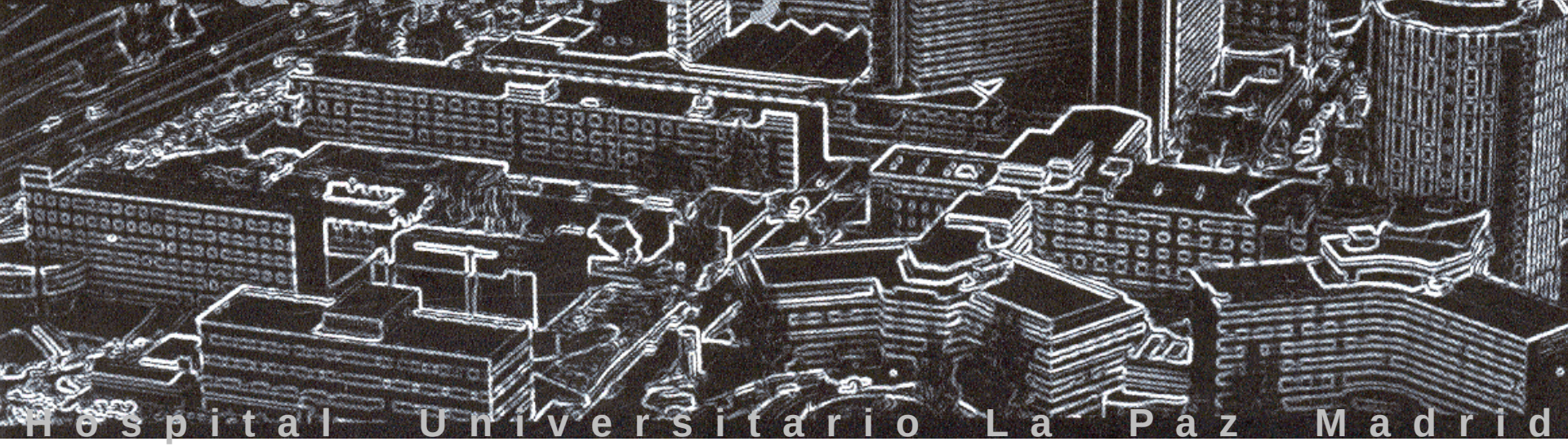


Alteraciones del metabolismo tiroideo en los trastornos del neurodesarrollo

Evidencias en modelos animales

José Carlos Moreno, *MD, PhD*

INGEMM - Instituto de Genética Médica y Molecular

Hospital Universitario La Paz. Madrid.

VIII Jornada Neurofisiológica

Hospital Ramón y Cajal, Madrid. 29 y 30 de Noviembre 2012

Tesis de la Charla (s)

Hipotiroidismo cerebral fetal

Permanente
Grave

Déficits Psicomotores

Trastornos Cognitivos

Cretinismo

Tesis de la Charla

Hipotiroidismo cerebral fetal

Permanente
Grave

Déficits Psicomotores

Trastornos Cognitivos

Trastornos del Neurodesarrollo

Cretinismo

TDAH

TEA

Tesis de la Charla

Hipotiroidismo cerebral fetal

Permanente
Grave

?

Déficits Psicomotores

Trastornos Cognitivos

Trastornos del Neurodesarrollo

Cretinismo

TDAH

TEA

Tesis de la Charla

Hipotiroidismo cerebral fetal

Permanente
Grave

Transitorio?
Leve?
Especifico de circuitos neuronales?

Déficits Psicomotores

Trastornos Cognitivos

Trastornos del Neurodesarrollo

Cretinismo

TDAH

TEA

Esquema de la Charla

- **Hormonas tiroideas y desarrollo cerebral**

  Hormonas tiroideas y desarrollo cerebral

  Genes diana de T3 en cerebro

  Hormonas tiroideas y embarazo

- **2 modelos animales de alteración tiroidea en TDAH.**

  Modelo Post-Receptor de T3.

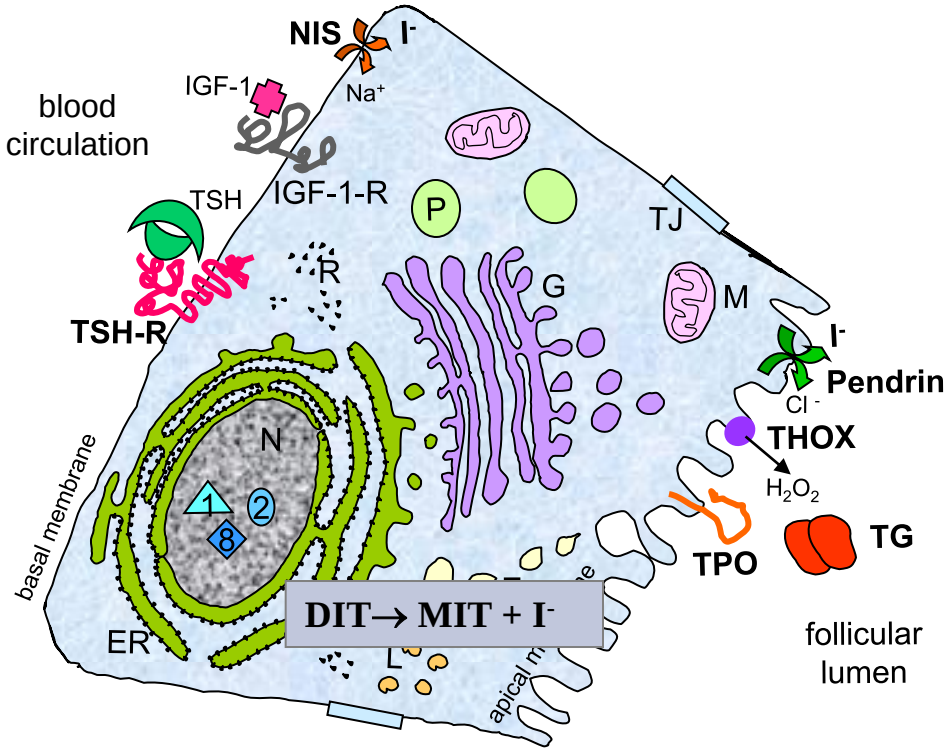
  Modelo Receptor de T3

  Modelo Pre-receptor de T3.

- **Evidencias alteración Tiroidea y TND en humanos.**

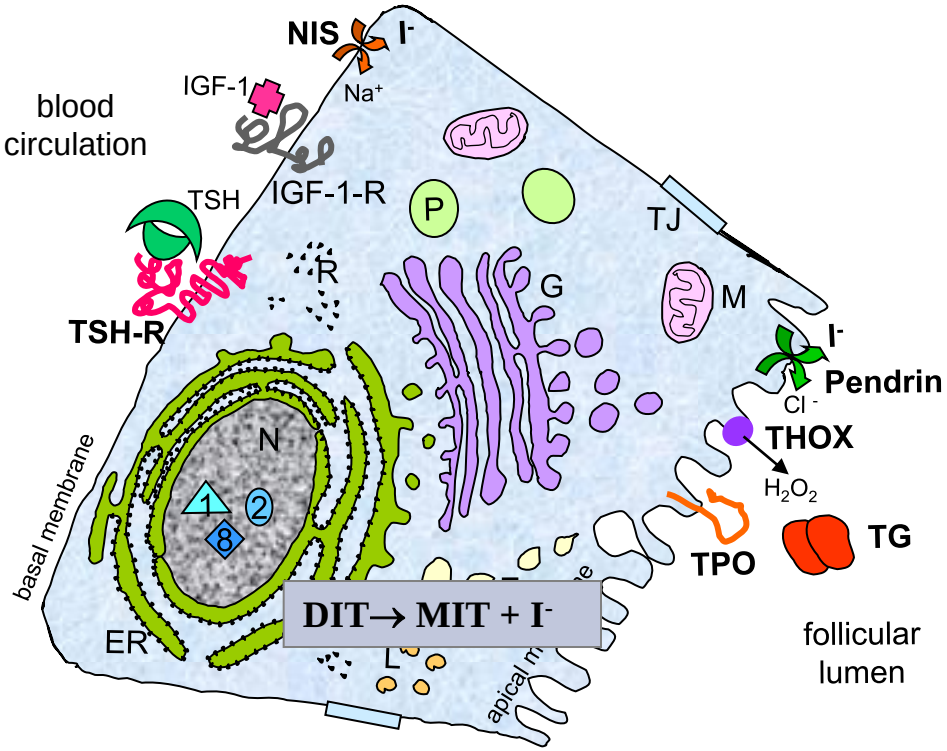
Fundamentos

Síntesis de las h. tiroideas (T4, T3)



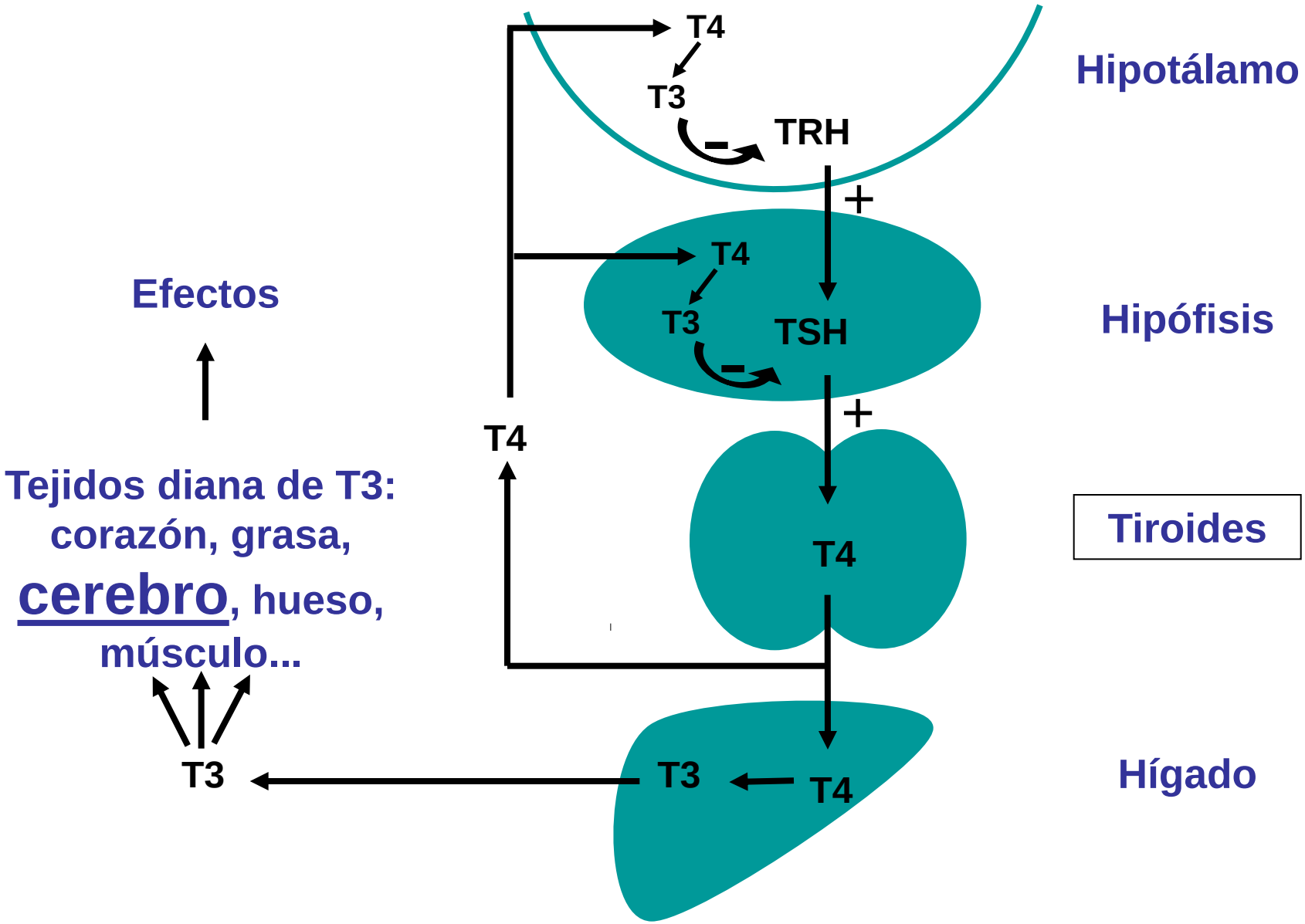
Fundamentos

Síntesis de las h. tiroideas (T4, T3)



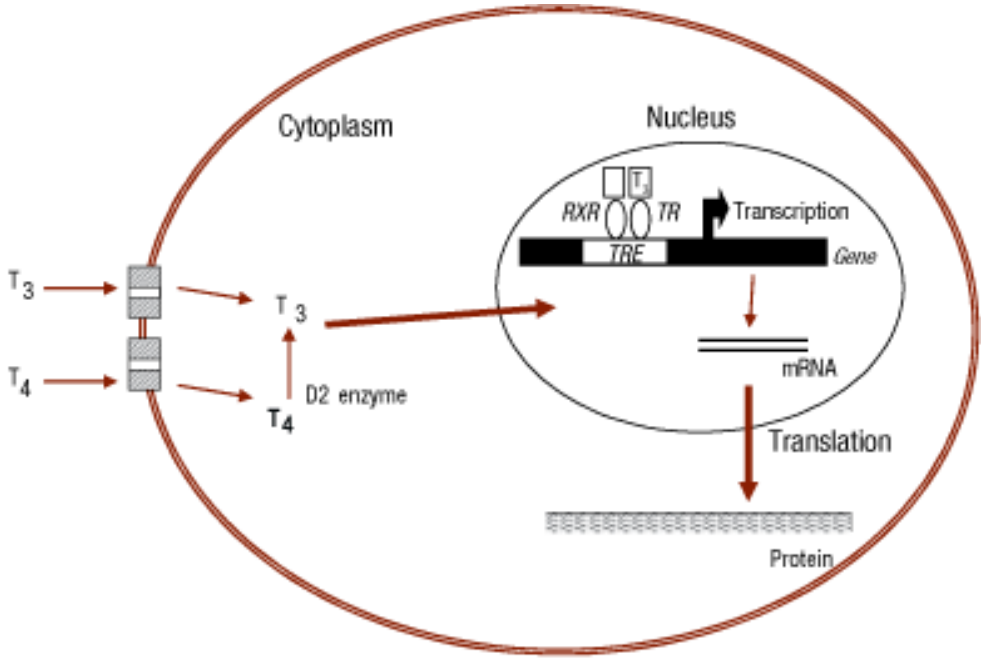
La hormonogénesis tiroidea es completamente **dependiente de los aportes externos de yodo (I^-)** .

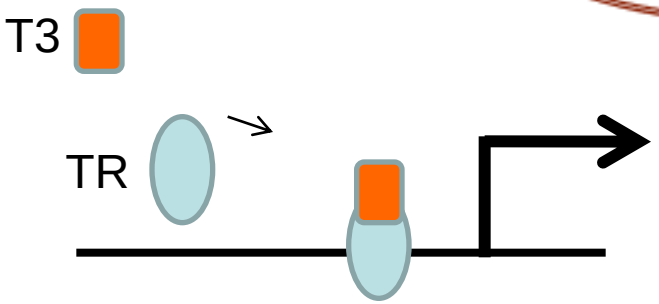
Eje Hipotálamo-Hipófiso-Tiroideo



Fundamentos

Acciones celulares de las h. tiroideas (T4, T3)

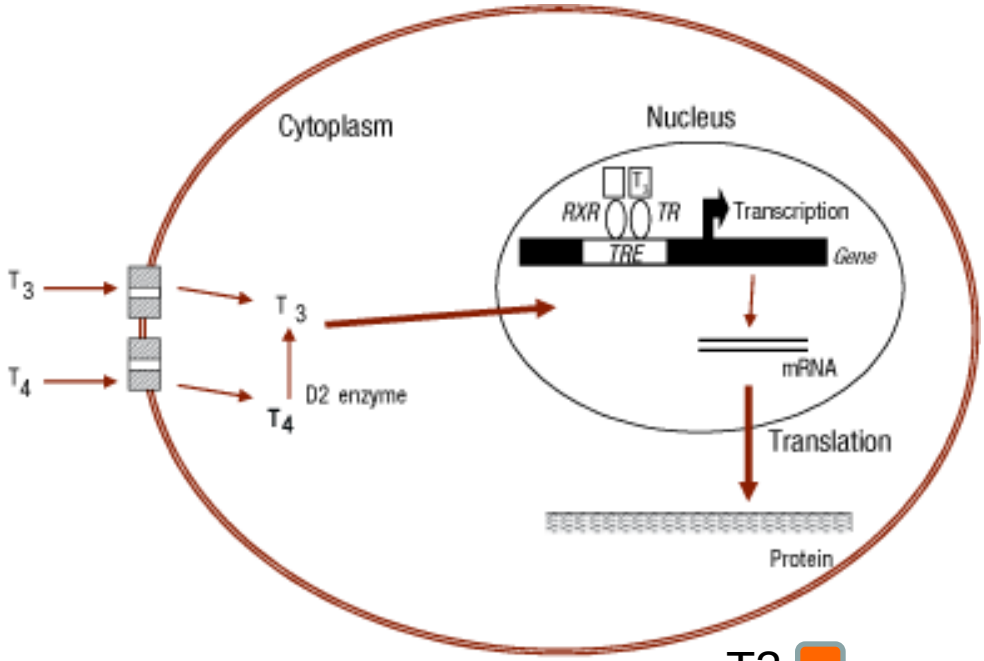


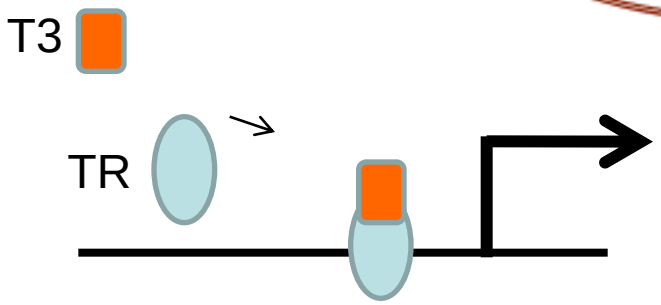


Regulación positiva

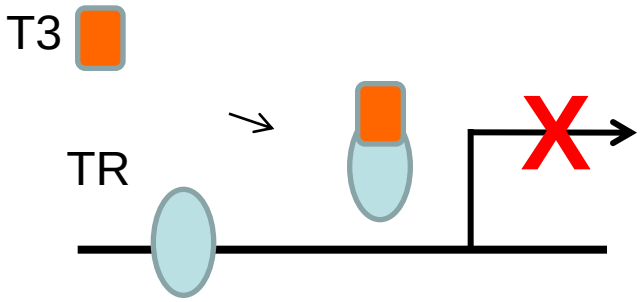
Fundamentos

Acciones celulares de las h. tiroideas (T4, T3)





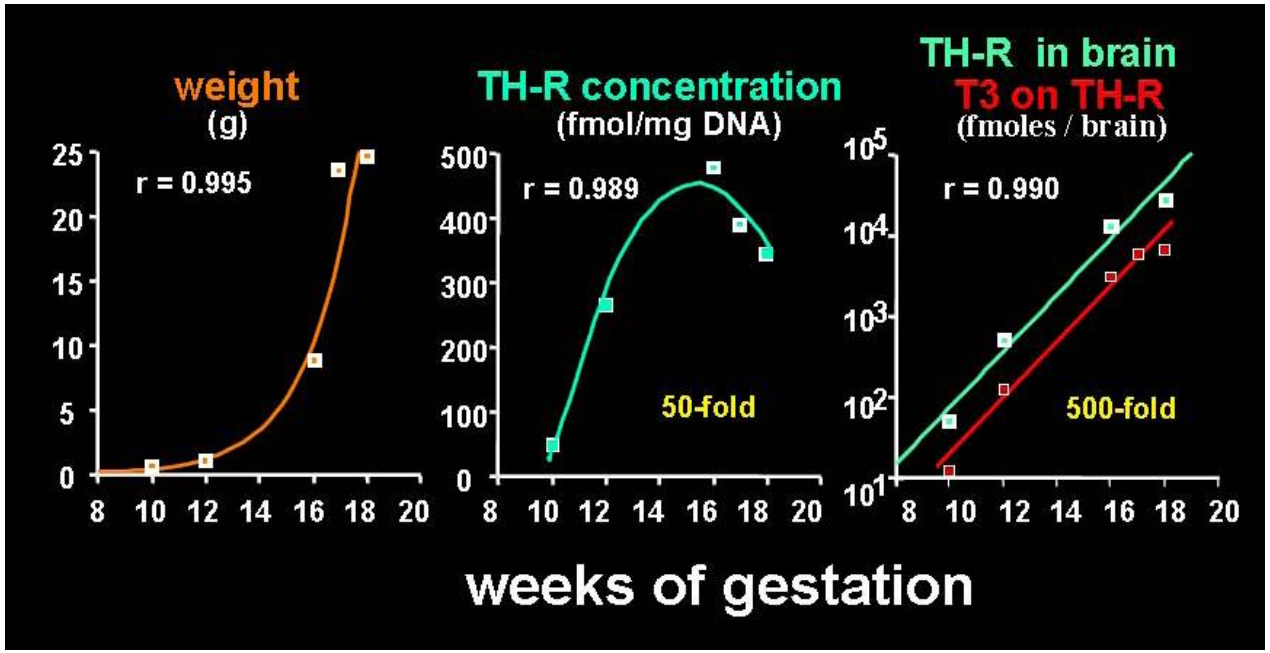
Regulación positiva



Regulación negativa

Ontogenia de TR en cerebro fetal humano

TR y T3 en el cerebro fetal humano

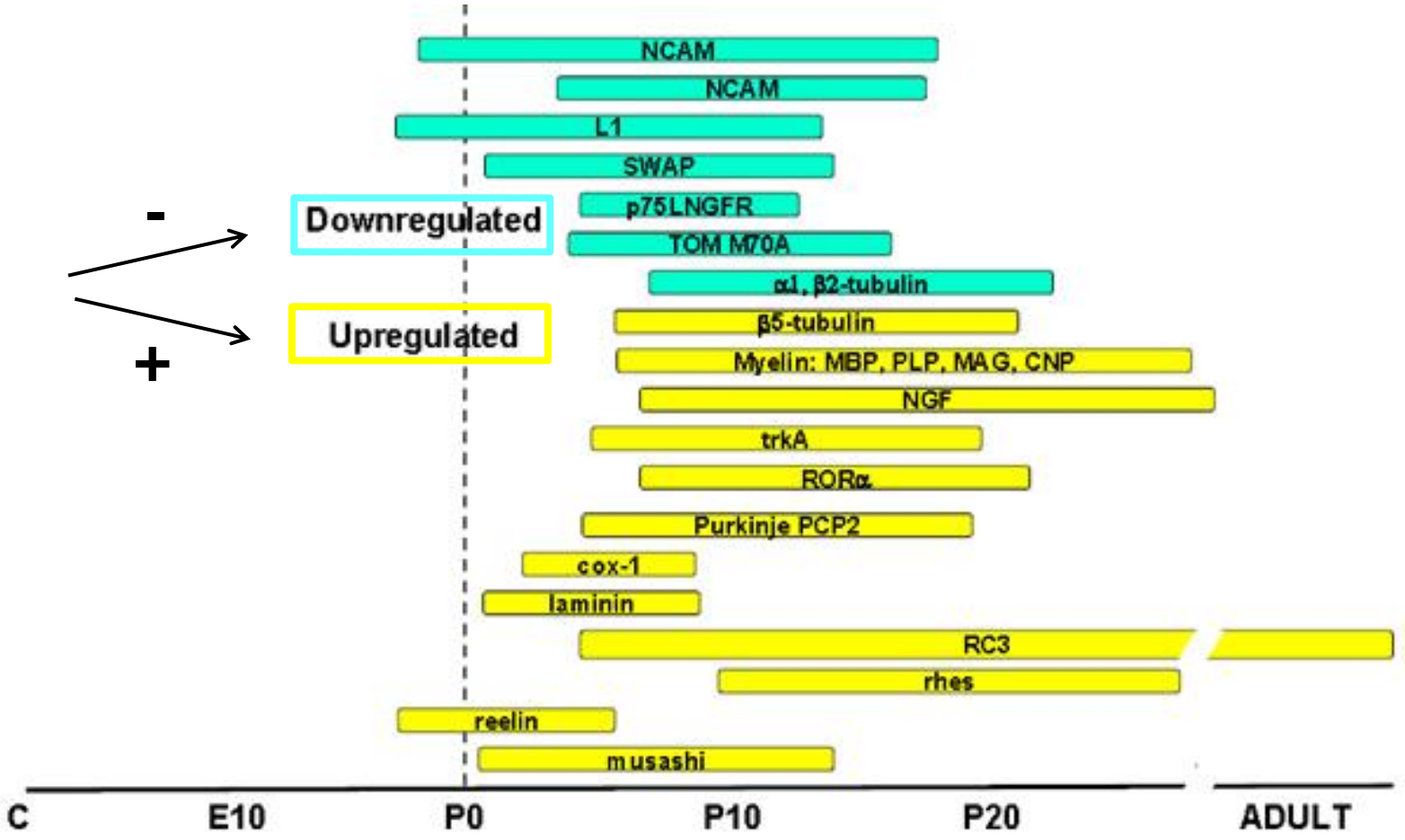


Bernal & Pekonen, 1984

Ensayos de binding de T3 y TR

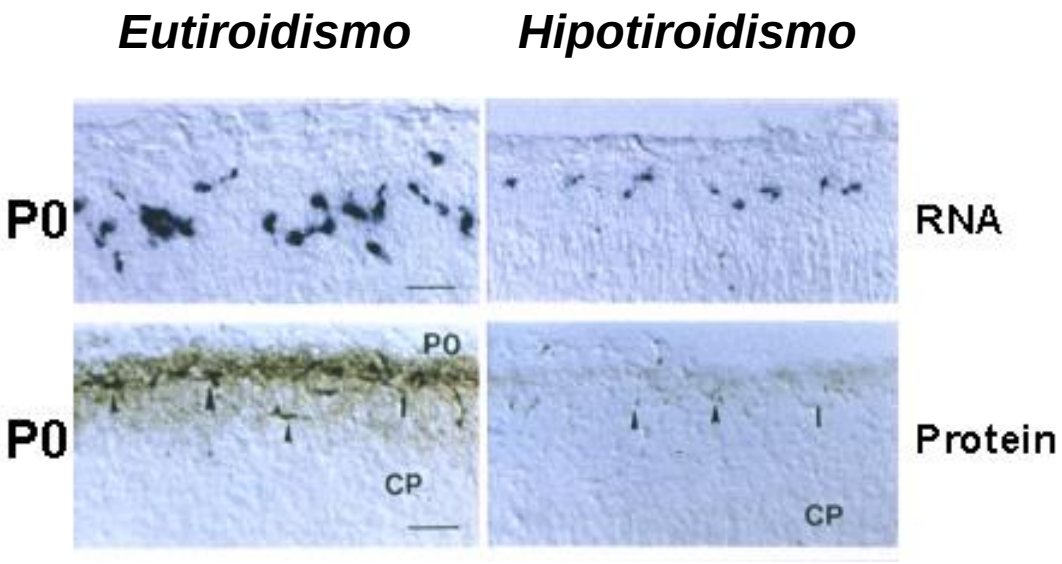
Regulación génica cerebral por T3

Expresión génica cerebral T3-dependiente postnatal



T3 en cortex cerebral

Regulación de Reelina por hormona tiroidea

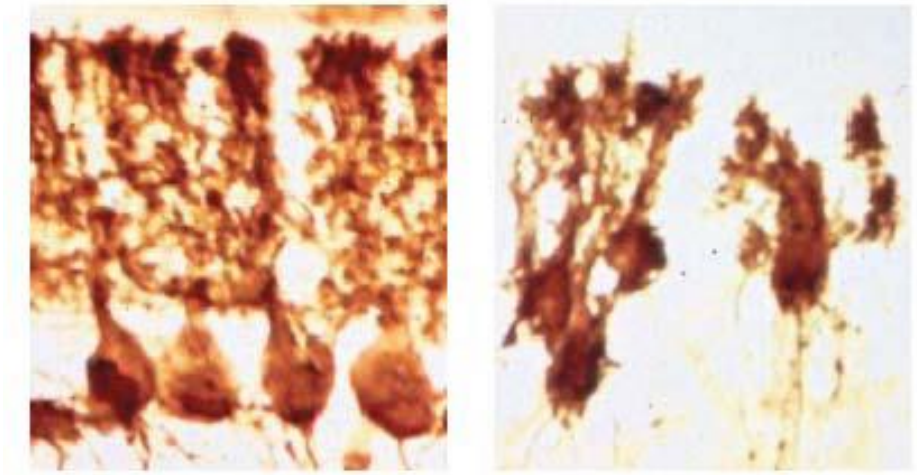


Alvarez-Dolado *et al*,, 1999

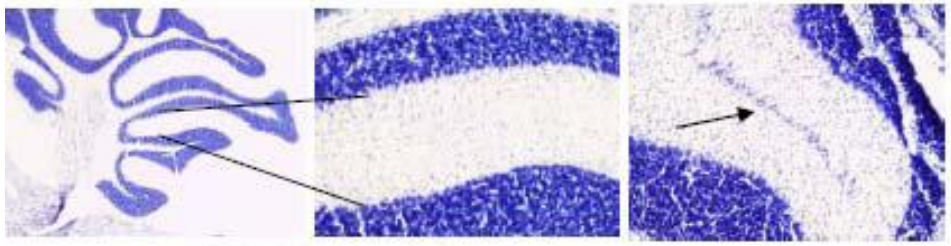
T3 en cerebelo

Cambios morfológicos en el hipotiroidismo neonatal (murino)

Eutiroidismo *Hipotiroidismo*



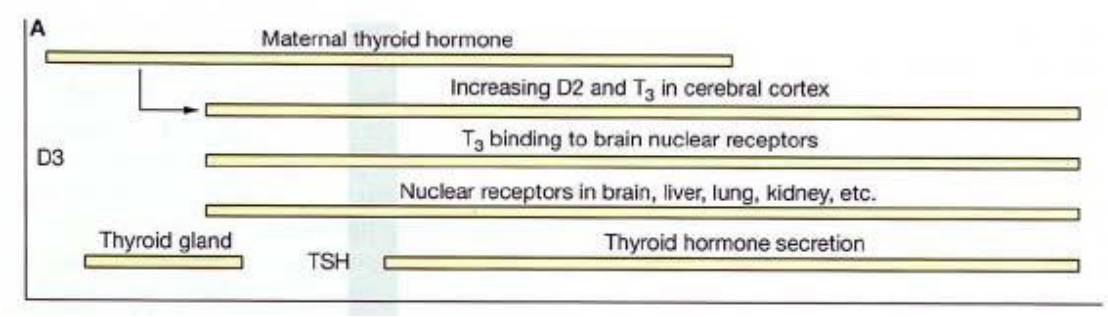
Células de Purkinje



Capa granular externa

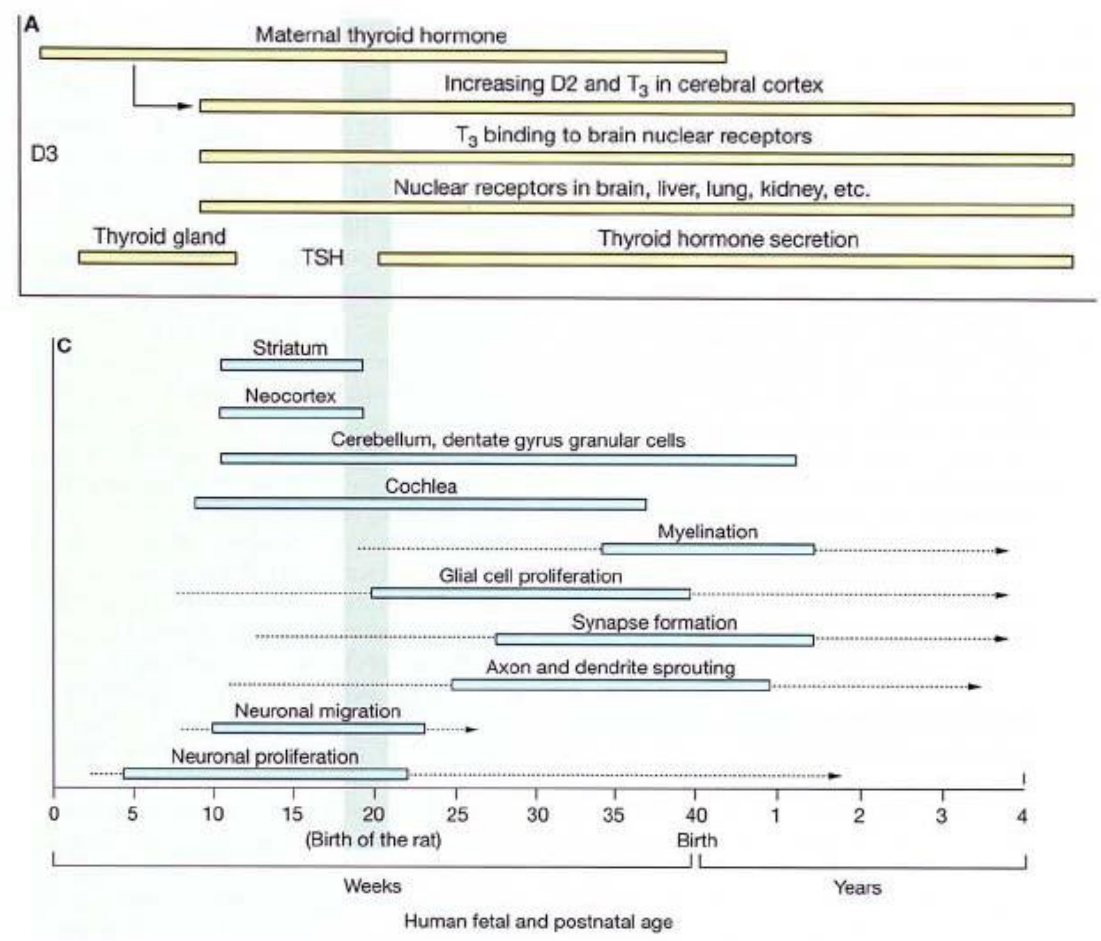
SNC y eventos T3-dependientes

Implicaciones del "timing" del hipotiroidismo celular



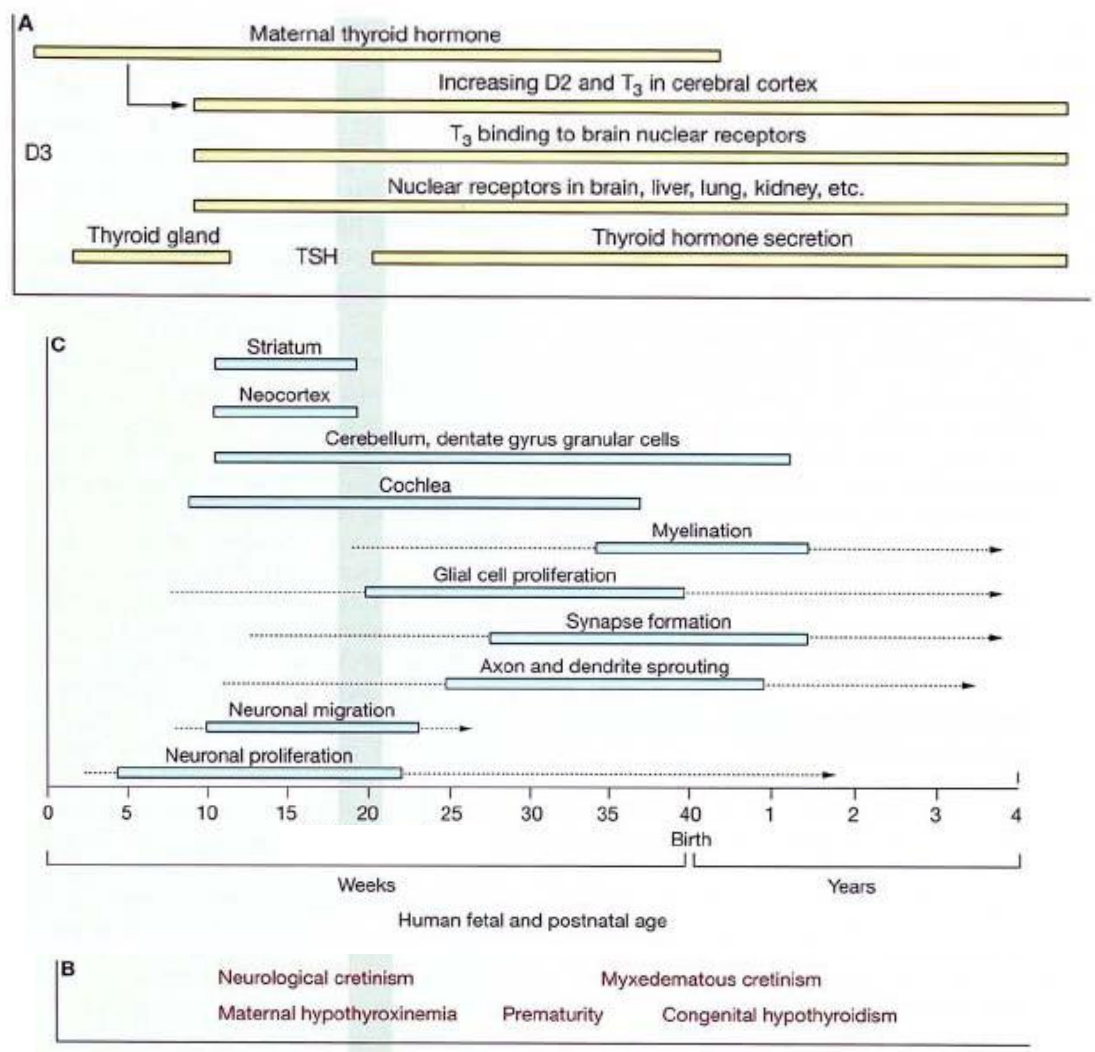
SNC y eventos T3-dependientes

Implicaciones del "timing" del hipotiroidismo celular



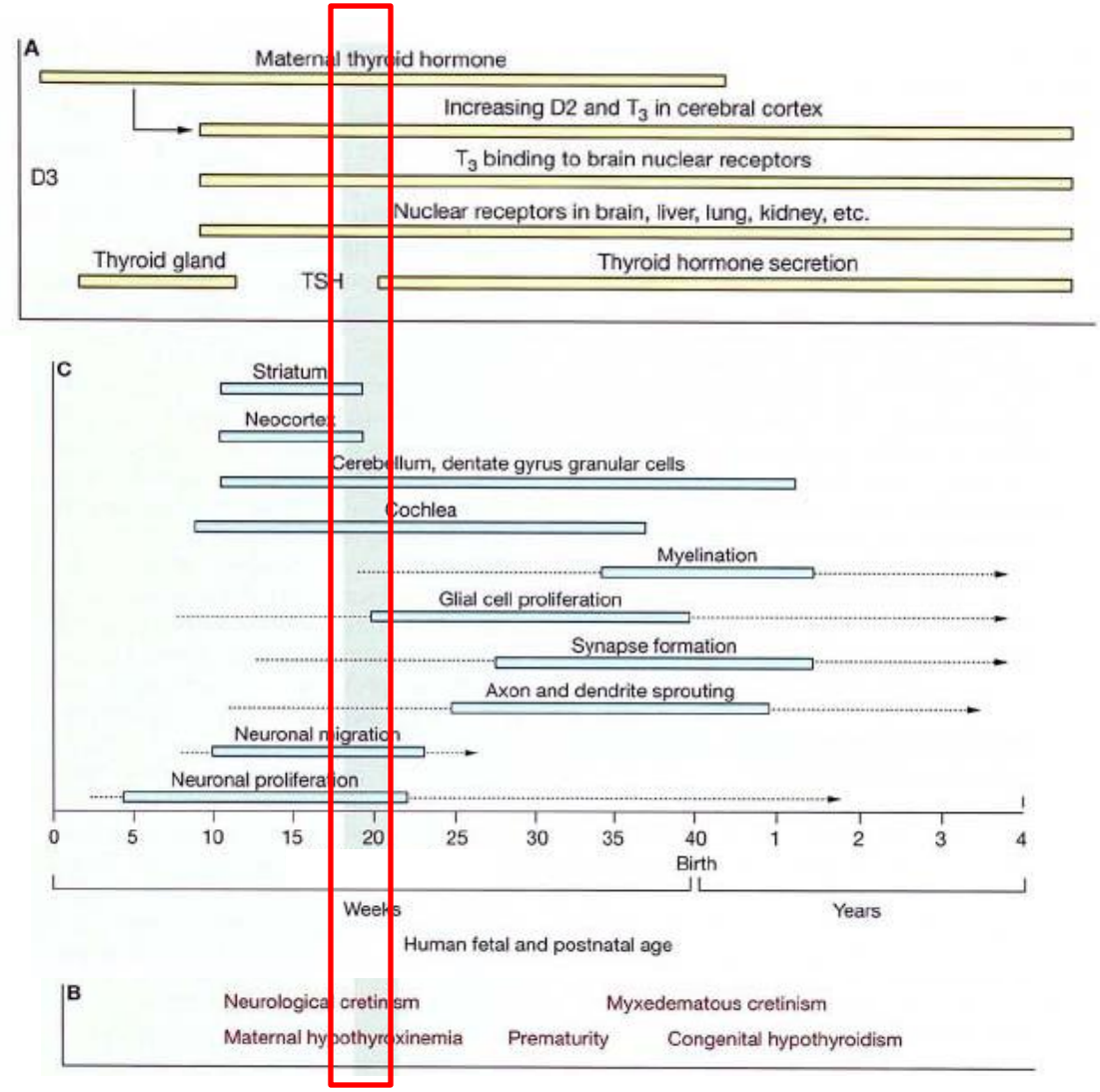
SNC y eventos T3-dependientes

Implicaciones del "timing" del hipotiroidismo celular



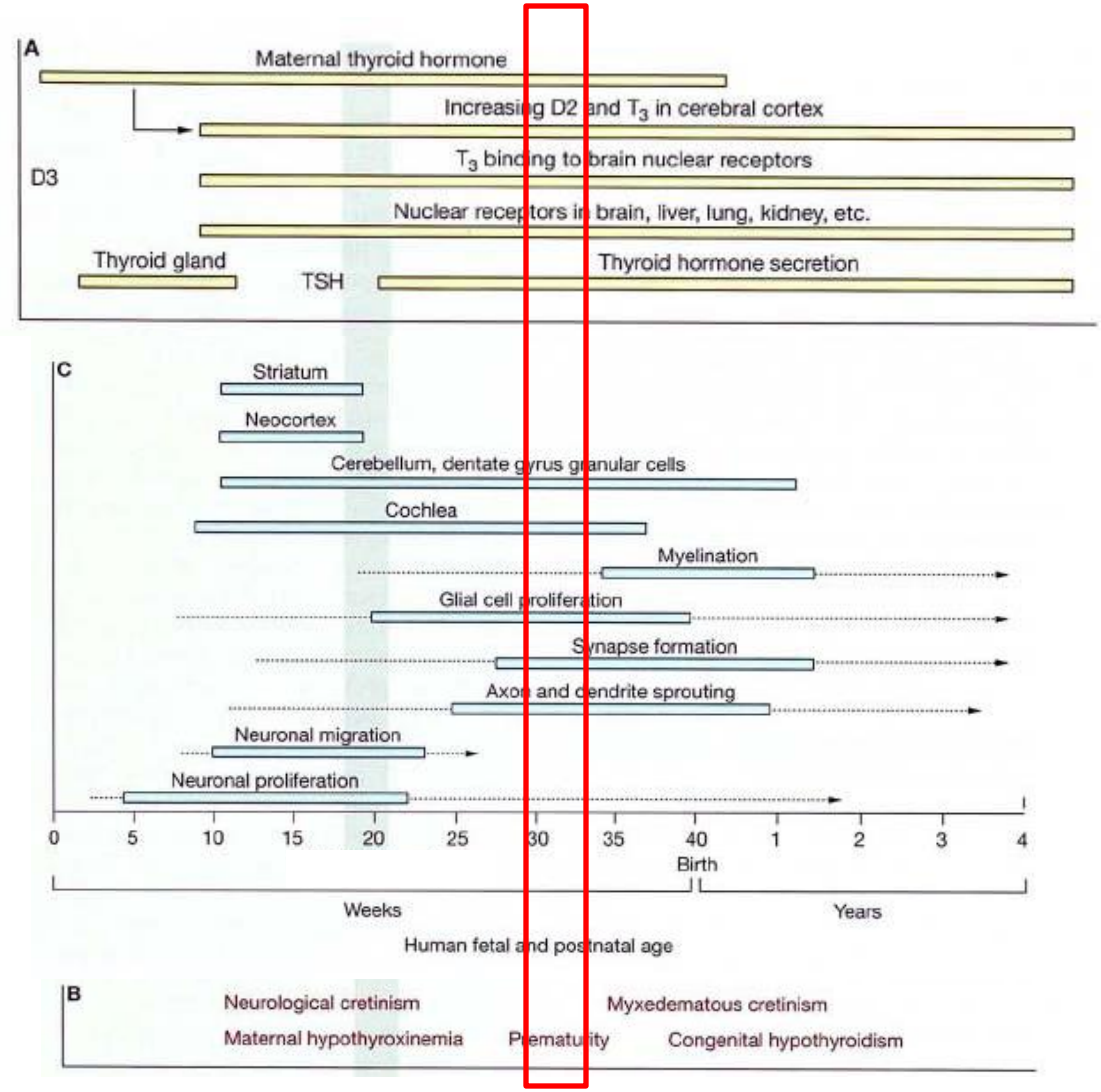
SNC y eventos T3-dependientes

Implicaciones del "timing" del hipotiroidismo celular



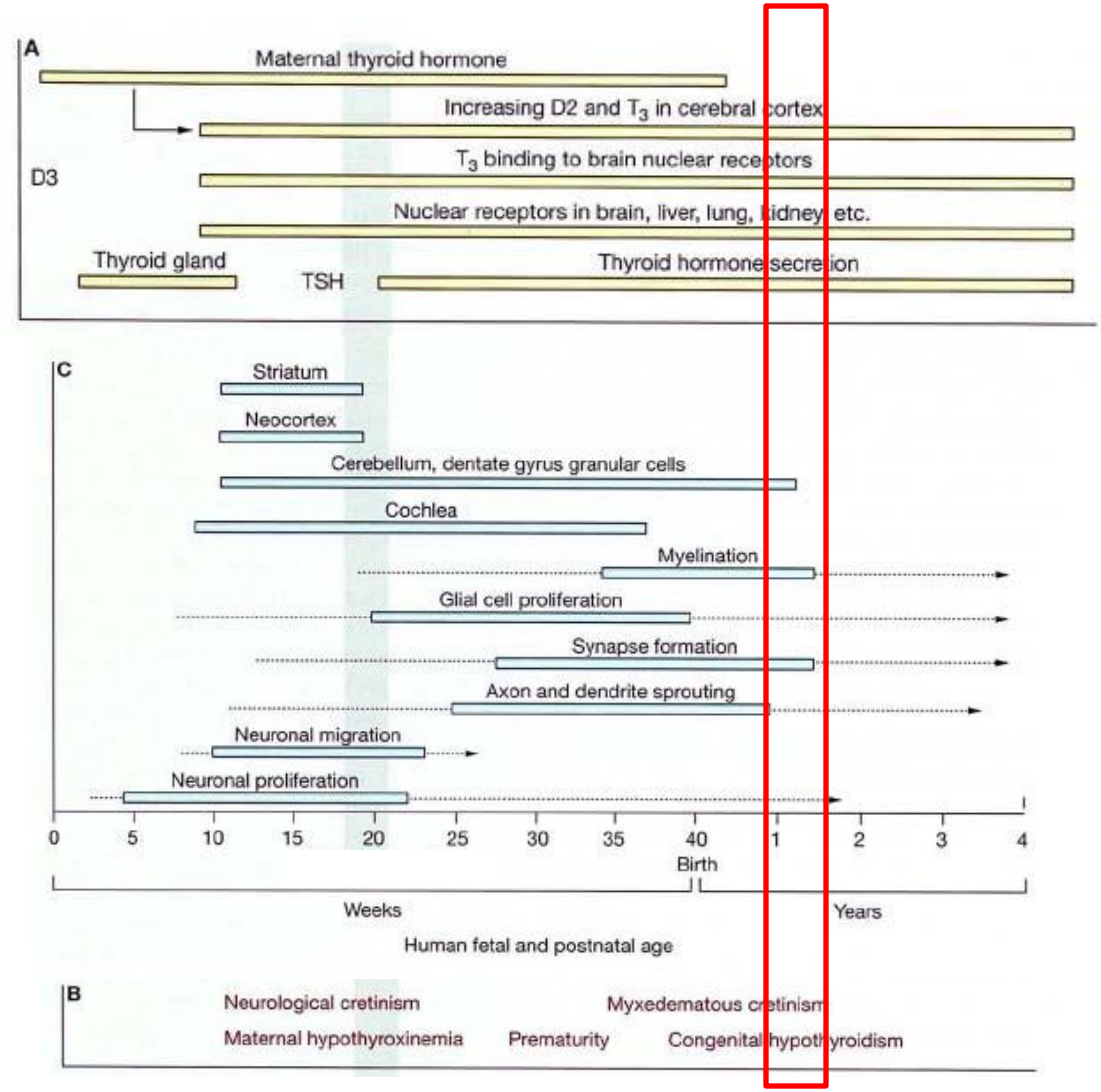
SNC y eventos T3-dependientes

Implicaciones del "timing" del hipotiroidismo celular



SNC y eventos T3-dependientes

Implicaciones del "timing" del hipotiroidismo celular



Defectos de hormonas tiroideas y trastornos del Neurodesarrollo:

TDAH

TDAH y hormonas tiroideas

Fenotipos y genética del TDAH

Fenotipos

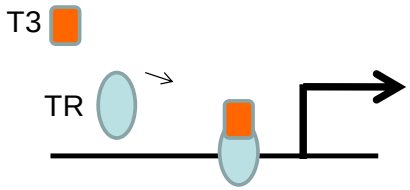
- Hiperactividad, falta de atención, impulsividad o falta de control.
- 5% de la población (*criterios diagnósticos* !).
- Subtipos: TDAH / TDA; +/- déficits cognitivos.

Etiología

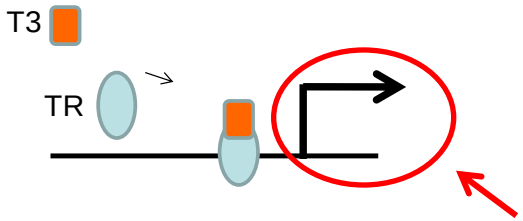
- ***Ambientales***: def. de yodo, disrupción endocrina por xenobióticos.
- ***Genética:*** *Vía Dopaminérgica*: *DAT1, DRD4-5, COMT, SNAP25.*

  Predisposición genética: ***CNVs***: *16p13 dupl*.
- ***Genético-ambiental*.**

Modelos animales de TDAH

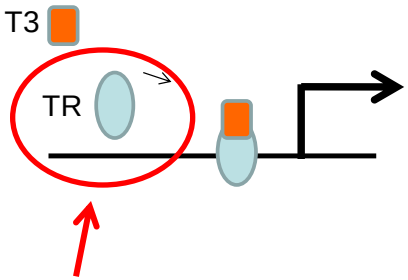


Modelos animales de TDAH



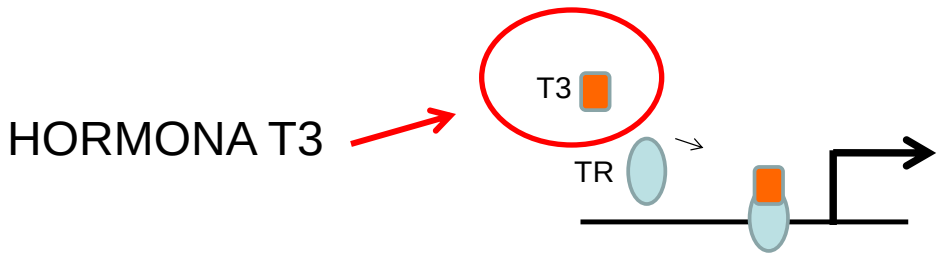
GEN DIANA de T3

Modelos animales de TDAH

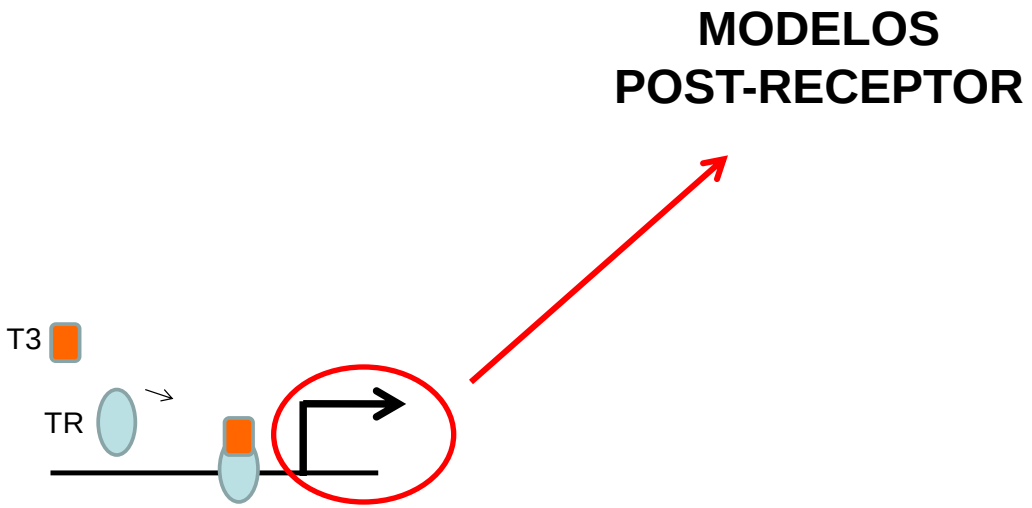


RECEPTOR de T3

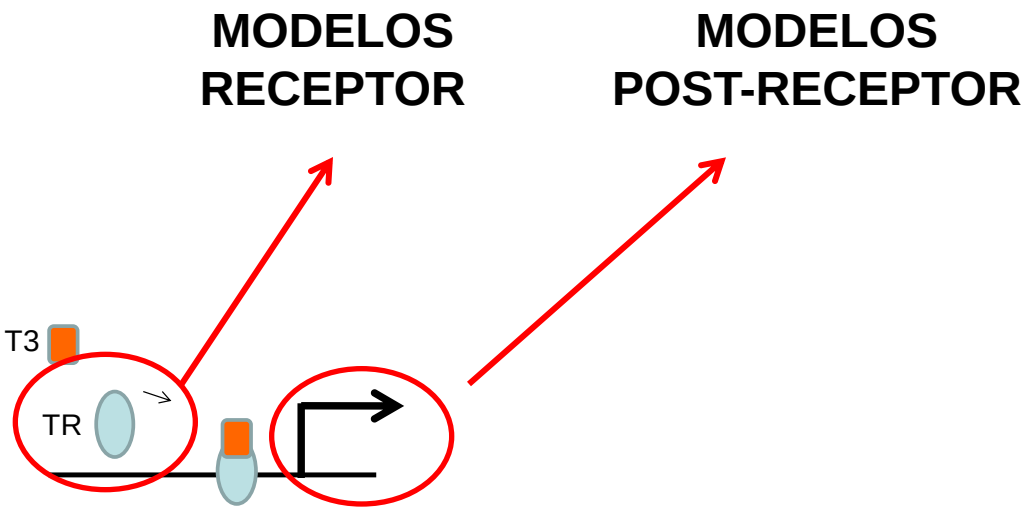
Modelos animales de TDAH



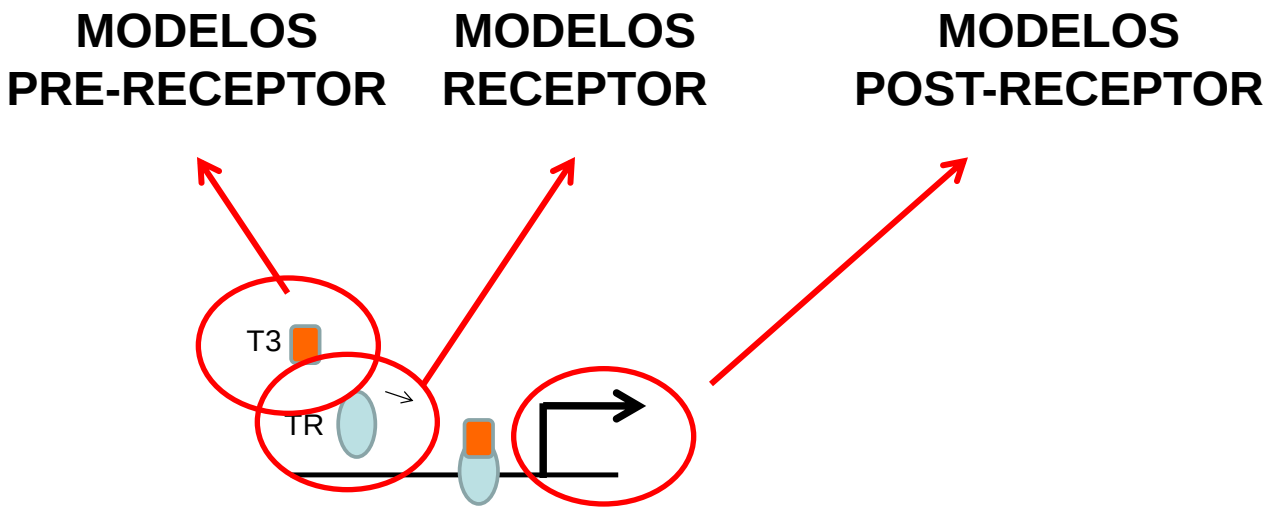
Modelos animales de TDAH



Modelos animales de TDAH



Modelos animales de TDAH



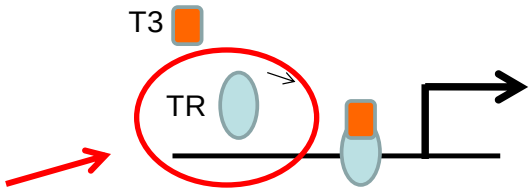
Modelos animales de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) **5:** 282–297



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

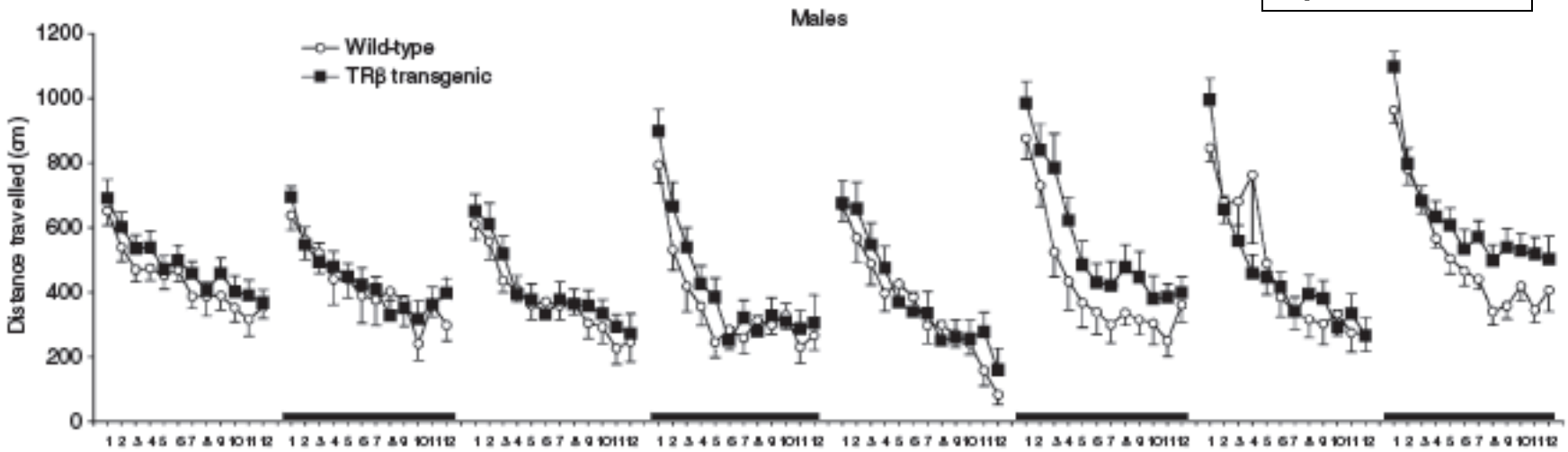
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** *282–297*

Hiperactividad

Open field test



Modelo animal de TDAH

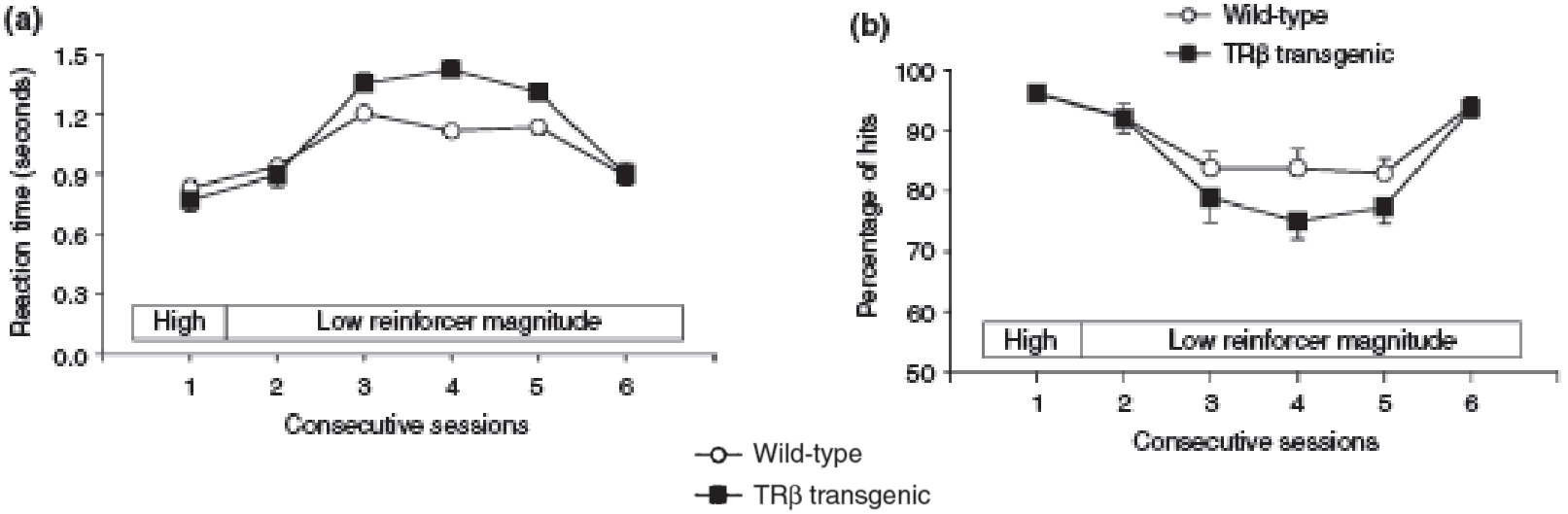
Mutación en R de T3 y fenotipo TDAH en ratón

Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** *282–297*

Déficit de atención



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

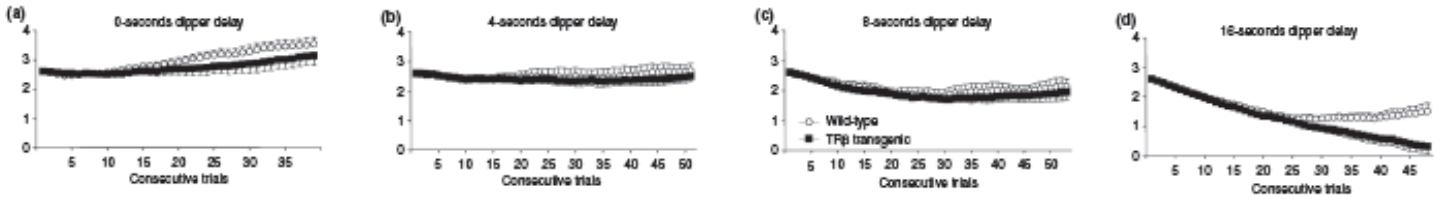
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** *282–297*

Impulsividad

Delay-of-gratification test



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

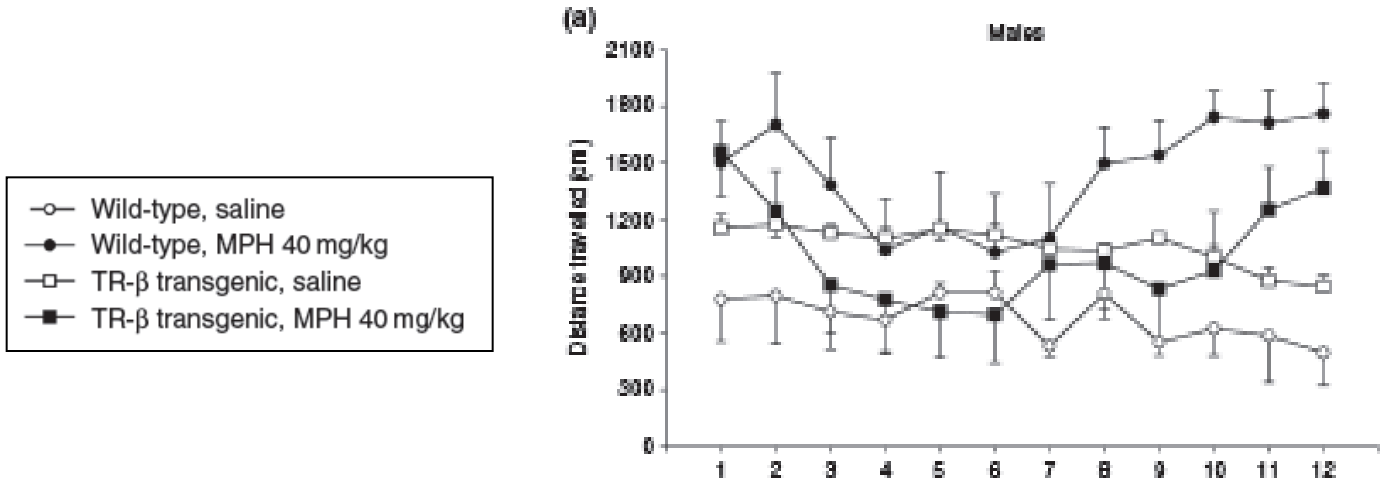
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** *282–297*

Respuesta al metil-fenidato (MPH)

Open field test



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

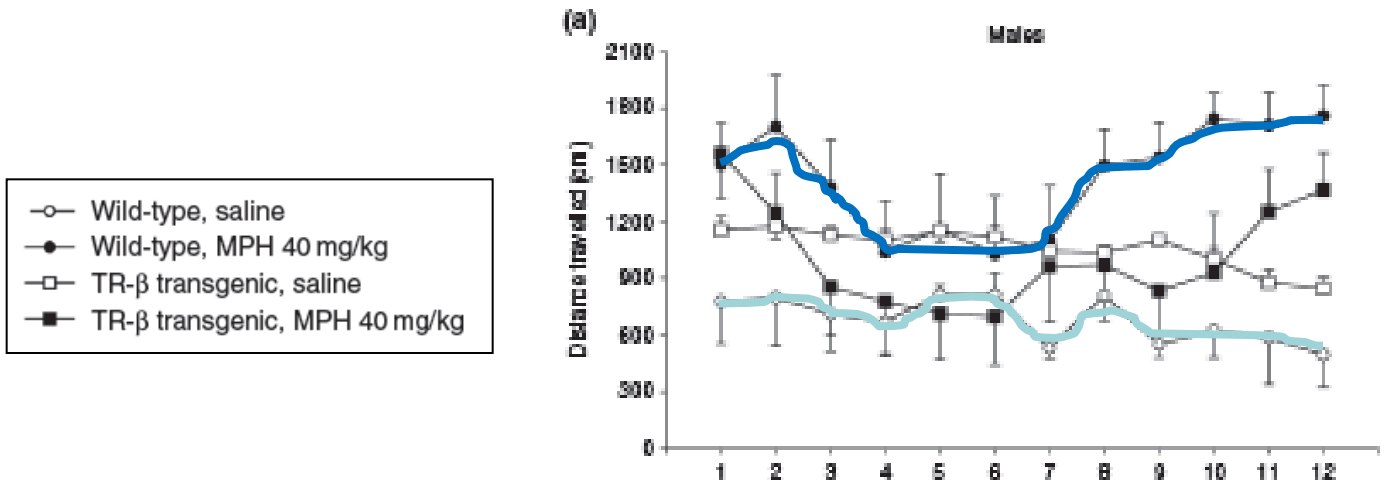
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** 282–297

Respuesta al metil-fenidato (MPH)

Open field test



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

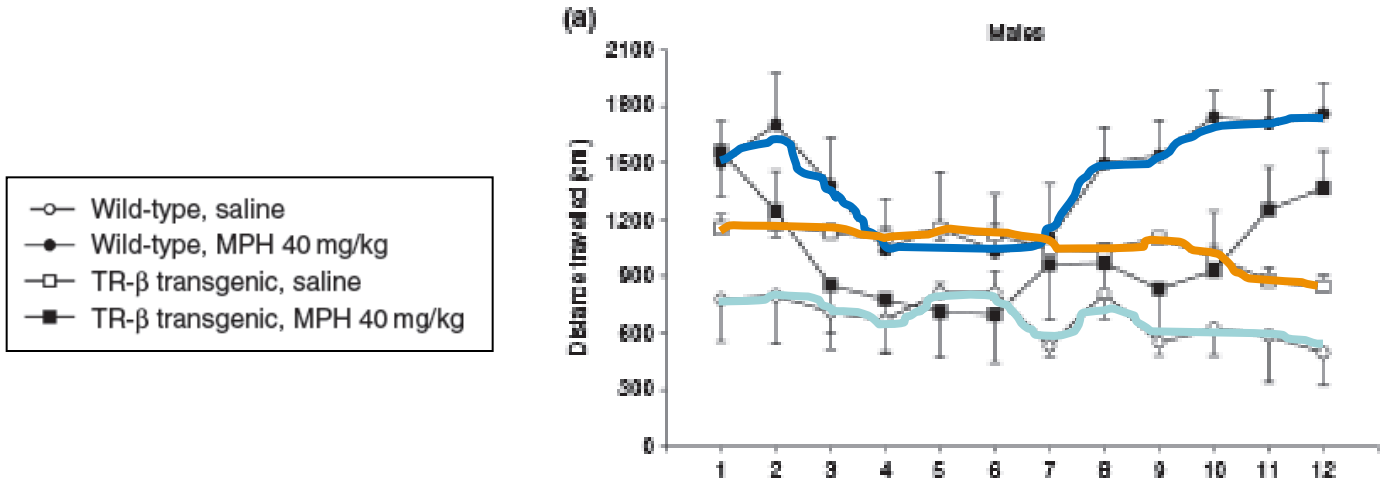
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** 282–297

Respuesta al metil-fenidato (MPH)

Open field test



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

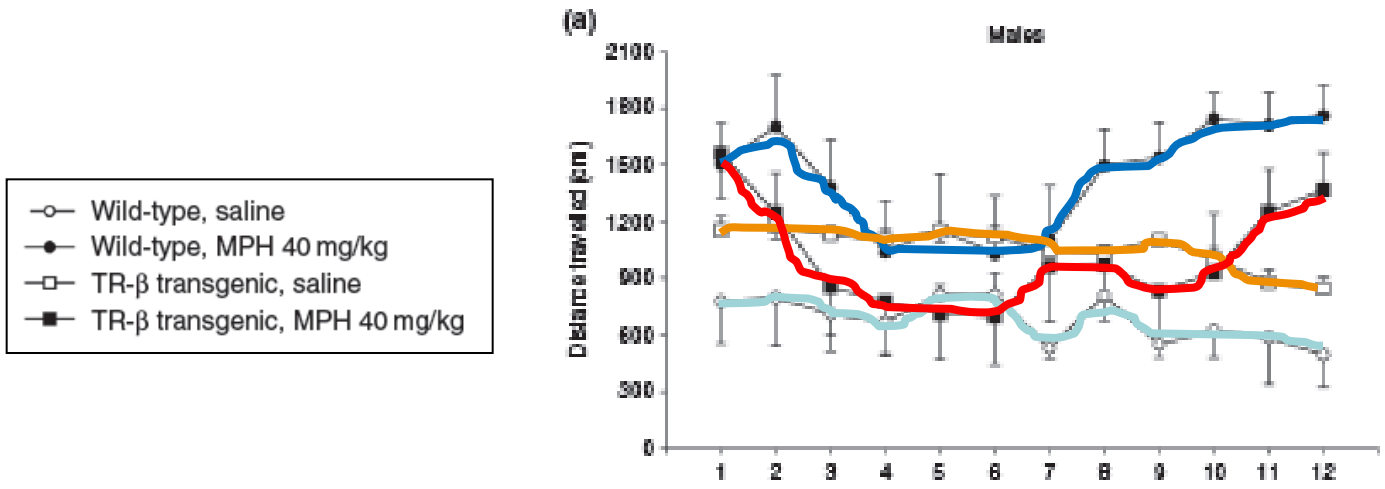
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** 282–297

Respuesta al metil-fenidato (MPH)

Open field test



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

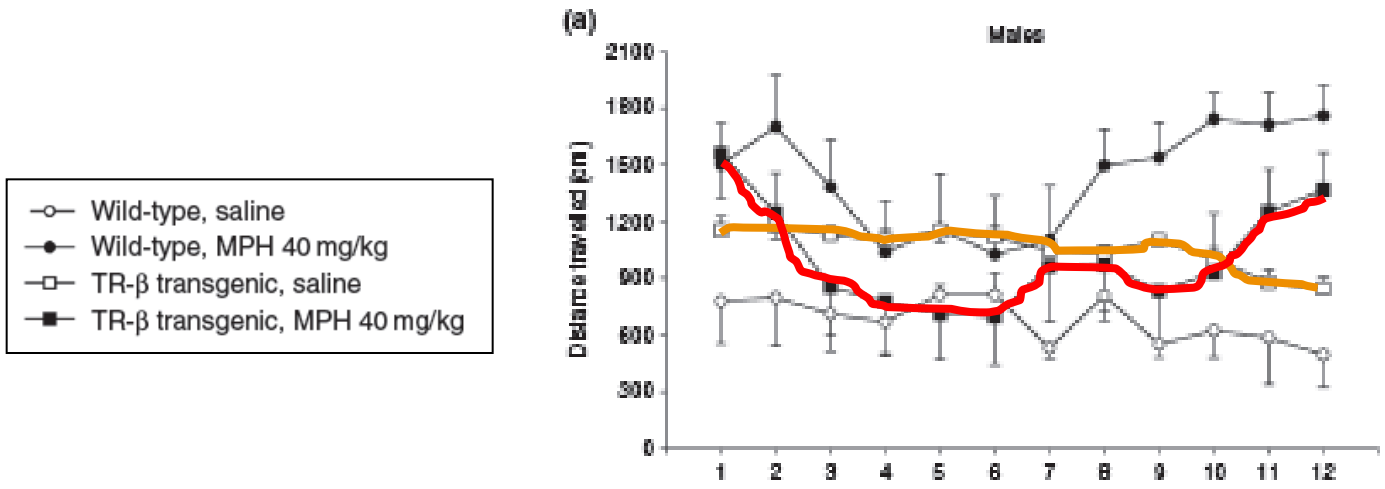
Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive

W. B. Siesser[†], J. Zhao[‡], L. R. Miller[‡], S.-Y. Cheng[¶] and M. P. McDonald[*,†,‡,§]

Genes, Brain and Behavior (2006) ***5:*** 282–297

Respuesta al metil-fenidato (MPH)

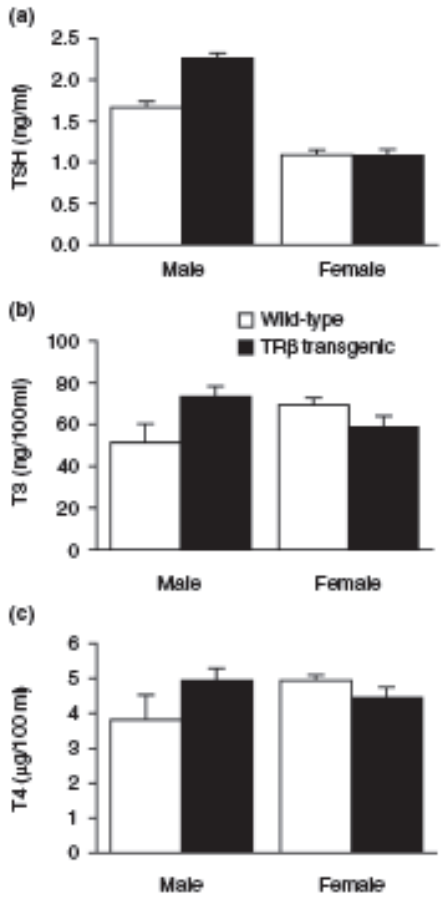
Open field test



Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

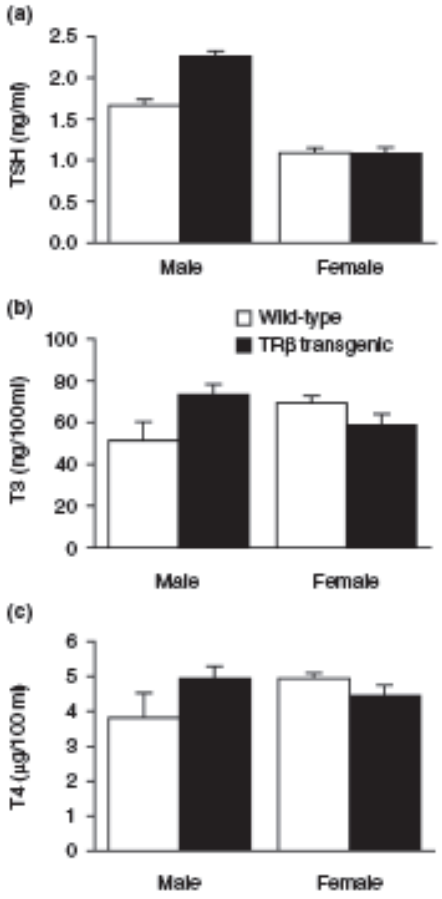
Perfil hormonal (transitorio)



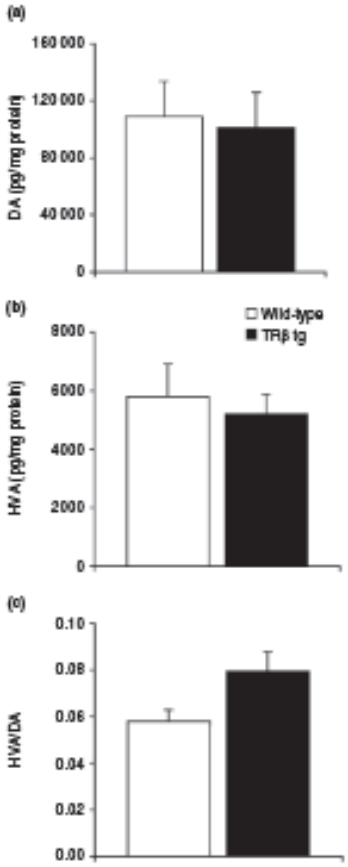
Modelo animal de TDAH

Mutación en R de T3 y fenotipo TDAH en ratón

Perfil hormonal (transitorio)



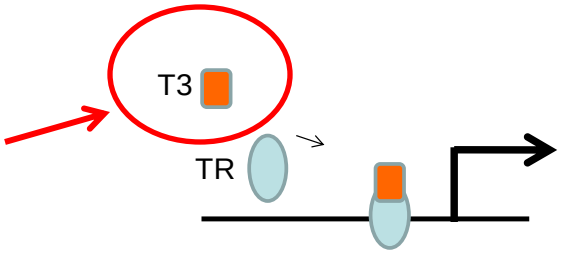
Metabolismo dopamina



Turnover incrementado *(alteración transporte de Dopamina)*

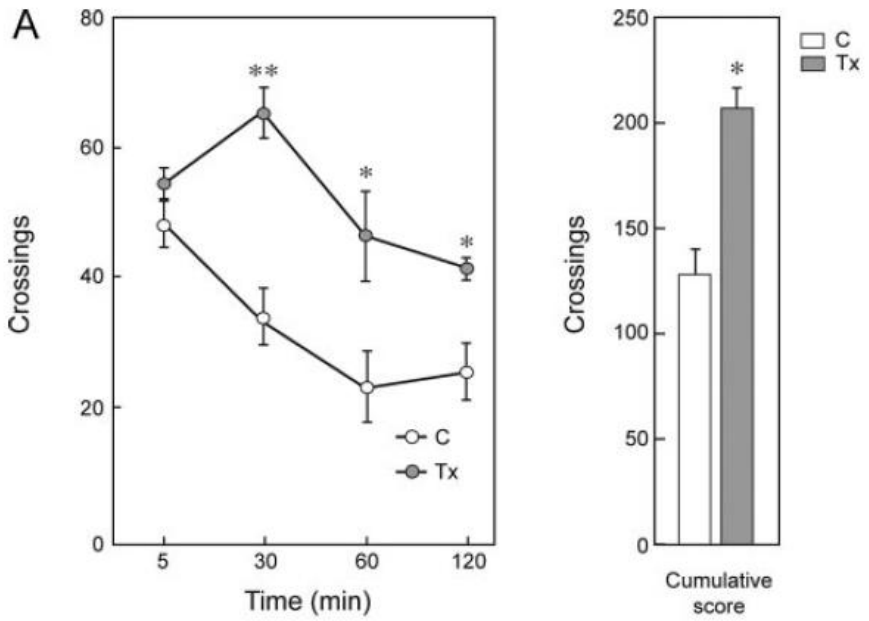
Modelos animales de TDAH

Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism



Modelo de hiperactividad en ratas

Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism



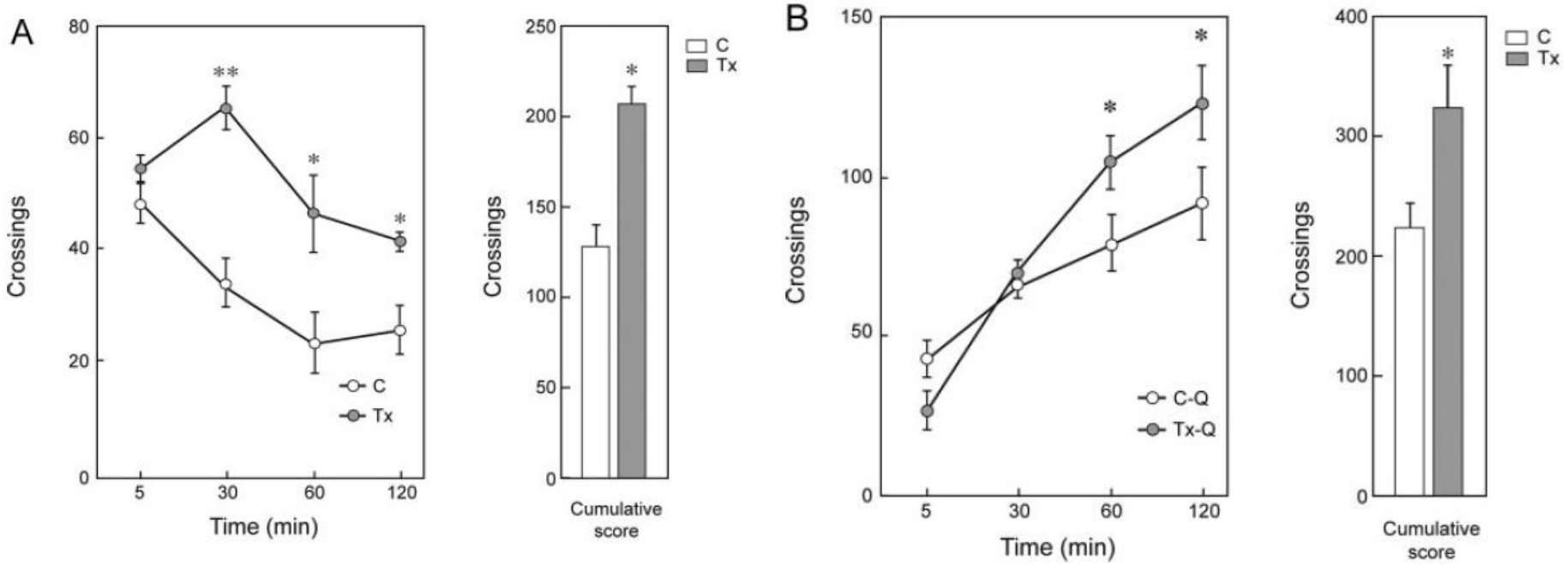
Congenital hypothyroidism increases locomotor activity.

Modelo de hiperactividad en ratas

El Receptor de Cannabinoides CB1

Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism

+ Quinpirol

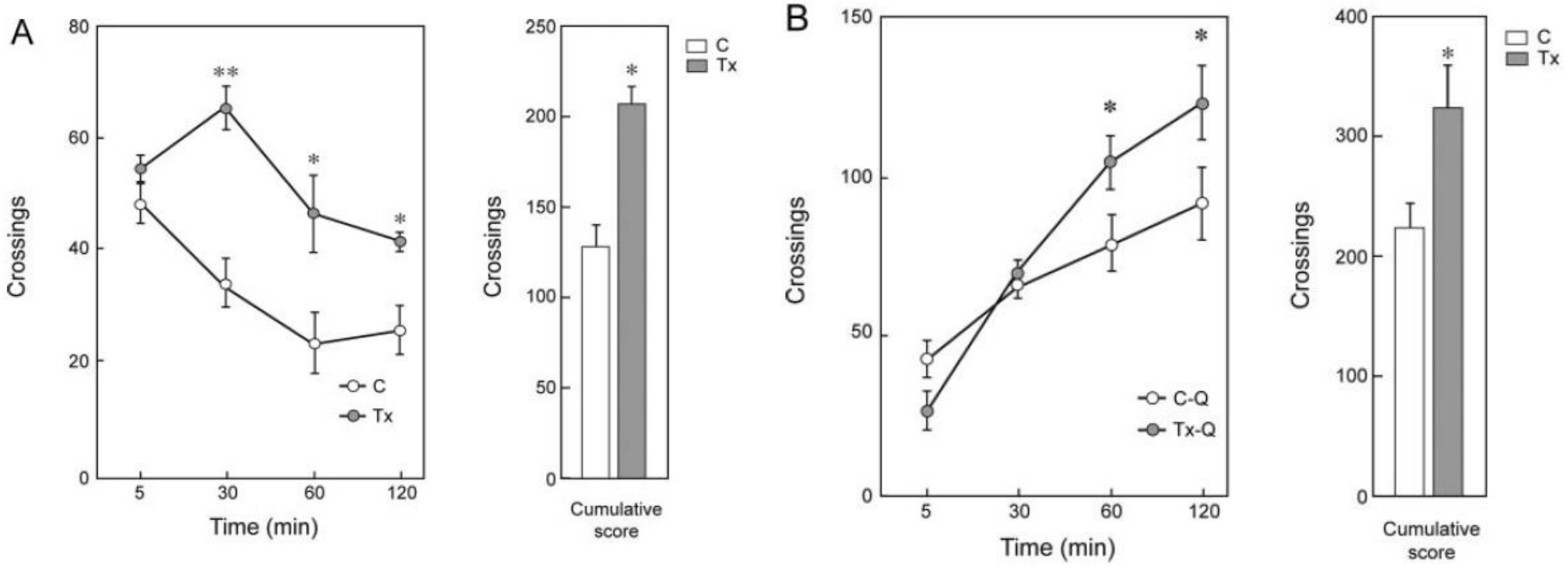


Congenital hypothyroidism increases locomotor activity.

Modelo de hiperactividad en ratas

Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism

+ Quinpirol

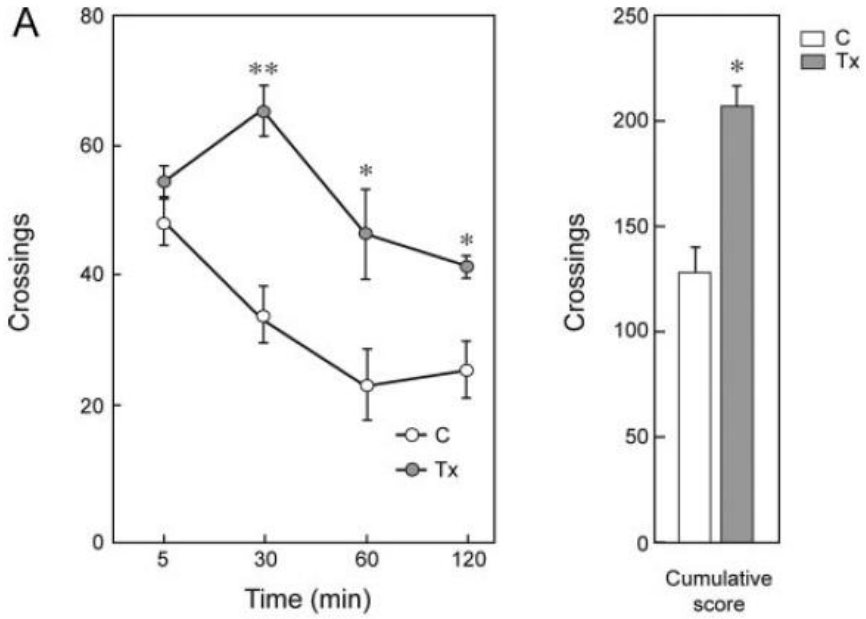


Congenital hypothyroidism increases locomotor activity.

Modelo de hiperactividad en ratas

El Receptor de Cannabinoides CB1

Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism

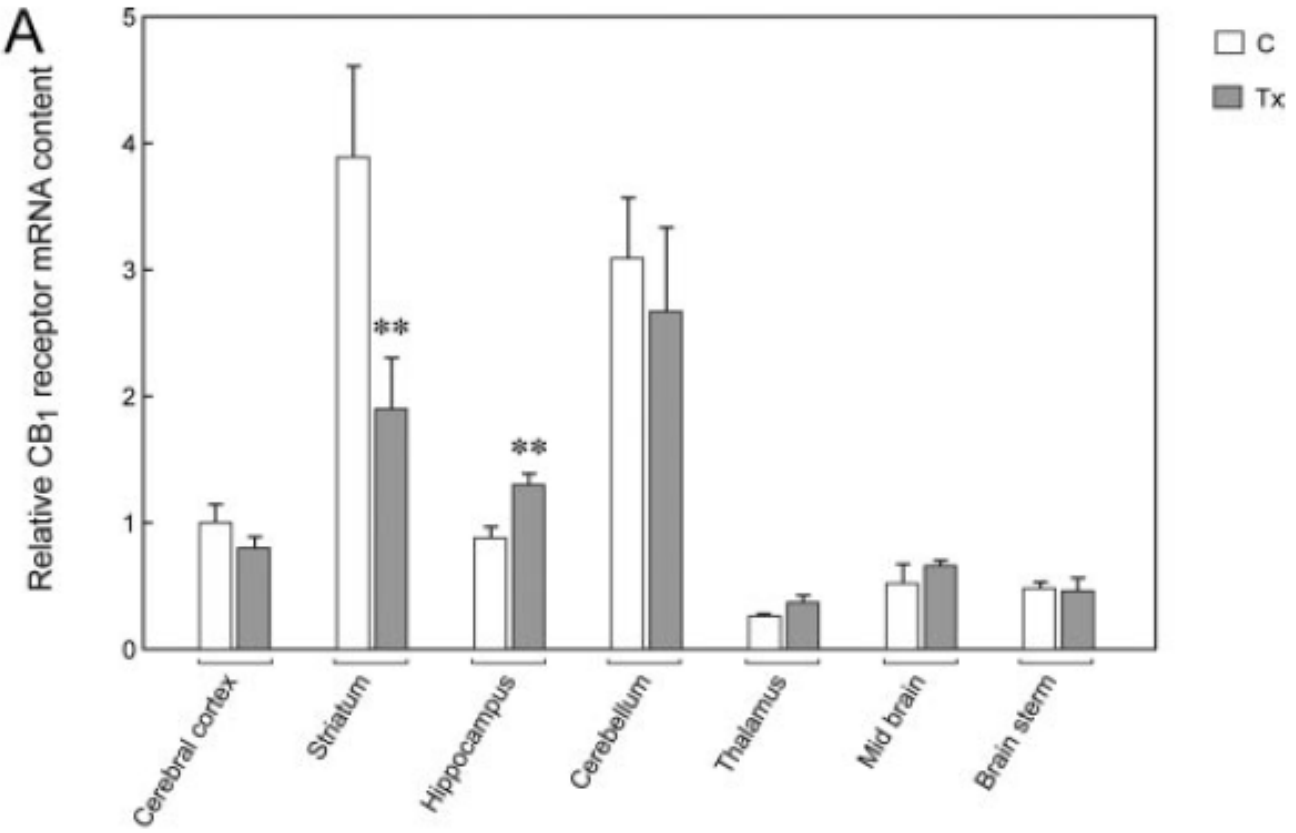


Congenital hypothyroidism increases locomotor activity.

Modelo de hiperactividad en ratas

El hipotiroidismo reduce la expresión del mRNA de CB1

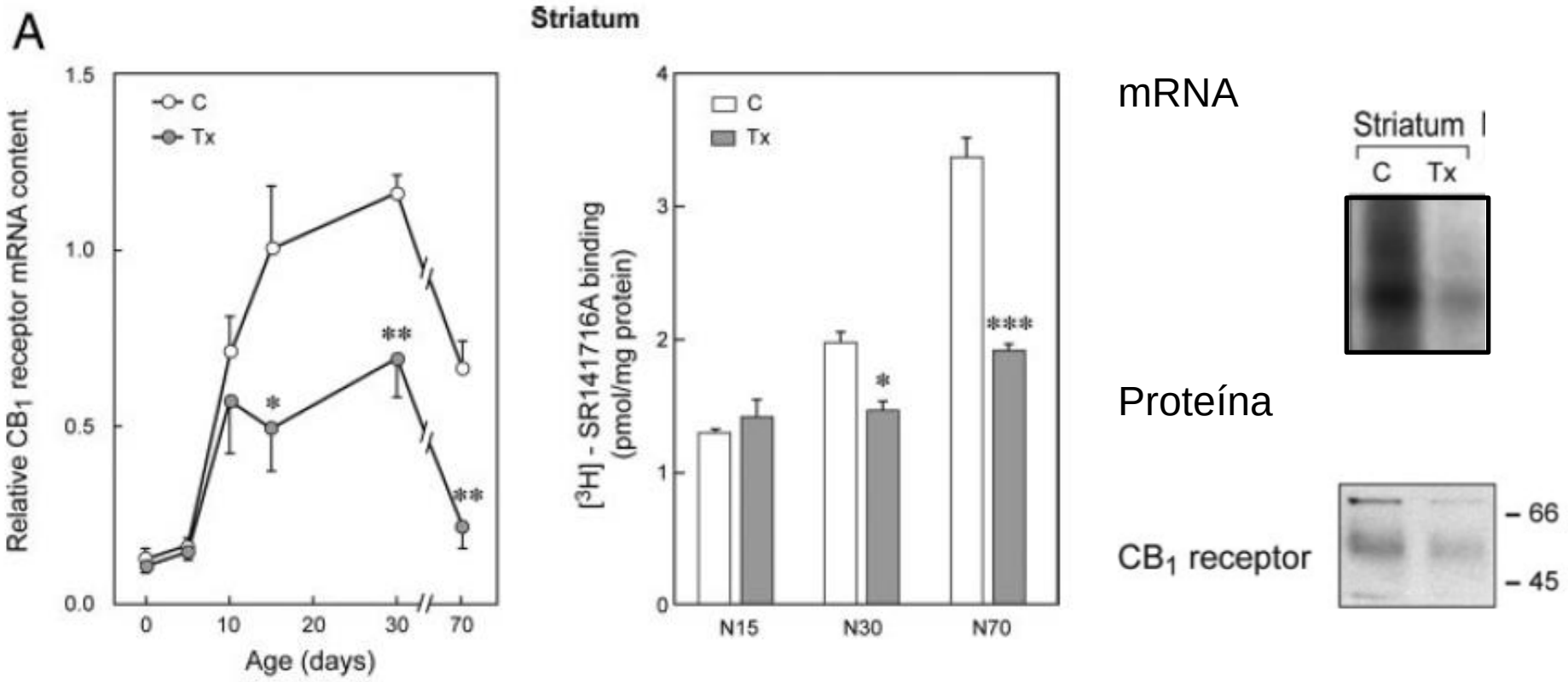
Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism



Modelo de hiperactividad en ratas

El hipotiroidismo reduce CB1 mas intensamente con la edad

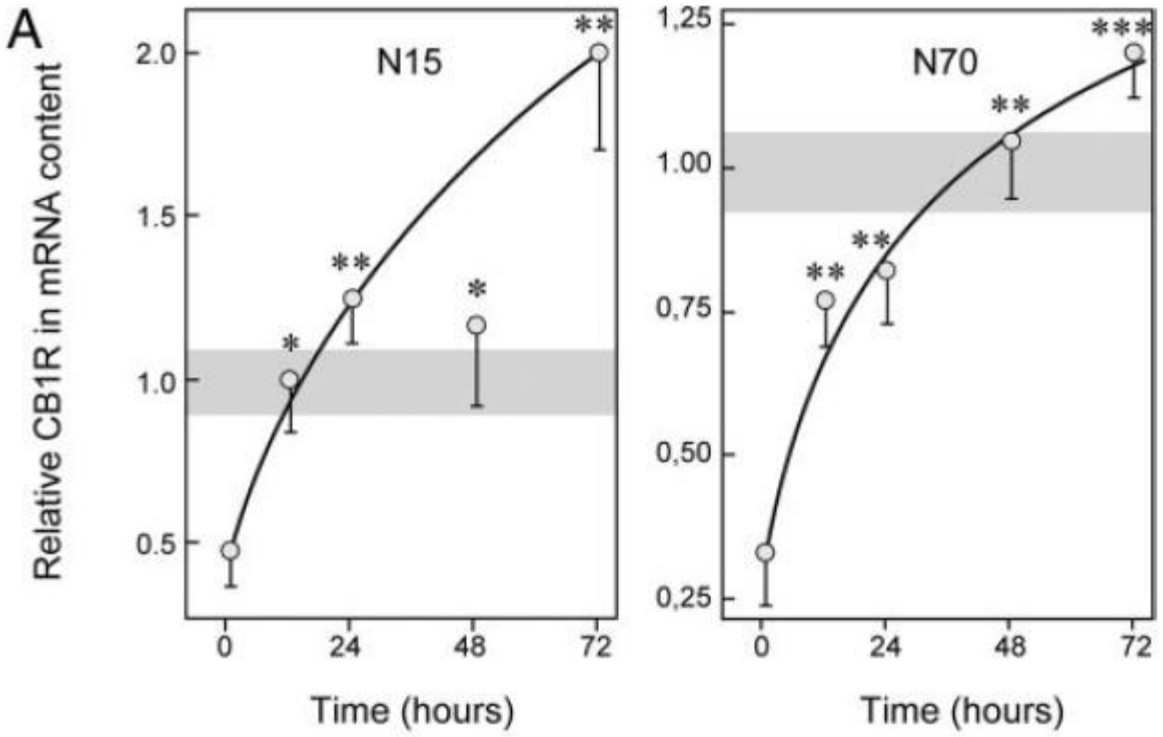
Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism



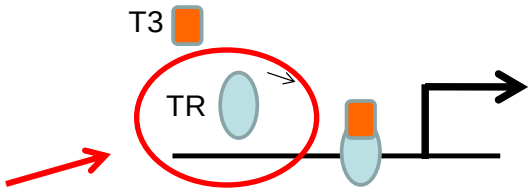
Modelo de hiperactividad en ratas

El hipotiroidismo tratado con T3 incrementa el CB1

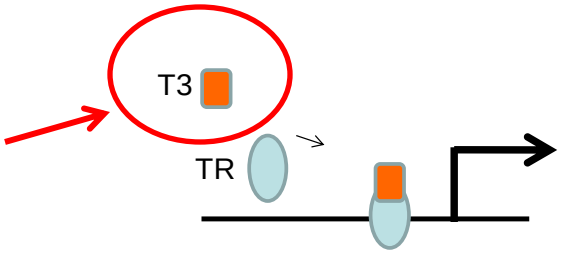
Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism



“Modelos” humanos de TDAH



“Modelos” humanos de TDAH



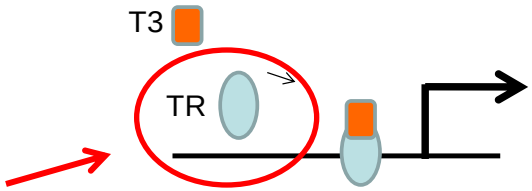
TDAH y hormonas tiroideas

TDAH y <u>Resistencia Generalizada a hormonas tiroideas</u>

ATTENTION DEFICIT–HYPERACTIVITY DISORDER IN PEOPLE WITH GENERALIZED RESISTANCE TO THYROID HORMONE

Peter Hauser, M.D., Alan J. Zametkin, M.D., Pedro Martinez, M.D., Benedetto Vitiello, M.D., John A. Matochik, Ph.D., A. James Mixson, M.D., and Bruce D. Weintraub, M.D.

Conclusions. In our study sample, attention deficit–hyperactivity disorder is strongly associated with generalized resistance to thyroid hormone. (N Engl J Med 1993; 328:997-1001.)



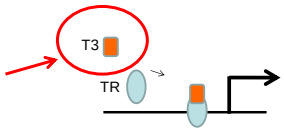
TDAH y hormonas tiroideas

Deficiencia de yodo, hipotiroxinemia materna y TDAH

Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild-Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries

F. VERMIGLIO, V. P. LO PRESTI, M. MOLETI, M. SIDOTI, G. TORTORELLA, G. SCAFFIDI, M. G. CASTAGNA, F. MATTINA, M. A. VIOLI, A. CRISÀ, A. ARTEMISIA, AND F. TRIMARCHI

The Journal of Clinical Endocrinology & Metabolism 89(12):6054–6060



- 2 regiones **A** (deficiente en yodo) y **B** (suficiente) en Italia.
- Perfil tiroideo en embarazadas al final 1 trimestre.
- n=16 niños de madres en las regiones A ó B.
- Inteligencia Wechsler: WISC-III, y screening TDAH (DSM-IV) a los niños a los 18 meses y a los 8-10 años.

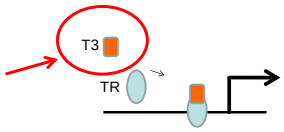
TDAH y hormonas tiroideas

Deficiencia de yodo, hipotiroxinemia materna y TDAH

Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild-Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries

F. VERMIGLIO, V. P. LO PRESTI, M. MOLETI, M. SIDOTI, G. TORTORELLA, G. SCAFFIDI, M. G. CASTAGNA, F. MATTINA, M. A. VIOLI, A. CRISÀ, A. ARTEMISIA, AND F. TRIMARCHI

The Journal of Clinical Endocrinology & Metabolism 89(12):6054–6060



- 2 regiones **A** (deficiente en yodo) y **B** (suficiente) en Italia.
- Perfil tiroideo en embarazadas al final 1 trimestre..
- n=16 niños de madres en las regiones A ó B.
- Inteligencia Wechsler: WISC-III, y screening TDAH (DSM-IV) a los niños a los 18 meses y a los 8-10 años.

- **68.7%** de niños en A con **TDAH.**
- **Total IQ: 92** en A *vs.* **110** en B.
- **63%** de niños TDAH de madres con Hipotiroxinemia gestacional

TEA y hormonas tiroideas

Fenotipos y genética de los TEA

Fenotipos

- Déficits de interacción social, desarrollo del lenguaje, comportams. e intereses repetitivos y esterotipias.
- Prevalencia: 0.1% (*criterios DSM-IV*).
- Subtipos: +/- déficits cognitivos. Clasificac. por "*endofenotipos*".

Etiología

- Ambientales: def. yodo, ***disrupción endocrina por xenobioticos***.
- Genética: *NGLN3-4, SHANK3, CNTNAP2, MECP2, AHI1.*

  Predisposición genética: ***CNVs*** *(16p11.2, 15q13, 17p11).*
- Genético-ambiental.

TEA y hormonas tiroideas

Autismo y metabolismo de h. tiroideas

Iodine deficiency as a cause of autism

Journal of the Neurological Sciences 276 (2009) 202

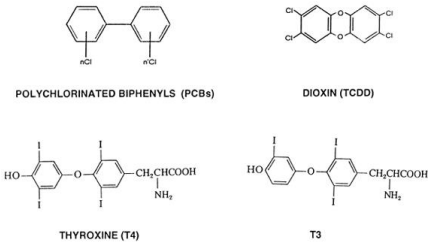
Autism: Transient *in utero* hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents

Gustavo C. Román *

Journal of the Neurological Sciences 262 (2007) 15–26

Neurodevelopment and Endocrine Disruption

Theo Colborn June 2004 • Environmental Health Perspectives



Institute of Medical
Molecular Genetics

Thyroid Molecular Laboratory. INGEMM

INGEMM

IdiPAZ
www.idipaz.es

Dasha Gorbenko
Theo Visser
ErasmusMC

Hospital Universitario La Paz
SaludMadrid
Comunidad de Madrid

SaludMadrid

Hospital Universitario Ramón y Cajal
Comunidad de Madrid

ciberer
CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED DE ENFERMEDADES RARAS

novo nordisk®

Causas moleculares

Paso transplacentario y de BHE fetal

Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation

Pere Berbel,[1] José Luis Mestre,[2,*] Asunción Santamaría,[1,3] Inmaculada Palazón,[4] Ascensión Franco,[1] Marisa Graells,[5,†] Antonio González-Torga,[6] and Gabriella Morreale de Escobar[7]

THYROID
Volume 19, Number 5, 2009

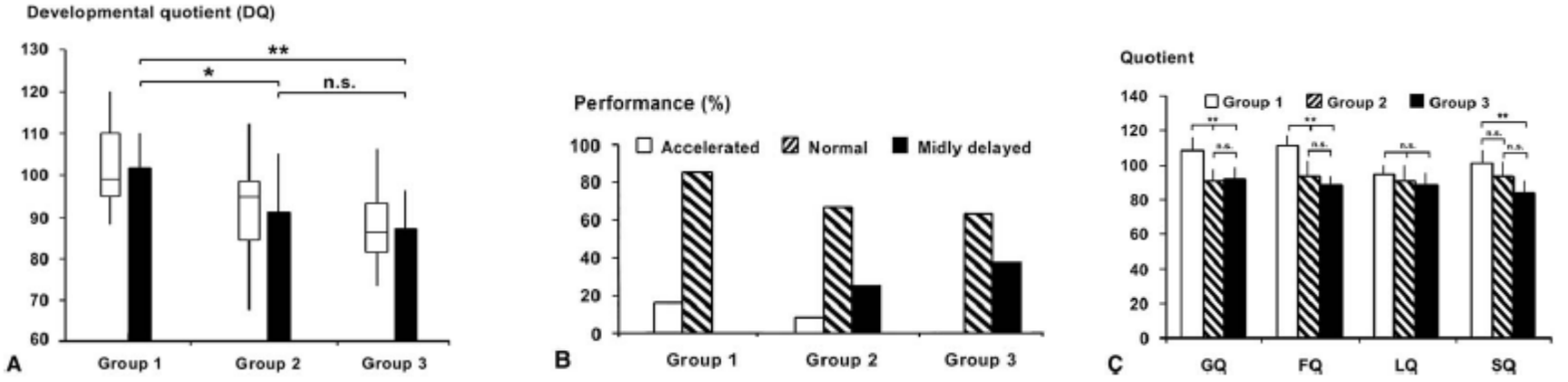
TEA y hormonas tiroideas

Hipotiroxinemia y defectos de socialización

Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation

Pere Berbel,[1] José Luis Mestre,[2,*] Asunción Santamaría,[1,3] Inmaculada Palazón,[4] Ascensión Franco,[1] Marisa Graells,[5,†] Antonio González-Torga,[6] and Gabriella Morreale de Escobar[7]

THYROID
Volume 19, Number 5, 2009



TEA y hormonas tiroideas

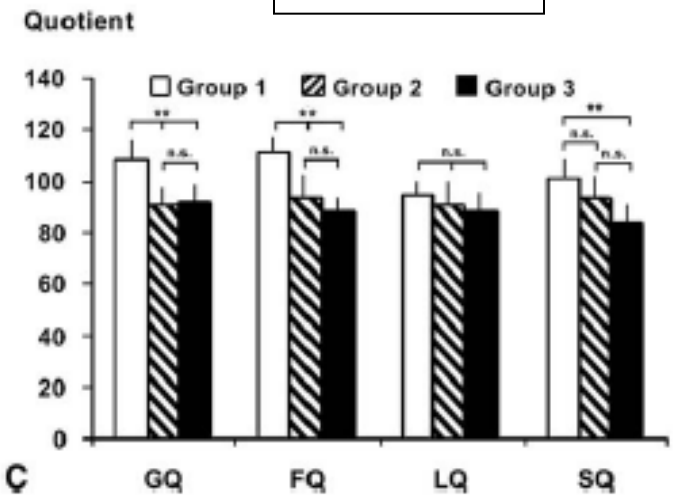
Hipotiroxinemia y defectos de socialización

Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation

Pere Berbel,[1] José Luis Mestre,[2,*] Asunción Santamaría,[1,3] Inmaculada Palazón,[4] Ascensión Franco,[1] Marisa Graells,[5,†] Antonio González-Torga,[6] and Gabriella Morreale de Escobar[7]

THYROID
Volume 19, Number 5, 2009

18 meses



Implicaciones:

34. Peterson CC, Slaughter VP, Paynter J 2007 Social maturity and theory of mind in typically developing children and those on the autism spectrum. J Child Psychol Psychiatry 48:1243–1250.

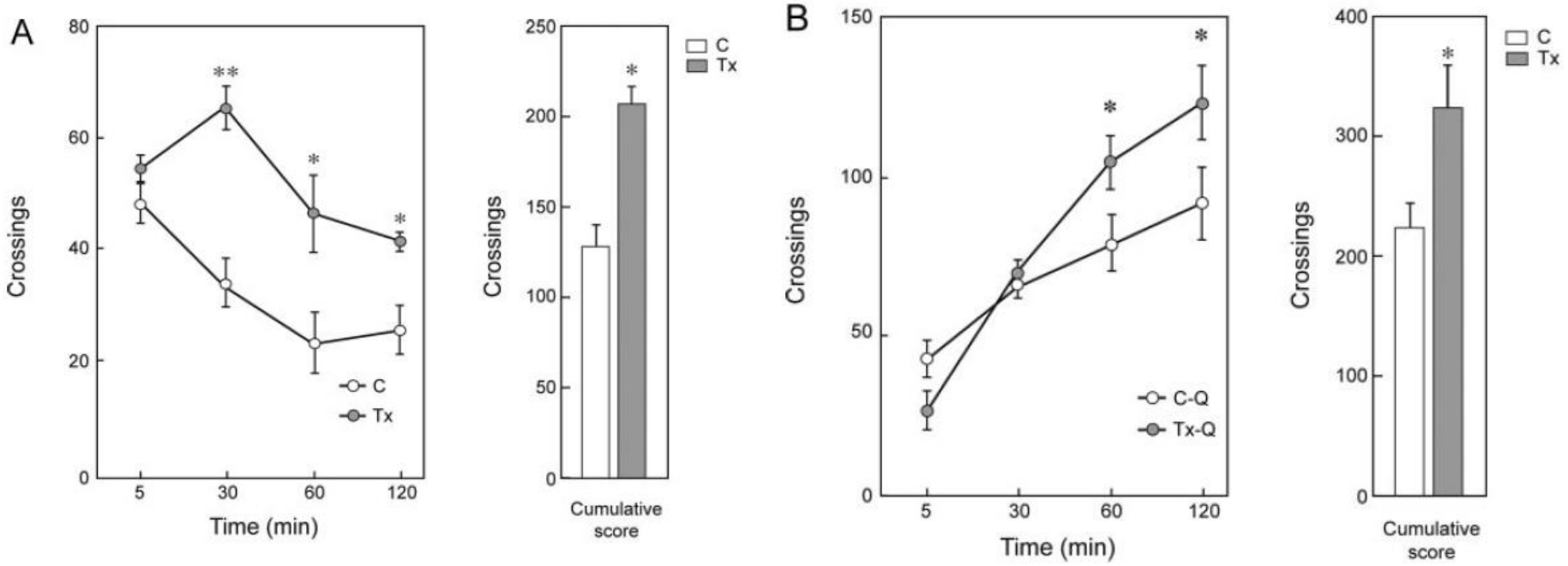
35. Johnson MH, Siddons F, Frith U, Morton J 1992 Can autism be predicted on the basis of infant screening tests? Dev Med Child Neurol 34:316–320.

Modelo de hiperactividad en ratas

El Receptor de Cannabinoides CB1

Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism

+ Quinpirol



Congenital hypothyroidism increases locomotor activity.

Defectos tiroideos y neurodesarrollo

The genetics of neurodevelopmental disease

Kevin J Mitchell

Current Opinion in Neurobiology 2010, 21:1–7