JCI The Journal of Clinical Investigation

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J Clin Invest. 1972;51(4):788-795. https://doi.org/10.1172/JCI106873.

Research Article

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ABSTRACT Previous work has demonstrated that acute pneumococcal infections in man and in the rhesus monkey are accompanied by accelerated metabolic disposal of L-thyroxine (T_4). In order to study the influence of acute pneumococcal infection on the kinetics of hormone distribution, the early cellular uptake of T_4 (CT_4), reflecting the net effect of plasma and cellular binding factors, was assessed in rhesus monkeys from the differences in instantaneous distribution volumes of T_4-^{131}I and albumin-^{125}I during the first 60 min after their simultaneous injection. Hepatic and renal uptakes of ^{131}I were also determined. Plasma binding of T_4 was assessed by measuring the per cent of free T_4 (% FT_4) in serum. Six monkeys were studied 12 hr (INF-12) and seven 24 hr (INF-24) after intravenous inoculation with *Diplococcus pneumoniae;* seven controls were inoculated with a heat-killed culture. CT_4 at 60 min as per cent administered dose was 31.5 ±2.0 (mean ±SE) in INF-12 and 33.0 ±0.8 in INF-24, values significantly greater than control (22.4 ±1.3). By contrast, mean % FT_4 was identical in control and INF-12 (0.028 ±0.002 and 0.028 ±0.001) and variably increased in INF-24 (0.034 ±0.003). Thus, in the infected monkeys CT_4 and % FT_4 were not significantly correlated. The increased CT_4 in the infected monkeys could not be ascribed to an increase in vascular permeability and did not correlate with the magnitude of fever. Although the increased CT_4 could not be accounted for by increased hepatic or renal uptake of hormone, hepatic and renal T_4 spaces were increased, results consistent with increased binding by these tissues. Our data indicate that the cellular uptake of T_4 is increased early in acute pneumococcal infection and suggest that this results from a primary enhancement of cell-associated binding factors for T_4.

INTRODUCTION

In man and in the rhesus monkey, the metabolic disposal of thyroid hormone, as judged from the disappearance from serum of ^{131}I-labeled L-thyroxine (T_4)[1] after attainment of distribution equilibrium, has been shown to be accelerated during acute pneumococcal infections (1, 2). In the study conducted in the rhesus monkey (2), it was further noted that the concentration in serum of labeled T_4 8 hr affer its injection, that is, before attainment of distribution equilibrium, was often lower in the infected monkeys than in the control monkeys, suggesting more rapid disappearance of hormone during its early distributive phase as well. Recent work has established that the early distributive kinetics are determined by both plasma and cellular binding factors, the former retarding and the latter enhancing distributive disappearance of hormone from plasma (3–7). Since acute pneumococcal infection could influence early distributive kinetics through either mechanism, the present study was undertaken to examine this question more closely in the rhesus monkey infected with *Diplococcus pneumoniae*. Advantage was taken of the technique of Oppenheimer, Bernstein, and Hasen (4) for assessing the early cellular uptake of T_4 from the differences in the instantaneous distribution volumes of administered labeled T_4 and labeled albumin.

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Received for publication 13 August 1971 and in revised form 21 October 1971.

[1] *Abbreviations used in this paper:* AFT_4, absolute free T_4 concentration; CT_4, cellular uptake of T_4; % FT_4, per cent free T_4; INF-12, monkeys studied 12 hr after inoculation with *D. pneumoniae;* INF-24, monkeys studied 24 hr after inoculation with *D. pneumoniae;* T_4, L-thyroxine; TCA, trichloroacetic acid.

METHODS

Conditioned male rhesus monkeys (*Macaca mulatta*) weighing between 2.7 and 3.8 kg were maintained on monkey chow[2] containing 1.6 ppm iodine and an ad lib. water intake for several months before study. Monkeys were placed in primate chairs 5–7 days before study during which period rectal temperatures and complete blood counts were obtained. Those monkeys with normal basal parameters and no clinical signs of illness were inoculated intravenously with a culture containing approximately 4×10^8 Type I-A viable *Diplococcus pneumoniae*[3] (13 monkeys) or with an equal volume of the culture that had been killed by heating to 57.5°C for 30 min (7 monkeys). Rectal temperatures, complete blood counts, and cultures of venous blood were obtained at 12 or 24 hr after inoculation.

At either 12 or 24 hr after inoculation, the monkeys received an intravenous injection of 10 μCi of ^{131}I-labeled T_4[4] and 10 μCi of ^{125}I-labeled human serum albumin[4] in 1.0 ml of 1% (w/v) human serum albumin. Blood samples of approximately 1.0 ml were obtained by saphenous venipuncture at 10-min intervals for 50 min after injection of the labeled materials; a final 10 ml blood sample was obtained at 60 min after injection. At this time the monkeys were sacrificed by injecting intravenously a highly concentrated pentobarbital solution.[5] The liver, both kidneys, and the thyroid gland were rapidly removed, flushed with chilled 0.85% NaCl solution, blotted on filter paper, and weighed.

The concentrations in serum of protein-bound ^{131}I and ^{125}I (T_4-^{131}I and albumin-^{125}I) were determined by subjecting 250-μl samples of serum to trichloroacetic acid (TCA) precipitation as previously outlined (2). Counting standards that had been prepared from the injection solutions immediately after administration were also precipitated with TCA. Samples and standards were counted in a dual-channel well-type scintillation counter with corrections being made for the contribution of the ^{131}I to the ^{125}I counting rate in each sample.

In the present study complete urine collections could not be obtained to assess to what extent metabolism of the T_4-^{131}I had occurred. Accordingly, to minimize the possibility of significant metabolism of T_4-^{131}I influencing its disappearance from serum, blood samples were obtained for only 60 min after injection. This is much shorter than the 4-hr period employed in man by Oppenheimer, Bernstein, and Hasen (4), and was decided upon in view of the approximately fourfold greater metabolic clearance rate of T_4 per kilogram of body weight in the rhesus monkey (2). In any event, to evaluate the possible extent to which the injected T_4-^{131}I might be metabolized by way of deiodination during the 60 min period of study, the accumulation of non-TCA-precipitable ^{131}I in serum was monitored and the thyroidal uptake of ^{131}I at 60 min was measured by counting the entire gland as described below.

The early cellular uptake of T_4 (CT_4) was calculated as described by Oppenheimer, Bernstein, and Hasen (4). Briefly, the extent to which the distribution volume of T_4-^{131}I exceeds that of albumin-^{125}I at any time before significant metabolism of T_4-^{131}I has occurred is considered as representing the cellular component of exchangeable T_4. The distribution volumes of T_4-^{131}I and albumin-^{125}I at any given time were calculated as the quotients of the injection doses and their simultaneous concentrations in serum. CT_4, as per cent administered dose of T_4-^{131}I at a given time, was then calculated as the product of the concentration of T_4-^{131}I in serum and the difference in the distribution volumes of T_4-^{131}I and albumin-^{125}I at that time.

Hepatic and renal uptakes of ^{131}I at 60 min were estimated as follows. Slices of 200–300 mg were prepared with a Stadie-Riggs microtome, blotted, weighed, and hydrolyzed in a standard volume of hot 2 N NaOH. The entire thyroid gland was also hydrolyzed. As previously described (4), the contribution of ^{131}I from residual blood to the observed ^{131}I counting rate in the tissue was estimated from the counting rate of albumin-^{125}I in the tissue and the ratio of the ^{131}I to the ^{125}I counting rate in the final (60 min) serum sample. Net organ uptake of ^{131}I was then calculated as the product of the corrected ^{131}I counting rate in the tissue and the total organ weight, and expressed as a per cent of the administered T_4-^{131}I; the weight of both kidneys was employed in calculating renal uptake. Hepatic and renal T_4 spaces were calculated as the quotient of the net organ uptake of ^{131}I and the concentration of T_4-^{131}I in the 60 min serum sample. In most experiments, hepatic and renal uptakes of ^{131}I were also assessed by counting suspensions of the entire liver or both kidneys in a standard volume of 2 N NaOH in a small animal whole body gamma counter using counting standards of similar geometry.

The per cent of free T_4 (% FT_4) was determined in a diluted aliquot of the 60 min serum sample employing the equilibrium dialysis method previously described in detail (8, 9). In accordance with the suggestion of Schussler and Plager (10), the commercial T_4-^{131}I used in this determination was first dialyzed against a large volume of distilled water for 18 hr at 6°C to remove iodide and other degradation products. Serum total T_4 concentration was determined by the method of Murphy and Pattee (11).[6] Absolute free T_4 concentration (AFT_4) in serum was then calculated as the product of serum total T_4 and % FT_4.

Statistical analyses were performed according to methods described by Snedecor and Cochran (12). Parameters in monkeys studied 12 hr (INF-12) and 24 hr (INF-24) after inoculation with the viable culture were compared to those in monkeys inoculated with the heat-killed culture (control) using the t test for unpaired values. The disappearances of T_4-^{131}I and albumin-^{125}I from serum seemed to conform to a single exponential function between 10 and 60 min. Mean best fit regression curves were calculated for each monkey group by the method of least squares. Linearity of these curves was confirmed statistically. Differences in the slopes of the regression curves were compared by the t test. Correlation coefficients (r) were calculated to assess the relationship between CT_4 and body temperature and CT_4 and % FT_4 in infected monkeys. Probability values (P) were then obtained from standard tables for t and r.

RESULTS

Intravenous inoculation of rhesus monkeys with a culture containing approximately 4×10^8 viable *D. pneumoniae* (Type I-A) has previously been shown to result in a well defined 2–3 day febrile illness with signs

[2] Obtained from Ralston Purina Co., St. Louis, Mo.

[3] Organisms were mouse passed to maintain virulence and encapsulation, stored at −70°C in fortified brain-heart infusion broth, and thawed immediately before inoculation.

[4] Obtained from Abbott Laboratories, Chemical Marketing Div., North Chicago, Ill.

[5] Lethane obtained from A. J. Buck & Co., Baltimore, Md.

[6] Performed by the Boston Medical Laboratory, Waltham, Mass.

TABLE I

Effects of Acute Infection with Diplococcus pneumoniae on Early Cellular Uptake of T_4-^{131}I (CT_4) and on Serum Total T_4, % Free T_4 (% FT_4), and Absolute Free T_4 (AFT_4)

Monkey No.	Weight	Temperature*	CT_4,‡ % administered dose T_4-^{131}I	Serum T_4	% FT_4§	AFT_4
	kg	*°F*		*μg/100 ml*		*ng/100 ml*
Controls						
1	3.1	99.8	20.6	7.0	0.033	2.3
2	3.6	100.6	29.2	4.5	0.023	1.0
3	3.2	99.4	21.7	7.0	0.025	1.7
4	2.7	98.8	18.6	10.5	0.033	3.4
5	2.9	100.6	22.4	8.0	0.034	2.7
6	3.4	100.2	20.0	8.0	0.024	1.9
7	3.5	99.0	24.1	6.0	0.022	1.3
Mean	3.2	99.8	22.4	7.3	0.028	2.0
SE	0.1	0.3	1.3	0.7	0.002	0.3
INF-12						
8	3.8	101.6	31.8	5.0	0.031	1.5
9	2.8	102.4	28.8	6.5	0.028	1.8
10	3.4	104.0	41.0	8.5	0.025	2.1
11	3.5	101.8	29.5	8.5	0.026	2.2
12	3.0	100.6	28.0	8.0	0.025	2.0
13	3.2	100.8	29.9	8.0	0.031	2.4
Mean	3.3	101.9	31.5	7.4	0.028	2.0
SE	0.1	0.5	2.0	0.6	0.001	0.1
INF-24						
14	2.9	103.3	34.6	2.5	0.050	1.2
15	3.5	103.8	31.3	3.5	0.039	1.3
16	3.2	104.3	32.1	4.5	0.023	1.0
17	3.1	105.0	33.6	4.5	0.039	1.7
18	3.7	101.8	33.0	4.9	0.026	1.3
19	3.5	104.6	30.3	5.5	0.034	1.9
20	3.8	102.7	36.2	4.2	0.031	1.3
Mean	3.4	103.6	33.0	4.2	0.034	1.4
SE	0.1	0.5	0.8	0.4	0.003	0.1
P values						
Control vs. INF-12		<0.01	<0.01	NS	NS	NS
Control vs. INF-24		<0.001	<0.001	<0.01	NS	NS

NS, not significant.

* Rectal temperatures obtained immediately before injection of T_4-^{131}I and albumin-^{125}I between 0800 and 1000 hr.

‡ Values represent those at 60 min after injection of T_4-^{131}I and albumin-^{125}I.

§ Values shown represent mean of duplicate determinations.

of infection usually appearing within 8–16 hr (2). In the present study monkeys given such an inoculum were found to have a modest leukocytosis and fever within 12 hr. Rectal temperatures were higher in monkeys studied 24 hr after infection (Table I). In those monkeys receiving viable organisms blood cultures obtained at 12 or 24 hr after inoculation grew *D. pneumoniae* in pure culture, providing further documentation of disseminated infection.

Fig. 1 depicts the mean best fit regression curves for the disappearances from serum of albumin-^{125}I and T_4-^{131}I in the seven control monkeys and in the six studied 12

hr and seven studied 24 hr after infection. The calculated slopes of the mean albumin-^{125}I regression curves did not differ significantly in control and infected monkeys (control, −0.0018; INF-12, −0.0019; INF-24, −0.0017). The initial volumes of distribution of albumin-^{125}I obtained by backward extrapolation of the disappearance curves were also similar in infected (112 ml in INF-12 and 119 ml in INF-24) and control (109 ml) monkeys. The small differences observed may have been related in part to variations in the mean body weights of these groups (Table I).

In contrast to the disappearance from serum of albumin-^{125}I, the slopes of the mean best fit regression curves for the disappearance from serum of T_4-^{131}I over 60 min were greater in the infected (−0.0034 in INF-12 and −0.0035 in INF-24) than in the control (−0.0025) monkeys ($P < 0.02$). Thus, in the infected monkeys the early fractional disappearance rate of T_4-^{131}I was selectively increased relative to that of albumin-^{125}I. Confirmation that this early disappearance of T_4-^{131}I from serum reflected distributive phenomena rather than metabolic disposal was obtained from the following observations. First, no net accumulation of non-TCA–precipitable ^{131}I in serum was noted in the control or infected monkeys during the 60 min period of study, based on a comparison with the proportion of non-TCA–precipitable ^{131}I in the injection standard (4–6%). Second, the thyroidal uptake of ^{131}I was similar in all groups (< 1% of the administered dose of T_4-^{131}I). Finally, from our previous study (2), mean values for the fractional metabolic disposal rate of T_4 were 46% per day or 0.032% per min in control monkeys and 83% per day or 0.058% per min in infected monkeys; these values comprise only 6% and 7% respectively of the values for early fractional disappearance rate (control, 0.58% per min; mean infected, 0.79% per min).

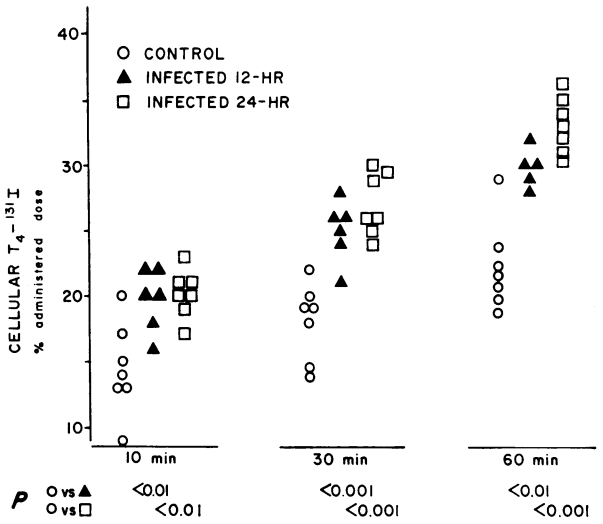

FIGURE 2 Individual values for the early cellular uptake of T_4-^{131}I (CT_4) in the seven control monkeys and in the six studied 12 hr and the seven studied 24 hr after inoculation with viable *Diplococcus pneumoniae*. CT_4 was significantly increased in the infected monkeys at 10 min, as well as at 30 and 60 min after injection of the T_4-^{131}I.

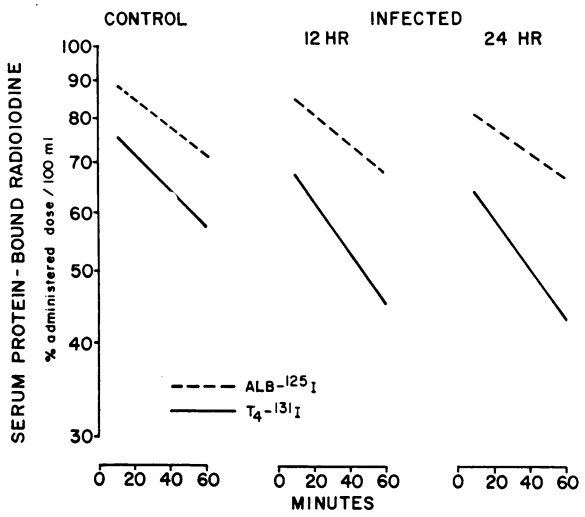

FIGURE 1 Mean best fit regression curves for the disappearances from serum of albumin-^{125}I and T_4-^{131}I over a 60 min period after injection of the labeled materials for the seven control monkeys and for the six studied 12 hr (INF-12) and the seven studied 24 hr (INF-24) after inoculation with viable *Diplococcus pneumoniae*. Concentrations of albumin-^{125}I and T_4-^{131}I in serum as protein-bound radioactivity were determined at 10-min intervals after injection of the labeled materials. Linearity of each curve was confirmed statistically (r at least > 0.66, P at least < 0.01). Slopes of the mean albumin-^{125}I regression curves did not differ significantly among the groups (control, −0.0018; INF-12, −0.0019; INF-24, −0.0017). Slopes of the mean T_4-^{131}I regression curves were greater in the infected monkeys (control, −0.0025; INF-12, −0.0034; INF-24, −0.0035) ($P < 0.02$).

The values for the early cellular uptake of T_4 (CT_4) are presented in Table I and depicted in Fig. 2. In the monkeys inoculated with the viable *D. pneumoniae* culture, CT_4 was significantly increased at all times studied (P at least < 0.01). The increase was evident at 10 min after injection of T_4-^{131}I; the values, expressed as per cent administered dose of T_4-^{131}I, were 14.3 ±1.3 (mean ±SE) in control, 19.6 ±1.0 in INF-12, and 20.3 ±0.6 in INF-24. At 30 min, the values were 18.1 ±1.1 in control, 24.9 ±1.0 in INF-12, and 27.1 ±0.9 in INF-24; and at 60 min, 22.4 ±1.3 in control, 31.5 ±2.0 in INF-12, and 33.0 ±0.8 in INF-24. The ratio of CT_4 in the infected monkeys to that in the control monkeys remained essentially constant at 10, 30, and 60 min (INF-12, 1.37, 1.38, and 1.41 respectively; INF-24, 1.42, 1.50, and 1.47 respectively).

In the infected monkeys, CT_4 was not significantly

correlated with body temperature (r for CT_4 at 60 min and rectal temperature in °F, 0.45 with $P > 0.05$).

The values for serum total T_4, % FT_4, and AFT_4 are presented in Table I. Serum total T_4, expressed as micrograms per 100 ml, was not appreciably different in control monkeys and those studied 12 hr after infection (control, mean 7.3 ±SE 0.7; INF-12, 7.4 ±0.6); serum T_4, however, was significantly reduced in INF-24 (4.2 ±0.4, $P < 0.01$). % FT_4 in serum, reflecting the binding of T_4 in plasma, did not differ significantly in the three groups (control, mean 0.028 ±SE 0.002; INF-12, 0.028 ± 0.001; INF-24, 0.034 ±0.003). Individual values, how-

TABLE II

Effects of Acute Infection with Diplococcus pneumoniae on Hepatic and Renal ^{131}I Uptakes and T_4 Spaces

Monkey No.	Hepatic Uptake % administered dose T_4-^{131}I	Hepatic Uptake % CT_4	Hepatic Space	Renal Uptake % administered dose T_4-^{131}I	Renal Uptake % CT_4	Renal Space
			ml			*ml*
Controls						
1	11.5	55.8	22.2	2.1	10.2	4.0
2	14.8	50.7	28.3	3.7	12.7	6.8
3	13.9 (12.7)	64.1	24.0	3.5 (4.1)	16.1	6.0
4	9.0 (12.3)	48.4	13.9	1.7 (1.9)	9.1	2.6
5	12.1 (15.0)	54.0	22.0	1.7 (2.1)	7.6	2.7
6	7.9 (9.8)	39.5	13.5	2.3 (2.5)	11.5	4.2
7	15.3 (13.8)	63.8	26.3	3.0 (3.8)	12.4	5.3
Mean	12.1	54.8	21.5	2.6	11.4	4.5
SE	1.1	3.3	2.2	0.3	1.0	0.6
INF-12						
8	13.4	42.0	33.4	3.3	10.3	6.9
9	10.3 (9.5)	35.8	21.8	2.7 (2.5)	9.4	4.9
10	15.0 (13.8)	36.6	34.6	4.7 (5.3)	11.5	11.8
11	17.1 (19.2)	58.0	41.6	3.0 (3.4)	10.2	7.3
12	16.5 (17.0)	58.9	29.7	3.9 (3.5)	13.9	8.2
13	11.2 (13.7)	37.5	23.4	3.2 (4.2)	10.7	6.7
Mean	13.9	44.8	30.7	3.5	11.0	7.6
SE	1.1	4.4	3.0	0.3	0.6	0.9
INF-24						
14	12.5	36.1	28.5	3.3	9.5	7.5
15	10.2	31.9	22.2	2.8	8.9	6.1
16	14.1 (16.1)	43.9	30.4	3.1 (2.9)	9.6	6.7
17	17.3 (14.5)	51.5	39.5	4.7 (5.9)	13.9	10.7
18	14.3 (11.9)	43.3	33.1	3.4 (3.0)	10.3	7.9
19	17.6 (18.2)	58.0	38.7	2.5 (2.3)	8.3	5.5
20	19.7 (20.5)	54.4	47.1	4.1 (3.8)	11.3	9.9
Mean	15.1	45.6	34.2	3.4	10.3	7.8
SE	1.2	3.6	3.1	0.3	0.8	0.7
P values						
Control vs. INF-12	NS	NS	<0.05	NS	NS	<0.02
Control vs. INF-24	NS	NS	<0.01	NS	NS	<0.01

NS, not significant.
Values in parentheses represent uptake obtained by counting whole organ in whole body counter.

ever, were variably increased in INF-24. When CT_4 was compared to % FT_4 at 60 min in the individual infected monkeys, no significant correlation was noted (r for CT_4 and % FT_4 at 60 min, -0.26 in INF-12 and 0.19 in INF-24). Values for AFT_4, expressed as nanograms per 100 ml, did not differ significantly in the three groups, but were somewhat lower in INF-24 owing to the reduction in serum total T_4 (control, mean 2.0 ±SE 0.3; INF-12, 2.0 ±0.1; INF-24, 1.4 ±0.1).

The values for net hepatic and renal ^{131}I uptakes and T_4 spaces at 60 min after injection of T_4-^{131}I are presented in Table II. In the control monkeys, net hepatic and renal uptakes, expressed as per cent administered dose of T_4-^{131}I, were 12.1 ±1.1 (mean ±SE) and 2.6 ±0.3 respectively; hepatic uptake accounted for 54.8 ±3.3% of the CT_4 at 60 min, and renal uptake, 11.4 ±1.0%. In the infected monkeys, mean hepatic and renal uptakes were only slightly greater than the control values; hepatic uptake tended to account proportionally for less of the CT_4 than in the control monkeys (INF-12, 44.8 ±4.4%; INF-24, 45.6 ±3.6), whereas the contribution of renal uptake to the CT_4 was essentially unchanged. Comparable values were obtained when hepatic and renal uptakes were determined by counting suspensions of the whole organs in a small animal whole body gamma counter. In the control monkeys, hepatic and renal T_4 spaces, expressed as milliliters, were 21.5 ±2.2 (mean ±SE) and 4.5 ±0.6 respectively. In the infected monkeys, the corresponding values were all significantly greater and averaged 30.7 ±3.0 ($P < 0.05$) and 7.6 ±0.9 ($P < 0.02$) in INF-12 and 34.2 ±3.1 ($P < 0.01$) and 7.8 ±0.7 ($P < 0.01$) in INF-24.

DISCUSSION

The results of our study indicate that the early cellular uptake of T_4 (CT_4), as estimated from the differential disappearance from serum of T_4-^{131}I and albumin-^{125}I, is increased early in the course of acute pneumococcal infection in the rhesus monkey. An increase in the fraction of T_4-^{131}I in the cellular compartment, that is, outside the distribution volume of albumin-^{125}I, was evident at both 12 and 24 hr after inoculation with the viable *D. pneumoniae* culture and was not associated with a significant change in the early distribution volume of albumin-^{125}I. In the absence of complete urine collections, the extent of T_4-^{131}I metabolism could not be estimated directly during the 60 min period of study. However, significant deiodination of T_4-^{131}I seemed an unlikely explanation for the more rapid disappearance of injected hormone in the infected monkeys since no accumulation of non-TCA–precipitable ^{131}I in serum was observed and thyroidal ^{131}I uptake was barely detectable in both control and infected monkeys at 60 min. Furthermore, employing data obtained in a previous study (2), it was calculated that metabolic disposal of T_4 could account for only 6–7% of the early disappearance of hormone in both control and infected groups. Finally, the increase in CT_4 was evident as early as 10 min after injection of the labeled T_4 in the infected monkeys. These features strongly suggest that the observed change in early T_4-^{131}I kinetics in the infected monkeys reflects alterations in distribution rather than accelerated metabolic disposal of hormone.

Serum total T_4 concentration was not statistically different in control monkeys and in those studied 12 hr after infection. In the latter, an increase in CT_4 was already evident. A significant reduction in serum total T_4, however, was noted in the monkeys studied 24 hr after infection. This sequence of events suggests that the increased secretion of thyroid hormone that has been observed to occur during acute pneumococcal infection (2) may be a compensatory response to a decline in the concentration of circulating hormone resulting from an increase in cellular uptake.

The increase in CT_4 in the infected monkeys preceded a detectable decrease in plasma binding as reflected by the % FT_4 in serum. Furthermore, CT_4 and % FT_4 were not significantly correlated when these parameters were compared within each group. These results are consistent, therefore, with a primary enhancement of cellular uptake of T_4. It is noteworthy that in several other acute infections changes in the metabolic disposal of T_4 have been reported to occur in the absence of appropriate alterations in the binding of hormone in plasma (13, 14).

Considerable evidence indicates that the liver and, to a lesser extent, the kidney are the major sites for the early cellular uptake of T_4 (3–7). In the control monkeys, these organs accounted for approximately two-thirds of the total cellular uptake of T_4-^{131}I at 60 min after injection. However, in the infected monkeys, the increase in CT_4 did not appear to result from either increased hepatic or renal uptake, since hepatic uptake tended to account proportionally for less of the total CT_4 in the infected monkeys while the contribution of renal uptake was nearly identical with that in the control monkeys. The results therefore suggest increased T_4 uptake by, as yet unidentified, extrahepatic and extrarenal sites early in this infection. Nevertheless, the increased hepatic and renal T_4 spaces observed in the infected monkeys are consistent with increased binding of hormone by these tissues. Furthermore, the present results do not exclude a significant role for liver and kidney in the metabolic disposal of hormone. A qualitatively similar alteration in the distributive kinetics of T_4 has been observed in response to an intravenous injection of salicylate in man (15). In this circumstance, accelerated early (3 hr) disappearance of T_4-^{131}I from plasma was also

not accounted for by increased hepatic uptake or by decreased plasma binding of T_4 alone.

The importance of the liver as a major site for the early uptake of T_4 may reside in the relative permeability of its sinusoidal bed that could permit rapid equilibration with the circulating T_4-protein complex in plasma (7, 16). Other tissues, such as muscle, are thought to equilibrate more slowly with these complexes due to the smaller pore size of their capillaries (17). It is possible, therefore, that pneumococcal infection might enhance T_4 uptake by ordinarily slowly equilibrating tissue by increasing small vessel permeability as part of the inflammatory response. However, the similarity of the slopes for the albumin-^{125}I disappearance curves in the infected and control monkeys in our study does not support a significant generalized increase in vascular permeability. Furthermore, the ratio of CT_4 in the infected monkeys to that in the control monkeys remained essentially constant at 10, 30, and 60 min, whereas if an increase in permeability were the sole mechanism responsible the ratio should have progressively declined. Thus, at least early in disseminated pneumococcal infection, a simple increase in capillary pore size does not appear to be an important factor in increasing the cellular uptake of hormone. Rather the data are more in keeping with a primary enhancement of cell-associated binding factors for T_4 in this infection. The mechanism ultimately responsible for this alteration is not known. An important role for fever appears unlikely in view of the lack of correlation between CT_4 and body temperature in the infected monkeys.

With respect to the physiologic significance of the increased cellular uptake, it should be pointed out that an increase in cellular uptake need not necessarily be followed by an acceleration of the metabolic disposal of hormone or by an induction of hormonal effect. Whether or not these metabolic consequences occur would presumably depend upon the nature of the cellular binding sites affected, that is, whether or not the sites are metabolically linked (7). Nevertheless, in view of the previous observation of accelerated metabolic disposal of hormone in the infected rhesus monkey (2), it is not unreasonable to suppose that this latter phenomenon might bear some relationship to the increase in cellular uptake observed in the present study. What role these alterations subserve in the adaptive response of the host to pneumococcal infection has not been established. It has been suggested that one way in which thyroid hormone might have adaptive value is by serving as a source of relatively oxidized iodine for bacterial iodination which appears to be an important microbicidal mechanism in the granulocyte (2, 18).

ACKNOWLEDGMENTS

In conducting the research reported herein, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences–National Research Council.

The authors are indebted to Sp4. Gary M. Cook and Sp5. Boyd W. Hevener for expert technical assistance, to Mrs. Phebe Summers for assistance in preparation of the figures and in performing statistical analyses, and to Mrs. Ann Clabaugh, Mrs. Phylis Rinehart, and Mrs. Edith Cusher for secretarial help.

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