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Iodine excess

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Several mechanisms are involved in the maintenance of normal thyroid hormone secretion, even when iodine intake exceeds physiologic needs by a factor of 100. The sodium–iodide symporter system contributes most to this stability. Faced with an iodine excess, it throttles the transport of iodide into the thyroid cells, the rate-limiting step of hormone synthesis. Even before the iodine symporter reacts, a sudden iodine overload paradoxically blocks the second step of hormone synthesis, the organification of iodide. This so-called Wolff–Chaikoff effect requires a high ($\geq 10^{-3}$ molar) intracellular concentration of iodide. The block does not last long, because after a while the sodium–iodide symporter shuts down; this allows intracellular iodide to drop below 10^{-3} molar and the near-normal secretion to resume. In some susceptible individuals (e.g., after radioiodine treatment of Graves' disease or in autoimmune thyroiditis), the sodium–iodide symporter fails to shut down, the intracellular concentration of iodide remains high and chronic hypothyroidism ensues. To complicate matters, iodine excess may also cause hyperthyroidism. The current explanation is that this happens in persons with goitres, for example, after long-standing iodine deficiency. These goitres may contain nodules carrying a somatic mutation that confers a 'constitutive' activation of the TSH receptor. Being no more under pituitary control, these nodules overproduce thyroid hormone and cause iodine-induced hyperthyroidism, when they are presented with sufficient iodine. These autonomous nodules gradually disappear from the population after iodine deficiency has been properly corrected. More recent studies suggest that chronic high iodine intake furthers classical thyroid autoimmunity (hypothyroidism and thyroiditis) and that iodine-induced hyperthyroidism may also have an autoimmune pathogenesis.

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The thyroid gland of human adults secretes about 80 µg thyroxine per day, corresponding to 52 µg iodine, an amount of iodine the gland must take up daily in order to remain in balance. It is generally assumed that in adults this is the case at a dietary iodine intake between 100 and 150 µg per day. Intakes of up to 600 µg per day in the European Union and 1100 µg per day in the United States are declared as tolerable for adults.¹ Therefore, higher values are, by definition, excessive, but the above cut-off figures are arbitrary, since most individuals tolerate higher intakes, while a few already have untoward effects at lower intakes. The average dietary iodine intake varies widely from one individual and one population to the other, and it may exceed 5000 µg per day, for example, in populations consuming seaweed.² Some responses of the thyroid to excess iodine occur only in glands with pre-existing pathology, while others are seen in apparently normal glands. Some effects occur at iodine intakes that are far in excess; others are observed at intakes that are above physiological needs, but below the tolerable doses as defined above. Finally, it must be recognised that identical iodine excess may cause hyperthyroidism in some persons and hypothyroidism in others.

This review is concerned not only with the effects of clearly excessive iodine intakes, but it will also discuss the effects of planned iodine supplementation that raises iodine intake from severely deficient to high-normal values. The present article updates previous reviews on how the thyroid gland reacts to excess iodine intakes and how it copes with it.^{3–5}

Mechanisms of the thyroid to counteract iodine excess

As outlined above, the spectrum of iodine excess is confusing: hypothyroidism or hyperthyroidism with or without goitre, euthyroid goitre and silent or manifest autoimmune thyroid disease. This bewildering spectrum can only be understood with the knowledge of the physiological and biochemical bases discussed in detail in the subsequent sections. In view of the many functions of thyroid hormone, it is not surprising that several mechanisms assure homeostasis of hormone secretion in the face of widely varying iodine intakes (Table 1).

Thyrotropin

Thyrotropin intervenes in many ways in the adaptation of the thyroid gland to varying iodine supply. The interaction is straightforward and easy to understand in the case of iodine deficiency: with increasing iodine deficiency, serum thyroxine decreases and serum TSH rises.^{6,7} In the case of iodine excess, the interaction appears more complex; for example, the decrease of the sodium–iodide symporter (NIS; see below) in iodine excess may be due to autoregulation, while its increase in iodine deficiency is TSH dependent. The subsequent sections discuss these complex interactions.

The sodium–iodide symporter (NIS)

The thyroid gland relies on a mechanism to accumulate iodide from plasma against a concentration gradient that can vary between 1:2 and 1:80, depending on whether the gland is quiescent or

Table 1

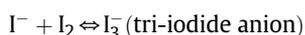
Overview of the different mechanisms that contribute to maintain (near) normal thyroid function in iodine deficiency and iodine excess. The dominant role of the sodium–iodide symporter (NIS) is evident. The contribution ranges from 0 (none) to +++ (important). TSH is not listed; it interacts in a complex way with these mechanisms. See text for details.

	Role in iodine excess	Role in iodine deficiency
Sodium-iodide symporter	+++	+++
Wolff-Chaikoff effect	+++ (Only in acute short excess)	0
Block of hormone secretion from stores	++	0
Redistribution of organic iodine in colloid	+	++
Secretion of non-hormonal iodine	++	0

stimulated.^{8,9} A special glycoprotein located in the basal cell membrane of thyrocytes accomplishes this astonishing feat. This NIS ('iodide pump') loads itself with two sodium cations and one iodide anion at the exterior surface of the basal cell membrane. Driven by the electrochemical Na⁺ gradient, it transports its load across the basal cell membrane from the exterior into the interior of the cell.¹⁰ The NIS system is highly adaptable and contributes by far the most to a constant hormone secretion over a wide range of iodine supply.^{11,12} In the thyroid of iodine-deficient rats, it maintains an iodide gradient (extracellular: intracellular) of 1:60 when the pituitary is intact, compared with 1:5 after hypophysectomy, attesting to pituitary control of NIS in iodine deficiency.⁸ TSH stimulation of NIS probably operates through the insulin/phosphoinositid-3-kinase pathway.¹³ On the other hand, excess iodine throttles NIS by autoregulation (see next section below). It is no exaggeration to say that, for any given level of iodide intake, the activity of NIS determines the intracellular iodide concentration, and therefore NIS plays a role in virtually every subsequent metabolic step of iodine within the thyroid.

The Wolff–Chaikoff effect

A single injection of 500 µg of iodide in the rat (a dose exceeding the daily iodine requirement by a factor of 100) paradoxically blocks incorporation of iodide into the tyrosyl residues of thyroglobulin – the first step in thyroid hormone biosynthesis (organification).¹⁴ This TSH-independent autoregulatory block (called the Wolff–Chaikoff effect) relies on a high ($\geq 10^{-3}$ molar) intracellular concentration of iodide^{15,16}; its exact biochemical mechanism remains controversial. It could be explained by the following tri-iodide reaction:



At high iodide concentration, this reaction is pushed to the right by mass action and thereby sequesters I₂, the latter supposedly being an intermediary in the organification of iodide.³ Interference by iodide with the active site of thyroid peroxidase^{17,18} or with the production of inositol triphosphate and Ca²⁺ as messengers of TSH action¹⁹ are the other possible mechanisms of the Wolff–Chaikoff block. The Wolff–Chaikoff block is short lived, because the biosynthesis of NIS is rapidly shut down, intracellular iodide drops below 10⁻³ molar and organification of iodine resumes.^{10,20} This impressive drop in the NIS activity occurs by a TSH-independent autoregulation^{8,16,17,20–25}, which appears to operate at the transcriptional and/or post-transcriptional level.^{17,23,24}

Block of hormone secretion from colloid stores

In the follicular lumen, the thyroid gland stores a large quantity of hormone in the form of thyroxyl residues of thyroglobulin. When hormone synthesis is blocked, for example, by a thio-urea drug, hormone secretion drops only after significant amounts of this stock are used up; this takes several weeks in human. By contrast, excess iodine lowers serum thyroxine almost instantaneously; this suggests that it not only blocks synthesis (the Wolff–Chaikoff effect proper), but also blocks secretion of stored preformed hormone. In human, this effect is particularly pronounced and prolonged in stimulated glands, and it explains the rapid action of high doses of iodine in Graves' disease.^{3,25–27} This secretory block may operate through adenylate cyclase, one of the messenger systems for TSH.^{19,28,29}

Redistribution of organic iodine

In the first steps of hormone synthesis, tyrosyl residues of thyroglobulin are iodised to mono-iodotyrosyl (MIT), then to diiodotyrosyl (DIT). In the final reaction, DIT couples with another DIT to thyroxine (T4; four iodine atoms per molecule) or with a MIT to triiodothyronine (T3; three iodine atoms). In iodine abundance, DIT predominates over MIT, which favours T4 biosynthesis, the latter being hormonally less active than T3. Thus, a euthyroid state is maintained despite an increased amount of iodine taken up by the gland.^{30–32} This mechanism is probably of some importance in the

case of iodine excess as well as in iodine deficiency; in the latter case, it favours T3 over T4 synthesis and thereby assures euthyroidism at lesser expense in iodine.

Secretion of non-hormonal iodine

As outlined above, MIT, DIT, T3 and T4 are all part of thyroglobulin, which is stored in the form of colloid in the follicles. For T3 or T4 secretion, thyroglobulin is hydrolysed to its constituent amino acids. MIT and DIT are also set free as non-hormonal by-products, and their iodine can be secreted as non-hormonal iodine (mostly iodide), thereby ridding the gland of excess iodine.^{27,32–34}

Consequences of iodine excess

Iodine excess in persons with a normal thyroid gland

Most persons tolerate a chronic excess of 30 mg up to 2 g iodide per day, without clinical symptoms, but a detailed analysis reveals a persistent drop of serum T4 and T3 of 25% and 15%, respectively, and a rise of TSH of 2 mU⁻¹; all values, though, remain well within the normal range, and there are no clinical signs of thyroid dysfunction or goitre, even though sonographic thyroid volume is slightly increased.^{25,35–39} Formal dose–effect studies have not been performed, but slight changes of TSH and T4 have already been observed after administration of 500 µg iodide daily for 28 days.

Thus, the adaptation of the normal thyroid gland to iodine excess is good, though not perfect, since T4 and TSH values suggest a slight decrease in thyroid hormone secretion. The main adaptation to iodine excess is by NIS, the other mechanisms listed in [Table 1](#) each contributing its share.

Iodine-induced hypothyroidism

Sometimes the above regulatory mechanisms fail and iodine excess causes frank clinical hypothyroidism. The following states predispose to iodine-induced hypothyroidism:

- Graves' disease after treatment with radio-iodine or partial thyroidectomy⁴⁰, but not after anti-thyroid drug treatment⁴¹
- After partial thyroidectomy for benign nodules⁴²
- In the presence of autoimmune thyroiditis, whether classical Hashimoto's disease or the post-partum variant.^{43,44} Even minimal doses of iodine (250 µg per day) cause hypothyroidism in 20% of patients^{45,46}

The common denominator of the states predisposing to iodine-induced hypothyroidism probably is a slightly elevated TSH or persistent thyroid-stimulating antibodies, which keep the NIS activated and intra-thyroidal iodide concentration high, thereby preventing an escape from the Wolff–Chaikoff effect.

Iodine-induced hyperthyroidism (IIH)

Even modest increases in iodine supply can trigger hyperthyroidism in some individuals. The phenomenon was the main argument of opponents of iodised salt in the 1920s in Switzerland, but a careful search for IIH cases was at that time negative, probably because iodine supplementation by salt was started at the very low dose of 3.75 parts per million.⁴⁷ That the argument was not to be taken lightly was realised decades later, when ill-conceived supplementation through iodised salt in Zimbabwe and eastern Zaire (The Democratic Republic of Congo) resulted in a significant number of cases of severe and long-lasting IIH.^{48,49} Although this form of hyperthyroidism occurs already at iodine intakes below 300 µg per day (i.e., by far not fulfilling the criteria of excess iodine as defined above), its pathogenesis will be discussed here.

The pathogenesis of IIH was clarified in a classical study: four euthyroid patients with a single autonomous nodule from the slightly iodine-deficient Brussels region received a supplement of 500 µg iodide daily. This caused a slow but constant increase of thyroid hormone and after 4 weeks the patients had become hyperthyroid.⁵⁰ Later studies confirmed the initial interpretation that the nodules were originally kept in check by the low iodine intake; having escaped from TSH controls, they produced excess hormone when presented with enough iodine. The escape of the nodules from TSH control is due to a 'constitutive' somatic mutation of the TSH receptor in the nodules, which keeps it activated even in the absence of TSH.^{51,52} This form of IIH was originally seen mainly in persons who harbour nodular goitres, that is, predominantly in elderly people after long exposure to iodine deficiency. The nodular goitres disappear slowly after iodine supplementation and the incidence of hyperthyroidism decreases over the years.^{53,54} Interestingly, persons with multinodular goitres residing in iodine-replete Boston reacted the same way, but much higher doses of iodine (up to 180 mg) were required.⁵⁵

Recent data have suggested that autonomous nodules are not the only pathogenetic explanation for IIH. Denmark, a moderately iodine-deficient country, introduced iodised salt at a dose that was calculated to increase iodine intake by only 50 µg per day. Unexpectedly, the increased incidence rate of hyperthyroidism was found mainly in the 20- to 39-year olds (where nodules are rare), and it was attributed to thyroid autoimmune disease.⁵⁶ Others have observed IIH in entirely normal glands.^{57,58} A review concluded that IIH may occur in endemic goitre, non-endemic goitre, after Graves' disease, and in patients with a normal thyroid gland.⁴

Three years after starting supplementation with iodised salt in China, the prevalence of overt hyperthyroidism in three regions was 1.6%, 2.0% and 1.2%, irrespective of whether the achieved iodine supplementation was mildly deficient (population refused to use iodised salt), more than adequate (population used the prescribed iodised salt) or excessive (population consumed iodised salt in addition to iodine containing drinking water).^{59–61} The study began only after iodine supplementation had been given for 3 years. Therefore, it does not allow estimating the incidence of IIH during the first 3 years of supplementation. In the same three communities, the cumulative 5-year incidences of overt hyperthyroidism for the 4th to 8th year of supplementation were 0.4%, 1.2% and 1.0%. At first glance, this seems to indicate a very low risk of IIH, if any; however, it must be cautioned that the calculated 1-year incidence rates, namely 80, 240 and 200 per 100 000 per year, are much higher than the figures published in other countries.⁶²

Iodine supplementation and autoimmune thyroid disease

When mice of an autoimmunity-prone strain are first fed an iodine-deficient diet, and then switched to iodine excess, they dose-dependently develop ultrastructural thyroid cell damage suggesting autoimmune disease.⁶³ Large epidemiologic studies performed in the past decade in China, Turkey and Denmark suggest that supplementation with iodised salt increases the prevalence of autoimmune thyroid disease, be it clinical or subclinical hypothyroidism^{59,61}, or autoimmune hyperthyroidism⁵⁶ or both.⁶⁴ The phenomenon was dose-dependent: at three urinary iodine excretion levels (marginally low/more than adequate/excessive), the prevalence of subclinical hypothyroidism was 0.9%, 2.9% and 6.1%. Even though other studies found no effect of iodine supplementation on thyroid autoimmunity⁶⁵, the findings call for keen attention to avoid unnecessarily high iodine supplementation.

Iodine excess by organic iodine compounds

Topical disinfectants, radiographic contrast agents and certain drugs contain large amounts of iodine in organic form. In addition to having potentially the same effects as inorganic iodine, such as hyper- and hypothyroidism⁶⁶, they may have drug-specific effects. The anti-arrhythmic drug amiodarone and the contrast agent iopanoic acid both block the peripheral conversion of T₄ to T₃ and interfere with the binding of T₃ to its nuclear receptors.^{67,68} The thyroidal side effects of these compounds are very complex and out of the scope of the present article. For amiodarone, the reader is referred to a recent review.⁶⁹

Practice points

- Iodine excess may (but must not) be associated with hyperthyroidism, euthyroidism or hypothyroidism, all of them goitrous or non-goitrous.
- Thus, there are no clinical clues specifically pointing to iodine induction of a thyroid disturbance.
- A low radio-iodine uptake should raise suspicion, but this test has lost its status as a routine function test, since ultrasonography allows morphologic imaging of the gland without use of radioisotopes. Nonetheless, the test may be useful in certain cases: a low radioiodine uptake may (but must not) occur in moderate iodine excess, such as by iodised salt; it may also be typical for de Quervain's giant-cell thyroiditis, a condition unrelated to iodine intake. Moreover, the scintiscan may distinguish between hyperfunctioning or 'cold' nodules.
- A history searching for intake of iodine-containing substances (see below) is recommended in every patient with a thyroid disturbance.
- A high urinary excretion of iodine in a spot urine sample is the ultimate proof of iodine excess, but it is performed only by few laboratories involved in epidemiological research.

Roti⁷⁰ has compiled an exhaustive list of substances involved in iodine excess; frequent offenders are:

- Iodine-containing drugs, amiodarone being the prime offender. Older asthma syrups (may contain potassium iodide as a secretolytic).
- Iodopovidone, used for topical disinfection.
- Seaweed preparations containing up to 2 mg iodine per gram in protein-bound form available in dried form in health-food shops and popular parts of the diet in coastal regions of Japan.²
- Contrast agents for conventional radiography or computer tomography. Radiologists use up to 100 g or more of iodine in complex organic molecules. The iodine of most preparations is rapidly excreted.
- Erythrosine (food additive E127) containing 57% iodine and used, for example, to improve the colour of canned cherries or of candies.
- Iodised salt; (over-iodised by inadvertence).

Research agenda

- Meta-analysis of epidemiological studies searching for an explanation for the reported widely differing incidences of IIH after introduction of iodised salt.
- Studies to understand how an increasing iodine intake promotes incidence and prevalence of thyroid autoimmunity.

In summary

- The thyroid gland disposes of several control mechanisms to keep its hormone secretion constant, despite varying iodine intake.
- The most potent and flexible mechanism is provided by the sodium-iodide symporter, which controls the limiting step of thyroid hormone synthesis, namely the transfer of iodide from the extra- to the intracellular compartment.
- Other mechanisms are an immediate, albeit short-lived, block of iodine organification after a sudden massive iodine excess (the Wolff–Chaikoff effect), an equally short-lived arrest of thyroid hormone secretion from stores in the colloid, a preferential secretion of the less active T4 over T3, and dumping of excess iodine by secreting it in non-hormonal form.

- TSH participates in the control by interacting in a complex manner with these mechanisms.
- While most individuals suffer no disturbance from iodine excess, some persons develop thyroid dysfunction despite the manifold control systems.
- Iodine excess may cause hyperthyroidism, hypothyroidism, euthyroid goitre or thyroid autoimmunity.
- These effects are usually not only seen at iodine intakes vastly in excess, but may also occur near the upper recommended limit of 200 µg iodine per day.
- The iodine-induced disturbances are easily managed, and most are transient.
- IIH, in particular, disappears from the population within a few years of properly dosed iodine supplementation.
- Risk–benefit analysis clearly is in favour of iodine supplementation, but at the same time speaks for a careful dosing, avoiding median intakes above the upper recommended level.

Conflicts of interest

None.

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