Effects of Fever and Hyperthermia on Thyroid Function

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Thyroid hormones in man are affected by acute and chronic febrile states. To define these acute changes, we used a previously described rabbit model. Serum levels of T_3, rT_3, and T_4 were measured at 0, 2, 4, 6, and 24 hr following injection of 1 μg *E. coli* endotoxin, and during heat-induced hyperthermia. All rabbits receiving endotoxin developed fever with peaks at one hour ($\Delta T = 1.1°C$) and three hours ($\Delta T = 1.4°C$); they then defervesced to base levels at 6 hr. Similar temperature elevations occurred with heat-induced hyperthermia. Results show that endotoxin-induced fever produces changes similar to those reported during infections in man, and more rapidly than previously recognized. These include a prompt decrease in T_3, reciprocal rise in rT_3, and an initially reduced T_4 that rebounds above basal levels. These findings may represent suppressed TSH release, alteration of peripheral monodeiodination of T_4 from T_3 to rT_3, or enhanced clearance of T_3. Heat-induced hyperthermia, except for slight decrease in T_4 at 6 and 24 hr, had little effect on thyroid hormones.

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With the availability of radioimmunoassays for the measurement of L-triiodothyronine (T_3), 3,3′,5′-triiodothyronine (rT_3), and thyroxine (T_4), it has been possible to show the effects of acute and chronic febrile states on thyroid function. Recent reports have indicated that thyroid hormones in man are affected by acute and chronic febrile states (*1-3*). Serial studies in the acute stages of febrile illnesses have indicated a reduction of serum levels of thyroid hormones (*4-6*), which may be followed by a rebound hypersecretion during recovery (*2*). These reports describe relatively delayed effects of fever based on hormone data sampled at daily or longer intervals. Serum levels of T_3 have been observed to fall as early as the first day of septic fever (*7*). Specific data on serum T_4 levels are contradictory. Levels have been reported to fall (*1,4*), to remain unchanged (*3,5*), or to rise (*2,6*) during infectious disease. This variability has been attributed to the nature of the infectious agent and to the specific effect of the infectious process (*7*).

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While the effects of fever on thyroid hormones have been observed for some time, it has been only recently that the effects of increased body temperature have been reported. In 49 euthyroid patients with hyperpyrexia, serum T_3 levels were found to decrease gradually with increasing body temperature (*8*). Body temperatures of 38°C produced T_3 levels that were below normal, whereas temperatures of 40°C produced T_3 levels that were observed only in clinically hypothyroid patients.

To approach the question of the relationship between thyroid hormones, hyperthermia, and endotoxin-induced fever, we used a rabbit model previously described (*9*). To minimize contributions from a specific infectious agent, endotoxin was used to induce fever. Similar elevations of body temperature were achieved using heat-induced hyperthermia. Serum levels of T_3, rT_3, and T_4 were measured in samples obtained serially during hours immediately following endotoxin-induced fever, and at similar time intervals with heat-induced hyperthermia.

MATERIALS AND METHODS

Thirty-two previously conditioned New Zealand white

rabbits (2.8-3.2 kg) were placed in loose-fitting restraining stocks and their rectal temperatures monitored for 6 hr (9). Sixteen rabbits received 1 μg of endotoxin (*E. coli* 0127:B8*) by i.v. injection. The minimum dose of endotoxin to produce a 0.5° fever response at 4 hr after injection (MPD-4) was 0.004 μg/kg body weight. A dose of eighty times the minimum dose was given to ensure that all rabbits would develop significant fevers.

Eight rabbits were exposed to heat-induced hyperthermia. Their backs were first covered with folded hand towels; they were then wrapped in 55-watt heating pads. In order to effect increased body temperatures, it was also necessary to cover the ears with the heating pads. Both the animals and the heating pads were then draped with a folded blanket for further insulation. The heating pads were powered through individual autotransformers, initially set for full line voltage. By 2 hr, all rabbits had body temperatures elevated about 1°C from their basal temperatures. The voltage to the heating pad was then reduced to maintain elevated body temperature for an additional 2 hr. At 4 hr the heating pads and blankets were removed to allow body temperature to return to normal.

The remaining eight rabbits were similarly fitted in their restraining stocks but received a volume of saline equal to the volume of endotoxin given the treated rabbits. All animals were monitored sequentially for 6 hr. Blood samples were obtained from the central ear artery before endotoxin injection, and at 2, 4, 6, and 24 hr after. All samples from a particular rabbit were run in duplicate and were included in the same assay run to eliminate intraassay variation.

Serum levels of T_3 were measured by radioimmunoassay using a specific in-house T_3 antiserum that has less than 0.05% cross-reactivity with T_4. Polyethylene glycol was used for the separation of antibody-bound and free hormone. The interassay C.V. was 2.7%. Reverse T_3 was determined using a commercial radioimmunoassay kit.† The interassay C.V. was 12.0%. Serum levels to total T_4 were obtained using the Immunophase Free T_4 radioassay system.‡ The interassay C.V. was 2.9%.

Serum levels and percent changes were given as mean ± s.e.m. The Student's t-test was used to evaluate the significance of observed differences. Serum levels were compared with control values at 2, 4, 6, and 24 hr.

RESULTS

The 16 rabbits receiving endotoxin developed a biphasic fever curve with peaks at 1 hr (ΔT = 1.1°C), and 3 hr (ΔT = 1.4°C), and returned to base levels by the sixth hour after injection. Similar temperature elevation occurred in the eight rabbits with heat-induced hyperthermia. The temperatures of the control rabbits remained constant (Fig. 1).

The pretreatment levels of thyroid hormones in all rabbits varied. The total T_3 level range was 78-380 ng/dl; the total T_4 level range was 1.5-4.2 μg/dl; and the rT_3 levels ranged from 0-150 pg/ml. Changes in hormone levels as a function of endotoxin-induced fever or heat-induced hyperthermia are expressed graphically as percent of basal level (Figs. 2-4).

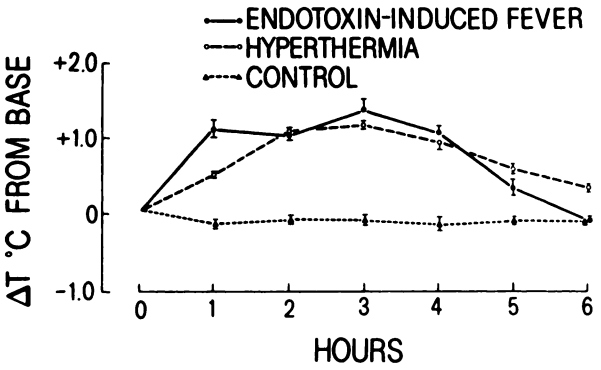

FIG. 1. Temperature changes in endotoxin-treated rabbits, heat-induced hyperthermia, and control animals. Rabbits receiving endotoxin developed a biphasic fever curve with peaks at 1 hr (ΔT = 1.1°C), at 3 hr (ΔT = 1.4°C), and with return to base levels at 6 hr.

There was no significant difference in total T_3 level between hyperthermic rabbits and controls. In the endotoxin-treated rabbits, total T_3 levels at 0 and 2 hr showed no significant difference. However, at 4 hr the febrile rabbits' total T_3 levels were 80% ± 2.8 s.e.m. of basal levels ($p < 0.05$), and at 6 hr were 51% ± 2.7 s.e.m. of basal levels ($p < 0.001$). The total T_3 levels of the febrile rabbits returned to only 77% ± 4.6 s.e.m. of basal levels by 24 hr ($p < 0.05$) (Fig. 2).

The rT_3 levels were measured at 0, 6, and 24 hr. The rT_3 levels of the control rabbits and those with heat-induced hyperthermia were essentially unchanged. At 6 hr, the rT_3 levels of the endotoxin-treated rabbits were

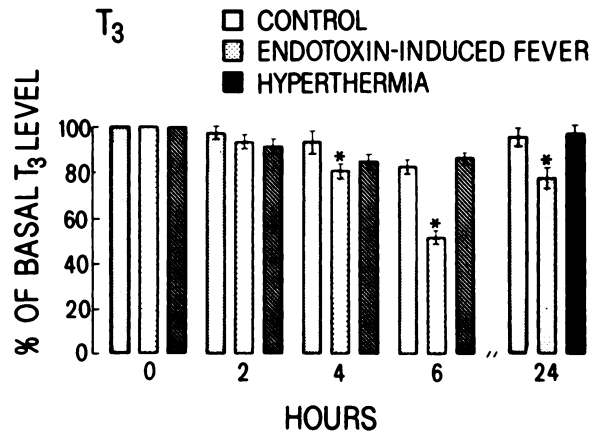

FIG. 2. Total T_3 levels in control animals, endotoxin-induced fever, and heat-induced hyperthermia. At 6 hr, total T_3 levels were 51% ± 2.7 s.e.m. of basal levels in endotoxin-treated animals ($p < 0.001$). There was no significant difference between hyperthermic rabbits and controls. (*) $p < 0.025$ at 4 and 24 hr, and $p < 0.001$ at 6 hr, compared with controls.

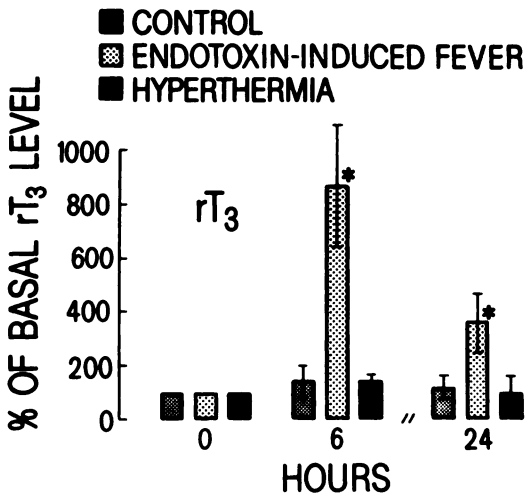

FIG. 3. rT_3 levels in control animals, endotoxin-induced fever, and heat-induced hyperthermia. At 6 hr, rT_3 levels were 870% ± 230 s.e.m. of basal levels in endotoxin-treated animals ($p < 0.001$). There was no significant difference between hyperthermic rabbits and controls. (*) $p < 0.001$ at 6 hr and $p < 0.05$ at 24 hr, compared with controls.

greatly increased to 870% ± 230 s.e.m. of basal levels ($p < 0.001$). At 24 hr, the rT_3 levels were still elevated ($p < 0.05$) (Fig. 3).

The T_4 levels of the endotoxin-treated rabbits showed a slight decrease at 6 hr, when the serum T_4 was 81% ± 3.4 s.e.m. of basal (not significantly different when compared with controls). At 24 hr the serum T_4 levels had rebounded to 173% ± 12.5 s.e.m. of the basal ($p < 0.05$). In the rabbits with heat-induced hyperthermia, there was a decrease in T_4 levels at 2 and 4 hr to 76% ± 3.2 s.e.m. of basal ($p < 0.05$), and it remained below basal at 6 and 24 hr. The T_4 levels of the control rabbits were not significantly different from basal levels throughout the 24-hr period (Fig. 4).

DISCUSSION

The effects of nonthyroidal illness on the pituitary-thyroid axis has been of interest for more than 20 years. 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 recent 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 both on the nature of the infectious agent and on 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 (*7*).

Our data from rabbits with endotoxin-induced fever fit this hypothesis. We were unable to measure rabbit TSH, but can infer a suppression of TSH release by the changes in the rabbits' T_4 levels. Interruption of T_4 release is more than adequate to account for the T_4 lost during the rabbits' febrile period. The 19% reduction in T_4 levels between 0 and 6 hr is equivalent to a drop of 0.5 μg/dl. This corresponds to an absolute loss of 0.85 μg T_4 for a 3-kg rabbit with a blood volume of 55.6 ml/kg (*12*). A normal 3-kg rabbit, with a T_4 production rate of 1.74 μg T_4/kg-day (*13*), would release 1.31 μg T_4 during a 6-hr period; this is more than the 0.85 μg lost by a febrile rabbit. An abrupt end of the suppression by removal of the febrile stimulus could explain the rebound of T_4 above basal levels.

Most circulating T_3 is derived from monodeiodination of T_4 in the peripheral tissues. The metabolic clearance rate of T_3 is 17 times that for T_4 in rabbits (*13*), so a relatively small change in T_3 production or clearance rates reported in man (*14*) could account for the greater reduction in serum T_3 levels, compared with serum T_4 levels.

The relationship between the time course of endotoxin-induced fever and serum T_3 levels was complex. Two hours after induction of endotoxin fever, during the period of body-temperature increase, there was no significant change in serum T_3 levels. At 4 hr, however, the febrile rabbits' serum T_3 levels were 80% of basal ($p < 0.05$) and the fevers were decreasing. The fevers resolved to normal during 4–6 hr, while the serum T_3 levels continued to decline to 51% of basal levels ($p < 0.001$). The

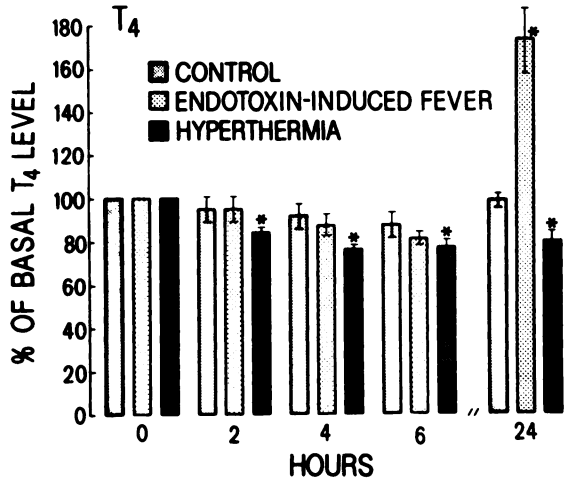

FIG. 4. Total T_4 levels in control animals, endotoxin-induced fever, and heat-induced hyperthermia. At 6 hr, total T_4 levels were 81% ± 3.4 s.e.m. of basal levels in endotoxin-treated animals ($p < 0.05$). At 24 hr this had rebounded to 173% ± 12.5 s.e.m. ($p < 0.05$). In hyperthermic rabbits, total T_4 levels were decreased to 76% ± 3.2 s.e.m. ($p < 0.05$), and remained depressed at 6 and 24 hr. (*) For hyperthermia, $p < 0.005$ at 2 hr, $p < 0.001$ at 4 hr, $p < 0.025$ at 6 hr, and $p < 0.010$ at 24 hr, compared with controls. (*) For endotoxin-induced fever, $p < 0.050$ at 24 hr.

drop in serum T_3 levels was coincident with the resolution of the fevers and suggests a possible role of thyroid hormones in modulating the febrile response.

Although the basal levels varied widely, the percentage reduction in T_3 levels was similar in all animals with endotoxin-induced fever. The lowest basal T_3 level observed (78 ng/dl) was reduced to 46 ng/dl (50% of basal) at 6 hr, and the highest T_3 level (380 ng/dl) was reduced to 132 ng/dl (37% of basal) at 6 hr.

While the primary monodeiodination of T_4 results in T_3, monodeiodination from the tyrosyl ring to rT_3 may also occur. In patients with acute illness, serum rT_3 levels are known to rise, whereas serum T_3 levels fall (*15*). This alteration in peripheral monodeiodination from production of a hormonally active compound to an inactive one is assumed to be due to an inhibition of peripheral T_3 formation with similar inhibition of reverse T_3 clearance. In our rabbits with endotoxin-induced fever, serum levels of rT_3 were greatly increased 6 hr after fever induction. At 24 hr the serum rT_3 levels had decreased, but still remained above basal levels.

From our data it appears that elevation of the basal body temperature produces a slight decrease in serum T_4 at 6 and 24 hr. During endotoxin-induced fever, rapid changes in thyroid hormones are observed, paralleling those reported during infectious illness in man. These findings include a reduced T_3 level, rT_3 levels that exhibit a reciprocal rise, and T_4 levels that are initially reduced and then rebound above basal levels. These findings suggest that an infectious febrile illness could cause an early suppression of TSH release and consequent decrease in T_4 secretion. With a subsequent reduction in the rate of T_4 conversion to T_3 and a concurrent increase in production of rT_3, there is an attempt at energy conservation by the formation of a hormonally inactive metabolite in place of a hormonally active compound.

Previous studies of the alteration of thyroid hormone levels during acute infectious illness in man have measured hormone levels at daily or longer intervals and have not documented rapid changes in less than 24 hr. By sampling during the hours immediately following induction of endotoxin fever and heat-induced hyperthermia, this study demonstrates rapid alteration of thyroid hormone levels, and may suggest a role of thyroid hormones in modulating the febrile response.

FOOTNOTES

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‡ Corning Medical, Medfield, MA.

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