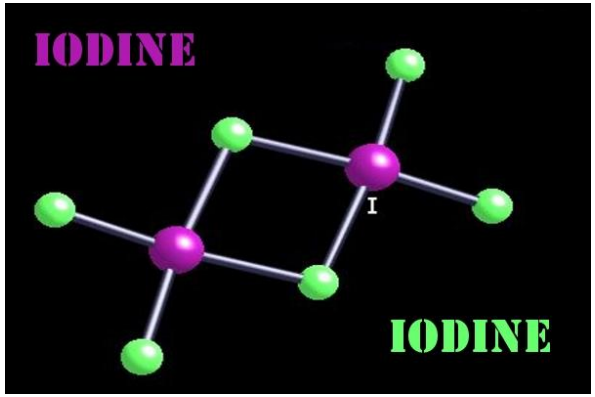
Iodo Therapy as Orthomolecular approach to treat different diseases

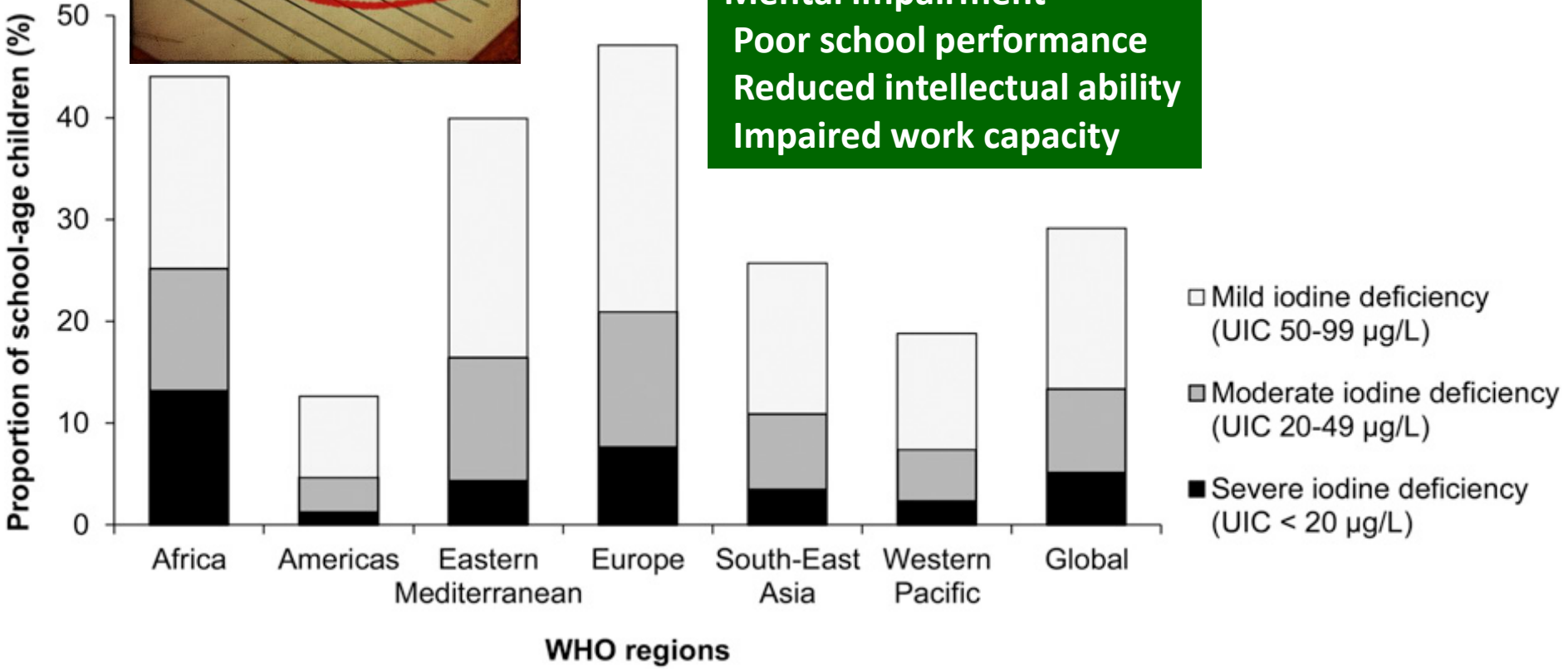
CARLY DOMINIQUE MD



Orthoiodosupplementation is the daily amount of iodine essential for whole body sufficiency.

Proportion (percentage) of SAC estimated to be at risk for mild, moderate, and severe iodine deficiency, by WHO region, 2011.

Mental impairment
Poor school performance
Reduced intellectual ability
Impaired work capacity



Global Iodine Status in 2011 and Trends over the Past Decade. Maria Andersson, Vallikkannu Karumbunathan, and Michael B. Zimmermann. 2012 American Society for Nutrition. First published online February 29, 2012; doi:10.3945/jn.111.149393.

Minimum iodine intake guidelines according to the World Health Organization

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	110 mcg*	110 mcg*		
7–12 months	130 mcg*	130 mcg*		
1–3 years	90 mcg	90 mcg		
4–8 years	90 mcg	90 mcg		
9–13 years	120 mcg	120 mcg		
14–18 years	150 mcg	150 mcg	220 mcg	290 mcg
19+ years	150 mcg	150 mcg	220 mcg	290 mcg

* Adequate Intake (AI)

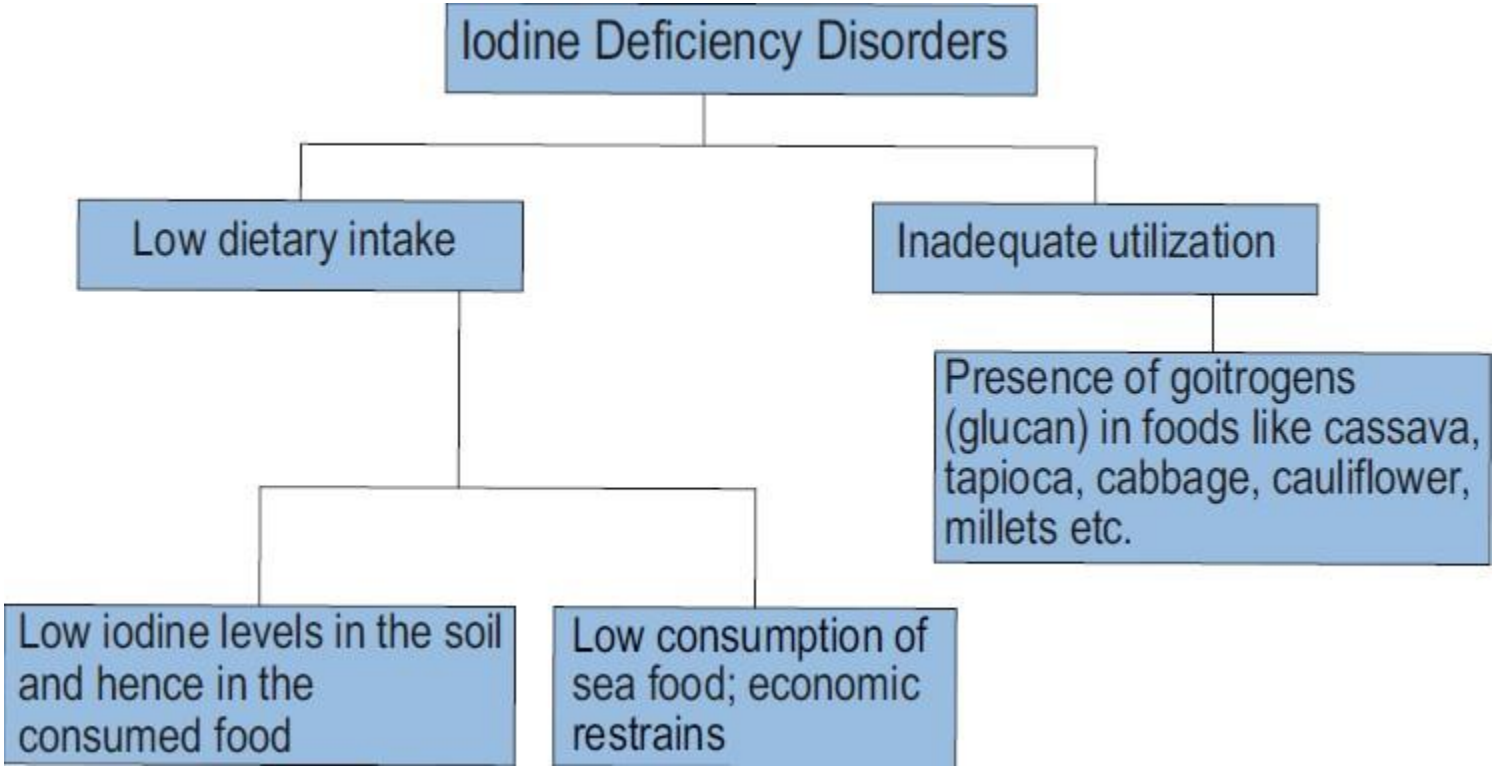
Table 1. **Epidemiological criteria for assessing iodine nutrition based on median urinary iodine (UI) concentrations in school-age children**

Median UI (μg/l)	Iodine intake	Iodine nutrition
< 20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimal
200–299	More than adequate	Risk of iodine-induced hyperthyroidism within 5–10 years following introduction of iodized salt in susceptible groups
⩾ 300	Excessive	Risk of adverse health consequences (iodine induced hyperthyroidism, autoimmune thyroid diseases)

Source (5).

Iodine deficiency in Europe A continuing public health problem, World health Organisation 2007

Causes of iodine deficiency disorders



Iodine, Iodine metabolism and Iodine deficiency disorders revisited. Farhana Ahad, Shaiq A Ganie. REVIEW ARTICLE. Year : 2010 | Volume : 14 | Issue : 1 | Page : 13-17.

Table 1: Sources of Iodine*

Soil	
$NaIO_3$	Sodium Iodine
$NaIO_4$	Sodium periodate
Seaweed / Algal Phytoplankton	
KI	Potassium Iodide
NaI	Sodium Iodide
I_2	Iodine
I'	Iodide
Seawater	
I'	Iodide

* Adapted from: Patrick L. Iodine: Deficiency and therapeutic considerations. Altern Med Rev 2008; 13: 116-127.

The Top Ten Iodine Rich Foods

10. Strawberries

Serving size – 1 cup –
13mcg iodine (9% RDA)

9. Navy beans

Serving size – 1/2 cup
32mcg iodine (21% RDA)

8. Potatoes, with skin

Serving size – 1 medium
60mcg iodine (40% RDA)

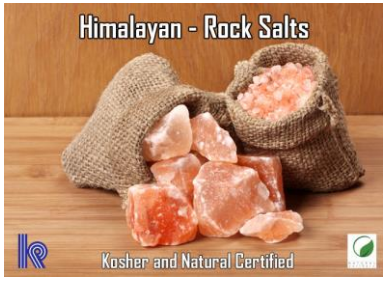
7. Turkey Breast

Serving size – 3oz
34mcg iodine (23% DRA)

6. Eggs

Serving size – 1 large
25mcg iodine (17% RDA)

5. Himalayan Crystal Salt



One gram of himalayan salt
+/-500/mcg of iodine.

4. Cod

Serving size – 3oz
100mcg iodine (66% RDA)

3. Yogurt

Serving size 1 cup
100mcg iodine (66% RDA)

http://www.iodinesupplement.org/iodine-rich-foods/

The Top Ten Iodine Rich Foods

2. Cranberries

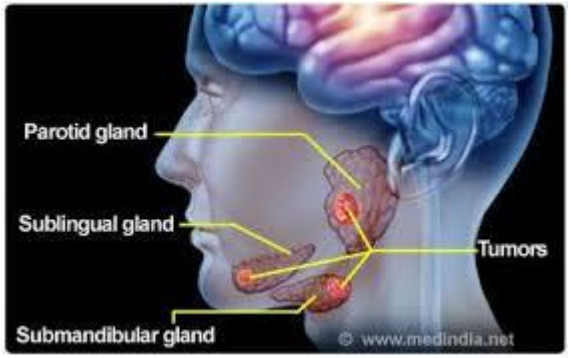
Serving size – 1 cup –
400 mcg iodine (267% RDA)

1. Seaweed

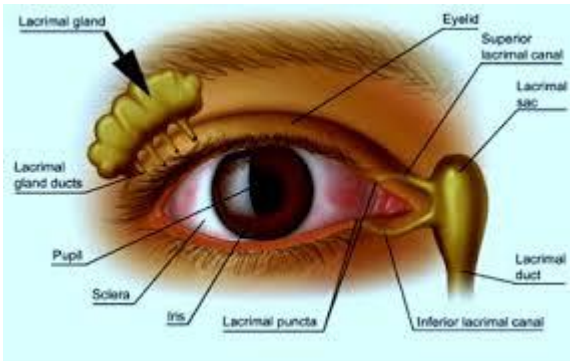
Serving size – ¼ oz
16 to 3000 mcg iodine
(16 to 2000 % RDA)

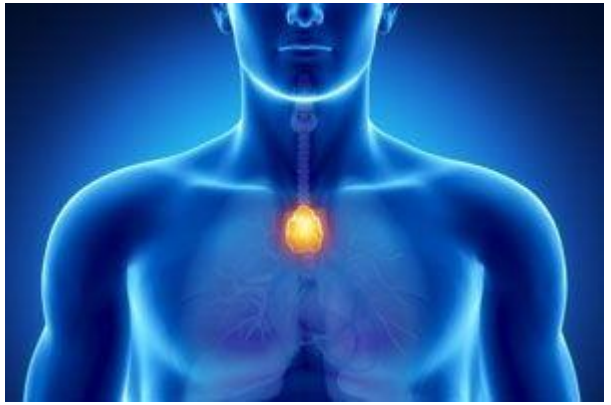
http://www.iodinesupplement.org/iodine-rich-foods/

NIS protein has been demonstrated in :



- The salivary glands,
- Stomach,
- Enterocytes
- Lactating breast,
- Breast cancer cells
- Prostate cancer cells
- lacrimal glands,
- Thymus.
- Pancreas
- Kidneys





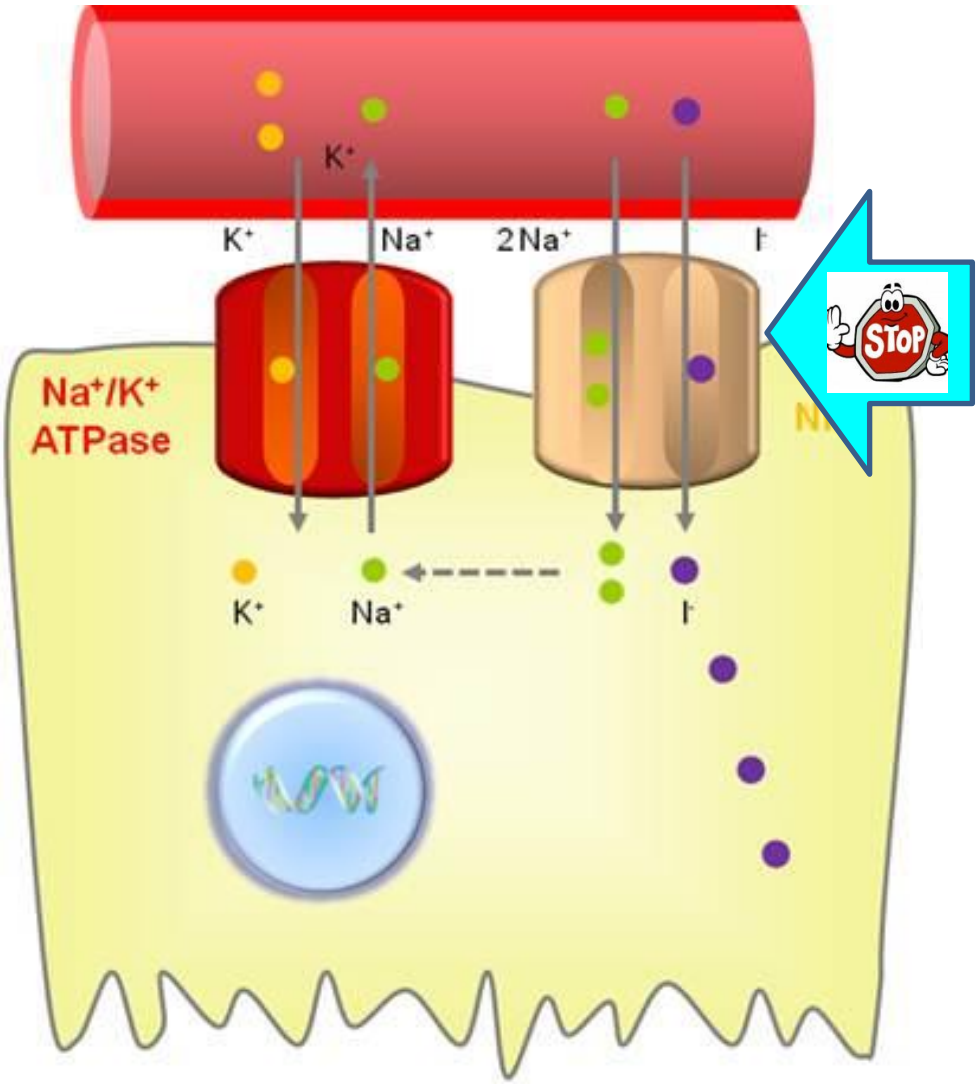
Reagents that modulate iodide uptake

Reagent	IUA	NIS
TSH	↑	↑
Iodine	↓	↓
T4 and T3	↓	↓
Perchlorate	↓	N
TPO inhibitor (MNI and PTU)	N	N, ↓

IUA, iodide uptake activity; NIS, sodium iodide symporter expression; TSH, thyrotropin; T3, triiodothyronine; T4, thyroxine; TPO, thyroperoxidase, MMI, methimazole; PTU, propylthiouracil; N, no change.

Sodium Iodide Symporter in Health and Disease. Daniel H.Y. Shen, Richard T. Kloos, Ernest L. Mazzaferri, and Sissy M. Jhiang. THYROID. Volume 11, Number 5, 2001

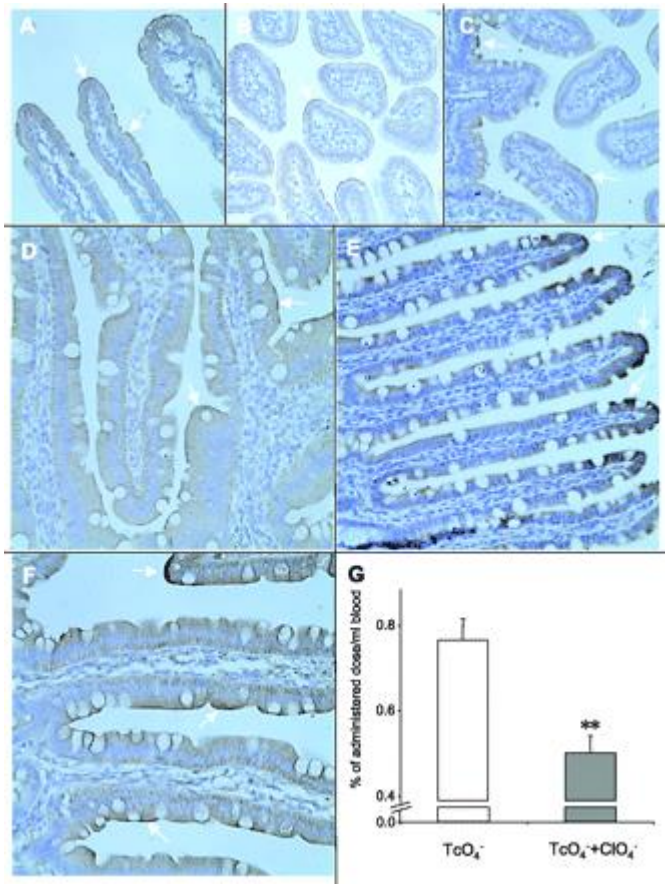
NIS blocking agents



- Organochlorides
- Bromides
- Nitrate
- Fluorides
- T4/T3
- Thyocyanates
- Iodine

The Na+/I– symporter mediates active iodide uptake in the intestine

NIS is expressed on the apical surface of small intestine enterocytes

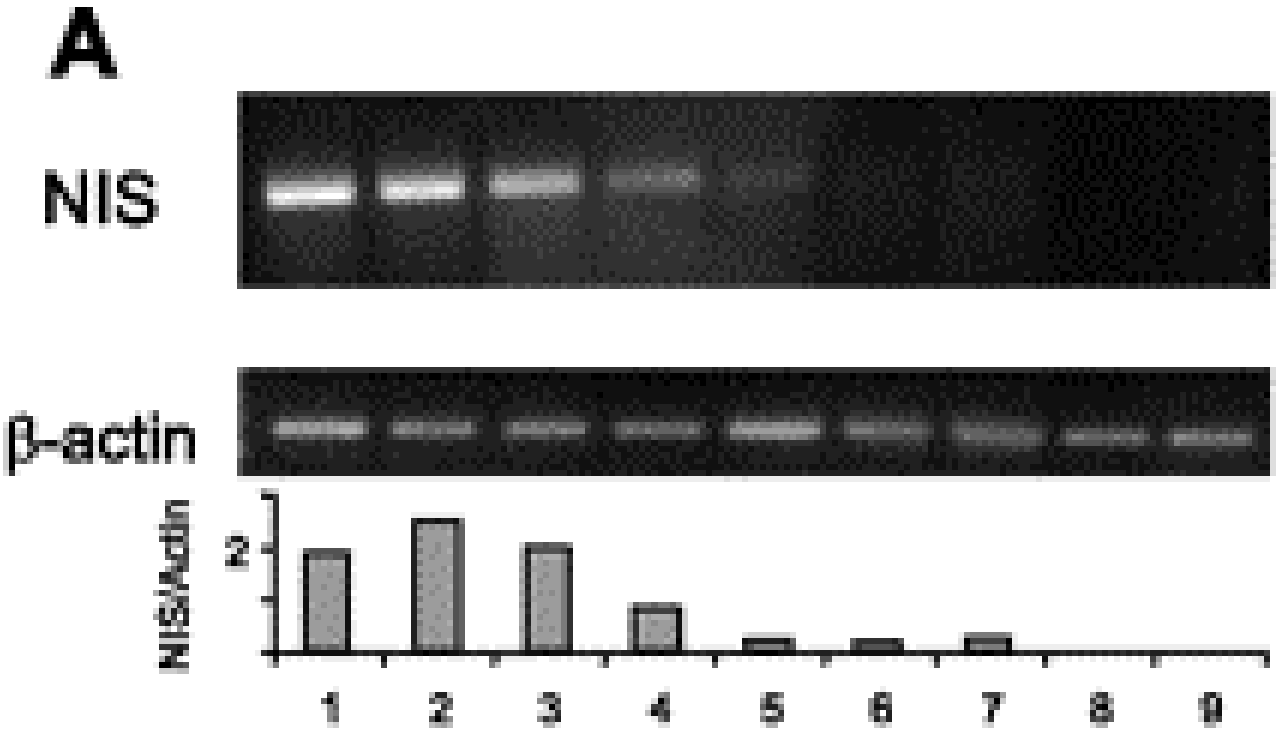


Imunohistochemistry with anti-NIS antibody.
NIS expression was clearly apparent along the entire length of the small intestine exclusively on the apical surface of the enterocytes.

To investigate at the functional level whether the absorption of I– is mediated by NIS in vivo, we administered pertechnetate (99mTcO4–) [a widely used NIS substrate with a shorter half-life than 125I– (48)] alone and, after a 2-h washout time, 99mTcO4– together with the NIS inhibitor ClO4– to four rats via duodenal catheterization, and collected blood samples. Nine minutes after administration, the absorption of 99mTcO4– in the animals simultaneously treated with ClO4– was inhibited by 27.4% to 47.9% as compared with those treated with 99mTcO4– alone.

The Na+/I– symporter mediates active iodide uptake in the intestine. Juan Pablo Nicola , Cécile Basquin , Carla Portulano , Andrea Reyna-Neyra , Monika Paroder , Nancy Carrasco. American Journal of Physiology - Cell Physiology Published 1 April 2009 Vol. 296 no. C654-C662

NIS is more abundantly expressed toward the tip of the villus

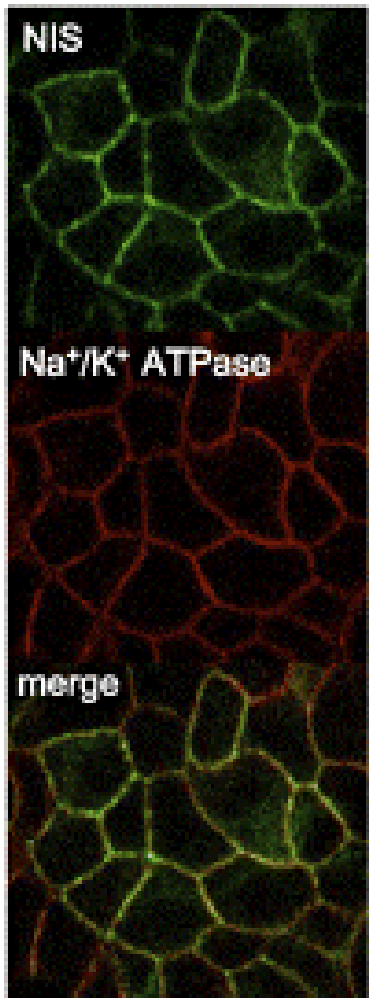


NIS mRNA (standardized relative to β-actin mRNA expression) was clearly enriched (~5- to 6-fold) in cells from the tip of the villus

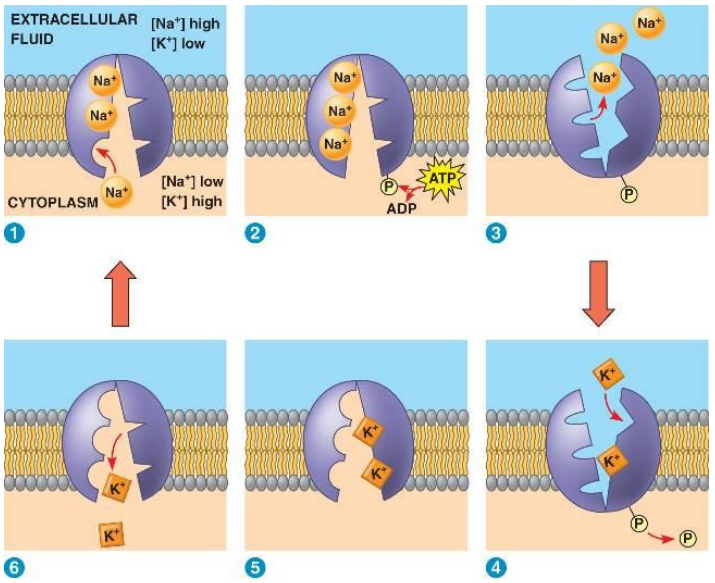
To assess our initial observation that NIS is more abundantly expressed toward the tip of the villus, we isolated nine fractions of epithelial cells, from the villus tip to the crypt.

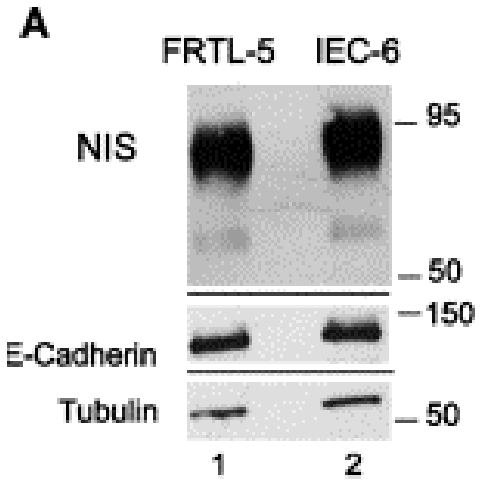
The Na+/I− symporter mediates active iodide uptake in the intestine. Juan Pablo Nicola , Cécile Basquin , Carla Portulano , Andrea Reyna-Neyra , Monika Paroder , Nancy Carrasco. American Journal of Physiology - Cell Physiology Published 1 April 2009 Vol. 296 no. C654-C662

Enterocyte NIS location



Overlay of the two images is shown at bottom. NIS is clearly localized at the plasma membrane of IEC-6 cells and colocalized with the Na+/K+ ATPase signal

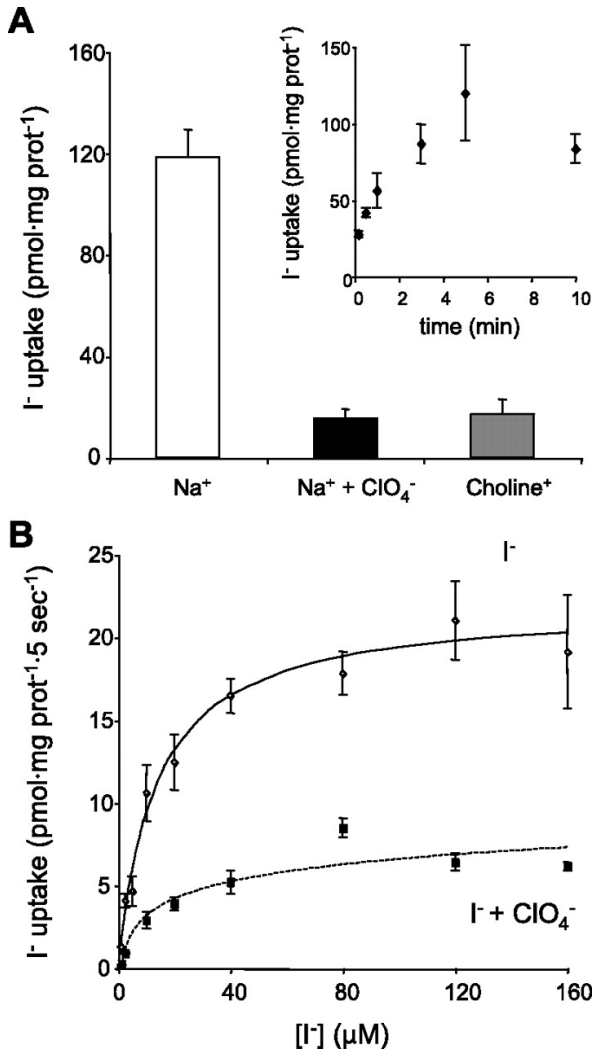




IEC-6 cells was actually slightly higher than in rat thyroid-derived FRTL-5 cells. Given that NIS must be in the plasma membrane for I− uptake to take place.

The Na+/I− symporter mediates active iodide uptake in the intestine. Juan Pablo Nicola , Cécile Basquin , Carla Portulano , Andrea Reyna-Neyra , Monika Paroder , Nancy Carrasco. American Journal of Physiology - Cell Physiology Published 1 April 2009 Vol. 296 no. C654-C662

Brush border membrane vesicles display pronounced NIS-mediated I– uptake

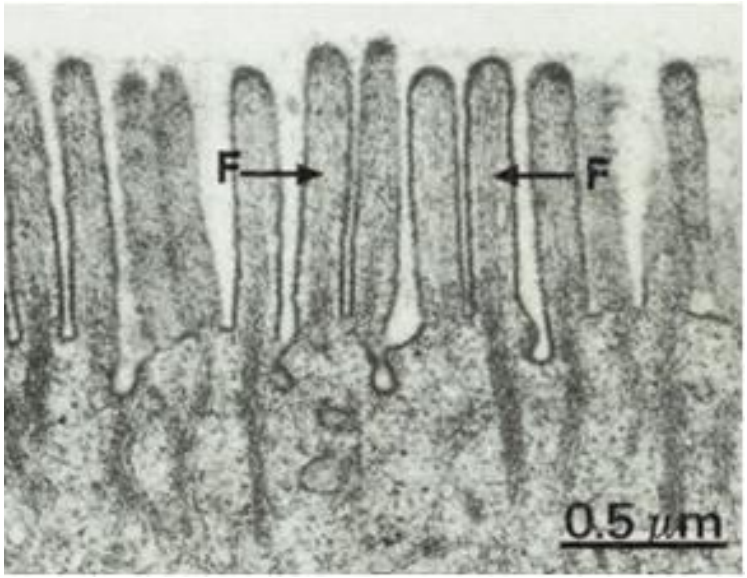


I– uptake in rat small intestine brush border membrane vesicles (BBMV).

A: steady-state I– uptake assays (5-min time points; see inset for time course) in BBMV (50 µg) were carried out with 20 µM I–/140 mM Na+ (white bar), 20 µM I–/140 mM Na+/40 µM ClO4– (black bar), and 20 µM I–/140 mM choline (gray bar) as described in materials and methods. I– transport displayed NIS-specific characteristics, i.e., Na+ dependence and ClO4– sensitivity. Inset: time course of I– uptake in BBMV. Transport saturated at 5 min.

B: initial rates (5-s time points) of I– uptake were determined at the indicated I– concentrations and a constant concentration of Na+ (140 mM) in the absence (solid line) or presence (dotted line) of 40 µM ClO4–.

The Na+/I– symporter mediates active iodide uptake in the intestine. Juan Pablo Nicola , Cécile Basquin , Carla Portulano , Andrea Reyna-Neyra , Monika Paroder , Nancy Carrasco. American Journal of Physiology - Cell Physiology Published 1 April 2009 Vol. 296 no. C654-C662

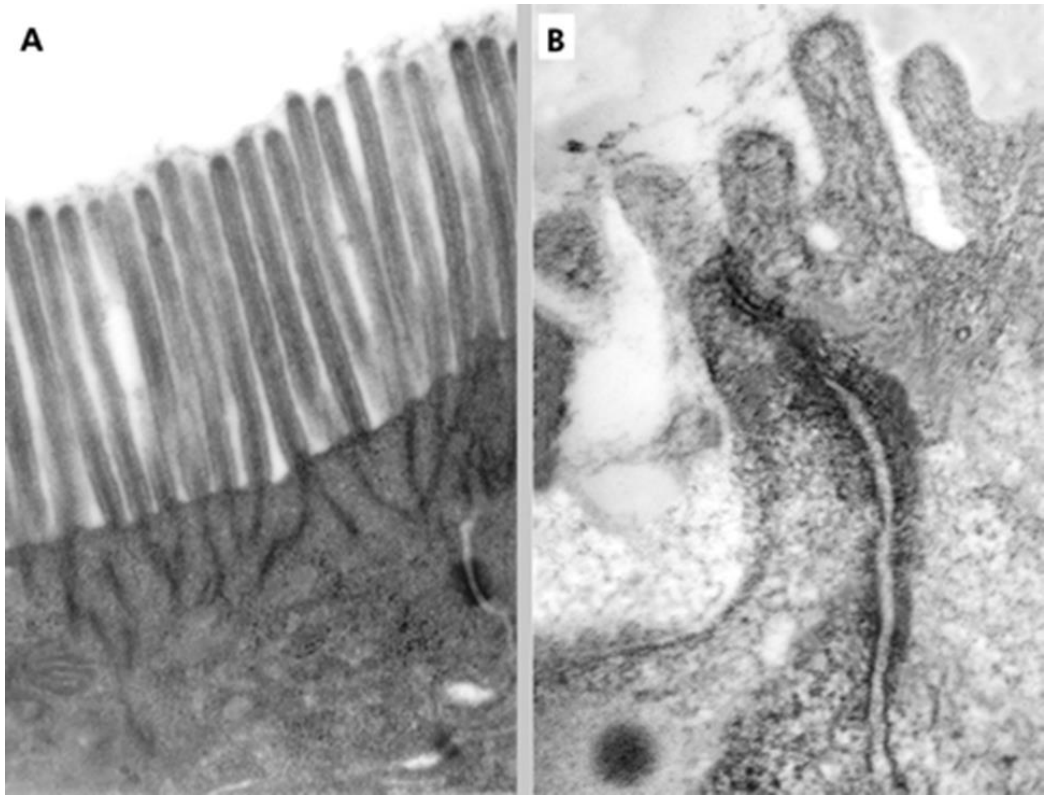


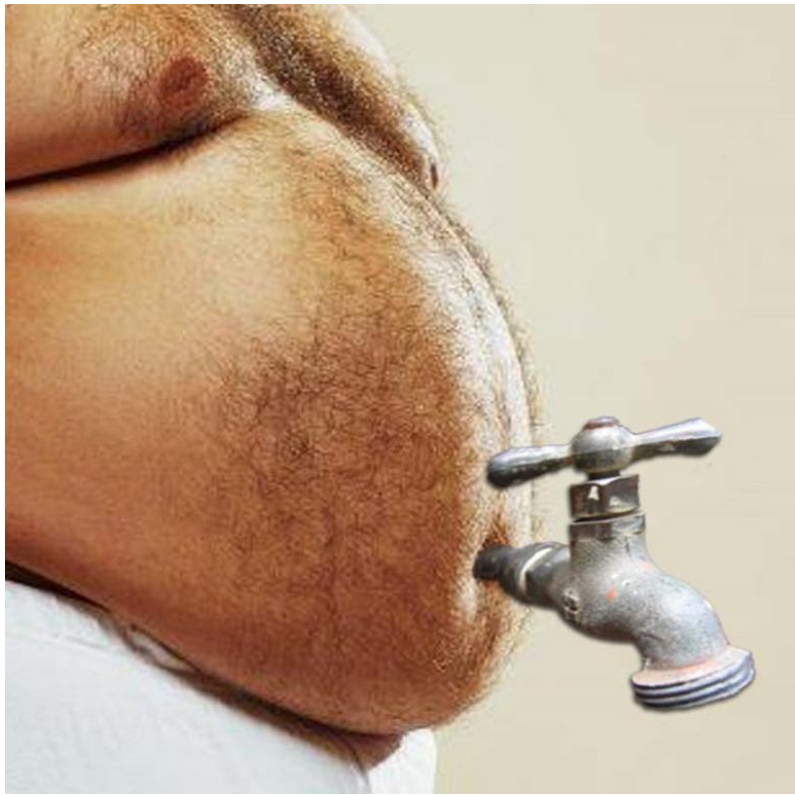
Those data do not rule out the possible participation of transporters other than NIS, such as anion exchangers, in the translocation of I– from the intestinal lumen into the enterocytes, a notion consistent with the observed partial inhibition of 99mTcO4– absorption by ClO4–

NIS may be thought of as a kind of I^- metabolism master molecule, participating in the anion's translocation from its intestinal absorption to its uptake in the thyroid, lactating breast, salivary glands, and gastric mucosa. In these last two tissues, NIS activity causes I– to return to the gastrointestinal lumen, from which the anion, as part of an I– conservation system, is again absorbed via NIS in the small intestine. Finally, in light of our recent demonstration that NIS mediates active transport of ClO4– , intestinal NIS is clearly a conduit for this environmental pollutant to enter the bloodstream.

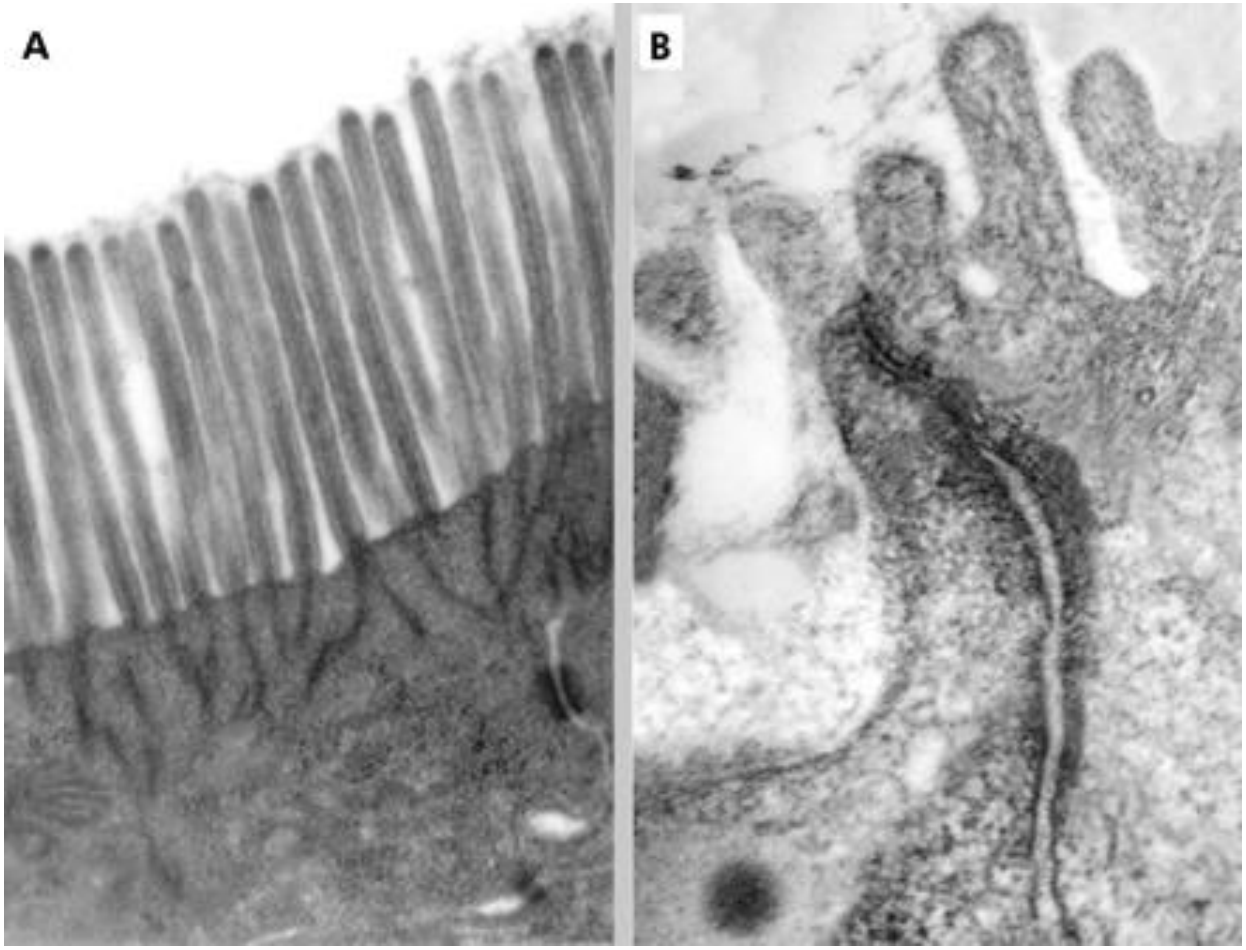
The Na+/I– symporter mediates active iodide uptake in the intestine. Juan Pablo Nicola , Cécile Basquin , Carla Portulano , Andrea Reyna-Neyra , Monika Paroder , Nancy Carrasco. American Journal of Physiology - Cell Physiology Published 1 April 2009 Vol. 296 no. C654-C662

Gut iodine absorption





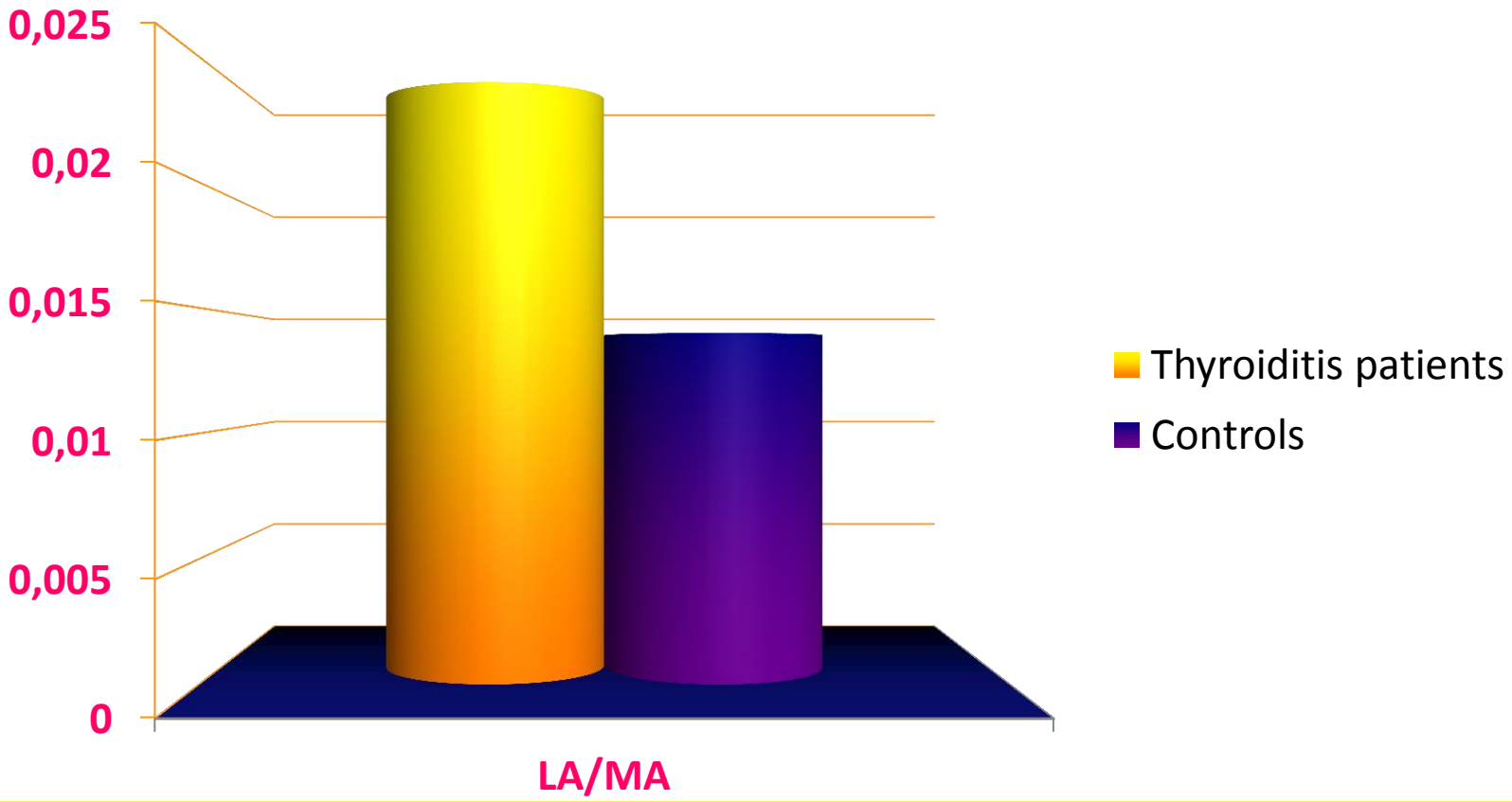
Ultrastructural changes in enterocytes in subjects with Hashimoto's thyroiditis



(A) Transmission electron microscopy (TEM) of a normal duodenal mucosa in a sample from a healthy control subject. Both microvilli and the visible tight junction (TJ) are normal with respect to thickness and height. Original magnification: 24 000×. (B) TEM micrograph showing features of adjacent enterocytes in a mucosal sample from a thyroiditis affected patient. TJ complexes are characterised by dilated intercellular spaces; some microvilli are also visible, clearly shorter and thicker than normal. Original magnification: 60 000×.

Ultrastructural changes in enterocytes in subjects with Hashimoto's thyroiditis. F C Sasso, O Carbonara, R Torella, A Mezzogiorno, V Esposito, L deMagistris, M Secondulfo, R Carratu, D Iafusco, M Carteni. Gut 2004;53:1878-1880 doi:10.1136/gut.2004.047498.

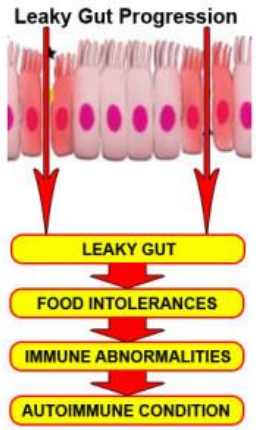
Alteration in intestinal mucosal permeability (IP) evaluated by the lactulose/mannitol (LA/MA) test.



Hashimoto thyroiditis present similar pathogenetic mechanisms of cellular damage, a cell mediated autoimmunity induced by Th1 cytokines.

Ultrastructural changes in enterocytes in subjects with Hashimoto's thyroiditis. F C Sasso, O Carbonara, R Torella, A Mezzogiorno, V Esposito, L deMagistris, M Secondulfo, R Carratu, D Iafusco, M Carteni. Gut 2004;53:1878-1880 doi:10.1136/gut.2004.047498.

Discov Med. 2012 Nov;14(78):321-6.

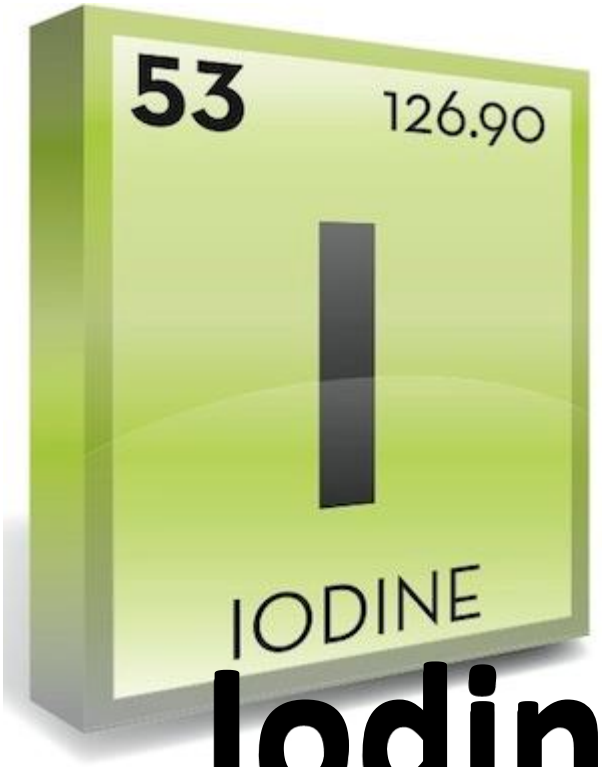


Does the gut microbiota trigger Hashimoto's thyroiditis?

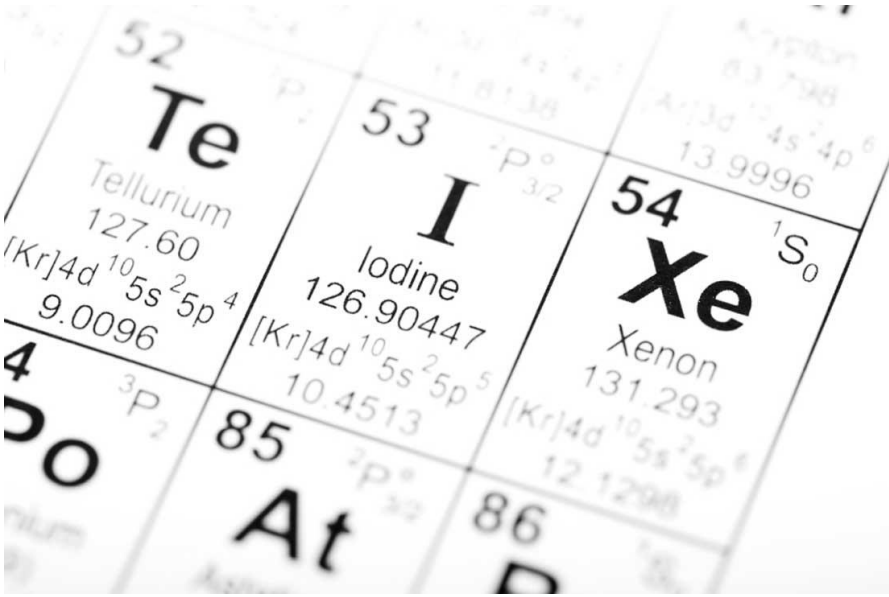
Mori K1, Nakagawa Y, Ozaki H.

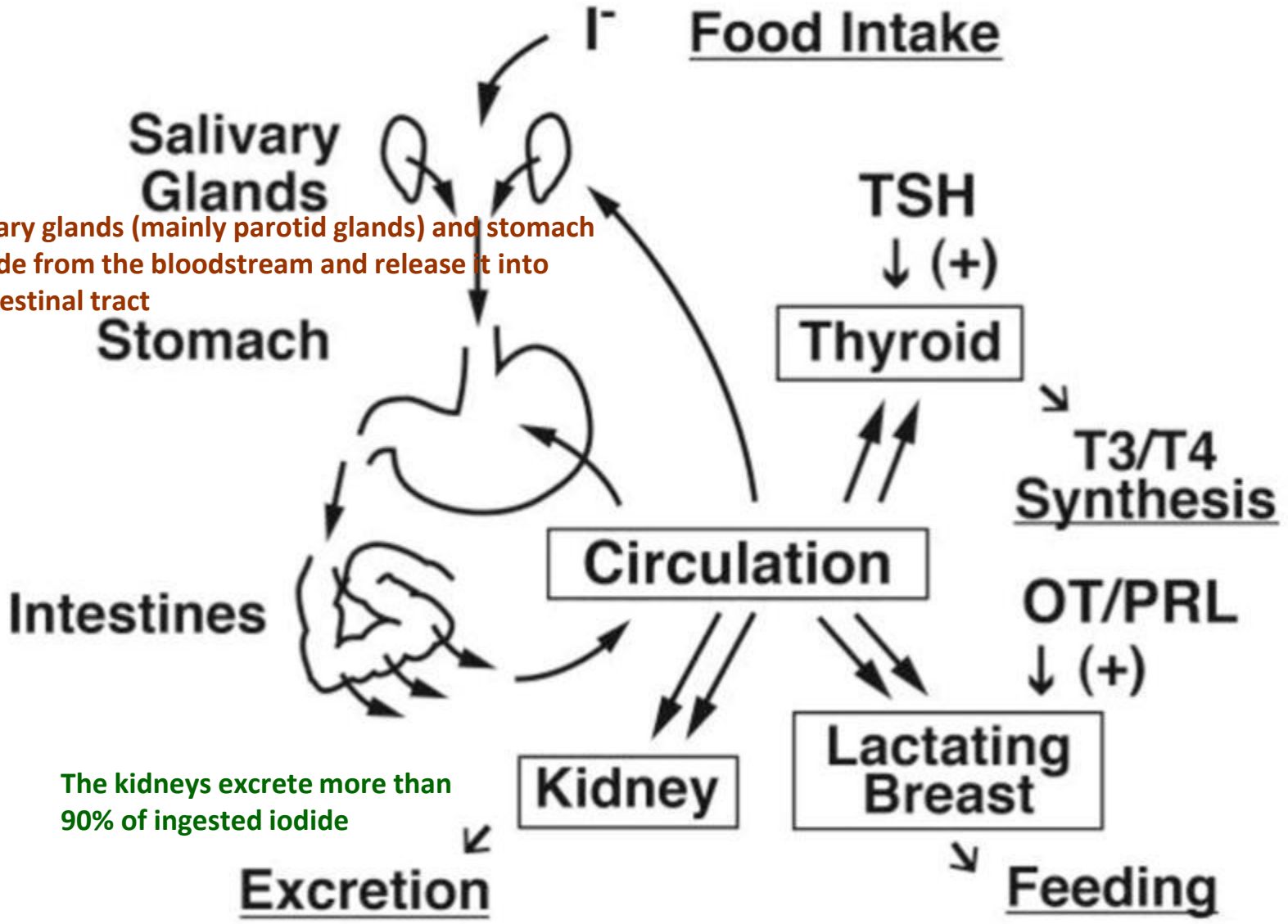
Abstract

Hashimoto's thyroiditis is an organ-specific autoimmune disease in which both genetic predisposition and environmental factors serve as the trigger of the disease. A growing body of evidence suggests involvement of viral infection in the development of Hashimoto's thyroiditis. However, not only pathogenic microorganisms but also non-pathogenic commensal microorganisms induce proinflammatory or regulatory immune responses within the host. In accordance, series of studies indicate a critical role of intestinal commensal microbiota in the development of autoimmune diseases including inflammatory bowel diseases, type 1 diabetes, rheumatoid arthritis, and multiple sclerosis. In contrast, the role of the gut and indigenous microorganisms in Hashimoto's thyroiditis has received little attention. Whereas activation of innate pattern recognition receptors such as Toll-like receptors and disturbed intestinal epithelial barrier may contribute to thyroiditis development, only a few studies have addressed a link between the gut and Hashimoto's thyroiditis and provided just indirect and weak evidence for such a link. Despite this unsatisfactory situation, we here focus on the possible interaction between the gut and thyroid autoimmunity. Further studies are clearly needed to test the hypothesis that the gut commensal microflora represents an important environmental factor triggering Hashimoto's thyroiditis.



Iodine metabolism

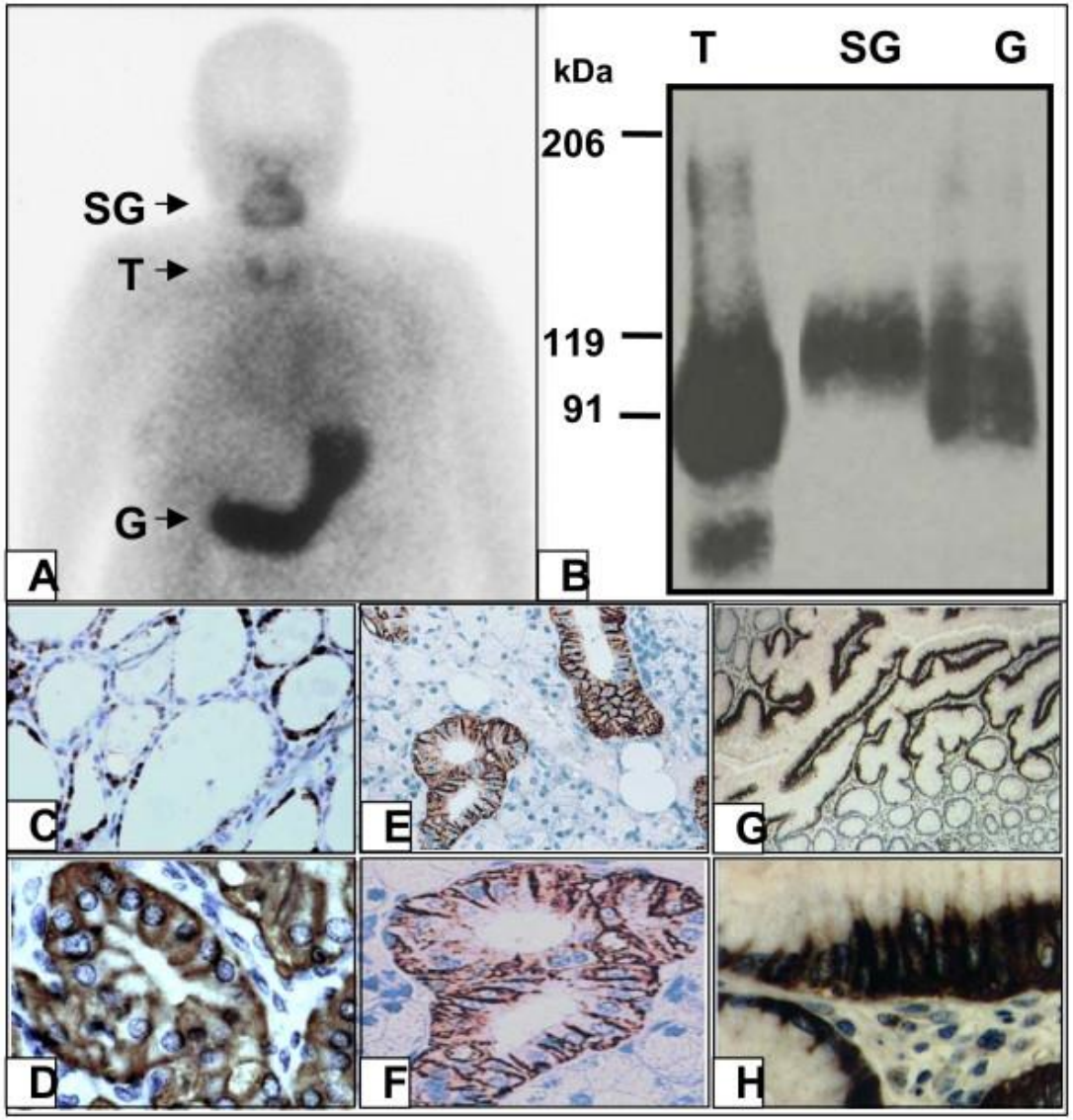




The salivary glands (mainly parotid glands) and stomach take iodide from the bloodstream and release it into gastrointestinal tract

The kidneys excrete more than 90% of ingested iodide

The Sodium Iodide Symporter (NIS): Regulation and Approaches to Targeting for Cancer Therapeutics. Takahiko Kogai and Gregory A. Brent. Pharmacol Ther. Sep 2012; 135(3): 355–370.



A: Radioiodide accumulation in NIS-expressing human tissues (SG: salivary glands, T: thyroid, G: stomach) 2 hours after ^{99m}Tc-pertechnetate administration.

B: Immunoblot analyses of human NIS expression in a Graves' thyroid (T), normal salivary glands (SG), and normal gastric mucosa (G).
C: Normal thyroid .

D: Graves' thyroid, strong basolateral NIS staining of the follicular epithelial cells .

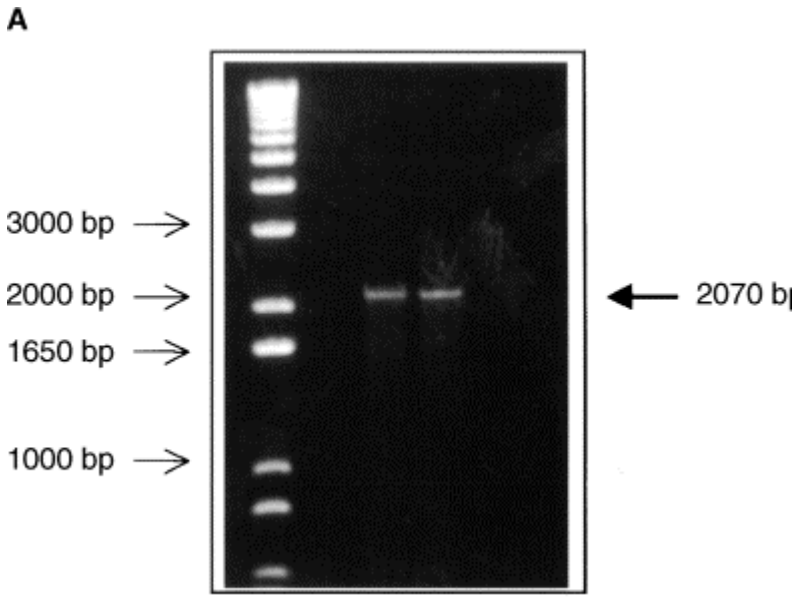
E: Salivary gland .

F: Basolateral NIS staining in the salivary ductal cells.
cells

G: Gastric mucosa. H: Basolateral NIS staining of the gastric mucin-secreting

Expression of the Na^+/I^- symporter (NIS) is markedly decreased or absent in gastric cancer and intestinal metaplastic mucosa of Barrett esophagus. Áron Altorjay, Orsolya Dohán, Anna Szilágyi, Monika Paroder, Irene L Wapnir and Nancy Carrasco. *BMC Cancer* 2007, 7:5

Expression of the sodium iodide symporter in human kidney



Polymerase chain reaction (PCR) amplification of cDNA derived from human Graves' thyroid tissue (lane 1) and normal human kidney tissue (lane 2) using a pair of hNIS-specific oligonucleotide primers designed to amplify full-length hNIS cDNA (2070 bp; A).

The authors found variable levels of hNIS gene expression in different kidney segments, the most prominent hNIS-specific immunoreactivity was observed in the distal tubular system, with lower staining in the proximal tubules and no hNIS-specific immunostaining in the glomeruli.

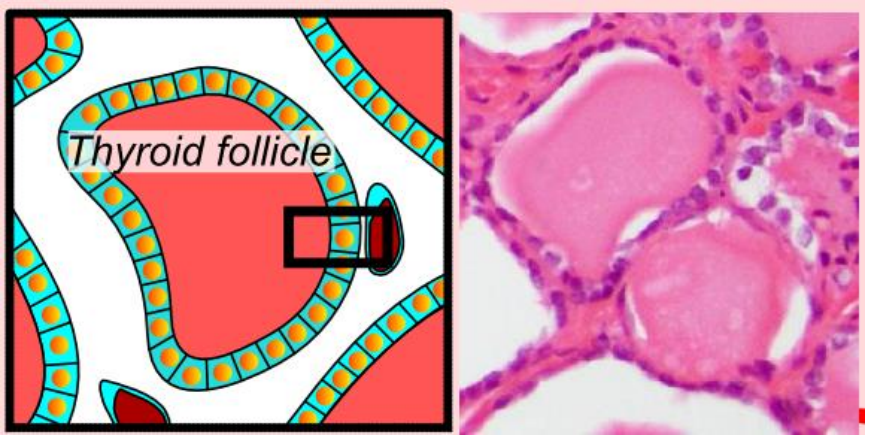
Renal iodide transport may be, at least in part, an active process driven by NIS. Further studies, in particular in vivo studies, are needed to determine that iodide transport in the kidney is mediated by hNIS and to address its exact function, possible immunologic relevance, and the regulatory mechanisms involved in balancing iodide clearance.

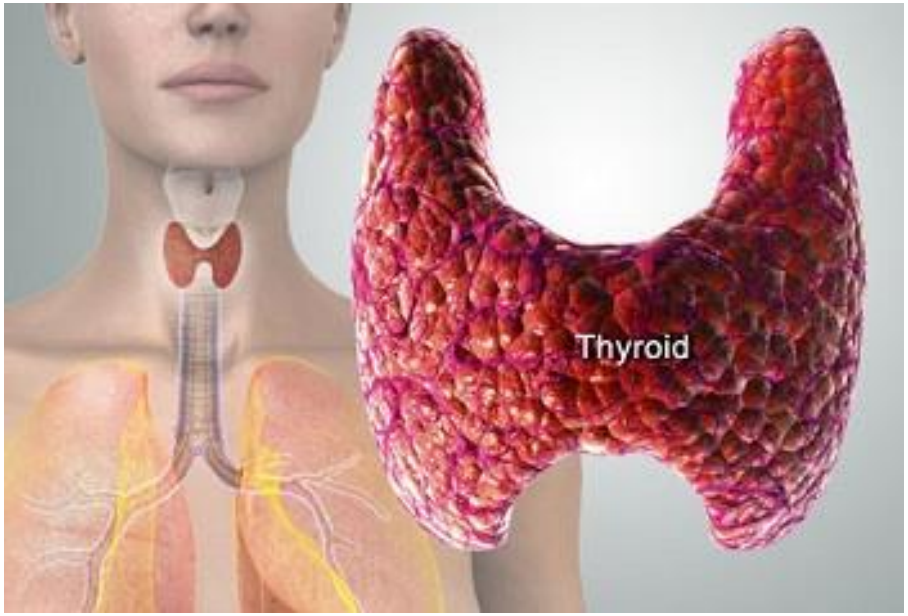
Expression of the sodium iodide symporter in human kidney. Christine Spitzweg, Charyl M Dutton, Maria R Castro, Elizabeth R Bergert, John R Goellner, Armin E Heufelder and John C Morris. Kidney International (2001) 59, 1013–1023.


Thyroid
SCIENCEphotoLIBRARY

Physiology of iodide metabolism and NIS

The thyroid contains 70–90% of the iodide in the body (9–10 mg) and this iodide accumulation is dependent on NIS expressed on the basolateral membrane of thyroid follicular cells.





The Sodium Iodide Symporter (NIS): Regulation and Approaches to Targeting for Cancer Therapeutics. Takahiko Kogai and Gregory A. Brent. Pharmacol Ther. Sep 2012; 135(3): 355–370.

Extracellular space

Na$^+$/glucose cotransporter

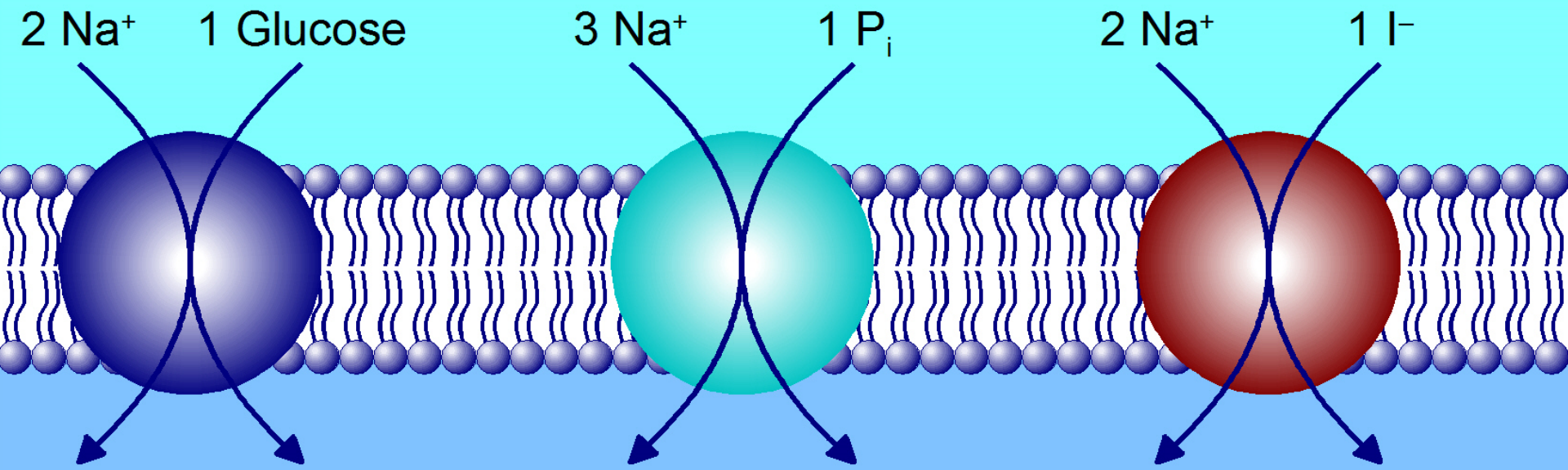
SGLT1

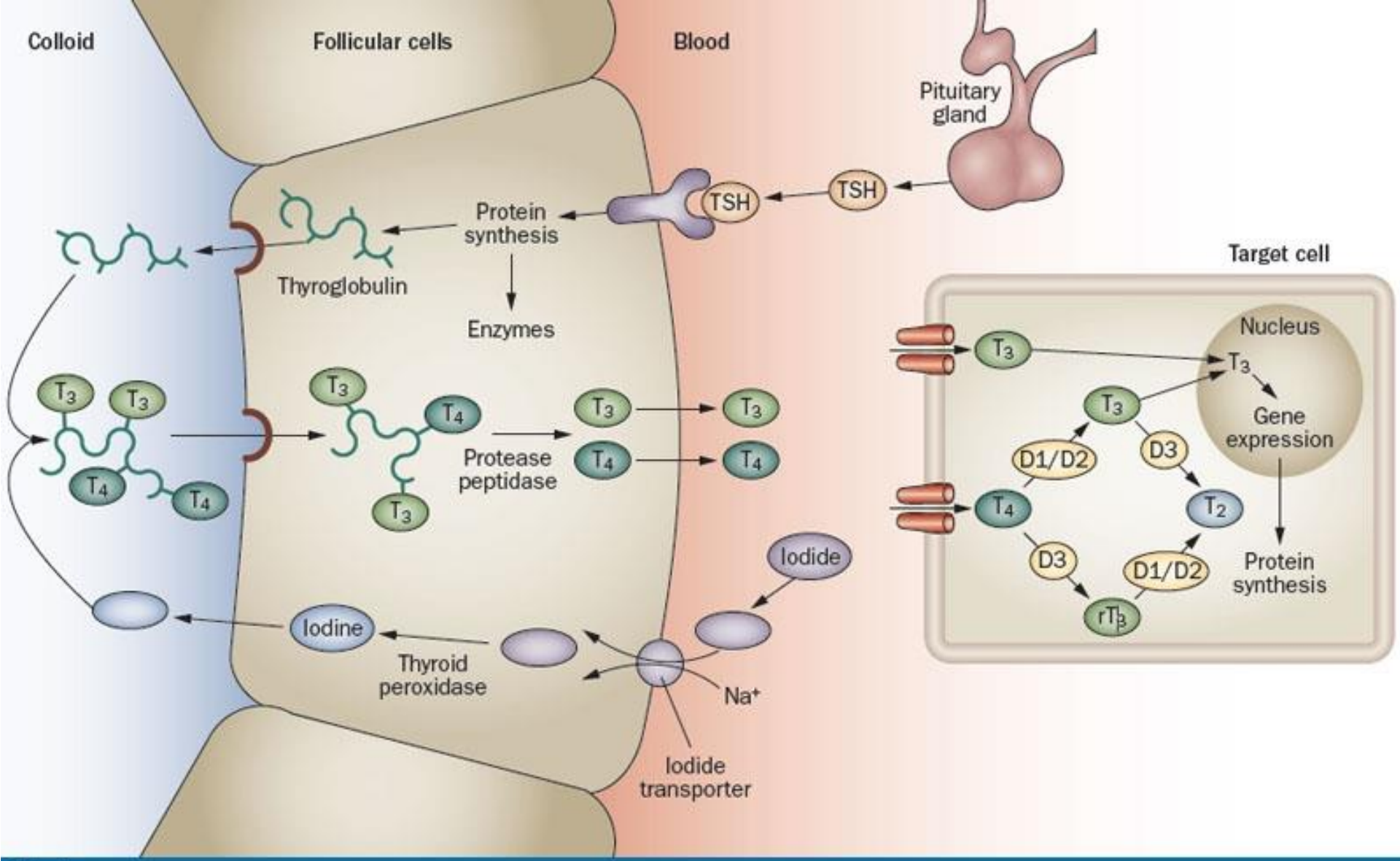
Na$^+$/phosphate cotransporter

NaPi IIa/b

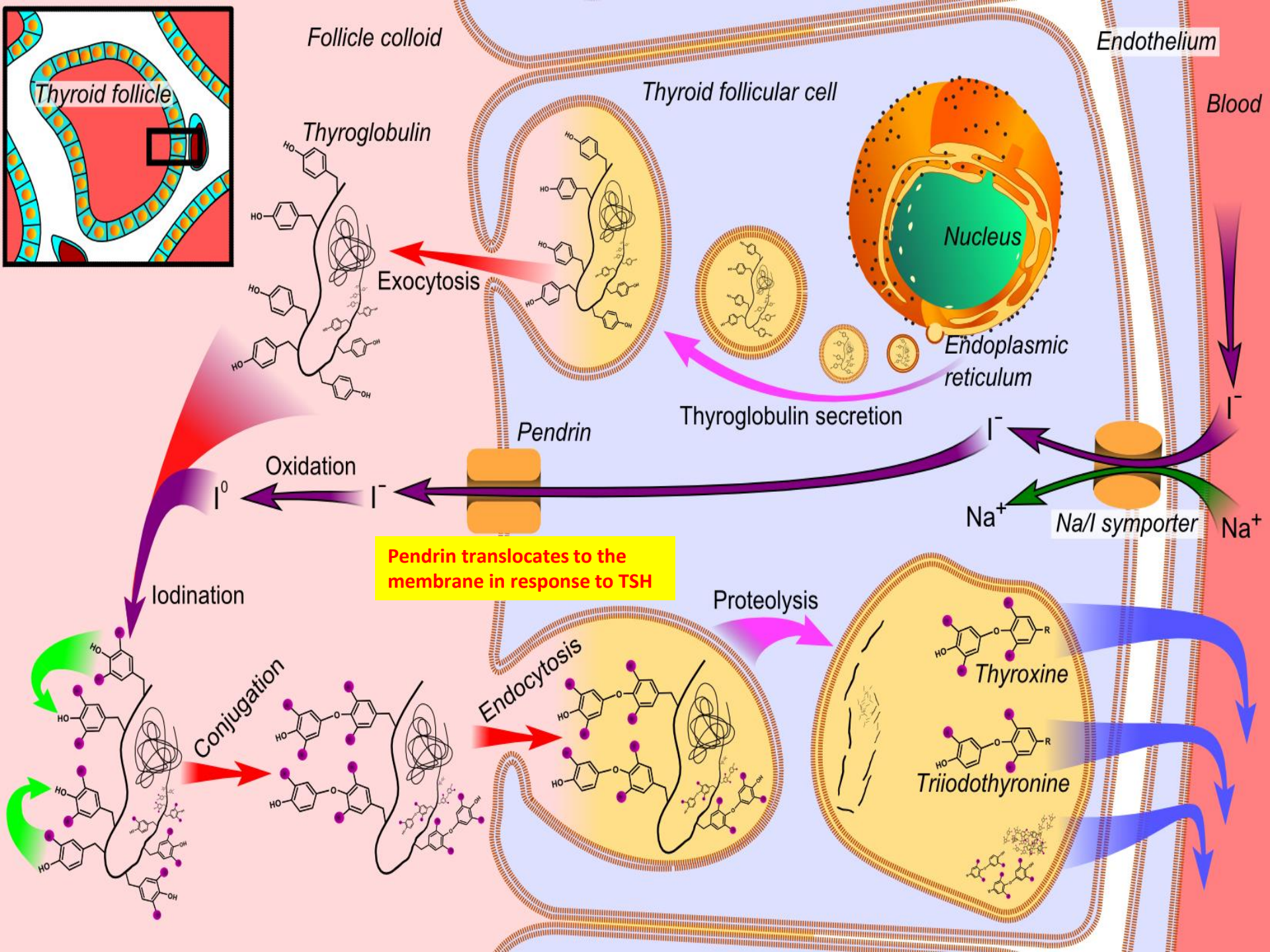
Na$^+$/iodide symporter

NIS





Synthesis of thyroid hormones. Thyroid hormones are synthesized in follicular cells of the thyroid gland from tyrosine residues within the thyroglobulin molecule. T4 and T3 molecules are... then cleaved and released into the circulation. T3, the physiologically active form of thyroid hormone, can also be formed from the monodeiodination of T4. T4 is converted to T3 predominantly by type I iodothyronine deiodinase. Abbreviations: D1, type I iodothyronine deiodinase; D2, type II iodothyronine deiodinase; D3, type III iodothyronine deiodinase; rT3, reverse T3. **http://www.medscape.org/viewarticle/712517_4**

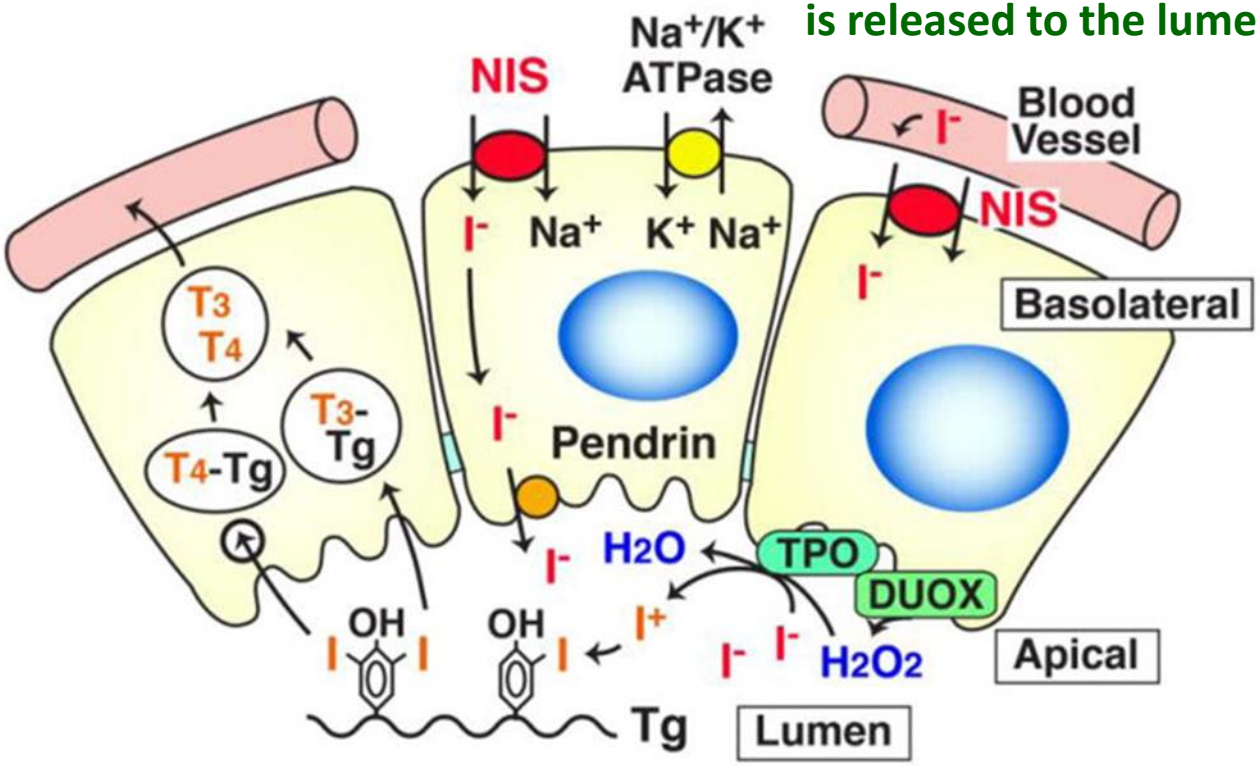

Thyroid follicle
Follicle colloid
Endothelium
Thyroid follicular cell
Blood
Thyroglobulin
Exocytosis
Nucleus
Endoplasmic reticulum
Thyroglobulin secretion
Pendrin
Oxidation
I^0
I^-
I^-
I^-
Na^+
Na^+
Na/I symporter
Pendrin translocates to the membrane in response to TSH
Iodination
Conjugation
Endocytosis
Proteolysis
Thyroxine
Triiodothyronine

Physiology of iodide metabolism and NIS

NIS is a glycosylated protein, transporting 2 Na+ and one I–, dependent on the Na+ gradient maintained by Na+/K+ ATPase.

NIS activity produces the iodide concentration gradient from blood to NIS-expressing cells, up to 30 to 50 fold.

Iodide taken up into the thyroid follicular cell by NIS, is released to the lumen via pendrin.



I- is oxidized by thyroid peroxidase (TPO) with hydrogen peroxide (H2O2) produced mainly by dual oxidase-2 (DUOX2), and binds to tyrosine residues of Tg accumulated in the lumen.

The Sodium Iodide Symporter (NIS): Regulation and Approaches to Targeting for Cancer Therapeutics. Takahiko Kogai and Gregory A. Brent. Pharmacol Ther. Sep 2012; 135(3): 355–370.

Eur J Endocrinol. 2006 Jul;155(1):17-25.

Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects.

De Groef B[1], Decallonne BR, Van der Geyten S, Darras VM, Bouillon R.

OBJECTIVE:

Perchlorate is a known competitive inhibitor of the sodium/iodide symporter (NIS). Possible thyroid-related effects of environmental perchlorate have created great health concerns, especially in the US, resulting in a debated reference dose (RfD) of 0.0007 mg/kg per day in d
in
lit

M

W
te
w
2(

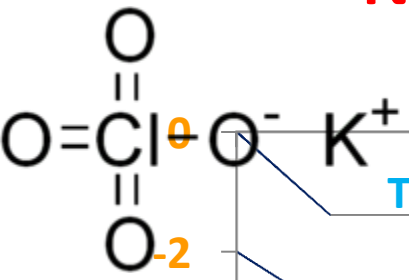
R

Th
pe

CONCLUSIONS:
Iodine uptake inhibition and any potential downstream effect by perchlorate are highly dependent on the presence of other environmental NIS inhibitors and iodine intake itself. These potential confounders should therefore be considered in future studies and calculations for risk assessment

ur
calculations show that nitrate and thiocyanate, acquired through drinking water or food, account for a much larger proportion of iodine uptake inhibition than perchlorate. Furthermore, the iodine uptake inhibitory effects of nitrate and thiocyanate - as defined by their legally accepted maximal contaminant levels in drinking water - exceed the potential effect of the proposed RfD for perchlorate by far.

Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08.



- High perchlorate n = 1939
- Low perchlorate n = 2084
- Hight êrchlorate and tiocyanate and low iodine n = 62

Concomitant exposure to perchlorate, thiocyanate, and low iodine markedly reduces thyroxine production. This highlights the potential importance of examining the combined effects of multiple agents when evaluating the toxicity of thyroid-disrupting agents.

Environ Res. 2013 May;123:17-24. Epub 2013 Mar 7. Steinmaus C, Miller MD, Cushing L, Blount BC, Smith AH.

Environ Med. 2013 Oct;55(10):1171-8

Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study.

Goldner WS[1], Sandler DP, Yu F, Shostrom V, Hoppin JA, Kamel F, LeVan TD. J Occup.

OBJECTIVE:

Evaluate the association between thyroid disease and use of insecticides, herbicides, and fumigants/fungicides in male applicators in the Agricultural Health Study.

METHODS:

W
hy
ap
RI

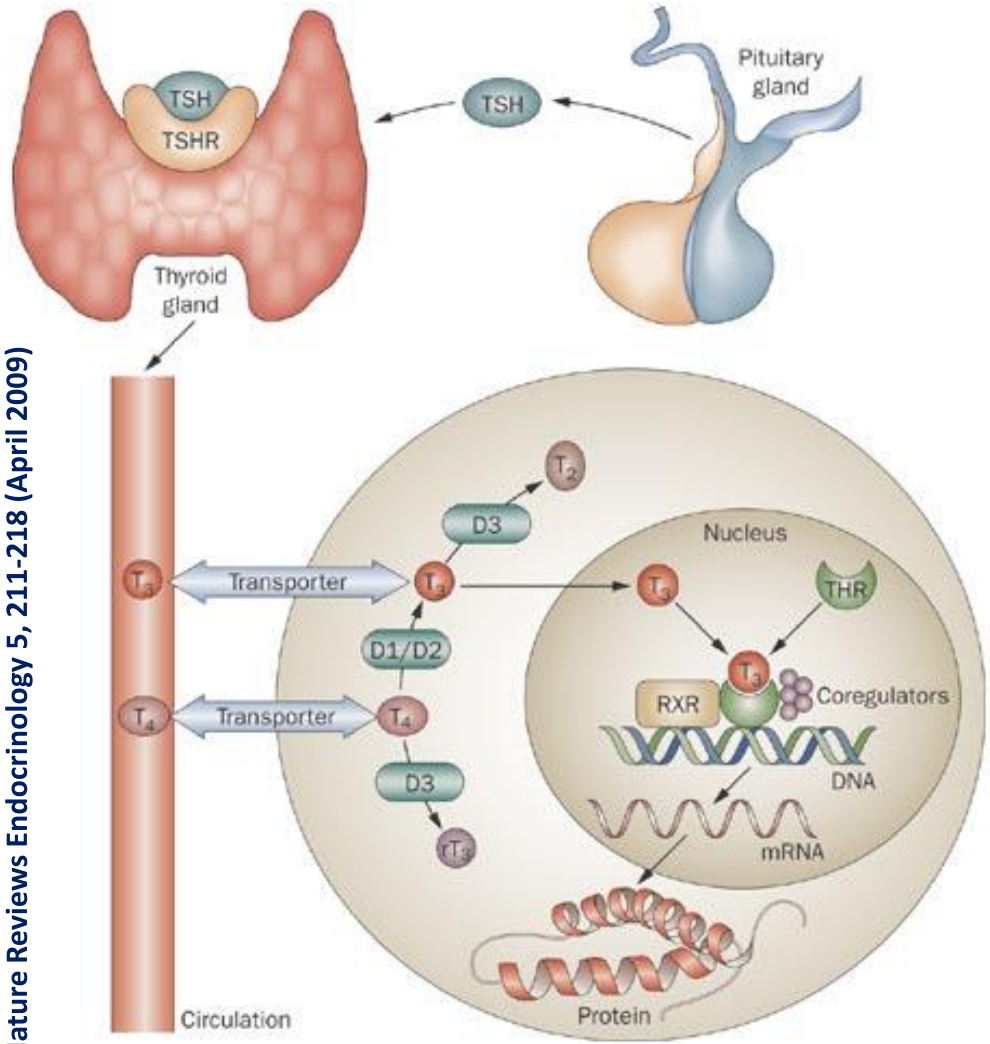
Th
di
tr
al
di

CONCLUSION:

There is an association between hypothyroidism and specific herbicides and insecticides in male applicators, similar to previous results for spouses.

organophosphates diazinon and malathion; and the carbamate carbofuran. Exposure-response analysis showed increasing odds with increasing level of exposure for the herbicides alachlor and 2,4-D and the insecticides aldrin, chlordane, DDT, lindane, and parathion.

Deiodinase activities in thyroids and tissues of iodine-deficient female rats.



Nature Reviews Endocrinology 5, 211-218 (April 2009)

Severe iodine deficiency is characterized by :

1. goiter.
2. preferential synthesis, and secretion of T(3) in thyroids.
3. hypothyroxinemia in plasma and tissues, normal or low plasma T(3)
4. slightly increased plasma TSH

Endocrinology. 2013 Jan;154(1):529-36. doi: 10.1210/en.2012-1727. Epub 2012 Nov 9

High occurrence of thyroid multinodularity and low occurrence of subclinical hypothyroidism among tobacco smokers in a large population study.

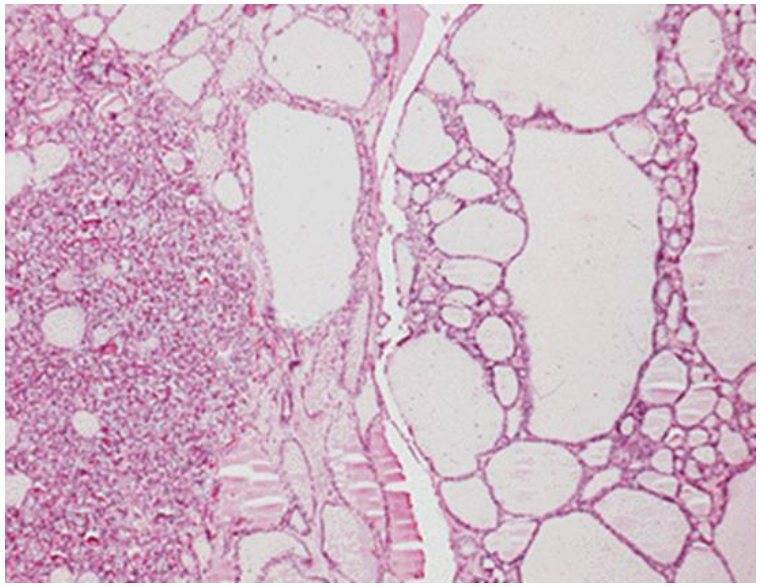
The prevalence of elevated TSH levels was markedly reduced among smokers (OR 0·47; 95% CI 0·33–0·67).

No association was found between smoking and hyperthyroidism.

The observed associations seem to be explainable by the blocking of iodine uptake and organification in the thyroid by thiocyanate, a degradation product of cyanide in tobacco smoke.

Journal of Endocrinology (2002) 175, 571–576

High occurrence of thyroid multinodularity and low occurrence of subclinical hypothyroidism among tobacco smokers in a large population study.



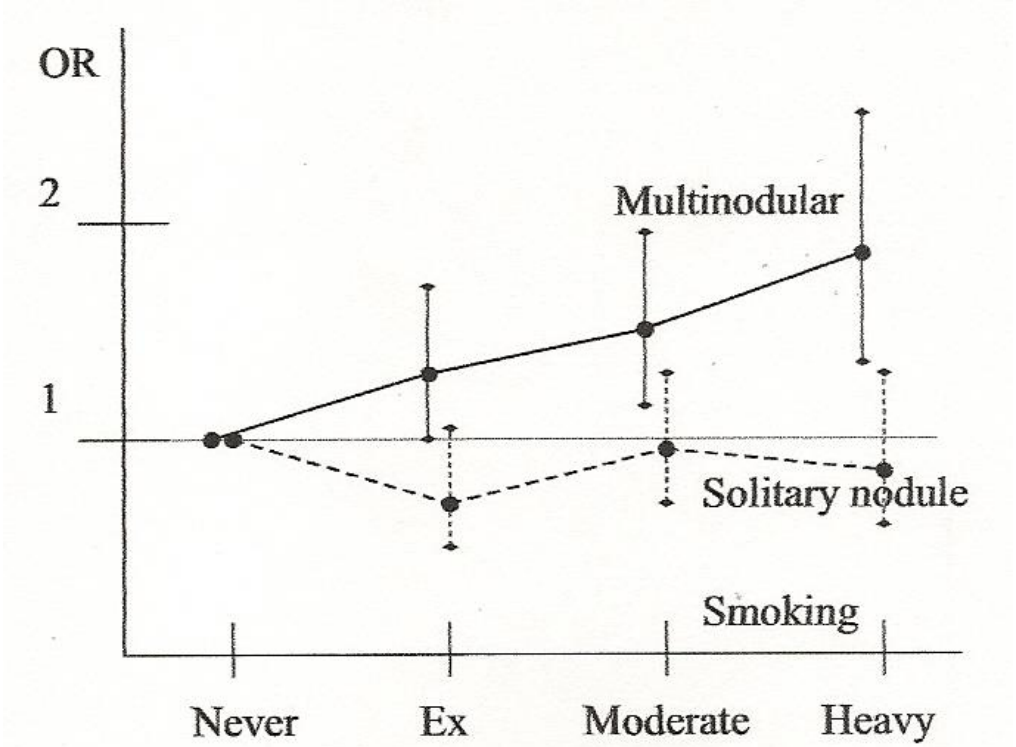


Figure 1 The association between tobacco smoking and multiple nodules or a solitary nodule in the thyroid at an ultrasonographic investigation of 4412 unselected Danes with no previous thyroid disease. Vertical bars represent 95% CI. OR values are significantly different from those who have never smoked if the CI does not include 1.

Journal of Endocrinology (2002) 175, 571–576

The association between smoking and multinodular appearance of the thyroid gland at ultrasonography.

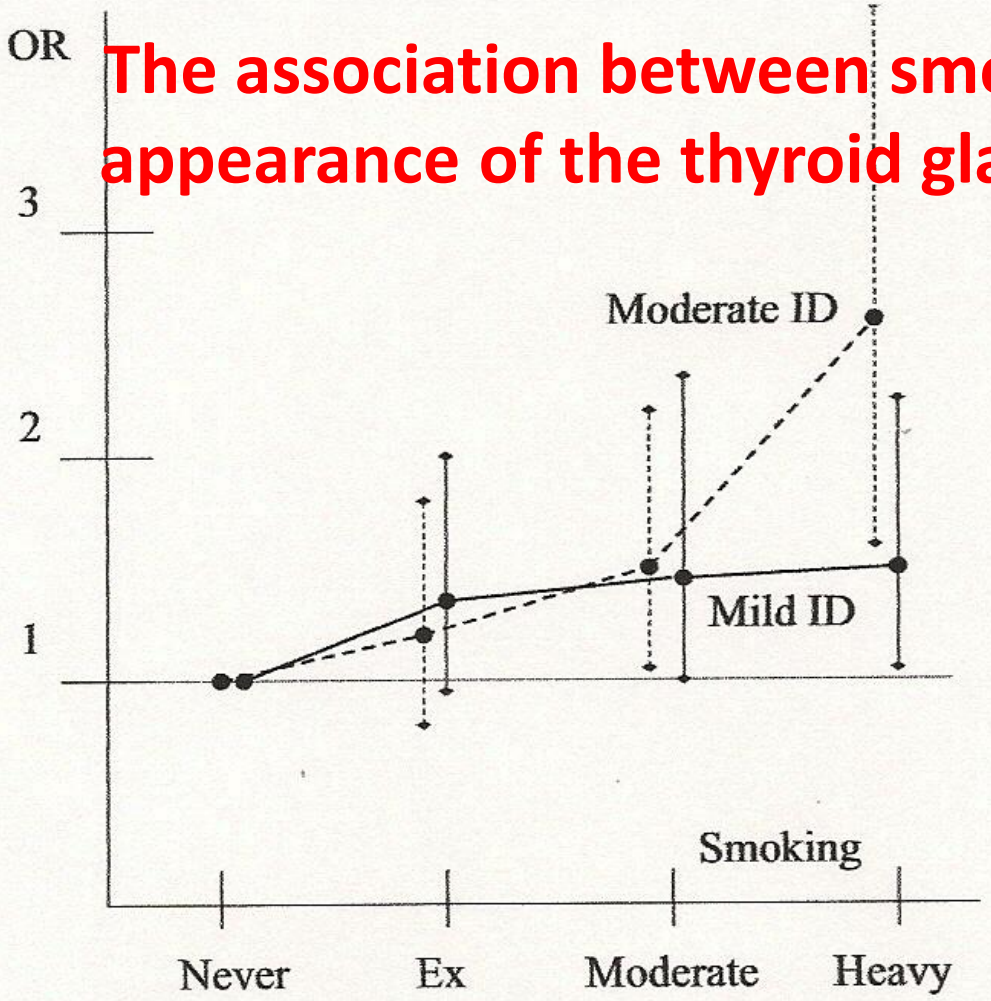
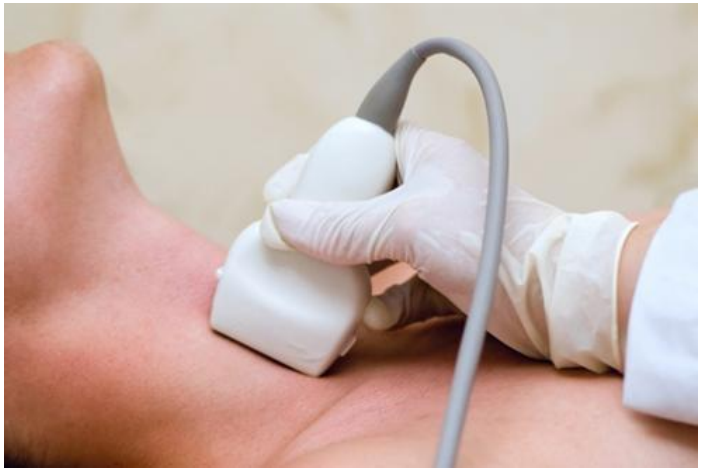


Figure 2 The association between smoking and multinodular appearance of the thyroid gland at ultrasonography. Data from a logistic regression analysis including 4412 unselected Danes without previous thyroid disease from two regions with slightly different degrees of iodine deficiency (ID). OR values are adjusted for age and gender. Vertical bars represent 95% CI. OR values are significantly different from those who have never smoked if the CI does not include 1.



Journal of Endocrinology (2002) 175, 571–576

Eur J Epidemiol. 2008;23(6):423-9. doi: 10.1007/s10654-008-9255-1. Epub 2008 Apr 26.

The impact of smoking on thyroid volume and function in relation to a shift towards iodine sufficiency.

Vejbjerg P[1], Knudsen N, Perrild H, Carlé A, Laurberg P, Pedersen IB, Rasmussen LB, Ovesen L, Jørgensen T.

Abstract

The aim of the study was to investigate whether the influence of smoking on thyroid volume and function changes in relation to a higher iodine intake in the population. The study comprised a total of 8,219 individuals each examined in one of two separate cross-sectional studies performed before (n = 4,649) and after (n = 3,570) a mandatory iod
de
thy
sti
sin
be
ioc
rat
1.5
to
ioc
thy
sufficiency a decline in the impact of smoking on thyroid volume was seen. The effect of smoking on hormonal level was unchanged after the iodization. Thus the effect of smoking on thyroid volume seems to be dependent on iodine intake, whereas the effect on function seems mainly to depend on other factors.

In areas approaching iodine sufficiency a decline in the impact of smoking on thyroid volume was seen. The effect of smoking on hormonal level was unchanged after the iodization. Thus the effect of smoking on thyroid volume seems to be dependent on iodine intake, whereas the effect on function seems mainly to depend on other factors.

Smoking and thyroid. Wilmar M. Wiersinga. Clinical Endocrinology. Volume 79, Issue 2, pages 145–151, August 2013

Summary

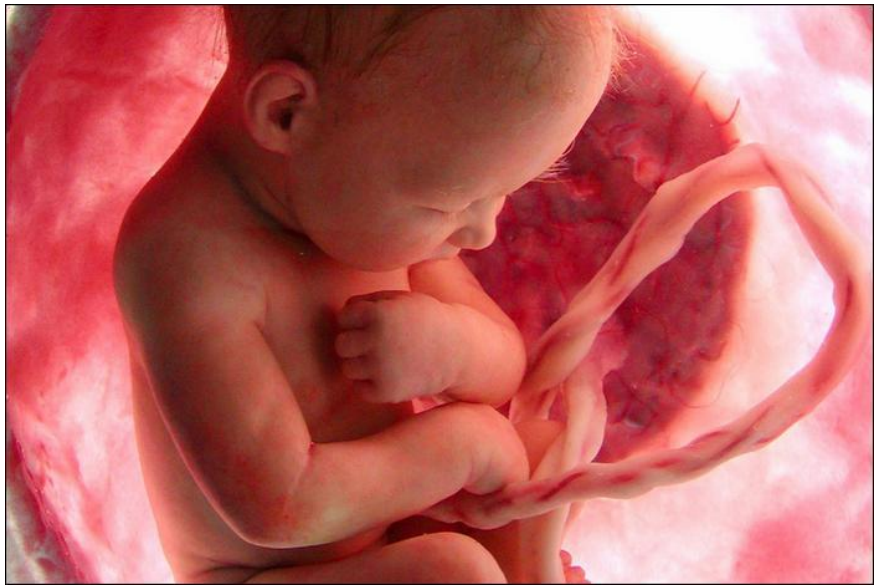
Current smoking in population surveys is associated with a slight dose-dependent fall of serum TSH, likely secondary to a rise of serum FT4 and FT3 induced by activation of the sympathetic nervous system; it is independent of iodine intake. In contrast, the slightly greater thyroid size in smokers is observed in iodine-deficient but not in iodine-sufficient areas and caused by

The slightly greater thyroid size in smokers is observed in iodine-deficient but not in iodine-sufficient areas and caused by competitive inhibition of thyroidal iodide uptake by thiocyanate. Smokers have an increased prevalence of nontoxic goitre and thyroid multinodularity, at least in iodine-deficient areas.

recurrence rate of Graves' hyperthyroidism, a higher risk on Graves' ophthalmopathy after 131I therapy and a less favourable outcome of GO treatment with steroids or retrobulbar irradiation. The observed associations with smoking likely indicate causal relationships in view of consistent associations across studies, the presence of dose–response effects and disappearance of associations after cessation of smoking.

The Spectrum of Iodine Deficiency Disorders

- Foetus Abortions
- Stillbirths
- Congenital Anomalies
- Increased Perinatal Mortality
- Increased Infant Mortality
- Neurological Cretinism
  - Mental deficiency
  - Deaf-mutism
  - Spastic diplegia
  - Squint
- Myxedematous Cretinism
  - Mental deficiency
  - Dwarfism
  - Psychomotor Defects



Health Consequences of Iodine Deficiency. Umesh Kapil. Sultan Qaboos Univ Med J. 2007 December; 7(3): 267–272.

The Spectrum of Iodine Deficiency Disorders

Neonate

- Neonatal goiter
- Neonatal hypothyroidism

Child and Adolescent

- Goiter
- Juvenile hypothyroidism
- Impaired mental function
- Retarded physical development

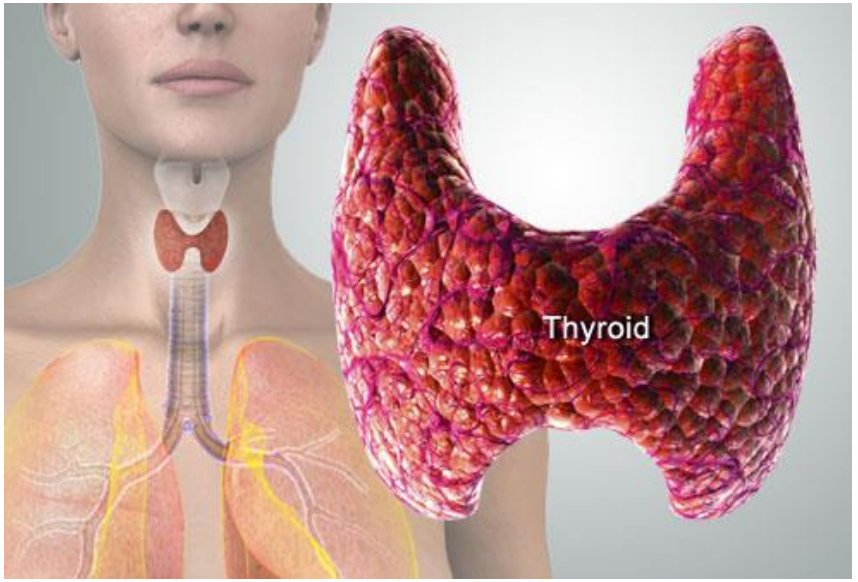
Adult

- Goiter with complications

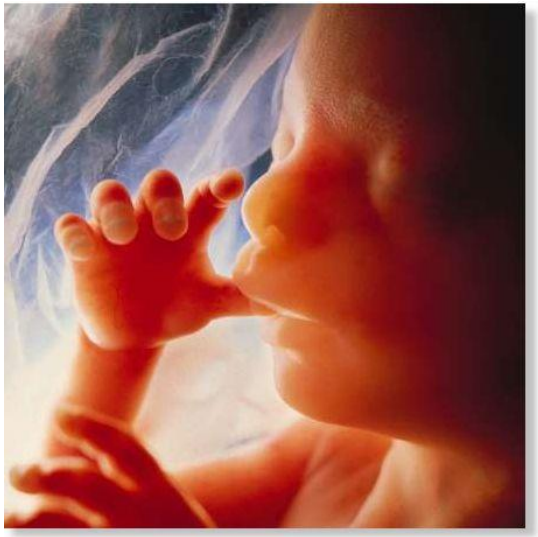
- Hypothyroidism
- Impaired mental function

Health Consequences of Iodine Deficiency. Umesh Kapil. Sultan Qaboos Univ Med J. 2007 December; 7(3): 267–272.

Iodine deficiency during pregnancy



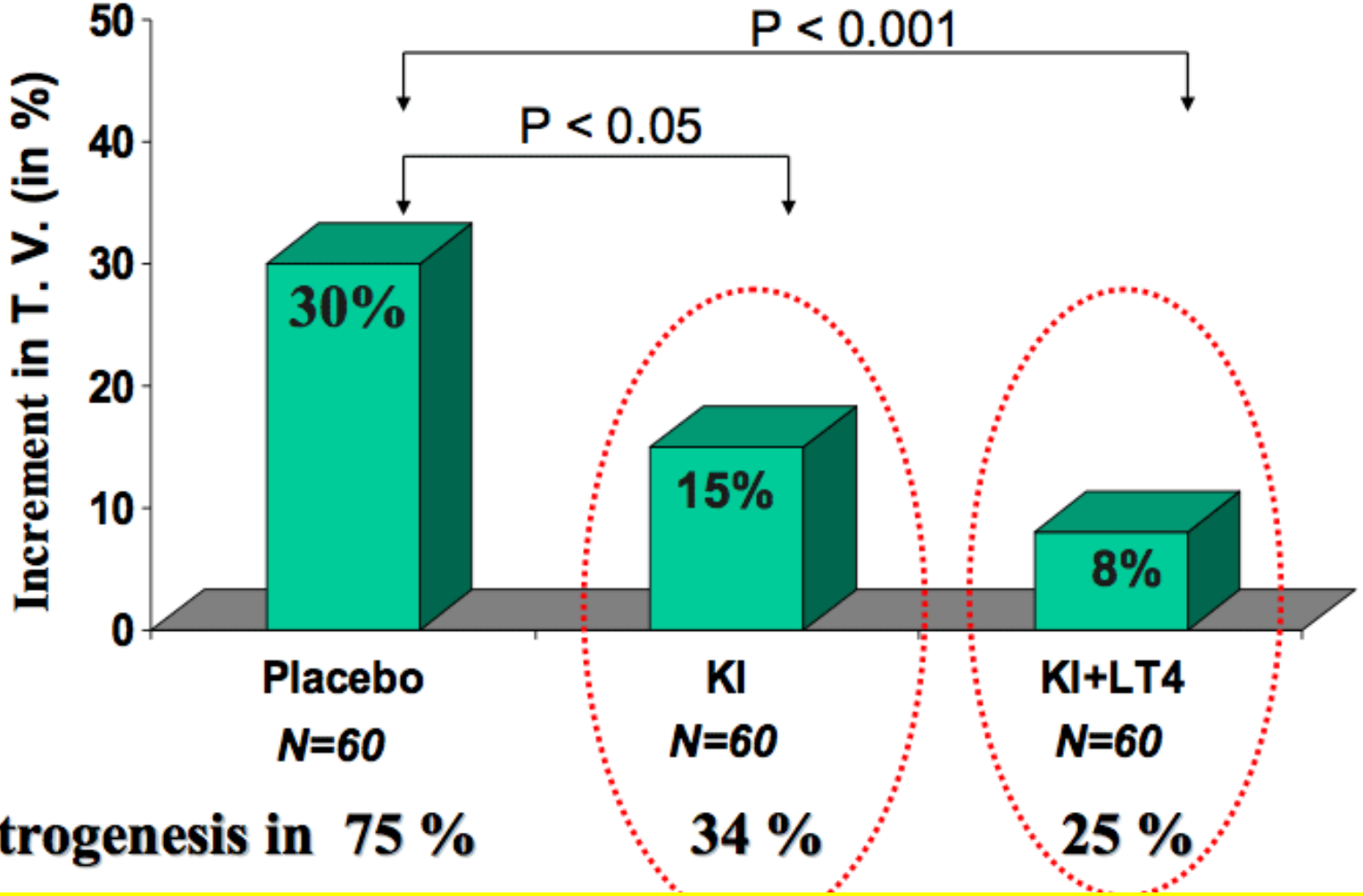
For pregnant women who have a marginal iodine nutrition status, the disruption of the thyroid due to exposure to organochlorines could induce iodine deficiency and result in negative effects on the brain of the developing fetus.



Kevin M. Sullivan. Environ Health Perspect. Apr 2008; 116(4): A155

Iodine & Thyroid Volume in Pregnancy

Randomized clinical trial with placebo versus KI (100 µg iodine/day) or KI + l-T4 (100 µg iodine/day and 100 µg T4/day) given during pregnancy in women with moderate iodine deficiency and laboratory features of thyroidal stimulation.



In the placebo-treated group, TV increased by a mean 30% and goiter formation occurred in 75% of the women. In both actively-treated groups, the increments in TV were significantly reduced (to only 15% and 8%), as was goiter formation

How can we diagnose iodine deficiency

- 1) the urinary iodine (UI) concentration (microg l) is not interchangeable with 24 h UI excretion (microg per 24 h);

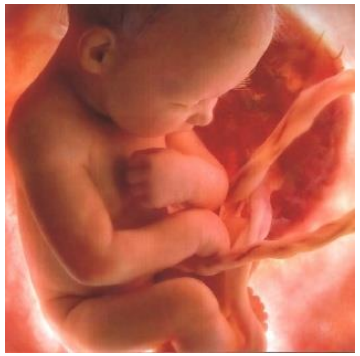
- 2) the concentration of iodine in a spot or casual urine sample cannot be used to diagnose iodine deficiency in an individual

Evaluating iodine deficiency in pregnant women and young infants-complex physiology with a risk of misinterpretation.
Laurberg P1, Andersen S, Bjarnadóttir RI, Carlé A, Hreidarsson A, Knudsen N, Ovesen L, Pedersen I, Rasmussen L.
Public Health Nutr. 2007 Dec;10(12A):1547-52; discussion 1553

The effects of iodine deficiency in pregnancy and infancy.

Zimmermann MB.

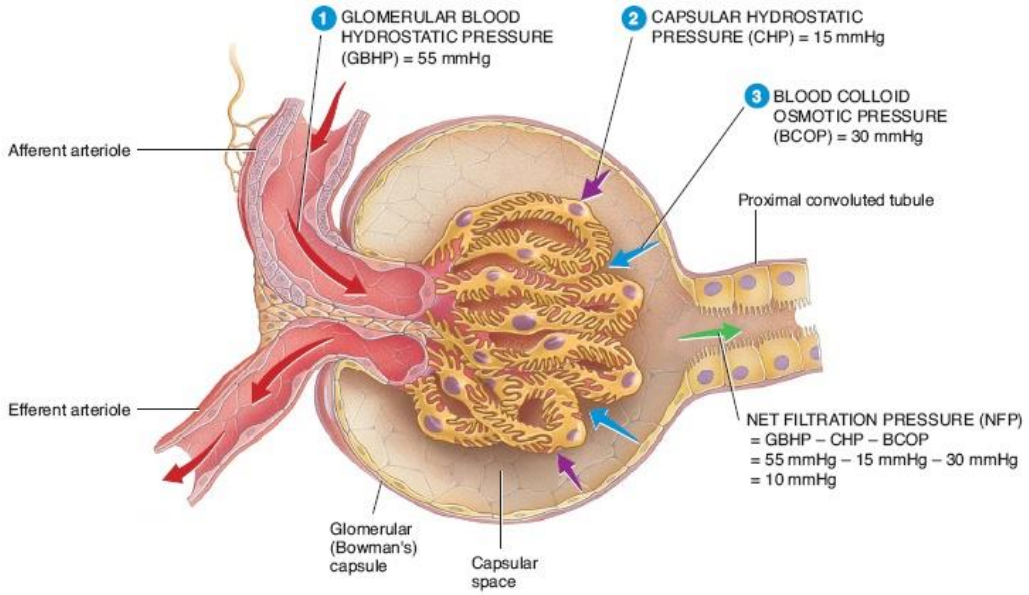
Paediatr Perinat Epidemiol. 2012 Jul;26 Suppl 1:108-17.



Abstract

Iodine requirements are increased ≥ 50% during pregnancy. Iodine deficiency during pregnancy can cause maternal and fetal hypothyroidism and impair neurological development of the fetus. The consequences depend upon the timing and severity of the hypothyroidism; the most severe manifestation is cretinism. In moderate-to-severely iodine-deficient areas, controlled studies have demonstrated that iodine supplementation before or during early pregnancy eliminates new cases of cretinism, increases birthweight, reduces rates of perinatal and infant mortality and generally increases developmental scores in young children by 10-20%. Mild maternal iodine deficiency can cause thyroid dysfunction but whether it impairs cognitive and/or neurologic function in the offspring remains uncertain. Two meta-analyses have estimated that iodine-deficient populations experience a mean reduction in IQ of 12-13.5 points. In nearly all regions affected by iodine deficiency, salt iodisation is the most cost-effective way of delivering iodine and improving maternal and infant health.

Glomerular filtration is increased during pregnancy

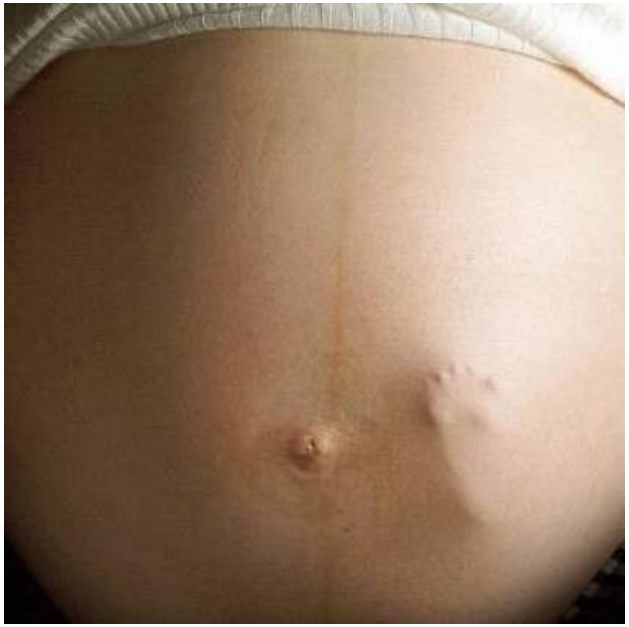


Increased renal blood flow and glomerular filtration rate lead to an increase in the excretion of plasma iodide, and as a result, dietary iodide requirements are increased from 150 micrograms/day for a normal adult to 250 micrograms/day for a pregnant or lactating woman.

Clinical Controversies in Screening Women for Thyroid Disorders During Pregnancy.
Frances A. Wier, CNM, MS, Cindy L. Farley, CNM, PhD. J Midwifery Womens Health. 2006;51(3):152-158.

Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review

IODINE REQUIREMENTS IN PREGNANCY



The WHO/UNICEF recommendation for iodine intake during pregnancy is 250 μg/d.

Recommended Nutrient Intake for iodine of 150 μg/d for nonpregnant women.
The iodine requirement during pregnancy is sharply elevated :

1) because of an increase by ≈50% in maternal thyroxine (T4) production to maintain maternal euthyroidism and to transfer thyroid hormone to the fetus,
2) because iodine needs to be transferred to the fetus for fetal thyroid hormone production, particularly in later gestation,
3) because of a probable increase in renal iodine clearance (RIC).

Michael B Zimmermann. Am J Clin Nutr February 2009 vol. 89 no. 2 668S-672S

The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review.

Zimmermann MB. Thyroid. 2007 Sep;17(9):829-35.

Author information

Laboratory for Human Nutrition,
Swiss Federal Institute of Technology, Zürich, Switzerland.

Abstract

Iodine is required for the production of thyroid hormones, which are essential for normal brain development, and the fetus, newborn, and young child are particularly vulnerable to iodine deficiency. The iodine requirement increases during pregnancy and recommended intakes are in the range of 220-250 microg/day. Monitoring iodine status during pregnancy is a challenge. New recommendations from World Health Organization suggest that a median urinary iodine concentration >250 microg/L and <500 microg/L indicates adequate iodine intake in pregnancy. Based on this range, it appears that many pregnant women in Western Europe have inadequate intakes. A recent Swiss study has suggested that thyroid-stimulating hormone concentration in the newborn is a sensitive indicator of mild iodine deficiency in late pregnancy. The potential adverse effects of mild iodine deficiency during pregnancy are uncertain. Controlled trials of iodine supplementation in mildly iodine-deficient pregnant women suggest beneficial effects on maternal and newborn serum thyroglobulin and thyroid volume, but no effects on maternal and newborn total or free thyroid hormone concentrations. There are no long-term data on the effect of iodine supplementation on birth outcomes or infant development. New data from well-controlled studies indicate that iodine repletion in moderately iodine-deficient school-age children has clear benefits: it improves cognitive and motor function; it also increases concentrations of insulin-like growth factor 1 and insulin-like growth factor-binding protein 3, and improves somatic growth.

Thyrotropin screening in newborns may be useful in assessing iodine status in late pregnancy

Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review

TABLE 2

Thyrotropin concentrations in newborns (days 3 and 4 after birth) from eastern Switzerland measured before the increase in salt iodine concentration from 15 to 20 mg/kg (1992–1998) and after the increase (1999–2004)[1]

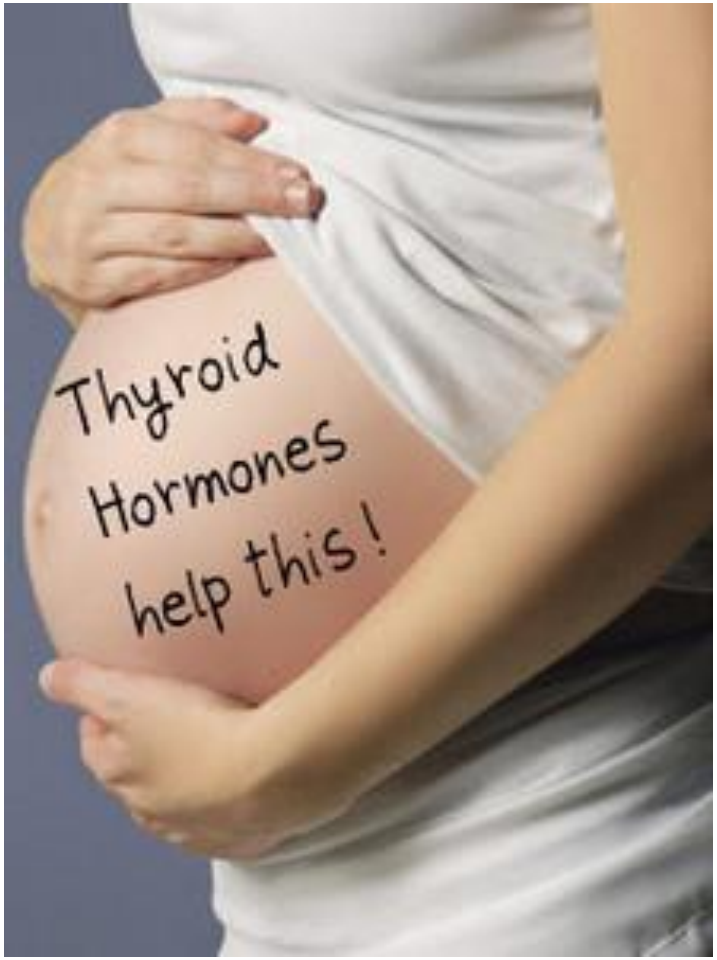
	1992–1998	1999–2004
Iodine status of pregnant women	Mild iodine deficiency	Iodine sufficiency
Median urinary iodine in pregnant women (μg/L)	138	249
No. of newborns	259,035	218,665
Prevalence of thyrotropin >5 mU/L in newborns (%)	2.9	1.7

Newborn thyrotropin concentrations, obtained with the use of a sensitive assay from blood samples collected 3–4 d after birth, is a sensitive indicator of even mild iodine deficiency in pregnancy.

WHO recommends that a <3% frequency of thyrotropin values >5 mU/L indicates iodine sufficiency in a population

Michael B Zimmermann. Am J Clin Nutr February 2009 vol. 89 no. 2 668S-672S

The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status.



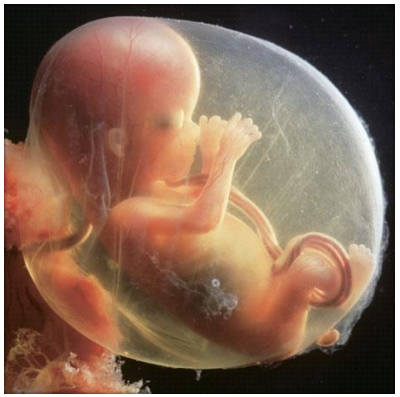
The main change in thyroid function associated with the pregnant state is the requirement of an increased production of thyroid hormone that depends directly upon the adequate availability of dietary iodine and integrity of the glandular machinery.

Physiologic adaptation takes place when the iodine intake is adequate, while this is replaced by pathologic alterations when there is a deficient iodine intake.

Pregnancy acts typically, therefore, as a revelator of underlying iodine restriction.

Best Pract Res Clin Endocrinol Metab. 2004 Jun;18(2):133-52

EFFECTS OF MILD-TO-MODERATE MATERNAL IODINE DEFICIENCY ON THE OFFSPRING



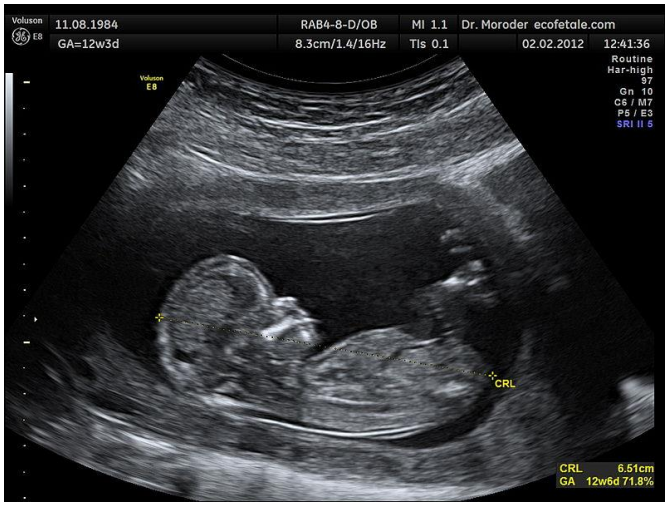
In moderate-to-severely iodine-deficient areas, controlled studies have demonstrated that iodine supplementation before or during early pregnancy :

1. eliminates new cases of cretinism,
2. increases birth weight,
3. reduces rates of perinatal and infant mortality
4. generally increases developmental scores in young children by 10-20%.

Two meta-analyses have estimated that iodine-deficient populations experience a mean reduction in IQ of 12-13.5 points.

Michael B Zimmermann. Am J Clin Nutr February 2009 vol. 89 no. 2 668S-672S

IODINE DEFICIENCY: EFFECTS ON NEUROLOGIC DEVELOPMENT AND FUNCTION



Severe iodine deficiency during pregnancy causes maternal and fetal hypothyroxinemia .

Thyroid hormone is required for normal neuronal migration, myelination, and synaptic transmission and plasticity during fetal and early postnatal life and hypothyroxinemia during these critical periods causes irreversible brain damage with mental retardation and neurologic abnormalities .

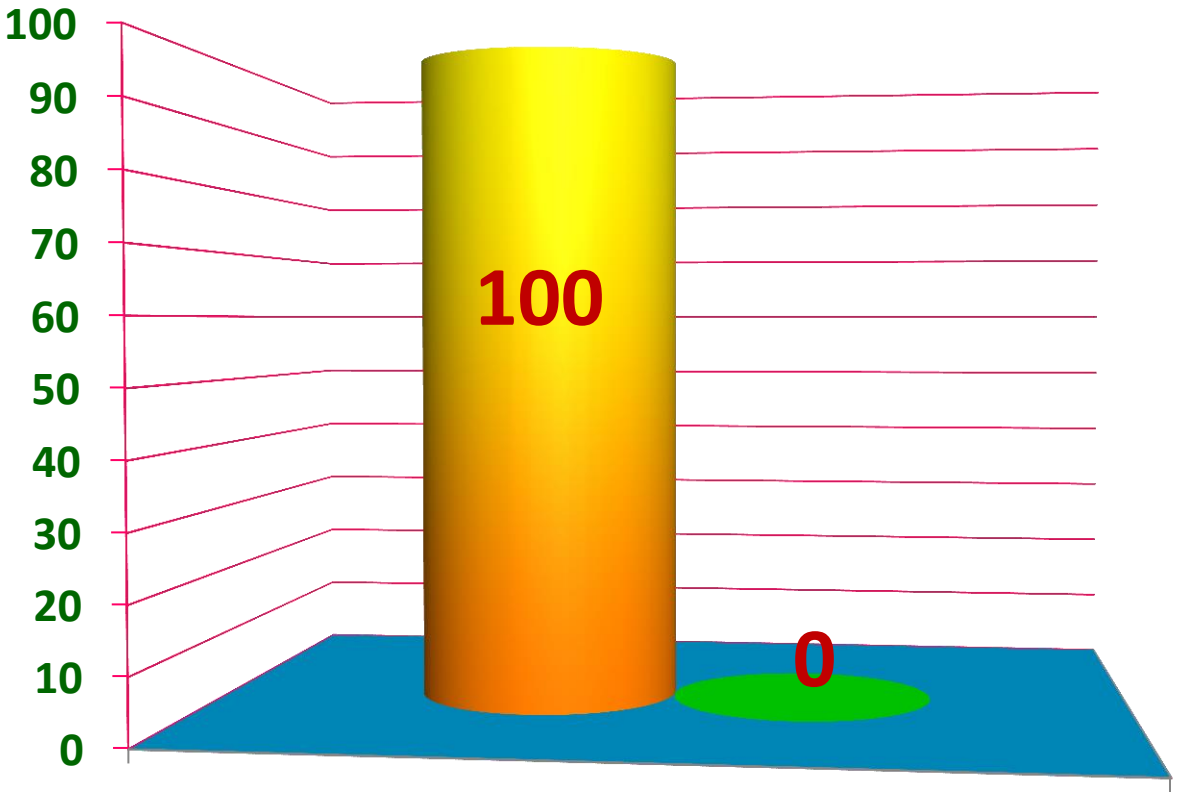
The consequences depend on the timing and severity of the hypothyroxinemia.

FT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psychomotor development (RR): 5.8, 95% CI: 1.3-12.6).

Clin Endocrinol (Oxf). 1999 Feb;50(2):149-55

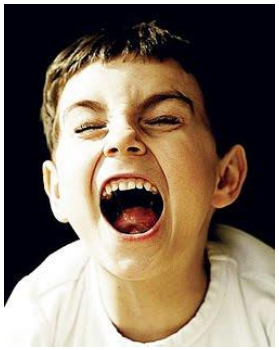
Michael B Zimmermann. Am J Clin Nutr February 2009 vol. 89 no. 2 668S-672S

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.



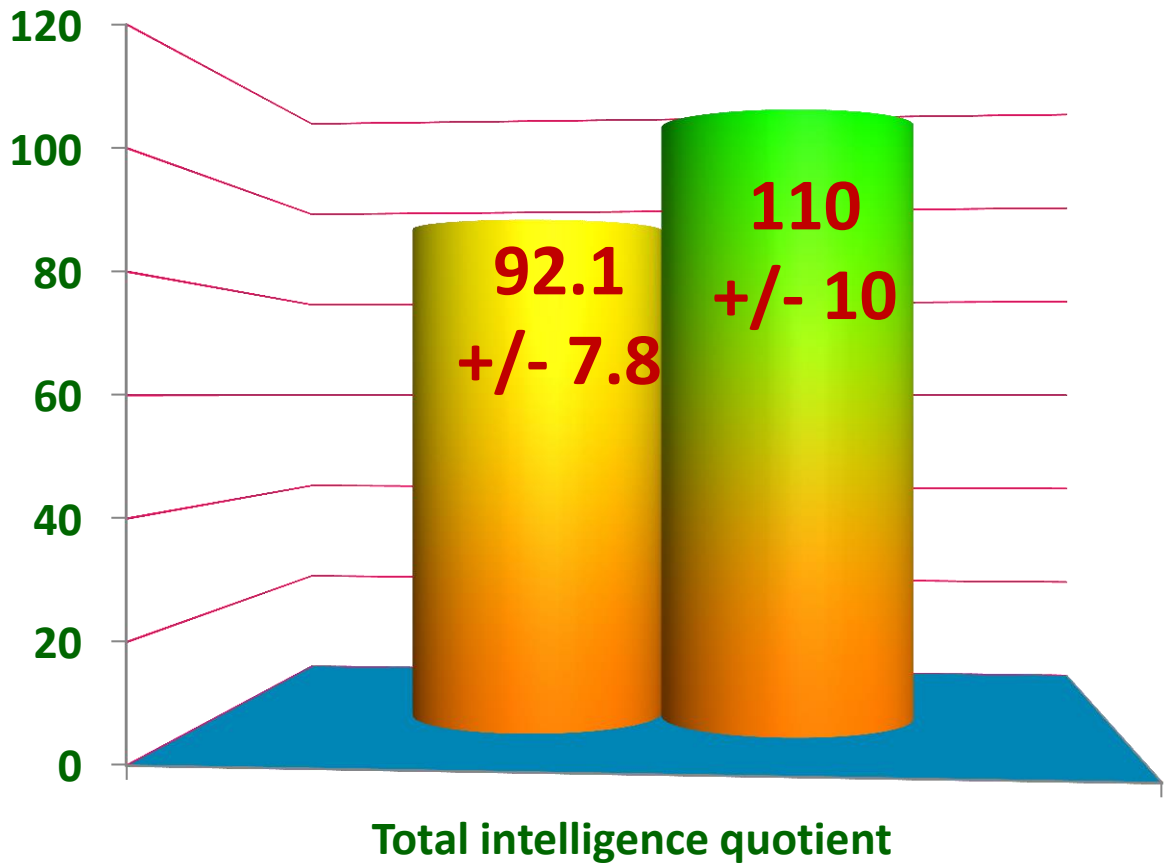
Moderate Iodine deficient area

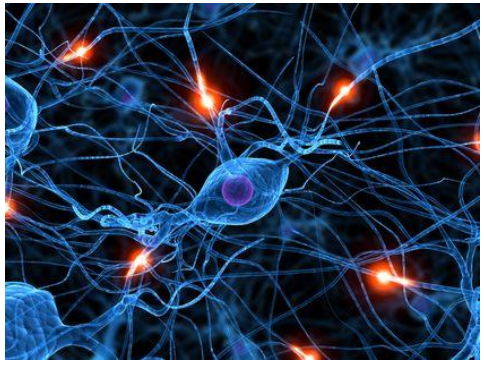
Marginally Iodine sufficient area



Over a period of almost 10 yr, we carried out a prospective study of the neuropsychological development of the offspring of 16 women from a moderately iodine-deficient area and of 11 control women from a marginally iodine-sufficient area whose thyroid function had been monitored during early gestation.

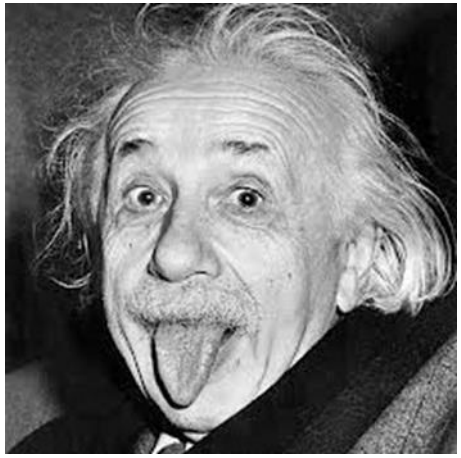
Vermiglio F, and Coll. J Clin Endocrinol Metab. 2004 Dec;89(12):6054-60





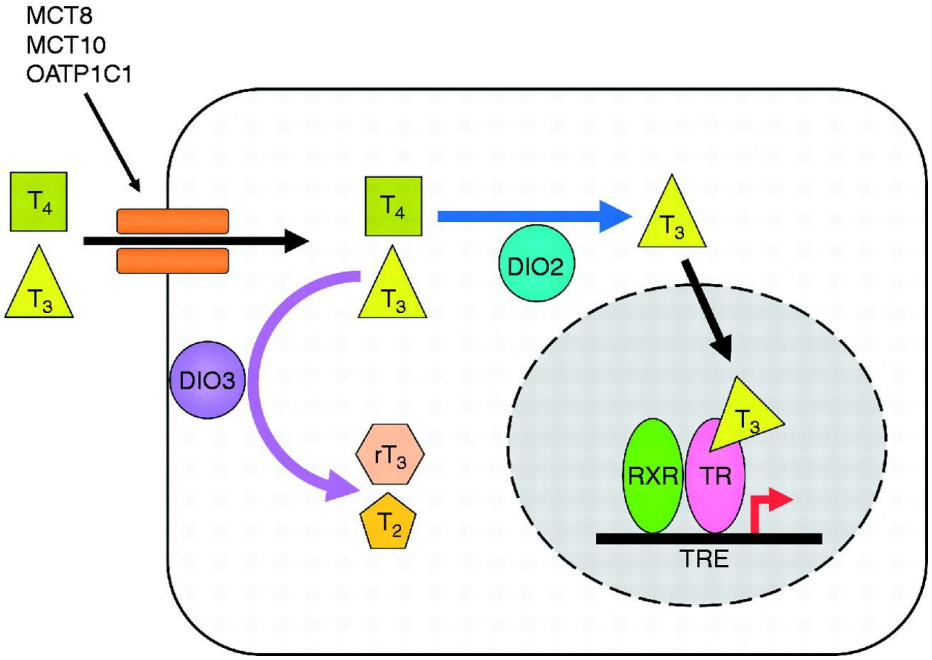
moderately iodine-deficient area

marginally iodine-sufficient area



Over a period of almost 10 yr, we carried out a prospective study of the neuropsychological development of the offspring of 16 women from a moderately iodine-deficient area and of 11 control women from a marginally iodine-sufficient area whose thyroid function had been monitored during early gestation.

Vermiglio F, and Coll. J Clin Endocrinol Metab. 2004 Dec;89(12):6054-60



So far, a similar prevalence of ADHD has been reported only in children with generalized resistance to thyroid hormones. This might suggest a common ADHD pathogenetic mechanism consisting either of reduced sensitivity of the nuclear receptors to thyroid hormone (generalized resistance to thyroid hormones) or reduced availability of intracellular T3 for nuclear receptor binding.

The latter would be the ultimate consequence of maternal hypothyroxinemia (due to iodine deficiency), resulting in a critical reduction of the source of the intracellular T3 available to the developing fetal brain.

Vermiglio F, and Coll. J Clin Endocrinol Metab. 2004 Dec;89(12):6054-60

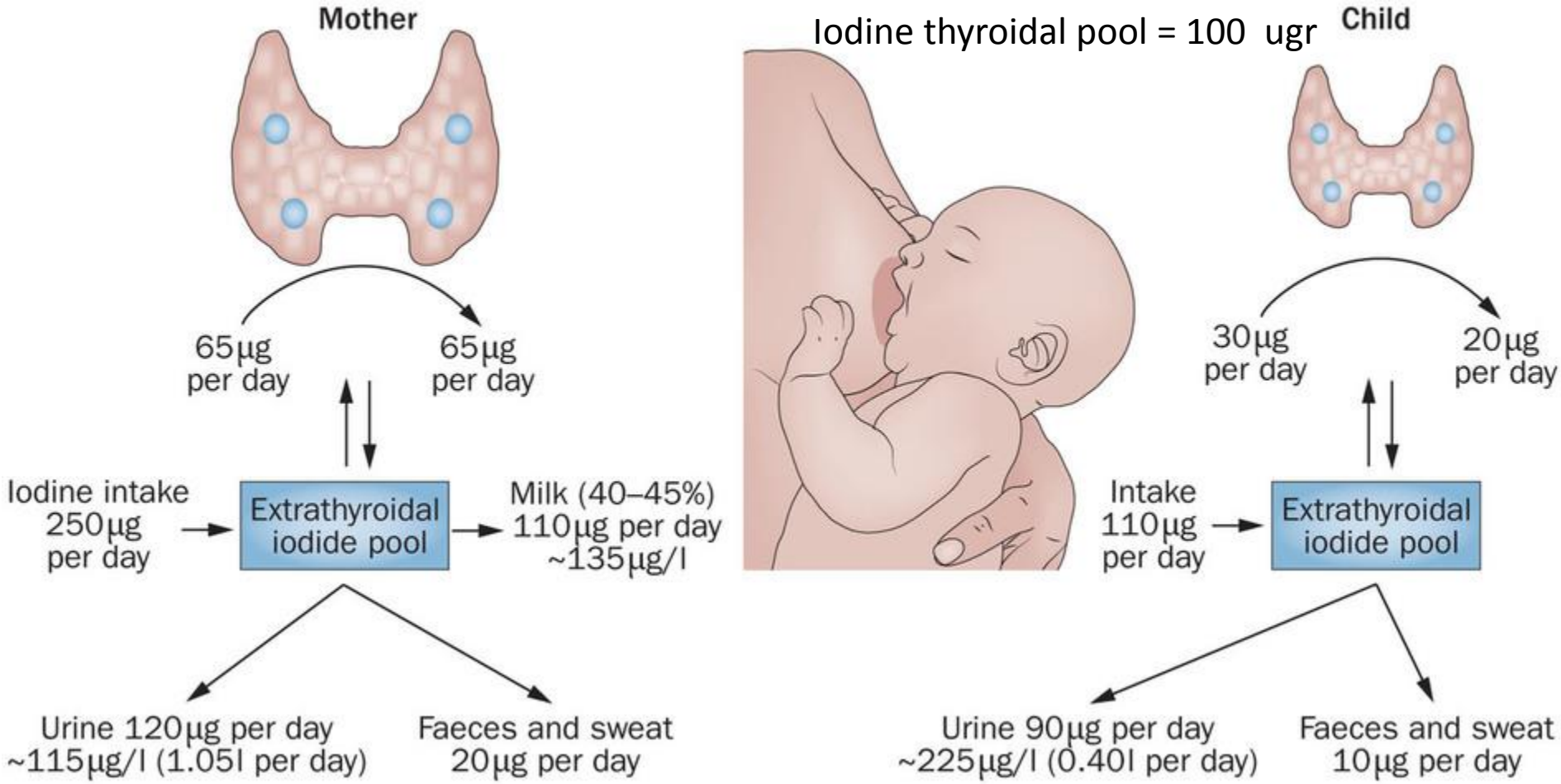
Iodine and breastfeeding

The current WHO/ICCIDD/UNICEF recommendation for daily iodine intake (250 microg for lactating mothers) has been selected to ensure that iodine deficiency dose not occur in the postpartum period and that the iodine content of the milk is sufficient for the infant's iodine requirement.

Adequate concentration of iodine in breast milk is essential to provide for optimal neonatal thyroid hormone stores and to prevent impaired neurological development in breast-fed neonates.

Clin Endocrinol (Oxf). 2009 May;70(5):803-9. doi: 10.1111/j.1365-2265.2008.03442.x. Epub 2008 Oct 6.
Breastfeeding and maternal and infant iodine nutrition. Azizi F, Smyth P.

Nutrition: Breast milk—a gateway to iodine-dependent brain development



Iodine from the diet is fundamental for brain development. Via milk, infants receive 40–45% of the iodine in their mother's diet during breastfeeding

Peter Laurberg & Stine Linding Andersen. Nature Reviews Endocrinology (2014) doi:10.1038/nrendo.2014.3 Published online 28 January 2014

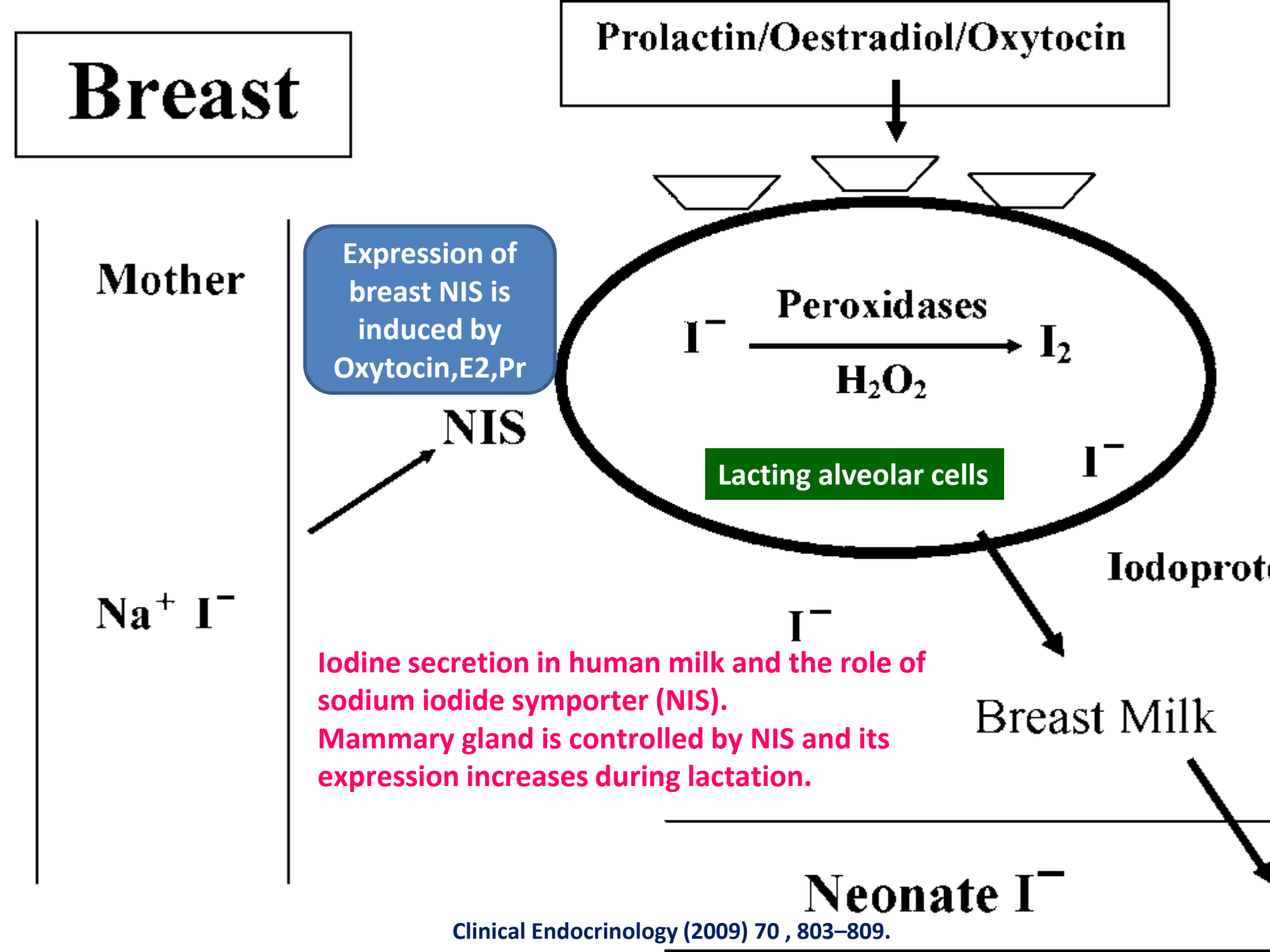
mgNIS expression in human breast cancer

Breast histology	Number of samples	mgNIS-positive	Estrogen-receptor-positive
Normal breast (reductive mammoplasty)	8	0 (0%)	ND
Invasive carcinomas	23	20 (87%)	56%
Ductal carcinoma in situ	6	5 (83%)	ND
Noncancerous in the vicinity of tumor	13	3 (23%)	ND
Gestational tissues	3	3 (100%)	ND

ND, not determined.

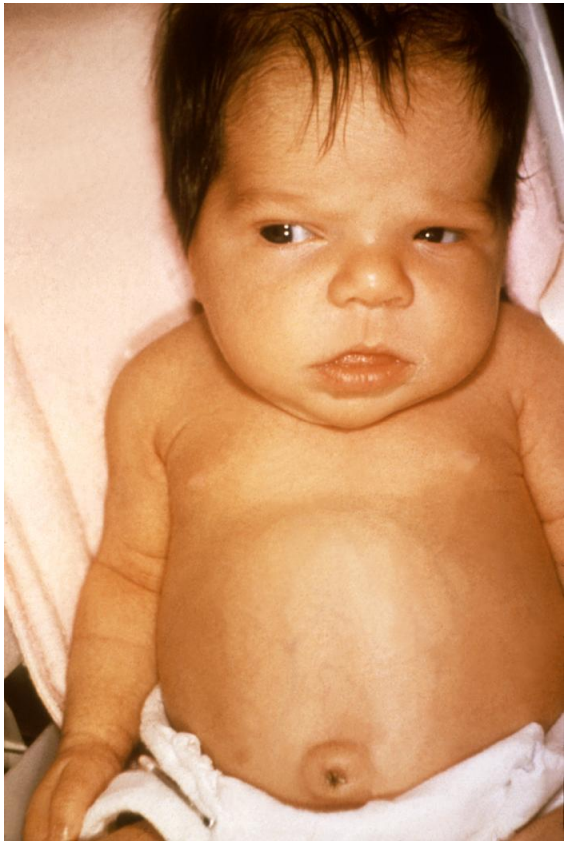
The mammary gland iodide transporter is expressed during lactation and in breast cancer.

NATURE MEDICINE • VOLUME 6 • NUMBER 8 • AUGUST 2000 871-878



Clinical Endocrinology (2009) 70 , 803–809.

Breastfeeding and maternal and infant iodine nutrition



The infant also needs a supply of iodine for normal thyroid activity, vital for brain development in the first 2 years of life.

The neonatal full-term thyroid gland contains about 100 µg of iodine under conditions of iodine sufficiency.

Breastfeeding and maternal and infant iodine nutrition. Fereidoun Azizi and Peter Smyth. Clinical Endocrinology (2009) 70 , 803–809.

Smoking during the period of breastfeeding increases the risk of iodine deficiency-induced brain damage in the child.

J Clin Endocrinol Metab. 2004 Jan;89(1):181-7. Iodine nutrition in breast-fed infants is impaired by maternal smoking. Laurberg P, Nøhr SB, Pedersen KM, Fuglsang E.

Iodine nutrition in breast-fed infants is impaired by maternal smoking

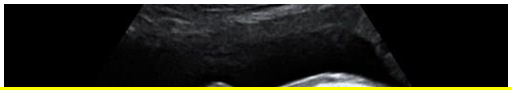
Lack of iodine for thyroid hormone formation during the fetal stage and/or the first years of life may lead to developmental brain damage.
During the period of breastfeeding, thyroid function of the infant depends on iodine in maternal milk.

In smokers, iodine transfer into breast milk correlated negatively to urinary cotinine concentration. Smoking mothers had significantly higher serum levels of thiocyanate, which may competitively inhibit the sodium-iodide symporter responsible for iodide transport in the lactating mammary gland. Smoking during the period of breastfeeding increases the risk of iodine deficiency-induced brain damage in the child. Women who breastfeed should not smoke, but if they do, an extra iodine supplement should be considered.

Smoking and nonsmoking mothers had identical urinary iodine on d 5 after delivery, but smoking was associated with reduced iodine content in breast milk.

J Clin Endocrinol Metab. 2004 Jan;89(1):181-7

Thyroglobulin in smoking mothers and their newborns at delivery suggests autoregulation of placental iodide transport overcoming thiocyanate inhibition.



Maternal smoking increased the degree of iodine deficiency in parallel in the mother and the fetus, as reflected by increased Tg levels. However, placental iodide transport seemed unaffected despite high thiocyanate levels, suggesting that thiocyanate-insensitive iodide transporters alternative to NIS are active or that NIS in the placenta is autoregulated to keep iodide transport unaltered.

Eur J Endocrinol. 2013 Apr 15;168(5):723-31.

Effect of iodine deficiency on brain function

Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

1040 first-trimester pregnant women. Children of women with an iodine-to-creatinine ratio of less than 150 µg/g were more likely to have scores in the lowest quartile for verbal IQ (odds ratio 1·58, 95% CI 1·09—2·30; p=0·02), reading accuracy (1·69, 1·15—2·49; p=0·007), and reading comprehension (1·54, 1·06—2·23; p=0·02) than were those of mothers with ratios of 150 µg/g or more.

Our results show the importance of adequate iodine status during early gestation and emphasise the risk that iodine deficiency can pose to the developing infant, even in a country classified as only mildly iodine deficient. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention.

Sarah C Bath PhD , Colin D Steer MSc , Prof Jean Golding FMedSci , Pauline Emmett PhD , Prof Margaret P Rayman Dphil.
The Lancet, Volume 382, Issue 9889, Pages 331 - 337, 27 July 2013

Information processing, fine motor skills, and visual problem solving are improved by iodine repletion in moderately iodine-deficient schoolchildren.

Compared with placebo, iodine treatment significantly improved performance on 4 of 7 tests: rapid target marking, symbol search, rapid object naming, and Raven's Coloured Progressive Matrices ($P < 0.0001$).

Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. Michael B Zimmermann, Kevin Connolly, Maksim Bozo, John Bridson, Fabian Rohner, and Lindita Grimci. Am J Clin Nutr January 2006 vol. 83 no. 1 108-114.

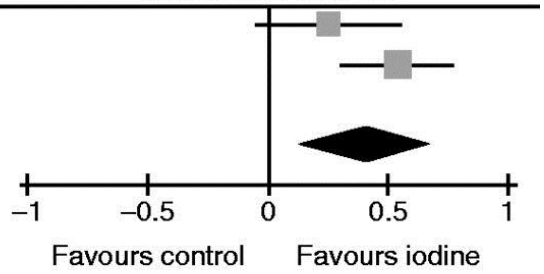
Forest plots showing effect of iodine supplementation on cognitive function (global cognitive index) in school-age children in mild-to-moderate iodine deficiency: (a) unadjusted SMD of the change from baseline (b) Adjusted

(a)

	Iodine			Control				SMD	SMD
Study or subgroup	Mean	S.D.	Total	Mean	S.D.	Total	Weight %	IV, random, 95% CI	IV, random, 95% CI
Gordon *et al.* 2009	0.7	2.5	84	0.1	2.3	82	43.7	0.25 (–0.06, 0.55)	
Zimmermann *et al.* 2006	4.8	6.2	159	1.4	6.3	151	56.3	0.54 (0.32, 0.77)	
Total (95% CI)			243			233	100.0	0.41 (0.13, 0.70)	

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 2.30$, df = 1 ($P = 0.13$); $I^2 = 56\%$

Test for overall effect: $Z = 2.84$ ($P = 0.005$)

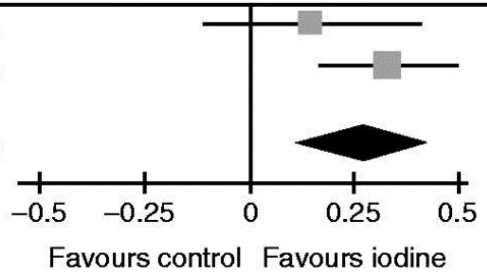


(b)

		Iodine		Control		SMD	SMD
Study or subgroup	SMD	S.E.M.	Total	Total	Weight %	IV, random, 95% CI	IV, random, 95% CI
Gordon *et al.* 2009	0.148	0.132	84	82	34.8	0.15 (–0.11, 0.41)	
Zimmermann *et al.* 2006	0.331	0.085	159	151	65.2	0.33 (0.16,0.50)	
Total (95% CI)			243	233	100.0	0.27 (0.10, 0.44)	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.36$, df = 1 ($P = 0.24$); $I^2 = 26\%$

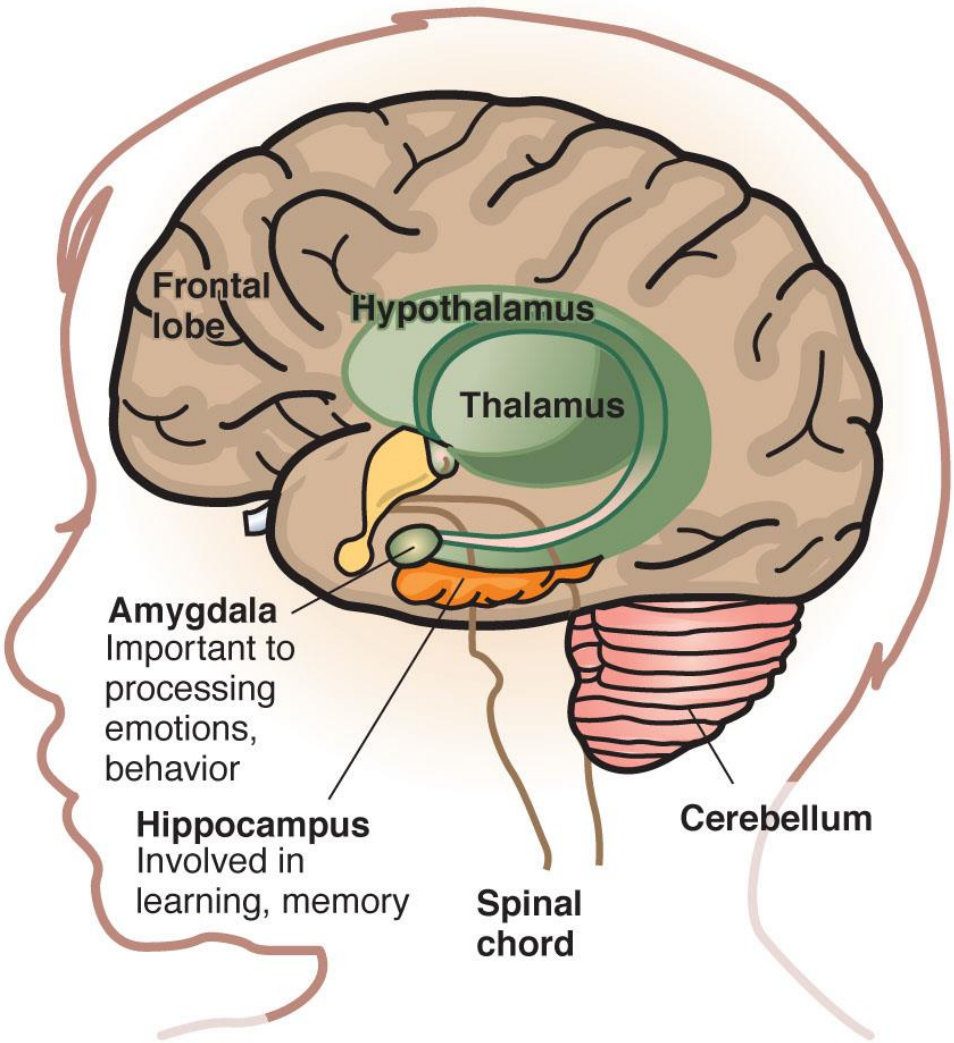
Test for overall effect: $Z = 3.07$ ($P = 0.002$)



Taylor P N et al. Eur J Endocrinol 2014;170:R1-R15

Autism and the brain

The areas of the brain affected by autism, which stems from abnormal brain development:



Affect on brain cells (neurons)

- Cells are smaller, more densely packed in certain areas
- Have shorter, less developed branches

Source: The Journal of NIH Research

Arch Med Res. 2013 Oct;44(7):555-61. doi: 10.1016/j.arcmed.2013.09.012. Epub 2013 Oct 10.

Iodine deficiency in Egyptian autistic children and their mothers: relation to disease severity.

Hamza RT[1], Hewedi DH, Sallam MT

Because autism may be a disease of early fetal brain development, maternal hypothyroxinemia (HT) in early pregnancy secondary to iodine deficiency (ID) may be related to etiology of autism. The aim of the study was to assess the iodine nutritional status in Egyptian autistic children and their mothers and its relationship with disease characteristics.

METHODS:

Fifty autistic children and their mothers were studied in comparison to 50 controls. All subjects were subjected to clinical evaluation, measurement of urinary iodine (UI), free triiodothyronine (fT3), free tetraiodothyronine (fT4) and thyroid-stimulating hormone (TSH) along with measurement of thyroid volume (TV). In addition, electroencephalography (EEG) and intelligence quotient (IQ) assessment were done for all autistic children.

RESULTS:

Of autistic children and their mothers, 54% and 58%, respectively, were iodine deficient. None of the control children or their mothers was iodine deficient. UI was lower among autistic patients ($p < 0.001$) and their mothers ($p < 0.001$). Childhood Autism Rating Scale (CARS) score correlated negatively with UI ($r = -0.94$, $p < 0.001$). Positive correlations were detected between autistic patients and their mothers regarding UI ($r = 0.88$, $p < 0.001$), fT3 ($r = 0.79$, $p = 0.03$), fT4 ($r = 0.91$, $p < 0.001$) and TSH ($r = 0.69$, $p = 0.04$). Autism had a significant risk for association with each of low UI (OR: 9.5, 95% CI: 2.15-33.8, $p = 0.02$) and intake of noniodized salt (OR: 6.82, 95% CI = 1.36-34.27, $p = 0.031$).

CONCLUSIONS:

ID is prevalent in Egyptian autistic children and their mothers and was inversely related to disease severity and could be related to its etiology.

The Interaction of Agricultural Pesticides and Marginal Iodine Nutrition Status as a Cause of Autism Spectrum Disorders

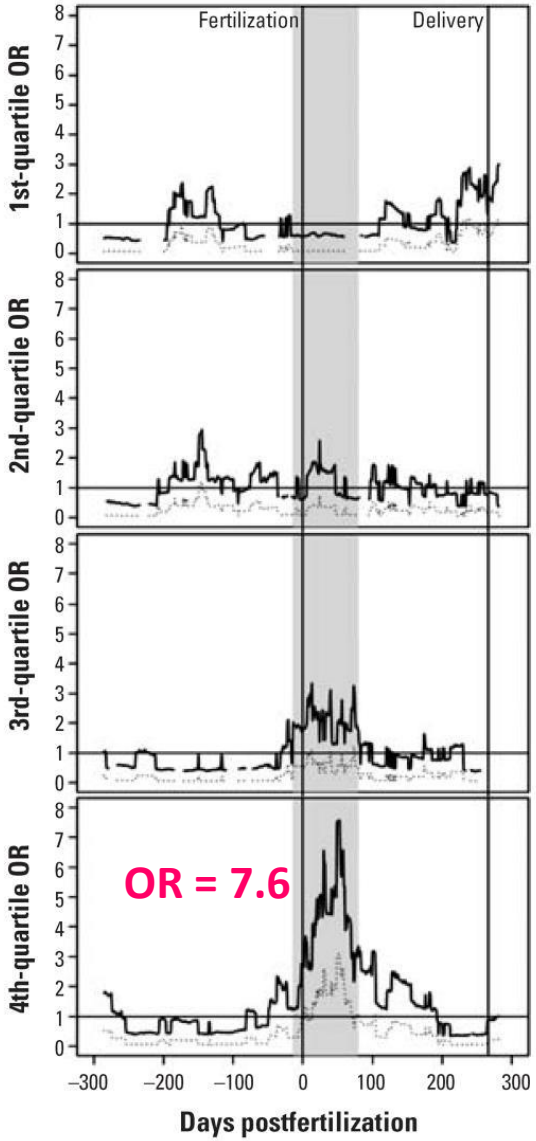
There is a relationship between agricultural pesticides and autism spectrum disorders (ASD).

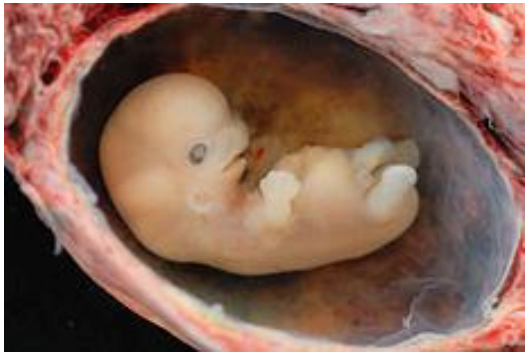
Organochlorines are associated with ASD.

One possible mechanism for this relationship is through thyroid disruption.

Kevin M. Sullivan. Environ Health Perspect. Apr 2008; 116(4): A155

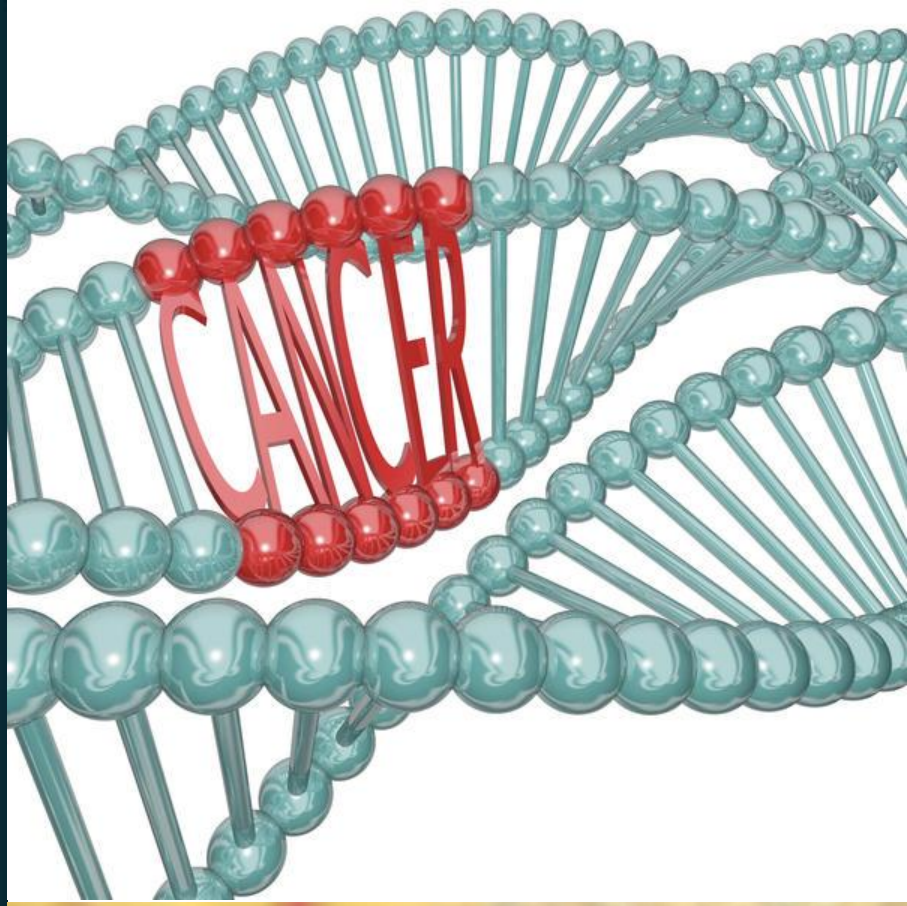
Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley

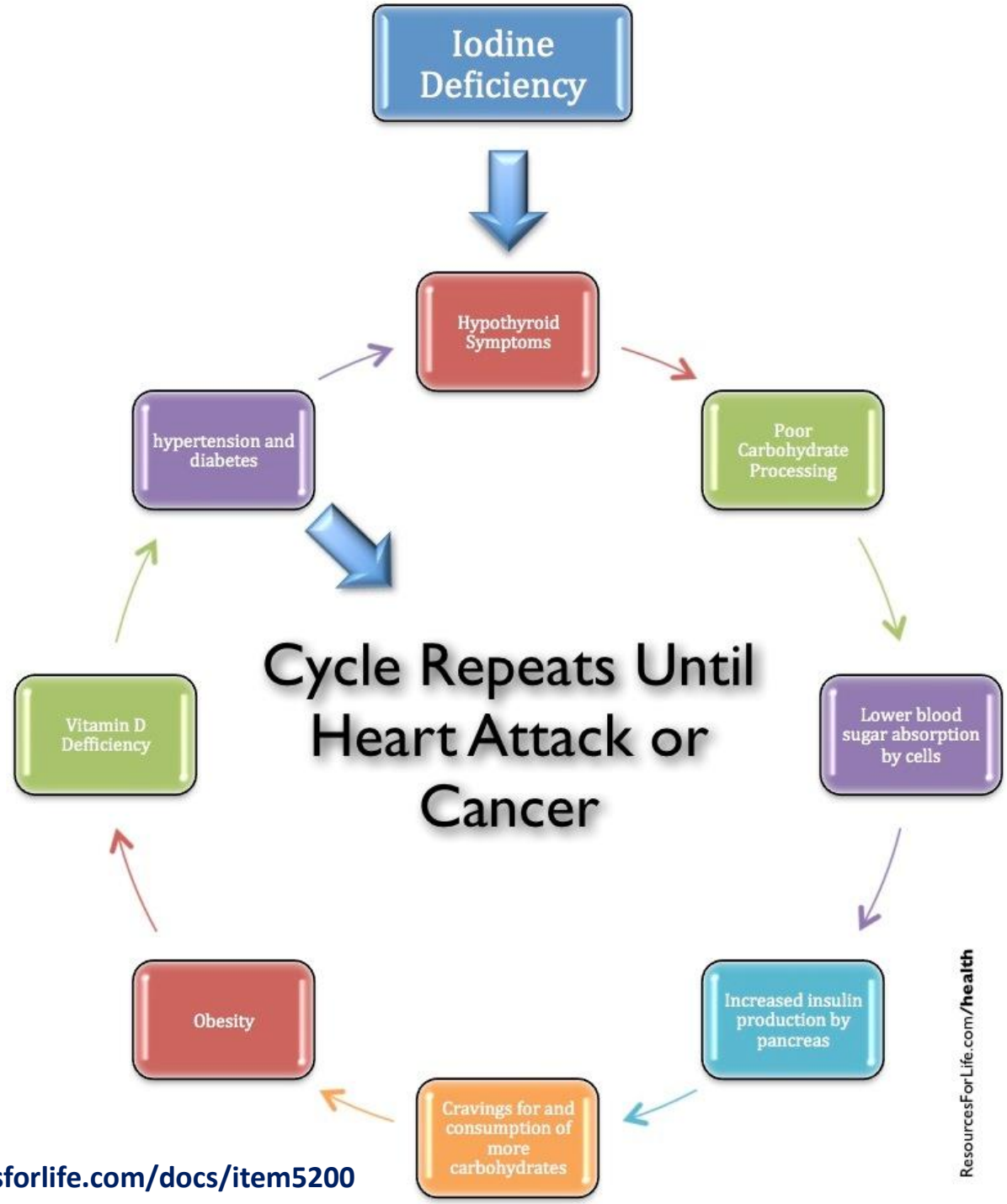




Using a 500-m radius around residential locations, we allowed the 8-week temporal window to be centered anywhere between 300 days before and 300 days following estimated date of conception.

Environ Health Perspect. Oct 2007; 115(10): 1482–1489.


CANCER



http://www.resourcesforlife.com/docs/item5200

Thyroid. 2009 Oct;19(10):1099-104.

Iodine treatment in children with subclinical hypothyroidism due to chronic iodine deficiency decreases thyrotropin and C-peptide concentrations and improves the lipid profile.

Zimmermann MB[1], Aeberli I, Melse-Boonstra A, Grimci L, Bridson J, Chaouki N, Mbhenyane X, Jooste PL.

Abstract

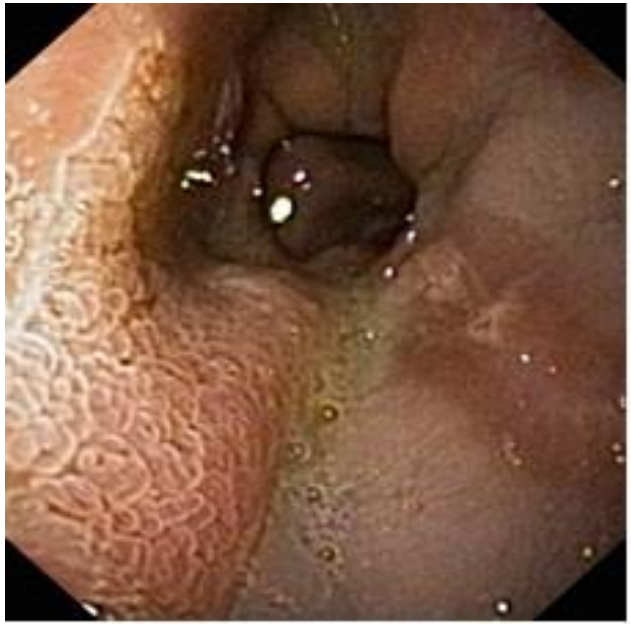
BACKGROUND:

Chronic iodine deficiency (ID) increases thyrotropin (TSH) concentrations and produces a thyroid hormone pattern consistent with subclinical hypothyroidism (ScH). ScH may be associated with ca
ch
pe
M
In
M
40
io
of
RE
M
tr
to
lip
treatment had no significant effect on concentrations of high-density lipoprotein cholesterol, triglycerides, or C-reactive protein.

CONCLUSIONS:

Correction of ID-associated ScH improves the insulin and lipid profile and may thereby reduce risk for cardiovascular disease. This previously unrecognized benefit of iodine prophylaxis may be important because ID remains common in rapidly developing countries with increasing rates of obesity and cardiovascular disease

Expression of the Na+/I- symporter (NIS) is markedly decreased or absent in gastric cancer and intestinal metaplastic mucosa of Barrett esophagus.

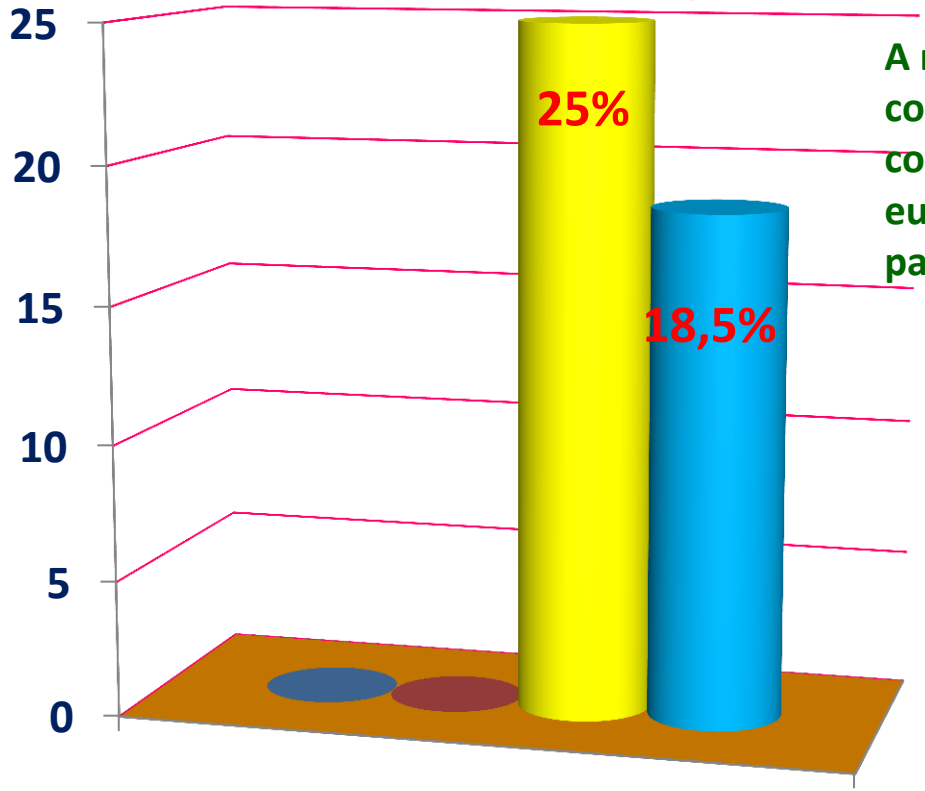


Those findings underscore the prognostic and diagnostic significance of the absence of NIS expression in gastric alterations when intestinalization or cancer occurs.

The introduction of NIS immunohistochemical tests in gastric mucosa samples may be of considerable diagnostic value in Barrett esophageal and gastric polyps to evaluate intestinal metaplasia, and as an additional early molecular marker in the diagnosis of precancerous or/and cancerous gastroesophageal lesions.

Expression of the Na^+/I^- symporter (NIS) is markedly decreased or absent in gastric cancer and intestinal metaplastic mucosa of Barrett esophagus. Áron Altorjay, Orsolya Dohán, Anna Szilágyi, Monika Paroder, Irene L Wapnir and Nancy Carrasco. *BMC Cancer* 2007, 7:5

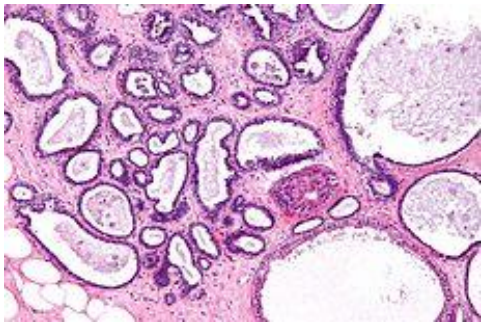
The effect of supraphysiologic levels of iodine on cyclic mastalgia



A randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted with 111 otherwise healthy euthyroid women with a history of breast pain.

Placebo
1,5 mg I2/d
3 mg I2/d
6 mg I2/d

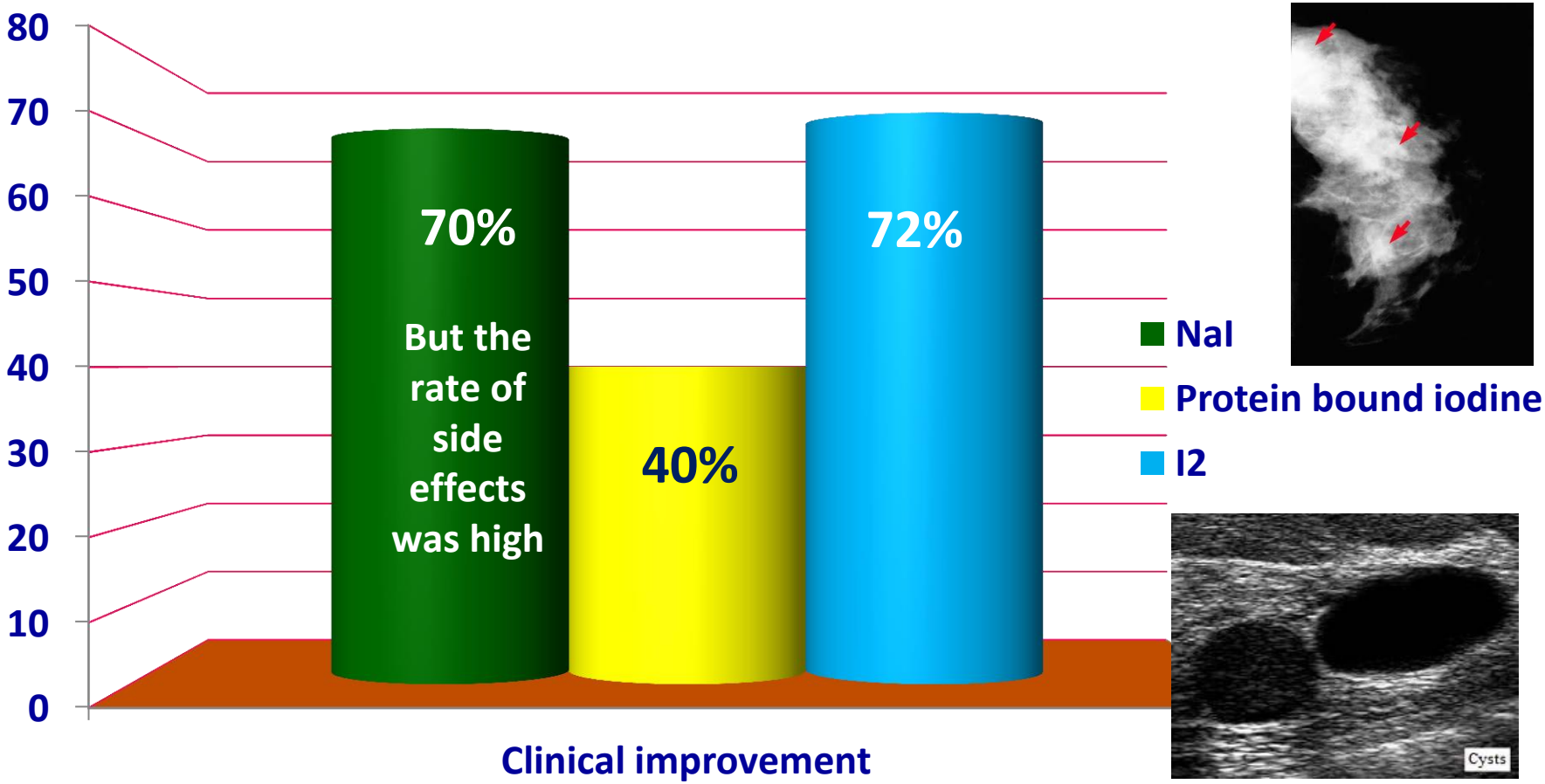
Reduction (%) in nodularity, breast pain , tenderness after 5 month therapy



All doses were associated with an acceptable safety profile. No dose-related increase in any adverse event was observed.

The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. Kessler JH. Breast J. 2004 Jul-Aug;10(4):328-36.

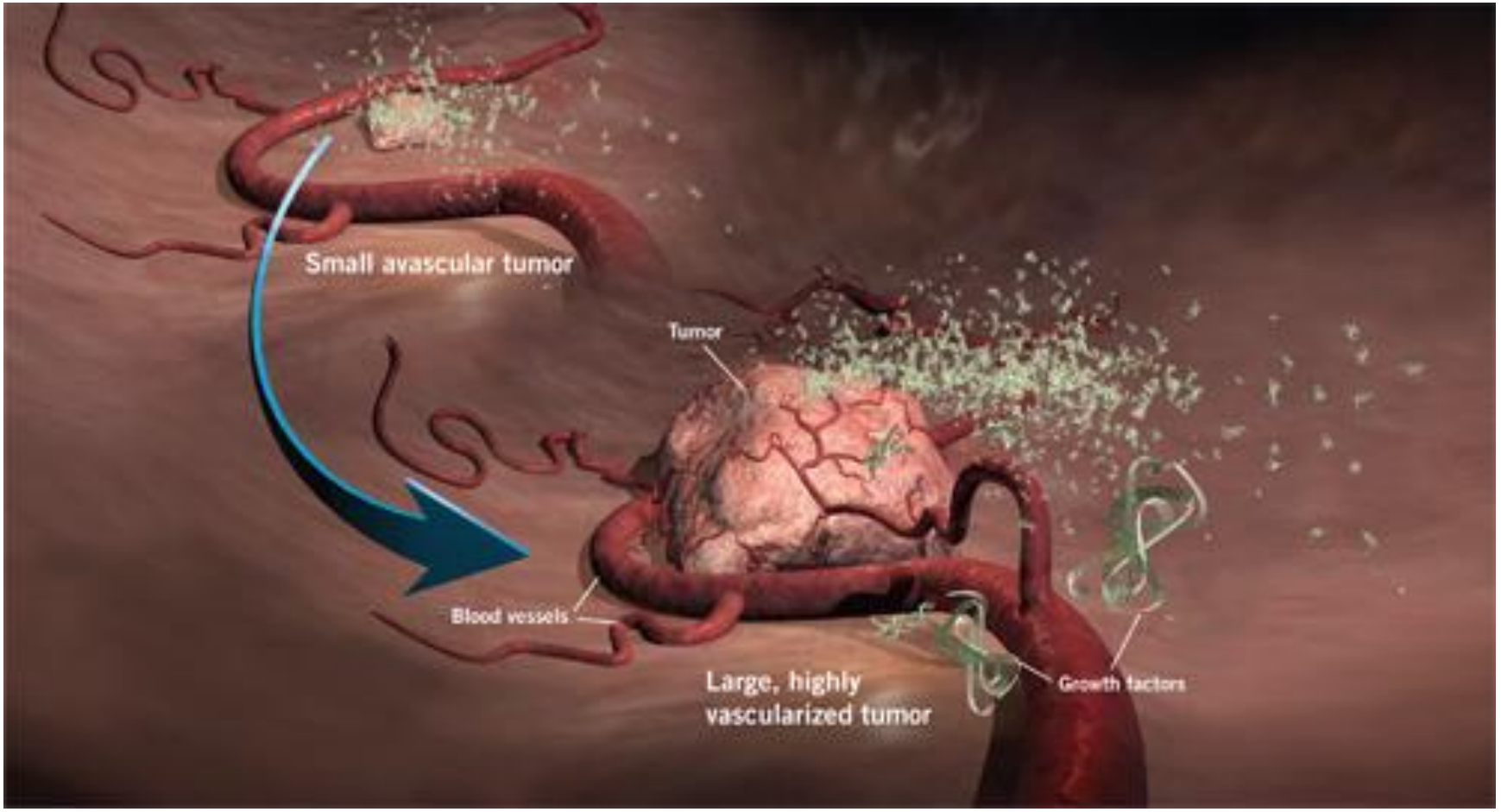
Iodine replacement in fibrocystic disease of the breast



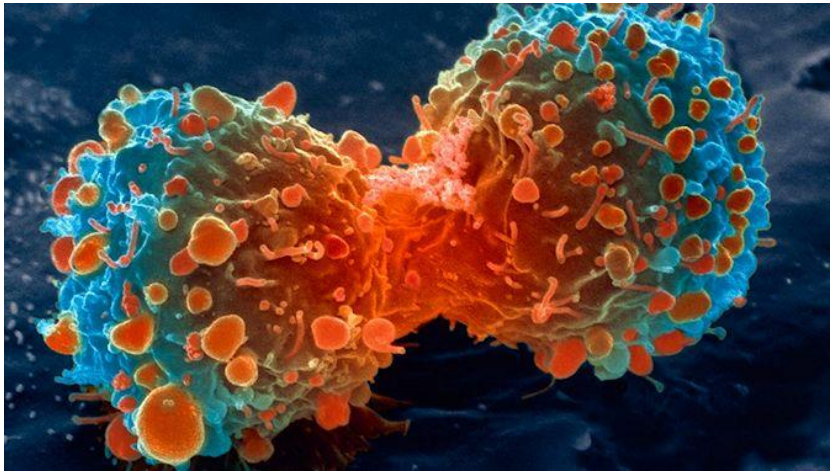
Molecular iodine is non thyrotropic and was the most beneficial

Can J Surg. 1993 Oct;36(5):453-60. Iodine replacement in fibrocystic disease of the breast.
Ghent WR, Eskin BA, Low DA, Hill LP

Antitumoral effects of iodine



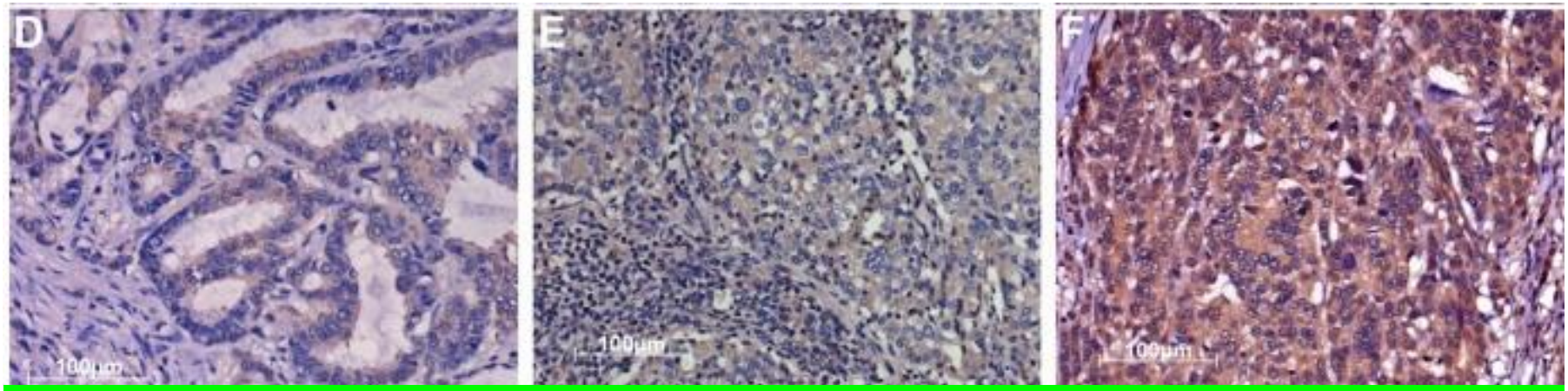
Antitumoral effects of iodine



- APOPTOSIS
- IODINE ALTERS GENE EXPRESSION
- PROLIFERATIVE RATE
- CELL VIABILITY
- CELL METASTASIS
- VEGF

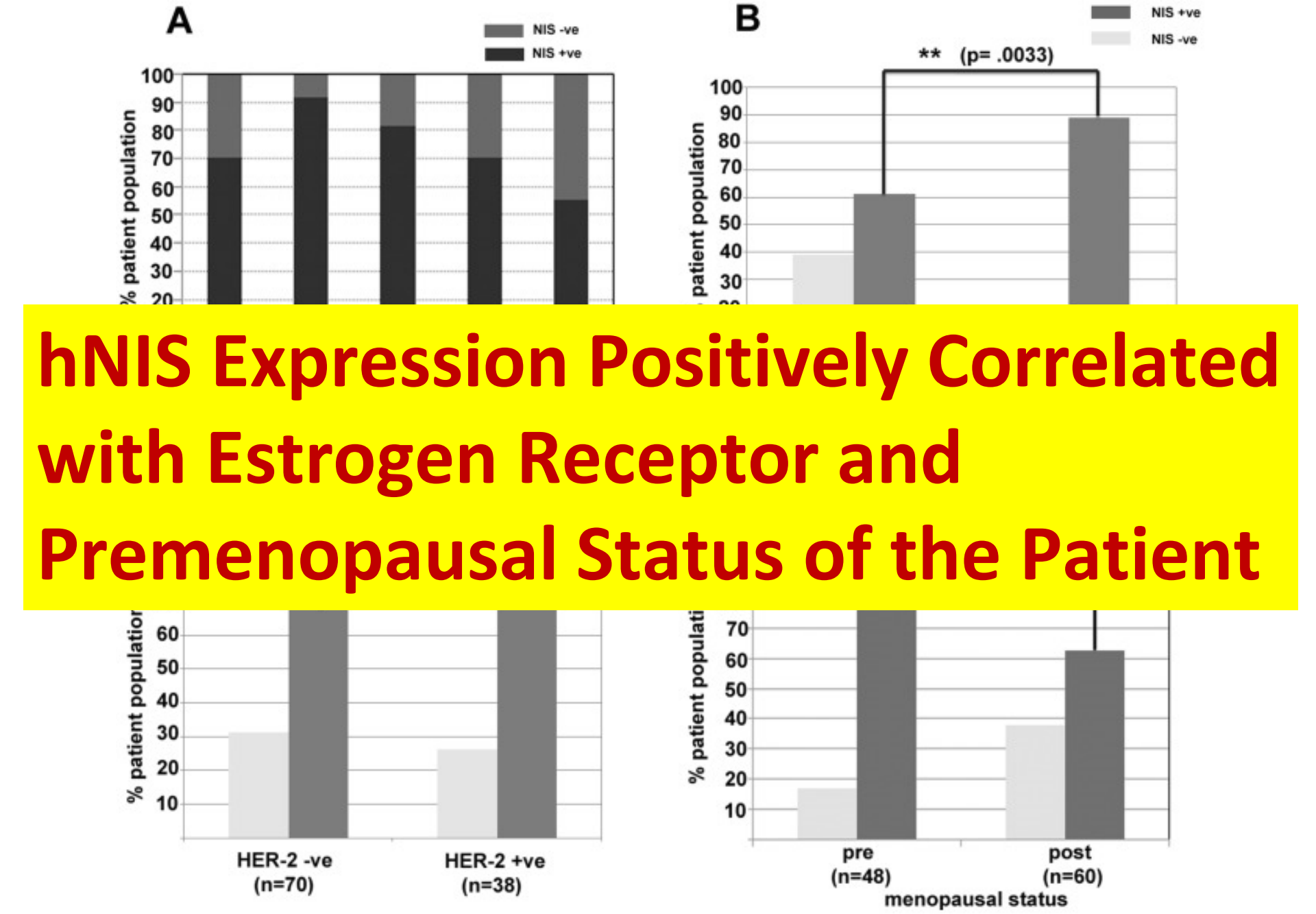
Quantitative Immunohistochemical Analysis Reveals Association between Sodium Iodide Symporter and Estrogen Receptor Expression in Breast Cancer.

Human sodium iodide symporter (hNIS) gene over-expression is an alternative target molecule for breast cancer diagnosis and targeted radio-iodine treatment.



hNIS expression in ER+ve, PgR+ve, HER2-ve subtype representing 0, 1+ and 2+ score respectively.

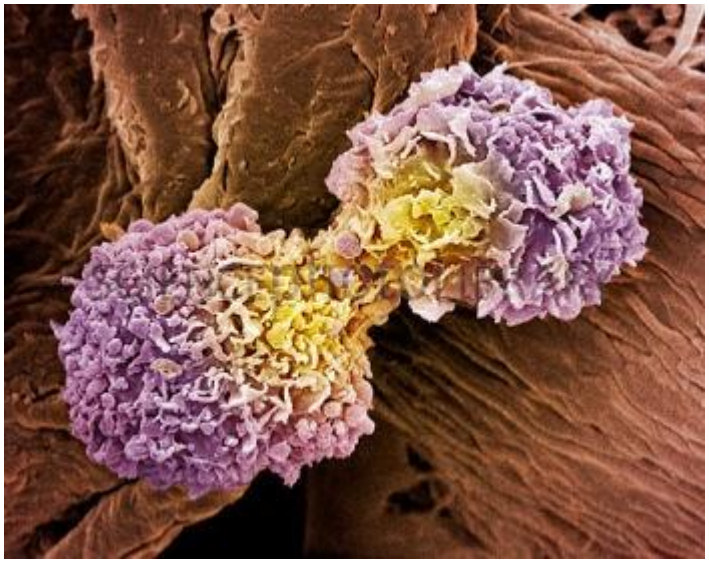
Sushmita Chatterjee, and Coll. PLoS One. 2013; 8(1): e54055. Published online Jan 14, 2013. doi: .1371/journal.pone.0054055



hNIS Expression Positively Correlated with Estrogen Receptor and Premenopausal Status of the Patient

Sushmita Chatterjee, and Coll. PLoS One. 2013; 8(1): e54055. Published online Jan 14, 2013. doi: .1371/journal.pone.0054055

Quantitative Immunohistochemical Analysis Reveals Association between Sodium Iodide Symporter and Estrogen Receptor Expression in Breast Cancer.

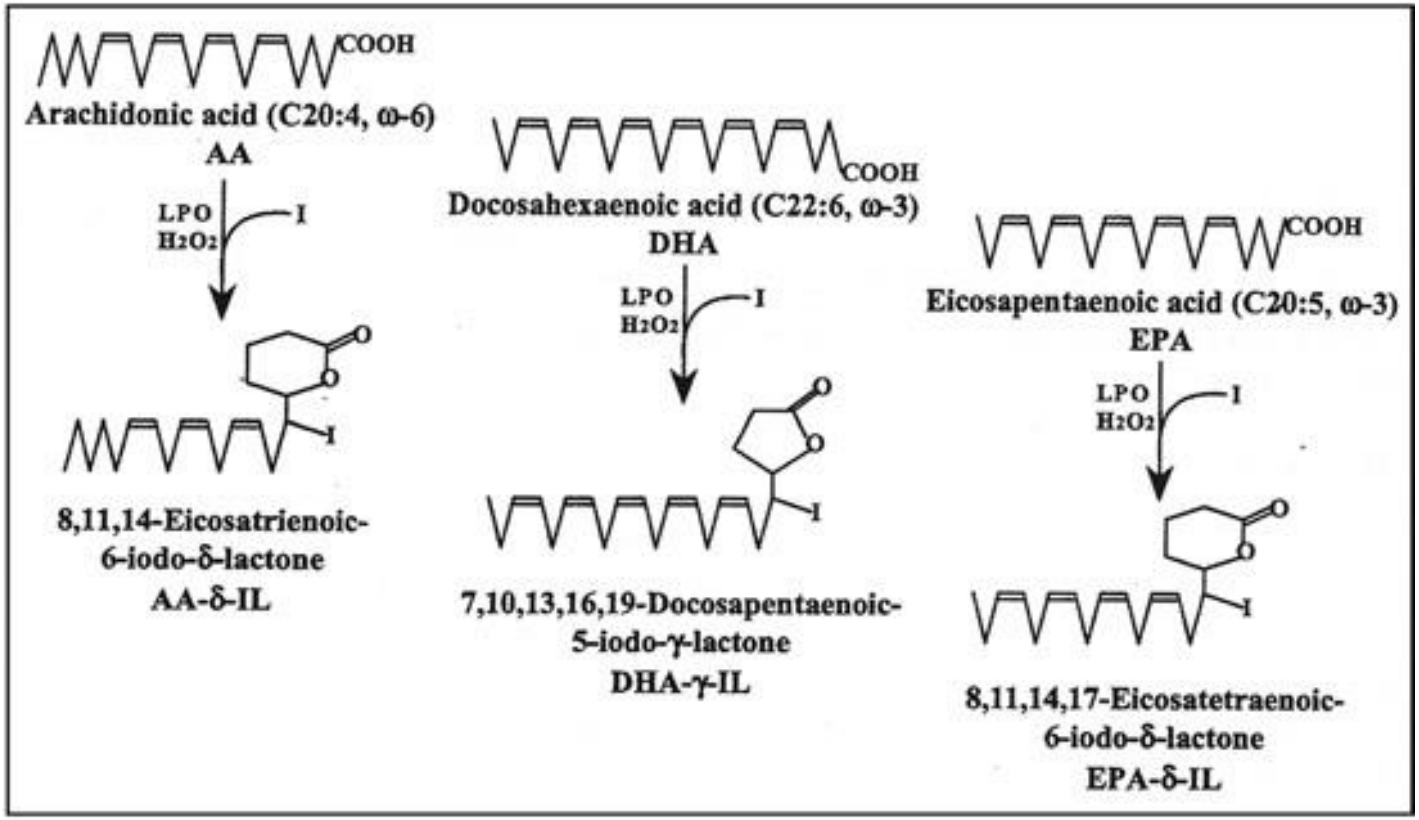


hNIS protein expresses in 70% cases of breast cancer, but the expression significantly varies among the subtypes of breast cancer. Highest frequency and intensity of hNIS expression is found in ER+ve, PgR+ve, HER2-ve subtype suggesting that hNIS expression is strongly associated with ER expression.

The quantitative immunohistochemistry image analysis method reported here will further help in patient stratification and potentially benefit global clinical assessment where hNIS mediated targeted 131I radio-ablative therapy is aimed.

Sushmita Chatterjee, and Coll. PLoS One. 2013; 8(1): e54055. Published online Jan 14, 2013. doi: .1371/journal.pone.0054055

6-iodo-5-hydroxy-eicosatrienoic acid (δ-iodolactone)



δ-Iodolactone seems to be the main iodocompound which can inhibit growth and induce apoptosis in B-CPAP cells as well as in MCF 7 breast cancer cells

The role of iodine and δ-iodolactone in growth and apoptosis of malignant thyroid epithelial cells and breast cancer cells. Roland Gärtner, Petra Rank, Birgit Ander. HORMONES 2010, 9(1):60-66

Antineoplasic effect of iodine involves 6-IL formation and PPARγ induction

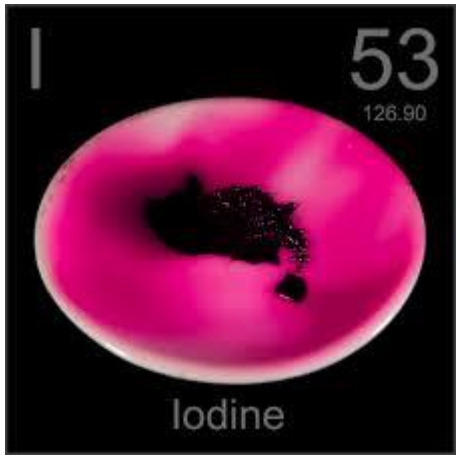
Tumoral tissue contains significantly higher concentrations of arachidonic acid than normal mammary tissue and the I2 treatment is accompanied by a 12-fold increase in 6-IL formation.

	AA (nmol/g)	6-IL (nmol/g)
MG	1.70 ± 0.5	---------
MG + I_2	1.54 ± 0.3	0.13 ± 0.1
Tumor	6.22 ± 0.8*	---------
Tumor + I_2	5.31 ± 1.0*	1.92 ± 0.3*

- Studies in mammary cancer demonstrated that moderately high concentrations of molecular iodine have a antiproliferative and apoptotic effect either in vivo as in vitro, however the cellular intermediated involved in these effects has not been elucidated.

Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

The β-iodolactone derived from eicosapentaenoic acid is more active in growth inhibition than β-iodolactone from arachidonic acid

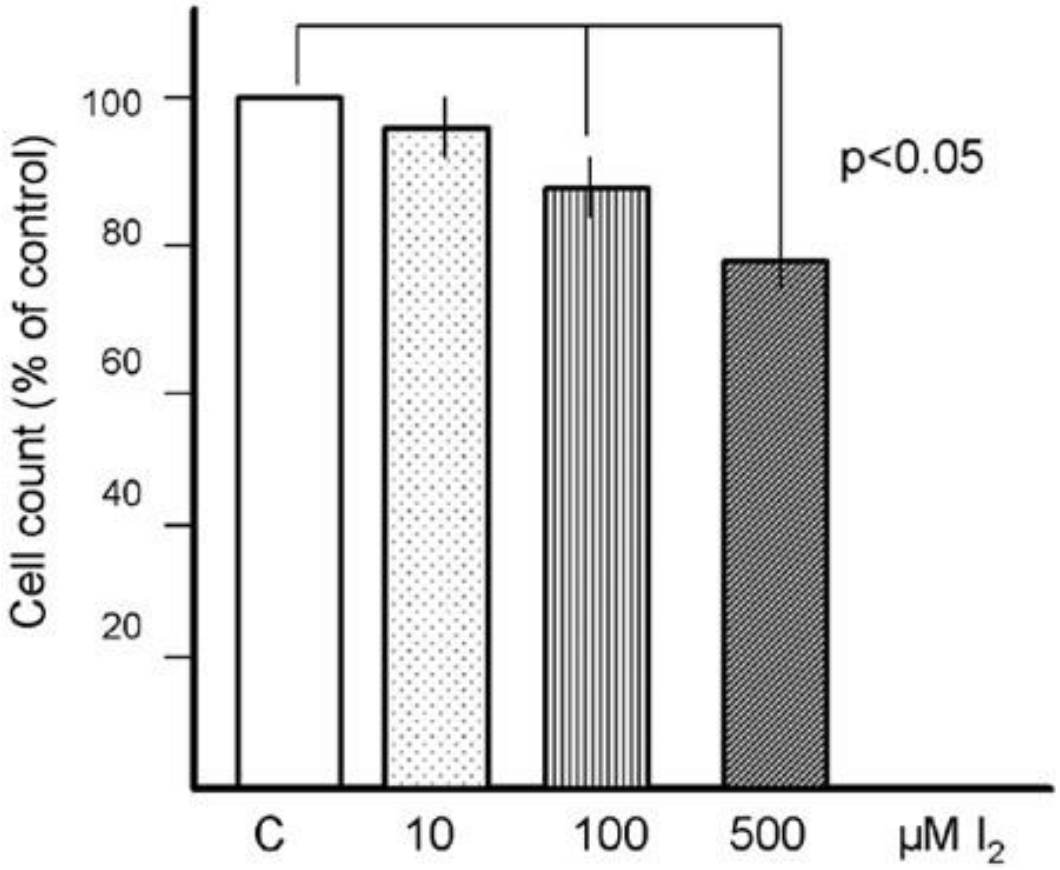


The β-iodolactone derived from eicosapentaenoic acid is more active in growth inhibition than β-iodolactone from arachidonic acid, but the β-iodolactone from docosahexaenoic acid was ineffective.

This indicates the specificity of different iodolactones and might explain why fish and iodide consumption is important for maintaining normal thyroid volume.

The role of iodine and δ-iodolactone in growth and apoptosis of malignant thyroid epithelial cells and breast cancer cells. Roland Gärtner, Petra Rank, Birgit Ander. HORMONES 2010, 9(1):60-66

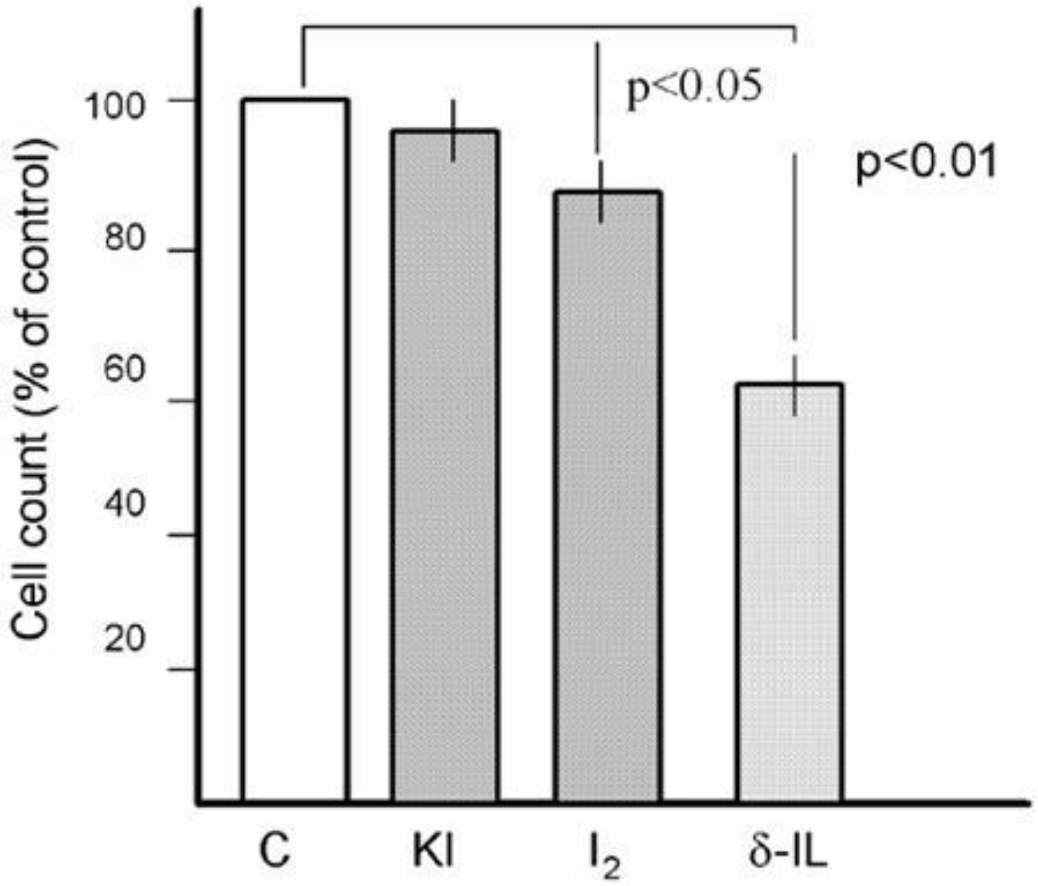
Dose-dependent effect of iodine on growth of C-BAP thyroid carcinoma cells



Dose-dependent effect (10, 100 and 500 µM) of iodine (I2) on growth of C-BAP thyroid carcinoma cells. Cells were incubated for 24 hours and then cell number counted in a Coulter Counter. Reduction of cell number with 100 µM and 500 µM I2 was significant ($p<0.05$), in comparison to controls (C).

The role of iodine and δ-iodolactone in growth and apoptosis of malignant thyroid epithelial cells and breast cancer cells.
Roland Gärtner, Petra Rank, Birgit Ander. HORMONES 2010, 9(1):60-66

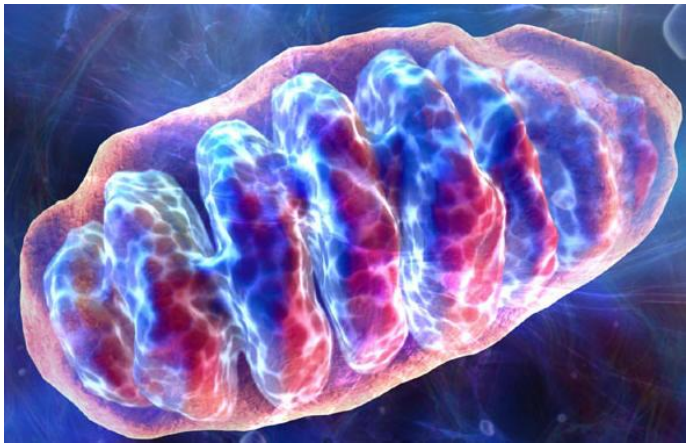
Effect of iodide, iodine and δ-iodolactone on MCF-7 mammary carcinoma cells



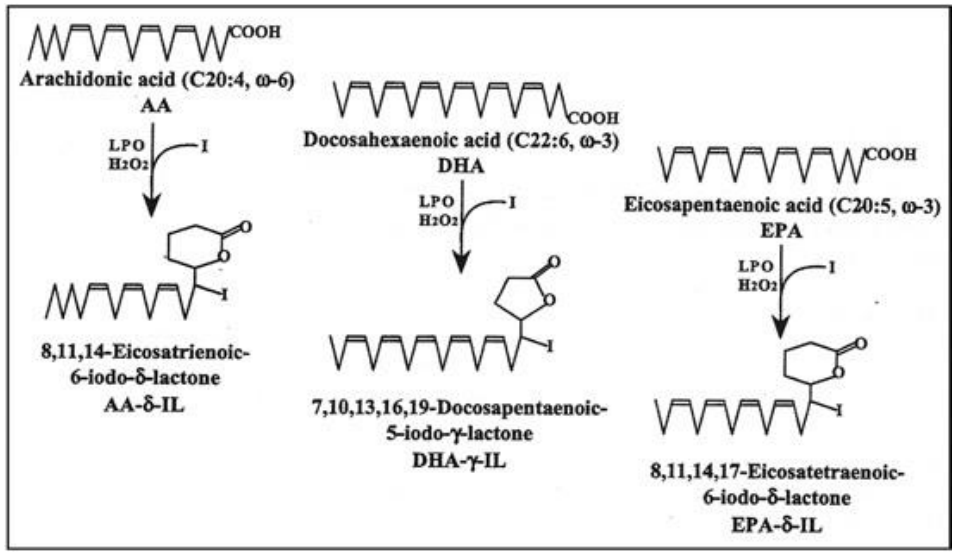
Effect of iodide (KI 100 µM), iodine (100 µM) and δ-iodolactone 5 µM (δ-IL5) and 10 µM (δ-IL 10) on MCF-7 mammary carcinoma cells. Cells were incubated for 24 hours and then cell number counted in a Coulter Counter. Inhibition with 100 µM I2 and 5 µM δ-iodolactone was significant ($p<0.01$), in comparison to controls (C).

The role of iodine and δ-iodolactone in growth and apoptosis of malignant thyroid epithelial cells and breast cancer cells.
Roland Gärtner, Petra Rank, Birgit Ander. HORMONES 2010, 9(1):60-66

Uptake and antitumoral effects of iodine and 6-iodolactone in differentiated and undifferentiated human prostate cancer cell lines.

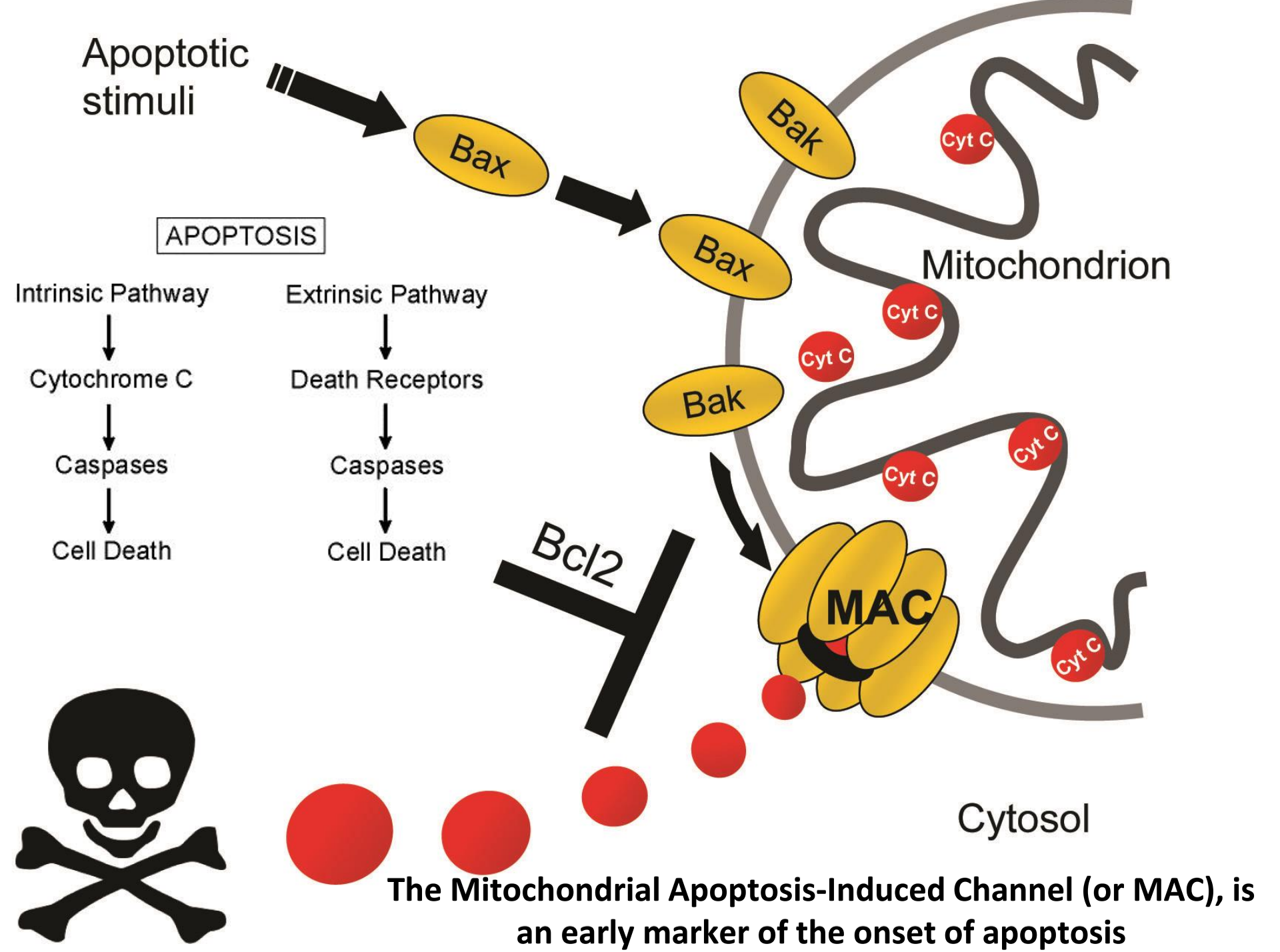


In the three cell lines both forms of iodine (I(-)) and iodine (I(2)) activated the intrinsic apoptotic pathway (increasing the BAX/BCL-2 index and caspases).



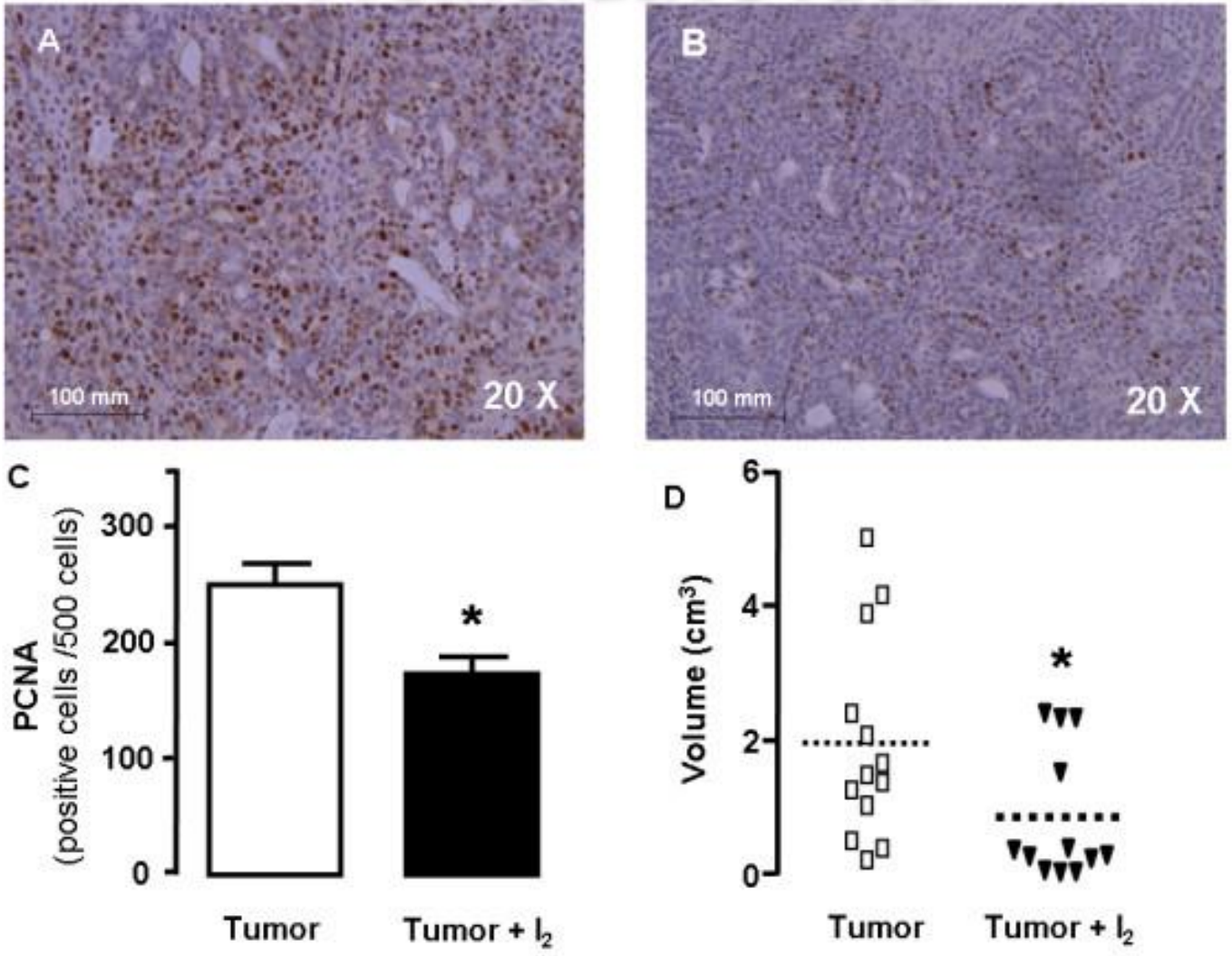
Non-cancerous (RWPE-1) and cancerous (LNCaP, DU-145) cells, as well as nude mice xenotransplanted with DU-145 cells were used as cancer models.

Uptake and antitumoral effects of iodine and 6-iodolactone in differentiated and undifferentiated human prostate cancer cell lines. Aranda N, Sosa S, Delgado G, Aceves C, Anguiano B. Prostate. 2013 Jan;73(1):31-41. doi: 10.1002/pros.22536. Epub 2012 May 10



The Mitochondrial Apoptosis-Induced Channel (or MAC), is an early marker of the onset of apoptosis

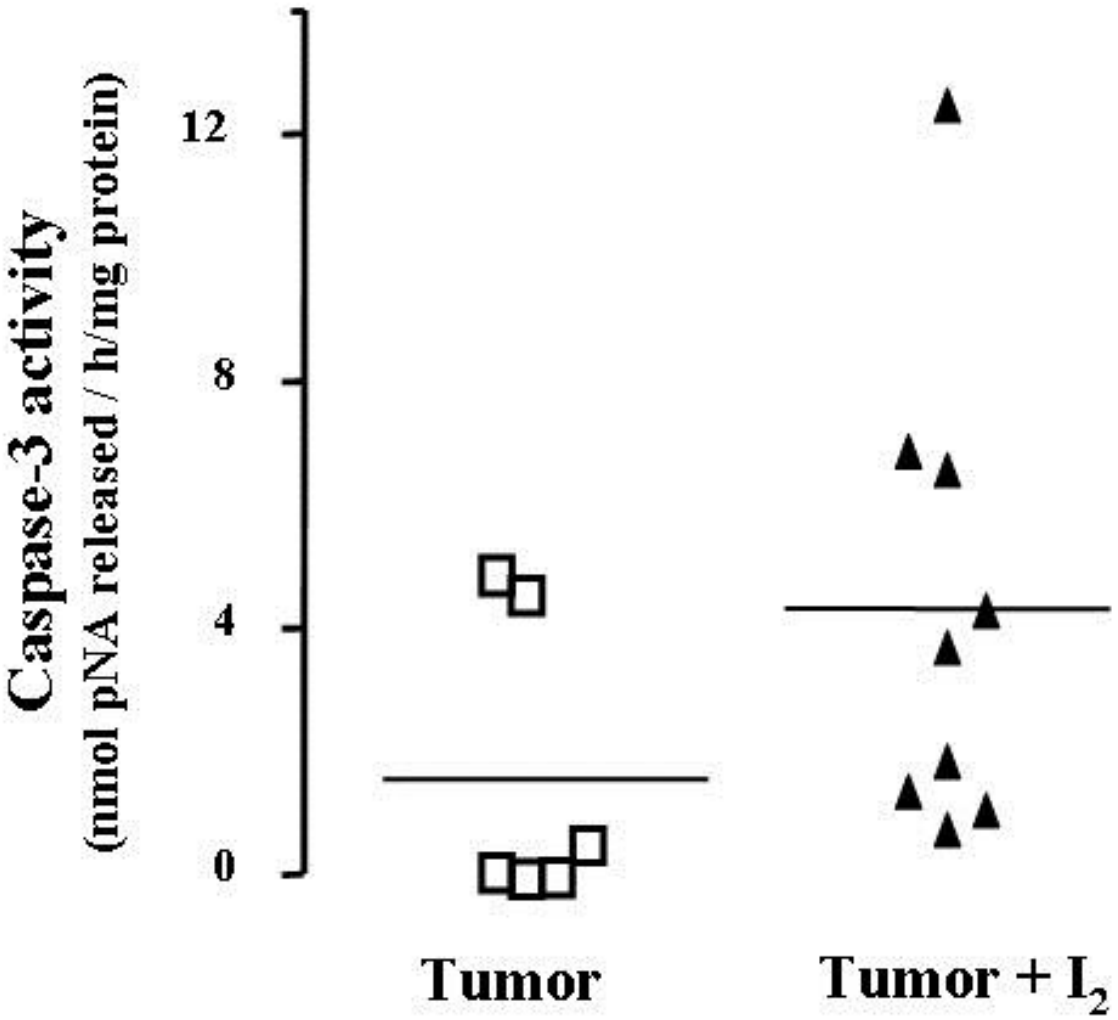
Proliferative rate



Immunohistochemical presence of PCNA-positive cells in tumors from control (A) and I2-supplemented rats (B); PCNA-positive cells were revealed with diaminobenzidine (brown stain) and counterstained with hematoxylin (purple stain). C, quantification; D, size of tumors (Volume). Differences between experimental groups were analyzed using an unpaired t test. *indicates significant difference from the appropriate control ($p < 0.05$).

Mol Cancer. 2009; 8: 33.

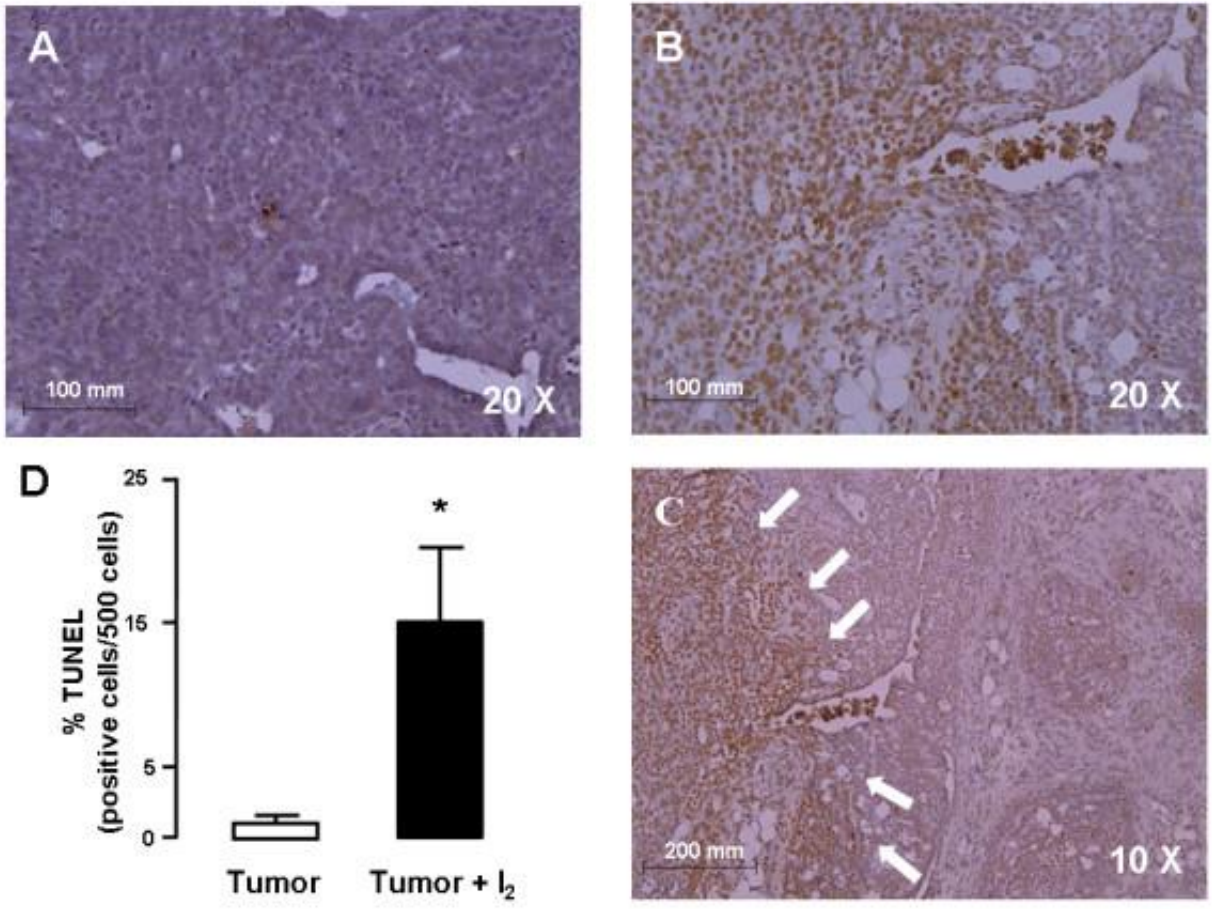
Caspase-3 activity



Individual tumors from control or I2-treated rats were assayed; horizontal line represents the mean of each group. Differences between experimental groups were analyzed using an unpaired t test. A tendency toward higher caspase-3 activity (p = 0.246) in I2-treated tumors was observed.

Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

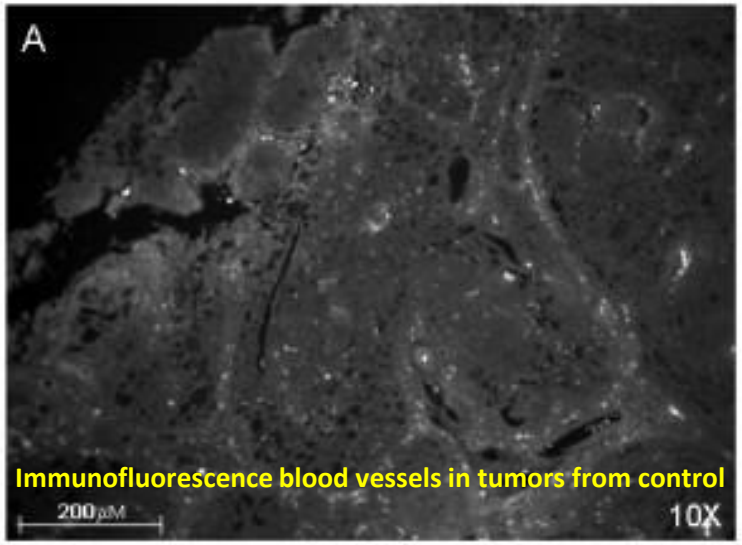
Apoptotic rate

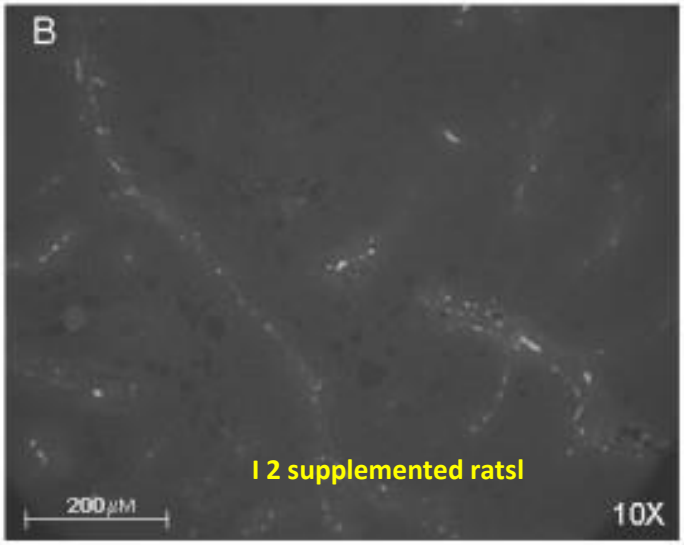


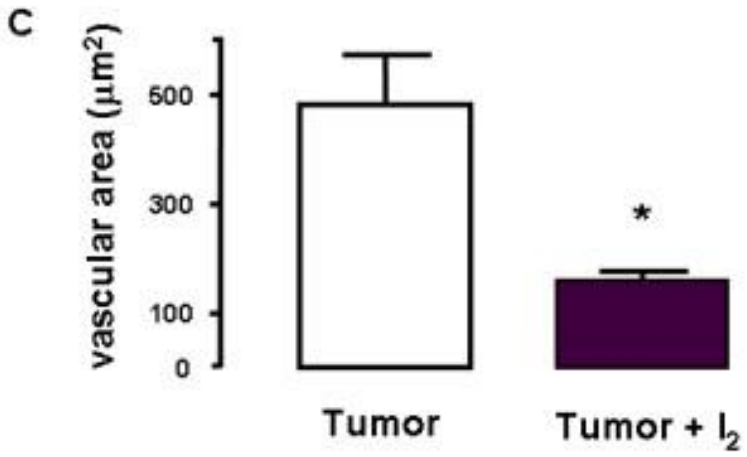
Representative sections of TUNEL-positive cells in tumors from control (A) or I2-treated rats (B), magnification 20×. C, Section of rat tumor treated with I2 that shows an extensive zone of TUNEL-positive cells (white arrows), magnification 10×. TUNEL-positive cells were revealed with diaminobenzidine (brown stain) and counterstained with hematoxylin (purple stain). D, TUNEL-positive cell quantification. The difference between experimental groups was analyzed using an unpaired t test. *indicates significant difference from the control ($p < 0.05$).

Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

Vascular area



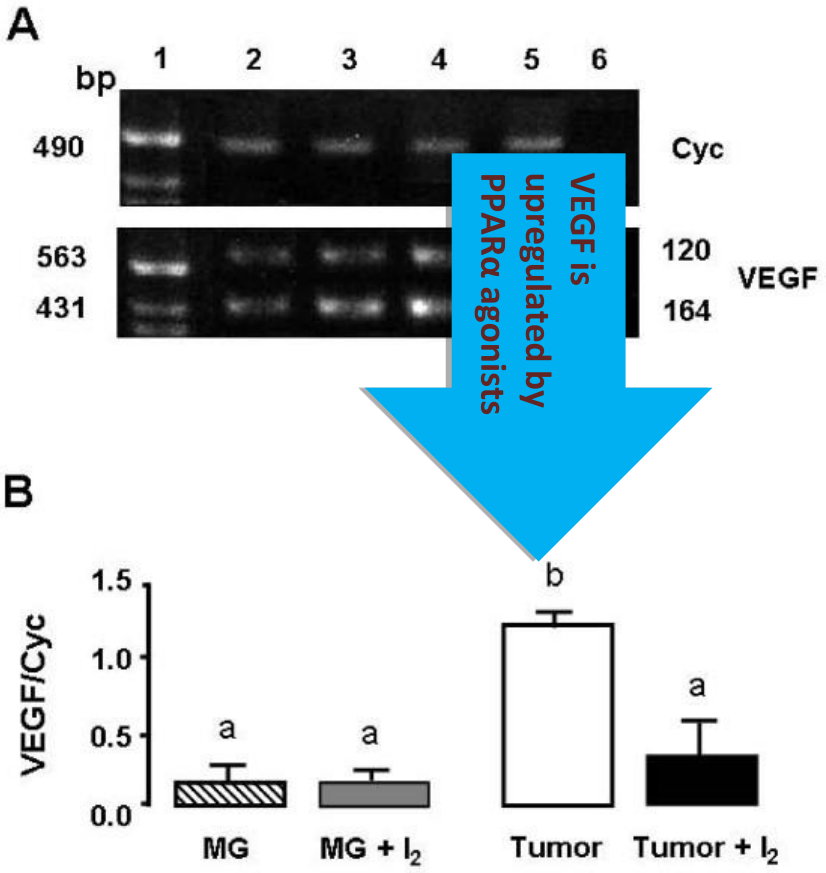




Immunofluorescence blood vessels in tumors from control (A) and I_2-supplemented rats (B). Vessel area was calculated as the total field area positively stained for the vascular marker (μm^2). C, quantification. Differences between experimental groups were analyzed using an unpaired t test. *indicates significant difference from the control ($p < 0.05$)

Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

Vascular Endothelial Growth Factor expression



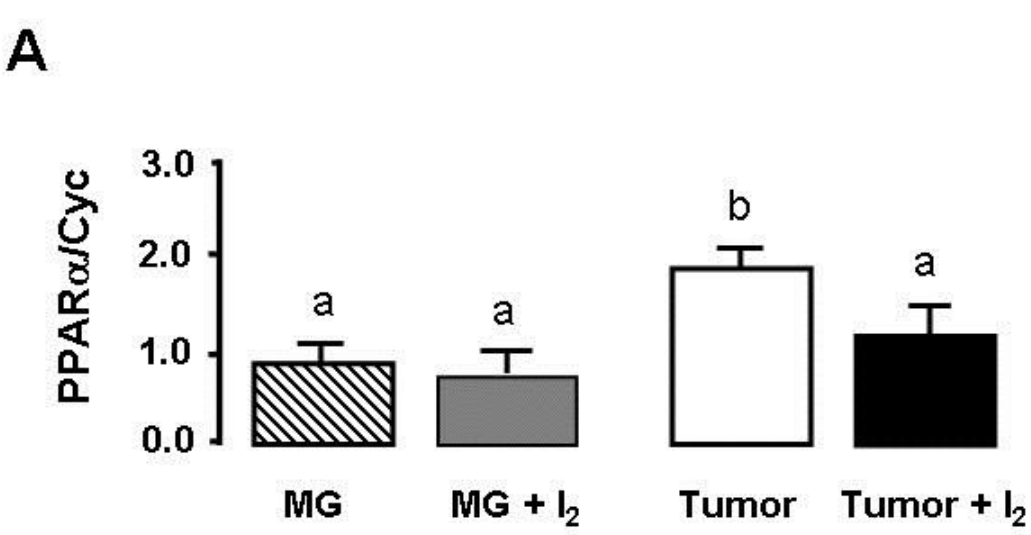
Isoforms of VEGF mRNA in normal (MG) or tumoral (tumor) mammary glands from control or I_2-treated rats were measured by the real time PCR method. A. Representative gel of amplicon of Cyclophilin (Cyc) and 120 and 164 isoforms of VEGF mRNA in 2% agarose gel stained with ethidium bromide. 1, ladder; 2, MG; 3, MG + I_2., 4, Tumor; 5, Tumor + I_2; 6, all the PCR reagents without RT sample. B. VEGF mRNA quantification. Cyclophilin (Cyc) served as internal control and was used to normalize for differences in input RNA. Data are expressed as the mean ± SD. Differences between experimental groups were analyzed using a one-way ANOVA and the Tukey-HSD Test. Means with different letters are significantly different ($p < 0.05$)

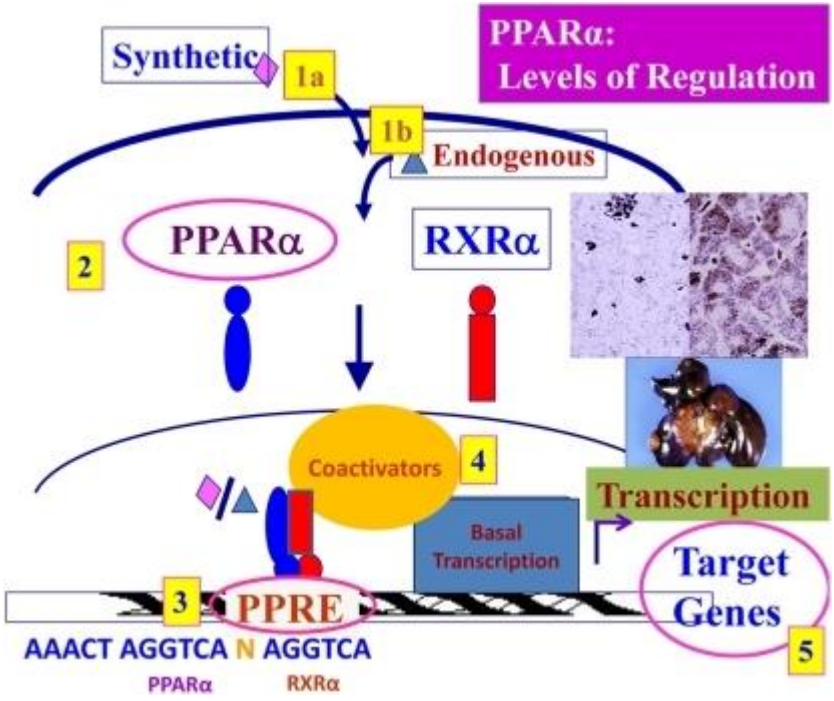
VEGF is a potent mitogen with high specificity for endothelia. The inhibition of PPARα expression might explain this effect

Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

PPAR expression

In mammary cancer cells PPARα is over-expressed, and its activation correlates with proliferation

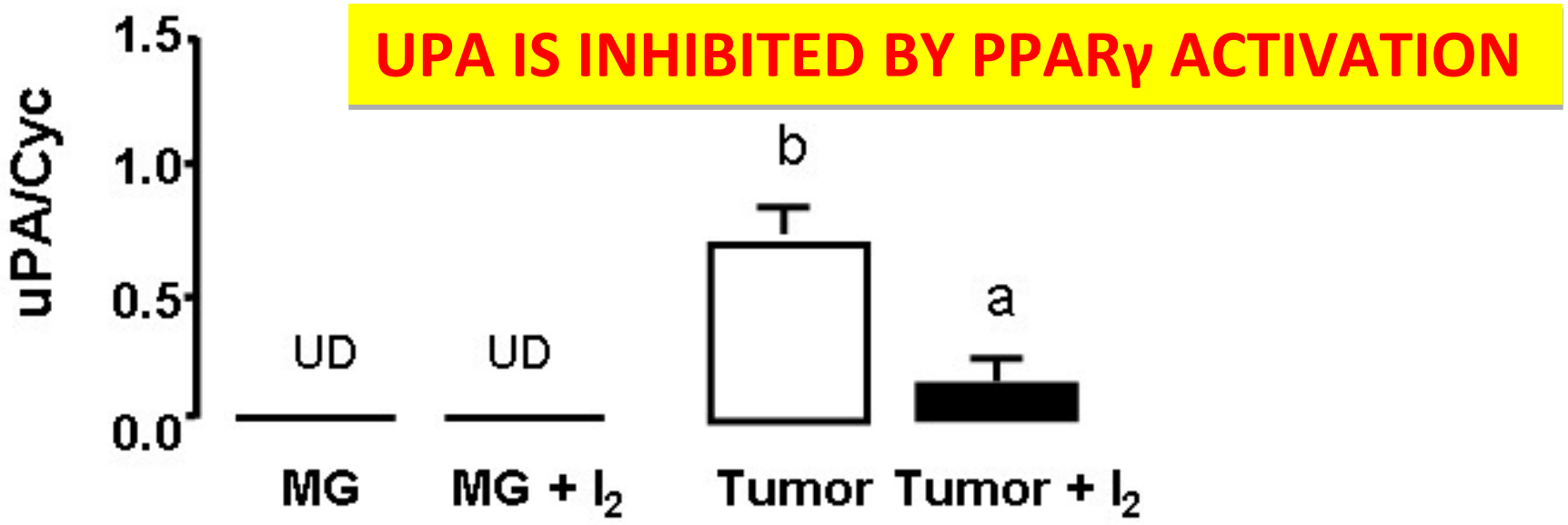




Isoforms of PPAR mRNA in normal (MG) or tumoral (tumor) mammary glands from control or I2-treated rats were measured by the real time PCR method. A, PPAR type alpha (PPARα).

Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

Urokinase Plasminogen Activator (uPA) expression

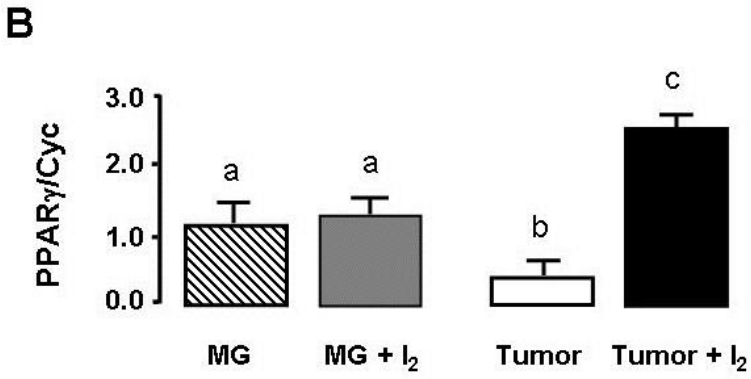


uPA mRNA in normal (MG) or tumoral (tumor) mammary glands from control or I2-treated rats were measured by the real time PCR method, and Cyclophilin (Cyc) served as internal control. UD, undetectable levels. Data are expressed as the mean ± SD. Differences between experimental groups were analyzed using a one-way ANOVA and the Tukey-HSD Test. Means with different letters are significantly different ($p < 0.05$)

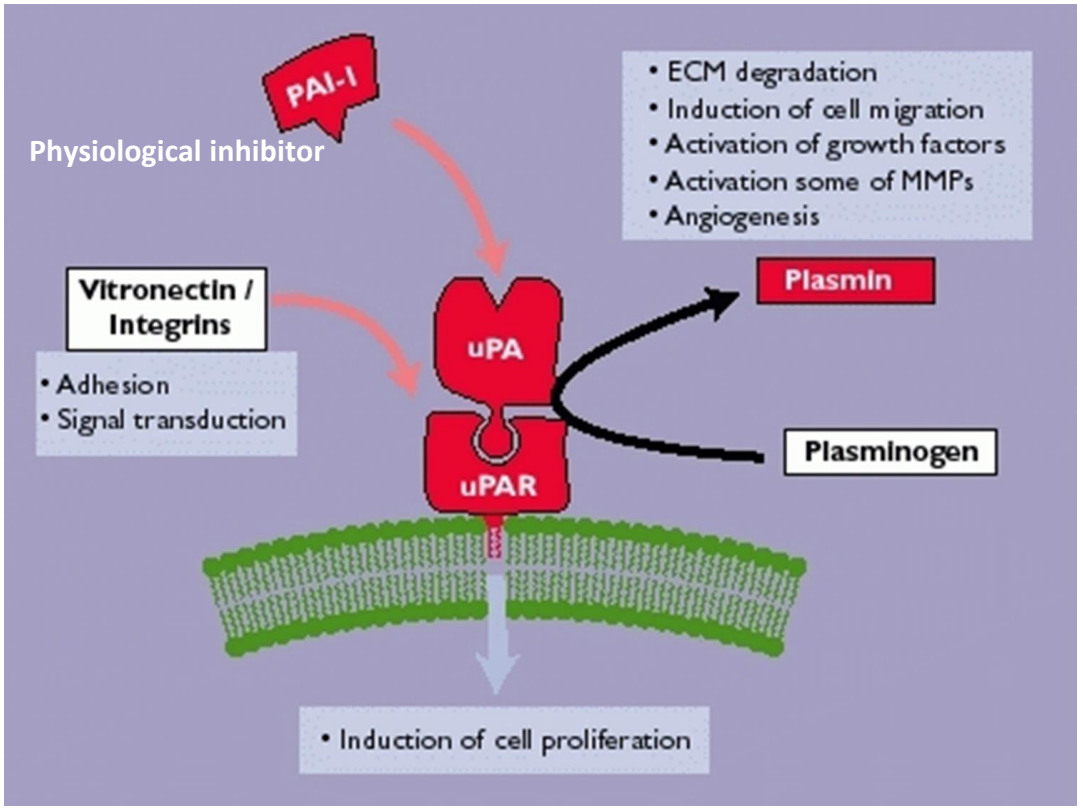
Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

PPAR expression

uPA is inhibited by PPARγ activation



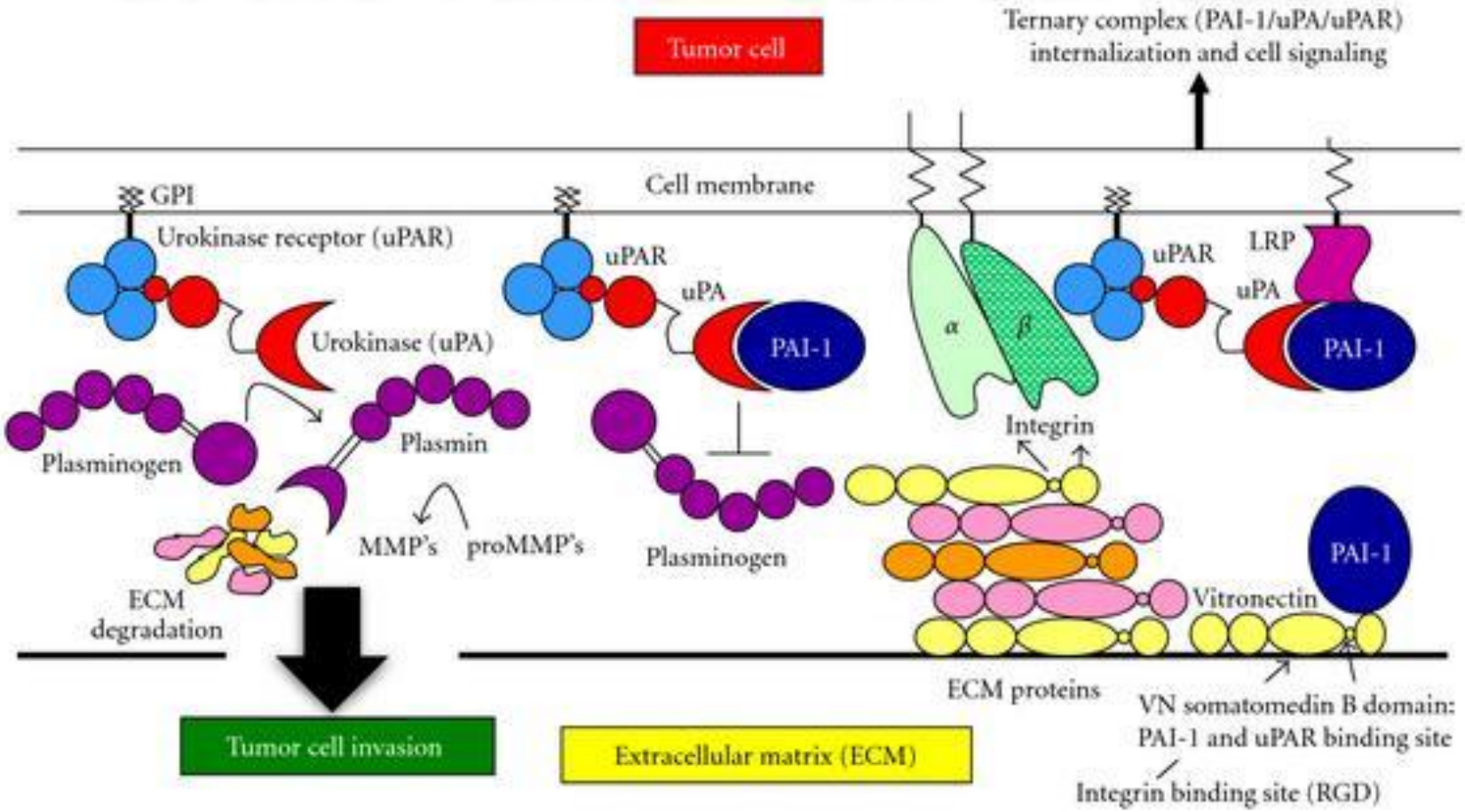
Isoforms of PPAR mRNA in normal (MG) or tumoral (tumor) mammary glands from control or I2-treated rats were measured by the real time PCR method.
B, PPAR type gamma (PPARγ).



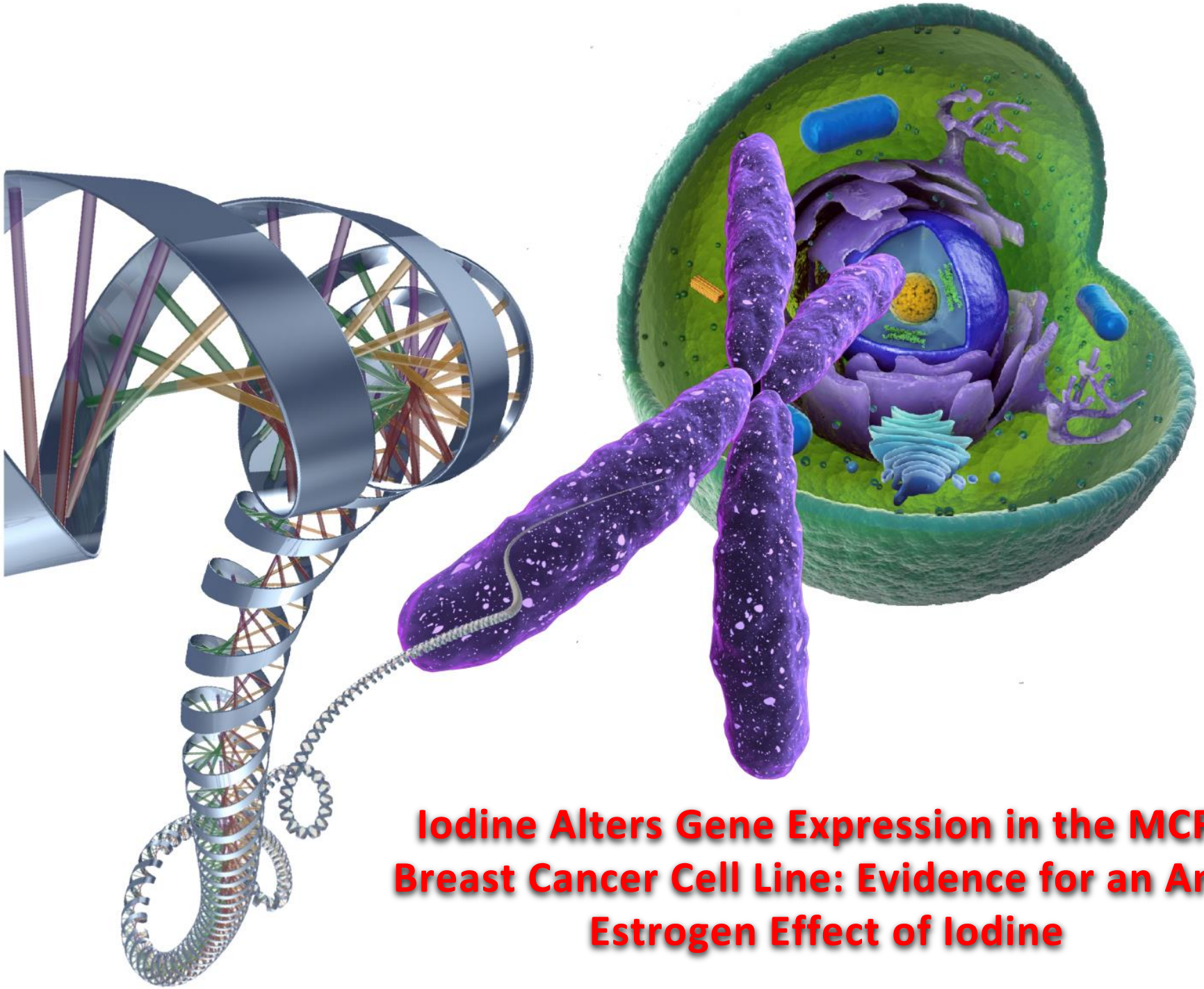
Antineoplastic effect of iodine in mammary cancer: participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). Carmen Aceves, Pablo García-Solís, Omar Arroyo-Helguera, Laura Vega-Riveroll, Guadalupe Delgado, and Brenda Anguiano. Mol Cancer. 2009; 8: 33.

Plasminogen Activator System at the Tumor Cell Surface

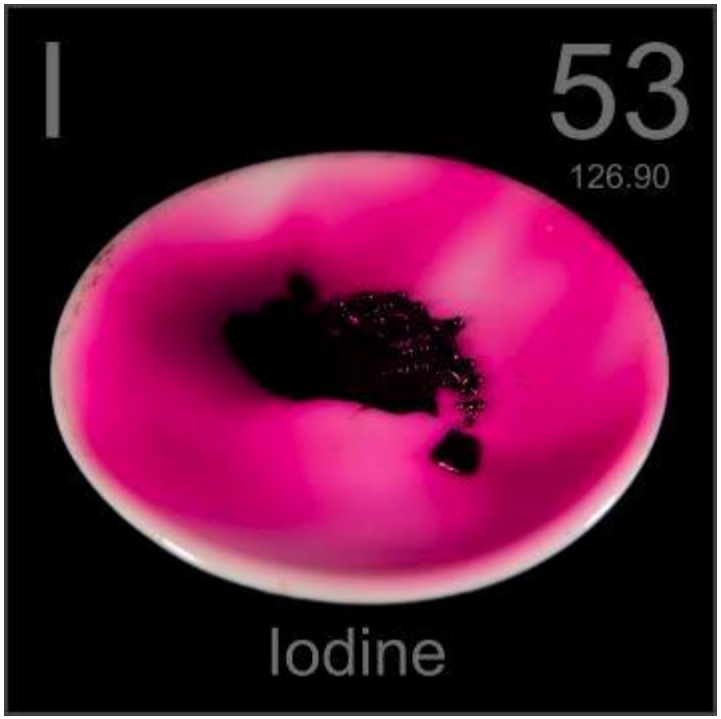
PPAR Research Volume 2009 (2009), Article ID 345320, 13 pages.



The catalytic activity of urokinase (uPA) is enhanced when bound to the cell surface by uPAR. uPA cleaves the zymogen plasminogen to its active form, the serine protease plasmin. Plasmin can subsequently activate matrix metalloproteases (MMP's) in the extracellular matrix (ECM) microenvironment. Thus, the uPA/uPAR complex and MMP activation contribute to tumor cell invasion and metastasis by degradation of ECM components.



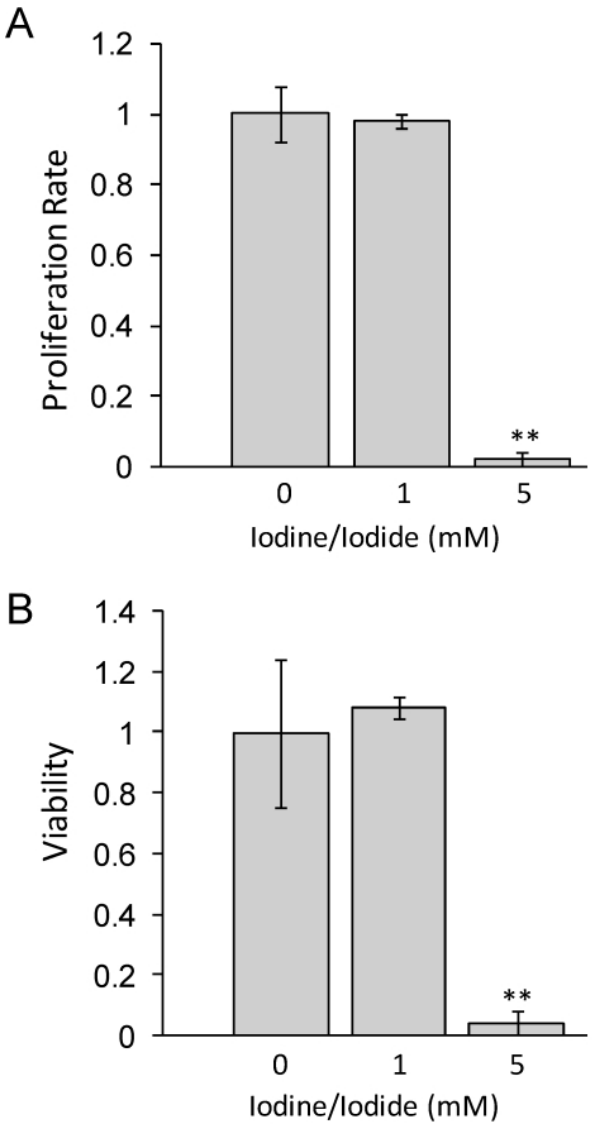
Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine



- **The impact of iodine therapy for the maintenance of healthy breast tissue has been reported in both animal and clinical studies yet the mechanisms responsible remain unclear**

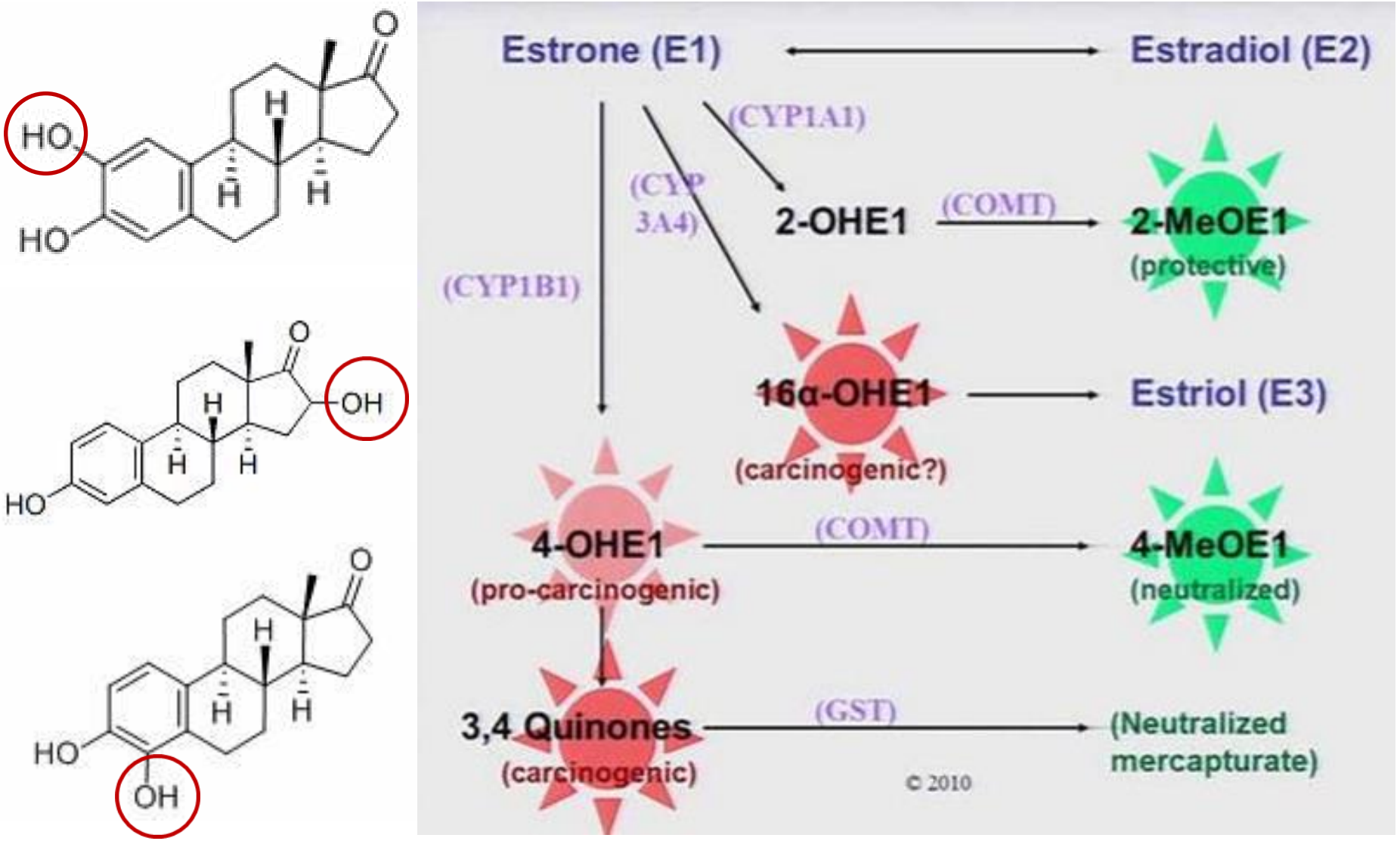
Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine. Frederick R. Stoddard, Ari D. Brooks, Bernard A. Eskin3, Gregg J. Johannes. Int J Med Sci 2008; 5(4):189-196.

Cell viability or proliferation at 48 hours



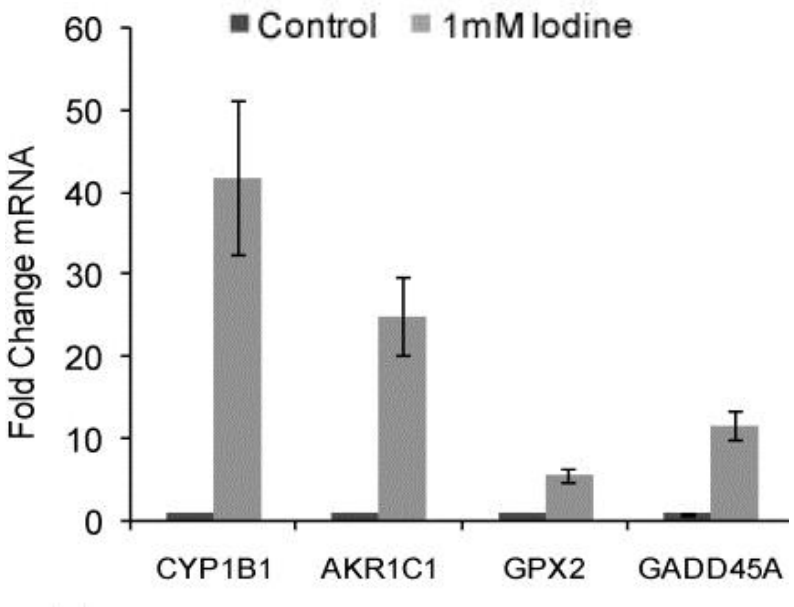
1 mM iodine/iodide does not impact cell viability or proliferation at 48 hours. MCF-7 cells were grown in RPMI-1640 supplemented with 1 µM tRA and 1 nM estradiol (control medium) or control medium supplemented with Lugol's iodine solution (5% iodine, 10% iodide) to a concentration of 1 mM iodine (1.0 mM iodine/iodide) or 5 mM iodine (5 mM iodine/iodide) for 48 hours and the effect on cell proliferation (A) and cell viability (B) was analyzed. Significant decrease in proliferation and viability was observed in the 5 mM iodine/iodide condition. Relative change in cell proliferation (A) and relative change in viability (B) for the control condition was set to one. Standard deviation is shown. ** denotes $P \leq 0.01$

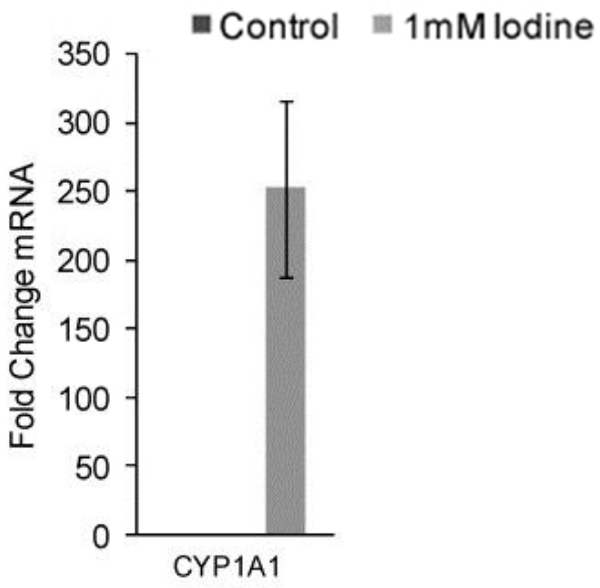
Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine. Frederick R. Stoddard, Ari D. Brooks, Bernard A. Eskin3, Gregg J. Johannes. Int J Med Sci 2008; 5(4):189-196.



Oestrogen detoxification pathway

Genes which are documented to be estrogen responsive

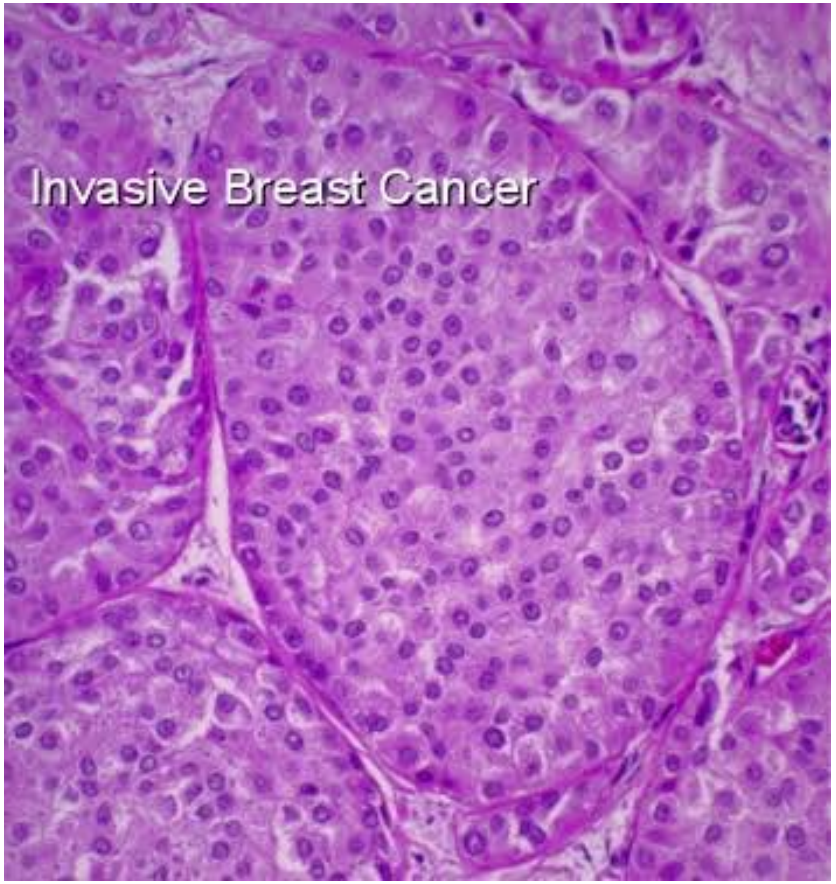




The importance of the CYP1A1/CYP1B1 ratio in-vivo is evident in the increased presence of 4-OH-E2 in breast cancer tissue compared to non breast cancer control

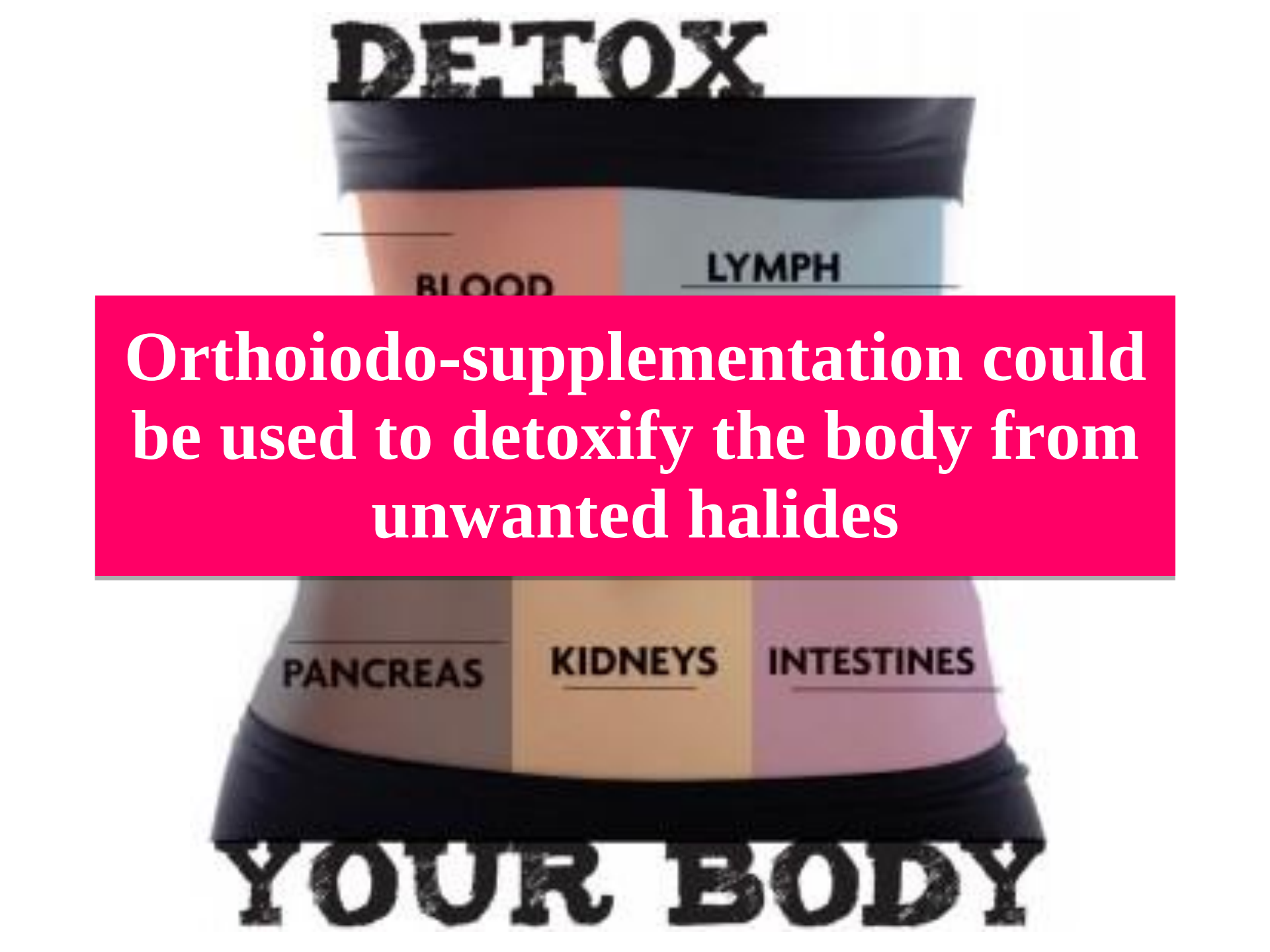
Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine. Frederick R. Stoddard, Ari D. Brooks, Bernard A. Eskin3, Gregg J. Johannes. Int J Med Sci 2008; 5(4):189-196.

Iodide-deficiency alters the structure and function of mammary gland alveolar cells and makes them highly sensitive to stimulation by estradiol



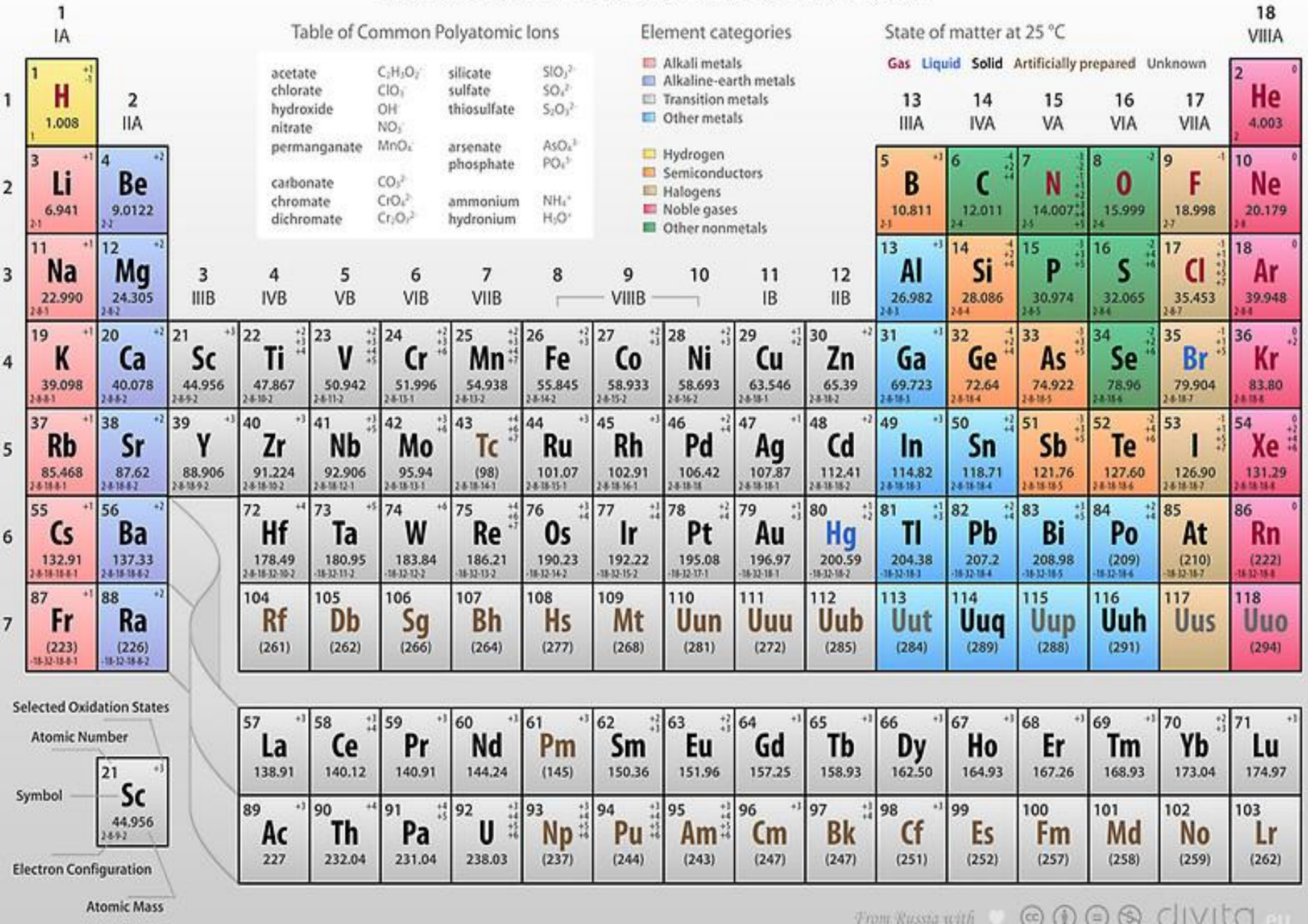
When rats are kept iodide-deficient, atrophy and necrosis takes place in the mammary gland and areas of dysplasia and atypia are seen. Administration of estradiol to iodide-deficient rats stimulates cell division in the gland and leads to the formation of alveoli. Continued stimulation by estradiol produces changes in the newly-formed alveolar cells. Their nucleoli are altered and show a separation of components.

Effect of iodide-deficiency on rat mammary gland. Strum JM.
Virchows Arch B Cell Pathol Incl Mol Pathol. 1979 May 31;30(2):209-20.

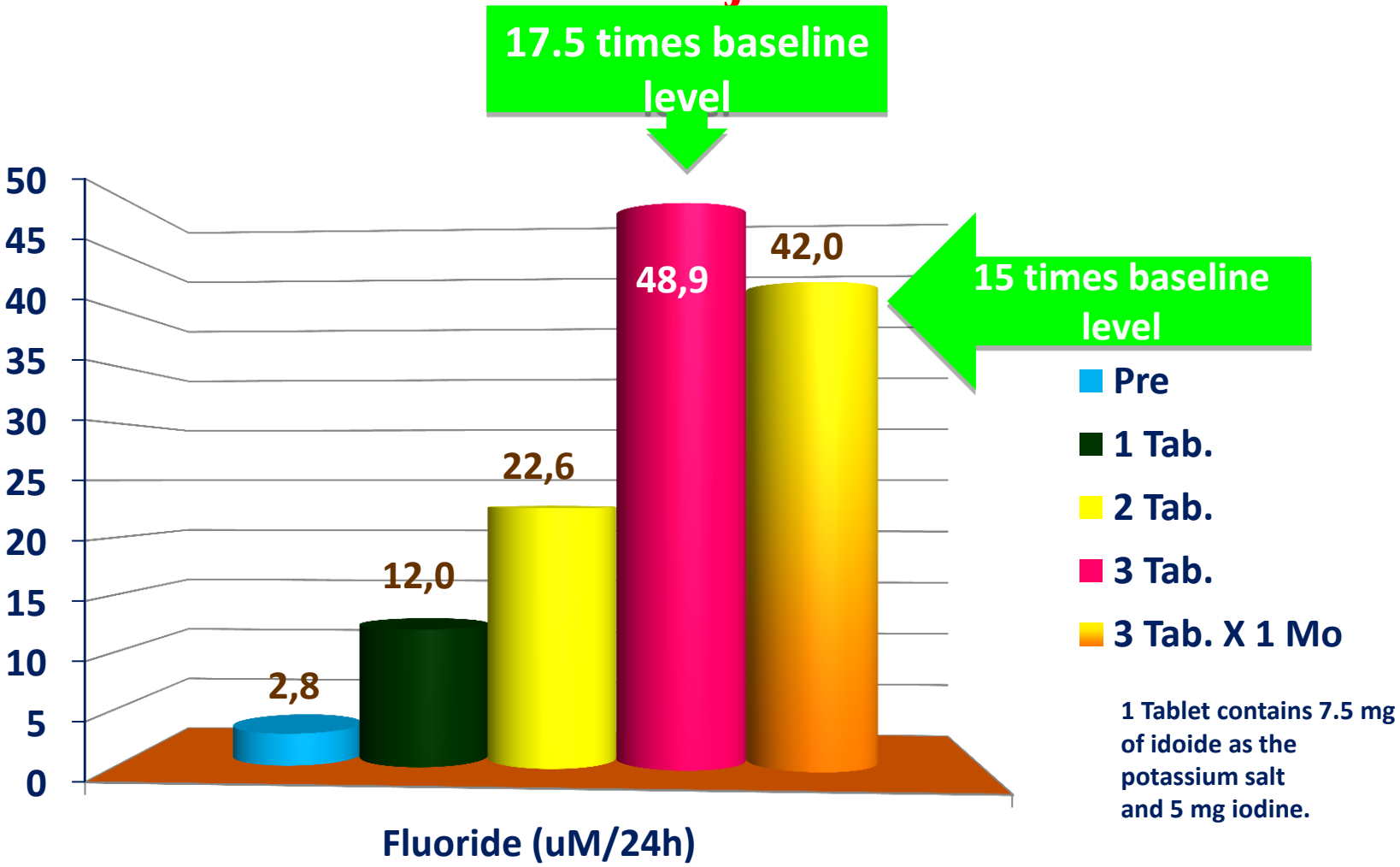


Orthoiodo-supplementation could be used to detoxify the body from unwanted halides

Mendeleev's Periodic Table of Elements



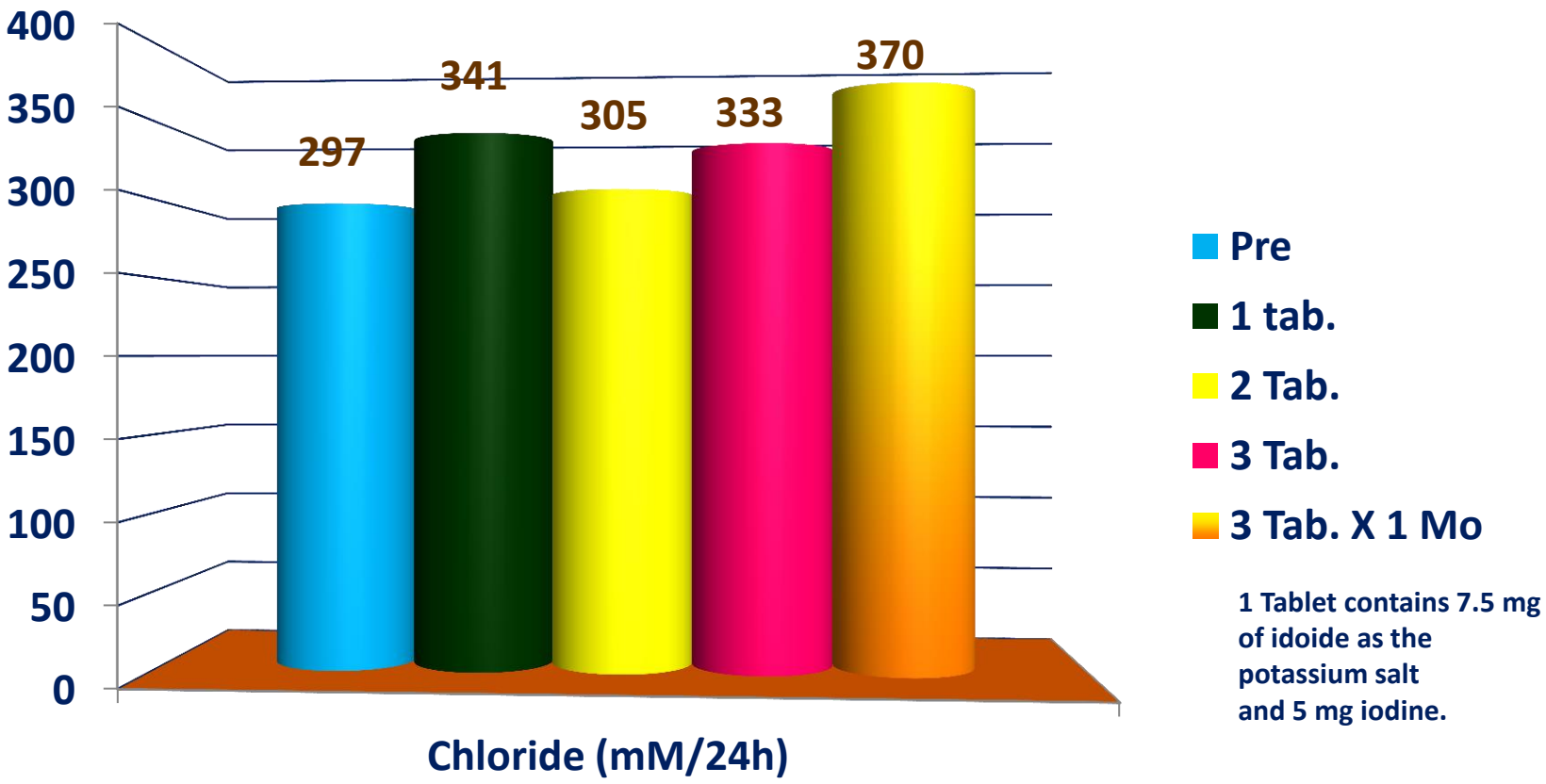
Effect of increasing intake of an Iodine/Iodide supplement, on urinary excretion of halides in a male subject.



These high levels persisted even after one month of supplementation at 3 tablets/day

Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al

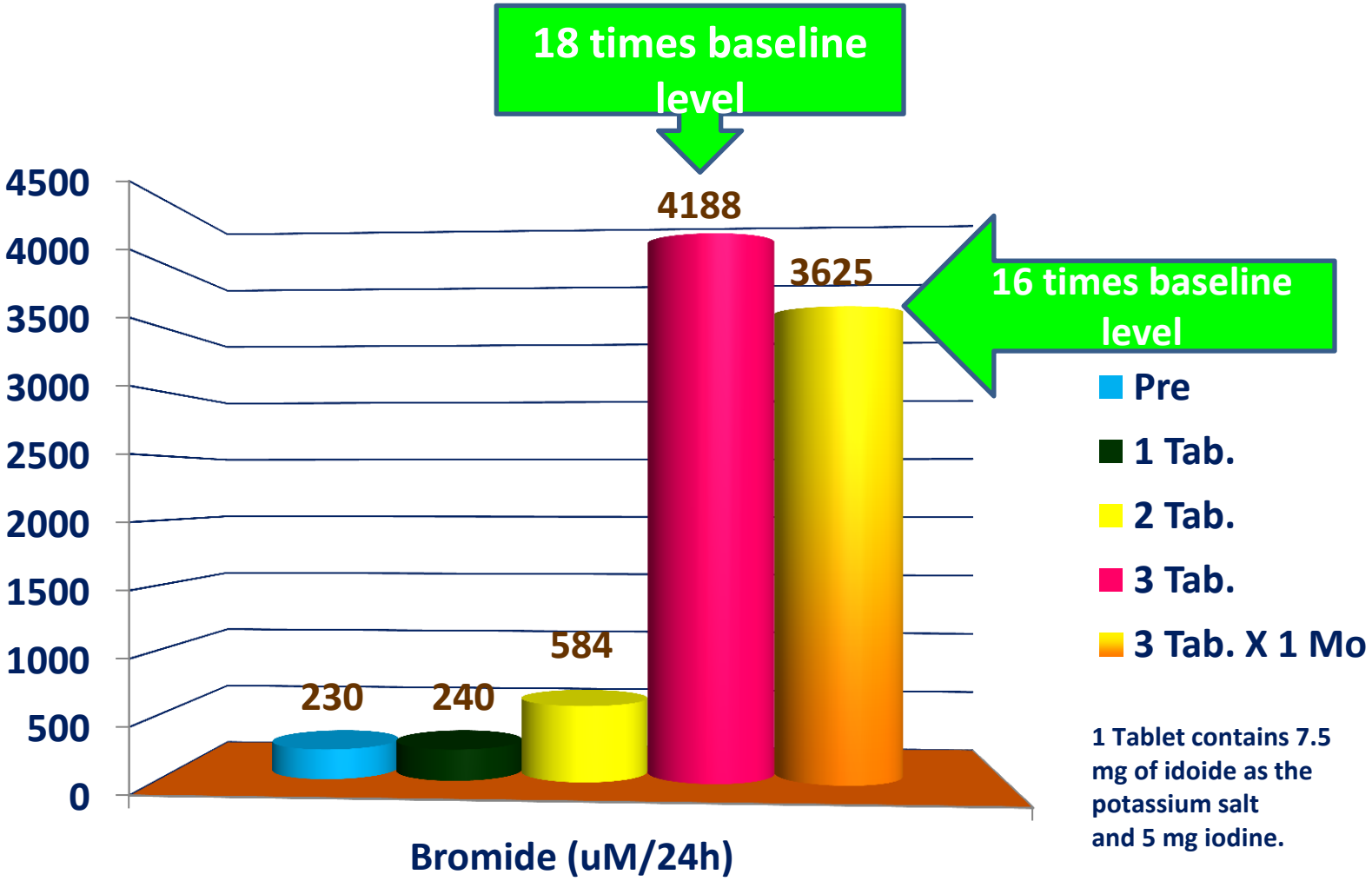
Effect of increasing intake of an Iodine/Iodide supplement, on urinary excretion of halides in a male subject.



1 Tablet contains 7.5 mg of idoide as the potassium salt and 5 mg iodine.

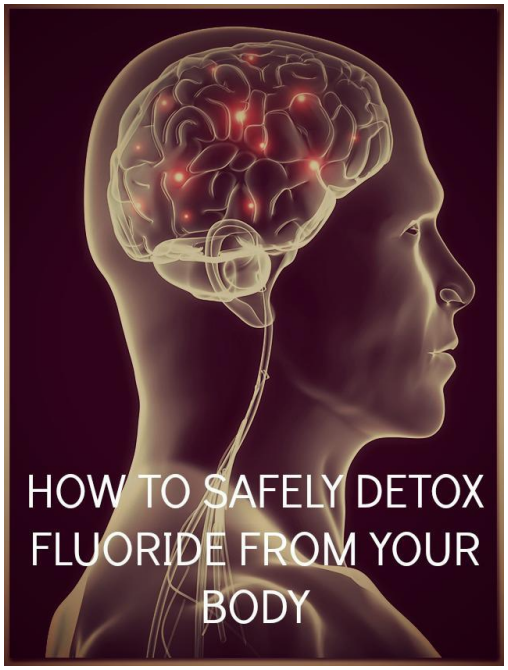
Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al

Effect of increasing intake of an Iodine/Iodide supplement, on urinary excretion of halides in a male subject.



Bromide concentration was 18.4 mg/24h, 3 times the ADI recommended by Van Leeuwen et al.

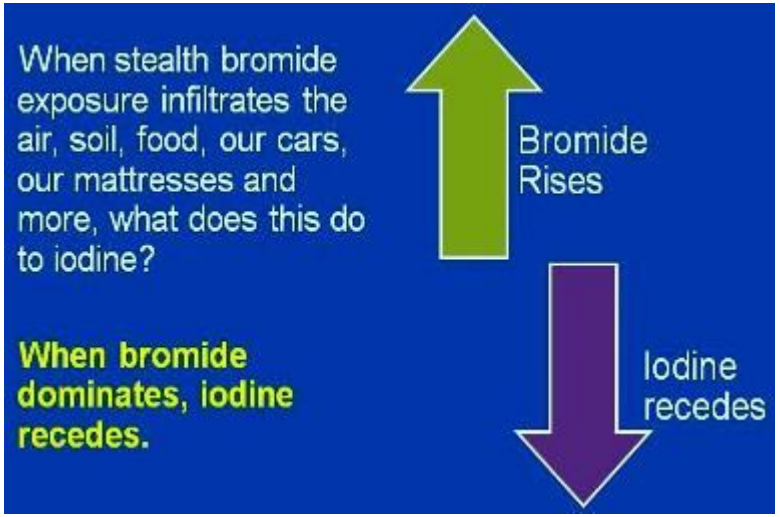
Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al



After one month, the estimated total amount of halide excreted was
24 mg fluoride
8700mg bromide.

It is unlikely that such large amounts of halides came from the thyroid gland.

It would seem that the whole body is being detoxified.



Orthoiodo-supplementation could be used under medical supervision to detoxify the body from unwanted halides in a manner similar to the use of EDTA for the detoxification of heavy metals.

Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al

Iodine-related bromide symptoms may include but are not limited to:

- eye lid twitching
- foot twitching
- tingling in hands or feet
- dark thoughts (e.g., there is no reason to live)
- depression (e.g., there is no reason to get out of bed)
- anxiety
- emotionality
- mouth and tongue sores and cuts or "sore mouth"
- "different" acne,"bromide acne," "acne-like eruptions" without "coniform." (Some iodine
- users found zinc helps bromide acne.)
- skin "cuts"
- hair loss
- brain fog
- leg and hip ache (feels like arthritis)
- rash (bromaderma)
- metallic taste
- sinus ache
- cherry angiomas
- runny nose
- headache
- sedation
- lethargy
- odd swallowing sensation (reported in old medical literature as "swollen glottis")
- body odor (bromos is Greek for stench)
- unusual urine odor
- dry mouth
- ureteral spasm, frequent urination (mistaken for urinary infection)

http://www.breastcancerchoices.org/bromidedetoxsymptomsandstrategies.html

Iodine-related bromide symptoms may include but are not limited to:

Bromide Uses

Pesticide
Computers
Some sodas
Some Gatorade
Fabrics
Dyes
Mattresses and furniture
Car interiors
Televisions

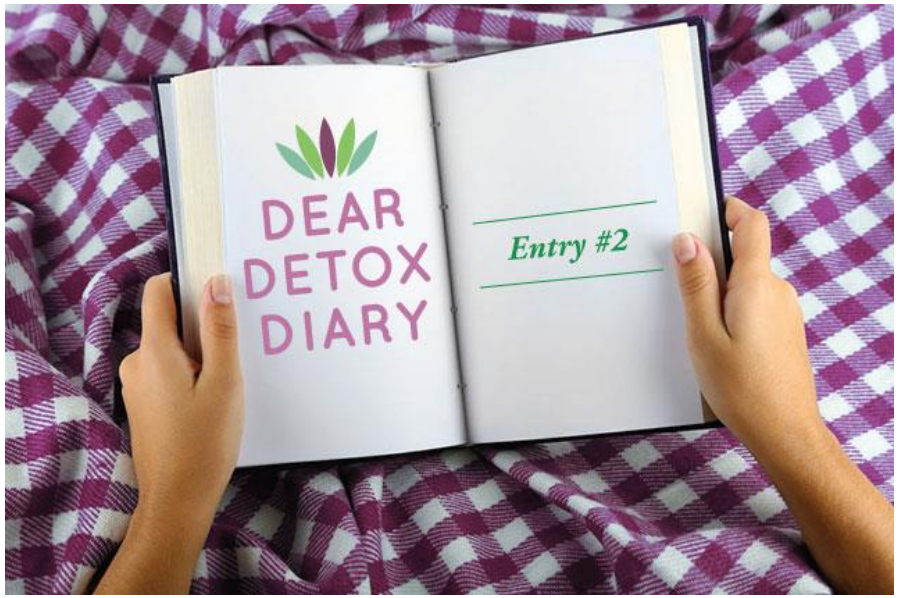
- Hot Tub Cleaners
- Some cosmetics
- Some Hair Products
- Extermination products
- Prescription drugs
- Cell Phones
- Fabric Softeners
- *Fire Retardants*

- **constipation**
- **vision changes**
- **irritability**
- **increased salivation**
- **dream changes**
- **hormone changes**
- **kidney pain**
- **breast tenderness (transient symptom reported to resolve)**

http://www.breastcancerchoices.org/bromidedetoxsymptomsandstrategies.html

Bromide Detox Strategies

- **1. Salt Loading.**
- **2. Stopping iodine for 48 hours to rest the kidneys.**
- **3. Reducing the iodine dose temporarily, then working back up.**
- **4. Taking several grams vitamin C spread out throughout the day along with the Iodine Companion Nutrients.**
- **5. Drinking more water.**
- **6. Pulse-dosing (stopping and restarting iodine therapy.)**
- **7. According to Iodine users with skin symptoms, adding 25 mg zinc often helps**



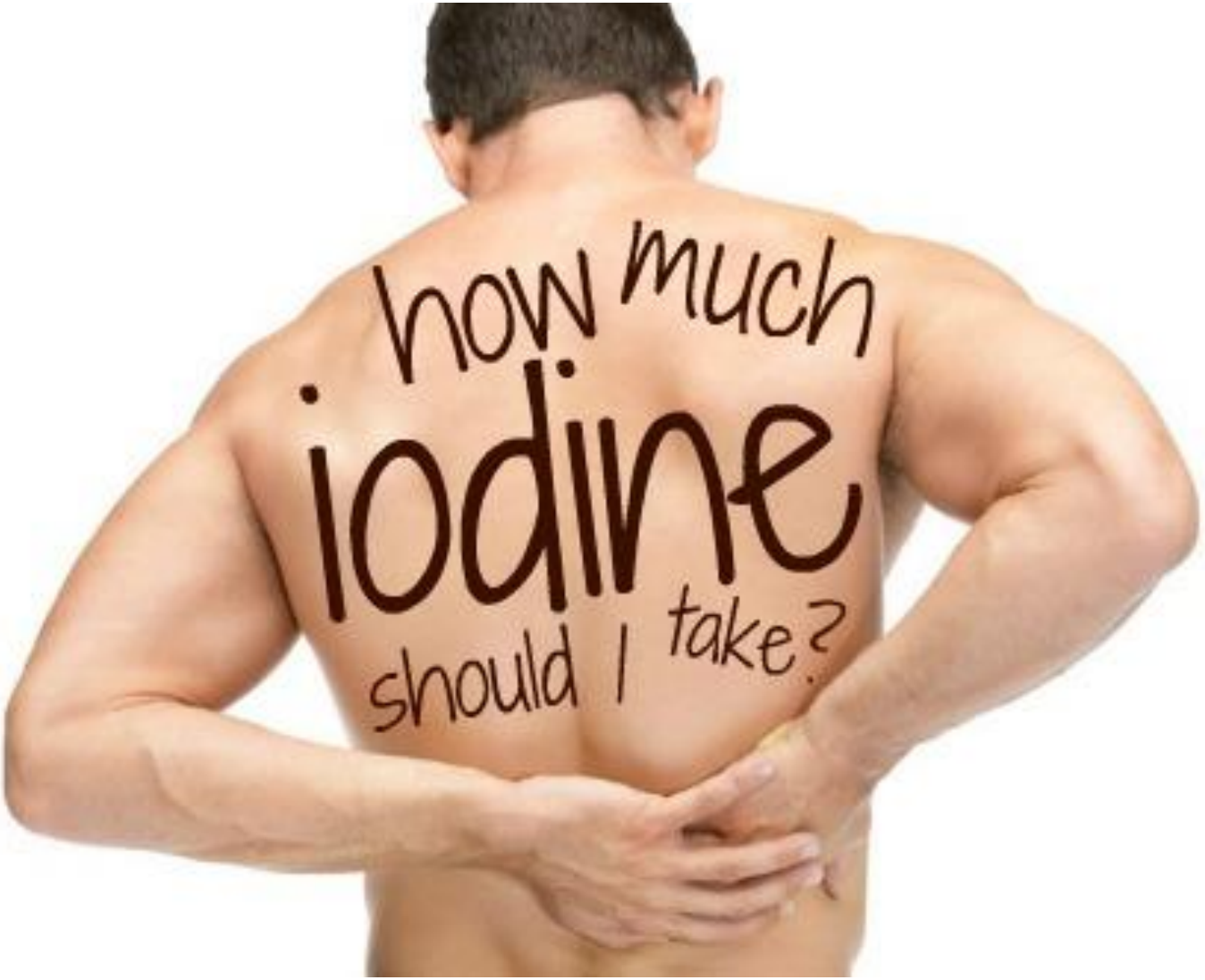
http://www.liveto110.com/dear-detox-diary-2/

Effect of increasing intake of an Iodine/Iodide supplement, on urinary excretion of halides in a male subject.

He did not reach iodine sufficiency even after one month on 3 tablets/day. Based on the results of the loading test, the body is considered iodine sufficient when at least 90% of the oral amount is excreted in the 24h urine collection. Urinary iodine levels in this subject were 149.6 uM/24h or 19 mg/24h representing only 51% of the dose.

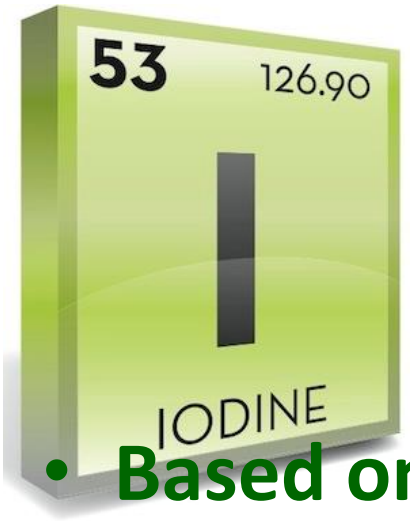
Iodide (uM/24h)

Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al


how much
iodine
should I take?

- **The RDA for iodine is based on the amount of iodine/iodide needed to prevent goiter, cretinism and hypothyroidism.**
- **The optimal requirement of the whole human body for iodine has never been studied.**

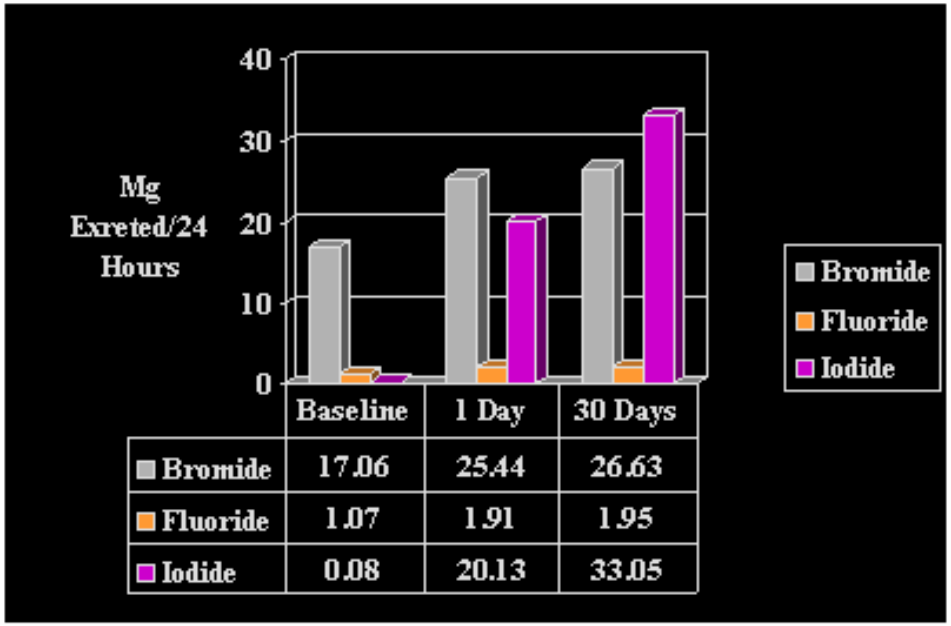
Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al



- **Based on a review of published data, we previously proposed that an amount of iodine 100 times the RDA would be required for iodine sufficient of the whole human body.**
- **This amount is equivalent to 2 drops of Lugol solution which contains 5 mg iodine and 7.5 mg iodide as the potassium salt.**

Abraham, G.E., et al, Othoiodosupplementation: Iodine Sufficiency of the Whole Human Body. The Original internist, 9:3041, 2002. Abraham, G.E., et al

Dr. Guy Abraham and his Colleagues have found the 24 Hour Iodine Loading test helpful in assessing a patient's iodine sufficiency.



	Baseline	1 Day	30 Days
Bromide	17.06	25.44	26.63
Fluoride	1.07	1.91	1.95
Iodide	0.08	20.13	33.05

Clinical Experience with Inorganic Non-radioactive Iodine/Iodide.
David Brownstein, M.D.

The principle is, if the body's level of iodine is adequate, most of the 50 mg iodine ingested at the start of the test will be excreted in the urine within 24 hours.

If the body shows insufficiency, a significant portion of the pre-test iodine dose will be retained by the body. The amount excreted in the urine will be low.

Doctor Abraham and his Colleagues find that any test result showing saturation lower than 90% suggests the patient is a candidate for iodine supplementation.

http://www.breastcancerchoices.org/loading.html


That's all Folks!
Any Question ?