



Gruppo di Ricerca Geriatrica

AGGIORNAMENTI IN ENDOCRINOLOGIA GERIATRICA
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IPOTIROIDISMO E FUNZIONI COGNITIVE

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ISTITUTO CLINICO S. ANNA

Ruolo degli ormoni tiroidei

Gli ormoni tiroidei modulano svariati processi metabolici attraverso alterazioni nel consumo di ossigeno tissutale e variazioni nel metabolismo di proteine, lipidi, carboidrati e vitamine.

Modulano, inoltre, i segnali endocrini attraverso la regolazione della sintesi di proteine implicate nella sintesi e degradazione di altri ormoni e fattori di crescita

Metabolismo degli ormoni tiroidei

Nel plasma, gli ormoni tiroidei sono legati a numerose proteine; una piccola percentuale di T_3 e T_4 esiste in forma libera.

Mentre il T_4 è interamente prodotto dalla tiroide, il T_3 è quasi totalmente prodotto dalla deiodiazione del T_4 in tessuti non tiroidei (fegato e rene). Le deiodiasi agiscono in vari siti, dando origine anche a forme inattive come il rT_3 o il T_2 .

L'espressione e l'attività delle deiodasi varia a seconda del tessuto e dell'età dell'individuo.

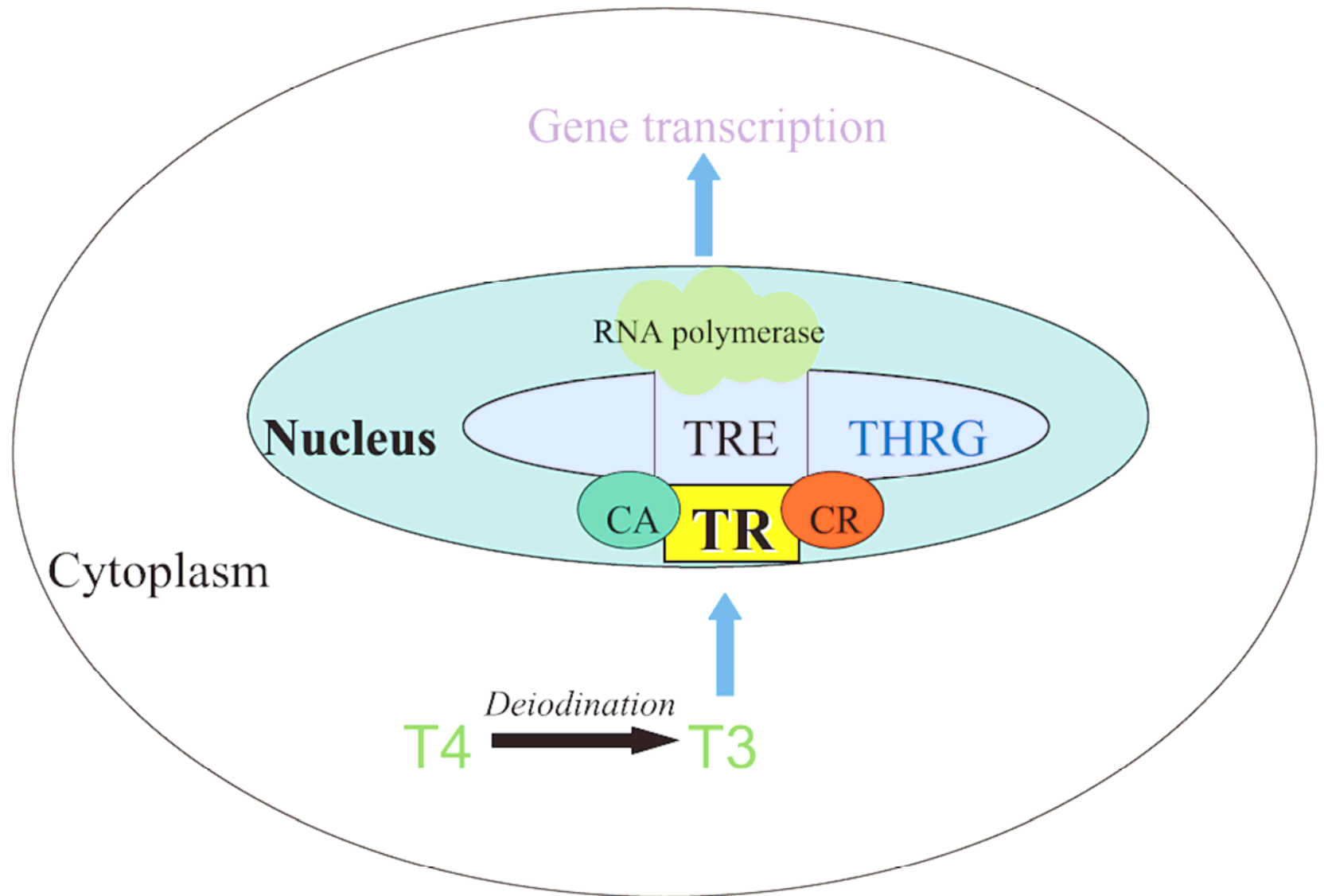


Figure 1 Transactivation of thyroid hormone responsive genes (THRG) through the binding of T3 to thyroid hormone receptors (TR) followed by T3-TR binding to the thyroid response element (TRE) located in the promoter regions of THRG. Transactivation is regulated by co-activators (CA) and co-repressors (CR) which bring about conformational changes in the DNA structure, altering the thyroid hormone responsive gene accessibility to RNA polymerase, the enzyme responsible for gene transcription.

Attività degli ormoni tiroidei

A livello cellulare, gli ormoni tiroidei sono essenziali per:

- Differenziazione
- Crescita
- Maturazione

I meccanismi sono specifici a livello cellulare, tissutale e di organo.

Gli ormoni tiroidei, con la loro azione integrativa, permettono il mantenimento dell'omeostasi cellulare durante le fasi di accrescimento e attività cellulare

Ormoni tiroidei (THs) e SNC

Gli ormoni tiroidei possono essere identificati nel SNC a partire dalla 10[°] settimana di gestazione.

Gli astrociti:

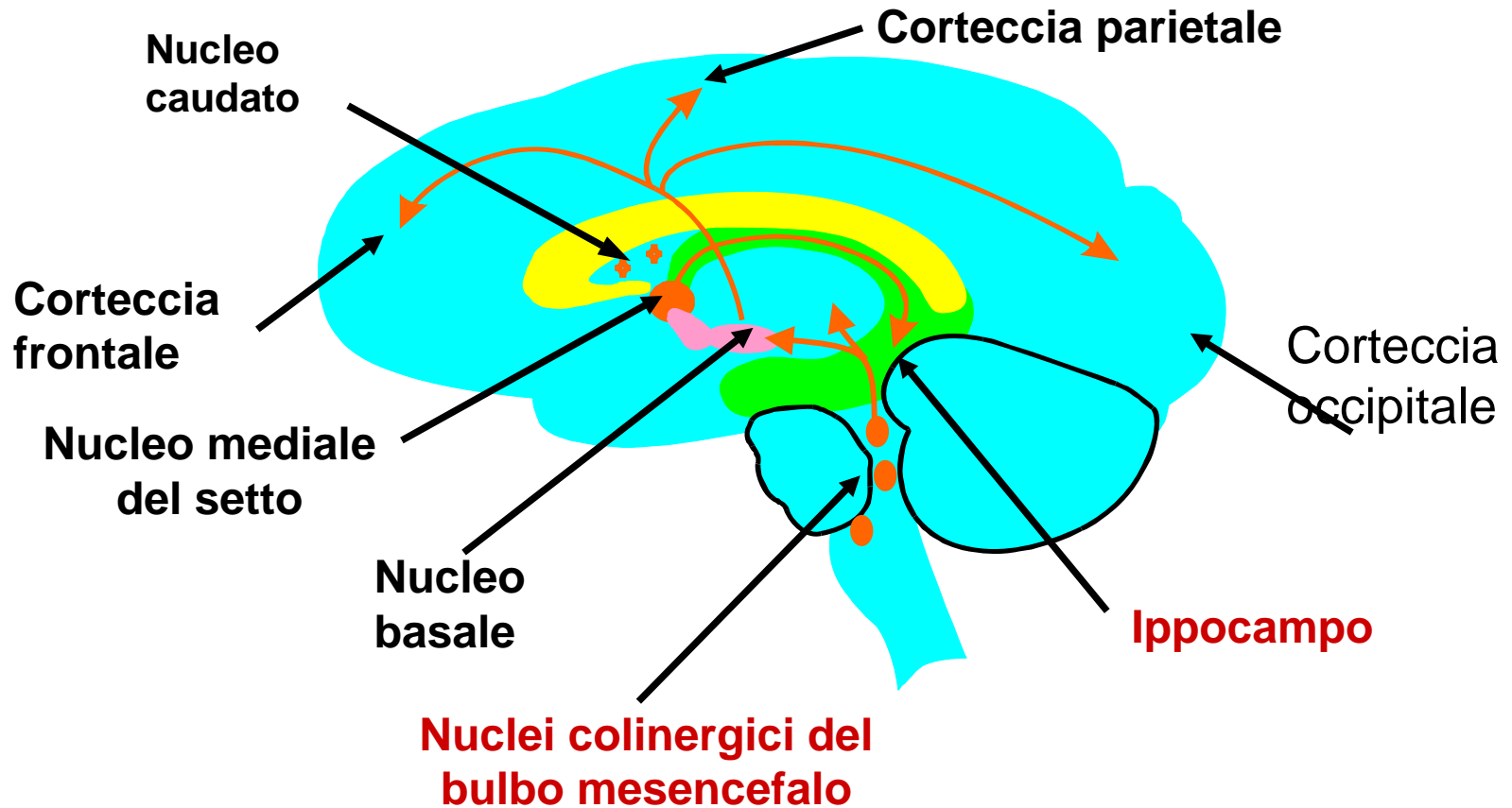
- posseggono recettori per gli ormoni tiroidei
- posseggono un trasportatore di glucosio THs-dipendente
- esprimono proteine strutturali sotto lo stimolo degli THs
- esprimono recettori β -adrenergici in maniera direttamente proporzionale alla presenza di THs

Ormoni tiroidei (THs) e SNC

Gli THs mediano la maturazione di specifiche aree cerebrali:

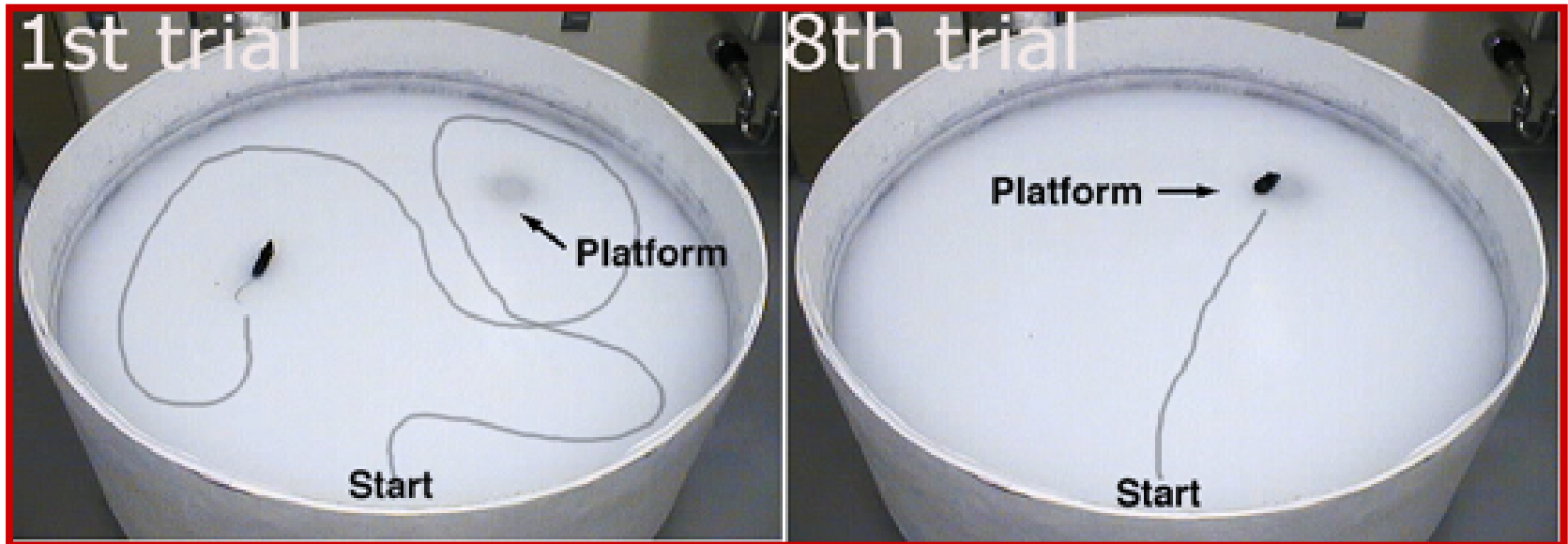
- 1) Topi resi ipotiroidei subito dopo la nascita sviluppano alterazioni della distribuzione neuronale a livello dell'ippocampo
- 2) Una specifica proteina dendritica (RC3) implicata nello sviluppo della connettività neuronale sinaptica è espressa dai neuroni corticali e striatali in maniera direttamente proporzionale alla concentrazione di THs
- 3) L'espressione delle MAPs (actina e tubulina) è THs-dipendente.

Ormoni tiroidei (THs) e acetilcolina (ACh)



Azione HTs sul NGF

Il watermaze di Morris



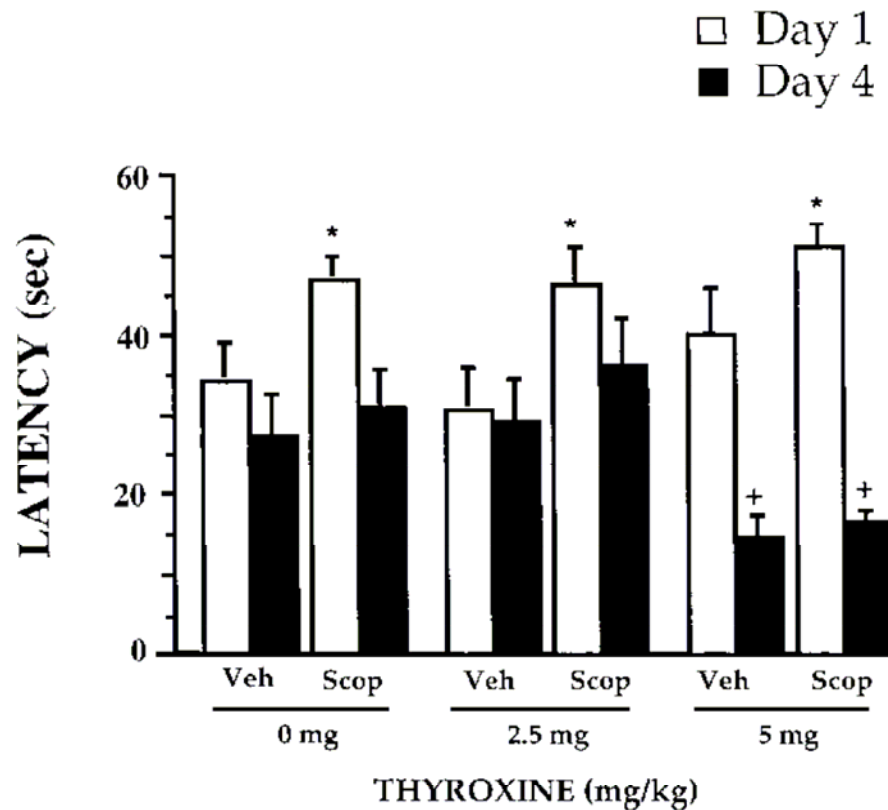
Valutazione degli effetti della somministrazione acuta e cronica di tiroxina sulle capacità cognitive del topo (vie colinergiche setto-ippocampali → apprendimento spaziale).

TIROXINA-VEICOLO

-

DEMENZA DA SCOPOLAMINA

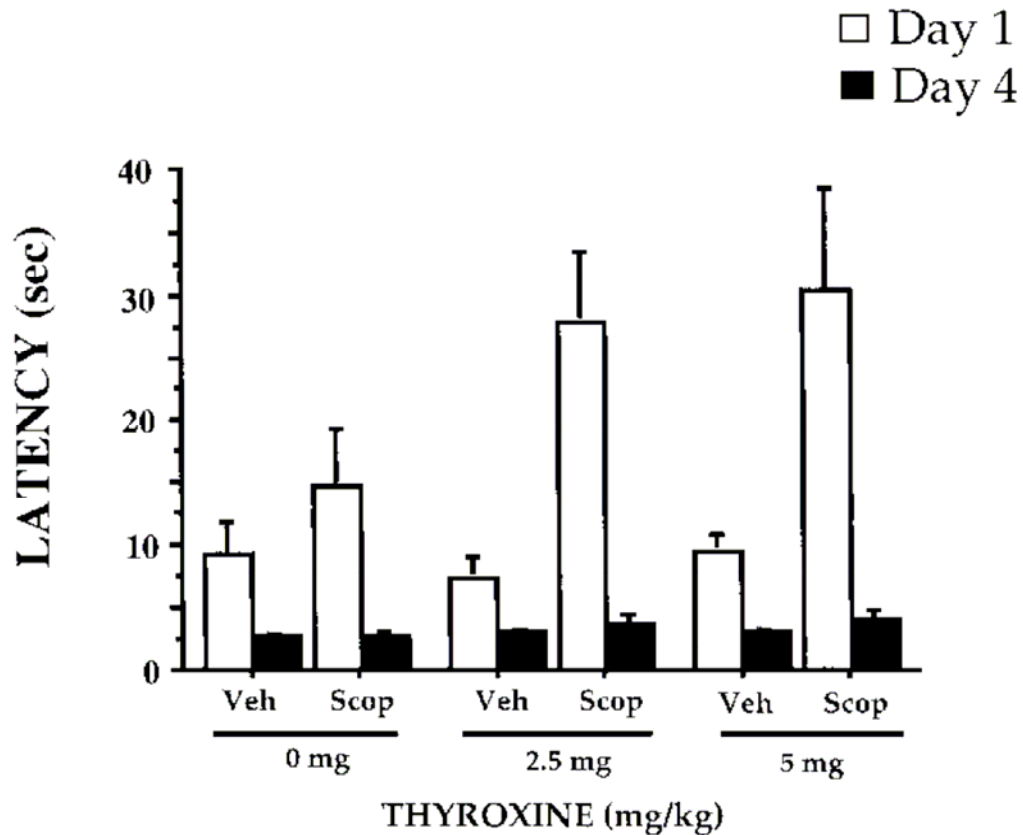
Somministrazione acuta di tiroxina



Il trattamento con tiroxina migliora la performance nel localizzare la piattaforma al 4° giorno.

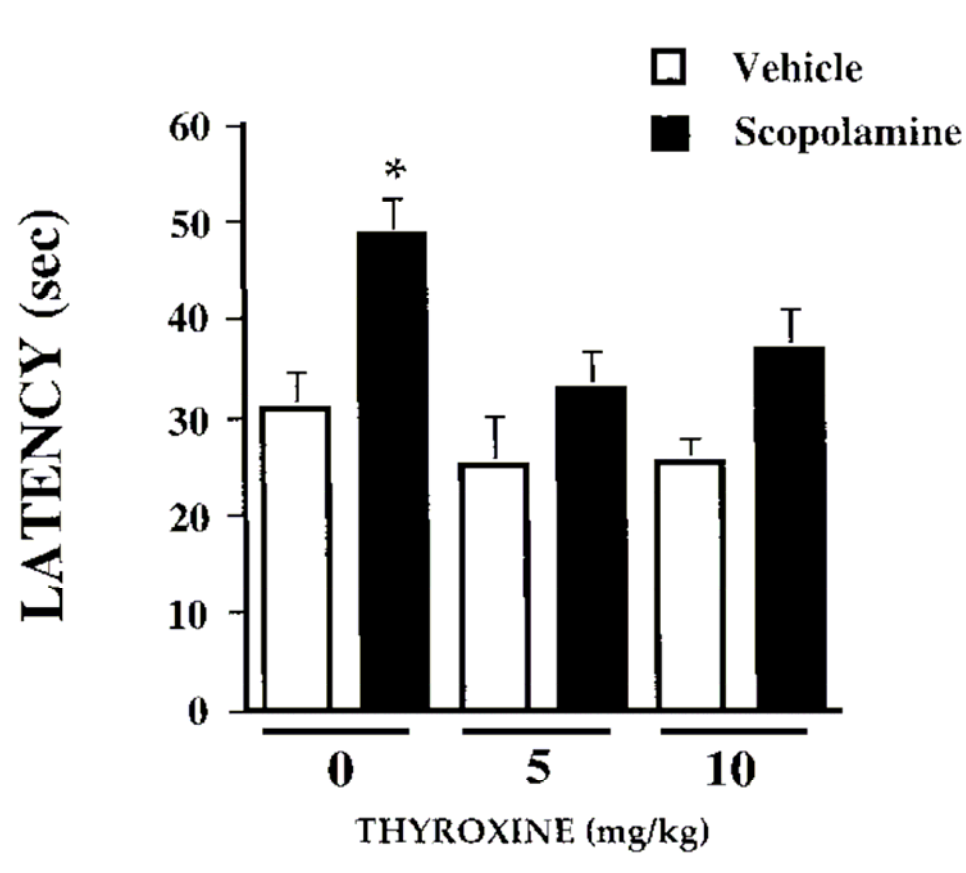
L'ormone tiroideo bilancia gli effetti della scopolamina.

Somministrazione acuta di tiroxina



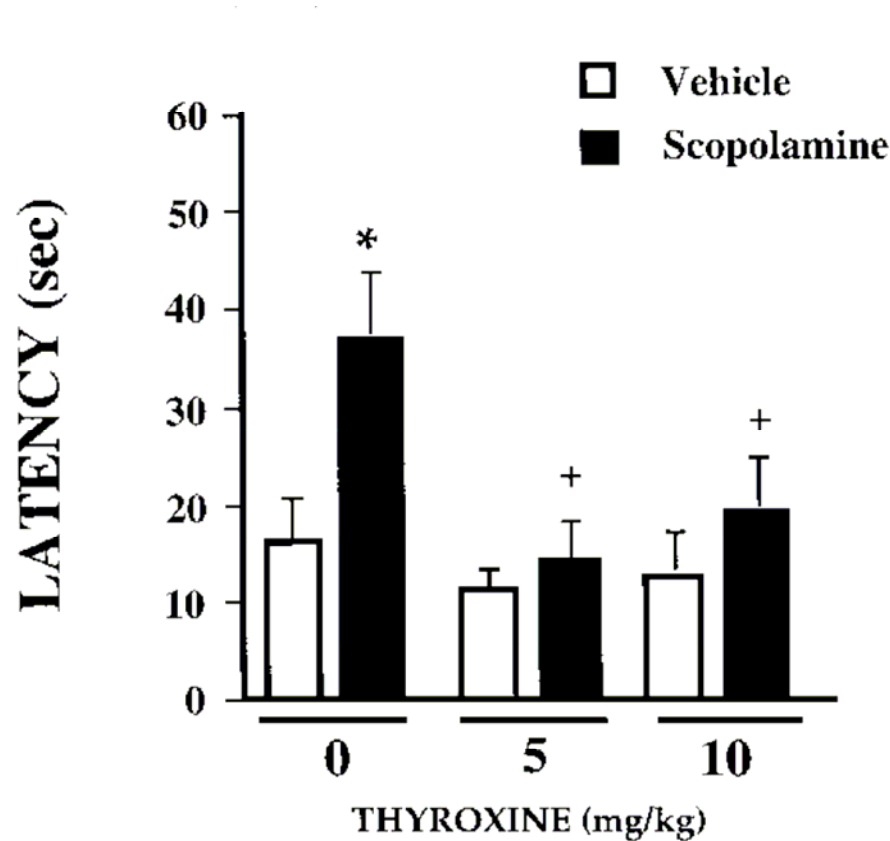
Se la piattaforma è resa visibile gli effetti della tiroxina vengono annullati. Il 4° giorno i topi sono ugualmente capaci di localizzare la piattaforma.

Somministrazione cronica di tiroxina



Il trattamento cronico con tiroxina migliora la performance nei topi trattati con scopolamina. Di per sé il trattamento cronico non produce effetti.

Somministrazione cronica di tiroxina



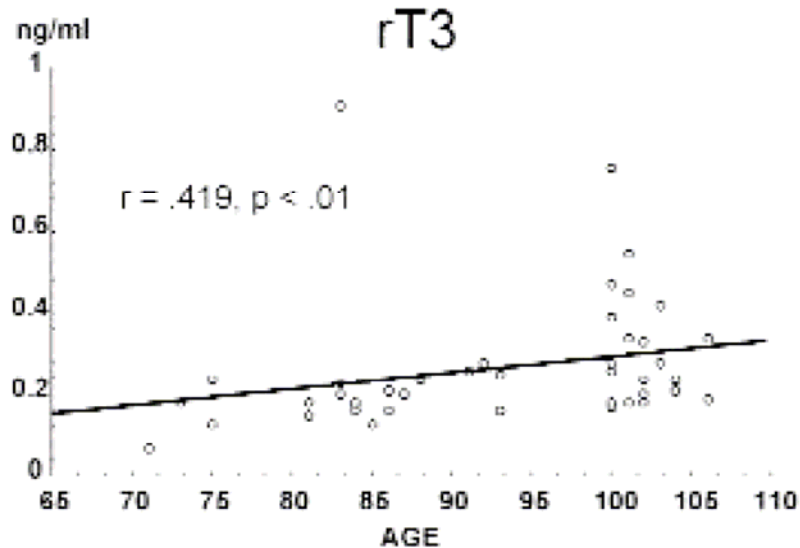
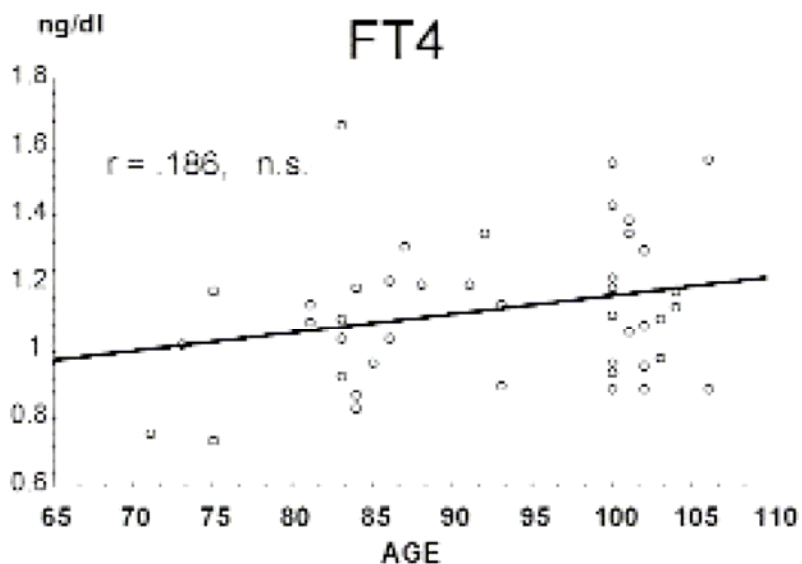
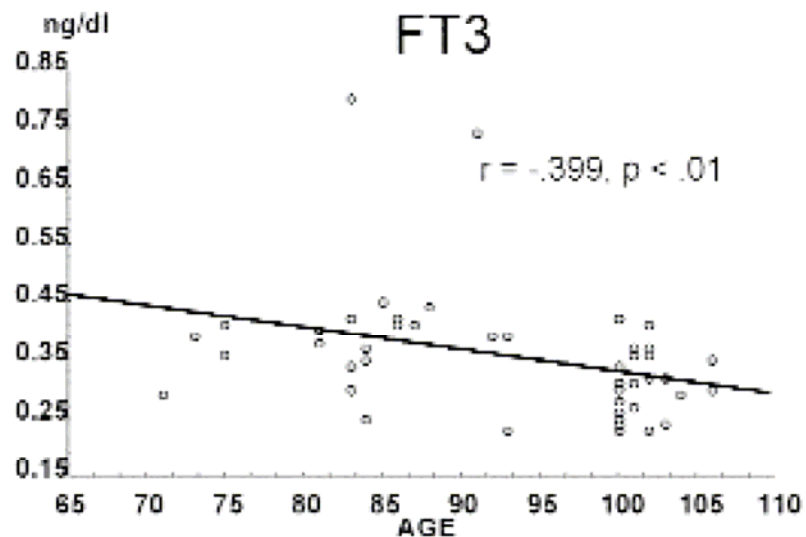
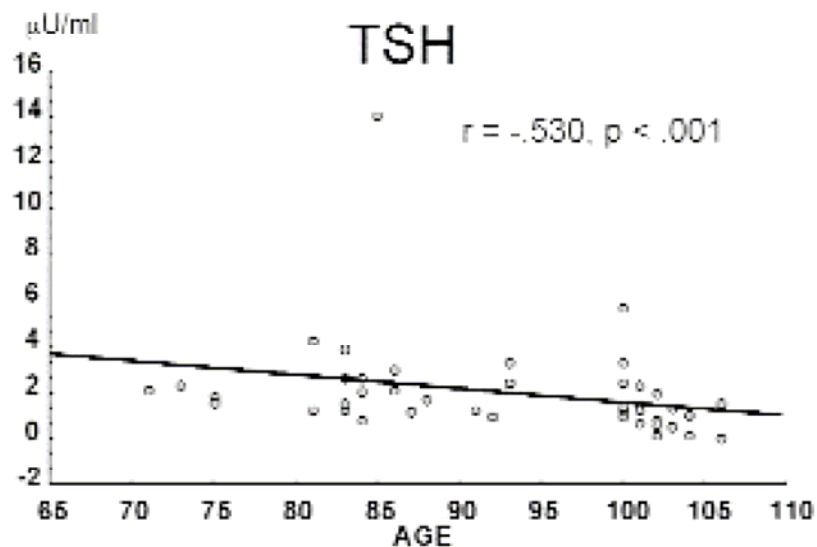
Se la piattaforma è resa visibile, gli effetti cronici della tiroxina sono efficaci solo nei topi trattati con scopolamina.

Invecchiamento e asse ipotalamo-ipofisi-tiroide

Negli anziani ospedalizzati è stata descritta un'elevata prevalenza di autoanticorpi anti-tiroide

Con l'avanzare dell'età si assiste a una modesta ma significativa riduzione età-dipendente della concentrazione sierica di TSH, riferibile ad una maggiore sensibilità delle cellule tireotrope nei confronti del feed-back negativo degli ormoni tiroidei o ad alterazioni dell'asse ipotalamo-ipofisi-tiroide

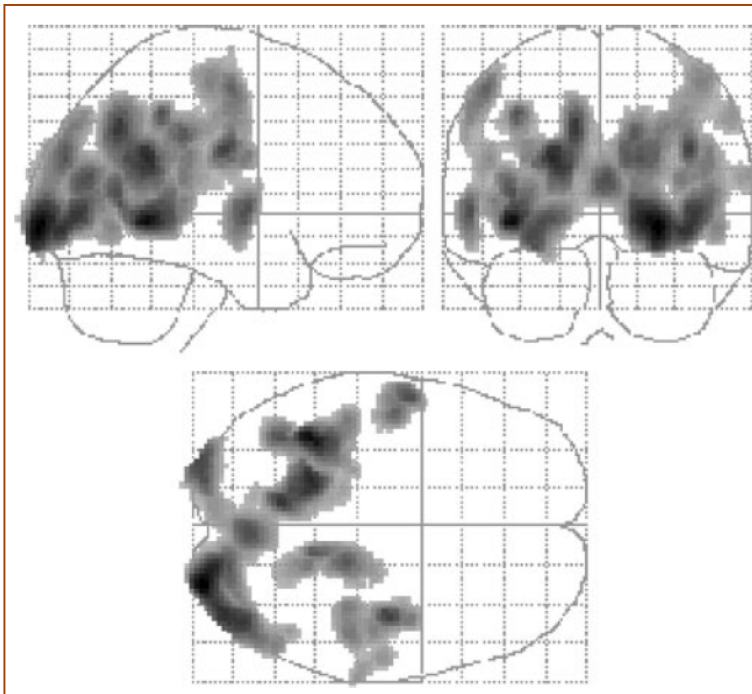
L'invecchiamento fisiologico, tuttavia, non sembra di per sé associarsi ad alterazioni della funzionalità tiroidea



Regional Cerebral Blood Flow in Patients with Mild Hypothyroidism

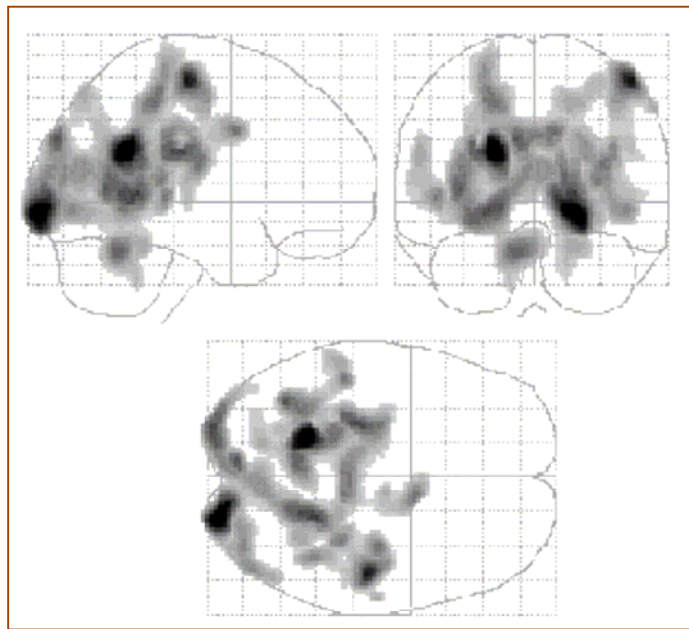
Yodphat Krausz, MD¹; Nanette Freedman, PhD¹; Hava Lester, PhD¹; J.P. Newman, PhD²; Gavriel Barkai, MD³; Moshe Bocher, MD¹; Roland Chisin, MD¹; and Omer Bonne, MD³

¹Department of Medical Biophysics and Nuclear Medicine, Hadassah–Hebrew University Medical Center, Jerusalem, Israel; ²Department of Neurology, Agnes Ginges Center for Human Neurogenetics, Hadassah–Hebrew University Medical Center, Jerusalem, Israel; and ³Department of Psychiatry, Hadassah–Hebrew University Medical Center, Jerusalem, Israel



Studio del flusso cerebrale con metodica SPECT in pazienti con lieve ipotiroidismo (TSH: $15,1 \pm 2,9$ mU/l).

BASALE: riduzione del flusso sanguigno cerebrale regionale nei lobi temporali e nella corteccia parieto-occipitale (BA 1, 3, 4, 18, 19, 23, 30, 31, 37, 41, 42)

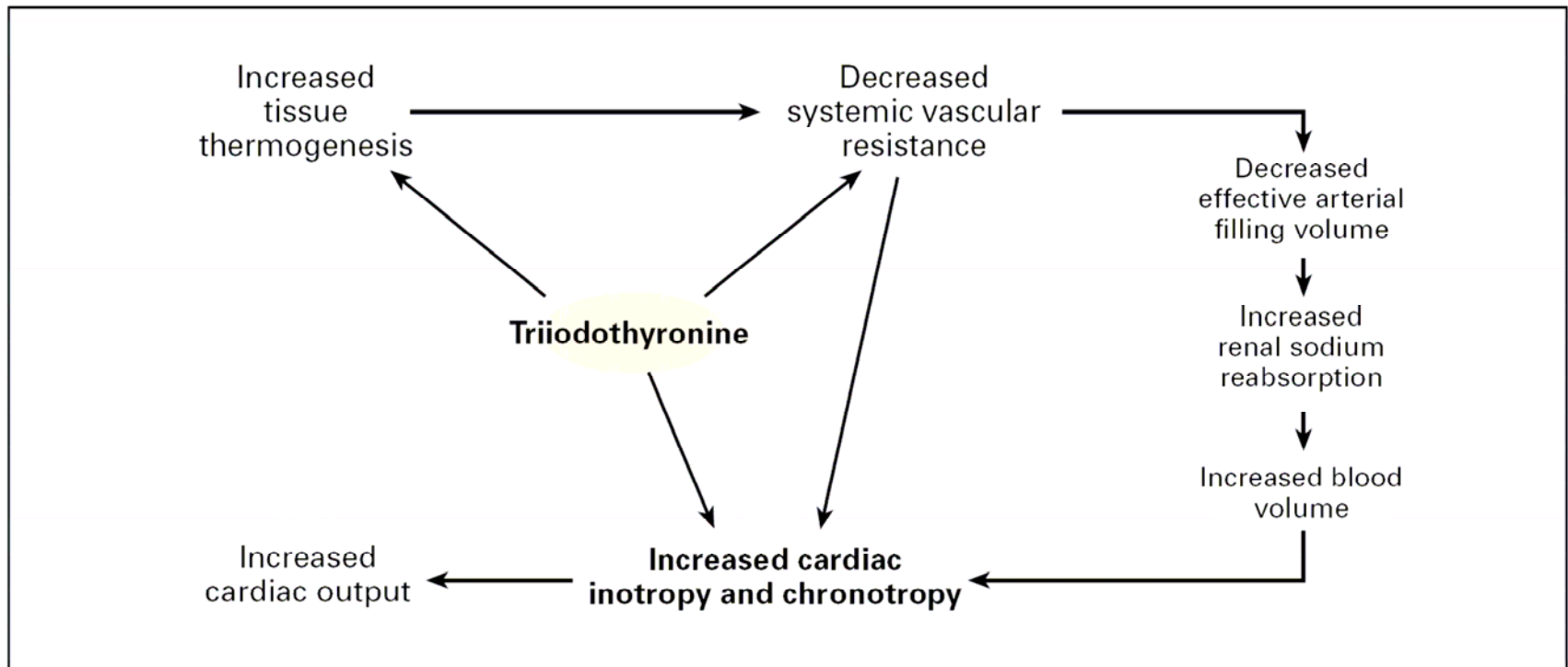


DOPO TRATTAMENTO (TSH: $1,7 \pm 1,2$ mU/L) persiste l'ipoperfusione cerebrale in BA 1, 3, 4, (giro pre e post-centrale), BA 18, 19 (giro occipitale inferiore, fusiforme e corteccia calcarina), BA 29, 41, 42 (insula) e BA 30, 31 (cingolo posteriore).

CONCLUSIONI: le vaste alterazioni del flusso sanguigno cerebrale regionale persistono anche dopo il ripristino dell'eutiroidismo.

Le regioni interessate mediano l'attenzione, la memoria, l'elaborazione visuo-spaziale e la velocità della risposta motoria suggerendo un ruolo degli ormoni tiroidei sul metabolismo cerebrale (\uparrow resistenza vascolare; \downarrow gittata cardiaca) anche se ciò non spiega la selettività di tali deficit.

Ormoni tiroidei e sistema cardiovascolare



Ormoni tiroidei (THs) e sviluppo del SNC

L'ipotiroidismo perinatale si associa a ritardo mentale (cretinismo). Il cretinismo endemico si caratterizza per alterazioni neurologiche (deficit corticale e dei gangli della base) motorie (rigidità con spasticità da disfunzione piramidale) e nello sviluppo cocleare

Nei topi l'ipotiroidismo fetale o neonatale produce alterazioni della connettività sinaptica, alterazioni neurotrasmettitoriali e demielinizzazione

L'ipotiroidismo murino conseguente a tiroidectomia post-natale determina riduzione dei livelli di glucosio a livello corticale (specialmente aree uditive)

Ormoni tiroidei (THs) e disturbi neurologici nell'adulto

Alterazioni sia neurologiche che comportamentali

- 1) Psicosi depressiva
- 2) Atassia cerebellare
- 3) Deficit mnesico
- 4) Allucinazioni
- 5) Delirium
- 6) Deliri
- 7) Assenza delle onde α all'EEG

Hypothyroidism Presenting as Psychosis: Myxedema Madness Revisited

Thomas W. Heinrich, M.D. and Garth Grahm, M.D.

*Department of Internal Medicine, Massachusetts General Hospital, Harvard Medical School,
Boston USA*

CASE REPORT

J Clin Psychiatry, 2003

Ms. A. 73 anni

Di carattere piuttosto introverso, non presenta significative limitazioni funzionali nelle IADL e BADL. Anamnesi patologica remota sostanzialmente muta, se si eccettua per un ipovisus sinistro presente da circa un anno e che si accentua nelle ore serali, per il quale non ha mai voluto eseguire accertamenti medici.

Da due settimane presenta allucinazioni uditive e visive (“una voce dentro di me mi annuncia i programmi della TV; vedo insetti che camminano sul soffitto”).

Giunta in PS:

Parametri vitali stabili.

Obiettività cardio-polmonare nella norma.

Cute secca e capelli sottili e fragili. Tiroide in sede.

Esame neurologico negativo per deficit focali, significativo ritardo nella fase di rilascio dei riflessi tendinei profondi. Vigile, collaborante ma con frequenti allucinazioni visive e uditive durante il colloquio.

Tc encefalo: leucoaraiosi.

TSH: 53 mUI/ml

FT₃: 1,1 ng/dl

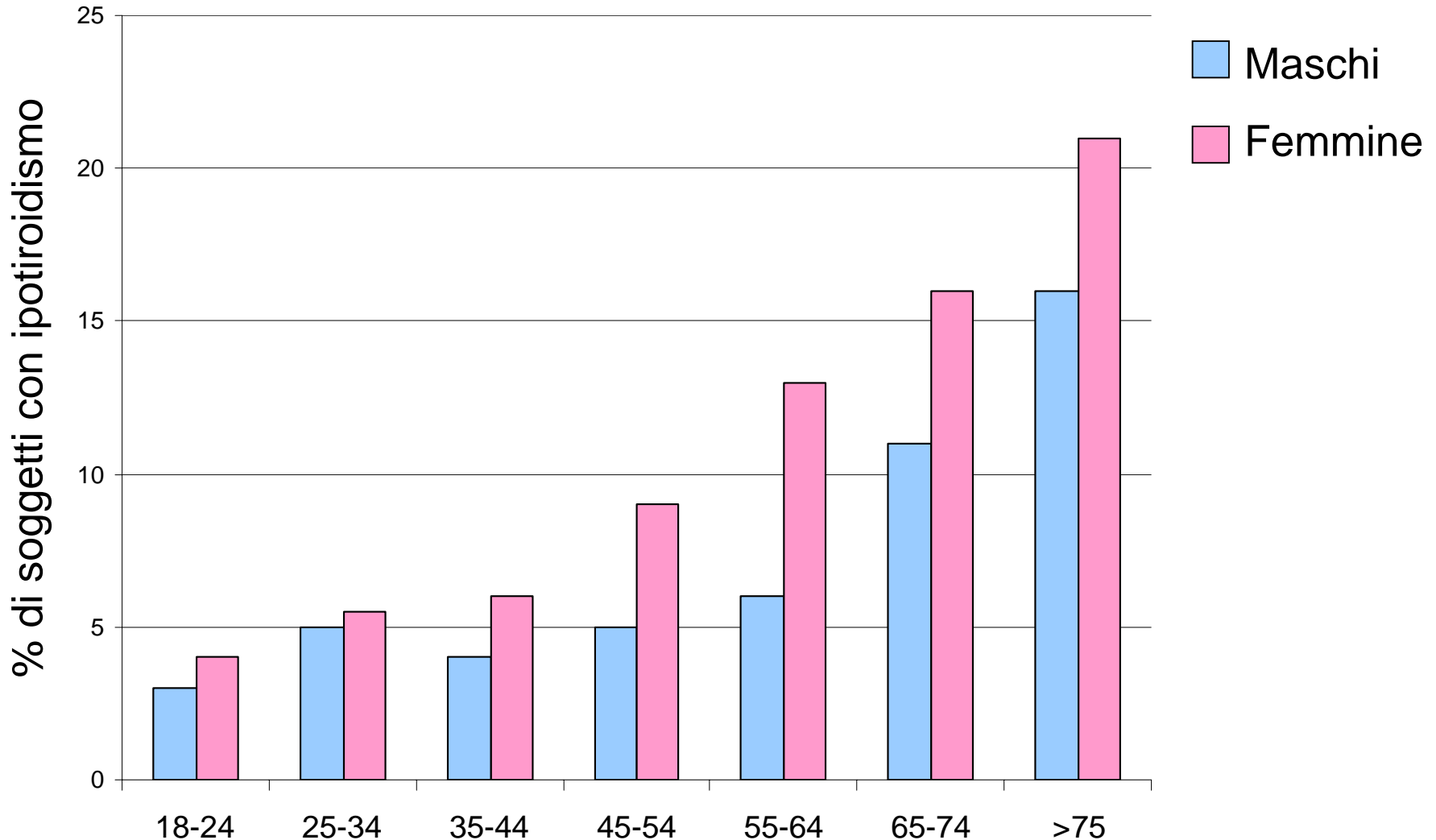
FT₄: 0,2 ng/dl

Trattata con L-tiroxina 25 mcg e risperidone 0,5 mg con regressione dei sintomi dopo 2 settimane.

Percentuale di soggetti con ipotiroidismo per sesso ed età

The Colorado Thyroid Disease Prevalence Study

(Arch Int Med; 2000;160:526-34)



Incidence and Causes of Nondegenerative Nonvascular Dementia

A Population-Based Study

David S. Knopman, MD; Ronald C. Petersen, MD, PhD; Ruth H. Cha, MS; Steven D. Edland, PhD; Walter A. Rocca, MD, MPH

Background: Information on the incidence of nondegenerative and nonvascular dementia is limited.

Design: We used the records-linkage system of the Rochester Epidemiology Project to ascertain incident cases of dementia in Rochester, Minn, from January 1, 1990, through December 31, 1994. To define causes of dementia, we reviewed all diagnoses, imaging study results, laboratory test results, and clinical courses, as recorded historically in the patient dossier.

Results: We found 560 incident cases of dementia, and 60 of them (10.7%) had onset before the age of 70 years (younger-onset group). Forty-three cases (7.7%) were due to nondegenerative nonvascular causes and represented 30.0% of the total in the younger-onset group, but only 5.0% of the total in the older-onset group (aged 70-99

years). The most common nondegenerative nonvascular causes were cancer with or without brain metastases (n=13), chronic alcoholism (n=7), and chronic mental illness (n=11). There were no cases of dementia due to normal-pressure hydrocephalus, subdural hematoma, hypothyroidism, vitamin B₁₂ deficiency, or neurosyphilis. There were 2 individuals with acute confusion due to subdural hematoma and 1 with hypothyroidism whose cognition normalized with therapy.

Conclusions: Nondegenerative nonvascular causes were more common than expected in patients with a younger onset of dementia. None of the patients with dementia reverted to normal with treatment of the putative reversible cause.

Arch Neurol. 2006;63:218-221

Sintomi psichiatrici dell'ipotiroidismo

Nei pazienti anziani, le alterazioni psichiatriche rappresentano spesso i sintomi d'esordio

Causa di errore diagnostico

I sintomi più comunemente presenti sono:

depressione, labilità emotiva, rallentamento ideo-motorio, deficit di memoria e di attenzione

Le alterazioni percettive possono coinvolgere il tatto, l'udito e la vista

CLINICAL STUDY

Thyroid and adrenal axis in major depression: a controlled study in outpatients

Jantien P Brouwer, Bente C Appelhof, Witte J G Hoogendijk⁴, Jochanan Huyser¹, Erik Endert², Cassandra Zuketto, Aart H Schene¹, Jan G P Tijssen³, Richard Van Dyck⁴, Wilmar M Wiersinga and Eric Fliers

Abstract

Objective: Major depressive disorder has been associated with changes in the hypothalamus–pituitary–thyroid (HPT) axis and with hypercortisolism. However, the changes reported have been at variance, probably related to in- or outpatient status, the use of antidepressant medication and the heterogeneity of depression. We therefore conducted a controlled study in unipolar depressed outpatients who had been free of antidepressants for at least 3 months.

Design: We assessed endocrine parameters in 113 depressed outpatients and in 113 sex- and age-matched controls.

Methods: Patients were included if they had a major depression according to a Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition (SCID-IV) and if they had a 17-item Hamilton rating scale for depression (HRSD) score of ≥ 16 . Endocrine parameters contained serum concentrations of TSH, (free) thyroxine, tri-iodothyronine, cortisol, thyroid peroxidase (TPO) antibody titre and 24-h urinary excretion of cortisol.

Results: The serum concentration of TSH was slightly higher in depressed patients as compared with controls ($P < 0.001$), independent of the presence of subclinical hypothyroidism and/or TPO antibodies ($n = 28$). All other HPT axis parameters were similar in both groups. The 24-h urinary cortisol excretion was similar in patients and controls. In atypical depression, serum cortisol was lower than in non-atypical depression ($P = 0.01$). Patients with neither melancholic depression nor severe depression ($\text{HRSD} \geq 23$) had altered endocrine parameters. Finally, serum TSH values could not be related to cortisol values.

Conclusion: When compared with matched control subjects, outpatients with major depression had slightly higher serum TSH, while urinary cortisol levels were similar. Furthermore, we observed lower serum cortisol in atypical depression than in non-atypical depression.

Comorbidità nel disturbo bipolare

Comorbid Condition	Mean Rate of Comorbidity (%)	Percentage Range Across Studies (%)
Any Axis I disorder	65	50–70
Substance use disorder	56	34–60
Alcohol abuse	49	30–69
Other drug abuse	44	14–60
Anxiety disorder	71	49–92
Social phobia	47	
PTSD	39	
Panic disorder	11	3–21
OCD	10	2–21
Binge-eating disorder	13	
Personality disorder	36	29–38
Migraine	28	15–40
Overweight	58	
Obesity	21	
Type 2 diabetes	10	
Hypothyroidism	9	

OCD = obsessive-compulsive disorders; PTSD = posttraumatic stress disorder.

Is Subclinical Thyroid Dysfunction in the Elderly Associated with Depression or Cognitive Dysfunction?

Lesley M. Roberts, PhD; Helen Pattison, PhD; Andrea Roalfe, MSc; Jayne Franklyn, MD, PhD; Sue Wilson, PhD; F.D. Richard Hobbs, MB ChB; and James V. Parle, MD

Background: Widespread use of automated sensitive assays for thyroid hormones and thyroid-stimulating hormone (TSH) has increased identification of mild thyroid dysfunction, especially in elderly patients. The clinical significance of this dysfunction, however, remains uncertain, and associations with cognitive impairment, depression, and anxiety are unconfirmed.

Objective: To determine the association between mild thyroid dysfunction and cognition, depression, and anxiety in elderly persons.

Design: Cross-sectional study. Associations were explored through mixed-model analyses.

Setting: Primary care practices in central England.

Patients: 5865 patients 65 years of age or older with no known thyroid disease who were recruited from primary care registers.

Measurements: Serum TSH and free thyroxine (T_4) were measured. Depression and anxiety were assessed by using the Hospital Anxiety and Depression Scale (HADS), and cognitive functioning was established by using the Middlesex Elderly Assessment of Mental State and the Folstein Mini-Mental State Examination. Comorbid conditions, medication use, and sociodemographic profiles were recorded.

Results: 295 patients met the criteria for subclinical thyroid dysfunction (127 were hyperthyroid, and 168 were hypothyroid). After confounding variables were controlled for, statistically significant associations were seen between anxiety (HADS score) and TSH level ($P = 0.013$) and between cognition and both TSH and free T_4 levels. The magnitude of these associations lacked clinical relevance: A 50-mIU/L increase in the TSH level was associated with a 1-point reduction in the HADS anxiety score, and a 1-point increase in the Mini-Mental State Examination score was associated with an increase of 50 mIU/L in the TSH level or 25 pmol/L in the free T_4 level.

Limitations: Because of the low participation rate, low prevalence of subclinical thyroid dysfunction, and other unidentified recruitment biases, participants may not be representative of the elderly population.

Conclusions: After the confounding effects of comorbid conditions and use of medication were controlled for, subclinical thyroid dysfunction was not associated with depression, anxiety, or cognition.

Psicosi

Dal 5 al 15% dei pazienti con ipotiroidismo presentano una forma di psicosi

I pazienti possono presentare allucinazioni visive e uditive, deliri, perseverazioni e disturbi paranoidei. Tipicamente, a differenza del delirium, non si hanno franche alterazioni dello stato di vigilanza



SINDROME DI CAPGRAS: il paziente vive come in un universo parallelo, dove impostori hanno preso il posto dei familiari

Neurocognitive Deficits in Hypothyroid Adults*

Cognitive Domain	Source, y	Impaired	Treatment Outcome	Measures
General intelligence	Crown, ⁵⁰ 1949	Yes	Improvement after 3 mo	RPM, MHV, SVT
	Haggerty et al, ⁵¹ 1986	Yes	No change after 8 mo	WAIS, DRS
	Mennemeier et al, ⁵² 1993	Yes	Not generally affected	WAIS-R
Complex attention and concentration	Mennemeier et al, ⁵² 1993	No	Improvement after 7 mo	PASAT
	Osterweil et al, ⁵³ 1992	Yes	Improvement after 5 mo	TMT (Part A), SDMT
	Whybrow et al, ⁵⁴ 1969	Yes	No change after 10.5 mo	TMT (Parts A and B)
Memory	Haggerty et al, ⁵¹ 1986	Yes	NA	WMS
	Mennemeier et al, ⁵² 1993	Yes	No change (but treatment may arrest further decline)	CVMT, FMT, RCFT, SRT, WMS
Perceptual and visuospatial function	Osterweil et al, ⁵³ 1992	Yes	Improvement	Inglis Paired Associates Learning Test
	Mennemeier et al, ⁵² 1993	Yes	Improvement	WAIS-R (Block Design and Object Assembly subsets)
	Osterweil et al, ⁵³ 1992	Yes	No improvement	Cube Copying
Language (expressive)	Mennemeier et al, ⁵² 1993	No	NA	Word Fluency Test
	Osterweil et al, ⁵³ 1992	Yes	No improvement	Word Fluency Test (Animals)
Language (receptive)	Osterweil et al, ⁵³ 1992	No	NA	Word Discrimination, Oral Reading
Executive/frontal system functions	Mennemeier et al, ⁵² 1993	No	NA	Go-No Go, Word Fluency Test, Luria <i>m</i> 's and <i>n</i> 's
	Whybrow et al, ⁵⁴ 1969	Yes	No change	Porteus Mazes
General screening	Osterweil et al, ⁵³ 1992	Yes	No movement	Modified Mini-Mental State Examination
	Peabody et al, ⁵⁵ 1986	Yes	Progressive decline	Mini-Mental State Examination
Motor function	Mennemeier et al, ⁵² 1993	No	No consistent change	Grip Strength

* Data pertain only to studies that focused on outcome following treatment. RPM indicates Raven Progressive Matrices Test; MHV, Mill Hill Vocabulary Scale; SVT, Shipley Vocabulary Test; WAIS, Wechsler Adult Intelligence Scale; DSR, Dementia Rating Scale (Mattis); WAIS-R, Wechsler Adult Intelligence Scale-Revised; PASAT, Paced Auditory Serial Addition Task; TMT, Trail-Making Test; SDMT, Symbol Digit Modalities Test; NA, not applicable; CVMT, Continuous Visual Memory Test; FMT, Milner Facial Memory Test; RCFT, Rey-Osterrieth Complex Figure Test; SRT, Selective Reminding Test (Buschke); WMS, Wechsler Memory Scale.

The association between Alzheimer's disease and thyroid disease in Rochester, Minnesota

F. Yoshimasu, MD; E. Kokmen, MD; I.D. Hay, MD, PhD; C.M. Beard, RN, MPH; K.P. Offord, MS;
and L.T. Kurland, MD, DrPH

Article abstract—To determine whether an association exists between Alzheimer's disease (AD) and thyroid disease, we carried out two studies in the population of Rochester, Minnesota. We reviewed medical records of a cohort of 198 women with histologically confirmed Hashimoto's thyroiditis (1935 to 1974) for evidence of subsequent dementia, applying the criteria used for dementia in a previous determination of incidence and prevalence rates in this population. From a total of 4,197 person-years of follow-up, eight cases of AD were diagnosed, whereas the expected number was 5.8. The standardized morbidity ratio was 1.37, which failed to reach statistical significance. The second study was a retrospective case-control comparison that sought any relationship between AD and all thyroid disorders, using a previously identified (1960 to 1979) AD cohort (N = 646) and their age- and sex-matched controls. For myxedema there was a positive association for AD without significance, whereas in Graves' disease there was a significant negative association for AD.

NEUROLOGY 1991;41:1745-1747

Thyroid Function in Patients With Alzheimer Disease: Implications on Response to Anticholinesterase Treatment

Elisabeth Kapaki, MD, George P. Paraskevas, MD,* Emily Mantzou, MSc,†
Apostolos Papapostolou, MD,* Maria Alevizaki, MD,† and Demetris Vassilopoulos, MD, PhD**

TABLE 1. TFTs at Baseline in AD Patients and Controls

	Controls	AD Patients (Entire Pretreated Group)	<i>P</i> (AD vs. Controls)
n (M/F)	24 (5/19)	28 (9/19)	NS*
Age (y)†	71.73 ± 7.81	74 ± 7.24	NS‡
MMSE	29 (26-30)	22 (16-25)	0.001§
T ₃ (ng/mL)	1.15 ± 0.22	1.17 ± 0.20	NS
T ₄ (μg/dL)	8.64 ± 1.94	9.85 ± 1.85	NS
fT ₃ †	5.42 ± 0.98	5.62 ± 0.91	NS
fT ₄ (pmol/L)†	16.01 ± 3.22	19.01 ± 3.28	0.0098
TSH (μU/mL)¶	1.15 (0.01-5.60)	1.40 (0.05-8)	NS
Anti-TPO (U/mL)¶	3.55 (1-321)	14.80 (5-3000)	0.00006

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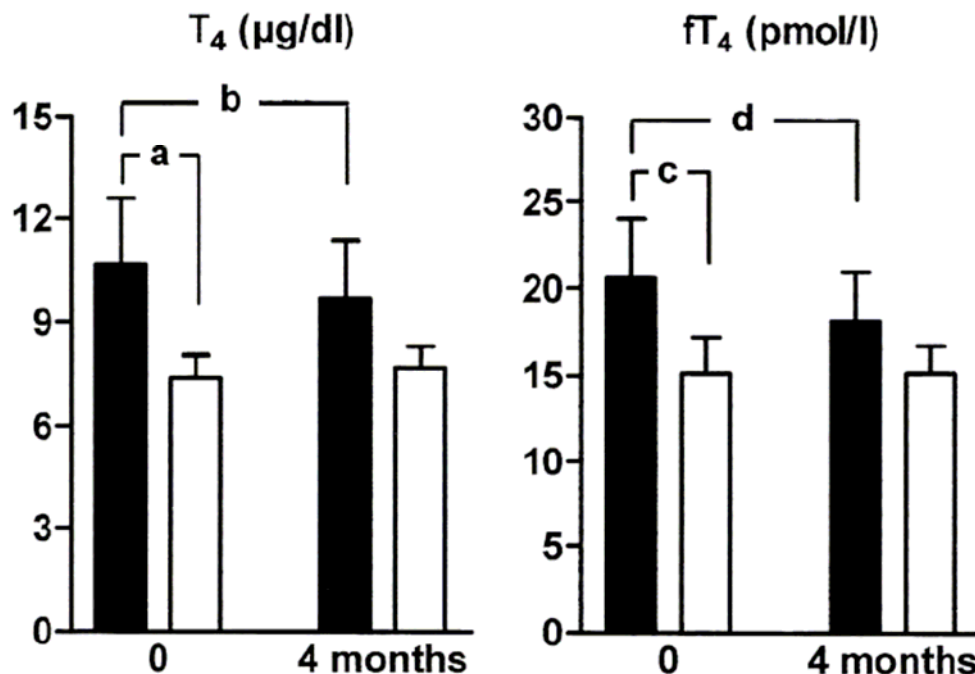


FIGURE 1. Adjusted means (SD) of T₄ and fT₄ levels in responders (black bars) and nonresponders (white bars) to AChE therapy at baseline and 4 months after treatment. ^a*P*=0.029, ^b*P*=0.045, ^c*P*=0.032, ^d*P*=0.0021.

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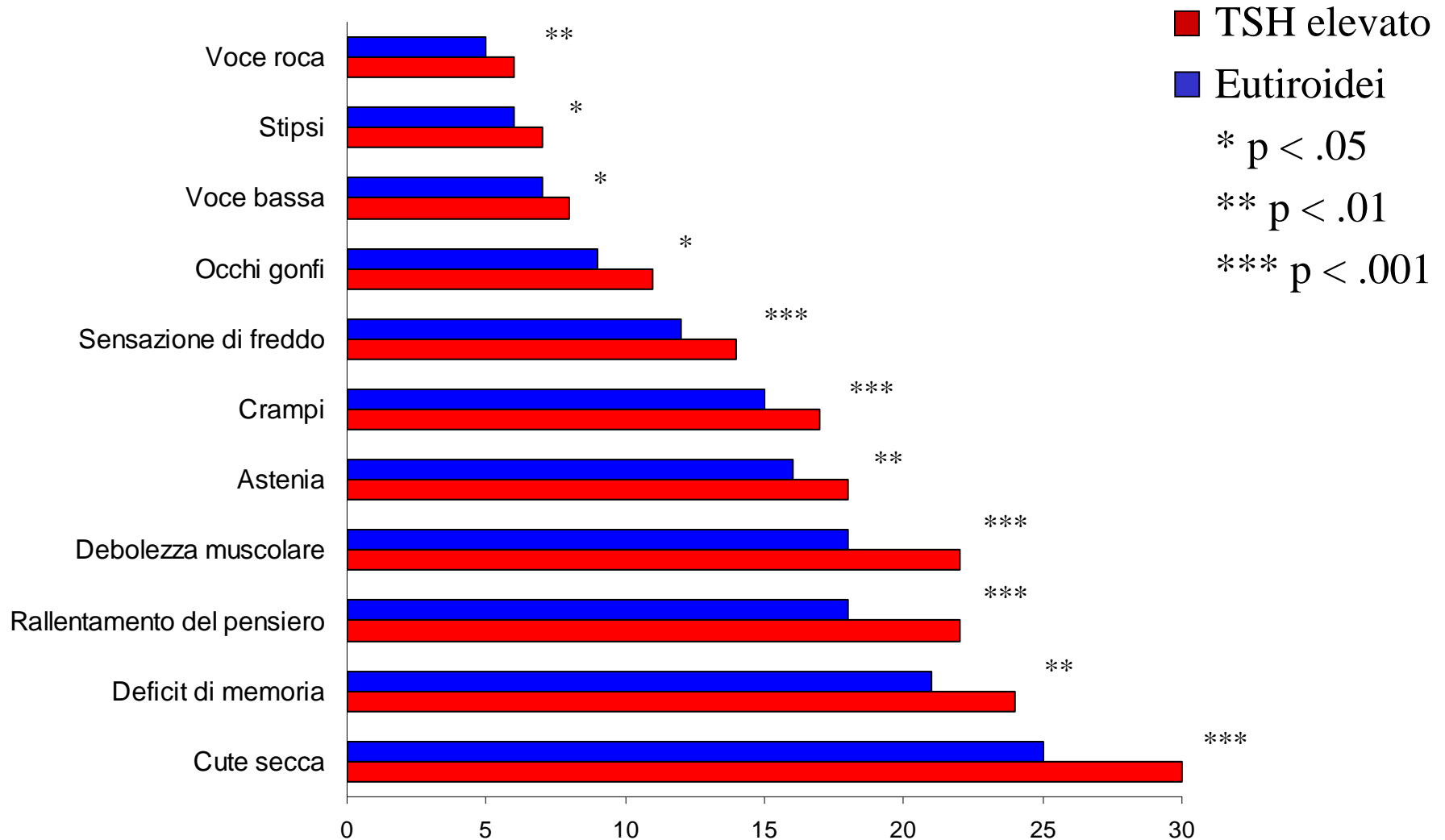
TABLE 2. TFTs Before and After Treatment With the Acetylcholinesterase Inhibitor Donepezil (n = 19)

	Before Treatment	After Treatment	<i>P</i> (Before vs. After Treatment)
T ₃ (ng/mL)	1.22 ± 0.20	1.16 ± 0.17	NS*
T ₄ (μg/dL)	9.85 ± 1.98	9.26 ± 1.58	0.038*†
fT ₃ §	5.89 ± 0.94	5.38 ± 0.60	0.027*
fT ₄ (pmol/L)§	19.17 ± 3.59 ^a	17.13 ± 2.6	0.0023*‡
TSH (μU/mL)‡	1.35 (0.40-8)	1.60 (0.39-7.2)	NS*
Anti-TPO (U/mL)‡	14.84 (5-2754) ^b	14.45 (5-2700) ^c	0.041
Anti-Tg (U/mL)‡	20.7 (8.60-2386)	18.95 (8.51-2250)	NS
MMSE	21 (14-24)	22 (13-24)	NS

Percentuale di soggetti eutiroidei e con elevato TSH che riportano ciascun sintomo

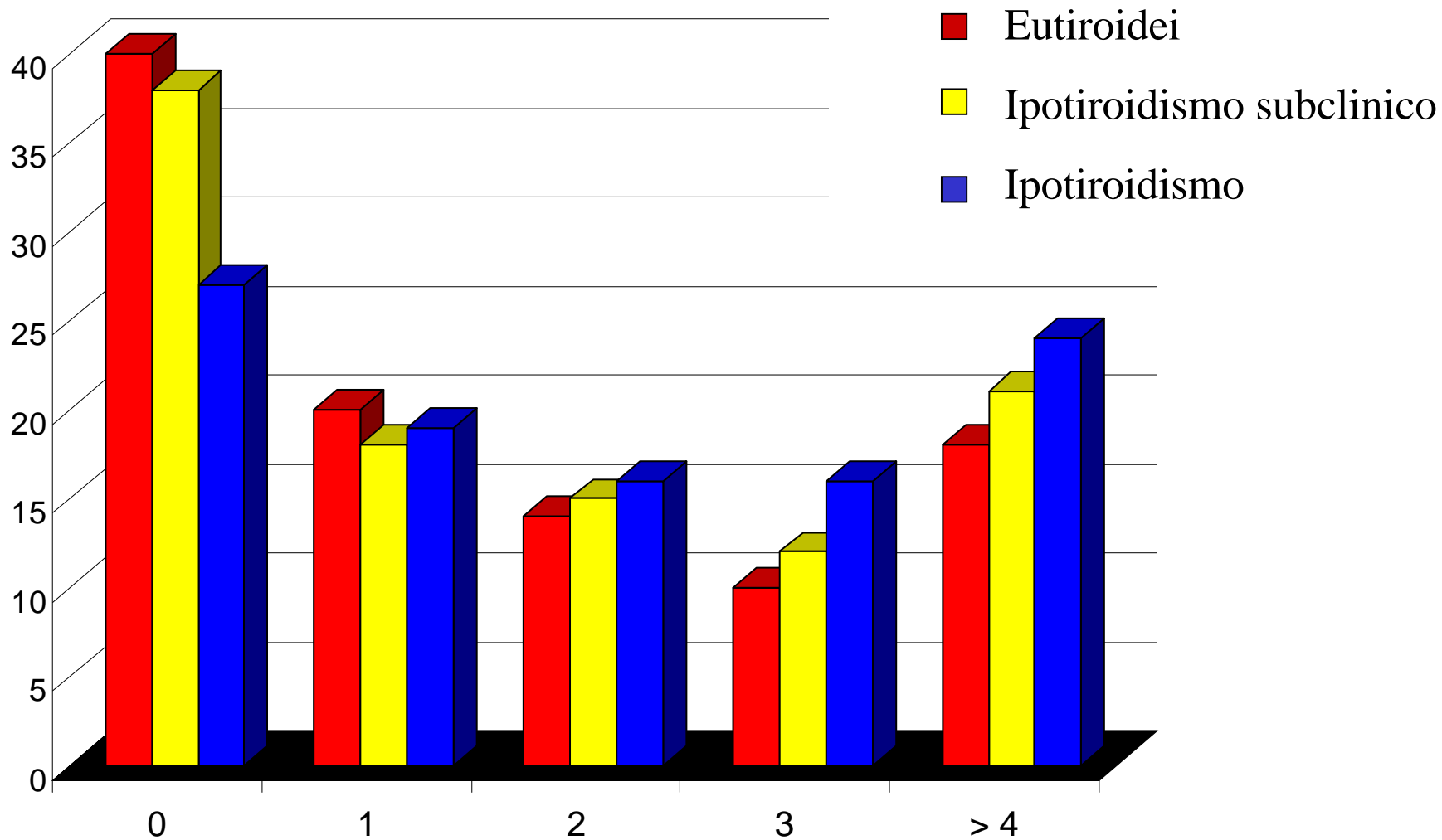
The Colorado Thyroid Disease Prevalence Study

(Arch Int Med; 2000;160:526-34)



Percentuale di soggetti che riportano 0, 1, 2, 3, 4 o più sintomi

(Arch Int Med; 2000;160:526-34)



Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

Conclusions In the general population of the oldest old, elderly individuals with abnormally high levels of thyrotropin do not experience adverse effects and may have a prolonged life span. However, evidence for not treating elderly individuals can only come from a well-designed, randomized placebo-controlled clinical trial.



Ceci n'est pas une pipe.