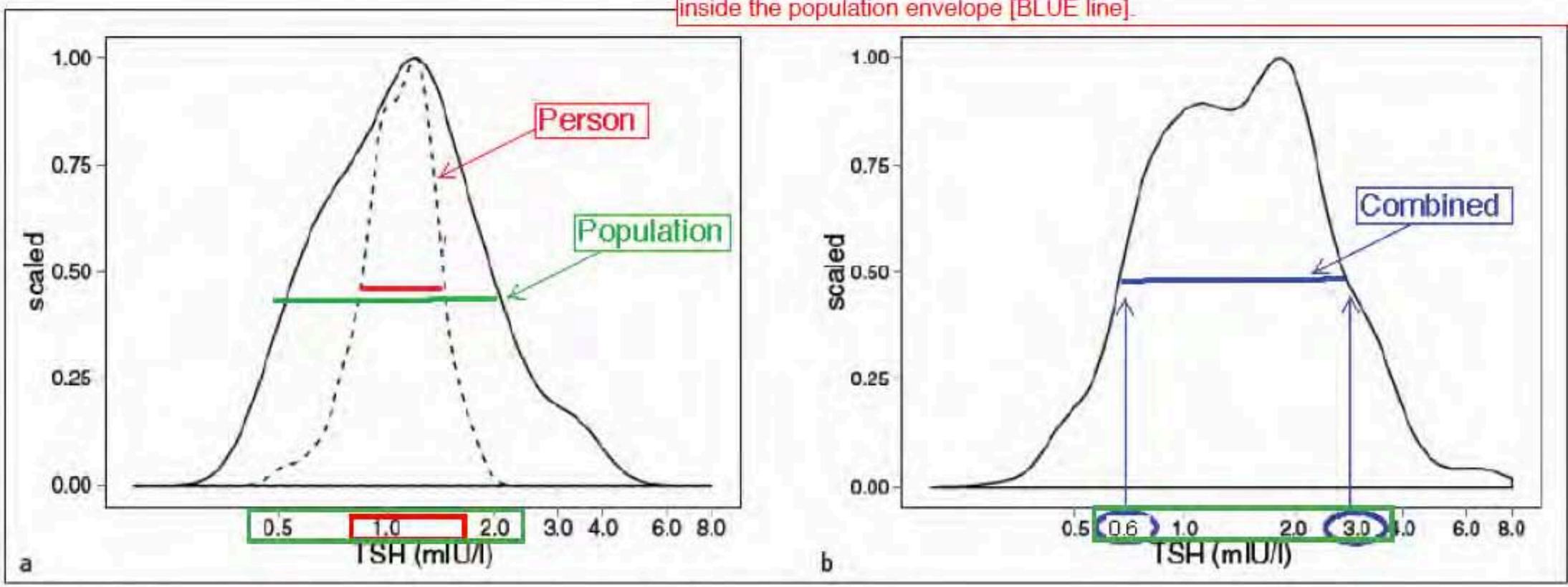

Fig. 2 Inter-individual (–) and intra-individual variation (---) of TSH
a) 65 euthyroid subjects; b) total collective (n = 399)

0013-7227/02/$15.00/0
Printed in U.S.A.

We might argue to use Total T4 as a measure rather than TSH. Andersen et al demonstrate that Total levels have the same problem in Overt Hypothyroid patients when followed over a 12 month period.

The Journal of Clinical Endocrinology & Metabolism 87(3):1068–1072

Narrow Individual Variations in Serum T_4 and T_3 in Normal Subjects: A Clue to the Understanding of Subclinical Thyroid Disease

STIG ANDERSEN, KLAUS MICHAEL PEDERSEN, NIELS HENRIK BRUUN, AND PETER LAURBERG

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High individuality causes laboratory reference ranges to be insensitive to changes in test results that are significant for the individual. We undertook a longitudinal study of variation in thyroid function tests in 16 healthy men with monthly sampling for 12 months using standard procedures. We measured serum T_4, T_3, free T_4 index, and TSH. All individuals had different variations of thyroid function tests ($P < 0.001$ for all variables) around individual mean values (set points) ($P < 0.001$ for all variables). The width of the individual 95% confidence intervals were approximately half that of the group for all variables. Accordingly, the index of individuality was low: $T_4 = 0.58$; $T_3 = 0.54$; free T_4 index = 0.59; TSH = 0.49. One test result described the individual set point with a precision of plus or minus 25% for T_4, T_3, free T_4 index, and plus or minus 50% for TSH. The differences required to be 95% confident of significant changes in repeated testing were (average, range): T_4 = 28, 11–62 nmol/liter; T_3 = 0.55, 0.3–0.9 nmol/liter; free T4 index = 33, 15–61 nmol/liter; TSH = 0.75, 0.2–1.6 mU/liter. Our data indicate that each individual had a unique thyroid function. The individual reference ranges for test results were narrow, compared with group reference ranges used to develop laboratory reference ranges. Accordingly, a test result within laboratory reference limits is not necessarily normal for an individual. Because serum TSH responds with logarithmically amplified variation to minor changes in serum T_4 and T_3, abnormal serum TSH may indicate that serum T_4 and T_3 are not normal for an individual. A condition with abnormal serum TSH but with serum T_4 and T_3 within laboratory reference ranges is labeled subclinical thyroid disease. Our data indicate that the distinction between subclinical and overt thyroid disease (abnormal serum TSH and abnormal T_4 and/or T_3) is somewhat arbitrary. For the same degree of thyroid function abnormality, the diagnosis depends to a considerable extent on the position of the patient's normal set point for T_4 and T_3 within the laboratory reference range. (*J Clin Endocrinol Metab* 87: 1068–1072, 2002)

Narrow Individual Variations in Serum T_4 and T_3 in Normal Subjects: A Clue to the Understanding of Subclinical Thyroid Disease

ENDOCRINE CARE

PowerPoint Slide for Teaching

The problem is no better for Subclinical Hypothyroid Patients. Free T4 changes for an Person [RED] will not be identified by the Population lab range [GREEN]

(Downloading may take up to 30 seconds. If the slide opens in your browser, select File -> Save As to save it.)

Click on image to view larger version.

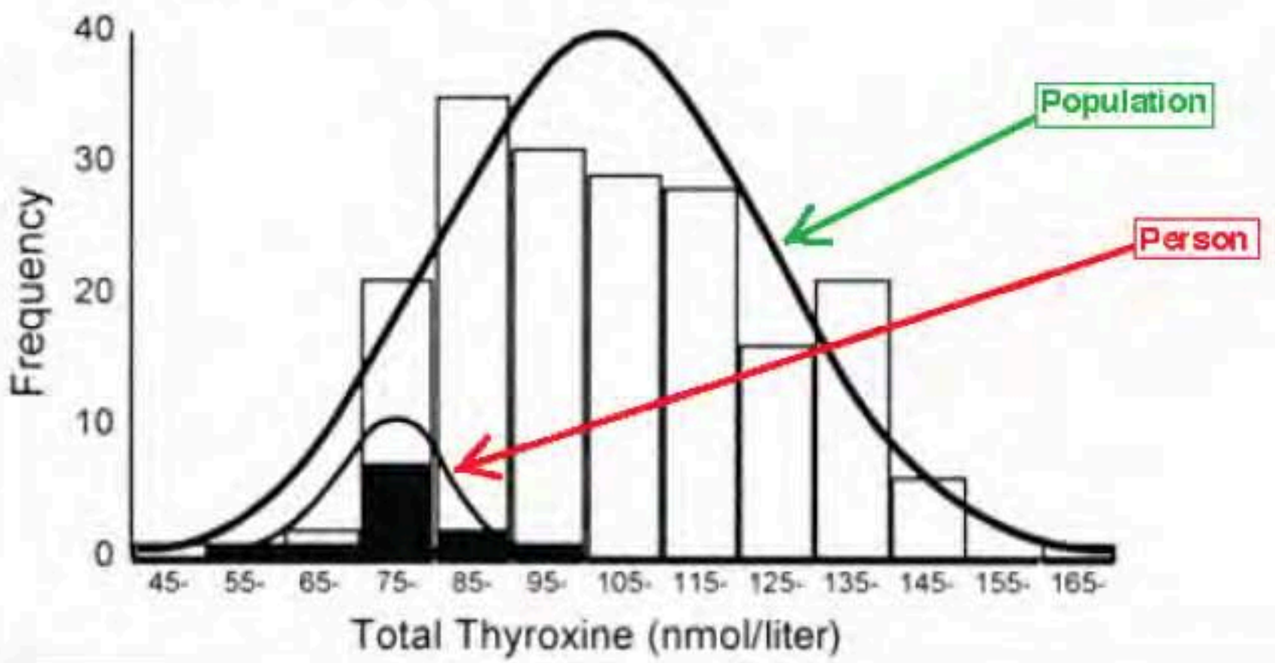

Figure 2.

The distribution of 12 monthly measurements of total T_4 in 15 healthy men (□) and in one individual, number 11 (▪). The distribution in one individual is about half the width of the distribution in the group.

>>100.04 1479683X - European Journal of Endocrinology] Narrow intra-individual variation of maternal thyroid function in pregnancy based on a longitudinal stu

In fact, every serum measure of Thyroid function demonstrates the same limitation.
Boas et al measured several of these Thyroid Function Tests in Pregnancy.

European Journal of Endocrinology (2009) 161 903–910 ISSN 0804-4643

CLINICAL STUDY

Narrow intra-individual variation of maternal thyroid function in pregnancy based on a longitudinal study on 132 women

Malene Boas[1], Julie Lyng Forman[2], Anders Juul[1], Ulla Feldt-Rasmussen[3], Niels Erik Skakkebæk[1], Linda Hilsted[4], Marla Chellakooty[1], Torben Larsen[5,6], Jørgen Falck Larsen[6], Jørgen H Petersen[1,2] and Katharina M Main[1]

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TSH, Total T4, Free T4, Total T3 and Free T3 all demonstrate narrower ranges for the Individual than the Population, making the use of Lab Normals problematic.

Table 3 Individuality indices and estimated variations within (intra-individual variation) and between (inter-individual variation) women at different times of gestation. Data are presented as transformed values (square root for TSH and thyroxine (T_4); log for free (FT_4), tri-iodothyronine (T_3), and free (FT_3).

	Gest. age (weeks)	S.D. within	S.D. between	Individuality index
TSH	10	0.13	0.33	0.39
	25	0.13	0.29	0.43
	40	0.13	0.30	0.42
T_4	10	0.45	0.85	0.53
	25	0.45	0.86	0.53
	40	0.45	1.03	0.44
Free T_4	10	0.07	0.11	0.63
	25	0.07	0.10	0.71
	40	0.07	0.11	0.63
T_3	10	0.08	0.16	0.53
	25	0.08	0.14	0.59
	40	0.08	0.16	0.52
Free T_3	10	0.07	0.11	0.61
	25	0.07	0.10	0.64
	40	0.07	0.11	0.59

Gest. age, gestational age.

Intra-individual variation of serum thyroxin and triiodothyronine in pregnancy.

W G Hölzel, W Deschner

Published October 1988

Hozel and Deschner in 1988 reported that Thyroid Lab Variation is the same for Pregnant and Non-Pregnant patients.

The Total T3 and T4 levels also did not change after 15 weeks of Gestation. My own 2004 Thyroid Study Patients showed the same behavior for Free T4 after 15 weeks.

Abstract

The mean concentrations of triiodothyronine (T3) and thyroxin (T4) in serum were increased in pregnancy, the increases for individuals remaining stable for week 16 to week 40 of gestation. For this period biological intra-individual variations of T3 and T4 in serum were estimated and compared with those of non-pregnant women. The average biological intra-individual CVs for T3 and T4 were of the same order for pregnant and non-pregnant women (6.9-8.4%). The ratios of the biological intra-individual CVs to the biological group CVs were 0.5 to 0.6. Individual values were normally distributed. There was no increase of the intra-individual variation with the lapse of time between two consecutively observed values. The estimated average biological intra-individual CVs were used to derive decision-making criteria in monitoring thyroid function during the 2nd and 3rd trimester of gestation.

PREGNANCY

0163-769X/97/$03.00/0
Endocrine Reviews

Daniel Glinoer is one of the pioneers exploring Thyroid Physiology, very early on elucidating the processes in Pregnancy.

Vol. 18, No. 3
Printed in U.S.A.

The Regulation of Thyroid Function in Pregnancy: Pathways of Endocrine Adaptation from Physiology to Pathology

DANIEL GLINOER

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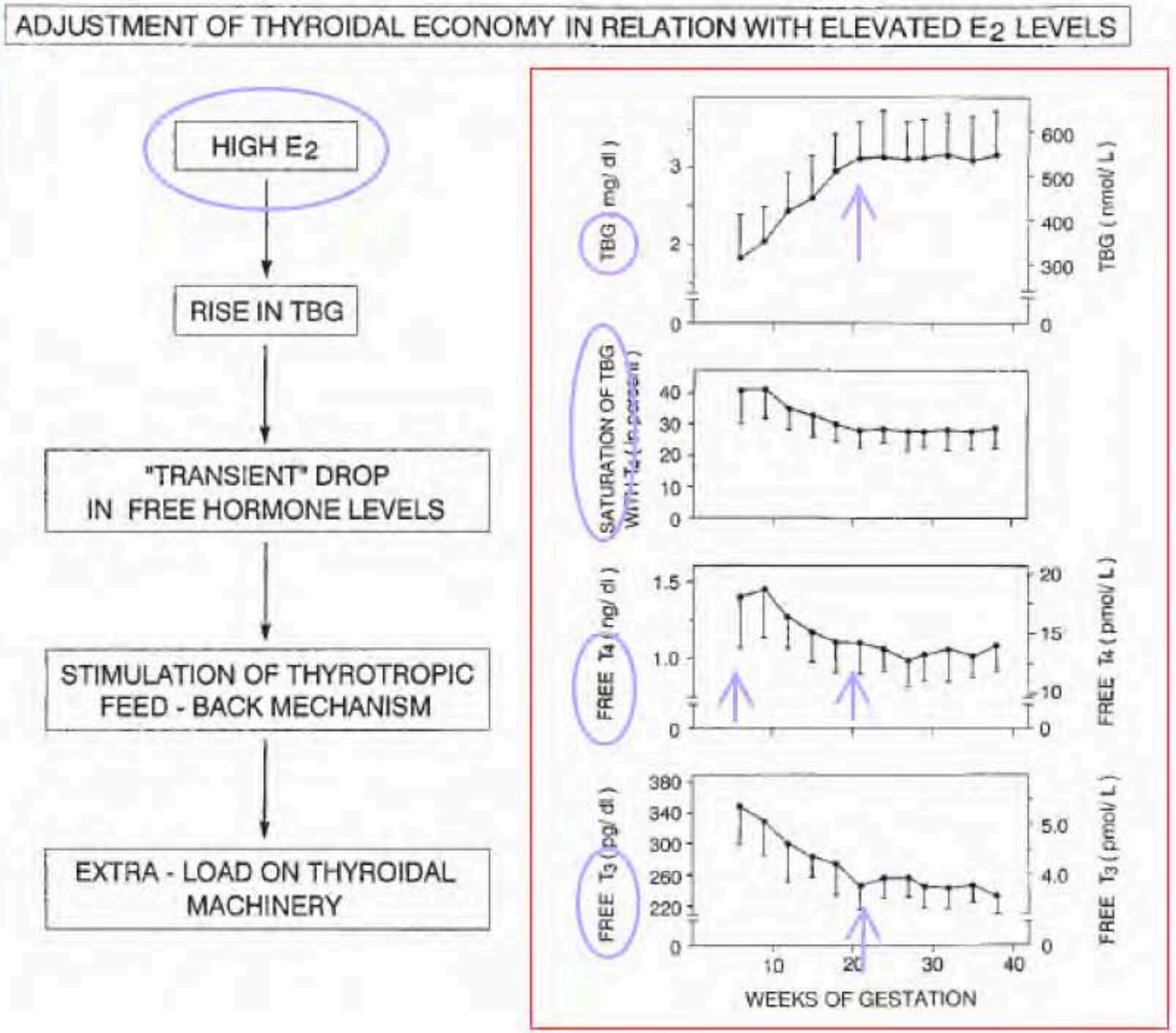
I. Introduction

THYROID disorders are observed 4- to 5-fold more frequently in women when compared with men, in particular during the childbearing period. It is therefore not unusual to encounter thyroid function abnormalities during a "routine" laboratory evaluation carried out for pregnant women. One of the aims of the present review is to underscore the rationale that allows for a correct interpretation of these alterations. Furthermore, pregnancy is accompanied by profound alterations in thyroidal economy, resulting from a complex combination of factors specific for the pregnant state: the rise in T_4-binding globulin concentrations, the effects of CG on the maternal thyroid, alterations in the requirement for iodine, modifications in autoimmune regulation, and the role of the placenta in deiodination of iodothyronines. Another aim of this review is to discuss the specific role attributed to each factor and delineate the main pathways of thyroidal adaptation, including physiology as well as pathophysiology in the pregnant state. Finally, the third aim is to discuss specific aspects of the management of hypothyroidism (related to established, subclinical, and preclinical hypothyroidism) and hyperthyroidism [both Graves' disease (GD) and gestational nonautoimmune transient thyrotoxicosis] when associated with pregnancy.

Hormone levels are not constant in Pregnancy, and Thyroid is no exception. In his 1997 paper, Glinoer summarized underlying processes.

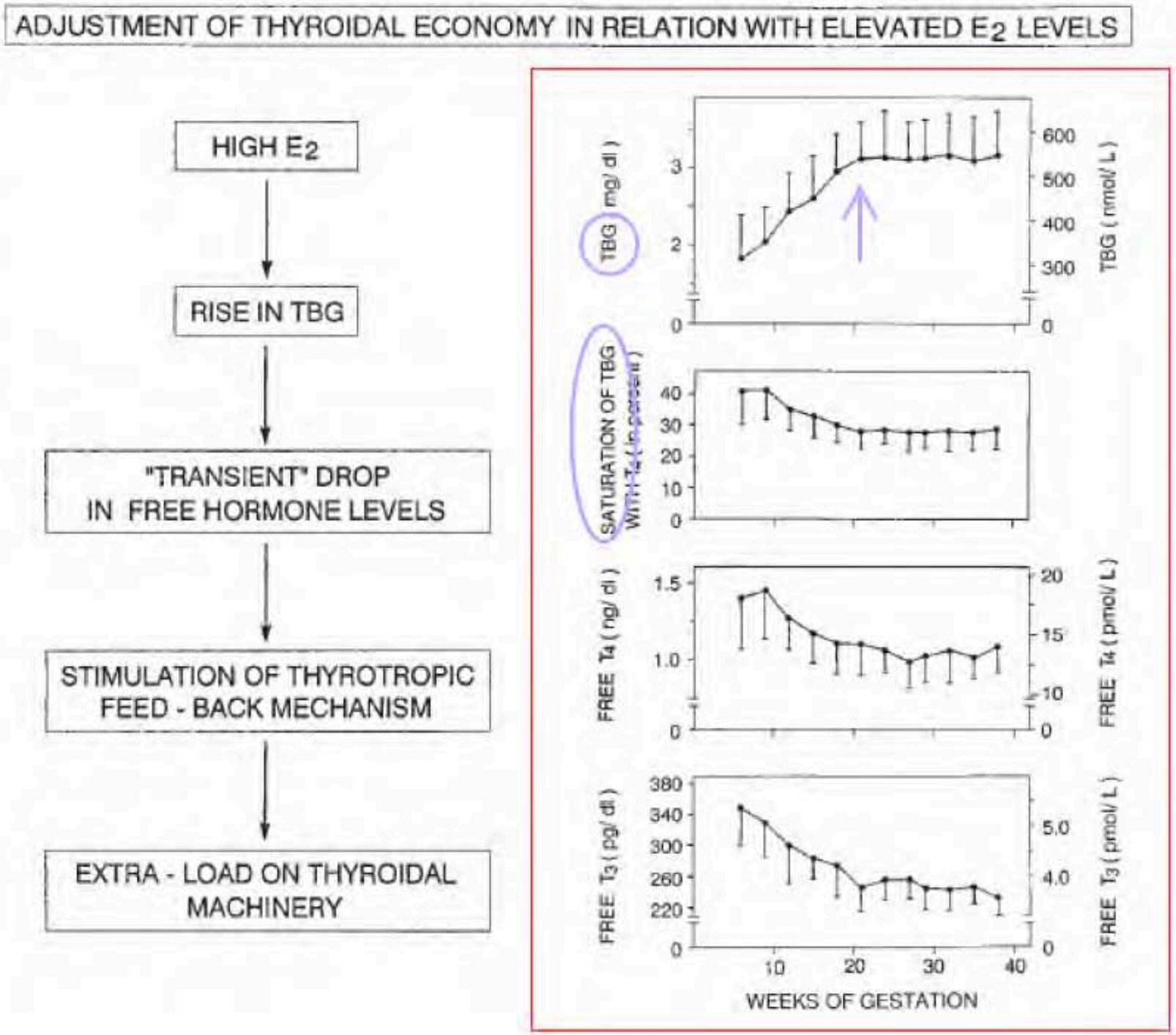
1) First, high Estradiol in Pregnancy increases steadily until 20 weeks and levels off.

FIG. 2. Schematic representation of the feedback regulatory mechanisms between the rise in TBG levels, the trend toward a reduction in free hormone concentrations, and the stimulation of the pituitary-thyroid axis. In the *right* part of the figure, data collected in 606 normal pregnancies in Brussels are illustrated, showing the progressive rise in serum TBG during the first part of gestation, accompanied by a progressive decrease in the free T_4 index (saturation level of TBG by T_4), and free T_4 and T_3 concentrations. Brussels being in an area with a restricted iodine intake, the quantitative reduction in free hormone concentrations observed in the second part of gestation is more pronounced than in areas without iodine deficiency. [Adapted with permission from D. Glinoer (36) © Plenum Publishing Corp.]



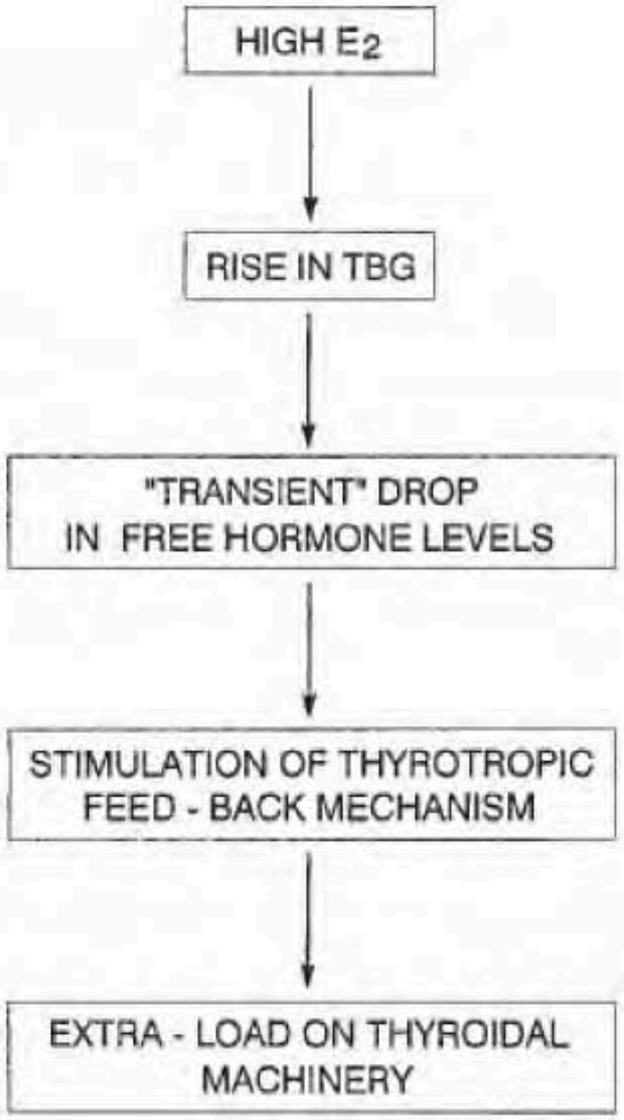
2) TBG binds Thyroid hormones, so its increase from Estrogen stimulation requires more Thyroxine to 20 weeks, and TBG saturation goes down.

FIG. 2. Schematic representation of the feedback regulatory mechanisms between the rise in TBG levels, the trend toward a reduction in free hormone concentrations, and the stimulation of the pituitary-thyroid axis. In the *right* part of the figure, data collected in 606 normal pregnancies in Brussels are illustrated, showing the progressive rise in serum TBG during the first part of gestation, accompanied by a progressive decrease in the free T_4 index (saturation level of TBG by T_4), and free T_4 and T_3 concentrations. Brussels being in an area with a restricted iodine intake, the quantitative reduction in free hormone concentrations observed in the second part of gestation is more pronounced than in areas without iodine deficiency. [Adapted with permission from D. Glinoer (36) © Plenum Publishing Corp.]



3) Free T4, which peaks at 10 weeks, decreases back towards pre-pregnancy values.

ADJUSTMENT OF THYROIDAL ECONOMY IN RELATION WITH ELEVATED E_2 LEVELS



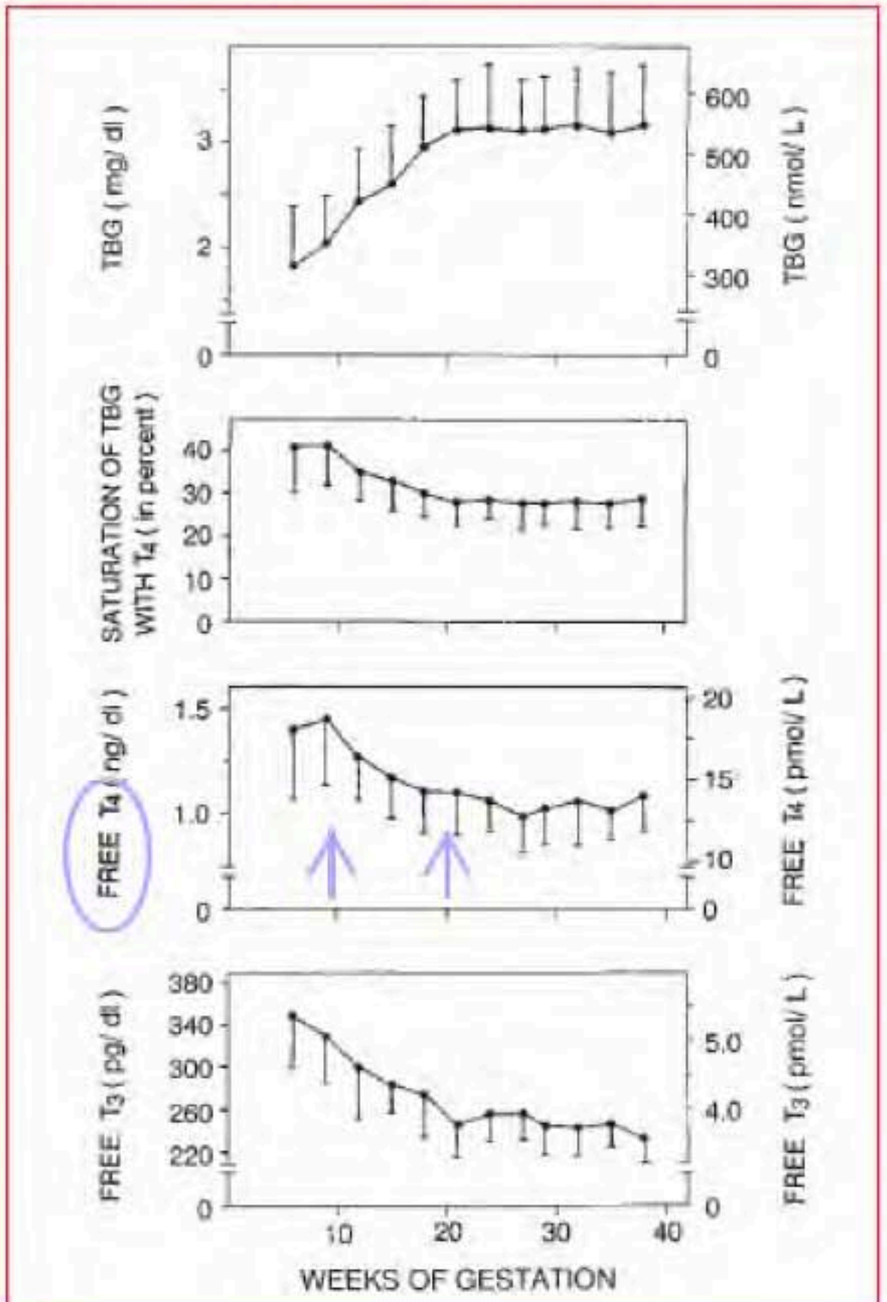
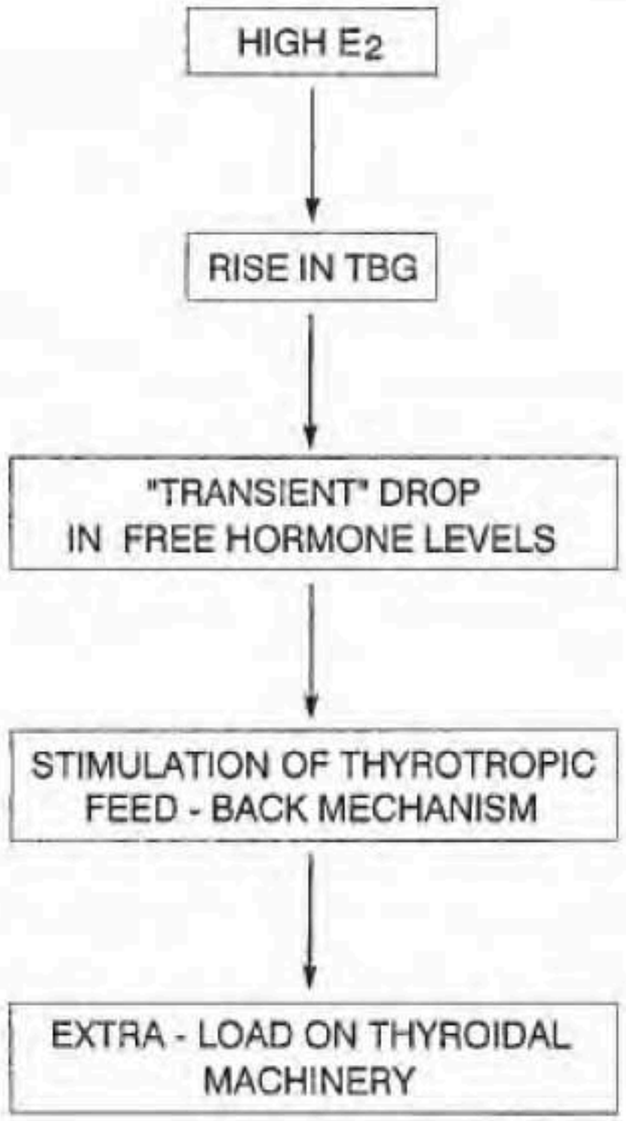


FIG. 2. Schematic representation of the feedback regulatory mechanisms between the rise in TBG levels, the trend toward a reduction in free hormone concentrations, and the stimulation of the pituitary-thyroid axis. In the *right* part of the figure, data collected in 606 normal pregnancies in Brussels are illustrated, showing the progressive rise in serum TBG during the first part of gestation, accompanied by a progressive decrease in the free T_4 index (saturation level of TBG by T_4), and free T_4 and T_3 concentrations. Brussels being in an area with a restricted iodine intake, the quantitative reduction in free hormone concentrations observed in the second part of gestation is more pronounced than in areas without iodine deficiency. [Adapted with permission from D. Glinoer (36) © Plenum Publishing Corp.]

4) Free T3 shows similar behavior.

ADJUSTMENT OF THYROIDAL ECONOMY IN RELATION WITH ELEVATED E_2 LEVELS



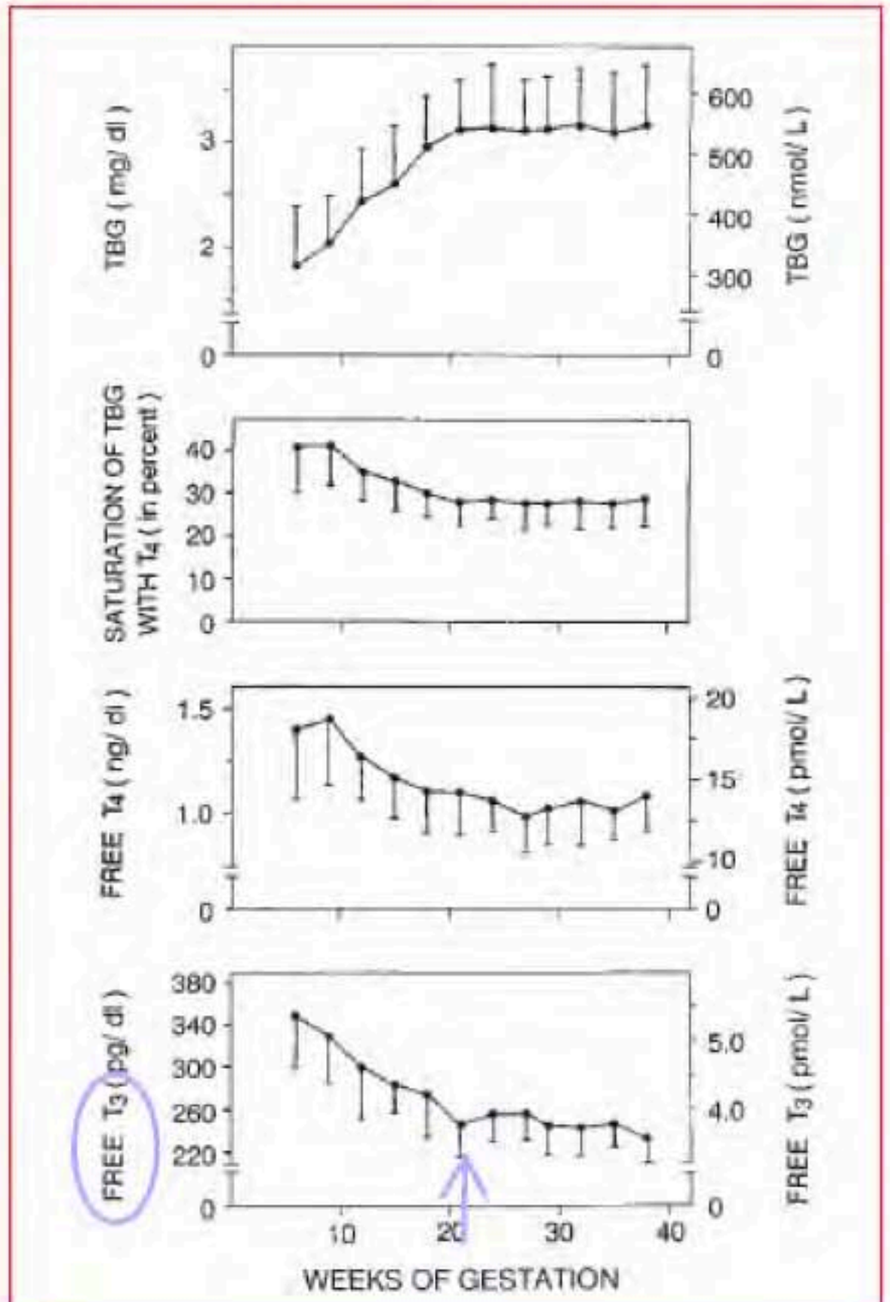
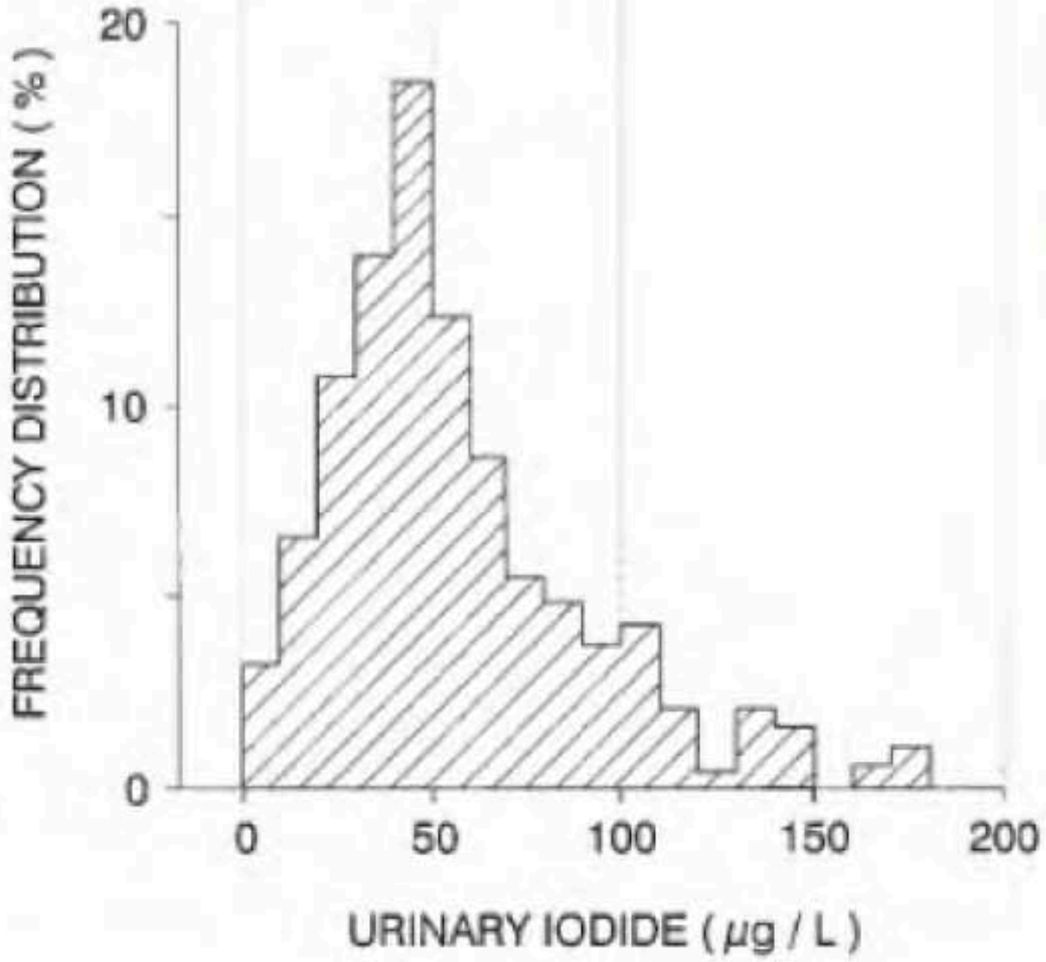


FIG. 2. Schematic representation of the feedback regulatory mechanisms between the rise in TBG levels, the trend toward a reduction in free hormone concentrations, and the stimulation of the pituitary-thyroid axis. In the *right* part of the figure, data collected in 606 normal pregnancies in Brussels are illustrated, showing the progressive rise in serum TBG during the first part of gestation, accompanied by a progressive decrease in the free T_4 index (saturation level of TBG by T_4), and free T_4 and T_3 concentrations. Brussels being in an area with a restricted iodine intake, the quantitative reduction in free hormone concentrations observed in the second part of gestation is more pronounced than in areas without iodine deficiency. [Adapted with permission from D. Glinoer (36) © Plenum Publishing Corp.]

Relative Hypothyroxinemia (Low Free T4 level) is one of the useful parameters that can be measured in Pregnancy.

Percent of women	43 %	42 %	15 %



take is marginally low. It is therefore important that clinicians correctly assess increased thyroidal stimulation (34, 160). In practice, four simple biochemical parameters have been identified and proven to be useful markers.

The first parameter is relative hypothyroxinemia. As already discussed, free T_4 levels tend to decrease slightly, even in pregnant women who have an adequate iodine supply. In women with iodine restriction, however, the early rise in total T_4 (associated with the rise in TBG) was shown to be inappropriately low, with free T_4 and T_3 levels progressively decreasing during the first part of gestation to stabilize at a low level (with an average decrement of 30%) in the second part of gestation (34, 131, 161). Under the environmental conditions that we investigated in Brussels before iodine supplementation was systematically introduced during pregnancy, it was observed that one third of pregnant women had free T_4 values near or below the lower limit of normal (34). It was also shown that there was a tendency for individuals to exhibit variable patterns of glandular adaptation. For instance, a woman whose serum free T_4 was already in the lower tertile of the population's range during early gestation had a greater than 80% risk of remaining in the lower part of the range during late gestation. Conversely, a woman with a serum free T_4 in the upper part of the population's range during the last months of pregnancy had a greater than 90% chance of having a serum free T_4 in the upper part of the range in early gestation, indicating that in

classified as: 1) <50 μg/liter (severe deficiency); 51–100 μg/liter (moderate deficiency); and 101–200 μg/liter (no obvious iodine deficiency). [Reproduced with permission from D. Glinoer (153). © Schattauer.]

Another parameter is the T3/T4 ratio, reflecting T3 adequacy and/or T4 inadequacy. This ratio is expected to remain unchanged throughout Pregnancy.

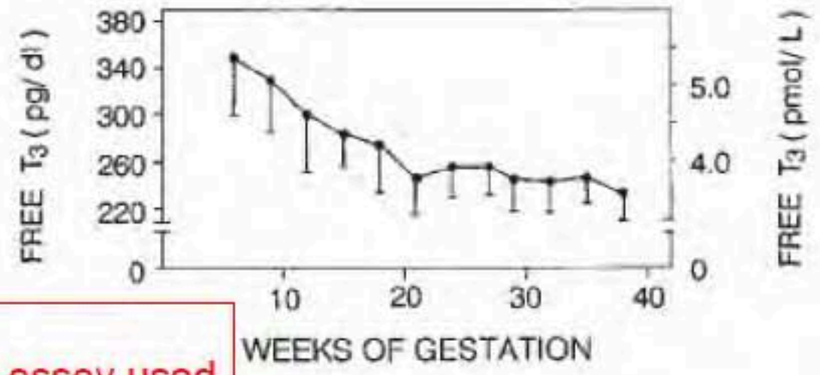
ments such as selenium. These factors combined with iodine deficiency tend to enhance the thyroidal alterations (89, 155). Thyroid function, in adults and children in areas with severe IDD varies: some subjects exhibit normal thyroid function parameters and others display variable degrees of hypothyroidism. Also, hypothyroidism plays a major role in reducing a woman's fertility and increasing the rate of miscarriage. When hypothyroid women become pregnant, thyroid function tends to deteriorate even further as gestation progresses. Endemic goiter is the most visible hallmark of severe iodine deficiency in these populations: in some villages, the prevalence of goiter may exceed 60–70% of all adults. Longstanding goiters are usually multinodular, and field observations

early enough during gestation (63, 125, 151).

The second parameter is preferential T_3 secretion, reflected by an elevated molar ratio of total T_3/T_4 in serum. It was mentioned previously that, owing to differences in the respective binding affinities of TBG for T_4 and T_3, the T_3/T_4 ratio tends to remain unchanged during pregnancy. Under conditions of a normal iodine intake, the serum T_3/T_4 ratio ranges between 10–22 ($\times 10^{-3}$) in euthyroid pregnant women (28, 59, 124, 162). In clinical and experimental conditions in which there is an increased stimulation of the thyroid gland, *e.g.* in GD (163) or after acute TSH stimulation (164), the T_3/T_4 ratio increases as the result of preferential T_3 production by the gland. The T_3/T_4 ratio also depends upon the extent of iodine depletion (*i.e.* a small intrathyroidal iodine pool) and has been shown to be useful for evaluating the degree of thyroidal stimulation in endemic iodine deficiency (165).

[Adapted with permission from D. Glinoer (36) © Plenum Publishing Corp.]

EXTRA - LOAD ON THYROIDAL MACHINERY



One of the controversies is what happens to Free Levels in Pregnancy.
Glinoer found that most pregnant women had levels that remained in the normal level for the assay used.

(46) in which the authors compared serum-free thyroid hormones in pregnant women at term and their newborns, using ten different commercially available kits. The data show the variability in free T_4 and T_3 concentrations obtained with different methods, but they also show that free hormone levels are always significantly lower than in nonpregnant women. Longitudinal studies based on reliable methodology (*i.e.* methods that are not influenced by changes in serum TBG and albumin levels) in large numbers of pregnant women without iodine deficiency have confirmed that serum free T_4 levels are lower by an average of 10–15% at delivery, in comparison with nonpregnant female subjects. Changes in free T_3 levels follow a parallel pattern. In most pregnant women, however, free hormone levels are maintained within the nonpregnant reference range (47, 48).

Women are considered to remain euthyroid during pregnancy, and the reason for the reduction (even though of small amplitude) in free hormone levels during the second half of gestation, observed in healthy women who have an adequate iodine supply, is not understood. The more drastic reduction in free hormone levels observed in women with iodine replex than usually considered. For instance, there are arguments to suggest that high estrogen levels over a prolonged period of time may modify the regulation of both basal and TRH-stimulated TSH release directly at the pituitary level (51–55). Also, as will be discussed later, high human CG levels down-regulate the TSH tone during early pregnancy. Finally, an apparent hypothyroid state might be compensated by an increased nuclear binding capacity for thyroid hormones in target cells (56).

The calculation of free T_4 indices (which is still very much in use in many countries) deserves a comment: these indices are established on the basis of the known physico-chemical properties of the thyroid hormone transport proteins, using the T_4/TBG ratio or the T_3 resin uptake test. One should remember that these estimations of free T_4 concentrations from indirect calculations do not always provide reliable results in pregnancy. The free T_4 index based on the T_3 resin uptake test shows only small fluctuations in pregnancy, while the index based on the T_4/TBG ratio yields values significantly lower than those found in nonpregnant women (23, 57).

HCG

HCG showing an inverse relation that supresses TSH by at least 0.5 mIU, This effect peaks at 10 weeks gestation (at the Pituitary). At the same time, HCG linearly increases Free T4 levels by net +30% to 10 weeks, a countering effect to TSH (at the Thyroid).

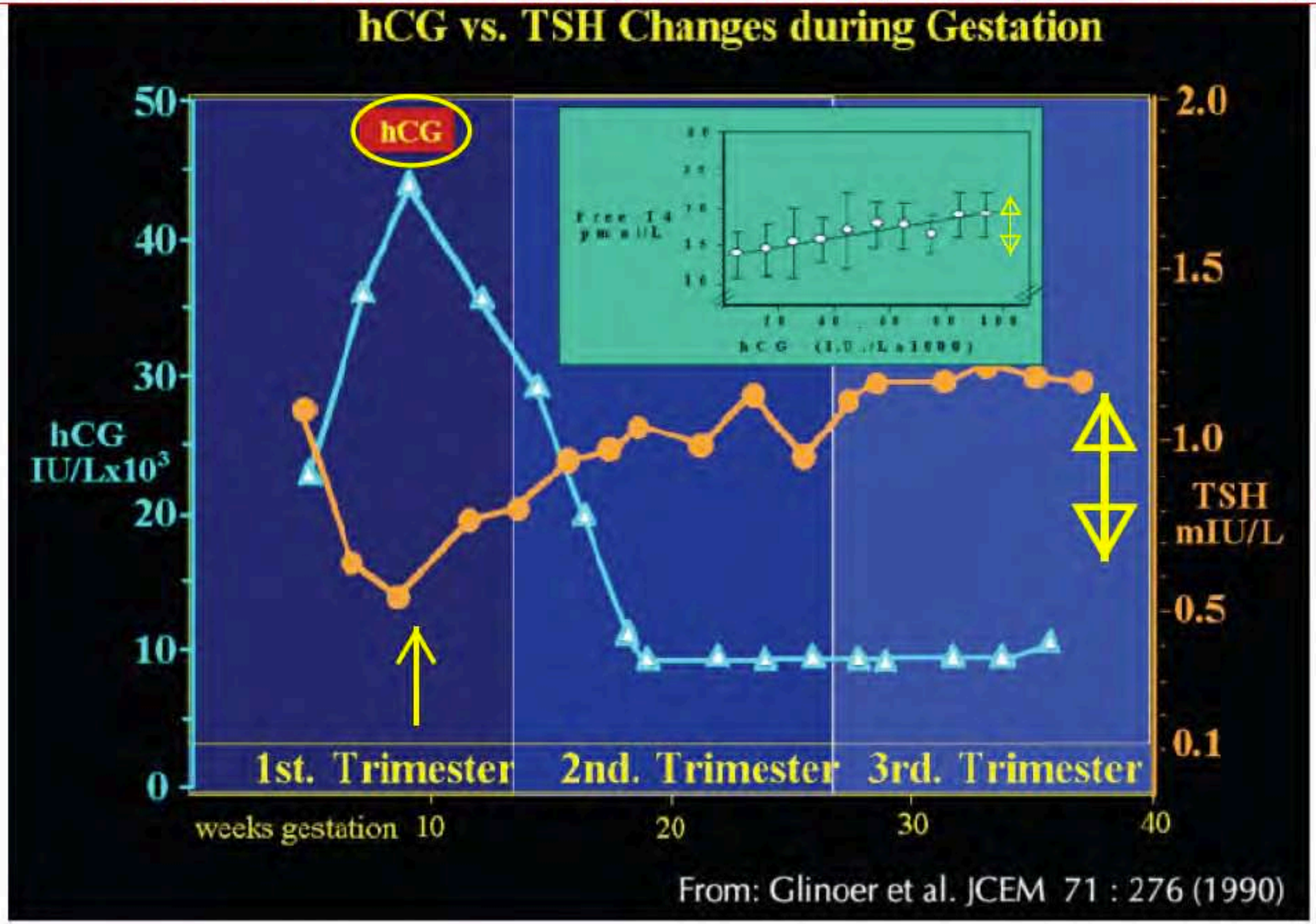


Figure 1. The pattern of serum TSH and hCG changes are shown as a function of

PREECLAMPSIA HYPERTENSION

BMJ. 2009; 339: b4336.
Published online 2009 Nov 17. doi: 10.1136/bmj.b4336: 10.1136/bmj.b4336
PMCID: PMC2778749
PMID: 19920004

Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study

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Accepted 2009 Jun 29.

Pre-eclampsia

TSH

FreeT3

Results In predelivery specimens of the Calcium for Pre-eclampsia Prevention cohort after the onset of pre-eclampsia, thyroid stimulating hormone levels increased 2.42 times above baseline compared with a 1.48 times increase in controls. The ratio of the predelivery to baseline ratio of cases to that of the controls was 1.64 (95% confidence interval 1.29 to 2.08). Free triiodothyronine decreased more in the women with pre-eclampsia than in the controls (case ratio to control ratio 0.96, 95% confidence interval 0.92 to 0.99). The predelivery specimens but not baseline samples from women with pre-eclampsia were significantly more likely than those from controls to have concentrations of thyroid stimulating hormone above the reference range (adjusted odds ratio 2.2, 95% confidence interval 1.1 to 4.4). Both in women who developed pre-eclampsia and in normotensive controls the increase in thyroid

They report that TSH increased 2 times as much and Free T3 decreased by 1/2 as much from baseline in Pre-Eclamptic Patients compared to normal Pregnant Patients.

We will have more to say about CardioVascular issues later.

etween baseline and predelivery specimens was strongly associated

y soluble fms-like tyrosine kinase 1 (P for trend 0.002 and <0.001,

Health Study, women with a history of pre-eclampsia in their first

UTERINE CONTRACTIONS

Am J Physiol Endocrinol Metab 304: E478–E485, 2013.
First published December 18, 2012; doi:10.1152/ajpendo.00346.2012.

Chronic levothyroxine and acute T_3 treatments enhance the amplitude and time course of uterine contractions in human

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Submitted 9 July 2012; accepted in final form 12 December 2012

Corriveau S, Pasquier JC, Blouin S, Bellabarba D, Rousseau É. Chronic levothyroxine and acute T_3 treatments enhance the amplitude and time course of uterine contractions in human. *Am J Physiol Endocrinol Metab* 304: E478–E485, 2013. First published December 18, 2012; doi:10.1152/ajpendo.00346.2012.—This study compares the functional consequences of levothyroxine (T_4) treatment during pregnancy as well as the acute affects of triiodothyronine (T_3) on spontaneous uterine contractile activities observed in vitro. Uterine biopsies were obtained from consenting women undergoing elective caesarean at term ($n = 28$). Spontaneous contractile activities from T_4-treated pregnant women ($n = 8$) were compared with control patients ($n = 20$) by isometric tension measurements. Effects of acute T_3 and T_4 on control tissues were also monitored. Area under the curve, amplitude, time to peak, duration, and frequency were quantified. In uterine strips from women treated for hypothyroidism, phasic uterine contractions of larger amplitude (+77%) were observed, with a prolonged duration at 90% relaxation (+138%) and reduced frequency (−55%) compared with values of the control group. The addition of exogenous T_3 in vitro on control strips induced a signif-

hypothyroidism properly during pregnancy, with the administration of adequate doses of T_4 (levothyroxine) (12, 21).

Uterine rhythmic contractile activities are essential for normal labor and delivery. Inadequate contractions can lead to labor abnormalities and will often result in C-sections with associated surgical risks for both mothers and newborns (35). The existence of a large-conductance calcium-activated potassium channel (BK_{Ca}) is demonstrated in pregnant human myometrium and is even shown to be involved in uterine quiescence (2, 17, 22). A modification in BK_{Ca} conductance is related to a change in the functionality of uterine contractile response (16, 25).

Several investigative groups have analyzed the effect of thyroid dysfunction on pregnant uterine tissue and in particular have observed an effect of low levels of T_4 on uterine contractile activities in gravid rats (24, 30). Hypothyroidism has also been found to reduce calcium channel function in pregnant rat uterine tissue (30). Given that calcium influx is an essential

Research Article

Free Thyroxine Level in the High Normal Reference Range Prescribed for Nonpregnant Women May Reduce the Preterm Delivery Rate in Multiparous

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Received 18 August 2011; Revised 23 October 2011; Accepted 24 October 2011

Academic Editor: Noriyuki Koibuchi

Here is some data on Thyroid and Preterm Delivery.
Torremonte et al reported a non-randomized retrospective study on Preterm Labor in Multiparas treated with Thyroid Hormone.
Free Thyroxine serum levels in the high-normal reference range for non-pregnant patients reduced Preterm Labor by -61%.

Preterm birth is the most common reason for perinatal morbidity and mortality in the western world. It has been shown that in euthyreotic pregnant women with thyroid autoimmune antibodies, L-Thyroxine replacement reduces preterm delivery rate in singleton pregnancies. We investigated in a nonrandomized retrospective observational study whether L-Thyroxine replacement, maintaining maternal free thyroxine serum level in the high normal reference range prescribed for nonpregnant women also influences the rate of preterm delivery in women without thyroid autoimmune antibodies. As control group for preterm delivery rate, data from perinatal statistics of the State of Baden-Württemberg from 2006 were used. The preterm delivery rate in the study group was significantly reduced. The subgroup analysis shows no difference in primiparous but a decline in multiparous by approximately 61% with L-Thyroxine replacement. Maintaining free thyroxine serum level in the high normal reference range prescribed for nonpregnant women may reduce the preterm delivery rate.

the thyroid gland as well [43].

In contrast to supraphysiological fT4 serum concentration seen in L-T4 replacement therapy, hyperthyroidism is defined as an excessive thyroid hormone production due to thyroid overactivity. The vast majority of cases of hyperthyroidism in pregnancy are induced by Graves' disease, toxic adenoma, or thyroid hormone resistance, where the negative feedback mechanism no longer functions. In these pathological conditions the overactive thyroid gland secretes both the metabolically inactive prohormone T4 and the metabolically highly active hormone T3 causing multiple symptoms. In Graves' disease, the intrathyroidal type-II deiodinase (D2), which activates thyroid hormone, has a 50 to 150 fold higher activity than in placenta and contributes significantly to the intrathyroidal T3 production and secretion [44]. Hyperthyroidism caused by Graves' disease and toxic multinodular goiter, high T3 concentrations are the result of excessive production and release from the thyroid gland and not of peripheral deiodination [45]. This explains why patients with Graves' disease or with toxic adenoma present symptoms of hyperthyroidism in contrast to patients taking L-T4 in a TSH suppressive dose. Additionally, in replacement therapy with a TSH suppressive L-T4 dose, T3 is derived completely from peripheral monodeiodination in the liver, kidney, or muscle because the thyroid gland is also suppressed. To achieve physiological levels of T3 in humans treated with L-T4, it is necessary to maintain fT4 levels at the higher end of the normal range [46, 47]. Only under pathological conditions, such as massive metastatic follicular thyroid cancer has T3 thyrotoxicosis by increased conversion of administered L-T4 been described [48]. L-T4 replacement

associated nausea was more pronounced, predominantly in the first trimester in only a few women. By reducing the L-T4 dosage, pregnancy-associated nausea resolved.

Their conclusion:

In summary, thyroid hormone replacement therapy aiming at holding maternal fT4 serum levels in the upper third of the reference range prescribed for nonpregnant women and controlling this therapy by determining fT4 seems to be safe and to have beneficial effects for both mother and fetus. In all probability it will reduce preterm birth rates in multiparous. These results have yet to be confirmed by further prospective randomized studies.

Acknowledgment

The authors want to thank Professor S. Kunz Chairman of the Advisory Board "Obstetrics and Gynecology" and Miss Susanne Rode from the Federal Office for Quality Assurance in Hospitals (GeQiK (R)) in Baden-Württemberg for providing us with data from the Perinatal Survey Baden-Württemberg. We would like to thank John M. Lindquist, Surgeon and General Practitioner, for language correction and proof-reading as native speaker.

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Myometrial contractile strain at uteroplacental separation during parturition

Dyer et al demonstrated some time ago that Placental Separation after Delivery has some extreme requirements:

1) Maximal Myometrial Contraction. Placental seperation requires increased radial strain of +450% and circumferential strain of -75%. Thyroxine Deficiency would likely produce sub-optimal contractions and delayed placental delivery.
2) Uterine Fetal and Amniotic Fluid volume normally inhibits these maximal contractions guarding against premature abruption.

T.W. Deyer, MS,[a] J.A. Ashton-Miller, PhD,[a, b, c] P.M. Van Baren, MD,[d] and M.D. Pearlman, MD[d, e]

Ann Arbor, Michigan

OBJECTIVE: A simplified geometric model of the uterine wall during the second and third stages of labor was created to estimate the magnitude of myometrial strain associated with the initiation of placental separation.

STUDY DESIGN: The uterine wall was modeled as an isovolumetric, incompressible spherical shell whose overall radius decreased and mural thickness increased on uterine muscle contraction after delivery of the fetus. Either a 3.5-MHz or a 5-MHz ultrasonography probe was used to measure the change in uterine mural thickness of 14 healthy patients from just before delivery to the time of initial separation of the placenta. The measured change in uterine wall thickness was then used to calculate its average radial and circumferential strain with a simple mathematic model.

RESULTS: Placental separation occurred at radial and circumferential strains (mean ± SD) of 450% ± 182% and –75% ± 11%, respectively. These strains are consistent with the known maximal contractile strains achievable by smooth muscle.

CONCLUSION: Placental separation is likely associated with maximal myometrial contractile strain. Before birth the presence of the fetal and amniotic fluid volumes usually renders such contractile strains unachievable, thereby helping to guard against premature placental separation. (Am J Obstet Gynecol 2000;183:156-9.)

ata***.pdf

American Thyroid Association (ATA)

Statement on Early Maternal Thyroidal Insufficiency:
Recognition, Clinical Management and Research Directions

The American Thyroid Association and the American Association of Clinical Endocrinologists have been educating us about Thyroid Insufficiency in Pregnancy for some time.

For over one hundred years, it has been clear that adequate maternal iodine nutrition and, more recently, adequate maternal thyroid hormone is necessary during and after pregnancy to assure the health of the mother and her offspring. Adequate maternal iodine nutrition must be maintained during pregnancy to meet the increased demand for thyroid hormone production that occurs with pregnancy. Maternal iodine supplies in the United States and in most of the developed world are now sufficient to prevent the occurrence of cretinism and severe mental retardation from iodine deficiency. However, there are still additional adverse outcomes for maternal health, maintenance of pregnancy, and child development that may occur as a result of overt maternal hypothyroidism, as well as subclinical hypothyroidism (normal serum thyroxine concentration and elevated serum TSH concentration), maternal hypothyroxinemia (depressed serum free thyroxine concentration), and the presence of thyroid autoantibodies.

Key research findings include:

They highlight wo Clinical findings:

- Pregnant mothers with overt or subclinical hypothyroidism are at an increased risk for premature delivery.

- Pregnant mothers with detectable thyroid autoantibodies and normal thyroid function are at an increased risk for miscarriage and for postpartum thyroid disease including thyroiditis, hyperthyroidism (Graves' Disease) and also hypothyroidism.

- The offspring of mothers with thyroid hormone deficiency or thyroid stimulating hormone elevation during pregnancy may be at risk of mild impairment in their intellectual function and motor skills.

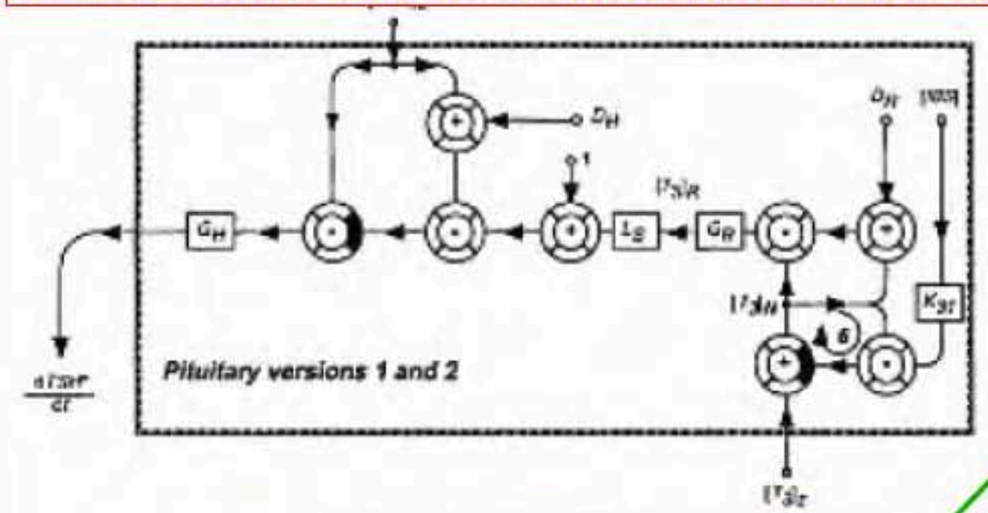
- Pregnant women being treated with thyroid hormone replacement often require a 30-50% increase in their thyroid hormone dose.

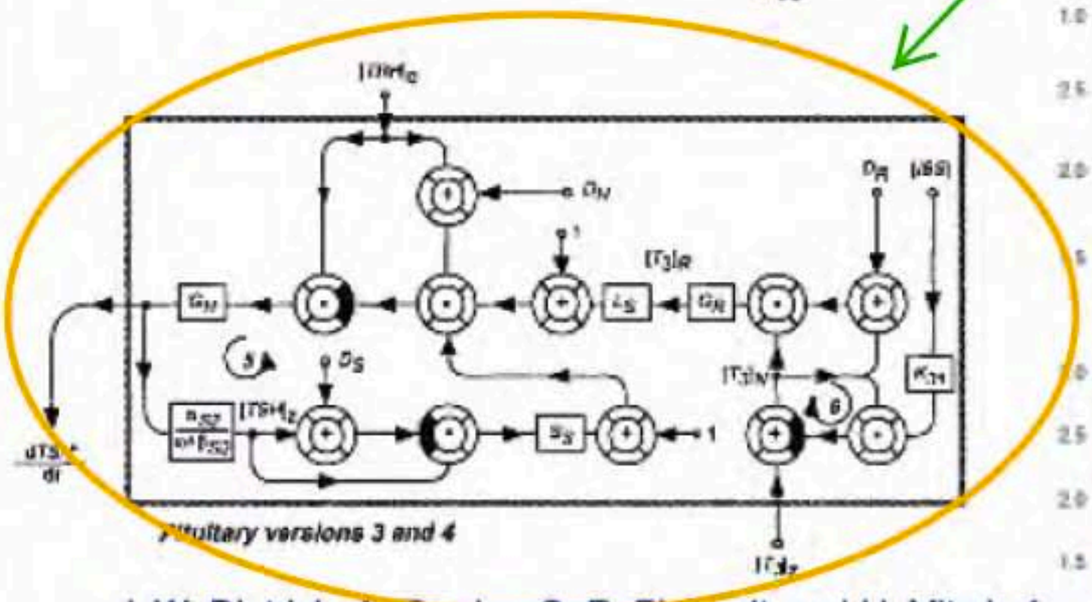
Taking a look at the Hormone Cortisol and Thyroid

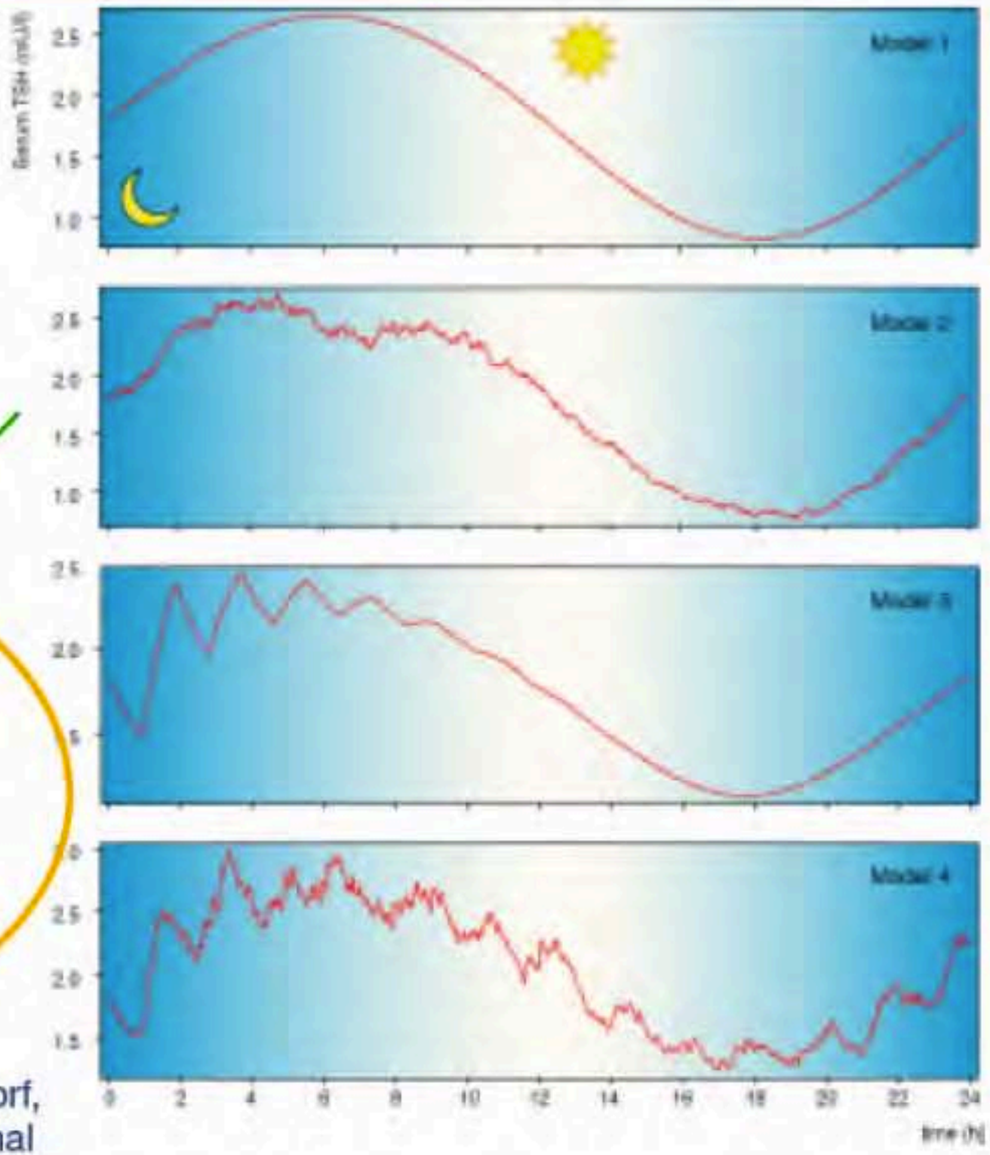
CORTISOL

Pulsatile TSH Secretion

Deitrich and Researchers in Germany have worked thru a rather complicated feedback control structure for Thyroid hormone production.

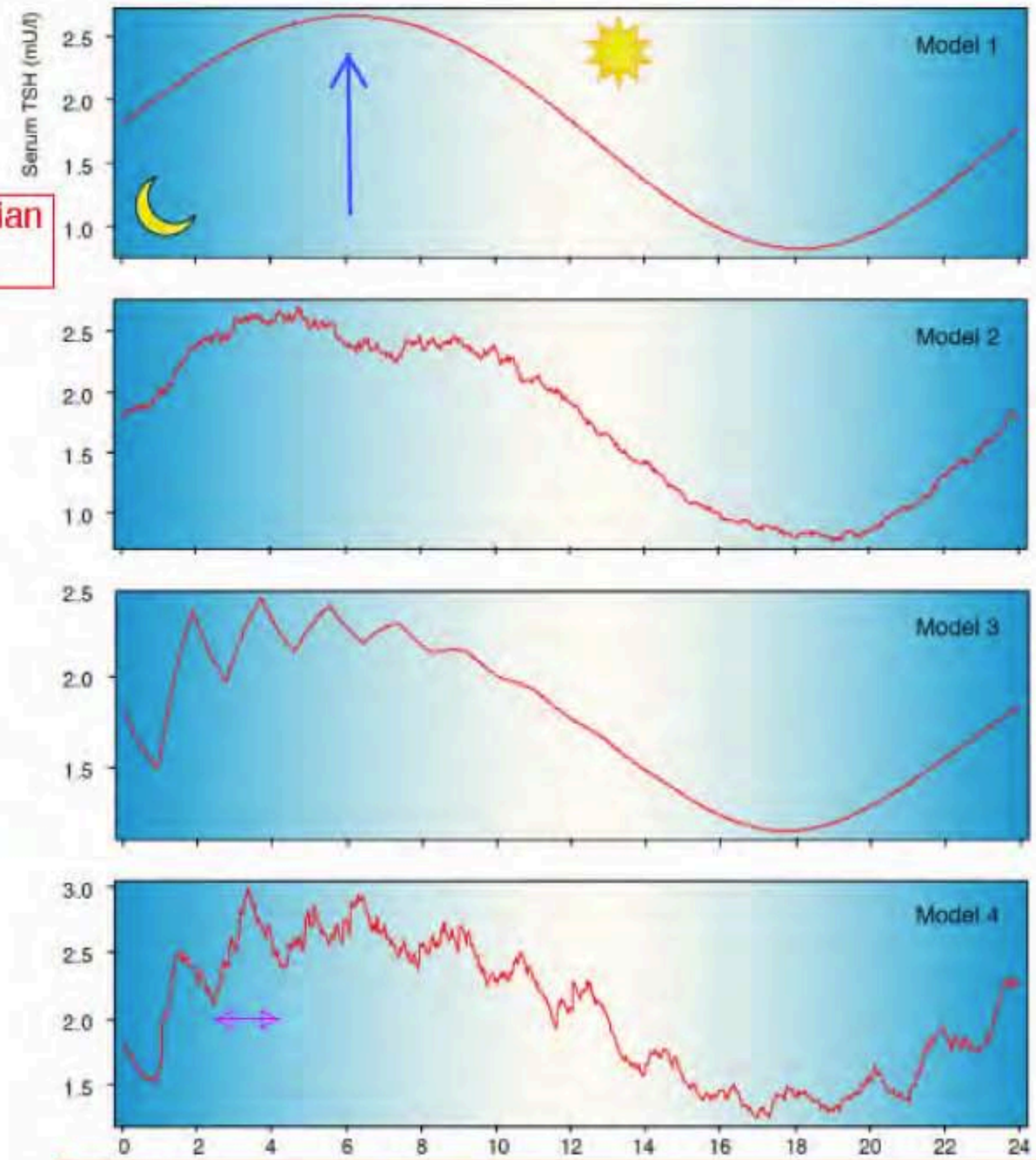






J. W. Dietrich, A. Tesche, C. R. Pickardt, and U. Mitzdorf, "Thyrotropic feedback control: evidence for an additional ultrashort feedback loop from fractal analysis," Cybernetics and Systems, vol. 35, no. 4, pp. 315–331, 2004.

Diurnal & Ultraradian Variations



Dietrich et al

In addition to the 12-hour diurnal cycle peaking near midnite (blue), they show a 2-hour ultra-short 2 (purple) and a several-minute pulsatile variation in TSH.

FIGURE 3 | Pulsatility of TSH secretion. Secretion of thyrotropin is subject to circadian and ultradian variation. Shown are results of computer simulations with circadian input only (model 1), additional stochastic afferences (model 2), additional ultrashort feedback of TSH secretion (model 3), and combined stochastic input and ultrashort feedback (model 4). Statistical properties and fractal geometry of model 4 is identical to that of natural time series, while the simpler models differ (10).

Functional Thyroid Disorders, Part I

By David Brady, DC, ND, DACBN

http://www.chiroweb.com/archives/18/07/03.html

Thyroid disorders are among the most commonly encountered metabolic disorders in private practice. The strong tendency for thyroid disorders to cause musculoskeletal symptoms make the understanding of these disorders even more critical to the practicing chiropractor.

David Brady has produced a nice discussion online about Thyroid Disorders, in particular Cortisol that is involved in Thyroid regulation as Alan McDaniel has described.

In this two-part article, I will attempt to provide the reader with an overview of thyroid disorders, along with suggestions on proper diagnosis and treatment. I will explain why conventional medicine does not recognize many cases of thyroid disease, and why many patients diagnosed with thyroid disease do not respond to conventional therapy. Part I will provide information on hypothyroidism, with Part II providing information on hyperthyroidism and thyroid cancer. A follow-up article on fibromyalgia will discuss the current state of research and treatment of this complex metabolic disorder, including the strong role that thyroid dysfunction plays in many cases of fibromyalgia and fibomyalgia-like disorders.

Normal amounts of Cortisol are necessary to Produce T3 from T4.
1) **Low-Cortisol** inhibits T3 from T4, decreasing the T3/T4 ratio.

A study which is much more cost effective than the Barnes test to evaluate adrenal function is the "adrenal stress index," a urinary and salivary test which measures cortisol at several times during the day, as well as DHEA. This test is offered by many functional medicine labs. Adrenal function is critical in the conversion of T4 to T3, which is 10 times more active than T4, in peripheral tissues. This conversion of T4 to T3 is influenced by adrenal cortisol, iron, selenium, B12 and magnesium. Too much cortisol in the system can induce a conversion of T4 to an improper form of T3 called reverse T3 (rT3), as shown in **Figure**

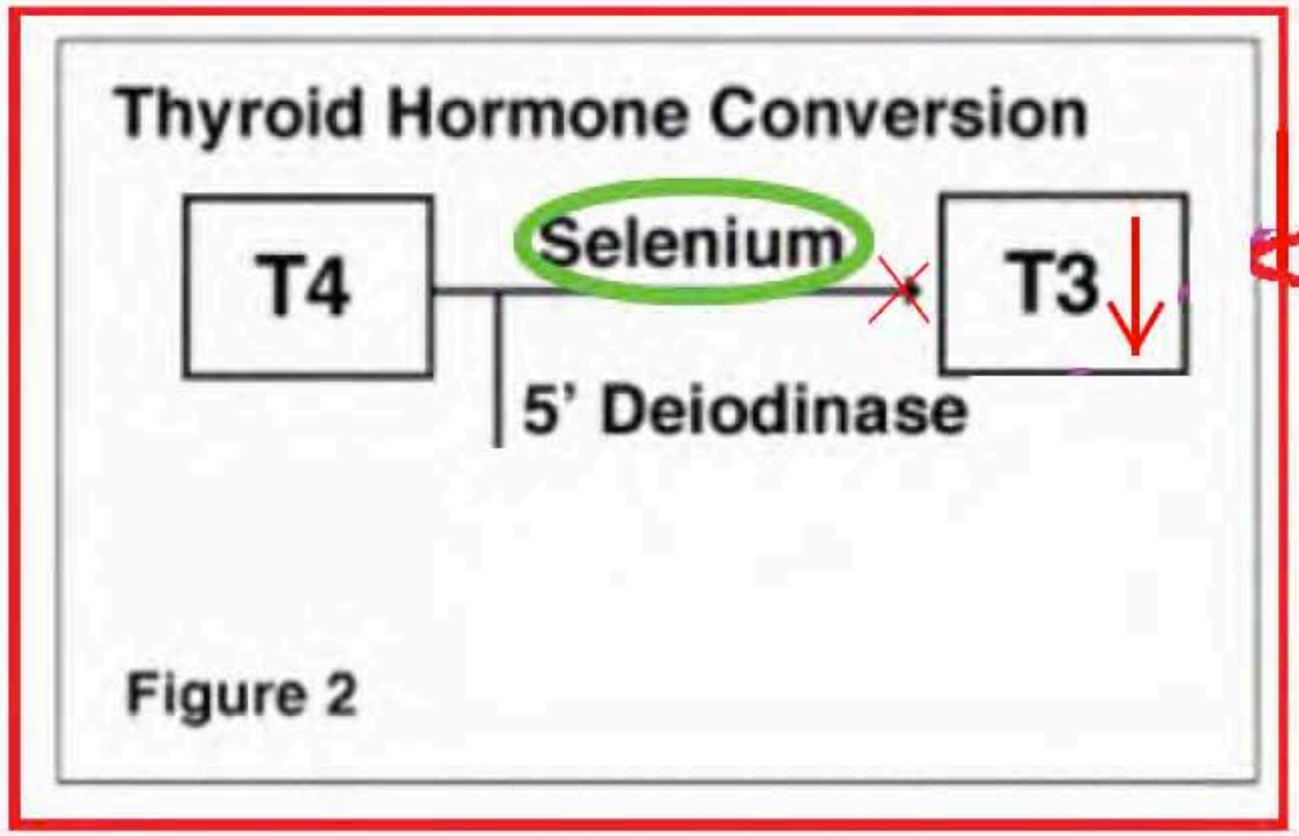


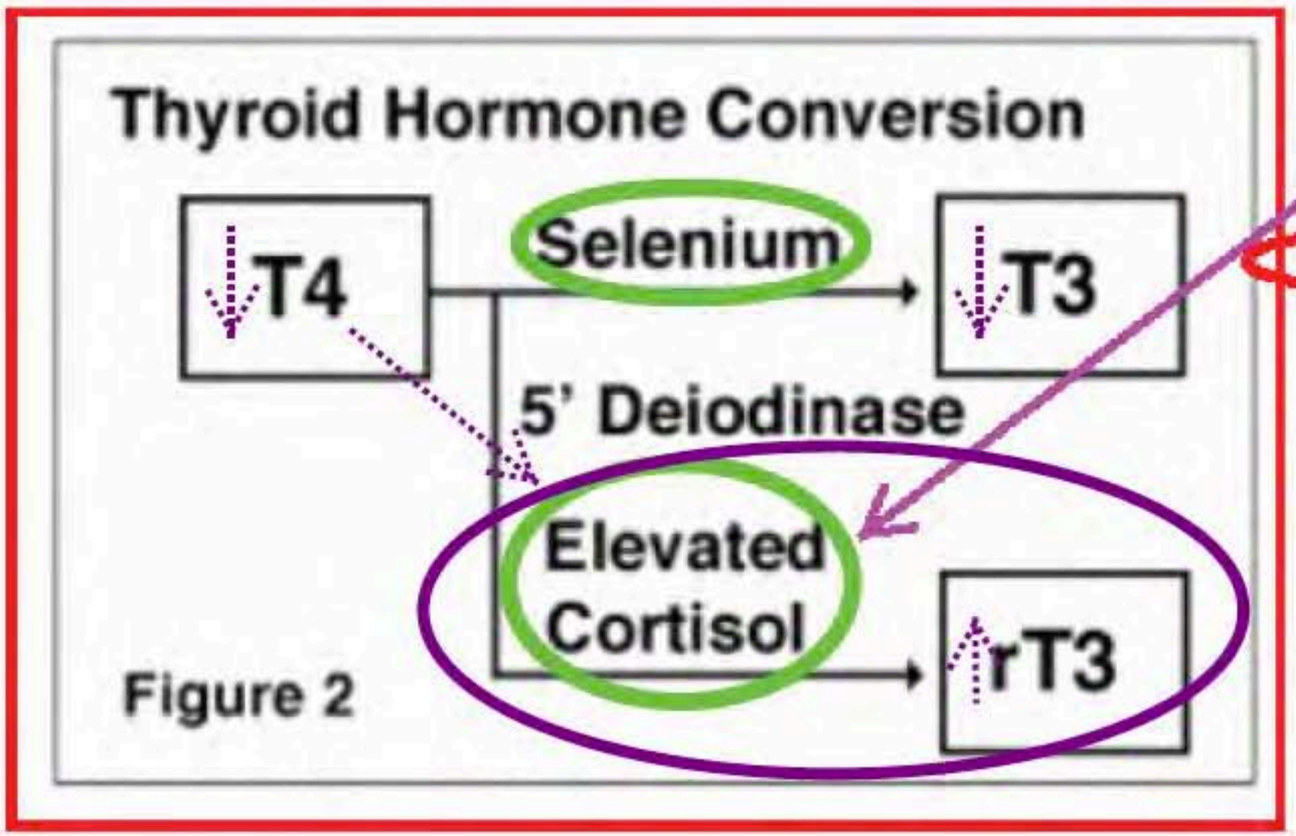
Figure 2

Lo Cortisol lowers T3

Reverse T3 is not recognized by peripheral thyroid hormone receptors and has little to no activity on cellular metabolism. Too little cortisol, or other nutrients listed above, can result in a slowed conversion of T4 to T3. Therefore, borderline hypoadrenalism or hyperadrenalism can result in functional hypothroidism and persistently low axillary temperatures, even when the patient is on significant dosages of exogenous thyroid hormones. Adrenal dysfunction can be addressed with stress reduction, proper sleep, the use of

Normal amounts of Cortisol are necessary to Produce T3 from T4.
2) **Hi-Cortisol** lowers both T4 and T3 levels, thru increased T4 degredation.

A study which is much more cost effective than the Barnes test to evaluate adrenal function is the "adrenal stress index," a urinary and salivary test which measures cortisol at several times during the day, as well as DHEA. This test is offered by many functional medicine labs. Adrenal function is critical in the conversion of T4 to T3, which is 10 times more active than T4, in peripheral tissues. This conversion of T4 to T3 is influenced by adrenal cortisol, iron, selenium, B12 and magnesium. Too much cortisol in the system can induce a conversion of T4 to an improper form of T3 called reverse T3 (rT3), as shown in **Figure**



Hi Cortisol lowers T4 & T3 (stress)

Reverse T3 is not recognized by peripheral thyroid hormone receptors and has little to no activity on cellular metabolism. Too little cortisol, or other nutrients listed above, can result in a slowed conversion of T4 to T3. Therefore, borderline hypoadrenalism or hyperadrenalism can result in functional hypothroidism and persistently low axillary temperatures, even when the patient is on significant dosages of exogenous thyroid hormones. Adrenal dysfunction can be addressed with stress reduction, proper sleep, the use of

1) Low Blood volume increases hormone concentration, so test levels may be interpreted in hypovolemic patients as normal when they are actually low.
2) As we will see later, some hypothyroid states produce adverse effects at the cellular level in the Pituitary and Hypothalamus, which decreases TSH. There is a chicken-egg problem here.

Serum studies often miss cases of mild hypothyroidism, because hypothyroid patients tend to have low blood volume, which produces a concentration effect, resulting in thyroid hormones being interpreted as normal when they are low. The TSH test, which would be expected to be high in cases of primary hypothyroidism, can also be falsely interpreted as normal since a hypothyroid state can produce adverse cellular effects upon the pituitary, resulting in decreased TSH production. The urinary excretion test of metabolites of thyroid and adrenal hormones, as well as electrolytes,[15] provides an alternative method of checking the function of the thyroid and adrenal glands. This test is preferred by many functionally minded clinicians for its ability to pick up milder cases of hypothyroidism, and its ability to relate thyroid to adrenal function. However, this test is quite expensive and has a very long turnaround time. It is important to evaluate adrenal status, since adrenal and thyroid function are so interdependent.

Since daylight affects Thyroid function, how about the seasons?

SEASON

It looks like Thyroid Levels fluctuate with season. An illustration in a Goat study shows a 50% higher T4, 50% lower TSH in Winter, reversed in the Summer. This may follow Cortisol Seasonal fluctuation, as Melatonin stimulation from the Pineal Gland in Sunlight lowers Cortisol.

Thyroid Fluctuates with Season

The J. Anim. Plant Sci. 27(3):2017

Winter
TT4-Hi / TSH&THI-Low

Summer
TT4-Low / TSH&THI Hi

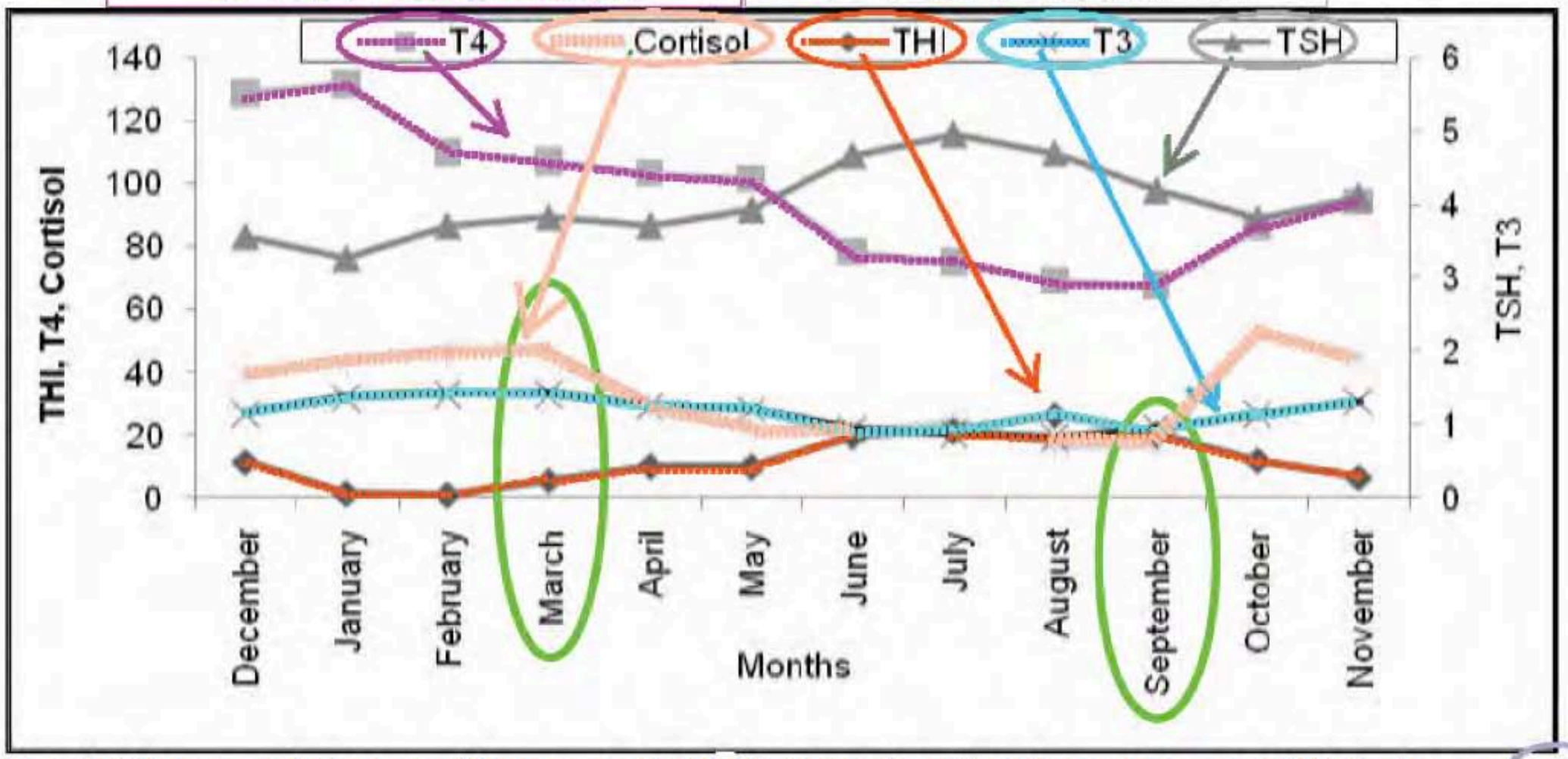


Figure 1. The annual change of the serum TSH, T_4, T_3 and cortisol hormones and THI in Angora goat.

Early in my career I counseled a patient on Nutrition. She looked at me saying, "You know a lot about Nutrition ...for a Doctor!"

In the MD world we have relegated Nutrition to non-Physicians. It turns out that has been unwise, and it is certainly not about the Food Pyramid.

NUTRITION

Measures of Iodine absorption show sharp declines in the past 50 years. 30 years ago Iran instituated Nationwide Iodine supplementation becuase of their identified Hypothyroid epidemic related to Iodine Deficiency.

REVIEW ARITICLE

Appropriate Iodine Nutrition in Iran: 20 Years of Success

Hossein Delshad, Ladan Mehran, and Fereidoun Azizi*

ocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract- Iodine is a trace element in the human body, its only known function is the synthesis of thyroid hormones. Effects of iodine deficiency, termed iodine deficiency disorders (IDD), include endemic goiter, hypothyroidism, cretinism, decreased fertility rate, increased infant mortality and mental retardation. 2.2 billion people worldwide are at risk for IDD. Of these, 30-70% have goiter and 1-10% have cretinism. Two decades ago the I.R. Iran was among the countries most severely affected by iodine deficiency, but during the last two decades has made much progress in the development of universal salt iodization strategies and IDD prevention, and since 1996 meets all WHO/UNICEF/ICCIDD criteria for the sustainable elimination of iodine deficiency.

Acta Medica Iranica 2010; 48(6): 361-366.

Key words: Iodine; deficiency; goiter thyroid hormones

Introduction

Iodine is a trace element present in the human body in

1846, Provost and Maffini proposed the theory of the role of iodine deficiency in the development of goiter. For the first time, Boussingault in Southern America

Introduction

Iodine is a trace element present in the human body in minute amounts. It's only confirmed role is the synthesis of thyroid hormones. Iodine is obtained primarily through the diet.

Dietary iodine is taken up readily from the gut in the form of iodide and then it is concentrated in the thyroid gland through blood circulation. In the follicle cells of the thyroid gland, 4 atoms of iodine are incorporated into each molecule of thyroxin (T_4) and 3 atoms into each molecule of triiodothyronine (T_3). These hormones are essential for neuronal and sexual development, growth and for regulating the metabolic rate, body heat, and energy (1). Consequently, severe iodine deficiency impairs thyroid hormonogenesis.

If the physiologic requirements of iodine are not met, a series of functional and developmental abnormalities occur, including thyroid function abnormalities, endemic goiter, cretinism, decreased fertility rate, increased perinatal death and infant mortality which are grouped under the general term of iodine deficiency disorders (IDD) (2-4).

1846, Provost and Maffini proposed the theory of the role of iodine deficiency in the development of goiter. For the first time, Boussingault in Southern America suggested the usage of iodized salt in the treatment of goiter, but information on the extensive usage of preventive methods was not available until the 20th century. Marine and Kimball achieved the first successful experience in the campaign against iodine deficiency in Ohio through prescription of iodized salt (7).

Worldwide, iodine deficiency is the leading cause of preventable mental retardation (8,9). Twenty-nine percent of the world's population, living in approximately 130 countries, is estimated to live in areas of iodine deficiency . Of these persons, 30-70% have goiter and 1-10% have cretinism (10-15).

The recommended dietary allowance (RDA) is 150 µg/day of iodine for adults and adolescents, 250 µg/day for pregnant and lactating women and 90-120 µg/day for children aged 1-11 years. The adequate intake for infants is 110-130 mcg/day (16- 20). Replacement of iodine is most easily achieved by using iodized salt. Salt has been selected as the medium for iodine supplementation

Iodine Nutrition:

In Pregnancy, it is now recommended that 150mcg of extra Iodine be taken every day.
In fact, 60% of Prescription Prenatal Vitamins contain ZERO mcg of Iodine.

Optimal iodine nutrition is particularly important during pregnancy and lactation. It appears by and large that iodine nutrition in the United States is adequate, although new data suggest that some women of reproductive age in the US may be at risk for slightly deficient intake. Iodine supplementation in pregnancy and during lactation is strongly encouraged. Total daily iodine intake is suggested to be at a level of 220 mcg/day for pregnant women and 290 mcg/day for lactating women, respectively. It is recommended that all pre-natal vitamin-mineral supplements for use during pregnancy contain at least 150 mcg/day iodine.

Physiol Rev 94: 355–382, 2014
doi:10.1152/physrev.00030.2013

THYROID HORMONE REGULATION OF METABOLISM

Back to the paper by Rashmi Mullur and Yan-Tun Liu. Their description of Thyroid Metabolism contains some fascinating findings.

1) Thyroid receptor subunits, as for other Nuclear Protein Receptors, demonstrate Isforms that modulate different function. Different tissues produce disparate function on stimulation.

2) Nutriition intake modulates Thyroid Hormones signaling, thru Epigentic modification of the histone complexes of DNA at promotor and inhibitor receptor complex sites. Nutrition thus causes changes in the DNA control of cellular function.

Rashmi Mullur, Yan-Yun Liu, and

Department of Medicine, VA Greater
David Geffen School of Medicine at UC

Mullur R, Liu Y-Y, E
94: 355–382, 2014. doi: 10.1152/physrev.00030.2013. Thyroid hormone (TH) is required for normal development as well as regulating metabolism in the adult. The thyroid hormone receptor (TR) isoforms, α and β, are differentially expressed in tissues and have distinct roles in TH signaling. Local activation of thyroxine (T_4), to the active form, triiodothyronine (T_3), by 5′-deiodinase type 2 (D2) is a key mechanism of TH regulation of metabolism. D2 is expressed in the hypothalamus, white fat, brown adipose tissue (BAT), and skeletal muscle and is required for adaptive thermogenesis. The thyroid gland is regulated by thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). In addition to TRH/TSH regulation by TH feedback, there is central modulation by nutritional signals, such as leptin, as well as peptides regulating appetite. The nutrient status of the cell provides feedback on TH signaling pathways through epigentic modification of histones. Integration of TH signaling with the adrenergic nervous system occurs peripherally, in liver, white fat, and BAT, but also centrally, in the hypothalamus. TR regulates cholesterol and carbohydrate metabolism through direct actions on gene expression as well as cross-talk with other nuclear receptors, including peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways. TH modulates hepatic insulin sensitivity, especially important for the suppression of hepatic gluconeogenesis. The role of TH in regulating metabolic pathways has led to several new therapeutic targets for metabolic disorders. Understanding the mechanisms and interactions of the various TH signaling pathways in metabolism will improve our likelihood of identifying effective and selective targets

nutrients

MDPI

Low protein diets and low essential amino acid intake leads to Thyroid Hormone abnormalities.

Review

Effects of Dietary Protein on Thyroid Axis Activity

Ewelina Pałkowska-Goździk *, Katarzyna Lachowicz and Danuta Rosołowska-Huszcz

Department of Dietetics, Faculty of Human Nutrition and Consumer Sciences, Warsaw University of Life Sciences WULS-SGGW, 159c Nowoursynowska Str., 02-776 Warsaw, Poland; katarzyna_lachowicz@sggw.pl (K.L.); danuta_rosolowska_huszcz@sggw.pl (D.R.-H.)

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Received: 15 September 2017; Accepted: 18 December 2017; Published: 22 December 2017

Abstract: Thyroid hormones (TH) are essential for the normal development and function of every vertebrate. The hypothalamic-pituitary-thyroid (HPT) axis is regulated to maintain euthyroid status. One of the most influential environmental factors that determines HPT axis activity is nutrition. Both food availability and substrate diversity affect thyroid hormone economy. The present paper aims to summarize literature data concerning the influence of the amount and the type of protein on thyroid axis activity. This review sheds light on the contribution of a low-protein diet or insufficient intake of essential amino acids to TH abnormalities. We believe that the knowledge of these dependencies could improve the results of nutritional interventions in thyroid axis disorders and enhance the efficiency of animal breeding.

Sympathetic Stimulation and Hypertension in the Pyridoxine-Deficient Adult Rat

CHERAMADATHIKUDYIL S. PAULOSE, SUBAH PACKER, AND NI

Vitamin B6 (Pyridoxine) Deficiency is associated with Hypertension, supression of TSH and other products at the Hypothalamus.
In rats, but not in Humans, repleting B6 normalizes Blood Pressure and TSH level, as well as Seratonin, Norepinephrine & Epinephrine.

SUMMARY Pyridoxal phosphate is the coenzyme of various decarboxylases involved in the formation of monoamine neurotransmitters such as γ-aminobutyric acid, serotonin, dopamine, and norepinephrine. Adult male Sprague-Dawley rats placed on a pyridoxine-deficient diet for 8 weeks showed significant hypertension compared with pyridoxine-supplemented controls. Hypothalamic contents of pyridoxal phosphate, γ-aminobutyric acid, and serotonin in the pyridoxine-deficient rats were significantly lower than those in pyridoxine-supplemented controls. Hypertension was associated with sympathetic stimulation. Treatment of pyridoxine-deficient rats with a single dose of pyridoxine (10 mg/kg body weight) reversed the blood pressure to normal levels within 24 hours, with concomitant restorations of hypothalamic serotonin and γ-aminobutyric acid as well as the return of plasma norepinephrine and epinephrine to normal levels. Also, pyridoxine treatment reversed the hypothalamic hypothyroidism observed in pyridoxine-deficient rats. These results indicate an association between pyridoxine deficiency and sympathetic stimulation leading to hypertension.
(Hypertension 11: 387–391, 1988)

KEY WORDS • pyridoxine • serotonin • γ-aminobutyric acid • norepinephrine • blood pressure

THE crucial role played by pyridoxine in the nervous system is evident from the fact that the putative monoamine neurotransmitters such as γ-aminobutyric acid (GABA), serotonin (5-

areas of the rat brain.[4–6] We have also demonstrated the hypothalamic origin of hypothyroidism in the pyridoxine-deficient rat.[7] Various reports have indicated a relationship between pyridoxine status and hypertension

Thyroid function during B-vitamin supplementation of patients on antiepileptic drugs

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Received 16 March 2005; received in revised form 20 May 2005; accepted 5 Januar
Available online 8 Februar 2006

Vitamin B Deficiency appears to lower TSH at the Pituitary, by inhibiting TRH (Thyroid Releasing Hormone) secretion at the Hypothalamus.

Anti-epileptics tend lower B-vitamins. Supplement in Humans on anti-epileptic drugs does not normalize Thyroid levels, in contrast to animals Thyroid does normalize.

Abstract

Objectives: Patients on antiepileptic drugs (AEDs) may have low serum concentrations of thyroxine, with or without a compensatory increment in thyroid-stimulating hormone (TSH). Furthermore, patients on AEDs often have hyperhomocysteinemia and low concentrations of vitamins B_6, B_2 and folate. Previously, an inverse relationship between thyroxine and homocysteine concentrations has been observed. In animals, deficiency of vitamin B_6 has been found to impair the hypophyseal release of TRH. We have studied the effect of B-vitamin supplements on thyroid function in patients on AEDs.

Design and methods: Thirty-two patients on AEDs were identified with hyperhomocysteinemia and low folate, B_6 and B_2. They were supplemented with pyridoxine, riboflavin and folic acid for 30 days.

Results: At baseline, the patients had low serum concentrations of free thyroxin and slightly elevated TSH. On day 30 of the B-vitamin supplements, homocysteine had decreased, however, the thyroid parameters remained unchanged.

Conclusions: Hyperhomocysteinemic patients on AEDs have indications of hypothyroidism, however, supplementation with B-vitamins does not improve their thyroid function.

Keywords: Carbamazepine; Epilepsy; Phenytoin; Pyridoxal 5-phosphate; Riboflavin; Thyroid-stimulating hormone; Thyroxine; Triiodothyronine

Introduction

Low serum concentrations of thyroxine and normal or slightly elevated serum thyroid-stimulating hormone (TSH) have been observed in patients on antiepileptic drugs (AEDs) [1–4]. Most patients were clinically euthyroid, despite low

of thyroid function are not fully understood. Patients on inducer AEDs appear to have an accelerated degradation of thyroxine in extra-thyroidal tissues, primarily the liver [9–11]. Furthermore, AEDs may alter the hypothalamic feedback response to low thyroxine, causing inadequate secretion of thyroid-stimulating

Effects of tri-iodothyronine, cortisol and transcriptional inhibitors on vitamin D3-enhanced thyrotrophin secretion by rat pituitary cells in vitro ...

http://joe.endocrinology-journals.org/cgi/content/abstract/121/3/451

Getting Started Latest Headlines

Journal of Endocrinology, Vol 121, Issue 3, 451-458

Work by MC d'Emden and JD Wark some time ago indicated that Vitamin D influences Thyroid Function.
-Vitamin D3 enhances TRH secretion.
-This is modulated by T3.

Articles

Effects of tri-iodothyronine, cortisol and transcriptional inhibitors on vitamin D3-enhanced thyrotrophin secretion by rat pituitary cells in vitro

MC d'Emden and JD Wark

The hormone 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) has been shown to selectively enhance agonist-induced TSH release in the rat thyrotroph in vitro. The interaction of 1,25-(OH)2D3 with tri-iodo-thyronine (T3) and cortisol was studied in primary cultures of dispersed anterior pituitary cells. TRH (1 nmol/l)-induced TSH release over 1 h was enhanced by 70% (P less than 0.01) following exposure to 10 nmol 1,25-(OH)2D3/l for 24 h. Pretreatment with T3 (1 pmol/l-1 mumol/l) for 24 h caused a dose-dependent inhibition of TRH-induced TSH release. Net TRH-induced TSH release was inhibited by 85% at T3 concentrations of 3 nmol/l or greater. Co-incubation with 1,25-(OH)2D3 resulted in enhanced TRH-induced TSH release at all T3 concentrations tested (P less than 0.001). The increment of TRH-induced TSH release resulting from 1,25-(OH)2D3 pretreatment was equivalent in the presence or absence of maximal inhibitory T3 concentrations. At 1 nmol T3/l, there was a two- to threefold relative increase in 1,25-(OH)2D3-enhanced TRH-induced TSH release. Incubation with cortisol (100 pmol/l-100 nmol/l) had no effect on basal or TRH-induced TSH release, nor did it alter 1,25-(OH)2D3-enhanced TRH-induced TSH release when added 24 h before, or at the time of addition of 1,25-(OH)2D3. Actinomycin D and alpha-amanitin abolished 1,25-(OH)2D3-enhanced TSH secretion. These data demonstrate that the action of 1,25-(OH)2D3 in the thyrotroph required new RNA transcription, and was not affected by cortisol. In the presence of T3, the response of the thyrotroph to TRH induced by 1,25-(OH)2D3 was increased. We have shown that 1,25-(OH)2D3 has significant effects on the action of TRH and T3 in vitro. These findings support the proposal that 1,25-(OH)2D3 may modulate TSH secretion in vivo.

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Done

Acta Endocrinol (Copenh). 1986 Nov;113(3):329-34

Thyroid hormones modulate Steroid Hormones. As an example, DHEAS level is found to be lower in Hypothyroid Patients.

Effect of vitamin D3 loading and thyroid hormone replacement therapy on the decreased serum 25-hydroxyvitamin D level in patients with hypothyroidism.

Bársony J, Lakatos P, Földes J, Fehér T.

Abstract

Twelve hypothyroid subjects, 13 healthy and 12 healthy women with a slight deficiency of vitamin D were studied to distinguish seasonal changes from the thyroxine-dependent ones. Serum 25-hydroxyvitamin D levels of hypothyroid patients were lower than those of healthy individuals when the sera were obtained in the autumn. In hypothyroid patients a single oral dose of 100,000 IU vitamin D3 resulted in a smaller increase in 25-hydroxyvitamin D concentration than in controls having subclinical exogenous vitamin D deficiency. Substitution therapy with thyroid hormone, started in our study always in autumn, increased the 25-hydroxyvitamin D concentration in hypothyroid patients, which was opposite to the autumn-to-spring variation of this hormone observed in healthy controls. The increase of 25-hydroxyvitamin D, dehydroepiandrosterone and its sulphate values following substitution therapy in the hypothyroid patients may indicate that thyroid hormone(s) is (are) involved in the regulation of steroid hormone synthesis.

This brings us to the the Sex Steroids.
A look at Thyroid influence on Progesterone.

SEX HORMONES

T3 stimulates progesterone.pdf

1 / 1 Sticky Note Text Edits Show

Progesterone and T3

ANSWER FROM 2 SOURCES

Thyroid and Progesterone modulate each other in both directions.
T3 stimulates Progesterone at the Ovary.
Progesterone stimulates T3 and T4 at the Thyroid.

T3 significantly stimulated progesterone release **(P < 0.01)** from luteal cells and this could be blocked by cycloheximide, indicating a protein mediator for the T3 effect.

T3 > P

Progesterone receptors bind with the hormone and the gland responds by producing T3 and T4.

When progesterone deficiency occurs, the hormone is unable to bind to receptors in the thyroid gland.

P > T3, T4

Both Directions

Thyroid hormone stimulates progesterone release from human ...

ncbi.nlm.nih.gov

Progesterone and Thyroid Relationship - Thyroid Advisor

thyroidadvisor.com

A turn to Thyroid's role in Infection.

INFECTION

Thyroid hormone Structures

Thyroxine T4 is a bi-phenol that contains 4 Iodine atoms.

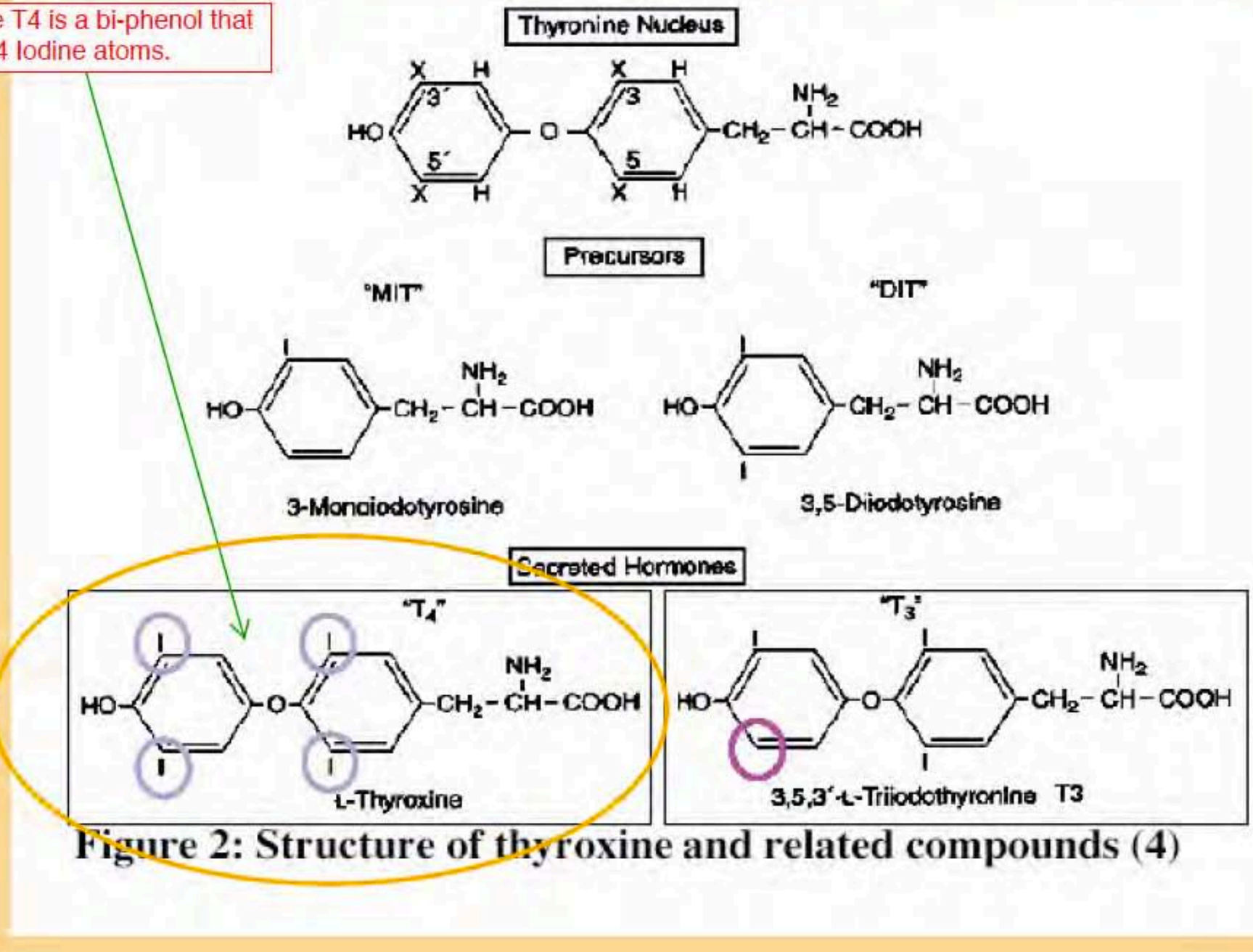


Figure 2: Structure of thyroxine and related compounds (4)

Thyroid hormone Structures

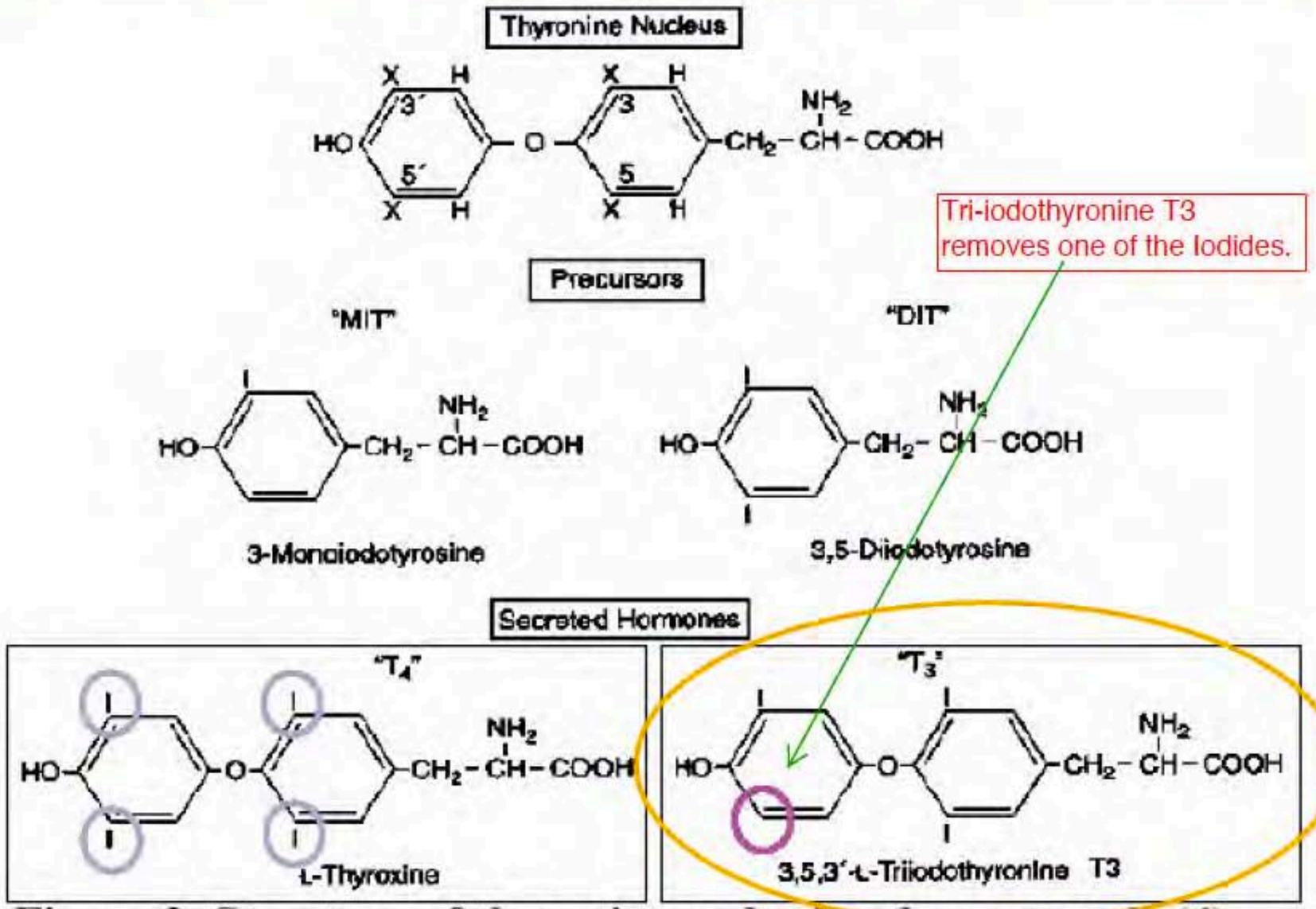


Figure 2: Structure of thyroxine and related compounds (4)

Structural mechanism for the carriage and release of thyroxine in the blood

TBG-T4 -> TBG + T4

Zhou and al presented the structure of TBG recently. TBG is a carrier protein that binds most of T4 (99% TBG-T4) releasing it to keep an adequate supply of unbound Free (T4)

Aiwu Zhou*, Zhenquan Wei, Randy J. Read, and Rob

Departments of Haematology and Medicine, Cambridge Institute fo
Cambridge CB2 2XY, United Kingdom

Edited by Robert Huber, Max Planck Institute for Biochemistry, Martinsried, Germany, and approved July 14 2006 (received for review May 17, 2006)

The hormones that most directly control tissue activities in health and disease are delivered by two noninhibitory members of the serpin family of protease inhibitors, thyroxine-binding globulin (TBG) and corticosteroid-binding globulin. The structure of TBG bound to tetra-iodo thyroxine, solved here at 2.8 Å, shows how the thyroxine is carried in a surface pocket on the molecule. This unexpected binding site is confirmed by mutations associated with a loss of hormone binding in both TBG and also homologously in corticosteroid-binding globulin. TBG strikingly differs from other serpins in having the upper half of its main β-sheet fully opened, so its reactive center peptide loop can readily move in and out of the sheet to give an equilibrated binding and release of thyroxine. The entry of the loop triggers a conformational change, with a linked contraction of the binding pocket and release of the bound thyroxine. The ready reversibility of this change is due to the unique presence in the reactive loop of TBG of a proline that impedes the full and irreversible entry of the loop that occurs in other serpins. Thus, TBG has adapted the serpin inhibitory mechanism to give a reversible flip-flop transition, from a high-affinity to a low-affinity form. The complexity and ready triggering of this conformational mechanism strongly indicates that TBG has evolved to allow a modulated and targeted delivery of thyroxine to the tissues.

placement of the binding site of thyroxine within a β-barrel of TBG. This presumed site has been consistently backed by a series of modeling, linkage, and domain-exchange studies (12–15), but it does not explain why thyroxine is released by the serpin conformational change or why mutations distant to the site result in a loss of binding. It also does not explain how a conformational change that is irreversible in other serpins has been adapted by TBG to give the reversible binding of thyroxine and to allow its tissue-targeted release. To answer these questions, we determined the crystal structure of TBG bound to thyroxine.

Results and Discussion

Plasma-derived TBG is heterogeneous and resistant to crystallization, so the recombinant nonglycosylated form of the molecule was prepared by expression in *Escherichia coli*, with subsequent crystallization and x-ray diffraction as detailed in *Materials and Methods*. The resulting 2.8-Å structure of TBG complexed with tetra-iodo thyroxine is shown in Fig. 1. The molecule is well ordered in the structure with an R factor of 0.235 and R_{free} of 0.284 and with good geometry (for statistics, see Table 2, which is published as supporting information on the PNAS web site) except for three residues at the N terminus, one at the C

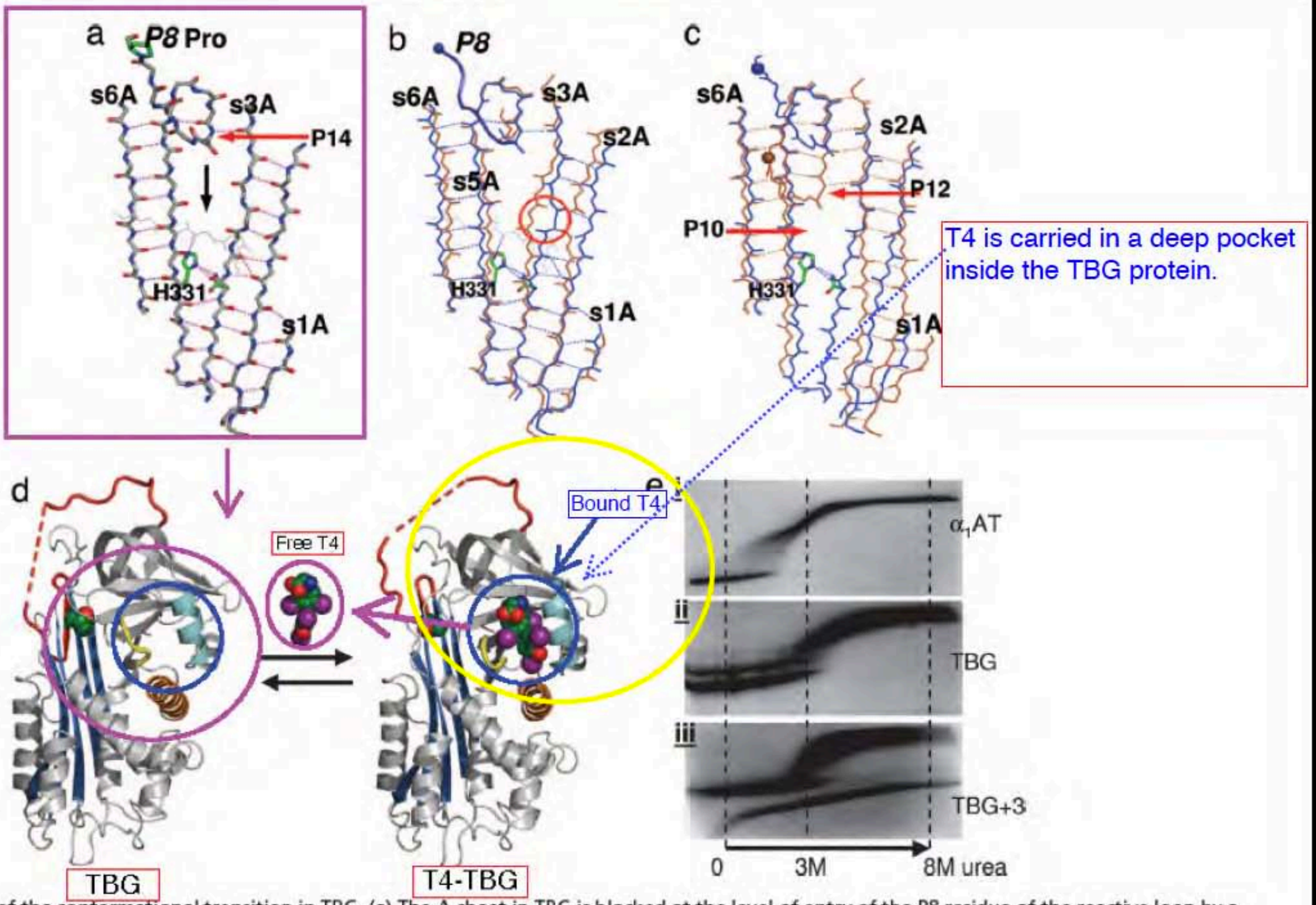
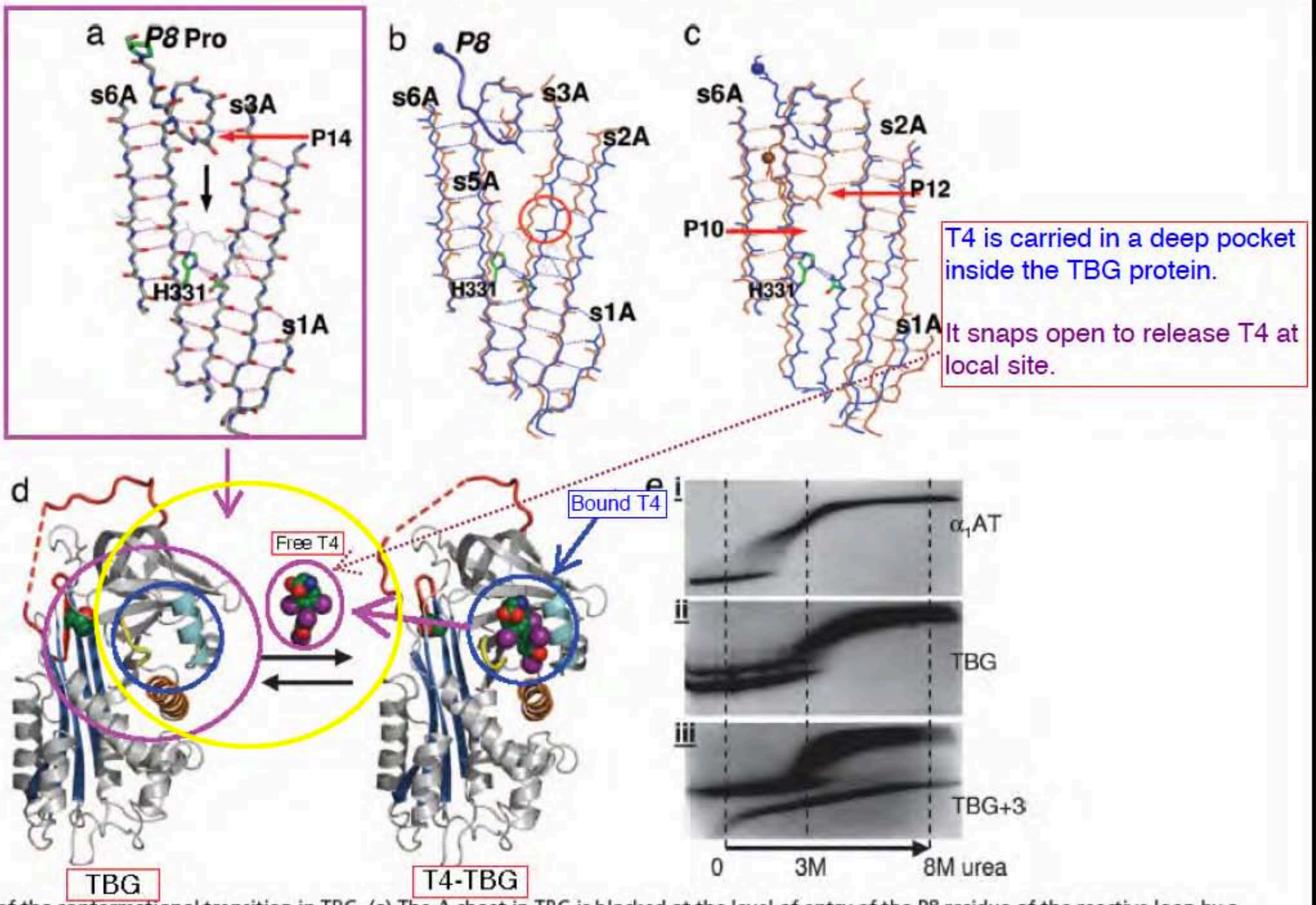


Fig. 5. Reversibility of the conformational transition in TBG. (*a*) The A-sheet in TBG is blocked at the level of entry of the P8 residue of the reactive loop by a



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The opening of the TBG "Catchers Mitt" can be stimulated by local proteases that hydrolyse a single amino acid site. These proteases are produced locally by White Blood Cells, releasing Free T4 outside the cell. Iodide levels also increase inside the WBC.

I[illegible]flammatory process might have an important p[illegible]ed by inflammation caused hormone release from CBG and t[illegible]has known anti-inflammatory action. The potential role of increased T_4 or T_3 release from TBG is less obvious. Over 30 yr ago, Klebanoff (15) explored the antibacterial effect of iodine in a myeloperoxidase system. Although iodide was 200 times more effective than chloride, the much larger available concentration of chloride made the role of iodide less attractive. Subsequent experiments by Klebanoff and Green (16), however, demonstrated that activated leukocytes rapidly degrade T_4 and T_3 and greatly increase the iodide concentration within the cell. Others demonstrated an accelerated disappearance of T_4 and T_3 from plasma in pneumococcal infection in man (17) and in monkeys (18). It is tempting to postulate, as Jirasakuldech *et al.* (9) have done, that localized release of T_4 from TBG by limited proteolysis might play a role in pathological, and even in physiological, processes. Very rough calculations suggest that release in a few hours of about half of the bound T_4 in a relatively small volume of infected tissue might, if leukocytes can deiodinate T_4 quickly, provide enough iodide and iodine for significant bactericidal activity. An important corollary is that this release would take place at specific anatomical sites in response to some initiating event, such as an infection or an inflammatory response to trauma. (See Ref. 19 in their report.) The authors also raise the interesting possibility that this phenomenon may explain the increased free to bound T_4 ratio and other abnormalities seen in nonthyroidal illness, and the rapid fall in serum T_4 that may occur during acute inflammation [their Refs. 26 and 20, and work from their own laboratory (Ref. 11 , still in press)].

Jacob Robbins The Journal of Clinical Endocrinology & Metabolism Vol. 85, No. 11 3994-3995

Iodide is an anti-bacterial and acts as an antiseptic.

Local Iodinases rapidly convert Free T4 to T3, releasing Iodide outside the WBC, as well increasing Iodide levels inside the WBC.

Secreted Hormones

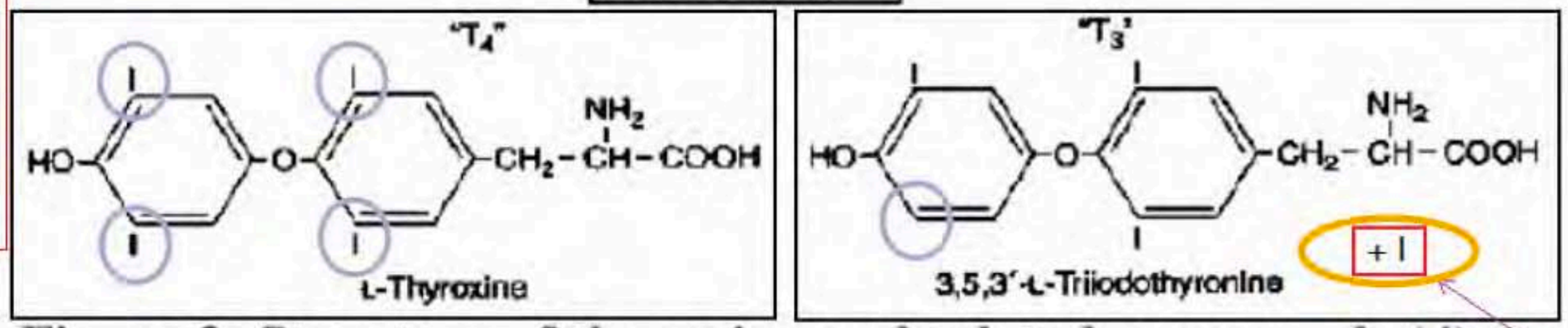

Figure 2: Structure of thyroxine and related compounds (4)

T4 ---> T3 + I

local antiseptic

Psychiatric illness is a serious problem.

I want to touch on Thyroid Hormones in Depression and Anxiety.

MOOD

Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor α1 can be ameliorated by T3 treatment

César Venero,[1,4] Ana Guadaño-Ferraz,[2,4] Ana Isabel Herrero,[1] Kristina Nordström,[3] Jimena Manzano,[2] Gabriella Moreale de Escobar,[2] Juan Bernal,[2,6] and Björn Vennström[3,5]

[1]Psychobiology Department, Universidad Nacional de Educación a Distancia, 28040 Madrid, Spain; [2]Instituto de Investigaciones Biomédicas "Alberto Sols," CSIC-UAM, 28029 Madrid, Spain; [3]Department of Cell and Molecular Biology, Karolinska Institute, S-171 77 Stockholm, Sweden

In this adult rat model by Venero et al with a Thyroid Receptor Mutation that elicits anxiety, memory, and locomotor dysfunction, T3 treatment was necessary and sufficient to normalize the deficits.
This correlates with GABA neuron strutural changes in the Hypocampus, and improved cerebellar development.

the role of unliganded thyroid hormone receptor α1 (TRα1) in neuronal tissues, we introduced a mutation into the mouse TRα1 gene that lowers affinity to thyroid hormone (TH) 10-fold. The resulting heterozygous mice exhibit several distinct neurological abnormalities: extreme anxiety, reduced recognition memory, and locomotor dysfunction. The anxiety and memory deficiencies were relieved by treatment with high levels of TH in adulthood, an effect that correlated with a normalization of GABAergic inhibitory interneurons in the hippocampal CA1 region. In contrast, a post-natal TH treatment was necessary and sufficient for ameliorating the adult locomotor dysfunction. Here, the hormone treatment normalized the otherwise delayed cerebellar development. The data thus identify two novel and distinct functions of an unliganded TRα1 during development and adulthood, respectively.

Published by Cold Spring Harbor Laboratory Press April 2005

[*Keywords*: Thyroid hormones; nuclear receptors; cerebellum; hippocampus; GABA]

Thyroid affects the Sympathetic System (Norepinephrine)

Close interaction between thyroid hormones and the noradrenergic system also has been examined. Brain T_3 is primarily localized in the central noradrenergic systems, with axonal anterograde transport of T_3 from the locus ceruleus. T_3 is processed and accumulated in the noradrenergic system, carried via axonal transport, then delivered from nerve cell bodies to its neuronal targets.[5,7] T_3 thus functions as a coneurotransmitter with norepinephrine.

Cellular energy metabolism. We recently reported that thyroid hormones' antidepressant effect may be related to brain cellular energy metabolism. Thyroid hormones increase cellular levels of adenosine triphosphate (ATP) and phosphocreatine (PCr) in the hypothyroid brain.[5] Brain imaging —phosphorus-31 nuclear magnetic resonance spectroscopy (31P-MRS)—of subjects with MDD shows decreased brain levels of ATP and increased PCr.[21]

Our group showed that the antidepressant effect of T_3 augmentation of SSRIs is correlated with significant increases in ATP levels and decreases in PCr. This effect—which appears to represent re-normalization of brain bioenergetics in treatment responders—did not occur in nonresponders (Iosifescu et al, presented at APA, 2004).

The effect of thyroid hormones on bioenergetic metabolism is compatible with the hypothesized effects on noradrenergic and serotonergic systems.[5,7] These mechanisms may represent different links in the same chain of events.

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▼ References

The Cardiology Community appears to ignore the amazing evidence that Thyroid improves Cardiac function.

CARDIOVASCULAR

J Clin Endocrinol Metab. 2008 April; 93(4): 1172–1174.
doi: 10.1210/jc.2008-0291
PMCID: PMC2291496

Thyroid Hormone Treatment to Mend a Broken Heart

T3 Triiodothyronine

Irwin Klein and Sara Danzi

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Beginning in development and extending to adult physiology, a close relationship exists between the thyroid gland and the heart (1). Both thyroid and cardiac anlage migrate together during ontogeny. This intimacy continues into adult life when changes in thyroid function produce the classic cardiovascular and hemodynamic findings of hyper- and hypothyroidism (2). The important physiological link is affirmed by the predictable changes in cardiovascular function that occur across the entire range of thyroid disease states. Hyperthyroidism produces increased heart rate and cardiac contractility and lowers systemic vascular resistance resulting in a marked increase in cardiac output (2,3). In contrast, hypothyroidism results in impaired left ventricular (LV) contractile and relaxation functions, increased systemic vascular resistance, and low cardiac output, similar to that seen with congestive heart failure (1,4,5). There are numerous parallels between hypothyroidism and heart failure, including decreased serum thyroid hormone, especially T_3 levels (6). The significance of this is reinforced by studies of biopsied LV myocardium showing alterations in expression of thyroid hormone-responsive genes that are similar in hypothyroidism and heart failure. These changes include the genes encoding the proteins that regulate calcium cycling, β1-adrenergic receptors, and the myosin heavy chain contractile proteins (4).

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serum T_3 levels in heart failure and a variety of other cardiac disease states (6,7,8). In both children and adults undergoing cardiac surgery with cardiopulmonary bypass and in patients after uncomplicated acute myocardial infarction, there is a predictable fall in serum T_3 (9,10,11). Controversy persists about the significance of these changes in serum thyroid hormone levels (12). It has been suggested that a low T_3 level after an acute myocardial infarction or in the course of chronic cardiac disease is somehow adaptive, reducing metabolic demands during these nonthyroidal illnesses. At the same time, multiple reports have demonstrated potential benefit of T_3 replacement in patients undergoing cardiac surgery, with acute myocarditis and, in the current issue of *JCEM*, with heart failure (8,9,10,13).

Iervasi *et al.* (7) and the cardiothoracic research group in Pisa have previously shown that low serum T_3 levels are the single most significant predictor of cardiovascular and all-cause mortality in adults with heart disease. Although the basis for this observation is not entirely clear, preclinical studies have suggested that a variety of cardiac pathological processes, including acute myocardial infarction, lead to impaired LV function and a concomitant fall in serum T_3 (14). In those studies, T_3 replacement improved LV function and restored myocyte gene expression to euthyroid levels, similar to that seen in the treatment of hypothyroidism (5).

In this context, the current *JCEM* report of the beneficial effects of T_3 replacement in human heart failure is especially interesting and serves as proof of the concept that altered thyroid hormone metabolism plays a pathogenic role in progression of cardiac disease states (13). The authors prospectively studied 20 heart

Both Hypothyroidism and Hyperthyroidism Increase Atrial Fibrillation Inducibility in Rats

Youhua Zhang, MD, PhD; Eduard I. Dedkov, MD, PhD; Diana Teplitsky, OMS-III; Nathan Y. Weltman, PhD; Christine J. Pol, PhD; Viswanathan Rajagopalan, PhD;

Atrial Arryhtmias are a common problem as evidenced by the use of dangerous blood thinners for prevention of thrombotic stroke. From Zhang et al in 2013 - both Low and High Thyroid serum levels are associated with Atrial Fibrillation in rat models.

Background—Evidence indicates that cardiac hypothyroidism may contribute to heart failure progression. It is also known that heart failure is associated with an increased risk of atrial fibrillation (AF). Although it is established that hyperthyroidism increases AF incidence, the effect of hypothyroidism on AF is unclear. This study investigated the effects of different thyroid hormone levels, ranging from hypothyroidism to hyperthyroidism on AF inducibility in thyroidectomized rats.

Methods and Results—Thyroidectomized rats with serum-confirmed hypothyroidism 1 month after surgery were randomized into hypothyroid (N=9), euthyroid (N=9), and hyperthyroid (N=9) groups. Rats received placebo, 3.3-mg L-thyroxine (T4), or 20-mg T4 pellets (60-day release form) for 2 months, respectively. At the end of treatment, hypothyroid, euthyroid, and hyperthyroid status was confirmed. Hypothyroid animals showed cardiac atrophy and reduced cardiac systolic and diastolic functions, whereas hyperthyroid rats exhibited cardiac hypertrophy and increased cardiac function. Hypothyroidism and hyperthyroidism produced opposite electrophysiological changes in heart rates and atrial effective refractory period, but both significantly increased AF susceptibility. AF incidence was 78% in hypothyroid, 67% in hyperthyroid, and the duration of induced AF was also longer, compared with 11% in the euthyroid group (all $P<0.05$). Hypothyroidism increased atrial interstitial fibrosis, but connexin 43 was not affected.

Conclusions—Both hypothyroidism and hyperthyroidism lead to increased AF vulnerability in a rat thyroidectomy model. Our results stress that normal thyroid hormone levels are required to maintain normal cardiac electrophysiology and to prevent cardiac arrhythmias and AF. (***Circ Arrhythm Electrophysiol.* 2013;6:952-959.**)

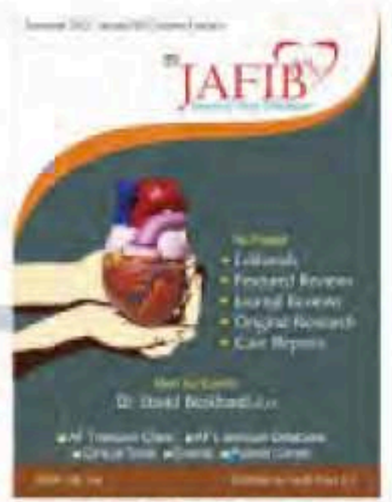
Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ electrophysiology ■ thyroid hormones

Kolettis and Tsatsouis in 2012, identified Subclinical Hypothyroid (defined as High TSH with traditionally considered normal T4 levels) as associated with Atrial Fibrillation.

JAFIB

Case Report

Journal of Atrial Fibrillation



WWW. jafib.com

Subclinical Hypothyroidism: An Overlooked Cause of Atrial Fibrillation?

Theofilos M. Kolettis, MD[a], Agathocles Tsatsoulis, MD[b]

Departments of [a]Cardiology and [b]Endocrinology, University of Ioannina, Greece.

Looking at the Ratio of Serum T3 to T4T4
A patient with untreated Subclinical Hypothyroid presented with a T3/T4 Ratio of 1.4.
On treatment with Levothyroxine with 50 mcg of LT4 the incidence of atrial fibrillation decreased and at 75 mcg dosing essentially stopped, evidencing a T3/T4 ratio of 0.3 under the normalized condition.

was excluded, based on repeated blood pressure recordings and on ambulatory monitoring; echocardiography, exercise stress testing, as well as blood biochemistry were normal. However, mild subclinical hypothyroidism was diagnosed based on thyrotropin (thyroid-stimulating hormone, TSH) values of 5.69mIU/L, with normal triiodothyronine(T3) (1.53ng/ml, laboratory reference values: 0.56-1.56ng/ml) and free(T4) (1.12ng/dl, laboratory reference values: 0.6-1.37ng/dl) values. She was treated with levothyroxin 50µg daily and her symptoms progressively resolved; during a 24-month follow-up, thyroid function

UNTREATED
T3/FT4 ratio = 1.4
TT3 97%
FT4 68%

Despite previous normal thyroid function tests (4 years prior to the index evaluation), subclinical hypothyroidism was diagnosed, based on TSH values of 7.67mIU/L with normal T3 (0.96ng/ml) and free T4 (0.68ng/dl). During the subsequent 6 months, he had three more episodes of persistent atrial fibrillation, despite levothyroxin 50µg daily and antiarrhythmic treatment, initially with sotalol 80mg t.i.d. and subsequently with propafenone 150mg t.i.d.; at that time, thyroid function tests had improved but were still abnormal, with TSH values of 5.36mIU/L, whereas T3 (0.80ng/ml) and free T4 (0.72ng/dl) remained within normal range. Levothyroxin was increased to 100µg daily, which normalized TSH values to 2.48mIU/L after 6 months, again with normal T3 (0.85ng/ml) and free T4 (1.00ng/dl) levels. During a further 12-month follow-up, only brief episodes of par-

TREATED
T3/FT4 ratio = 0.3
TT3 29%
FT4 52%

Corresponding Address : Theofilos M. Kolettis, MD, PhD, FESC, Associate Professor in Cardiology, University of Ioannina, Department of Cardiology, 1 Stavrou Niarxou Avenue, 45110 Ioannina, Greece.Tel: 30(265)1007227; Fax: 30(265)1007053; E-mail: thkolet@cc.uoi.gr

Elmer Press

Case Report

J Med Cases 2011;2(3):121-123

Thyroid Dysfunction is clearly associated with Atrial Arrhythmias. A demonstration about for a patient with the rhythm of Bigeminy is presented by Digklia et al.

Atrial Bigeminy Associated With Hypothyroidism: A Case Report

Antonia Digklia[a], Ioannis A. Voutsadakis[a, b]

Abstract

The effect of hypothyroidism on the cardiovascular system has been well documented. Hypothyroidism produces both systolic and diastolic dysfunction that can lead to cardiac arrhythmia and congestive heart failure. The consequences of acute hypothyroidism due to thyroid hormone withdrawal in previously thyroidectomized patients on cardiac function have been investigated only in a few studies. We describe a 65-year-old man, having previously undergone a thyroidectomy for thyroid cancer, in whom withdrawal of thyroid hormone led to cardiac arrhythmia manifested as bigeminy. It is the first report in the English literature where a short term overt hypothyroidism is associated with atrial bigeminy.

Keywords: Hypothyroidism; Cardiac arrhythmia; Atrial bigeminy; Thyroid cancer; Papillary

increased premature atrial beats and ventricular extra-systoles [1, 2]. In addition, because decreased peripheral vascular resistance cannot compensate for the increased heart rate, hypertension is often observed. In contrast, hypothyroidism produces sinus bradycardia and decreased cardiac contractility [3]. Paradoxically, this decreased contractility can lead to prolonged QT interval, heart blocks and other arrhythmias [4, 5].

Case Report

A 65-year-old man with papillary thyroid carcinoma of right lobe, stage T4 N1 M0, was initially treated with total thyroidectomy and postoperative radioiodine in two occasions 3 and 9 months after surgery. Thyroid hormone substitution was begun thereafter. A recurrence with ipsilateral regional lymph node metastases 1.5 years later was treated with right

Available online at www.sciencedirect.com

Thyroxine T4 is a potent arterial vasodilator.
There is clear evidence that the epidemic of Hypertension, particularly newer classifications of "Systolic Hypertension" can be correlated with low Thyroid levels.
Nagasaki et al described that Thyroxine treatment decreases arterial stiffness by normalization of Thyroid Function.

& BIOMEDICINE PHARMACOTHERAPY

http://france.elsevier.com/direct/BIOPHA/

Dossier: Hypertension and cardiovascular diseases: the rational approach

Decrease of arterial stiffness at common carotid artery in hypothyroid patients by normalization of thyroid function

Toshiki Nagasaki [a], Masaaki Inaba [a,*], Yasuro Kumeda [a], Misako Ueda [a], Yoshikazu Hiura [a], Hideki Tahara [a], Eiji Ishimura [a], Naoyoshi Onoda [b], Tetsuro Ishikawa [b], Yoshiki Nishizawa [a]

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Received 8 June 2004

Available online 15 December 2004

PLOS ONE

Recent descriptions of Thyroid treatments for Myocardial Infarction report improved outcomes.

From a paper by Rajagopalan et al in 2016:

RESEARCH ARTICLE

Safe Oral Triiodo-L-Thyronine Therapy Protects from Post-Infarct Cardiac Dysfunction and Arrhythmias without Cardiovascular Adverse Effects

Viswanathan Rajagopalan[1]*, Youhua Zhang[1], Kaie Ojamaa[2], Yue-feng Chen[1], Alessandro Pingitore[3], Christine J. Pol[1], Debra Saunders[4], Krithika Balasubramanian[4], Rheal A. Towner[4], A. Martin Gerdes[1]*

1 Department of Biomedical Sciences, New York Institute of Technology-College of Osteopathic Medicine, Old Westbury, New York, United States of America, 2 Feinstein Institute for Medical Research, Manhasset, New York, United States of America, 3 CNR Clinical Physiology Institute, Pisa, Italy, 4 Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, United States of America

* agerdes@nyit.edu (AMG); vrajagop@nyit.edu (VR)

Citation: Rajagopalan V, Zhang Y, Ojamaa K, Chen Y-f, Pingitore A, Pol CJ, et al. (2016) Safe Oral Triiodo-L-Thyronine Therapy Protects from Post-Infarct Cardiac Dysfunction and Arrhythmias without Cardiovascular Adverse Effects. PLoS ONE 11(3): e0151413. doi:10.1371/journal.pone.0151413

Editor: Yibin Wang, David Geffen School of Medicine at UCLA, UNITED STATES

Received: January 18, 2016

Safe Oral Triiodo-L-Thyronine Therapy Protects from Post-Infarct Cardiac Dysfunction and Arrhythmias without Cardiovascular Adverse Effects

Background

A large body of evidence suggests that thyroid hormones (THs) are beneficial for the treatment of cardiovascular disorders. We have shown that 3 days of triiodo-L-thyronine (T3) treatment in myocardial infarction (MI) rats increased left ventricular (LV) contractility and decreased myocyte apoptosis. However, no clinically translatable protocol is established for T3 treatment of ischemic heart disease. We hypothesized that low-dose oral T3 will offer safe therapeutic benefits in MI.

OPEN ACCESS

Their findings:

Citation: Rajagopalan V, Zhang Y, Ojamaa K, Chen Y-f, Pingitore A, Pol CJ, et al. (2016) Safe Oral Triiodo-L-Thyronine Therapy Protects from Post-Infarct Cardiac Dysfunction and Arrhythmias without Cardiovascular Adverse Effects. PLoS ONE 11(3): e0151413. doi:10.1371/journal.pone.0151413

Editor: Yibin Wang, David Geffen School of Medicine at UCLA, UNITED STATES

Received: January 18, 2016

Accepted: February 26, 2016

Published: March 16, 2016

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health, Bethesda, MD, under Award Number R01HL103671 (AMG). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Methods and Results

Adult female rats underwent left coronary artery ligation or sham surgeries. T3 (~6 μg/kg/day) was available in drinking water ad libitum immediately following MI and continuing for 2 month(s) (mo). Compared to vehicle-treated MI, the oral T3-treated MI group at 2 mo had markedly improved anesthetized Magnetic Resonance Imaging-based LV ejection fraction and volumes without significant negative changes in heart rate, serum TH levels or heart weight, indicating safe therapy. Remarkably, T3 decreased the incidence of inducible atrial tachyarrhythmias by 88% and improved remodeling. These were accompanied by restoration of gene expression involving several key pathways including thyroid, ion channels, fibrosis, sympathetic, mitochondria and autophagy.

Conclusions

Low-dose oral T3 dramatically improved post-MI cardiac performance, decreased atrial arrhythmias and cardiac remodeling, and reversed many adverse changes in gene expression with no observable negative effects. This study also provides a safe and effective treatment/monitoring protocol that should readily translate to humans.

Hypothyroid Cardiomyopathy: Echocardiographic Documentation of Reversibility

Reversable Cardiomyopathy,
The American Journal of the Medical Sciences,
July 1987 Volume 294 Number 1

BY MOHANDAS M. SHENOY, MBBS, FACP, JOEL M. GOLDMAN, MD, FACP

Idiopathic Cardiomyopathy is a dangerous problem in Pregnant women. But if you don't diagnosis it, it cannot be treated.
T3 treatment has been shown to ameliorate Acute Decompensated Cardiomyopathy.
These treatment results speak to a clinical paradigm to normalize T3/T4 and the ratios:
Levothyroxine (LT4) for elevated TSH (or Low FreeT4)
Liiothyronine (LT3) for acute symptomatic Low T3 (Low FreeT3)

ABSTRACT: The concept of hypothyroid heart disease remains controversial. Although hemodynamic abnormalities have been described, the presence of underlying abnormal cardiac structures has not been confirmed. The authors studied 20 hypothyroid patients using M-mode echocardiography before and after l-thyroxine therapy. Fifteen additional hypothyroid patients were studied using two-dimensional echocardiography to confirm the data of the first study. The findings were the same in both studies: during hypothyroidism, the interventricular septum is thickened, the ratio of septal thickness to left ventricular posterior wall thickening is increased, the right ventricular wall is thickened, regional wall motion of interventricular septum and right ventricular wall is decreased, and global function of the left ventricle is decreased. These findings are reversed with l-thyroxine therapy; they occur within 6 months of the development of hypothyroidism, but appear unrelated to elevated TSH levels. Whether the thickened interventricular septum and right ventricular wall represent true mus-

The concept of "myxedema heart"[1] has remained controversial for 60 years.[2] The original features were later attributed to pericardial effusion.[3] Hemodynamic abnormalities occur in hypothyroidism and are reversed after thyroid hormone therapy.[4–10] However, few studies have examined anatomic features before and after treatment.[11–13] Although anatomic abnormalities suggestive of a reversible cardiomyopathy were seen in hypothyroid adults,[11] these findings were not confirmed in adults[14] or hypothyroid children.[12] We performed a prospective echocardiographic study of hypothyroid adults before and after thyroid hormone therapy using M-mode echocardiography. Another group of hypothyroid patients was subsequently studied with two-dimensional echocardiography.

Patients

Study1: M-mode Echocardiography. Twenty adults in whom hypothyroidism was diagnosed by T_4 values less than 3.0 μg/dl were included; T_4 values below the level of detection (1.5 μg/dl) were assigned the value of 1.5 μg/dl. T_3 resin uptake values did not suggest protein-binding abnormalities. TSH values

Endocrinology. 1984 Sep;115(3):858-61.

Beta-adrenergic antagonist inhibition of hepatic 3,5,3'-triiodothyronine production.

Shulkin BL, Peele ME, Utiger

80% of the serum T3 is converted from T4 in the Liver. The beta blocker Labetalol is commonly used to treat measured Hypertension in Pregnancy.
It is of no small note that Beta-Andrenergic Blockers decrease levels of T3 by blocking their production in the Liver, lowering Blood Pressure. These are suprisingly not recent findings.

Abstract

beta-Adrenergic antagonists provide moderate symptomatic relief for most hyperthyroid patients, although these agents have no direct antithyroid effects. Propranolol administration results in modest declines in serum T3 concentrations in both hyperthyroid and normal subjects and also inhibits T4 to T3 conversion in various tissue preparations in vitro. Other beta-adrenergic antagonists have not been shown to consistently alter serum T3 concentrations in vivo or T3 production in vitro. To evaluate the ability of beta-adrenergic antagonists to inhibit T4-5'-deiodination, we measured T3 production from T4 in rat liver homogenates (10,000 X g supernatant) using 1 microM T4 in the presence of varying concentrations of the beta-adrenergic antagonists available in the United States. Each drug inhibited T3 production, and the dose-dependent responses were linear and parallel when plotted as percent inhibition vs. log dose concentration. The calculated drug concentrations required to produce 50% inhibition were: propranolol, 1.7 mM; pindolol, 6.7 mM; timolol, 11.5 mM; atenolol, 23.2 mM; metoprolol, 30.5 mM, and nadolol, 106.1 mM. The IC50 values were similar in the presence of 4 mM dithiothreitol. In separate studies, the ability of D- and L-propranolol to inhibit T3 production was compared with that of D,L-propranolol, the common form. Both D- and L-propranolol were as effective as the racemic mixture. The propranolol metabolites 4-hydroxypropranolol, 4-methylpropranolol, propranolol glycol, and N-desisopropyl propranolol were also effective inhibitors. Thus, beta-adrenergic antagonists inhibit T3 production in vitro. This inhibition is not related to beta-adrenergic antagonism per se, but is correlated with the lipid solubility of the drugs, which may explain the effects of propranolol on serum T3 in vivo.

There is amazing information within the last 5-10 years about the Brain and Thyroid Function. It is providing underlying paradigms for a wide variety of disease processes.

There is so much work being done, it is hard to keep up.

BRAIN

I introduce this using several papers.
First is work in Hungary by Mohacsik et al in Glial cells (astrocytes & tanocytes)

SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 215718, 16 pages
doi:10.4061/2011/215718

Review Article

Thyroid Hormone and the Neuroglia: Both Source and Target

Petra Mohácsik,[1] Anikó Zeöld,[1] Antonio C. Bianco,[2] and Balázs Gereben[1]

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Received 19 March 2011; Revised 31 May 2011; Accepted 17 June 2011

Academic Editor: Juan Bernal

Thyroid hormone plays a crucial role in the development and function of the nervous system. In order to bind to its nuclear receptor and regulate gene transcription thyroxine needs to be activated in the brain. This activation occurs via conversion of thyroxine to T3, which is catalyzed by the type 2 iodothyronine deiodinase (D2) in glial cells, in astrocytes, and tanycytes in the mediobasal hypothalamus. We discuss how thyroid hormone affects glial cell function followed by an overview on the fine-tuned regulation of T3 generation by D2 in different glial subtypes. Recent evidence on the direct paracrine impact of glial D2 on neuronal gene expression underlines the importance of glial-neuronal interaction in thyroid hormone regulation as a major regulatory pathway in the brain in health and disease.

Cabezas et al in Brazil reported on the structure of the Blood Brain Barrier itself.

frontiers in
CELLULAR NEUROSCIENCE

REVIEW ARTICLE
published: 04 August 2014
doi: 10.3389/fncel.2014.00211

Astrocytic modulation of blood brain barrier: perspectives on Parkinson's disease

Ricardo Cabezas[1], *Marcos Ávila*[1], *Janneth Gonzalez*[1], *Ramon Santos El-Bachá*[2], *Eliana Báez*[1], *Luis Miguel García-Segura*[3], *Juan Camilo Jurado Coronel*[1], *Francisco Capani*[4], *Gloria Patricia Cardona-Gomez*[5] *and George E. Barreto*[1]*

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[2] *Departamento de Biofunção, Universidade Federal da Bahia, Salvador, Brazil*
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[4] *Laboratorio de Citoarquitectura y Plasticidad Neuronal, Facultad de Medicina, Instituto de Investigaciones cardiológicas Prof. Dr. Alberto C. Taquini (ININCA), UBA-CONICET, Buenos Aires, Argentina*
[5] *Cellular and Molecular Neurobiology Area, Group of Neuroscience of Antioquia, Faculty of Medicine, SIU, University of Antioquia UdeA, Medellín, Colombia*

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The blood–brain barrier (BBB) is a tightly regulated interface in the Central Nervous System (CNS) that regulates the exchange of molecules in and out from the brain thus maintaining the CNS homeostasis. It is mainly composed of endothelial cells (ECs), pericytes and astrocytes that create a neurovascular unit (NVU) with the adjacent neurons. Astrocytes are essential for the formation and maintenance of the BBB by providing secreted factors that lead to the adequate association between the cells of the BBB and the formation of strong tight junctions. Under neurological disorders, such as chronic cerebral ischemia, brain trauma, Epilepsy, Alzheimer and Parkinson's Diseases, a disruption of the BBB takes place, involving a lost in the permeability of the barrier and phenotypical changes in both the ECs and astrocytes. In this aspect, it has been established that the process of reactive gliosis is a common feature of astrocytes during BBB disruption, which has a detrimental effect on the barrier function and a subsequent damage in neuronal survival. In this review we discuss the implications of astrocyte functions in the protection of the BBB, and in the development of Parkinson's disease (PD) and related disorders. Additionally, we highlight

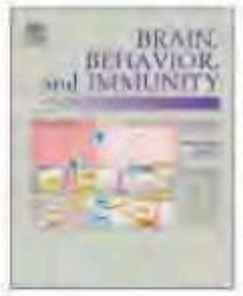
Brain, Behavior, and Immunity 60 (2017) 1–12

Varatharaj and Galea recently descibed the role of inflammation at the blood brain barrier.

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi



Invited Review

The blood-brain barrier in systemic inflammation

Aravinthan Varatharaj *, Ian Galea

Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Mailpoint 806, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, United Kingdom

ARTICLE INFO

Article history:
Received 8 January 2016
Received in revised form 6 March 2016
Accepted 15 March 2016
Available online 16 March 2016

Keywords:
Blood-brain barrier
Systemic inflammation
Lipopolysaccharide
Sickness behaviour
Delirium
Septic encephalopathy
Multiple sclerosis
Alzheimer's disease

ABSTRACT

The blood-brain barrier (BBB) plays a key role in maintaining the specialized microenvironment of the central nervous system (CNS), and enabling communication with the systemic compartment. BBB changes occur in several CNS pathologies. Here, we review disruptive and non-disruptive BBB changes in systemic infections and other forms of systemic inflammation, and how these changes may affect CNS function in health and disease. We first describe the structure and function of the BBB, and outline the techniques used to study the BBB *in vitro*, and in animal and human settings. We then summarise the evidence from a range of models linking BBB changes with systemic inflammation, and the underlying mechanisms. The clinical relevance of these BBB changes during systemic inflammation are discussed in the context of clinically-apparent syndromes such as sickness behaviour, delirium, and septic encephalopathy, as well as neurological conditions such as Alzheimer's disease and multiple sclerosis. We review emerging evidence for two novel concepts: (1) a heightened sensitivity of the diseased, versus healthy, BBB to systemic inflammation, and (2) the contribution of BBB changes induced by systemic inflammation to progression of the primary disease process.

Fluid and ion transfer across the blood–brain and blood–cerebrospinal fluid barriers; a comparative account of mechanisms and roles

- Stephen B. Hladky[1] &
- Margery A. Barrand[1]

Hladky and Barrand have a nice article describing the Neuroanatomy and the Blood Brain Barrier.

The following pulls with appreciation from all these articles.

Fluids and Barriers of the CNS **volume 13**, Article number: 19 (2016) | Download Citation

Abstract

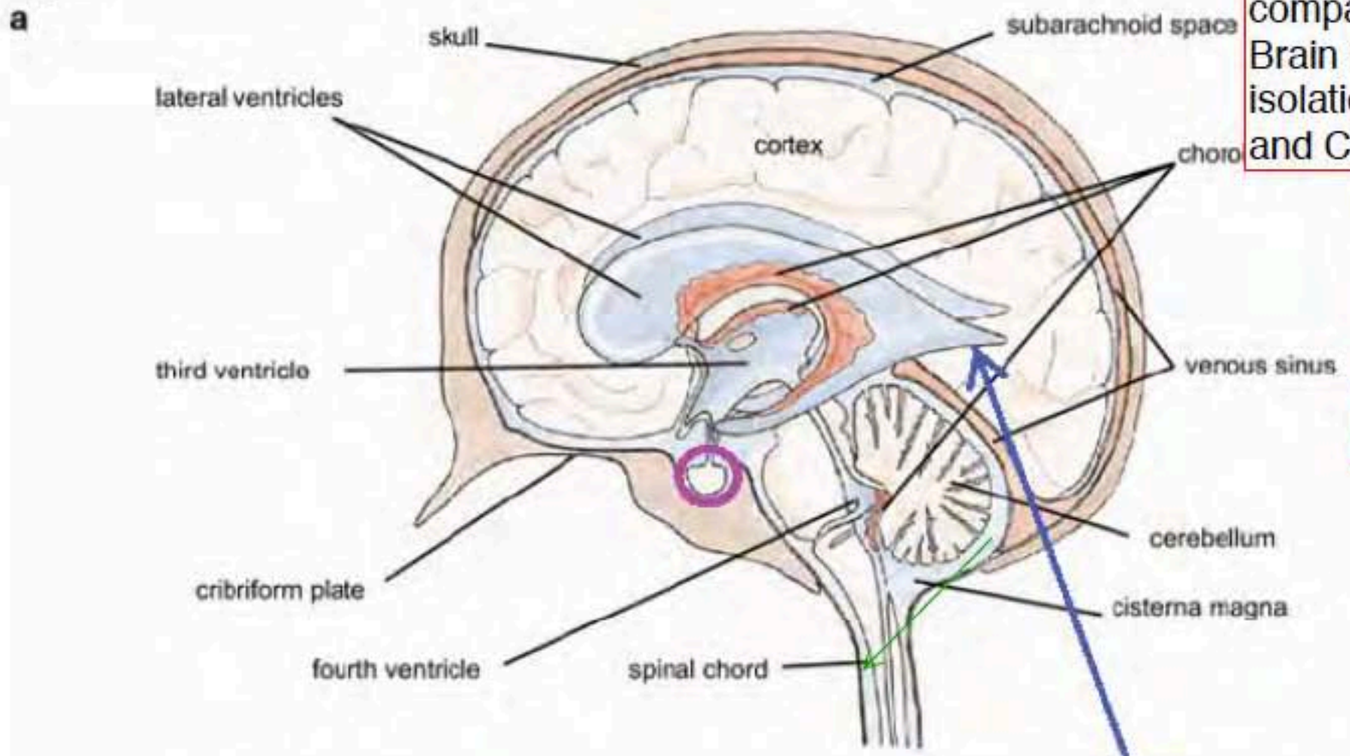
The two major interfaces separating brain and blood have different primary roles. The choroid plexuses secrete cerebrospinal fluid into the ventricles, accounting for most net fluid entry to the brain. Aquaporin, AQP1, allows water transfer across the apical surface of the choroid epithelium; another protein, perhaps GLUT1, is important on the basolateral surface. Fluid secretion is driven by apical Na^+-pumps. K^+ secretion occurs via net paracellular influx through relatively leaky tight junctions partially offset by transcellular efflux. The blood–brain barrier lining brain microvasculature, allows passage of O_2, CO_2, and glucose as required for brain cell metabolism. Because of high resistance tight junctions between microvascular endothelial cells transport of most polar solutes is greatly restricted. Because solute permeability is low, hydrostatic pressure differences cannot account for net fluid movement; however, water permeability is sufficient for fluid secretion with water following net solute transport. The endothelial cells have ion transporters that, if appropriately arranged, could support fluid secretion. Evidence favours a rate smaller than, but not much smaller than, that of the choroid plexuses. At the blood–brain barrier Na^+ tracer influx into the brain substantially exceeds any possible net flux. The tracer flux may occur primarily by a paracellular route. The blood–brain barrier is the most important interface for maintaining interstitial fluid (ISF) K^+ concentration within tight limits. This is most likely because Na^+-pumps vary the rate at which K^+ is transported out of ISF

Fig. 1

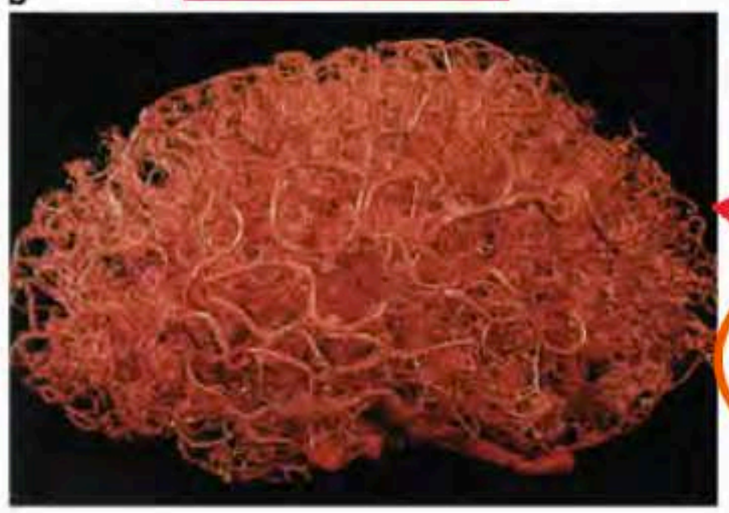
It is useful to visualize the different Thyroid compartments.
Brain Neurons and CSF are in Thyroid isolation, as is the Blood from Interstitial and Cellular fluid.

Brain Neurons & CSF are Encapsulated (Insulated)

These Brain Compartments are lined by two endothelial single layer blood–brain interfaces:



Brain Vasculature



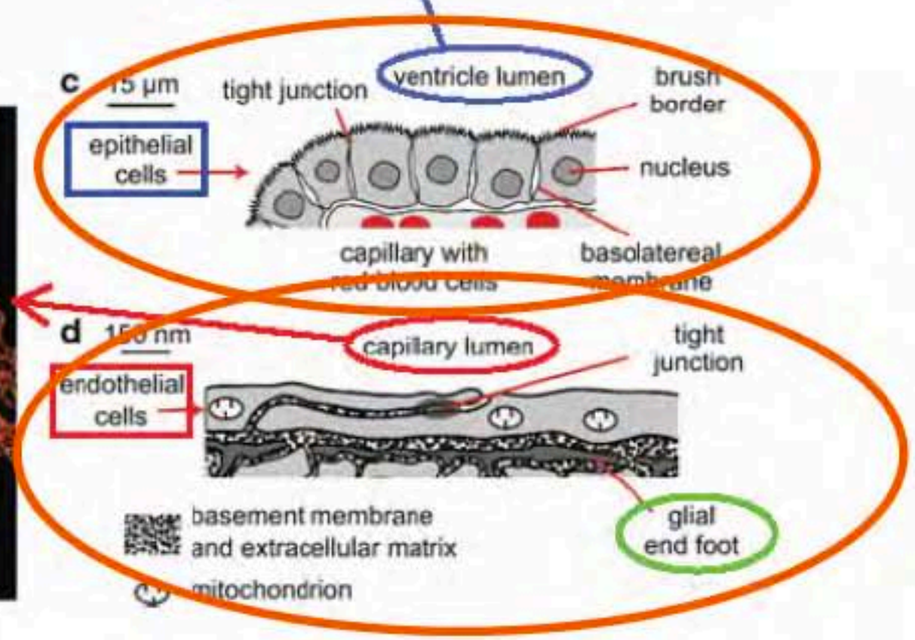
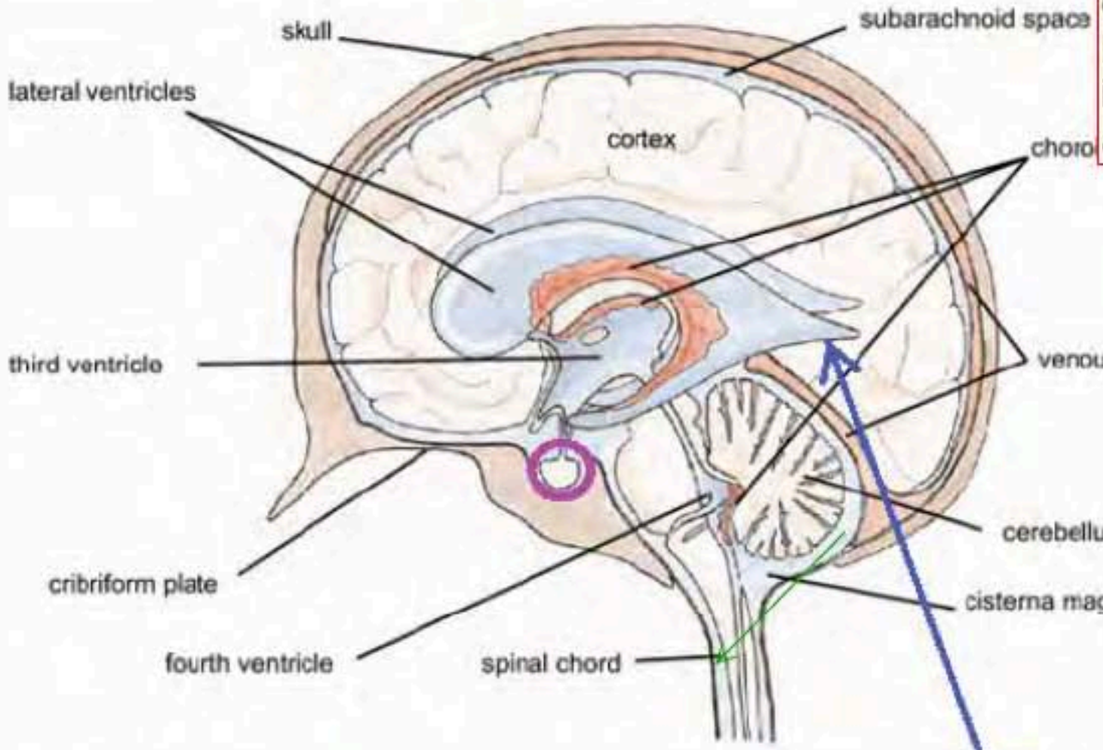


Fig. 1

a



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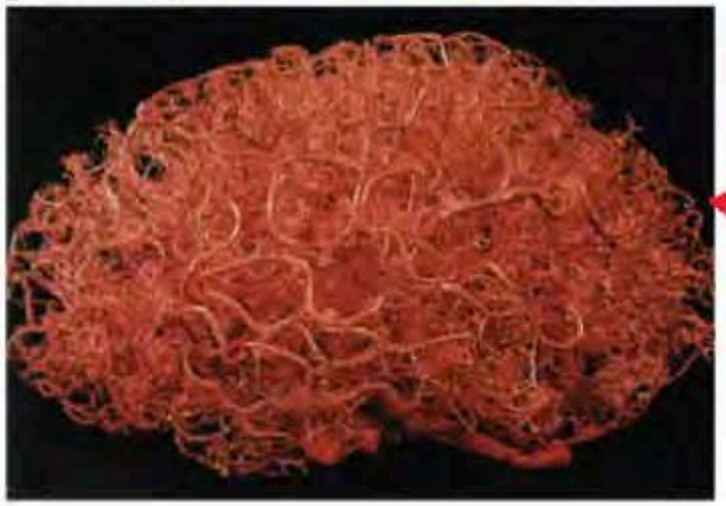
Brain Neurons & CSF are Encapsulated (Insulated)

These Brain Compartments are lined by two endothelial single layer blood–brain interfaces:

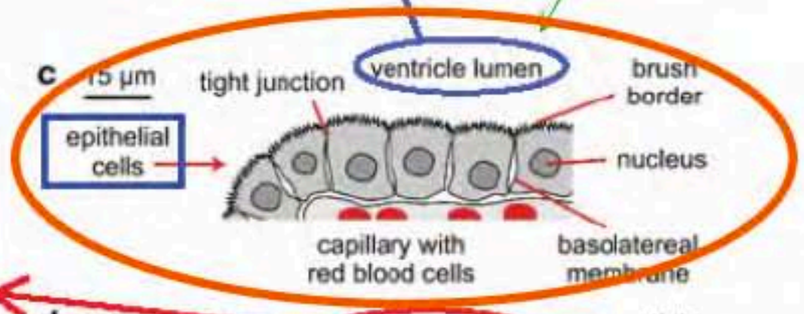
1) Choroid Plexus lining the ventricles has a layer of brush border cells separating Capillary Blood and CSF.

Brain Vasculature

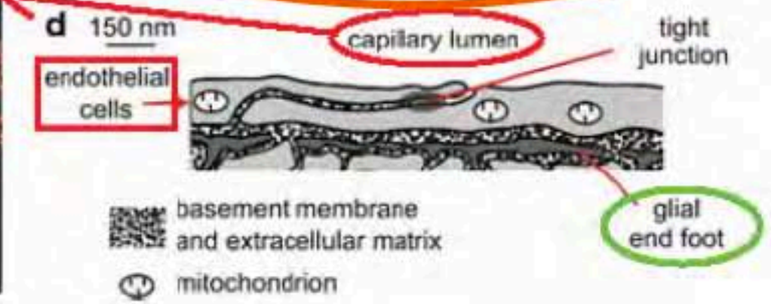
b



c



d



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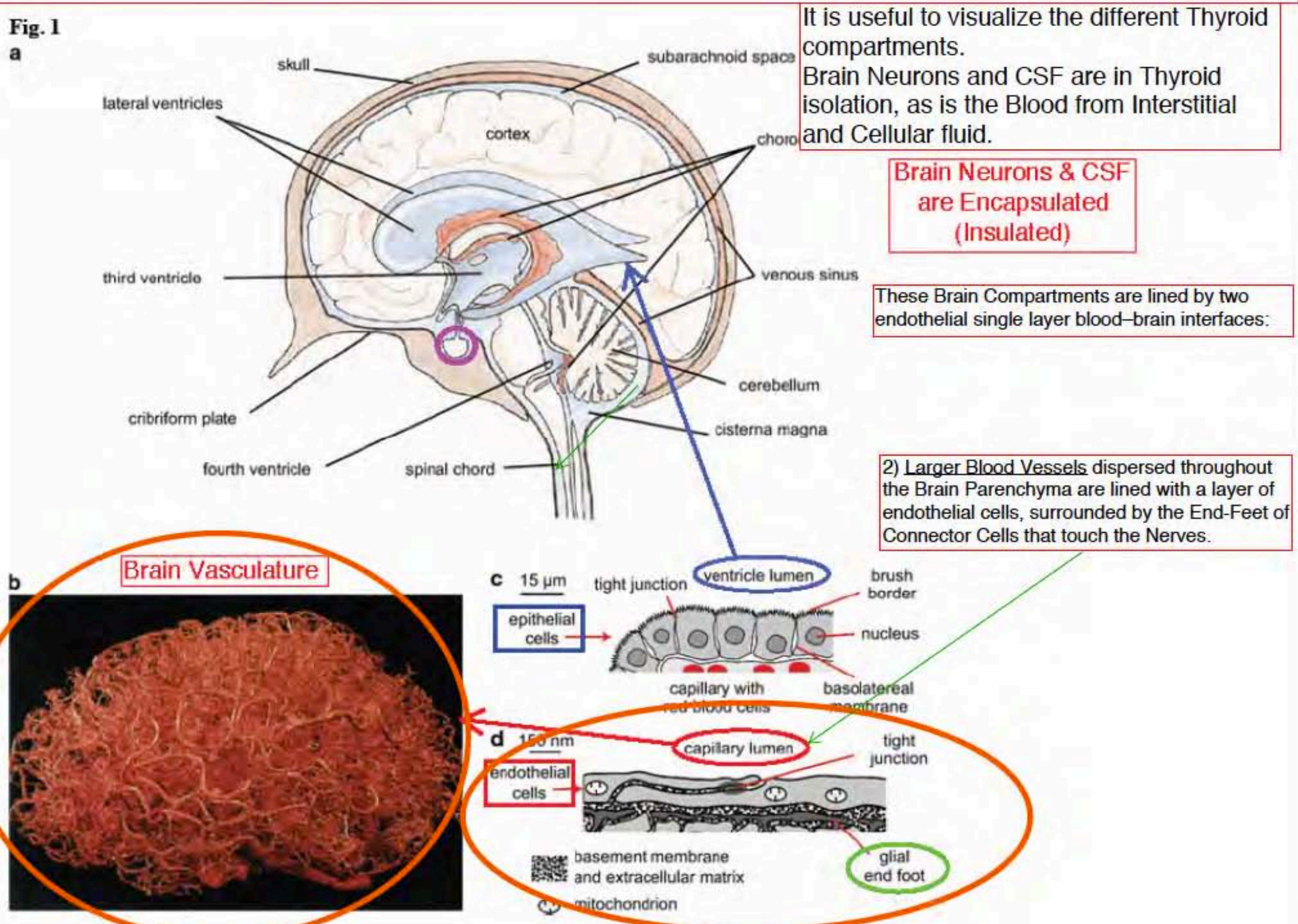

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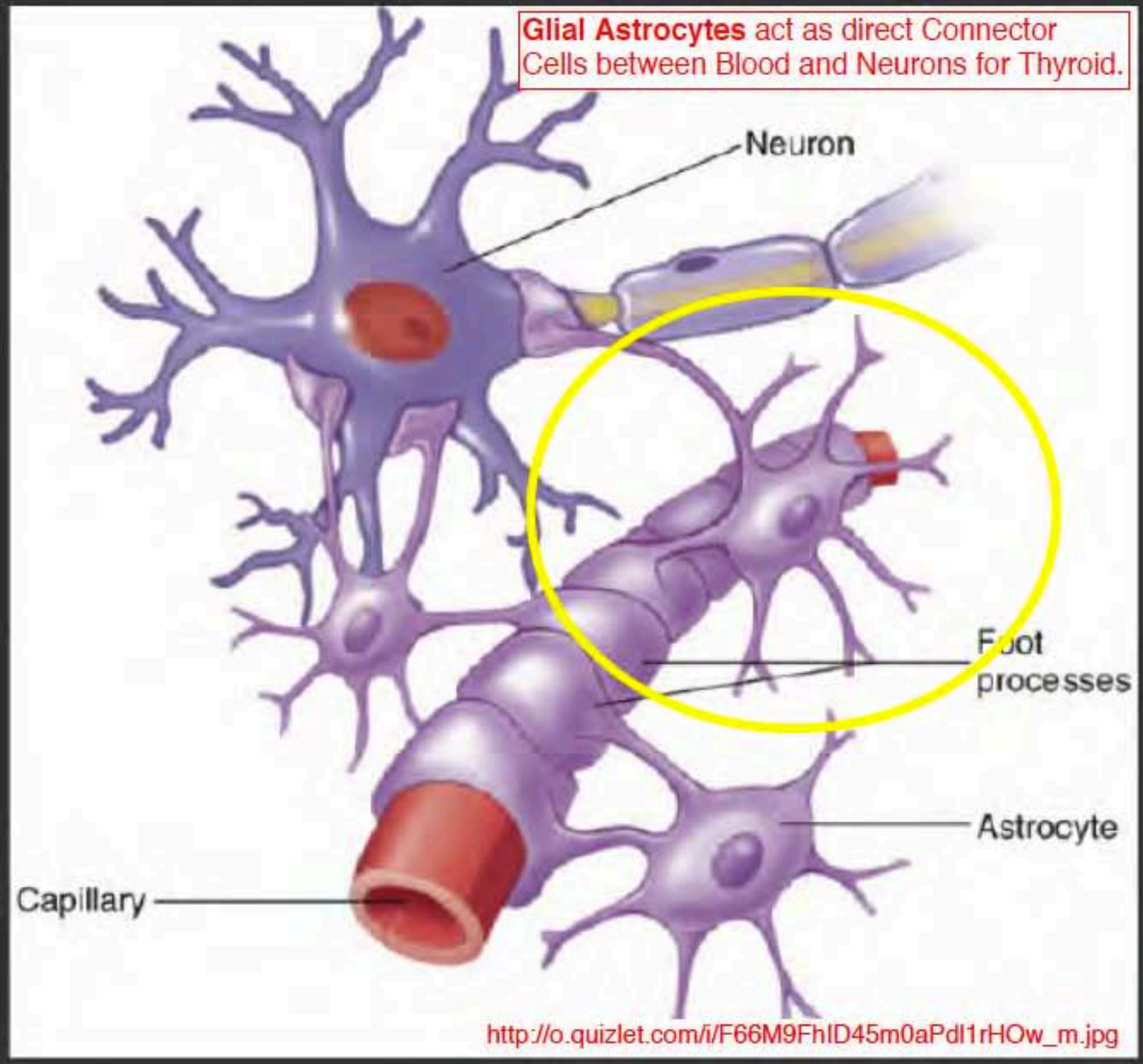
2) Larger Blood Vessels dispersed throughout the Brain Parenchyma are lined with a layer of endothelial cells, surrounded by the End-Feet of Connector Cells that touch the Nerves.


Glial Astrocytes act as direct Connector Cells between Blood and Neurons for Thyroid.
Neuron
Foot processes
Astrocyte
Capillary
http://o.quizlet.com/i/F66M9FhID45m0aPdI1rHOw_m.jpg

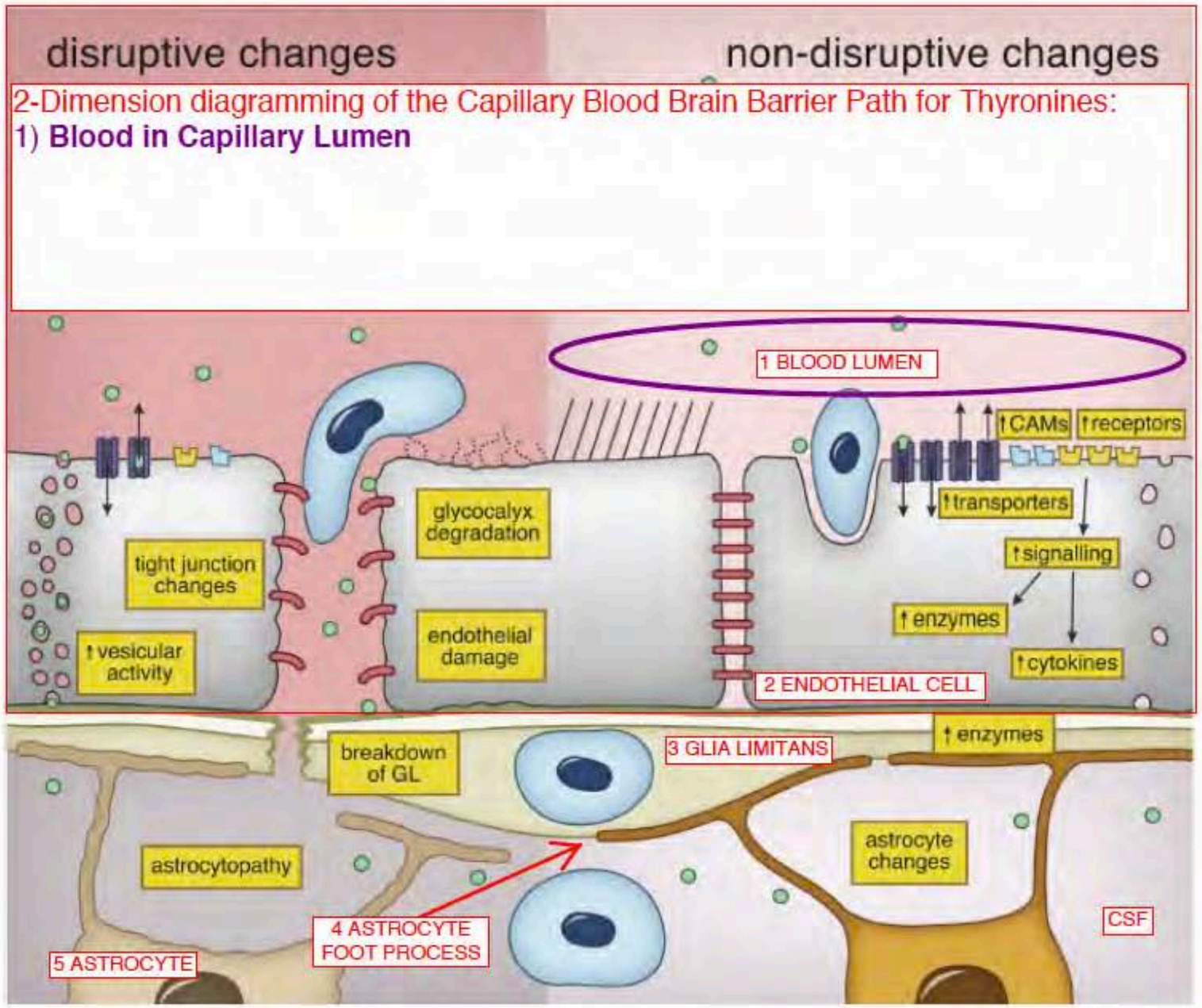
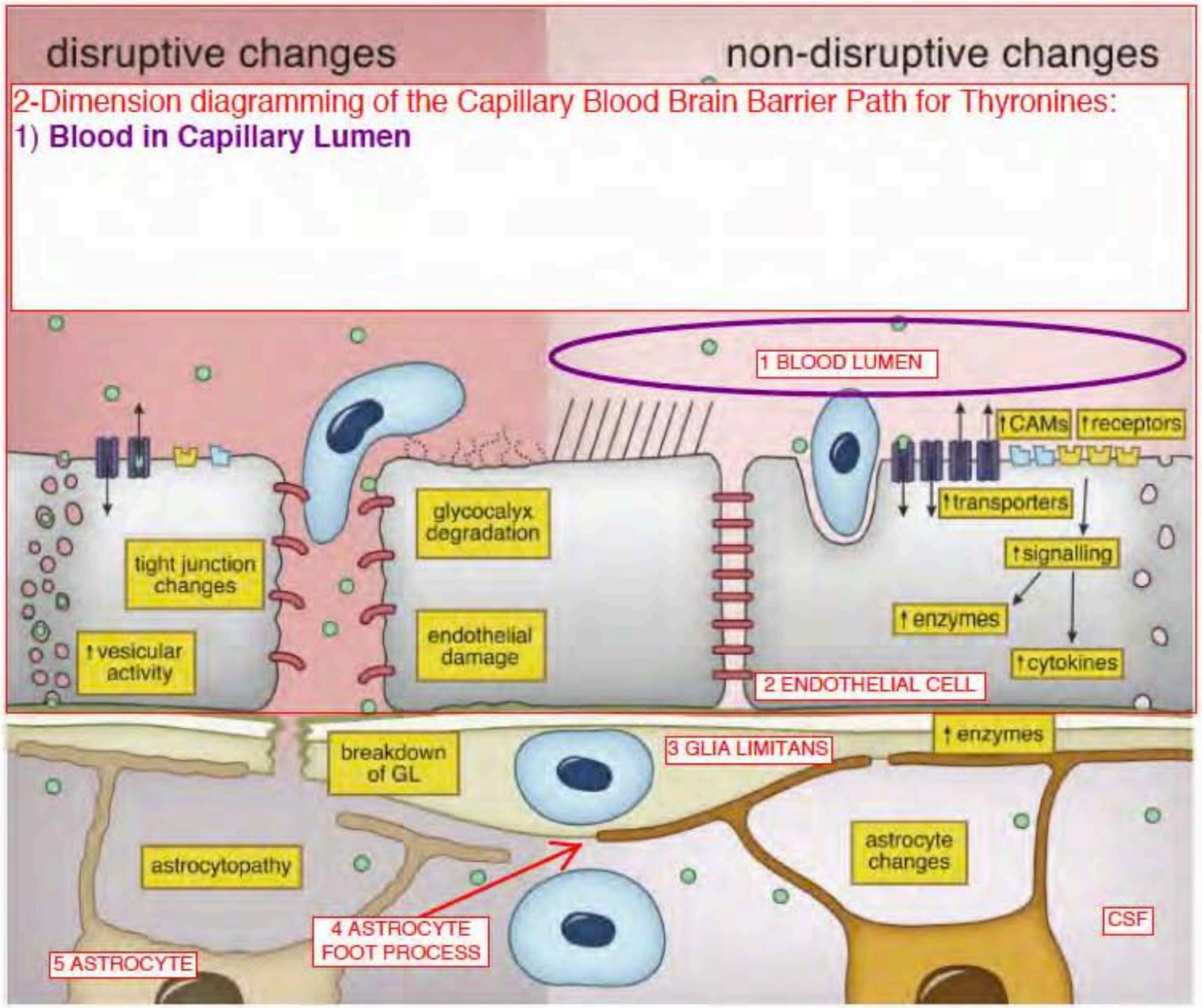


Fig. 2. Schematic illustration of disruptive and non-disruptive BBB changes during systemic inflammation. Relative proportions are not intended to be realistic. CAMs, cellular adhesion molecules; GL, glia limitans.



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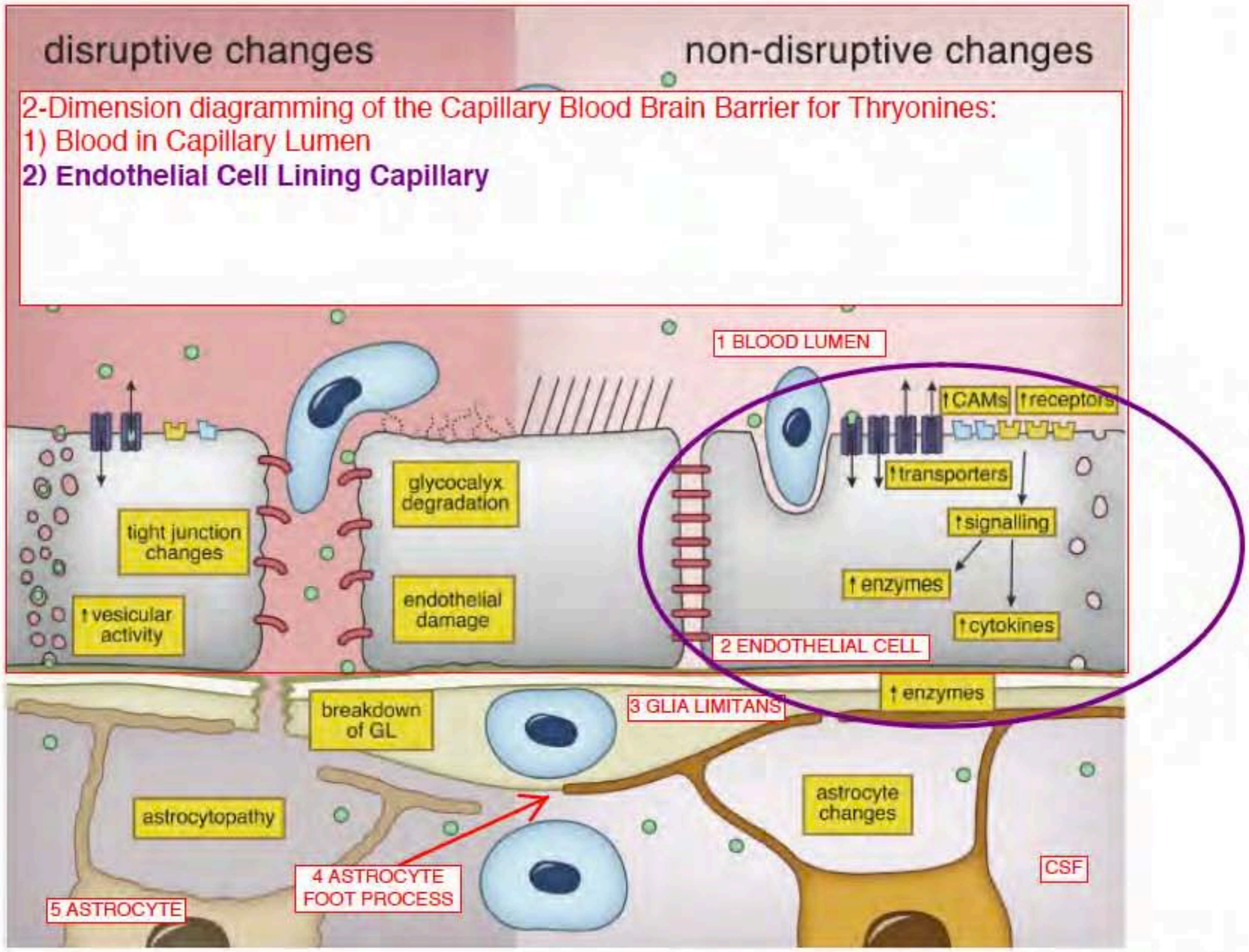

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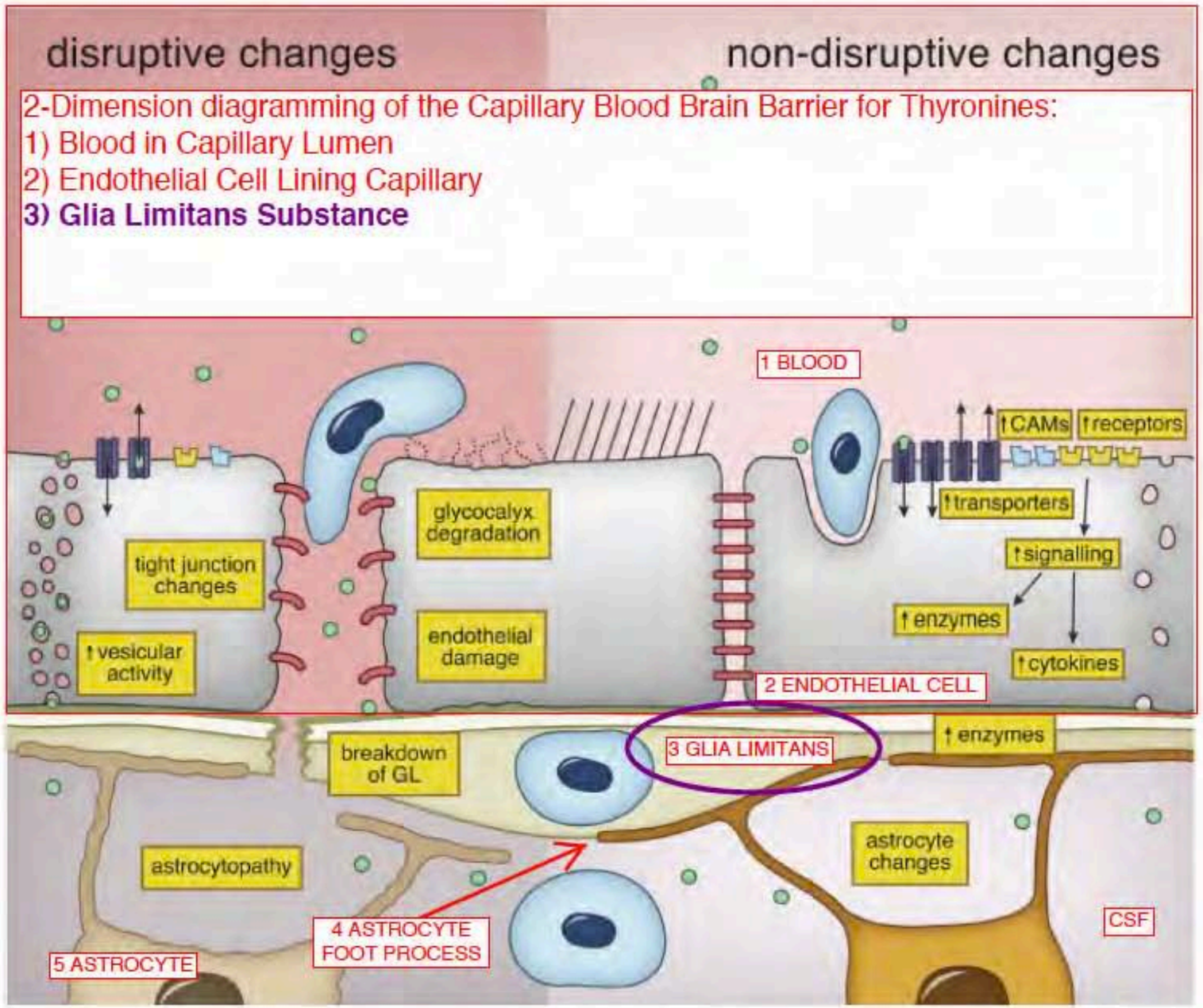

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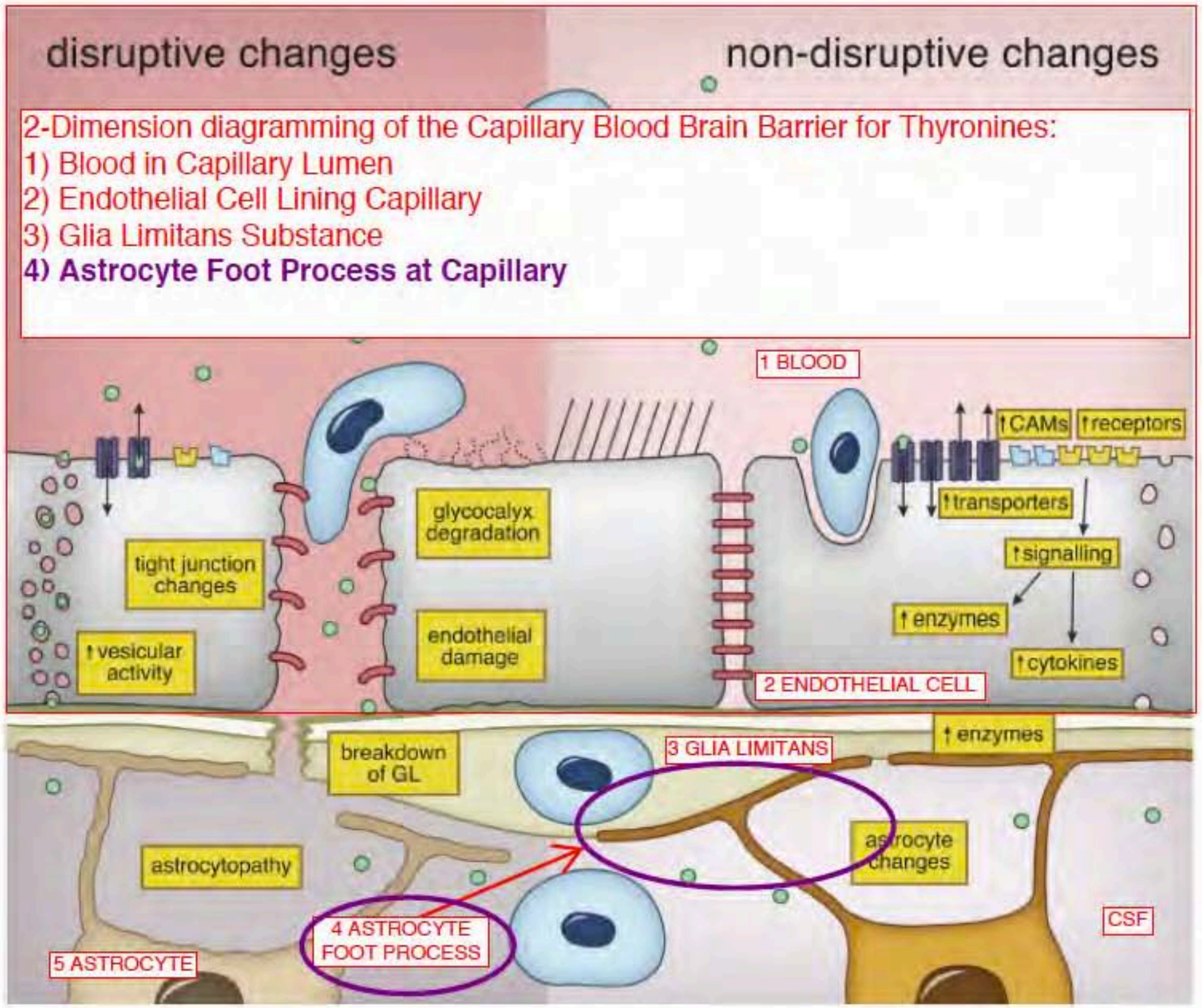

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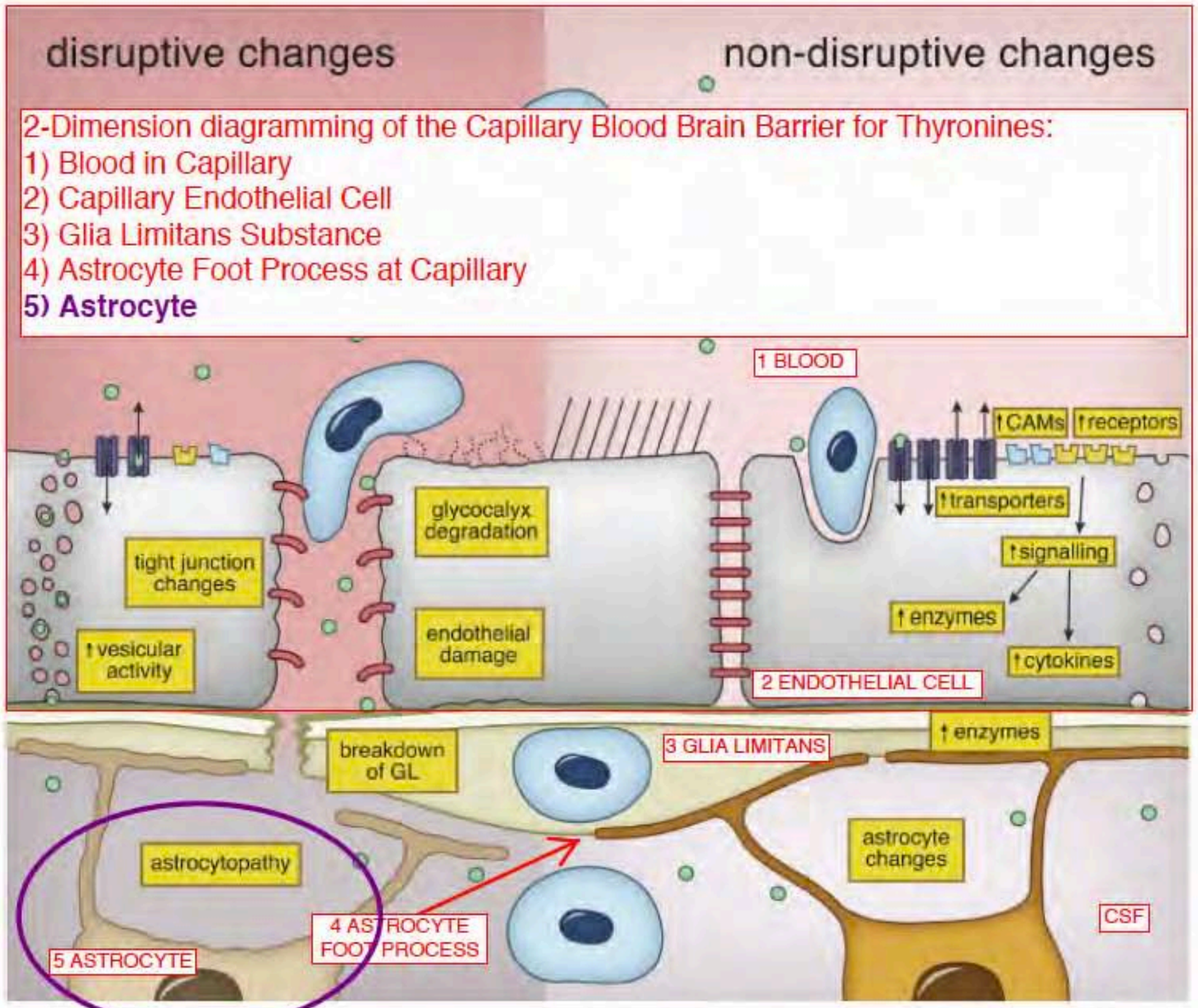


Fig. 2. Schematic illustration of disruptive and non-disruptive BBB changes during systemic inflammation. Relative proportions are not intended to be realistic. CAMs, cellular adhesion molecules; GL, glia limitans.

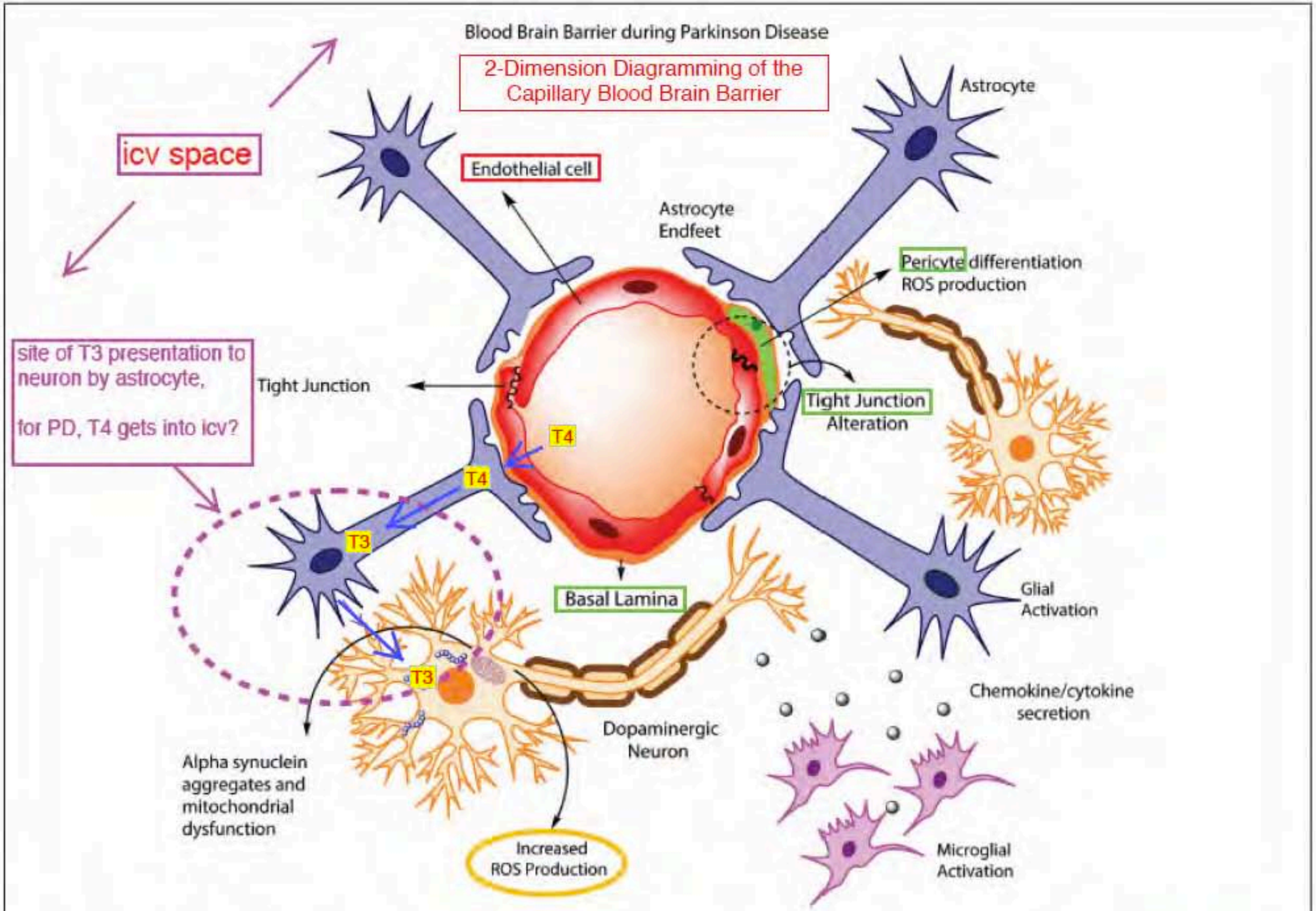


FIGURE 1 | BBB disruption in PD. During PD development, increased ROS production leads to the accumulation of α-synuclein in DAneurons, and this is accompanied by mitochondrial dysfunction and increased neuronal death. Concurrently, astrocyte and microglia became activated, promoting cytokine release, which in turn affects endothelial tight junctions, pericyte phenotype and BBB permeability.

Cazebas et al 2014

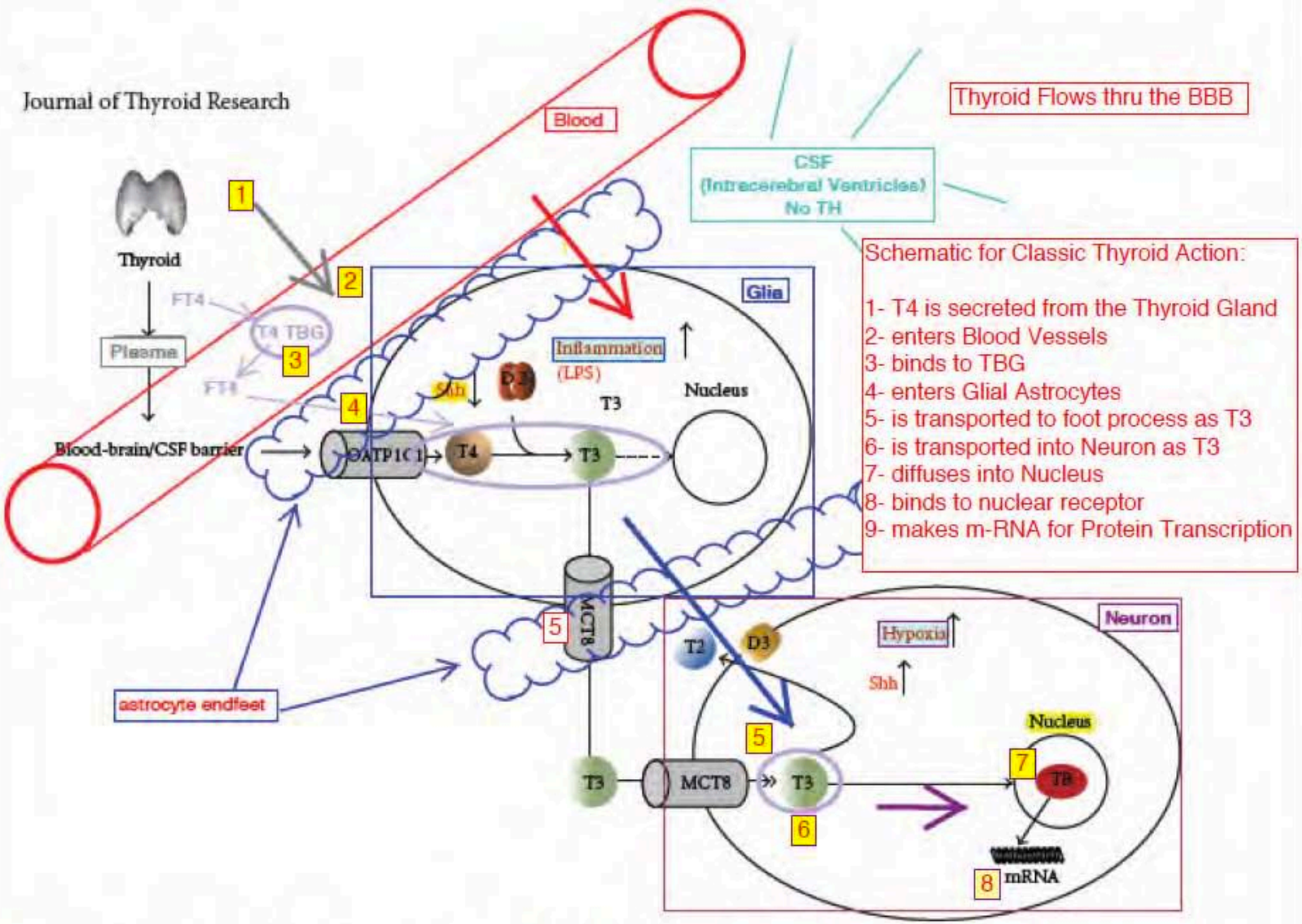
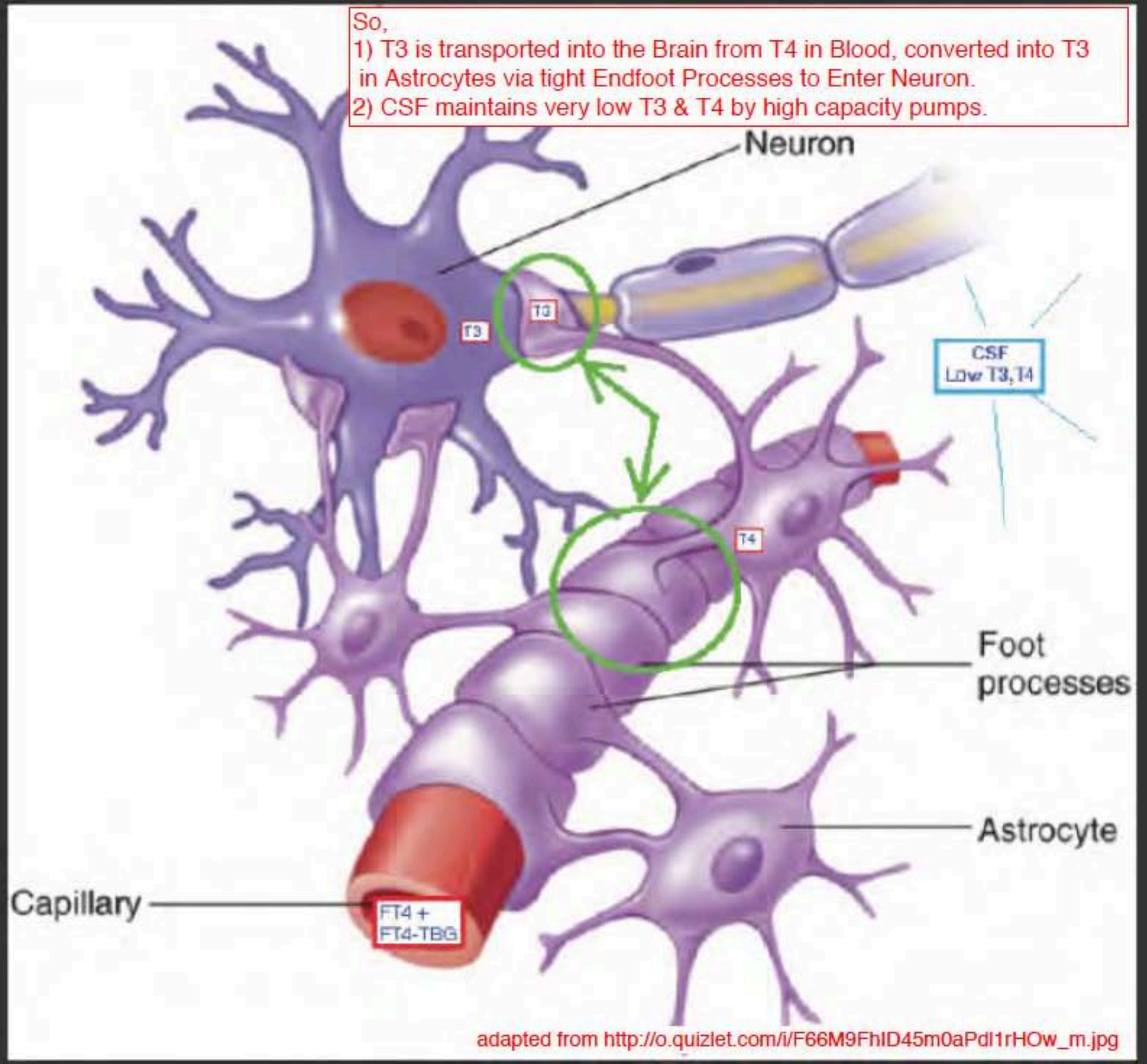


FIGURE 4: Proposed model of neuroglia-neuron interaction of thyroid hormone signaling in the brain. D2 activates the prohormone T4 in glial cells (astrocytes and tanycytes); the generated T3 exits the glial compartment and enters adjacent neurons, where it establishes a transcriptional footprint via liganding TR. Only the two best-characterized thyroid hormone transporters, OATP1C1 and MCT8, are indicated, but data are also accumulating on the role of LAT1 and LAT2 in the thyroid hormone transport both in neurons and astrocytes (discussed in Section 1). In the glial compartment LPS activates D2 transcription while sonic hedgehog (Shh) promotes D2 inactivation via WSB1—mediated ubiquitination; both hypoxia and Shh activate D3 gene transcription in neurons. Figure modified from Freitas et al. American Society for Clinical Investigation [23].

So,
1) T3 is transported into the Brain from T4 in Blood, converted into T3 in Astrocytes via tight Endfoot Processes to Enter Neuron.
2) CSF maintains very low T3 & T4 by high capacity pumps.



adapted from http://o.quizlet.com/i/F66M9FhID45m0aPdI1rHOw_m.jpg

CLINICAL IMPLICATIONS

Annals of Thyroid Research

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Research Article

TSH Should not be used as a Single Marker of Thyroid Function

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Received: August 07, 2018; **Accepted:** August 31, 2018; **Published:** September 07, 2018

Abstract

Context: Thyroid Stimulating Hormone (TSH) alone is often used as a primary marker to screen for thyroid function. Significant intra-individual variation of TSH concentrations occur in healthy individuals. Intra-individual sex and time-based variations pose the question of whether TSH can reliably screen for thyroid disorders.

Objective: To quantify the degree of diurnal fluctuations in TSH concentrations of healthy individuals and assess its diagnostic reliability. To propose preliminary sex and time dependent TSH reference intervals.

Design and Methods: Healthy volunteers (n=102) were recruited from 4 participating sites. Couplet (AM and PM) serum samples were drawn and analyzed for TSH concentration using immunoassay.

Results: Significant AM to PM increases in TSH levels for both men ($P < 0.0001$) and women ($P = 0.0003$) were noted.

Conclusion: TSH should not be used as a single marker for the assessment of thyroid function. We recommend that TSH be used in conjunction with Free Thyroxine (FT4), Free Triiodothyronine (FT3), and Total T3 measured by LCMS/MS.

Keywords: Thyroid stimulating hormone; Congenital hypothyroidism; Immunoassays; Thyroid function

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frontiers in Endocrinology

EDITORIAL
published: 05 June 2018
doi: 10.3389/fendo.2018.00291

Editorial: "Homeostasis and Allostasis of Thyroid Function"

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Keywords: thyroid hormones, thyronamines, homeostasis, allostasis, feedback regulation, hysteresis, TACITUS syndrome, syndrome T

Editorial on the Research Topic

Homeostasis and Allostasis of Thyroid Function

CURRENT CHALLENGES IN THYROIDOLOGY

A basic understanding of thyroid control involving pituitary thyrotropin (TSH) has become a cornerstone for the contemporary diagnosis of thyroid disorders. However, long-held simplistic interpretations of the classical feedback concept fall short of the elusive goal of a universally applicable and reliable diagnostic test. Diagnostic ambiguities may arise from the dynamic nature of thyroid

PROSPECTUS

Deeper insights in the physiology of thyroid function and its homeostatic control warrant a rethinking of diagnostic practice. The old paradigm employing TSH in the center of diagnostic work-up has to be replaced by a relational concept, where TSH is interlocked with FT4 and FT3, and multivariable distributions represent homeostatic equilibria (9, 30). This new approach allows for personalized interpretation of thyroid function and understands physiological influences as constituents of homeostatic/allostatic control modes (Hoermann et al.).

AUTHOR CONTRIBUTIONS