

## Iodine and Cobalt

### Overview

- Dietary iodine is largely converted to iodide in the digestive tract, where it is normally absorbed at >95% efficiency.
- Iodide is required for thyroid hormone biosynthesis, and is extensively recycled within the organism.
- The thiocarbamide group of plant-derived goitrogens possesses antithyroid activity.
- $^{131}\text{I}$  is sometimes used to treat animals with hyperthyroidism.
- Cobalt is an important constituent of vitamin B<sub>12</sub>.
- Cobalt deficiency in ruminant animals results in an inability to metabolize propionate, as well as an inability to reform tetrahydrofolate from N<sup>5</sup>-methyl-H<sub>4</sub> folate.
- Several physiologic processes require inorganic cobalt.
- Cobalt and iron may share the same transport system for intestinal absorption.
- Iron deficiency enhances intestinal Co absorption.

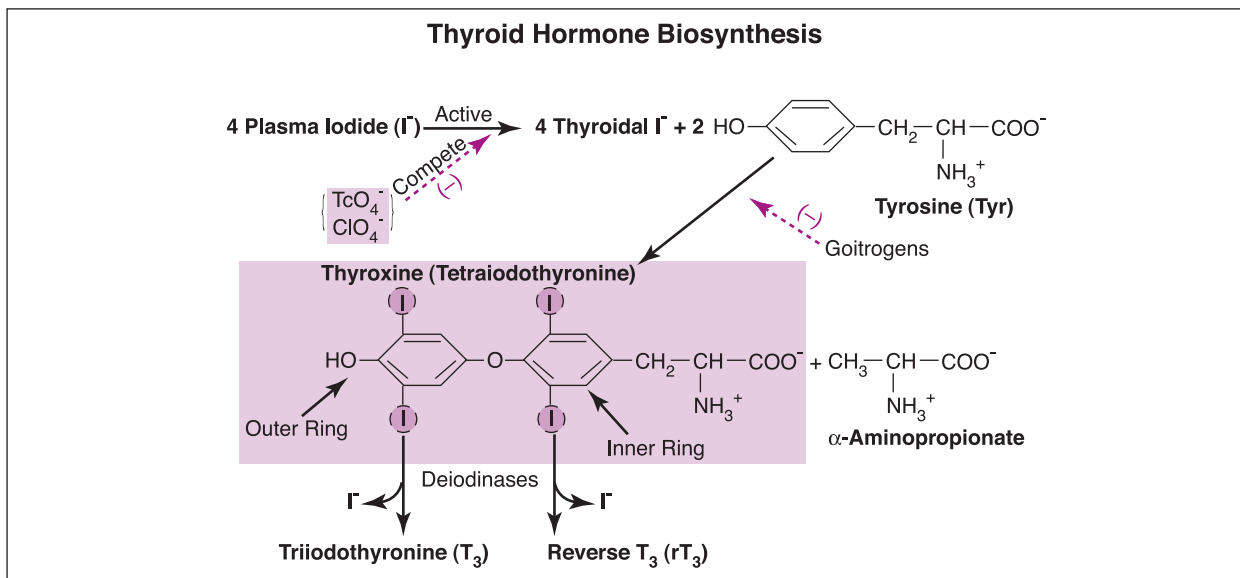
### Iodine (I)

The importance of **iodine** to mammalian thyroid metabolism has been recognized for over one-hundred years, and it is here that this trace element exerts its primary physiologic action. Within the thyroid iodine becomes a part of the **tri-** and **tetraiodothyronines**, which are the active thyroid hormones (**T<sub>3</sub>** and **T<sub>4</sub>**, respectively), as well as **reverse T<sub>3</sub>** (**rT<sub>3</sub>**), the inactive hormone (**Fig. 52-1**). The metabolism and endocrinology of these hormones, as well as discussions of hypo- and hyperthyroidism in animals, can be reviewed in **Engelking LR: Metabolic and Endocrine Physiology, Jackson, WY: Teton NewMedia**.

Goiter, an enlargement of the thyroid gland with hypertrophy and/or hyperplasia of the follicular epithelium, occurs largely in response to iodine deficiency. Young animals born to

dams on iodine-deficient diets are more likely to develop severe thyroid hyperplasia, and demonstrate signs of hypothyroidism. Iodine is a fairly benign trace element, which is thought to cause little harm at 10-20 times the recommended daily allowance. However, animal studies indicate that greater amounts can cause **toxicity** by ultimately inhibiting thyroid hormone biosynthesis, and causing goiter.

The richest natural **dietary sources** of iodine are fish, vegetables, meats, and eggs, while processed feeds and pet food products routinely include iodine as a supplement. **Dietary iodine** is normally converted to iodide (I<sup>-</sup>) in the digestive tract, which is then actively absorbed from the small intestine at a **>95%** efficiency. Iodide circulates in plasma largely bound to plasma proteins (though some is free). This element is actively concentrated from

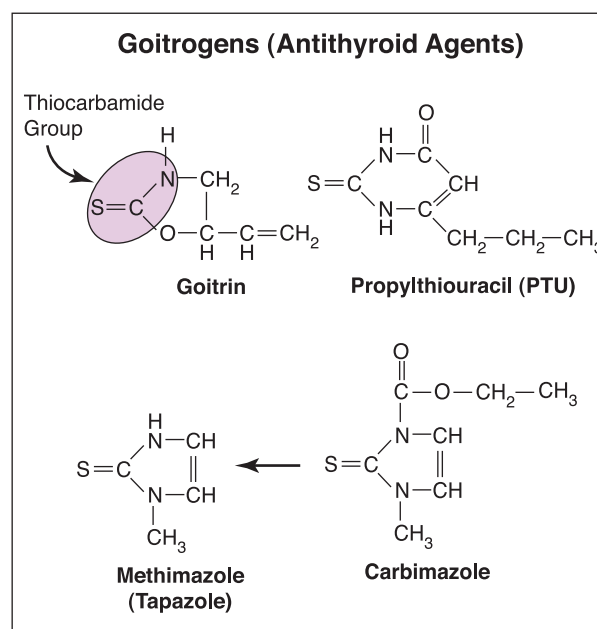
**Figure 52-1**

blood not only by follicular cells of the thyroid gland (which normally contain **>90% of  $I^-$  in the body** and maintain a **25:1 thyroid-to-plasma  $I^-$  concentration ratio**), but also by cells of the salivary and lactating mammary glands, as well as the choroid plexus (which produces cerebrospinal fluid). It is extensively recycled within the organism, and excreted mainly via urine.

### Goitrogens

While **iodine deficiency** has been associated with **goiter** in animals, it is not the only factor precipitating this condition. Genetic defects in thyroid hormone biosynthesis (thyroxinogenesis) occur, and **goitrogens**, which interfere with this process, are present to a variable degree in a number of plants from the family ***Brassicaceae***. **Thiocyanates**, which can be produced by ruminal degradation of cyanogenic glucosides from plants such as white clover (*Trifolium*), couch grass, and linseed meal, and by degradation of glucosinolates of *Brassica* crops, are associated with hyperplastic goiter in ruminant animals. **Goitrin (5-vinyloxazolidine-2-thione; Fig. 52-2)**, derived from these glucosinolates, inhibits thyroxinogenesis (i.e., thyroid hormone biosynthesis). The **thiocarbamide group** of goitrin (see Fig. 52-2) is

essential for antithyroid activity, and is used in drugs prescribed for the treatment of thyrotoxicosis. **Propylthiouracil (PTU)** and **methimazole (Tapazole)** are the two thiourylene antithyroid drugs available for use in the USA, while **carbimazole** is the alternative to PTU in Europe (where methimazole is generally unavailable). Animals rapidly convert carbimazole to methimazole *in vivo*, so that only methimazole is detectable in serum and the thyroid gland following carbimazole administration.

**Figure 52-2**

These compounds are actively concentrated by the thyroid gland, where they are thought to act to **inhibit thyroxinogenesis** through the following mechanisms:

- 1) By blocking incorporation of  $I^-$  into the tyrosyl groups in thyroglobulin (which is the thyroidal protein that normally binds thyroid hormones until they are secreted);
- 2) By preventing the coupling of iodotyrosyl groups (mono- and diiodotyrosines) into  $T_4$  and  $T_3$ ; and
- 3) Through direct interaction with the thyroglobulin molecule.

Antithyroid drugs are not thought to interfere with the thyroid gland's ability to concentrate or trap inorganic  $I^-$ , nor are they thought to block release of stored thyroid hormone into the circulation. Monovalent anions such as **perchlorate** ( $ClO_4^-$ ) and **pertechnetate** ( $TcO_4^-$ ) compete with  $I^-$  for thyroidal uptake, and they are also concentrated, like  $I^-$ , against a gradient (see **Fig. 52-1**). Technetium-labeled  $TcO_4^-$  is used clinically to monitor thyroid activity via thyroid scans.

**Radioactive iodine** provides a simple, effective, and relatively safe treatment for animals (mainly cats) with hyperthyroidism. The basic principle is that follicular cells of the thyroid do not differentiate between stable and radioactive iodine; therefore, radioiodine, like stable iodine, is concentrated by the thyroid gland following administration. The radioisotope most frequently used is  $^{131}I$ , which has a half-life of 8 days, and emits both  $\beta$  and  $\gamma$  radiation. The  $\beta$  particles are locally destructive, but usually spare adjacent hypoplastic thyroid tissue, parathyroid glands, and other cervical structures. The goal of  $^{131}I$  **therapy** is to restore euthyroidism with a single dose without producing hypothyroidism. With careful dosing, this therapy can be highly effective.

## Cobalt (Co)

Cobalt is an important constituent of **vitamin B<sub>12</sub>** (see Chapter 43), and as such, is required for two enzymatic reactions central to mammalian metabolism:

- 1) Synthesis of methionine from homocysteine to reform tetrahydrofolate ( $H_4$  folate) from  $N^5$ -methyl- $H_4$  folate, and thus allow the normal flow of folate metabolism (and thymidine synthesis; see Chapters 14-16 and 43); and
- 2) The rearrangement of methylmalonyl-CoA to succinyl-CoA which is important for converting propionate from microbial cellulose digestion, the terminal 3 carbons of odd-chain fatty acids from mitochondrial  $\beta$ -oxidation,  $\beta$ -aminoisobutyrate from pyrimidine degradation, and several amino acids from protein degradation, to a member of the tricarboxylic acid cycle (see Chapters 37 and 42).

Because **vitamin B<sub>12</sub>-deficiency** impairs the **methionine synthase** reaction, and thus DNA synthesis, cell division in bone marrow is impaired and **pernicious anemia** develops. This B-complex vitamin has also been associated with **myelin** and **carnitine** formation (**Table 52-1** and Chapters 43, 55, and 59).

Bacteria synthesize this vitamin, and **ruminant animals** appear to absorb only this form of Co. **Cobalt deficiency**, which causes anemia, anorexia, and wasting, is important in Australia, New Zealand, the UK and USA, and probably occurs in other areas of the world. The essential defect in ruminant Co deficiency is an inability to metabolize propionate. Where the deficiency is extreme, large tracts of land have been found to be unsuitable for raising ruminant animals, but apparently not horses.

Most Co absorbed has not been found to be in the form of vitamin B<sub>12</sub> in non-ruminant animals; likewise, only about 1/10<sup>th</sup> to 1/12<sup>th</sup> of Co in the mammalian organism is in vitamin

| <b>Table 52-1</b>   |  |
|---|--|
| <b>Cobalt-Dependent Processes</b>   |  |
| <b>Involving Vitamin B<sub>12</sub></b>   |  |
| *Rearrangement of methylmalonyl-CoA to succinyl-CoA   |  |
| Propionyl-CoA entry into gluconeogenesis  |  |
| Antipernicious anemia factor  |  |
| *Transfer of a methyl group from N <sup>5</sup> -methyl-H <sub>4</sub> folate to homocysteine in methionine formation |  |
| Purine, pyrimidine, and nucleic acid biosynthesis   |  |
| Reformation of folic acid   |  |
| Myelin formation  |  |
| Carnitine formation   |  |
| <b>Independent of Vitamin B<sub>12</sub></b>  |  |
| Stimulate glycylglycine dipeptidase activity  |  |
| Maintain erythropoiesis   |  |
| Stimulate bradykinin release  |  |
| Lower blood pressure  |  |
| Thyroxinogenic  |  |

\*Primary

form, and it is conceivable that inorganic Co may be released from B<sub>12</sub> during metabolism to enable other actions. For example, the activity of **glycylglycine dipeptidase** appears to require Co (Table 52-1). Additionally, **bradykinin** is released into the circulation in response to Co salt administration, and the blood pressure is lowered. Co salts also enhance proliferation of bone marrow **erythropoietic cells**, independent of vitamin B<sub>12</sub>. Large daily doses of **CoCl<sub>2</sub>** have been used to treat anemias that are refractory to Fe<sup>++</sup>, folate, and vitamin B<sub>12</sub>.

Studies in rats indicate that inorganic Co may help to support **thyroxinogenesis**. However, high doses of Co oxides and/or sulfides have been shown to produce proliferation of otherwise normal cells, and to cause cancer in animals at the injection site, or in muscle and follicular thyroid tissue. Although rare in animals, **Co-toxicity** is reportedly increased by thiamin and protein deficiencies.

Cobalt salts are soluble in neutral and

alkaline environments, and are thus more easily **absorbed** across the intestinal mucosa. Cobalt is thought to use the same intestinal transport systems as Fe<sup>++</sup>/Fe<sup>+++</sup> (see Chapter 48). Iron deficiency enhances Co absorption, and in rats iron appears to be the main regulator of intestinal Co uptake. Cobalt absorbed into intestinal mucosal cells is not invariably transferred to blood, and may be lost when intestinal cells are sloughed. In blood, inorganic Co is distributed attached to **albumin**. It initially deposits in liver and kidney tissue, and later in bone, spleen, pancreas, intestine, and other tissues. Liver, heart, kidney, and bone are considered to have the highest Co concentrations, which contrasts with the preferential accumulation of B<sub>12</sub>-cobalt in the liver, where 50-90% of this vitamin is stored (see Chapter 43). The **intestinal absorption efficiency** for Co is **63-97%**, and it is mainly eliminated through urine.

**Radiation** delivered from a distance is called teletherapy or external beam radio-

therapy. Orthovoltage x-ray and **cobalt-60** ( $^{60}\text{Co}$ ) machines have been extensively used in veterinary oncology.  $^{60}\text{Co}$  emits  $\gamma$ -rays with energy approximately six-times greater than orthovoltage x-ray units.  $^{60}\text{Co}$  units are in some cases being replaced by more modern linear accelerators.

### OBJECTIVES

- Understand why iodine is employed as a pet food supplement, and compare the intestinal absorption efficiency of this trace element to others.
- Explain how and why iodide is concentrated in the thyroid gland, and why it is also actively removed from blood by salivary and mammary glands.
- Identify dietary sources of iodine.
- Recognize normal routes of iodine elimination from the body.
- Explain how iodide is carried in blood.
- Describe the dietary and therapeutic sources of goitrogens, and identify how they are thought to interfere with thyroid function.
- Explain relationships between perchlorate, pertechnetate and iodide.
- Discuss the basis of using  $^{131}\text{I}$  to treat hyperthyroidism.
- Identify the structural relationship that exists between cobalt and vitamin  $\text{B}_{12}$ , and recognize two key enzymatic reactions that are dependent upon this complex.
- Recognize cobalt-dependent processes that do not involve  $\text{B}_{12}$ .
- Identify areas of the world possessing cobalt-deficient soils.
- Explain how cobalt is absorbed from the intestine, transported in plasma, stored and excreted from the body.
- Compare cobalt and iodide intestinal absorption efficiency to that for zinc, iron, copper, manganese and selenium.

### QUESTIONS

1. **All of the following are known to actively concentrate  $\text{I}^-$  from blood, EXCEPT the:**
  - a. Thyroid gland.
  - b. Pituitary gland.
  - c. Choroid plexus.
  - d. Salivary glands.
  - e. Lactating mammary glands.
  
2. **Which one of the following is an essential component of antithyroid drugs, propylthiouracil, methimazole, and carbimazole?**
  - a. Cobalt
  - b. Reverse  $\text{T}_3$
  - c. Selenium
  - d. Thiocarbamide group
  - e. Iodotyrosyl group
  
3. **Antithyroid drugs act by blocking:**
  - a. Tyrosine uptake into thyroid tissue.
  - b. Thyroglobulin synthesis.
  - c. Incorporation of  $\text{I}^-$  into tyrosyl groups in thyroglobulin.
  - d.  $\text{I}^-$  uptake into follicular cells of the thyroid.
  - e. Release of stored thyroid hormone into the circulation.
  
4. **The primary defect in ruminant Co-deficiency is the inability to:**
  - a. Produce bile.
  - b. Metabolize propionate.
  - c. Produce urine.
  - d. Metabolize acetate.
  - e. Synthesize thyroxine.
  
5.  **$\text{CoCl}_2$  therapy is sometimes used to treat:**
  - a. Hyperthyroidism.
  - b. Fatty liver syndrome.
  - c. Muscular dystrophy.
  - d. Vitamin E deficiency.
  - e. Anemia.
  
6. **Co appears to use the same intestinal transport system as:**
  - a. Sodium.
  - b. Potassium.
  - c. Iron.
  - d. Glucose.
  - e. Tyrosine.