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Compendium

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The Role of Iodine in Nutrition and Metabolism

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Abstract: *Iodine, which forms part of thyroid hormone, is essential for sustaining life in vertebrate animals. An absolute iodine requirement is difficult to determine because of adaptive responses to varying iodine intake. Excess or deficient iodine intake may result in altered thyroid metabolism. The magnitude and direction of the response to changes in dietary intake may also depend on previous iodine intake. Therefore, an understanding of the distribution, absorption, and metabolic fate of iodine is integral to the investigation of the role of iodine in disease states.*

The first description of iodine was by Bernard Courtois in 1811, when he saw a violet vapor arising from seaweed ash during the manufacture of gunpowder for Napoleon's army. The name *iodine*, from the Greek for "violet," was subsequently suggested by Joseph Louis Gay-Lussac. In 1895, Eugen Baumann identified iodine in thyroid glands, and by 1917, it was understood that thyroid gland enlargement (goiter) was caused by iodine deficiency and could be prevented by iodine supplementation. During the 1920s, oral iodine supplementation for goiter prophylaxis was introduced in Switzerland and the United States.[1]

Geologic Distribution of Iodine

Iodine occurs widely in trace amounts, mainly as iodide salts, with local concentrations depending on geologic and water conditions. Generally, the highest concentration of iodide (50 to 60 µg/L) is found in seawater; the concentration in freshwater is 1 to 10 µg/L. Iodide in seawater oxidizes and sublimes when exposed to air and is transported inland, where it is dissolved into water droplets that fall as rain. Leaching due to glaciation, flooding, and erosion depletes surface soils of iodide, resulting in most mountainous and some interior inland regions being deficient. Crops grown in these areas may be 10-fold lower in iodine content (~10 µg/kg) than those from iodine-sufficient regions.[1]

Food Sources

A 2003 report on the iodine content of food[2] found that the average (geometric mean) iodine content of 494 foods was 87 µg/kg. Geometric means of the iodine content of some specific food types are presented in **BOX 1**. Grain crops are generally poorer sources of iodine than vegetables. In some geographic locations, ingestion of seaweed and kelp contributes significantly to iodine intake.[1]

Physiologic Function of Iodine

The only known function of iodine in vertebrates is to form thyroid hormones, with approximately 70% to 80% of all the iodine in the body found in the thyroid gland.[1] Thyroxine (T_4) and triiodothyronine (T_3) are released from the thyroid gland in a ratio of about 40:1 (T_4:T_3). T_4 is considered to be a prohormone that requires conversion in peripheral tissues to active T_3 by selenium-dependent deiodinase enzymes. The deiodinase enzymes may also inactivate T_4 to produce reverse T_3 or convert T_3 to isomers of diiodothyronine (T_2).[1]

During lactation, the mammary glands concentrate iodine and secrete it into milk for the newborn. Other tissues take up small amounts of iodine, including the salivary glands, gastric mucosa, and choroid plexus. Iodine has no proven function in these tissues; however, there are suggestions of generalized immune system support.[1]

Hypothyroidism is common in dogs, and hyperthyroidism is common in cats. Clinical signs of hypothyroidism in dogs include lethargy, weight gain, alopecia, pyoderma, and seborrhea. Hyperthyroidism in cats is often characterized by weight loss, polyphagia, polydipsia/polyuria, and gastrointestinal signs. In addition, an enlarged, palpable thyroid gland may be present in cats.

Box 1. Geometric Means of Iodine Content in Food Types[2]

- Marine fish: 1455.9 µg/kg
- Freshwater fish: 102.8 µg/kg
- Leafy vegetables: 88.8 µg/kg
- Dairy: 83.9 µg/kg
- Other vegetables: 80.1 µg/kg
- Meat: 68.4 µg/kg
- Cereals: 56.0 µg/kg
- Fresh fruit: 30.6 µg/kg
- Bread: 17.0 µg/kg
- Water: 6.4 µg/L

Absorption

Most dietary iodine is an inorganic salt form of iodide that is absorbed directly in the stomach and duodenum. The iodate (IO_3^-) found in supplements is reduced in the gut to iodide (I^-) before absorption. Organic iodine is usually ingested only as T_4 supplements. Absorption of an oral dose of T_4 is variable; some is absorbed intact, and some is broken down and the iodine absorbed as iodide.[3]

Iodide is quickly absorbed in the stomach and small intestine, with an absolute bioavailability of >90%.[4] It is absorbed via an active transport protein in enteral mucosa called the *sodium-iodide symporter* (NIS). NIS is expressed on the apical surfaces of enterocytes as well as on many other cells, including thyroid follicular cells. NIS is down-regulated as the concentration of iodide from food increases.[5]

Tissue Uptake and Metabolism

Iodide absorbed from the gastrointestinal tract is transported to the bloodstream, from which it is rapidly taken up by the thyroid gland and the kidneys. The thyroid gland accumulates iodide depending on iodine and thyroid hormone status, whereas clearance by the kidneys is relatively constant, depending on glomerular filtration rate (GFR) and physiologic state. NIS located on the basal membrane in thyroid follicular cells is the key enzyme responsible for iodide accumulation. The specific activity of NIS is three to four times greater in thyroid tissue than in any other tissue in the body, effectively helping the thyroid gland preferentially accumulate and sequester iodide from the blood.[1,6] Iodide is concentrated in the cytosol of thyroid follicular cells to more than 40 times the level in plasma.[1]

In conditions of adequate to surplus dietary iodine supply, less than 10% of absorbed iodide is taken up by the thyroid. When dietary iodide is less abundant, the fraction of iodide taken up by the thyroid from the blood can exceed 80% of the plasma pool.[1] Thyroid-stimulating hormone (TSH) and plasma iodide regulate NIS expression in thyroid follicular cells, thereby determining iodide uptake by the thyroid gland. When thyroid hormone is low (hypothyroidism), TSH is increased, resulting in up-regulation of NIS expression. Conversely, during euthyroid or hyperthyroid states, TSH usually remains low and does not stimulate NIS expression. High concentrations of iodide in plasma directly decrease NIS expression.[7]

In the thyroid, iodide is moved to the colloid space via pendrin, a sodium-independent iodide/chloride transport protein. Thyroperoxidase enzyme then catalyzes organification, in which iodide is covalently bound to tyrosine residues in thyroglobulin either as monoiodotyrosine (MIT) or diiodotyrosine (DIT).[1] T_4 is formed from the combination of two DIT molecules, whereas T_3 is formed from one DIT and one MIT molecule. Increased TSH stimulates thyroglobulin proteolysis and subsequent release of thyroid hormones into circulation. Depending on overall iodine status, the colloid space stores enough covalently bound iodine in thyroglobulin to account for several weeks' to months' worth of hormone secretion.[1] This is a key point in determining responses to changes in iodine intake because this endogenous supply may blunt the response to diminished intake for long periods of time. Iodine turnover in the colloid space has been estimated at 1% per day in humans.

Distribution and Elimination

Absorbed iodide is distributed through the extracellular space with a half-life of approximately 10 h in plasma. The half-life may be shortened in iodine-deficient or hyperthyroid animals due to more rapid thyroid uptake and increased GFR. When dietary iodide intake is abundant, approximately 90% of ingested iodide is excreted in urine and the remainder in feces.[1] Renal iodide clearance remains constant as a percentage of filtered iodide in plasma, even in response to variable iodine intake. This results in decreased urinary iodide when iodine intake is low and increased urinary iodide when intake is high. Biliary conjugation of thyroxine may occur, with concomitant fecal elimination almost entirely as conjugated thyroid hormone. Enterohepatic recirculation of thyroid hormone is possible but varies by species, with no published information in dogs and cats.[1]

Key Facts

- Biologically, iodine is only required for thyroid hormone synthesis.
- Absolute requirements for iodine are difficult to estimate because:
  - Previous dietary iodine intake affects response to iodine supplementation.
  - The thyroid gland adapts to variable intake.
  - Other dietary compounds can interfere with measurement.
- Variable iodine intake may alter thyroid gland function and predispose animals to disease.
- Limiting iodine intake may aid in the management of hyperthyroidism in cats.

Recycling

Intrathyroidal and extrathyroidal recycling of iodide occurs after GI absorption and may be up- or down-regulated depending on the level of dietary iodine.[1,8] Mature thyroglobulin contains 0.1% to 1.0% iodine with six- to sevenfold more MIT and DIT than intact T_3 and T_4.[1] The inactive MIT and DIT released during proteolysis of thyroglobulin account for ~80% of recaptured intrathyroidal iodide that never leaves the gland due to efficient recycling mechanisms.[1,8]

Iodotyrosine deiodinase is the primary recycling enzyme; deficiencies of this enzyme have been associated with hypothyroidism, excessive renal iodine excretion, and goiter under conditions of presumed iodine sufficiency.[1,8] Extrathyroidal iodine recycling may occur when (1) absorbed iodide is excreted by salivary or gastric glands into the upper alimentary tract to be reabsorbed as previously described or (2) free iodide released from the conversion of T_4 to T_3 in peripheral tissues enters the general circulation, where it may be reused or eliminated.

Methods of Determining Iodine Nutritional Requirement

Four different parameters have been suggested for assessing and monitoring iodine status in human populations: urinary iodine

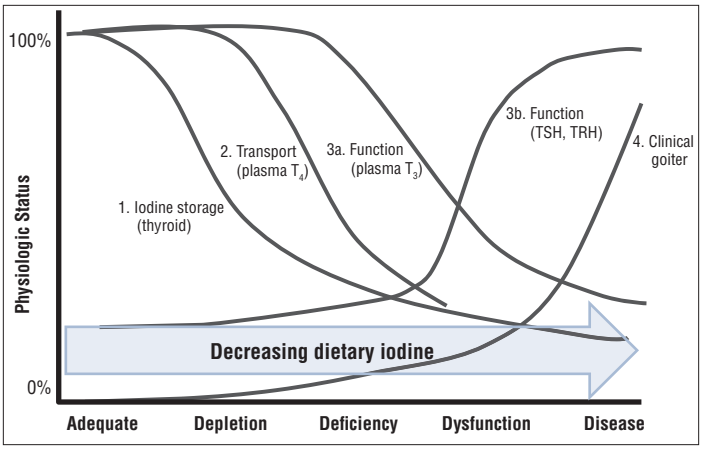

Figure 1. Effect of decreasing iodine intake on physiologic responses reflecting iodine status. Adapted with permission from: Iodine. In: Suttle NF. *Mineral Nutrition of Livestock*. 4th ed. Wallingford, UK: CAB International; 2010:306-333. *TRH* = thyrotropin-releasing hormone, *TSH* = thyroid-stimulating hormone.

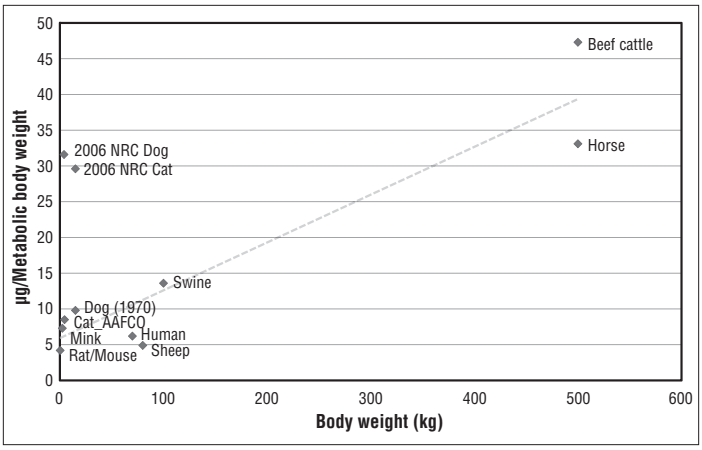

Figure 2. Recommended iodine intake per metabolic body weight (µg/kg$^{0.75}$) versus nontransformed body weight (µg/kg). The regression line drawn does not include the 2006 NRC values for dogs and cats. y = 0.0688x + 5.2594; R^2 = 0.9007

Data adapted from:

- Association of American Feed Control Officials, Inc. Official publication of the Association American Feed Control Officials. Oxford, IN: AAFCO; 2011.
- Institute of Medicine Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press; 2001.
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concentration, goiter rate, serum TSH, and serum thyroglobulin. These indicators display some complementary utility: urinary iodine is an indicator of recent iodine intake (days), thyroglobulin shows an intermediate response to changes in iodine intake (weeks to months), and changes in goiter rate reflect long-term iodine status (months to years). T_4 and TSH have some utility in certain populations but are not reliable indicators of iodine status.[1,9] Ideally, studies that use both direct (histopathology) and indirect measures of iodine status to estimate requirements for a species are preferred, but such studies are rarely performed.[10] Precise determination of iodine requirement in a species is difficult because of the multiple overlapping adaptation mechanisms, which create a continuum of responses (**FIGURE 1**). In addition, compounds found in dietary ingredients may interfere with iodine usage and confound requirement estimates. Examples include thiocyanate and perchlorate inhibition of NIS and soy goitrogen interference with organification. As such, to determine species requirements, it is probably most useful to perform multiple measurements over time with well-defined dietary constituents to get the most accurate assessment of iodine status. These same recommendations would probably also be beneficial in individual animals to determine clinical outcomes.

Recommended Iodine Intake

The recommended iodine intake across species appears to follow metabolic scaling for body weight (**FIGURE 2**). The recommended daily allowances for dogs and cats suggested by the National Research Council (NRC) in 2006 are in excess of NRC recommendations for other species, current AAFCO recommendations in cats, and earlier recommendations for dogs and cats based on metabolic body weight.[10–12] The dietary iodine requirement in cats has recently been suggested to be closer to 0.46 ppm than to the 1.3 ppm reported by the NRC.[10] The regression equation (graphed in **FIGURE 2**), without 2006 NRC values, yields a recommended dietary amount of 0.22 ppm for cats weighing 10 lb (4.5 kg) and 0.18 ppm for dogs weighing 44 lb (20 kg). General recommendations for iodine intake are listed in **BOX 2**.

Effects of Varying Iodine Intake on Thyroid Metabolism

The effects of varying iodine intake on thyroid metabolism must be evaluated in relation to prior iodine intake (acute and chronic), thyroid status, as well as the magnitude and direction of change relative to absolute requirement. Varying iodine intake has well-documented effects on human thyroid disorders (**FIGURE 3**), and data are starting to accumulate in companion animals. In humans, repletion of adequate iodine to the diet after chronic deficiency may result in iodine-induced thyrotoxicosis (Jod-Basedow phenomenon), whereas acute supplementation above the requirement in hyperthyroid or euthyroid individuals may result in hypothyroidism.

Feline hyperthyroidism has many similarities to iodine-induced thyrotoxicosis in humans, and an increased risk of hyperthyroidism

Box 2. Current Recommendations for Iodine Intake in Animals

- Feed wellness foods that meet, but are not in vast excess of, the dietary intake recommended by AAFCO.
- Avoid large variations in iodine content when changing foods (call the manufacturer if the iodine content is not listed), and perform multiple measures of iodine/thyroid status over time in animals with suspected disease.
- In cats with existing hyperthyroidism, limitation of iodine intake may return circulating thyroid hormone status to within normal reference ranges. The disease status of these animals should be monitored with multiple measures of thyroid status at appropriate intervals.

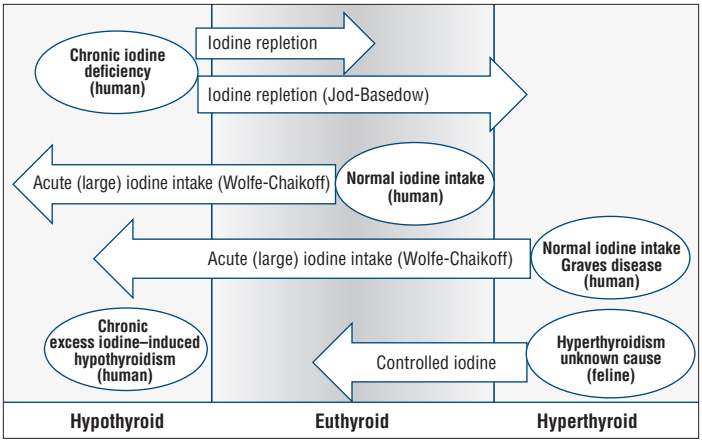

Figure 3. Effect of changes in iodine intake (*arrows*) in relation to current iodine and/or thyroid status (*ovals*).

in cats has been suggested to be related to dietary iodine concentration. Reported dietary risk factors include ingestion of canned foods,[13,14] specific flavors of canned foods (e.g., fish, giblets/liver),[15] increased variety in flavors of canned foods versus a monotonous flavor,[16] and lack of iodide supplementation in ingredient lists.[17] The effects of low (0.1 ppm), medium (2.2 ppm), and high (21 ppm) iodine intake on feline thyroid status were assessed in 2-week feeding trials,[18] which concluded that increased iodine intake resulted in decreased free thyroxine levels. In puppies, supplementation of iodine at 4.3 ppm above baseline (~0.2 ppm) from 45 to 90 days of age decreased thyroid hormone levels and altered bone metabolism.[19] These studies suggest that varying iodine intake in healthy dogs and cats may affect thyroid metabolism. It is unknown if these temporary changes affect iodine metabolism in such a way to result in permanent pathology.

Limiting iodine intake to slightly below the AAFCO recommendation has been found to decrease serum thyroxine levels in cats with existing hyperthyroidism and to enable achievement of a euthyroid state.[20,21] Reports of iodine content analyzed in commercial pet foods are limited to cat foods and indicate that variability is high, ranging from inadequate to excessive.[22,23] Commercial cat foods in New Zealand contained 0.19 to 21.2 ppm of iodine, whereas in Germany, a range of 0.22 to 6.4 ppm was noted.[22,23] Other reported values for iodine content of commercial cat foods range from undetectable amounts to 36.8 ppm.[17] There are few reported values for commercial dog foods, but because manufacturers use common ingredients across product lines, it is reasonable to postulate that similar variations in range exist in canine products.

Summary

Iodine metabolism is a complex interaction of physiologic responses superimposed on dietary intakes over time, resulting in a continuum of thyroid gland responses. Chronic iodine excess or deficiency may result in clinical disease.

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