Iodide-Induced Hypothyroidism: A Potential Hazard During Perinatal Life

Abstract. *The administration of iodide to pregnant and nursing rats induces hypothyroidism in the term fetus and neonatal rat through age 10 days as indicated by an increase in the serum concentration of thyroid-stimulating hormone and a decrease in the serum of thyroxine and triiodothyronine. Thyroid function returned to normal from age 18 through 60 days in spite of continued iodide administration, strongly suggesting that resistance to the inhibitory effect of iodide on thyroid hormone synthesis is developed at approximately 18 days of age. This perinatal rat model can be used to study the mechanisms responsible for iodide-induced hypothyroidism and goiter in human newborns whose mothers received iodide-containing medications during pregnancy.*

Iodide-induced hypothyroidism may occur in humans after long-term exposure to pharmacologic quantities of iodide. Such hypothyroidism usually occurs in patients with thyroid disease such as Hashimoto's thyroiditis (*1*) or previously treated Graves' disease (*2*), or a hemithyroidectomy for benign nodules (*3*); however, long-term iodide therapy in patients with chronic lung disease also may induce hypothyroidism (*4*). The hypothyroidism is transient in nature, and thyroid function usually returns to normal after the iodide treatment has been discontinued (*1-3, 5*).

The effect of pharmacologic quantities of iodide during perinatal life has not been systematically studied. Iodide readily crosses the placenta and could, therefore, affect fetal thyroid function. Iodide goiter and, rarely, hypothyroidism have been reported to occur sporadically in infants whose mothers received iodides during pregnancy for a variety of nonthyroid diseases or hyperthyroidism (*5*). The sporadic occurrence of neonatal goiter and hypothyroidism despite the relatively frequent use of iodide-containing medications was interpreted as evidence that only newborn infants with underlying thyroid disease are susceptible to the inhibitory effects of iodide on thyroid function in utero (*6*). Thyroid-stimulating immunoglobulins, antithyroid drugs such as propylthiouracil and methimazole, and other potential goitrogenic drugs also cross the placenta and could sensitize the fetal thyroid to the adverse effects of iodide on thyroid function. The finding that the administration of an iodine-containing dye used in amniofetography induced transient hypothyroidism in six of seven newborn infants studied (*7*) suggests the possibility that the normal fetal thyroid is sensitive to the adverse effect of iodide on thyroid hormone synthesis.

Long-term iodide administration to adult rats, in contrast to the reported observations in humans, does not result in hypothyroidism (*8*). Single doses of iodide administered to the rat cause a transient inhibition of thyroid hormone synthesis, the acute Wolff-Chaikoff effect (*9, 10*), that lasts approximately 48 hours. The resistance to long-term iodide administration is probably due to a decrease in the thyroid iodide transport capacity (*11*).

The maturation of the hypothalamic-pituitary-thyroid axis during the first 2 weeks of extrauterine life in the rat resembles human fetal function during weeks 16 to 40 of gestation (*12*). Since the effects of iodide during perinatal life cannot be studied in humans, iodide was administered to the pregnant and nursing rat, and the effects on fetal and neonatal rat thyroid function was evaluated.

Pregnant Sprague-Dawley rats were fed Purina Chow and either tap water alone (control group) or water containing 0.01 percent NaI (experimental group). The daily iodide intake per rat was estimated to be 1 to 2 mg. Blood was obtained from the dam and fetuses at term, and serum concentrations of thyroxine (T_4), triidothyronine (T_3), and thyroid-stimulating hormone (TSH) were measured by radioimmunoassay. Each measurement of serum concentration was made from pooled blood from all the fetuses in each litter. Since the mammary gland actively concentrates and secretes iodide into the milk, the lactating, nursing mothers were also given 0.01 percent NaI in their drinking water. After weaning, the young rats continued to receive 0.01 percent NaI in their water until 60 days of age. Blood was pooled from two or three rats at 1 and 5 days of age. In some experiments, thyroids were weighed and the concentrations of T_4 and T_3 were determined in ethanol extracts of the thyroid homogenates digested in trypsin at 37°C for 17 hours in the presence of propylthiouracil (*13*). All experiments were repeated at least twice.

As shown in Table 1, the concentration of TSH in the serum of term fetuses whose mothers were administered iodide was markedly increased compared to control fetuses whose mothers drank tap water alone. Serum T_3 and T_4 concentrations were undetectable in serums from fetuses in both groups, which is similar to the findings in previous studies (*12, 14*). The high concentrations of serum TSH in the iodide-treated groups persisted at 1, 5, and 10 days of age. When serum T_4 and T_3 concentrations could be reliably measured at 5 and 10 days of age in the control rats, they were significantly decreased compared to the iodide-treated rats. The intrathyroid concentrations of T_3 and T_4 in the 10-day-old rats were also significantly decreased in the iodide-treated group [T_4, 59 ± 11 μg/mg (mean ± standard error) compared to 31 ± 9 μg/mg, $P < .05$; T_3, 11 ± 1 compared to 5.5 ± 1 ng/mg, $P < .001$]. By age 18 days the serum TSH concentrations were still significantly increased in the iodide-treated rats, serum T_4 concentrations were the same in both groups, and serum T_3 concentrations were significantly increased in the iodide-treated rats, suggesting resistance to the inhibitory effects of iodide on hormone synthesis in these animals. At all ages, thyroid weights were similar in the control and iodide-treated rats, despite the increased serum TSH concentrations in the latter. The inhibitory effects of iodide

Table 1. Concentrations of TSH, T_4, and T_3 in serum of rats given pharmacologic quantities of iodide. The data are expressed as means ± standard error; probabilities are based on Student's *t*-test; N.D., not detectable.

Age (days)	*N*	TSH (μU/ml)		T_3 (ng/dl)		T_4 (μg/dl)	
		Iodide	Control	Iodide	Control	Iodide	Control
Fetus	4	362 ± 50	82 ± 8*	N.D.	N.D.	N.D.	N.D.
1	4	220 ± 64	51 ± 13†	N.D.	N.D.	0.7 ± 0.2	0.8 ± 0.2
5	12	223 ± 59	99 ± 14‡	N.D.	13 ± 2*	1.0 ± 0.06	1.6 ± 0.1*
10	7	497 ± 106	73 ± 10*	6 ± 2	27 ± 5*	2.6 ± 0.06	3.5 ± 0.1*
18	8	126 ± 13	74 ± 4*	69 ± 3	46 ± 6*	4.0 ± 0.1	4.1 ± 0.1
25	4	44 ± 2	50 ± 7				
35	6	85 ± 18	87 ± 7	101 ± 7	86 ± 4	4.6 ± 0.3	5.2 ± 0.2
60	7	35 ± 25	51 ± 12	99 ± 23	80 ± 10	3.5 ± 0.3	4.1 ± 0.1
Dam	4	60 ± 15	47 ± 14	69 ± 6	48 ± 4‡	3.5 ± 0.4	2.4 ± 0.3

*$P < .001$. †$P < .025$. ‡$P < .05$.

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were no longer observed in rats 25 days and older since serum T_4, T_3, and TSH concentrations were similar in both groups. Iodide administration had no effect on the serum concentrations of T_4 and TSH in the mothers, although a small but significant increase in serum T_3 was observed in the iodide-treated mothers.

These studies suggest that the perinatal rat thyroid is susceptible to the chronic inhibitory effects of iodide on thyroid hormone synthesis. Resistance to the iodide-induced hypothyroidism develops later in neonatal life. It appears that synthesis rather than release of T_4 and T_3 is impaired by excess iodide, since the concentrations of T_4 and T_3 in the thyroid are decreased in the iodide-susceptible neonates. Iodide may also inhibit thyroglobulin synthesis and degradation as reported in adult rats (*15*). The absence of goiter development in spite of the increased serum TSH concentration may be a result of the thyroid tissue being damaged by excess iodide administration, as has been reported in guinea pigs and hamsters (*16*).

Although the iodide intake in the rat was high, it was not much different from the pharmacologic doses administered to humans (150 to 880 mg per day). It may, therefore, be postulated that pharmacologic quantities of iodide administered to women during pregnancy and lactation may induce transient hypothyroidism in the fetus and the newborn. Damage to the developing neonatal brain by hypothyroidism and the significance of the early recognition of hypothyroidism during neonatal life have been emphasized (*17*). The present findings in the perinatal rat and the occurrence of human fetal hypothyroidism following iodide ingestion during pregnancy strongly suggest that pharmacologic doses of iodide should not be given to human pregnant and nursing mothers.

Upon completion of the present studies, it was reported that premature infants bathed with Betadine, an iodine-containing antiseptic agent, develop transient hypothyroidism (*18*). The similarity of these observations in humans to the present findings in the perinatal rat suggests that the perinatal rat provides an excellent model to study the mechanism whereby iodides induce hypothyroidism during perinatal life.

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Giant Interneurons Mediating Equilibrium Reception in an Insect

Abstract. *In the burrowing cockroach* Arenivaga, *two giant interneurons in each connective of the ventral nerve cord provide gravity orientation information. The interneurons receive input from plumb bob-like equilibrium receptors on the ventral surface of the cerci. Our results support the theory that the cerci of cockroaches are specialized equilibrium organs.*

Insects use modes of locomotion requiring precise equilibrium information, yet until recently they were considered to lack receptors such as statocysts sensitive specifically to spatial position and acceleration. Behavioral evidence supports the theory that during terrestrial locomotion proprioceptors at a variety of loci signal joint position and limb loading from which the central nervous system is able to extract information regarding spatial orientation (*1*). However, located on the cerci of certain crickets and cockroaches are pendulous sensilla which may serve that function (*2*, *3*). Those of the cricket show plane preference, and recordings made from the sensory neurons indicate that the impulse frequency is related to the angle of inclination of the sensilla and the animal (*4*). In this report we present physiologic evidence that giant interneurons in the ventral nerve cord of the polyphagid cockroach *Arenivaga* in conjunction with similar specialized sensilla on the cerci are integral parts of a receptor system signaling spatial position.

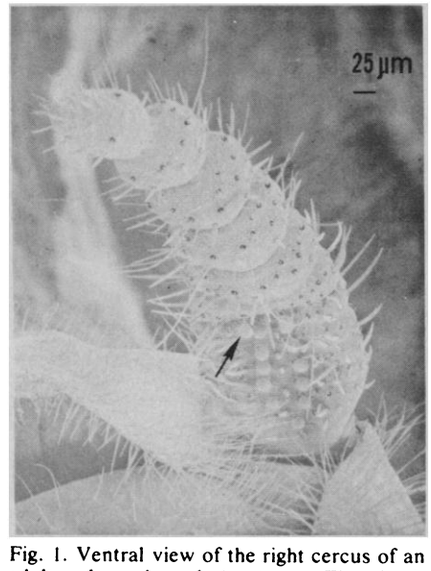

Fig. 1. Ventral view of the right cercus of an adult male cockroach *Arenivaga*. The plumb bob-like sensilla (note arrow) arranged in two rows are equilibrium receptors.

In addition to sensory hairs (trichobothria) and sensory bristles (sensilla chaetica), the ventral surfaces of the cerci of the burrowing cockroach *Arenivaga* sp. (*5*) possess sensory structures shaped like tiny plumb bobs. Those of adult animals are arranged in two rows of seven or eight sensilla (Fig. 1). Each sensillum consists of a dense sphere positioned at the distal end of a slender shaft which inserts into a singly innervated socket (*6*). To determine if interneurons are activated by changes in spatial position via these sensilla, we obtained electrophysiological recordings from the nerve cord during controlled displacement of the insect (*7*).

When the cockroach is maintained in the primary orientation, the giant interneurons are inactive except for sporadic

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