J. Pharm. Pharmacol. 1999, 51: 745–750
Received November 5, 1998
Accepted January 13, 1999

Influence of Dietary Iodine on Drug-induced Hypothyroidism in the Rat

M. L. BEYSSEN, J. F. LAGORCE, D. CLEDAT* AND J. BUXERAUD

*Department of Chemical Pharmacy and *Department of Analytical Chemistry, Faculty of Pharmacy, 87025 Limoges, France*

Abstract

Several compounds of pharmaceutical importance from a variety of chemical families, for example chlorpromazine and clomipramine, have been found to form charge-transfer complexes with iodine. We have investigated the influence of dietary iodine on thyroid-gland dysfunction induced by clomipramine, chlorpromazine or 2-thiazoline-2-thiol. We suggest that iodine is partly diverted from its metabolic pathway by complexation with drugs, and so the urinary concentration of iodide is increased.

Both chlorpromazine and clomipramine, at doses which do not inhibit thyroperoxidase, enhanced urinary iodine excretion when dietary iodine was restricted ($3{\cdot}94 \pm 0{\cdot}96\ \mu g$/day for chlorpromazine-tested rats, $3{\cdot}43 \pm 1{\cdot}33\ \mu g$/day for clomipramine-tested rats, compared with $2{\cdot}34 \pm 0{\cdot}11\ \mu g$/day in control rats). Concurrently, these pharmaceutical compounds increased the level of free thyroid-stimulating hormone (TSH) in comparison with controls and induced histological modifications in, and enlargement of, the thyroid gland.

We have demonstrated that drug-induced loss of iodine in the urine was associated with antithyroid action when iodine intake was limited.

Iodine plays a central role in thyroid physiology, being both a constituent of thyroid hormone and a regulator of thyroid gland function (Taurog 1991; Sundick et al 1992; Visser 1996). The metabolic activity of the thyroid gland of healthy individuals is disrupted by dietary iodine deficiency and by a variety of chemical compounds, especially those that inhibit thyroperoxidase. Many other compounds have been found to affect thyroid hormone synthesis without interfering directly with thyroperoxidase (Gaitan 1988; Capen 1992; Gittoes & Franklyn 1995). In previous studies (Raby et al 1990; Comby et al 1994; Lagorce et al 1995) we showed that many drugs which inhibit thyroperoxidase form charge-transfer complexes with iodine. If these molecules, which are also strong electron-donors, accumulate in the thyroid gland they would tend to sequester iodine, thereby mimicking iodine deficiency.

Because of the general increase in hypothyroidism, we wondered whether the administration of certain drugs, which have been shown to form charge-transfer complexes with iodine in-vitro, might induce iatrogenic thyroid disorder. We have studied three molecules with high formation constants for charge-transfer complexes with iodine (Table 1) but different activity towards thyroperoxidase: 2-thiazoline-2-thiol, an inhibitor of thyroperoxidase, clomipramine, devoid of action on thyroperoxidase, and chlorpromazine, a potential activator of thyroperoxidase (Gutmann & Keyzer 1967; Raby et al 1990; Thomes et al 1992; Kelder et al 1994).

Correspondence: J. F. Lagorce, Department of Chemical Pharmacy, Faculty of Pharmacy, 2 rue du Docteur Marcland, 87025 Limoges, France.

Materials and Methods

Animals, diets and treatments

Female Wistar rats were purchased from Iffa Credo (Lyon, France). Directly after weaning (at the age of 3 weeks), the rats were allocated to five groups. They were all housed under standard conditions but the groups were maintained on different diets or schedules as specified in Table 2.

LID rats received iodine-deficient pellets (modified Remington diet; UAR, Essone, France) and had free access to distilled water.

Table 1. Formation constants and lactoperoxidase activity.

	2-Thiazoline-2-thiol	Chlorpromazine	Clomipramine
Formation constant for complex[a] ($L\,mol^{-1}$)	2·527	3·168	4·545
Amount of drug inhibiting lactoperoxidase by 50%	0·13 mM	Activation	0[b]
Reference	Thomes et al (1992)	Raby et al (1990)	Raby et al (1990)

[a]Determined using Lang's method in CCl_4 at 20°C. [b]Without activity on lactoperoxidase.

Table 2. Codes used for dose-regimen schedules.

Code	Pellets	KI content of distilled drinking water
LID	Iodine-deficient pellets	0 $mg\,L^{-1}$
LID/KI	Iodine-deficient pellets	0·5 $mg\,L^{-1}$
COD	Conventional pellets	0 $mg\,L^{-1}$
EID	Conventional pellets	6·5 $mg\,L^{-1}$

LID/KI rats received iodine-deficient pellets and an iodine supplement of 0·5 $mg\,L^{-1}$ KI in the distilled drinking water. On this regimen, iodine intake was just sufficient to cover the needs of the organism.

COD rats received conventional pellets (AO4 diet; UAR, France) and distilled water.

EID rats received conventional pellets, with an iodine supplement of 6·5 $mg\,L^{-1}$ KI in distilled drinking water. LID then LID/KI rats received iodine-deficient pellets for three weeks with 1% $KClO_4$ in the drinking water; the diet was changed to LID/KI for four weeks.

Drugs were administered orally (10 $mg\,kg^{-1}$/day 2-thiazoline-2-thiol, chlorpromazine or clomipramine) to the different groups. Further experiments were conducted with 100 $mg\,kg^{-1}$/day 2-thiazoline-2-thiol on LID/KI rats, and with 10 or 100 $mg\,kg^{-1}$/day 2-thiazoline-2-thiol on LID then LID/KI rats.

The rats were killed by aortic exsanguination under ether anaesthesia. Serum was prepared for assay of triiodothyronine, tetraiodothyronine and thyroid-stimulating hormone (TSH). Thyroid glands were removed, weighed, and cut into 5-μm sections for histological examination.

Assay of iodine

Urine was collected for 24 h from rats in metabolic cages designed for animals of less of 300 g. The collection receptacle was carefully washed and rinsed with distilled water to eliminate possible traces of iodide, then heated to dryness. To eliminate daily fluctuations linked to factors external to the experimentation, urine was collected from a representative individual from each group.

Urinary iodine was determined by photometry based on the Sandell–Kolthoff reaction (Sandell & Kolthoff 1937), by use of a modified method described by Dunn et al (1993). Urine was digested with hydrochloric acid under mild conditions and iodine was determined manually from its catalytic activity on the reduction of ceric ammonium sulphate in the presence of arsenious acid. The reaction was stopped by adding brucine.

Hydrochloric acid solution (Benotti & Benotti 1963), arsenious acid solution and ceric ammonium sulphate solution (Dunn et al 1993) were prepared with Sigma-Aldrich (France) reagents and deionized water. Standard KI solutions containing 2, 5, 10, 15 and 20 μg iodine dL^{-1} were prepared from KI solution containing 1 μg elemental iodine mL^{-1} deionized water. The solution of brucine (Fluka) was prepared by dissolving brucine dihydrate (500 mg) in acetic acid (0·3%, v/v; 100 mL) (Gökmen & Dagh 1995).

Hydrochloric acid solution (750 μL) was added to urine (250 μL) and the mixture was incubated at 110°C for 50 min. Arsenious acid solution (1·75 mL) was added to the digested urine (400 μL) and left to stand for 15 min (approx.). Ceric ammonium sulphate solution (175 μL) was then added to each tube and rapidly vortex-mixed. Additions were performed at 10-s intervals. Exactly 25 min after addition of the ceric ammonium sulphate, brucine solution (1·25 mL) was added and the absorbance at 405 nm determined by spectrophotometry (Perkin-Elmer).

The analytical results were in line with those reported by other workers using different methods (Dunn et al 1993; May et al 1997). Accuracy and precision were sufficient for experimental monitoring purposes and urinary metabolites did not interfere with the iodine determination.

Thyroid endocrine status

Serum TSH levels were quantified using by use of TSH-specific enzymeimmunoassay kits

(Amersham). Concentrations of free triiodothyronine and tetraiodothyronine were determined in the hospital clinical biochemistry laboratory by use of radioimmunoassay kits.

Histology

Sections of thyroid gland were stained with haematoxylin, eosin and safran and examined under the microscope for histological changes and for mononuclear cell infiltration and follicular destruction. A pathological index was defined according to the criteria of Carayanniotis & Rao (1997).

Statistics

Results were expressed as means ± s.e.m. and tested for significant differences by analysis of variance or the Mann–Whitney *U*-test.

Results

Urinary iodine excretion

For rats on the LID diet, urinary iodine was below the detection threshold of our method. There was no interference between any of the three drugs and the assay. No change in urinary iodine levels was observed for rats on the COD or EID diets after administration of 2-thiazoline-2-thiol, chlorpromazine and clomipramine. Iodine excretion was 3·9 and 54 μg/day, respectively, for COD and EID rats.

For rats on the LID/KI regimen, urinary iodine was significantly increased by the drug treatment compared with control levels (Table 3). This increase was most marked at the high doses of 2-thiazoline-2-thiol, but there was no direct dose-dependence. The amount of iodine excreted was thought to have been limited by the availability of molecular iodine.

Table 3. Urinary iodine levels (μg/day) of rats maintained on iodine-deficient pellets with an iodine supplement of 0·5 mg L^{-1} KI in the distilled drinking water (LID/KI), after 3 and 6 weeks.

Drug	Dose (mg kg^{-1}/day)	Third week	Sixth week
Control	–	2·55 ± 0·14	2·34 ± 0·11
2-Thiazoline-2-thiol	10	3·77 ± 0·69*	3·78 ± 0·96*
2-Thiazoline-2-thiol	100	4·18 ± 0·56*	4·55 ± 1·02*
Chlorpromazine	10	3·83 ± 1·06*	3·94 ± 0·96*
Clomipramine	10	3·22 ± 1·04*	3·43 ± 1·33*

*$P < 0·05$ compared with control. Means and s.e.m. are given for 6 animals/group.

Table 4. Urinary iodine excretion (μg/day) of rats maintained on iodine-deficient pellets for three weeks initially with 1% $KClO_4$ in the drinking water and with distilled water containing 0·5 mg L^{-1} KI.

Drug	Dose (mg kg^{-1}/day)	Fourth week	Sixth week
Control	–	2·46 ± 0·79	2·44 ± 0·27
2-Thiazoline-2-thiol	10	3·77 ± 0·56*	3·96 ± 0·66**
2-Thiazoline-2-thiol	100	3·19 ± 0·66	3·12 ± 0·58*

*$P < 0·05$, **$P < 0·001$ compared with control. Means and s.e.m. are given for 6 animals/group.

Table 5. Thyroid/body index weight (mg/100 g) and serum-free triiodothyronine and tetraiodothyronine levels (pg mL^{-1}) of rats maintained on iodine-deficient pellets with an iodine supplement of 0·5 mg L^{-1} KI in the distilled drinking water (LID/KI).

Drug	Thyroid/ body index	Tetraiodo-thyronine	Triiodo-thyronine
Control	6·82 ± 0·73	5·65 ± 0·71	4·42 ± 0·26
2-Thiazoline-2-thiol	8·79 ± 0·93**	3·47 ± 0·58**	4·75 ± 0·34
Chlorpromazine	8·71 ± 0·42**	6·12 ± 1·65	5·67 ± 0·67
Clomipramine	8·71 ± 0·62**	6·32 ± 1·69	5·40 ± 0·48

**$P < 0·001$ compared with control. Means and s.e.m. are given for 6 animals/group.

When rats received iodine-deficient pellets for three weeks with 1% $KClO_4$ in the drinking water, and then 0·5 mg L^{-1} KI in the distilled water (LID then LID/KI), 2-thiazoline-2-thiol at 10 mg kg^{-1}/day induced a significant increase in urinary iodine (Table 4). The levels were not statistically different from values obtained without preliminary processing by an inhibitor of the iodide pump. Hypothyroidism induced by ingestion of $KClO_4$ (Saito et al 1983) or the strong inhibition of thyroperoxidase by 100 mg kg^{-1}/day 2-thiazoline-2-thiol (Thomes et al 1992) did not lead to any notable increase in urinary iodine.

Thyroid weight

The thyroid/body index weight of animals maintained on LID, COD or EID did not change after gavage with chlorpromazine or clomipramine. The index was significantly increased for animals maintained on LID/KI (Table 5). The thyroid/body index weight increased for animals treated with 2-thiazoline-2-thiol irrespective of the diet (Table 6).

Thyroid endocrine status

TSH levels in LID, COD and EID rats were, after treatment with chlorpromazine or clomipramine,

Table 6. Thyroid weight and endocrine status of rats treated with 2-thiazoline-2-thiol (10 mg kg^{-1} day).

Regimen	Thyroid/body index		Tetraiodothyronine		Triiodothyronine	
	Control	2-Thiazoline-treated 2-thiol (10 mg)	Control	2-Thiazoline-treated 2-thiol (10 mg)	Control	2-Thiazoline-treated 2-thiol (10 mg)
LID	10·35 ± 2·11	41·39 ± 5·97*	3·07 ± 0·45	ND	4·65 ± 0·34	3·13 ± 1·70
LID/KI	6·82 ± 0·73	8·79 ± 0·93*	5·65 ± 0·71	3·47 ± 0·58*	4·42 ± 0·26	4·75 ± 0·34
COD	5·77 ± 0·89	9·22 ± 0·99*	5·87 ± 0·86	4·57 ± 0·40*	4·97 ± 0·79	5·07 ± 0·66
EID	6·53 ± 0·84	11·80 ± 1·35*	8·70 ± 1·41	3·93 ± 0·25*	5·57 ± 0·78	4·63 ± 0·51

Female Wistar rats were maintained on four different dietary iodine regimens for a period of 6 weeks. LID rats received iodine-deficient pellets and had free access to distilled water. LID/KI rats received iodine-deficient pellets and an iodine supplement of 0·5 mg L^{-1} KI in the distilled drinking water. COD rats received conventional pellets and distilled water. EID rats received conventional pellets and an iodine supplement of 6·5 mg L^{-1} KI in the distilled drinking water. *$P < 0·05$ compared with control. Means and s.e.m. are given for 6 animals/group. ND = not determined.

comparable with those of controls. However, a significant increase in TSH was measured for most rats on the LID/KI regimen. This variability was attributed to the short duration of treatment. Administration of chlorpromazine or clomipramine did not lead to any significant alteration in free triiodothyronine and tetraiodothyronine levels in rats on any of the diets (Table 5).

On the LID regimen, administration of 2-thiazoline-2-thiol was accompanied by a sharp fall in free tetraiodothyronine, with triiodothyronine still detected in the serum (Table 6). For rats on the LID/KI, COD and EID diets, triiodothyronine levels were not altered, although free tetraiodothyronine decreased (Table 6). When rats were treated with 2-thiazoline-2-thiol an increase in TSH was measured for all diets. 2-Thiazoline-2-thiol at 10 mg kg^{-1}/day thus seemed to stimulate the gland to maintain normal production of triiodothyronine and tetraiodothyronine, and this was accompanied by an increase in thyroid weight. Tetraiodothyronine levels did not differ in the rats on the LID/KI, COD or EID diets. In complementary experiments we showed that 2-thiazoline-2-thiol induced a decrease in serum free tetraiodothyronine. For 2-thiazoline-2-thiol doses of 100 mg kg^{-1}/day, serum triiodothyronine and tetraiodothyronine levels were below the detection threshold of our assay. The goitre was also more pronounced at this dose than at the 10 mg kg^{-1}/day dose.

Histological analysis

The infiltration index was not affected by drug treatment. The hypothyroid state of rats treated with 2-thiazoline-2-thiol was indicated by thyrocyte hyperfunction. As with methimazole, thyroid stimulation was inhibited by iodine supplementation. On the COD and EID regimens, chlorpromazine enhanced synthesis leading to colloid enlargement. We observed few signs of thyrocyte hyperfunction in rats maintained on the LID/KI regimen, whereas the appearance of the thyroid of rats on the LID diet was comparable with that of controls, albeit with a more abundant colloid.

Treatment of LID, COD and EID rats with clomipramine had little influence on gland architecture compared with that of controls; slight hyperfunction was observed for treated rats maintained on the LID/KI regimen.

Discussion

2-Thiazoline-2-thiol, chlorpromazine and clomipramine are mainly excreted in the urine; all promoted elimination of iodine. This was particularly marked when iodine intake was limited (LID/KI), and was not found when iodine intake met physiological needs (COD and EID diets). This indicated that the escape of iodine in the urine was compensated by adaptation of the thyroid gland, probably by enhancing clearance of iodide to maintain normal gland requirements (Figure 1). This readjustment was rapid and did not require stimulation by TSH. The loss of iodine induced by drugs should not, therefore, have any clinical consequences in rats with adequate iodine intake. Clomipramine and chlorpromazine seem to have antithyroid activity only when dietary iodine just covered the needs of the organism. The consequences of the loss of iodine are not readily evaluated, because the drugs tested here have a variety of actions on thyrocytes and hormonal regulating systems (Kennedy et al 1997). Furthermore, the protein deficit on the Remington diet might delay the appearance of signs of hypothyroidism (Okamura et al 1981; Sanchez-Franco et al 1983). 2-Thiazoline-2-thiol has been shown to

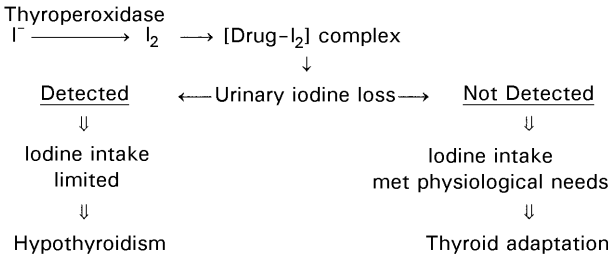

Figure 1. Schematic diagram of the interaction of drugs and iodine metabolism.

inhibit lactoperoxidase, and results obtained in-vivo indicate that the molecule also inhibits thyroperoxidase. 2-Thiazoline-2-thiol administration was accompanied by a dose-dependent fall in levels of triiodothyronine and free tetraiodothyronine. It acts initially on tetraiodothyronine synthesis, with a corresponding increase in TSH secretion. The appearance of goitre was one of the direct consequences of the impairment of hormone synthesis.

Chlorpromazine and clomipramine have not been found to inhibit lactoperoxidase, and at normal doses do not seem to inhibit thyroperoxidase in-vivo. Administration of either drug to rats on the iodine-deficient regimen did not enhance the hypothyroidism and had no influence on thyroid ultrastructure. Slight goitre and a small increase in TSH were observed in the rats on the LID/KI diet. The thyroid gland is slightly stimulated under these conditions. For rats on the COD and EID diets with adequate iodine intake, colloid enlargement on treatment with chlorpromazine could be accounted for by its activation of thyroperoxidase.

Our results are in agreement with those of Lombardi et al (1978) and Kirkegaard et al (1977) who observed an elevation in TSH in hypothyroid patients treated with chlorpromazine. These authors attributed this to an antidopaminergic action, without explaining why the phenomenon was not observed in healthy individuals. The lack of a change in urinary iodine levels in rats maintained on the COD and EID regimens was consistent with the formation of charge-transfer-type complexes between iodine and the tested drugs. The loss of iodine can be compensated for by an increase in iodide clearance from the thyroid, thereby maintaining normal metabolism. In this circumstance urinary iodine levels will not differ from control levels. When rats received iodine-deficient pellets for three weeks with 1% $KClO_4$ in the drinking water, and then the drink changed to 0·5 mg L^{-1} KI in distilled water, 100 mg kg^{-1}/day of 2-thiazoline-2-thiol did not lead to any significant increase in urinary iodine. In these circumstances the activity of thyroperoxidase seems to be as important as the iodine content of the thyroid gland. If we assume the capacity of thyroperoxidase to oxidize iodide to iodine is crucial, then drugs that form charge-transfer complexes with iodine will have antithyroid activity.

On the LID/KI regimen, the drug-induced increase in iodine excretion was stable with time, which would tend to rule out damage to the thyroid. This has been observed after therapy with radioactive iodine, which elicits liberation of excess iodine in the urine (Meller et al 1998). If this was so, we would have observed fluctuations in urinary iodine levels with time. Furthermore, thyroid ultrastructure was not altered by administration of 2-thiazoline-2-thiol, chlorpromazine or clomipramine. We also assumed that these molecules did not increase renal clearance of iodide.

The alteration in urinary iodine was not related to an increase in elimination of triiodothyronine and tetraiodothyronine. In this respect we found that for treatment with 2-thiazoline-2-thiol, high urinary iodine levels were associated with low levels of triiodothyronine and free tetraiodothyronine. It should also be borne in mind that in the rat, triiodothyronine and tetraiodothyronine are mainly eliminated in the stools (Distefano et al 1993). The physiological response of the gland to iodine deficiency will be rapid re-uptake of the iodide liberated on drug-induced deiodation of tetraiodothyronine. Similarly, the possible increase in thyroid hormone clearance, reported by Kennedy et al (1997) after administration of imipramine, would not be expected to alter urinary iodine levels.

We also ruled out the possibility that the increase in urinary iodine levels reflected an increase in iodine intake after administration of 2-thiazoline-2-thiol, clomipramine or chlorpromazine. Because clomipramine and chlorpromazine are known to lead to a gain in weight, we checked that the three drugs did not alter food intake in the rats during the course of the experiments.

Our results showed that when the iodine diet is just sufficient to cover the needs of the organism, clomipramine and chlorpromazine have antithyroid action. Although drugs such as 2-thiazoline-2-thiol induce loss of iodine from the organism, their action seems to stem more from inhibition of thyroperoxidase. Iatrogenic effects are currently classified in the fourth rank of priorities for medical research and dietary iodine is normal in five European countries only (Austria, Switzerland, Finland, Norway and Sweden). In regions where there is mild to severe iodine deficiency, treatment with clomipramine and chlorpromazine might have a significant impact on thyroid metabolism. Indeed,

as these molecules induce loss of iodine from the organism, their consumption will tend to mask the severity of the iodine deficiency.

References

Benotti, J., Benotti, N. (1963) Protein-bound iodine, total iodine, and butanol-extractable iodine by partial automation. Clin. Chem. 4: 408–416

Capen, C. C. (1992) Pathophysiology of chemical injury of the thyroid gland. Toxicol. Lett. 64/65: 381–388

Carayanniotis, G., Rao, V. P. (1997) Searching for pathogenic epitopes in thyroglobulin: parameters and caveats. Immunol. Today 18: 83–88

Comby, F., Lagorce, J. F., Buxeraud, J., Raby, C. (1994) Antithyroid action of ketoconazole: in-vitro studies and rat in-vivo studies. J. Pharm. Pharmacol. 46: 50–53

Distefano, J. J., Morris, W. L., Nguyen, T. T., Van Herle, A. J., Florsheim, W. (1993) Enterohepatic regulation and metabolism of 3,5,3′-triiodothyronine in hypothyroid rats. Endocrinology 132: 1665–1670

Dunn, J. T., Crutchfield, H. E., Gutekunst, R., Dunn, A. D. (1993) Two simple methods for measuring iodine in urine. Thyroid 3: 119–123

Gaitan, E. (1988) Goitrogens. Clin. Endocrinol. Metab. 2: 683–702

Gittoes, N. J. L., Franklyn, J. A. (1995) Drug-induced thyroid disorders. Pharmacoepidemiology 13: 46–55

Gökmen, I. G., Dagh, G. (1995) Determination of iodine concentration in human milk, cows' milk and infant formula and estimation of daily iodine intakes of infants. Analyst 120: 2005–2008

Gutmann, F., Keyzer, H. (1967) Study of phenothiazine– and chlorpromazine–iodine complexes. J. Chem. Phys. 46: 1969–1974

Kelder, P. P., De Mol, N. J., Fischer, M. J. E., Janssen, L. H. M. (1994) Kinetic evaluation of the oxidation of phenothiazine derivatives by methemoglobin and horseradish peroxidase in the presence of hydrogen peroxide. Implications for the reaction mechanisms. Biochim. Biophys. Acta 1205: 230–238

Kennedy, J. A., Jarrett, D. B., Wellby, M. L. (1997) Influence of imipramine on the hypothalamic/pituitary/thyroid axis of the rat. Metabolism 46: 1429–1434

Kirkegaard, C., Bjoerum, C. N., Cohn, D., Faber, J., Lauridsen, U. B., Nekup, J. (1977) Studies of the influence of biogenic amines and psychoactive drugs on the prognostic value of the TRH stimulation test in endogenous depression. Psychoneuroendocrinology 2: 131–136

Lagorce, J. F., Fatimi, J., Chabernaud, M. L., Marion, S., Buxeraud, J., Raby, C. (1995) Thirame: example of the thyroid toxicity of an agrochemical with strong electron-donor property. Int. J. Environ. Stud. 48: 221–229

Lombardi, G., Panza, N., Cei, S., Cosimato, F., Minozzi, M. (1978) Radioimmunoassay of thyrotropin-releasing hormone (TRH) in normal subjects, in abnormal thyroid states and under catecholaminergic influences. Acta Endocrinol. 87: 70–79

May, S. L., May, W. A., Bourdoux, P. P., Pino, S., Sullivan, K. M., Maberly, G. F. (1997) Validation of a simple, manual urinary iodine method for estimating the prevalence of iodine-deficiency disorders, and interlaboratory comparison with other methods. Am. J. Clin. Nutr. 65: 1441–1445

Meller, B., Lauer, I., Bahre, M., Richter, E. (1998) Influence of radioiodine therapy on urinary iodine excretion. Nuklearmedizin 37: 107–112

Okamura, K., Taurog, A., Krulich, L. (1981) Elevation of serum 3,5,3′-triiodothyronine and thyroxine levels in rats fed Remington diets: opposing effects of nutritional deficiency and iodine deficiency. Endocrinology 108: 1247–1256

Raby, C., Lagorce, J. F., Jambut-Absil, A. C., Buxeraud, J., Catanzano, G. (1990) The mechanism of action of synthetic antithyroid drugs: iodine complexation during oxidation of iodide. Endocrinology 126: 1683–1691

Saito, K., Yamamoto, K., Takai, T., Yoshida, S. (1983) Inhibition of iodide accumulation by perchlorate and thiocyanate in a model of the thyroid iodide transport system. Acta Endocrinol. 104: 456–461

Sanchez-Franco, F., Cacicedo, L., Morreale de Escobar, G., Escobar del Rey, F. (1983) Nutrition and iodine versus genetic factors in endemic goitre. J. Endocrinol. Invest. 6: 185–188

Sandell, E. B., Kolthoff, I. M. (1937) Microdetermination of iodine by catalytic method. Microchim. Acta 1: 9–25

Sundick, R. S., Bagchi, N., Brown, T. R. (1992) The role of iodine in thyroid autoimmunity: from chickens to humans: a review. Autoimmunity 13: 61–68

Taurog, A. (1991) Thyroid hormone synthesis. In: Braverman, L. E., Utiger, R. D. (eds) Wener's The Thyroid, 6th edn, J. B. Lippincott, Philadelphia, pp 51–97

Thomes, J. C., Comby, F., Lagorce, J. F., Buxeraud, J., Raby, C. (1992) Sites of action of 2-thiazoline-2-thiol on biogenesis of thyroid. Jpn J. Pharmacol. 58: 201–207

Visser, T. J. (1996) Pathways of thyroid hormone metabolism. Acta Med. Austriaca 23: 10–16