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Reduced Serum T_4 and T_3 and Their Altered Serum Binding after Burn Injury in Rats

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Total T_4 and T_3 concentrations are often suppressed in burned patients. To investigate the significance of such changes, we have characterized serum T_4 and T_3 after full-thickness scald burns (60% body surface under anesthesia) of 270-gm male Sprague-Dawley rats housed in a light:dark cycle of 14:10 hr. Groups ($N = 9–15$) of BURN, SHAM (anesthesia, fur clipped, no burn) and CON (controls) were sacrificed on postburn days 8 and 14. T_4 and T_3 (radioimmunoassay), free indices (FT_4I and FT_3I = respective total T_4 or T_3 × in vitro charcoal T_3 uptake, T_3U), and free concentrations (FT_4 and FT_3 = total T_4 or T_3 × respective equilibrium dialyzable fraction, T_4DF or T_3DF) were not different between CON and SHAM. Compared to SHAM, mean T_4 and FT_4I (by about 48% of respective SHAM means on both days), TT_3 (by 36, 43%), and FT_3I (by 38, 45%) (days 8, 14) were suppressed in BURN (all $p < 0.001$). T_4DF (both days) and T_3DF (day 14) were significantly elevated in BURN, demonstrating a deficit in serum binding, but T_3U was not. FT_4 (by 26, 22%) and FT_3 (by 33, 34%) (day 8, 14) were significantly lower in BURN. On either day, covariance analyses (BURN vs. combined CON+SHAM) correlated FT_4I or FT_3I with respective FT_4 or FT_3 (all $p < 0.001$, slopes not different in BURN vs. CON+SHAM), but the lower FT_4I and FT_3I in BURN significantly overestimated (all $p < 0.001$) the depression of respective FT_4 and FT_3 in BURN. Similarly to patients, burned rats exhibit suppressed circulating total and free T_4 and T_3 concentrations despite elevated dialyzable (free) fractions of T_4 and T_3. Because of failure of the T_3U to account for this serum binding abnormality, the results are most consistent with a burn-induced circulating inhibitor(s) for binding of T_4 and T_3, not only to transport proteins but also in vitro charcoal, perhaps similar to inhibitors previously described in the sera of patients with various nonthyroidal illnesses. The thermally traumatized rat appears to be a good model for thyroid changes in burns and other nonthyroidal illness.

In humans, a reduction in the circulating concentrations of bioactive thyroid hormones is characteristic of nonthyroidal illness (NTI) (14, 19, 26). In burned patients, similar to patients with other NTI, serum concentrations of 3,5,3′-triiodothyronine (T_3) and often tetraiodothyronine (T_4), as well as the indices of free hormonal concentrations, FT_3I and often FT_4I (index = total hormone concentration times T_3 uptake), are suppressed (2–4, 17). Serum free T_3 and often free T_4 (FT_3 and FT_4, determined as the product of T_4 or T_3 times the respective dialyzable free fraction) are suppressed in patients with major burns (3, 22) and FT_4I and FT_3I reflect the FT_4 and FT_3 respectively ($r > 0.93$) in a linear fashion (2, 22). Thus burns could be distinguished from controls equally well with FT_4I or FT_4 and with FT_3I or FT_3 values (22).

There is a T_4 and T_3 serum binding abnormality in the serum of burned patients, because the dialyzable fraction of T_4 (T_4DF) and of T_3 (T_3DF) and the in vitro T_3 charcoal uptake (T_3U) are elevated in burns (4, 22–24). These elevations were similar enough between T_3U and the dialyzable fractions to allow observation of the close relationship betwen indices and free concentrations mentioned above in human burn injury. Nevertheless, analysis of covariance indicated a statistically demonstrable underestimation of FT_4 and FT_3 by use of FT_4I and FT_3I, respectively, in burned patients compared to controls,

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indicating relatively less elevation of T_3U than of T_4DF or T_3DF in burns.

The present investigation sought to determine in an animal model whether concentrations of T_4 and T_3 respond to burns as in humans, whether there is a serum transport binding deficit, and whether such a binding abnormality might exhibit the same pattern of disparity in response to burn injury seen in humans between free indices and free concentrations of hormones.

MATERIALS AND METHODS

Adult male Sprague-Dawley rats were housed in a 14:10 hours light:dark cycle at a constant 22°C ambient temperature and fed tap water and standard laboratory chow ad libitum. During pentobarbital anesthesia, fur was clipped in the usual area of burn (SHAM) or additionally a full-thickness scald burn covering 60% of body surface was applied (BURN) in a standard manner (25). Unanesthetized and unclipped rats served as additional controls (CON). Animals were sacrificed in groups of 9 to 15 rats on postburn day (PBD) 8 or 14 to obtain trunk serum for analysis of T_4 and T_3 (radioimmunoassay) and T_3U (in vitro uptake of tracer 125 I-T_3 from serum directly onto charcoal matrix) (Diagnostic Products kits for T_4, T_3, and T_3U). Standard determinations were also made for equilibrium dialyzable fractions (T_4DF and T_3DF) of 125 I-tracer hormones added to serum then crossing a protein-impermeable membrane into buffer (at the Nichols Institute, San Pedro, California). The indices of free hormone concentrations (FT_3I and FT_4I) were the product of total concentration of hormone (T_3 or T_4) and the in vitro charcoal T_3 uptake (T_3U). The concentrations of free hormones (FT_3 and FT_4) were the product of total hormone (T_3 or T_4) multiplied by its respective dialyzable fraction (T_4DF or T_3DF). Comparisons among group means were made by the *t*-test for several means using the Bonferroni correction for multiplicity of comparisons, and differences in the relationship of free index to free concentration of hormones between groups were assessed with analyses of covariance.

RESULTS

The results for each group are shown in Fig. 1. Direct and derived hormonal values did not differ significantly between CON and SHAM groups. By PBD 14, mean weight gain of BURN (16%) was about half that (31%) of SHAM ($p < 0.01$). On either PBD 8 or 14, burn injury produced a significant suppression in thyroid hormones. In BURN, mean T_4 and FT_4I were about 52% of respective SHAM means on both PBD 8 and 14, T_3 was 64% (PBD 8) or 57% (PBD 14) of that in SHAM, and FT_3I was 62% (PBD 8) or 55% (PBD 14) of that in SHAM (all $p < 0.001$). T_4DF (both PBD 8 and 14) and T_3DF (day 14) were significantly elevated in BURN, demonstrating a deficit in serum binding, but T_3U was not elevated. Mean FT_4 was 74% (PBD 8) or 78% (PBD 14) and FT_3 67% (PBD 8) or 66% (PBD 14) of respective mean SHAM values, all significantly lower in BURN.

Figure 2 shows the relationships of FT_4I to FT_4 and FT_3I to FT_3 in BURN compared to the combined CON and SHAM groups. On either PBD 8 or 14, covariance analyses showed significant correlation (all $p < 0.001$) of FT_4I or FT_3I with respective FT_4 or FT_3, and the slopes were not different in BURN versus CON+SHAM. However, the excessively lower FT_4I and FT_3I in BURN significantly underestimated the respective FT_4 and FT_3 in BURN, with all vertical positional (intercept) differences at $p < 0.001$ versus CON+SHAM. The figures depict T_3U and the free indices (FT_4I and FT_3I) calculated on the conventional basis of the T_3U expressed as the fraction of total in vitro tracer 125 I-T_3 binding to the matrix after incubation. It has been suggested that expressing the T_3U as the tracer binding ratio (counts in matrix/counts in serum) might theoretically enhance the correspondence between FT_4I and FT_4 (see 26). However, reanalysis of the data with use of this modification of the T_3U did not improve this correspondence or change the results.

DISCUSSION

Burn injury in rats, as in patients, is capable of suppressing the total and free concentrations of circulating T_3 and T_4 and reducing the extent of serum binding of these hormones as reflected by increased dialyzable fractions. The overall response is similar in these two species in that while there is reduction of total T_3 and T_4 concentrations in burns, reduction of their bound fractions (elevation of their dialyzable fractions) may not restore their free concentrations (the biologically active forms) to normal. In this condition, burned patients (20) and rats (12) are not hypometabolic but have elevated O_2 consumption. Mainly on the basis of work in patients, this apparently paradoxical situation has tentatively been ascribed to a switch in control of resting metabolic rate from predominantly thyroidal influence to influence by augmented function of a composite hormonal system including sympathetic activity (1, 10, 11, 12, 20, 27), and plasma cortisol and glucagon concentrations (21) in burn injury and other hypermetabolic (febrile) nonthyroidal illnesses (NTI). Numerous questions which arise as to the nature of the interactions among thyroid hormone binding, free thyroid hormone concentrations, thyroid hormone production and degradation, peripheral conversion of T_4 to T_3, and activation of elements of sympathetic and other hormonal systems in NTI, might now profitably be addressed using the rat burn model.

The mechanism of the reduced iodothyronine binding in NTI is not well understood, although the observation is thought not to be explainable by reductions in serum thyronine-binding protein levels, but to involve a circulating inhibitor for binding of thyroid hormones to plasma proteins in many of these patients. The inhibitor has appeared variously to be non-ultrafilterable (28), an immunoglobulin (8), a heat-labile nondialyzable factor(s) possibly leaking into the circulation from injured tissues (7), a nondialyzable, non-immunoglobulin factor(s) (16), or an ether-extractable fat or fatty acid(s) (5). Particularly interesting is the factor(s) described by Oppenhei-

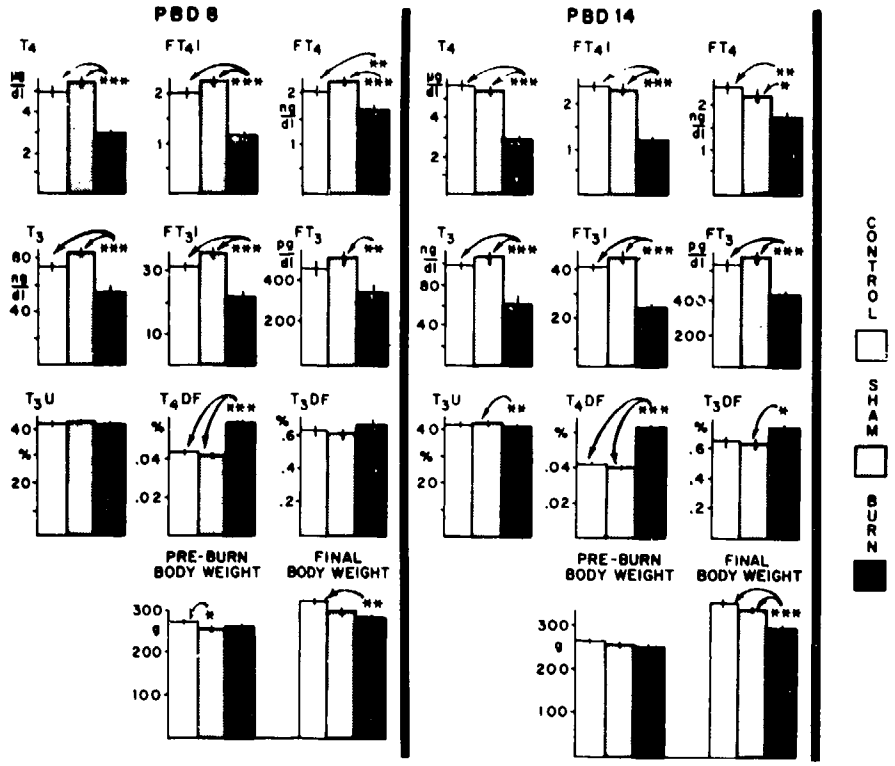

FIG. 1. Group means (± SE) for the measured variables in the three groups of rats on postburn day (PBD) 8 or 14. See text (Materials and Methods) for explanations of the symbols for the hormonal measurements.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

mer et al. (16) in sera of some NTI patients which appeared to inhibit iodothyronine binding not only to serum proteins, but also to charcoal matrix and to incubated rat hepatocytes, suggesting a broad range of action of the binding-inhibitor and its potential for pathophysiologic importance. Kaptein et al. (13) provided indirect evidence supporting decreased thyronine binding to tissues of NTI patients by demonstrating a slowed distribution (early-phase disappearance from serum) after injection of radiotracer T_4 or T_3. Studies showing decreased T_3 receptor binding in a number of conditions and decreased T_3 content in tissues from sick patients have been reviewed (26). It is thus possible that a binding inhibitor in NTI could further diminish the biologic effectiveness of the already reduced concentrations of free circulating thyroid hormones. The extensiveness of the binding defect and its metabolic significance might now be investigated in the rat burn model.

Whereas the rise in T_4DF and T_3DF was reflected by a less than proportional (though still quite significant) rise of mean T_3U in burned patients (4, 22), this disparity is even greater in the rats which showed no elevation of T_3U after burn injury (Fig. 1). This disparity of response between T_3U and the dialyzable fractions is further demonstrated by the positional difference in the vertical dimension between the broken (CON+SHAM) and solid (BURN) line in each panel of Figure 2, correlating the free indices (based on T_3U) with the respective free concentrations (based on the free fractions). We do not have independent measurements of serum thyronine binding proteins, though the content of binding proteins are the same whether the serum is subjected to the T_3U test or to dialysis.

Whatever the mechanism for the disproportionately lower free indices compared to free concentrations, it involves blunting of the rise in the T_3U expected from the rise in free fractions of T_4 and T_3. One explanation for this might be a burn-induced reduction in concentration of one of the serum proteins (thyroxine-binding prealbumin, TBPA) that binds a minor fraction of T_4 but not T_3, since burned patients exhibited a reduction in this protein (15). As discussed in a recent review (9), the T_3U is routinely performed under conditions in which the binding of T_4 to TBPA may be inhibited, and the resultant additional unbound T_4 might displace some of the labelled T_3 from the serum and augment the T_3U value. This would have occurred more in the controls than in the burns, resulting in apparent suppression of T_3U in the burns, if burned rats also have reduced TBPA. However, such an explanation seems inadequate, since it would not account for the disproportionality between the FT_3I and the FT_3 also seen in our burned rats compared to controls. Reported inability to detect any TBPA in rats (18) also suggests the need for another

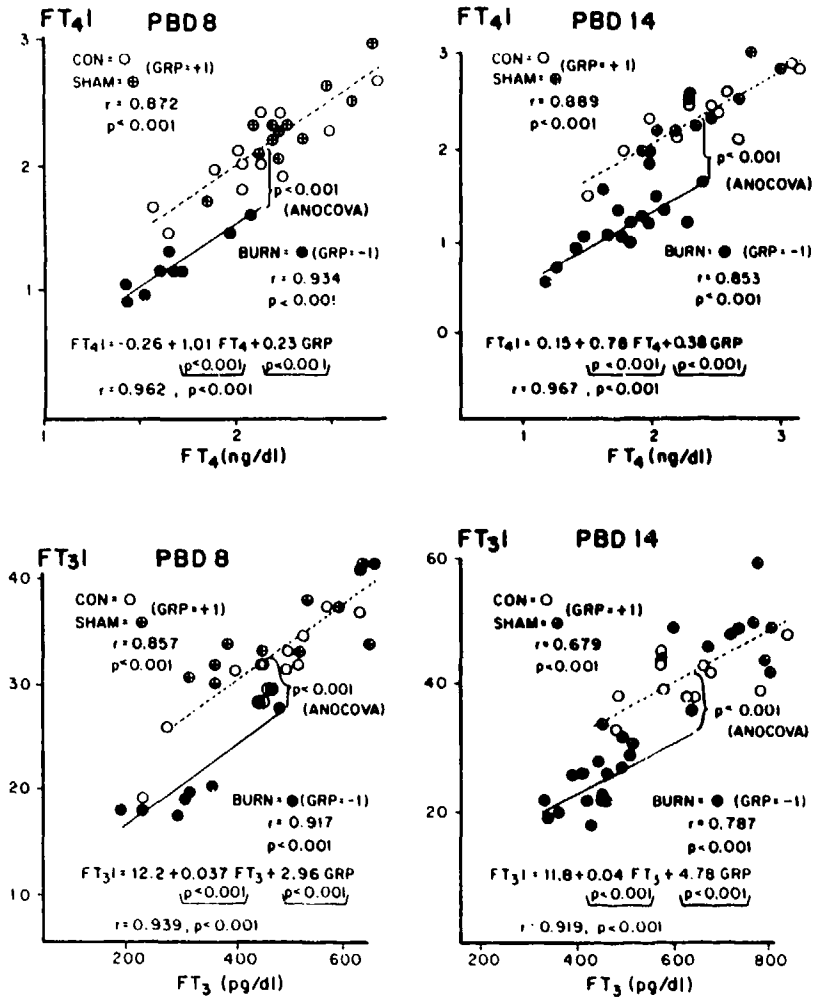

FIG. 2. Analysis of covariance (ANOCOVA) comparing the relationship of the free hormonal indices (FT_4I, FT_3I) to the respective free concentrations (FT_4, FT_3) between the combined CON+SHAM (dashed line) and the BURN (solid line) groups. GRP, grouping variable.

explanation. The pattern of response as related to the binding abnormality in our rats and in NTI could be explained by the presence of a binding inhibitor (16) which not only reduces the binding of iodothyronines to serum proteins (permitting greater dialysis of hormone through a membrane into buffer and greater binding of hormone to matrix in the T_3U test), but also reduces binding of iodothyronines to charcoal (preventing a rise in T_3U that otherwise would have resulted from decreased hormone binding to serum protein). This hypothesis could be further tested using the rat burn model.

The present findings of inability of the T_3U to represent the changes in T_4DF or T_3DF and the consequent disparity between FT_4I and FT_4, as well as between FT_3I and FT_3 in burned rats are similar (though apparently of greater magnitude) to those in burned patients, are also similar to those in other human NTI which often produce great disparity between FT_4I and FT_4 (6, 16, 28), and are compatible with a circulating factor inhibiting T_4 and T_3 binding to charcoal as suggested in patients with NTI (16). Thus the burned rat may provide a good model for study of the alterations of iodothyronine binding in NTI, as well as the pathophysiologic significance of reduced free thyronine concentrations in illness. Such studies would have clinical relevance in that suppressed free T_4 and T_3 have been correlated with deficient mental status and increased mortality in burned patients (22).

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DISCUSSION

DR. CLEON W. GOODWIN (New York Hospital Cornell Medical Center, New York, NY 10021): This paper represents another in a long series of elegant studies from the Army Burn Center in defining the metabolic and hormonal response to severe injury.

Wilmore and associates demonstrated that the catecholamines are the principal hormone system driving the postburn hypermetabolic response in humans. With Becker, Vaughan, and others, this group subsequently defined the role of thyroid hormones in this response. In these studies, thyroid hormone concentrations varied inversely with catecholamine concentrations during the sustained plateau of maximal metabolic expenditure. The glucocorticoids were found to be secondary in importance in predicting the increase in metabolic rate.

Now Doctor Shirani and his associates have begun to verify this hormonal response in an animal model of postinjury hypermetabolism. They have found that severe burns induce the same qualitative depression of major thyroid hormone concentrations as seen in humans, and propose that this animal model may be a useful tool for further dissecting this complex metabolic response.

However, the rat model may diverge from being a copy of the human response in several respects. In particular, a number of studies indicate that glucagon may play a more central role in initiating the cellular hypermetabolic response in the rat, and that alpha receptor agonists may be the participating catecholamine, not the beta agonist as seen in humans. I note that Doctor Shirani's coworkers have a paper in press concerning the role of glucagon in the postburn metabolic response in humans. I would ask the author if they have data available on these aspects of his animal model.

I have a few questions specifically about the model. Have you measured metabolic rate in these animals? When we used both an unclipped control and a sham-clipped uninjured animal, the sham process itself initiated a moderate but sustained rise in metabolic rate. However, you found no difference in the thyroid hormone response. How can you reconcile the fact that the shamming procedure produces a metabolic response but alters the thyroid concentrations not at all?

Why did your animal group sizes vary in number? Did some of the animals die before measurement? If so, how did you correct your design to allow for this?

How did you verify that these animals were not infected, since sepsis initiates its own metabolic alterations?

Finally, in terms of outcome, what do low levels of thyroid hormone really mean? Will hormone replacement alter survival or any other parameter of patient well being? This model will certainly allow you to carry out intervention trials to assess these possibilities.

In closing, this is a very elegant study in both its experimental design and statistical analysis. In particular, the authors have avoided the use of inappropriate techniques such as serial *t*-tests. I enjoyed the paper very much and look forward to future studies from this group.

DR. DONALD S. GANN (Rhode Island Hospital, Providence, 02902): I enjoyed this paper very much. I think it is easy to overlook the importance of being able to get into the laboratory and dissect out a problem, and I think that is what the authors have done in providing us with an animal model. It is an important step forward and one which we should not overlook.

I think it may be relevant also to the converse. If I understood what you were telling us, Doctor Shirani, it appears that the

burn situation may be an acute example of the euthyroid sick syndrome. That is a clinical situation with the same abnormalities that we have had described for us today, which has again defied explanation, because there has been no way of getting at what the inhibitor might be. So, I suspect what you are doing may be an important step forward for the endocrinologist as well as for the traumatologist.

I enjoyed the paper very much.

DR. KHAN Z. SHIRANI (Closing): Thank you for your kind comments. I will respond first to Doctor Gann. I think you are right, this being a model of sick NTI patients, what we see in the clinical setting. We so far have not had any animal model of sickness which will have most of the hormone changes that can be assessed in the laboratory in some systematic fashion. Although the burned rat may not be a perfect model, at least it is a comparable one which shows some of the thyroid hormone changes that are seen in patients with critical NTI and in burns.

In response to Doctor Goodwin's questions, glucagon may be a mediator of human burn hypermetabolism, in that hyperglucagonemia does correlate significantly with the hypermetabolic state, but in rats we do not have these measurements.

The rise in metabolic rate in fur-clipped sham animals is likely due to a lack of insulation. Whether such a mechanism applies to hormones needs further testing.

As far as outcome is concerned, should we treat these patients who have low FT_4I, FT_4, or FT_3? [Slide] In retrospect we looked at burn patients, and FT_4I shown on this slide is on the Y axis and days postburn on the X axis. The upper line shows the ones that survived burns and the lower line shows the ones that did not. Those that did not survive burns had lower FT_4I and total T_4 compared to the ones that did survive. In addition, FT_4I was also correlated with the level of obtundation, shown on the bottom panel of this slide as LO. Those who did not survive burn injury, shown by the upper line, had a worse level of obtundation compared to those that did survive the burn injury.

So we think it is possible that thyroid hormones do play some role in the survival of trauma patients, but we are not certain yet. For that purpose, we have initiated a prospective study in which we are looking in a randomized fashion at whether or not treatment with T_4 in such patients will improve their survival.

Thank you very much.