Effect of Endotoxin Fever on Plasma Clearance of Thyroxine and Tri-iodothyronine: Concise Communication

Michael K. Elson, Martin M. Oken, and Rex B. Shafer

VA Medical Center and University of Minnesota, Minneapolis, Minnesota

Endotoxin-induced fever in rabbits causes a rapid decrease in serum T_3, a reciprocal rise of 3,3′,5′-tri-iodothyronine (rT_3), and a less marked reduction in T_4 with a rebound at 24 hr. To answer the question whether the alteration in hormone levels was the result of a decrease in T_3 or T_4 production and release or of an increase in T_3 and T_4 metabolism, we measured the disappearance of $[^{125}I]T_4$ and $[^{125}I]T_3$ during endotoxin-induced fever and externally applied heat. Results showed no significant difference in disappearance of $[^{125}I]T_4$ or $[^{125}I]T_3$. This suggests that the rapid change in T_3 levels associated with endotoxin fever is due to an inhibition of thyroid production and peripheral conversion, and not to increased metabolism of hormones.

J Nucl Med 23: 241–244, 1982

Low serum T_3 and T_4 levels are common in infectious illness (*1–6*). The cause and physiologic significance of the low serum T_3 levels is still unknown. Using a rabbit model, we previously reported a rapid (within 4 hr) reduction in serum T_3 levels and a reciprocal rise in 3,3′,5′-tri-iodothyronine (rT_3) levels during endotoxin-induced fever (*7*). Serum T_4 levels showed a less marked reduction during endotoxin fever and rebounded above basal levels at 24 hr. No similar effects were observed with hyperthermia. These results raised the question of whether this rapid alteration of thyroid hormone levels was related to a decrease in hormone production and release or to an increase in metabolism. In an attempt to answer this question, we injected rabbits with high-specific-activity $[^{125}I]T_3$ or $[^{125}I]T_4$, induced fever with endotoxin or raised body temperature with externally applied heat, and then compared the disappearance of I-125 with that in controls.

MATERIALS AND METHODS

Twenty-four previously conditioned New Zealand white rabbits (3.0–4.1 kg) were placed in loose-fitting stocks and their rectal temperatures were monitored for 6 hr (*8*). Fever was induced in eight rabbits by i.v. injection of *E. coli* endotoxin.* The minimum dose of this endotoxin that will produce a 0.5 °C fever response at 4 hr after injection (MPD-4) was 0.004 μg/kg body weight. A dose of 80 times the MPD-4 was given to ensure that all rabbits would develop significant fevers. Hyperthermia was induced in eight additional rabbits by application of 55-W heating pads as previously reported (*7*). The remaining eight rabbits provided a control group.

Twelve of the rabbits were used to monitor $[^{125}I]T_4$ ($*T_4$) disappearance and twelve were used for $[^{125}I]T_3$ ($*T_3$) disappearance. Within each group, four rabbits were controls, four were injected with endotoxin, and four were heated with heating pads.

The $*T_3$ and $*T_4$ were carrier free† ($T_3 > 3300$ μCi/μg, $T_4 > 5500$ μCi/μg). The labeled hormones were each adsorbed to 10 ml of normal rabbit serum and dialyzed against a dilute buffer (10 n*M* PO_4, 150 m*M* NaCl, pH 7.4) until there was less than 1% free I-125 as demonstrated by Sephadex chromatography (*9*). The dialyzed sera carrying the $[^{125}I]T_3$ or $[^{125}I]T_4$ were sterilized by filtration through a 0.22-μ filter.

Each rabbit received 5–10 μCi of $*T_3$ or $*T_4$ intravenously in 1 ml of diluted normal rabbit serum. Rabbits that received endotoxin were injected with a labeled thyroid hormone at the same time. Seven to 10 min later, the zero-time sample was taken. Rabbits were bled from

Received July 29, 1981; revision accepted Oct. 19, 1981.

For reprints contact: Dr. Shafer, Nuclear Medicine Service (115), VA Medical Center, 54th St. and 48th Ave. So., Minneapolis, MN 55417

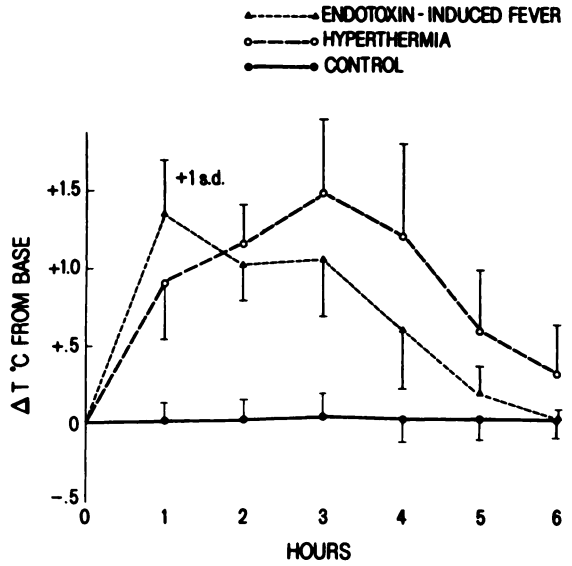

FIG. 1. Temperature changes in endotoxin fever, in heat-induced hyperthermia, and in control rabbits. Vertical bars represent 1 s.d.

the central ear artery. Samples were taken at 0, 2, 4, 6, and 24 hr. The samples were allowed to clot, then centrifuged, and the serum aspirated. Radioactivity levels in the sera were compared with that of the 0 sample and reported as percent.

The percentages for each treatment group are reported as mean ± one standard deviation. Student's unpaired two-tailed *t*-test was used to evaluate the significance of differences between between the control, endotoxin-fever, and hyperthermia groups.

RESULTS

The eight rabbits that received endotoxin developed significant fevers within one hour; it was sustained through 3 hr and then declined to basal levels by 6 hr. Similar temperature changes were reached in the eight rabbits with heat-induced hyperthermia. In the eight control rabbits the temperature remained constant (Fig. 1).

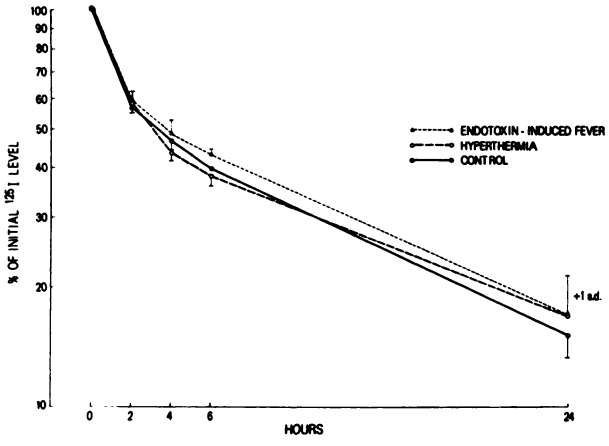

FIG. 2. Plasma disappearance of [^{125}I]T_4 in endotoxin fever, in heat-induced hyperthermia, and in control rabbits. Vertical bars represent 1 s.d.

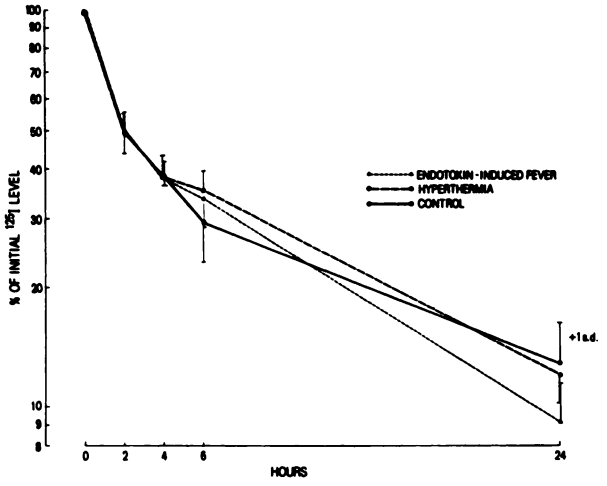

FIG. 3. Plasma disappearance of [^{125}I]T_3 in endotoxin fever, in heat-induced hyperthermia, and in control rabbits. Vertical bars represent 1 s.d.

There was no significant difference in the disappearance of *T_4 between the three groups of rabbits at 2, 4, and 24 hr. At 6 hr there was a difference between the endotoxin-fever group and the hyperthermia group ($p \leq 0.05$), but neither group was significantly different from the control group (Fig. 2).

There was no significant difference in the disappearance of *T_3 between the endotoxin-fever, hyperthermia, and control groups at 2, 4, 6, and 24 hr (Fig. 3).

Interference of residual radioactivity prevented quantitation of serum thyroid hormone levels during the plasma disappearance studies. However, comparative values of thyroid hormone levels during endotoxin-induced fever and externally applied heat are included in Table 1.

DISCUSSION

The effects of nonthyroidal illness on the pituitary-thyroid axis have been of clinical interest for more than 20 yr. A variety of animals and man have been studied for the effects of infectious illness, toxins, and other stress. The reports of these studies have been diverse and sometimes contradictory. Two reviews have critically examined the literature (*10,11*). Their conclusions may be summarized by the hypothesis that infectious illness causes an early suppression of TSH release and a consequent decrease in T_4 secretion. The rate of the peripheral conversion of T_4 to T_3 is also reduced. At the same time there is an overall increase in the metabolism of T_4 and T_3, but this increase is dependent upon both the nature of the infectious agent and the specific effect of the infectious illness. Serum levels of T_4 and T_3 drop during the acute phase of illness and may rebound above normal upon recovery.

TABLE 1. THYROID-HORMONE LEVELS DURING ENDOTOXIN-INDUCED FEVER AND EXTERNALLY APPLIED HEAT

Hours	Controls			Fever			Hyperthermia		
0	272 ± 36	23 ± 33	2.72 ± 0.81	203 ± 75	46 ± 49	2.6 ± 1.1	292 ± 52	72 ± 64	4.2 ± 1.0
2	274 ± 37	—	2.56 ± 0.71	184 ± 61	—	2.5 ± 1.1	265 ± 55	—	3.4 ± 0.8
4	255 ± 35	—	2.45 ± 0.70	164 ± 60	—	2.2 ± 1.0	244 ± 41	—	3.2 ± 0.7
6	247 ± 36	33 ± 28	2.37 ± 0.75	105* ± 45	403* ± 297	2.1 ± 1.0	250 ± 39	105 ± 100	3.2 ± 0.9
24	262 ± 35	27 ± 21	2.62 ± 0.72	153 ± 65	166 ± 150	4.5† ± 1.4	272 ± 30	67 ± 62	3.3 ± 1.0
	T_3 μg/dl	rT_3 pg/ml	T_4 μg/dl	T_3 μg/dl	rT_3 pg/ml	T_4 μg/dl	T_3 μg/dl	rT_3 pg/ml	T_4 μg/dl

* $p < 0.001$.
† $p < 0.05$.

We have previously demonstrated that endotoxin-induced fever in rabbits causes a rapid decrease in T_3 levels, which continues even as the fever decreases to normal (*7*). The T_3 levels return toward basal levels by 24 hr. There was a reciprocal rise of rT_3 levels. There was no such change in T_3 or rT_3 levels with hyperthermic rabbits and controls. The serum T_4 levels of endotoxin-fever rabbits decrease less impressively during the initial 6 hr but show a large rebound at 24 hr (to 173% of basal levels). Controls' serum T_4 levels are essentially unchanged, whereas the hyperthermic rabbits' serum T_4 levels decreased and remained below basal levels at 24 hr.

In the present study we measured the disappearance of $*T_4$ and $*T_3$ during endotoxin-induced fever and hyperthermia, compared with controls, to determine whether the rapid alteration in thyroid hormone levels was related to a reduction in hormone release or to an increase in metabolism. There was virtually no difference in the disappearance of $*T_4$ between the endotoxin-fever, hyperthermia, and control groups. The $*T_4$ remaining at 24 hr was in good agreement with that previously reported for New Zealand white rabbits: 16.7% ± 3.2 s.d. contrasted with 20% (*12*).

There was no difference in disappearance of $*T_3$ between endotoxin-fever, hyperthermia, and control groups. However, the amount of I-125 remaining at 24 hr is about ten times that previously reported (11.2% ± 3.0 s.d. versus 1.3%) (*12*). The [^{125}I]T_3 used in our study was labeled by exchange, so all iodine atoms of the T_3 would have an equal probability of being I-125. Consequently, any iodine in the T_3 metabolites would also be I-125. We measured the radioactivity in serum, so any circulating T_3 metabolites would be included in our measurements. Takagi et al. (*12*) measured the $*T_3$ by immunoprecipitation. However, it is doubtful whether the increased precision of immunoprecipitation can account for most of the tenfold difference. The explanation may lie with the actual dose of T_3 administered. Takagi et al. used 100 μCi of I-125-labeled T_3 that had a specific activity of 500 μCi/μg. This corresponds to 200 ng of T_3 administered to a 1.9-kg rabbit. Assuming a blood volume of 55.6 ml/kg (*13*) and serum T_3 levels of 137 ng/100 ml (*12*), the addition of 200 ng of T_3 would raise the serum T_3 level to over twice the basal level. Such a large dose may have influenced the excretion rate. We used a T_3 of higher specific activity and a lower dose of radioactivity, administering about 3 ng of T_3 to 3.6-kg rabbits. This would be about 1% of the endogenous T_3 and should impose a negligible burden on normal T_3 physiology.

Recently, Kaptein et al. (*14*) used pulsed tracer doses of labeled T_4 and T_3 to study alterations in peripheral thyroid-hormone metabolism in critically ill patients. Their results showed that the low T_3 values found in critical illness are related to a decreased T_3 production rate. In the present study, we have shown that the rapid reduction in T_3 levels related to endotoxin fever is not due to increased T_3 metabolism. This suggests that the observed changes in T_3 levels associated with endotoxin fever are due to an inhibition of thyroid production or peripheral conversion of T_3 and agrees with the demonstration by Kaptein et al. of reduced T_3 production in critically ill patients. The inhibition of T_3 production appears to be related to endotoxin fever and not to increased body temperature *per se*, since hyperthermia causes a reduction in T_4 levels but no change in T_3 levels.

FOOTNOTES

* *E. coli* 0127:B8, Difco, Detroit, MI.
† New England Nuclear, North Billerica, MA.

ACKNOWLEDGMENT

A portion of this paper was presented at the 28th Annual Meeting of the Society of Nuclear Medicine, Las Vegas, Nevada, June 1981.

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