
Effect of Altered Thyroid Status on the Transport of Hepatobiliary Radiopharmaceuticals

Dharampal N. Pahuja and Oliver P.D. Noronha

Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Parel, Bombay, India

The effect of induced hypothyroidism (by feeding an antithyroid drug—propylthiouracil) on the transport and clearance of the routinely used hepatobiliary radiopharmaceuticals—radioiodinated iodine-131 (^{131}I) rose bengal and technetium-99m-N-(4-n-butylphenyl-carbamoylmethyl) iminodiacetate, was studied in the rats. Hypothyroidism was associated with depressed growth and retarded clearance of these radiotracers from the in vivo system. Treatment of the hypothyroid rats with thyroxine (2–5 $\mu\text{g}/100\text{ g b.w. day}$) for 6 wk, restored these parameters towards normal values. These data suggest that delayed clearance of these hepatobiliary tracers could be related to reduced metabolic rate accompanied with the hypotonia and hypomotility of intestine normally observed in the hypothyroid state.

J Nucl Med 26:1168–1171, 1985

The liver is a major end-organ on which the thyroid hormones act, modifying various aspects of its cellular synthetic activity as well as its oxidative and metabolic functions. In turn, the liver metabolizes these hormones which are conjugated and excreted in bile (1). Pathological changes have been described in both hyper- and hypothyroidism. A large number of patients with thyroid dysfunction have been found to have biochemical and clinical abnormalities of liver function (2). A common form of liver injury leading to cholestatic hepatitis caused by the use of different drugs, including thiouracil, has also been noted (3). Caution has also been sounded in the case of unexplained jaundice to examine for hypothyroidism (4). In addition, hypothyroidism causes hypotonia of the gall bladder and an increased incidence of cholelithiasis (5). These pathophysiological alterations in the liver because of an abnormal thyroid-status could influence the fate of many drugs administered in the in vivo system.

Various types of technetium-99m ($^{99\text{m}}\text{Tc}$) agents are currently being used to elicit diagnostic information in nuclear medicine. These agents are normally administered intravenously into patients and the regional biochemistry and physiology of the organ system ascer-

tained by following the kinetics of the injected tracer. It is known that even drug-drug interactions can affect the so-called normal distribution pattern of radiopharmaceuticals (6). Furthermore, altered thyroid status is known to affect the metabolic homeostasis in the in vivo system. However, there is paucity of data in the literature regarding the effect of chronically induced hypo- and hyperthyroidism on the in vivo pharmacokinetics of hepatobiliary agents used in cholescintigraphic studies. This study was therefore initiated to examine the influence of chronic hypothyroidism on the transport of a currently used radiopharmaceutical $^{99\text{m}}\text{Tc}$ -N-(4-n-butylphenylcarbamoylmethyl) - iminodiacetate ($^{99\text{m}}\text{Tc}$]HIDA or $^{99\text{m}}\text{Tc}$]BIDA), and a previously used agent—iodine-131 rose bengal (^{131}I]RB) in the rats.

MATERIALS AND METHODS

Animals

Age-matched young male rats of Wistar strain weighing ~85–100 g were used in this study. The rats were fed normal colony diet containing 20% protein. The rats were divided into the following four groups:

1. Control (cont)—Normal colony diet.
2. Hypothyroid (Hypo)—Hypothyroidism was induced by feeding 0.1% propylthiouracil (PTU)* in the diet for 6 wk.

Received Aug. 14, 1984; revision accepted Jun. 20, 1985.

For reprints contact: Dharampal N. Pahuja, PhD, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Parel, Bombay-400 012, India.

TABLE 1
Effect of Induced Hypothyroidism and Thyroxine Treatment on Final Body Weight (b.w.) and Weights of Liver and Thyroid*

Group	b.w. (g)	Liver		Thyroid	
		Absolute weight (g)	Relative weight (g/100 g b.w.)	Absolute weight (mg)	Relative weight (mg/100 g b.w.)
Control	398 ± 35	12.5 ± 2.7	3.1 ± 0.4	34.0 ± 6.0	8.7 ± 2.2
Hypo†	174 ± 14†	7.1 ± 0.4†	4.1 ± 0.3†	96.0 ± 19.0†	57.0 ± 12.0†
Control + T ₄	470 ± 16†	14.0 ± 1.5†	2.9 ± 0.2†	31.0 ± 4.0†	6.5 ± 0.8†
PT ₄	393 ± 12	13.6 ± 0.7	3.4 ± 0.1	55.0 ± 6.0†	14.0 ± 1.5†
PTU + T ₄	350 ± 36	11.0 ± 2.0	3.0 ± 0.3	75.0 ± 18.0†	22.0 ± 4.0†

* Results are expressed as mean ± s.d. (n = 6–8).

† p < 0.05 – 0.005 compared with the control group.

3. Control + Thyroxine (cont + T₄)†—These rats were maintained on normal colony diet. Thyroxine (2 µg/100 g b.w. day) was given in drinking water for 6 wk.

4. Hypothyroid + T₄—Hypo rats were divided into two subgroups with respect to T₄ treatment.

(a) PT₄—Hypo. rats from group (2) were discontinued from PTU diet (6 wk), and were given T₄ (2 µg/100 g b.w. day) in drinking water for 6 wk along with normal colony diet.

(b) PTU + T₄—These rats were simultaneously given PTU (0.1%) in diet and T₄ (3–5 µg/100 g b.w. day) in drinking water for 6 wk. These rats were given a slightly higher dose of T₄ to compensate for the reduced intake of water.

Radiopharmaceuticals

Aqueous solutions of [¹³¹I]RB† with a specific activity of 2–10 mCi/g RB and [^{99m}Tc]BIDA were used. Iodine-131 rose bengal was diluted to the required concentration with physiologic saline before use. Technetium-99mBIDA was prepared by reconstituting the freeze-dried contents of Sn(II) p-BIDA† “kit” vial with 4.0 ml of Na^{99m}TcO₄ (~400 µCi) in physiological saline.

Each rat from the above group was injected i.v. under ether anaesthesia with 0.4 ml of the radiopharmaceuticals containing 40 µCi [^{99m}Tc]BIDA or 5 µCi [¹³¹I]RB. The rats were housed in individual metabolic cages after the administration of the tracers. They were killed by cardiectomy at 5, 30, and 60 min postinjection. Approximately 5–10 ml blood was collected by the cardiac puncture from the heart 30 sec before cardiectomy. The organs were excised, weighed and counted in a gamma-counter, and percent dose per organ calculated. Six to eight rats were taken for each time interval.

RESULTS

The results are summarized in Tables 1, 2, and 3. Table 1 gives the effect of induced hypothyroidism on

the general growth of the animal. Reduced gain in the body weight (b.w.) associated with the increased weights of the liver (g/100 g b.w.) and the thyroid gland (mg/100 g b.w.) is seen in the hypothyroid rats.

Hypothyroidism was confirmed in these rats by the significant reduction in the circulating levels of the thyroid hormones (cont: 2–4 µg%, hypo: 0.4–0.6 µg%, cont + T₄: 4–6 µg%, hypo + T₄: 2–5 µg%). These changes are restored to normal after their treatment with thyroxine.

Tables 2 and 3 show the biodistribution pattern of the two different types of hepatobiliary agents in important organs of the controls as well as experimental animals with respect to time. The biodistribution pattern during the first 60 min gives a fair picture of the time course of the agents in the different tissues. It also portrays the amount and rate of uptake of the agents in these tissues. It can be seen from Table 2 that the rate and amount of abstraction of [¹³¹I]RB from the blood by the liver is relatively retarded during the early phase (5 min) of transport in hypothyroid rats giving rise to elevated blood levels. A significant fraction of the injected dose is found in the liver as well as in the gut both in control and hypothyroid rats at 30 min postinjection. However, the levels are found to be higher in the livers of hypothyroid rats as compared to that of the controls. This increase is caused by the decreased rate of clearance into the small intestine. Peaking of the tracer activity (increased uptake) in the liver at ~30 min postinjection is noted only in the hypothyroid rats, which once again gives rise to elevated levels of [¹³¹I]RB in the liver. The retardation effect is also seen in the hypothyroid rats by the lower levels in the gut activity. This effect is seen to a better extent at 60 min postinjection.

Technetium-99m BIDA differs from [¹³¹I]RB in that the process of transport of both phases i.e., abstraction from the blood by the liver and clearance from the liver into the small intestine of the gut, is rapid. There is no peaking of the radiotracer activity in the liver as in [¹³¹I]RB. In hypothyroid rats, the rate of uptake of the

TABLE 2
Biodistribution of [¹³¹I]RB In Control and Hypothyroid Rats*

Tissue	5 min		30 min		60 min	
	Control	Hypo	Control	Hypo	Control	Hypo
Blood†	28.0 ± 3.3	46.4 ± 8.2‡	5.9 ± 0.9	7.6 ± 1.9	5.2 ± 1.0	4.8 ± 1.1
Liver	61.1 ± 3.8	48.5 ± 7.0‡	48.9 ± 7.2	63.3 ± 2.5‡	29.1 ± 6.7	49.9 ± 4.1‡
Gut	3.4 ± 0.7	3.3 ± 0.4	32.1 ± 7.4	18.2 ± 5.0‡	51.0 ± 7.5	36.0 ± 4.2‡
Kidneys	1.8 ± 0.4	1.9 ± 0.2	1.9 ± 0.3	2.0 ± 0.2	1.8 ± 0.5	2.0 ± 0.2

* Results are expressed as mean ± s.d. (n = 6–8).

† Blood volume is assumed to be 5% b.w.

‡ p < 0.05–0.005 compared with the control group.

agent from the blood into the liver during the early phase (5 min) is reduced. In addition, the rate of transport from the liver into the gut is markedly reduced. This occurrence is seen to a better extent at 30 min than that at 60 min postinjection (Table 3).

The alterations in the behavior of these radiotracers are highly significant (p < 0.05 to p < 0.005) in the hypothyroid rats with respect to both [¹³¹I]RB and [^{99m}Tc]BIDA. The kidney levels remain unaffected in the hypothyroid rats, thereby implying that there is no competition for the radiotracers by this excretory route in the experimental animals.

DISCUSSION

Normal functioning of the liver, a major target organ for thyroid hormone action, is disturbed in thyroid disorders. Reduced gain in body weight accompanied with the enlargement of the thyroid gland is noted in the hypothyroid rats. These rats also have smaller livers, although the relative liver weights (g/100g b.w.) are significantly higher in the hypothyroid rats (Table 1). These observations are consistent with our earlier reports (7,8). Such alterations have been explained by the higher protein and glycogen contents of the liver in the hypothyroid rats (8,9). All parameters are restored towards the control values after the hypothyroid rats are treated with thyroxine.

The hepatobiliary agent once administered into the blood circulation is avidly taken up by the liver parenchymal cells. Since the rat does not have a gall bladder, the agent is then transported into the small intestine, and thereafter, the large intestine of the gut. Therefore, the blood, liver, and gut (small and large intestine) constitute the major tissues of interest. The kidneys have also been included in order to evaluate its contribution if the tracer is excreted out by another excretory pathway in the experimental group of animals because of their altered physiologic status. Technetium-99mBIDA and [¹³¹I]RB are both hepatobiliary agents labeled with different tracers—^{99m}Tc and ¹³¹I. Both are routinely used in clinical practice. The former exists as an inorganic anion while the latter forms an organic anionic species in aqueous solution when normally used

as i.v. injectables. They differ in the rate of hepatobiliary excretion; [¹³¹I]RB is cleared at a slower rate as compared to [^{99m}Tc]BIDA in the control animals. Extensive studies regarding their radiobiologic profiles in normal rats have been reported recently (10,11).

The in vivo tissue distribution pattern of both these agents in the hypothyroid rats clearly indicates that the transport (i.e., uptake of the tracers from the blood by the liver parenchymal cells and excretion into the gut) is significantly retarded (Tables 2 and 3). The possibility that PTU per se may cause the delayed clearance of these radiotracers is not substantiated by our results. By supplementing thyroid hormone in drinking water to these rats (either after PTU withdrawal or simultaneously along with PTU) restored all the parameters towards control levels. In fact a similar pattern is also seen in the thyroidectomized rats. In the case of [¹³¹I]RB there is a peaking of the liver activity at 30 min postinjection. Such an effect is not observed with [^{99m}Tc]BIDA, because of its relatively faster in vivo transit time as compared to that of [¹³¹I]RB. The excretory retardation effect is seen to a greater extent during the early phase of the in vivo transit and gradually falls off over extended periods. The retardation of the transport of these tracers, however, does not affect the overall hepatobiliary characteristics, as seen by the total amount cleared by the hepatobiliary pathway and the unchanged pattern of uptake of the tracers by the urinary route (kidneys and bladder).

The delayed clearance of these hepatobiliary tracers could be related to the lowered basal metabolic rate accompanied with the reduced catabolism in the hypothyroid state. A delayed removal of glucose from the blood has been noted in hypothyroid rats (12). A marked diminution of gastrointestinal motility and hypotonia of the gall bladder leading to cholelithiasis has also been noted in the hypothyroid state (5,12). It is also possible that increased liver weight caused by higher contents of protein and glycogen may have some role to play in the ability of the hepatocytes to extract the radiopharmaceuticals in the state of altered blood flow (both hepatic and portal) in hypothyroid rats. The role of thyrotropin releasing hormone (TRH) in favouring the accumulation of tracer activity and delaying gall

TABLE 3
Biodistribution of [^{99m}Tc]BIDA In Control and Hypothyroid Rats*

Tissue	5 min		30 min		60 min	
	Control	Hypo	Control	Hypo	Control	Hypo
Blood†	2.8 ± 0.4	9.5 ± 2.5**	1.4 ± 0.7	2.8 ± 1.1	1.0 ± 0.7	2.5 ± 1.0
Liver	54.8 ± 4.9	64.0 ± 3.2	7.2 ± 2.2	28.4 ± 6.4‡	2.4 ± 0.8	10.5 ± 3.5‡
Gut	30.6 ± 4.3	13.5 ± 3.1**	83.8 ± 5.5	59.5 ± 7.4‡	91.4 ± 4.1	76.4 ± 5.8‡
Kidneys	1.8 ± 0.4	1.5 ± 0.4	2.2 ± 1.2	1.9 ± 0.6	2.0 ± 0.9	2.7 ± 0.9

* Results are expressed as mean ± s.d. (n = 6-8).

† Blood volume is assumed to be 5% b.w.

‡ p < 0.05-0.005 compared with the control group.

bladder emptying has been recently reported (13). Although we have not measured the circulating levels of TRH in our hypothyroid rats, it is known that thyroid hormone deficiency or its lack stimulates TRH release from the hypothalamus. In fact a twofold increase in TRH receptors has been observed in hypothyroid rats. The elevated levels are completely reversed by the treatment with the thyroid hormone (14). TRH has also been found to produce a variety of effects on the gastrointestinal tract including altered bile flow (13). Thus, TRH could have a major role to play in the delayed clearance of radiopharmaceutical activity from the blood and liver in these hypothyroid rats.

The biodistribution pattern of both these radiopharmaceuticals was also studied in the hypothyroid rats after they were treated with the thyroid hormone for 6 wk. This resulted in the restoration of the transport of both these hepatobiliary agents towards control values. However, no change was seen in the control rats treated with the thyroid hormone.

This study thus reveals that reduced gastrointestinal motility and hypotonia of the hepatobiliary route, either alone or accompanied with TRH effect, could be responsible for the retarded transport of these hepatobiliary radiopharmaceuticals in hypothyroidism. In short, it has been shown that: 1) Hypothyroidism in these animals results in the delayed clearance of both fast ([^{99m}Tc]BIDA) and relatively slower ([¹³¹I]RB) agents that are routinely used in clinical practice; 2) The retardation effect is seen to a significant extent at least during the first 60 min; and 3) supplementing T₄ to these rats restores the transport towards control levels. The clinical implications of this study, however, need further investigation.

FOOTNOTES

* Koch Light Laboratory, England.

† Sigma Chemical Co., USA.

‡ Radiopharmaceuticals Div., B.A.R.C., Bombay, India.

ACKNOWLEDGMENT

This study was supported in part by the International Atomic Energy Agency, Vienna.

REFERENCES

- Oppenheimer JH: Thyroid hormones in liver. *Mayo Clinic Proc* 47:854-863, 1972
- Klion FM, Segal R, Schaffner F: The effect of altered thyroid functions on the ultra structure of the human liver. *Am J Med* 50:317-324, 1971
- Patrick RS, McGee JO'D: Liver injury from drugs and toxins. In *Biopsy Pathology of the Liver*, Walker F, Neville AM, eds, London, Chapman and Hall Ltd., 1980, pp 140-167
- Schubert WK: Liver disease in infancy and childhood. In *Diseases of the Liver*, Schiff L., ed. Philadelphia, J.B. Lippincott Co., 1975, pp 1173-1245
- Kaunitz JD, Sleisenger MH: Effects of systemic and extra intestinal disease on the gut. In *Gastrointestinal Disease Pathology, Diagnosis, Management*. Sleisenger MH, Fordtran JS, eds, Philadelphia, W.B. Saunders Co., 1983, pp 369-404
- Spitznagle LA, Jay MJ: Factors influencing radiopharmaceutical distribution. In *Radiopharmaceuticals: Structure Activity Relationships*, Spencer RP, ed, New York, Grune and Stratton Inc., 1981, pp 130-139
- Pahuja DN, Ganatra RD, Shah DH: Effect of thionamides on adenylcyclase activity and phospholipogenesis in rat thyroids. *Biochem Pharmacol* 27:487-489, 1978
- Nadkarni GD, Deshpande UR, Pahuja DN: Effects of propylthiouracil, methimazole, and thyroidectomy on liver and plasma proteins: Differential response to thyroxine. *Exp Clin Endocrinol* 81:291-296, 1983
- Yatin MB, Wannemacher RW Jr, Banks WL Jr: Effects of thiouracil and of thyroidectomy on liver protein metabolism. *Endocrinology* 74:878-884, 1964
- Noronha OPD: Radiobiologic (tissue) profiles of ^{99m}Tc-diagnostics: Behavior of ^{99m}Tc-N-(p-butylphenylcarbamoylmethyl) iminodiacetic acid, (^{99m}Tc-p-butyl HIDA), in normal rats. *J Radioanalytical Nucl Chem Lett* 94:139-148, 1985
- Noronha OPD, Sewatkar AB: A reassessment of the hepatobiliary propensities of ¹³¹I-rose bengal in the rat. *Isotopenpraxis* 21:92-95, 1985
- Utiger RD: Hypothyroidism. In *Endocrinology Vol. 1*, De Groot L J, et al, eds. New York, Grune and Stratton, 1979, pp 471-488
- Shafer RB, Marlette JM, Morley JE: The effects of lipomul, CCK and TRH on gall bladder emptying. *Clin Nucl Med* 8:66-69, 1983
- De Lean A, Ferland L, Drouin J, et al: Modulation of pituitary thyrotropin releasing hormone receptor levels by estrogens and thyroid hormones. *Endocrinology* 100:1496-1504, 1977