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# EFFECT OF IMMUNIZATION ON THYROID FUNCTION AND THYROXINE BINDING BY RAT ORGANS

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KEY WORDS: immunization; thyroid gland; cyclic AMP; thyroid parenchyma.

Besides causing immunogenesis, an antigen which is an extraordinary factor for the living organism [3, 8], gives rise to a marked nonspecific neuroendocrine reaction. The concurrent development of these two processes in the course of evolution has become closely connected, but neurohumoral regulation of immune processes has been studied extremely inadequately [7,8]. The contradictory data obtained by investigation of the effect of administration of hormones in different periods of the immune response on the dynamics of antibody formation and on intercellular cooperation [2, 6, 9] demand a careful study of the hormonal background. A theory of neurohormonal regulation of antibody synthesis, in which the leading role is ascribed to the hypothalamo-hypophyseo-adrenocortical system, has been developed in Zdrodovskii's [6] and Rappoport's [10] laboratories. Relations between the functions of other neuroendocrine systems and, in particular, the thyroid system, and antibody formation have received much less study by present standards. There have been virtually no observations on thyroid function during the inductive phase of immunogenesis [2, 6, 9].

The object of the present investigation was to make a detailed study of thyroid function in the productive and, in particular, in the inductive phase, which determines all the subsequent events of immunogenesis [3, 7].

## EXPERIMENTAL METHOD

Experiments were carried out on 220 male albino rats weighing 150-180 g, divided into two groups. The animals of group 1 were immunized simultaneously with formol typhoid vaccine (suspension of 1 billion cells). The animals of group 2 (control) were injected with the same volume (0.2 ml) of 0.2% formalized physiological saline. Assimilation of $^{131}I$ was determined 1, 2, 3, 4, 7, 10, 15, 20, and 25 days after injection of the antigen, after subcutaneous injection of 0.5 μCi of the isotope, with a DCU-61 instrument. The level of protein-bound $^{131}I$ (PBI) in the blood serum and the coefficient of conversion of radioactive iodine were determined [12] on a Gamma (Hungary) instrument. On the 1st, 4th, and 20th days after the antigenic stimulus the content of cyclic AMP in the thyroid gland tissue was determined by means of a Cyclic AMP Assay Kit (Radiochemical Centre, Amersham, England) on a Mark III (The Netherlands) system. The total thyroxine ($T_4$) and triiodothyronine ($T_3$) in the blood serum were determined by means of Res-O-Mat $T_4$ and Ria-Mat $T_3$ kits (Byk Mallinckrodt, West Germany) on a Gamma 400 instrument (West Germany). The content of $^{131}I$-thyroxine (Polish Institute for Nuclear Research), injected subcutaneously in a dose of 1 μCi/

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TABLE 1. Effect of a Single Immunization on Uptake of $^{131}I$ by Rat Thyroid Gland (in % of injected dose of $^{131}I$), PBI Content (in % of one-tenth injected dose of $^{131}I$), Coefficient of Conversion of $^{131}I$ (in %), Content of Total $T_4$ (in μg/100 ml) and of Total $T_3$ in Blood Serum (in ng/100 ml blood serum), and Cyclic AMP Level (in pmoles/mg tissue) in Thyroid Tissue Homogenate (M ± m)

| Parameter | Intact animals | Time of investigation after injection of antigen, days | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 7th | 10th | 15th | 20th | 25th |
| Binding of $^{131}I$ by thyroid gland* | 41,2±3,6 | 50,2±8,7<br>48,2±5,8 | 46,1±3,8<br>46,1±4,1 | 36,1±3,2<br>25,9±6,1 | 33,8±3,2<br>18,5±3,8† | 34,2±3,7<br>22,2±4,3* | 37,2±3,5<br>35,3±5,3 | 38,9±3,0<br>49,1±4,8 | 42,7±3,8<br>60,3±6,8 | 42,3±4,1<br>58,5±4,6* |
| PBI content in blood serum | 1,03±0,17 | 1,19±0,17<br>1,06±0,21 | 1,01±0,16<br>0,87±0,24 | 0,83±0,14<br>0,35±0,12† | 0,77±0,15<br>0,18±0,04† | 0,81±0,17<br>0,32±0,11† | 0,84±0,12<br>0,93±0,24 | 0,95±0,19<br>1,38±0,22† | 1,09±0,17<br>1,61±0,22† | 1,16±0,20<br>1,51±0,21 |
| Coeff. of conversion of $^{131}I$ in blood* | 70,8±5,2 | 81,19±4,16<br>77,21±5,02 | 76,25±7,12<br>76,49±9,56 | 64,19±6,28<br>36,87±5,47† | 60,38±5,67<br>16,98±1,42† | 63,71±6,91<br>27,25±6,54† | 66,02±6,44<br>61,23±6,31 | 68,16±5,15<br>78,62±7,31 | 71,59±7,04<br>86,91±5,83† | 70,39±5,23<br>93,17±1,85* |
| Total $T_4$ content in blood serum | 3,81±0,41 | 3,77±0,54<br>4,13±0,28 | — | — | 3,46±0,26<br>2,32±0,39† | — | — | — | 3,60±0,39<br>4,82±0,52† | — |
| Total $T_3$ content in blood serum | 118,4±6,3 | 110,1±9,4<br>100,4±7,1 | — | — | 114,8±7,1<br>67,3±9,3† | — | — | — | 102,4±7,3<br>148,1±19,1 | — |
| Cyclic AMP content in thyroid gland | 86,2±6,8 | 823±67<br>708±71* | — | — | 854±71<br>588±65† | — | — | — | 803±98<br>1043±81* | — |

*Parameters studied 24 h after injection of $^{131}I$.
†$P \leq 0.05$.
Legend. Numerator — control; denominator — experiment.

TABLE 2. Binding of $^{131}I$-$T_4$ by Tissues of Organs (in % of injected dose per 100 mg weight of organ) as a Result of a Single Immunization of Animals with Typhoid Vaccine (M ± m)

| Organ | Time of investigation after injection of anitgen, days | | | | | |
|---|---|---|---|---|---|---|
| | 1st | | 4th | | 20th | |
| | control | expt. | control | expt. | control | expt. |
| Control | 0,207±0,019 | 0,191±0,013 | 0,227±0,017 | 0,182±0,021* | 0,258±0,027 | 0,301±0,029* |
| Liver | 0,231±0,021 | 0,228±0,022 | 0,324±0,023 | 0,261±0,011* | 0,291±0,021 | 0,396±0,031* |
| Spleen | 0,136±0,011 | 0,121±0,014 | 0,132±0,013 | 0,093±0,006* | 0,129±0,012 | 0,161±0,021* |

*$P \leq 0.05$.
Legend. Data for lymph nodes are not given because they are not statistically significant.

100 g body weight, was determined 24 h after injection of $^{131}$I-$T_4$ [4] on the 4th and 20th days of the immune response, in the spleen, liver, heart, and lymph nodes; labeled $T_4$ was injected 24 h before the investigation [12]. The numerical data were subjected to statistical analysis by the Wilcoxon–Mann–Whitney criterion [5].

## EXPERIMENTAL RESULTS

The results showed (Table 1) that during the 1st and 2nd days after injection of the antigen there was no significant change in thyroid function. By the 3rd-4th day of the observations the cyclic AMP content in the thyroid gland tissue of the immunized animals was considerably reduced (by 21.2%). The level of binding of $^{131}$I by the gland fell sharply. Iodine assimilation is known to be a passive process, the degree of which is determined by the intensity of hormone formation and by the release of thyroid hormone in the blood. To judge from the considerable fall in the blood PBI level by the 3rd (by 56.8%) and 4th days (by 76.6%), these processes have a low level of activity. The reason is evidently the low thyrotrophic function of the pituitary [11] at this period. This suggestion is confirmed by the fall in the thyroid cyclic AMP level, which was discovered, and which can be regarded as an indicator of thyrotrophic hormone activity in the blood [13]. On the 4th day after immunization, functional activity of the thyroid gland reached its lowest level, when the total $T_4$ content in the blood was reduced by 32.9% and the total $T_3$ content by 58.7%, and incorporation of $^{131}$I-$T_4$ by the tissues fell (Table 2), evidently on account of the more intensive binding of hormones with the serum globulin, for the number of binding sites on the globulin is increased at this time [14].

By the 7th day, parameters characterizing thyroid function continued to be significantly lowered, but this shift was not so great as at the previous time. The opposite trend of the response, evidently due to activation of the "feedback effect" [4], occurred in the productive period of immunogenesis, when the raised level of thyroid function led to stimulation of protein synthesis, which is highly sensitive to thyroid hormones [4]. The most marked changes were found on the 20th day of the experiment, when the cyclic AMP content in the thyroid tissue of the immunized animals was increased, along with an increase in total $T_4$ (by 33.9%) and $T_3$ (by 45.7%) of the blood serum and binding of labeled $T_4$ by the organs (Table 2).

The immune response, as we know, is divided into inductive and productive phases. The first period is evidently accompanied by a normal level of thyroid function. The decrease in thyroid activity toward the 3rd-4th day is probably due to elevation of the level of functioning of the adrenocorticotrophic system, with which thyroid function enjoys reciprocal relations [1].

The response of the thyroid to an antigenic stimulus, thus demonstrated, is regarded as a component of the nonspecific adaptive reaction of the organism to an extraordinary stimulus, such as an antigen [3, 4, 6, 9]. Responses of this sort are evidently an important condition for development of the immune response at the organismal level, ensuring the metabolic changes required for antibody synthesis and for the formation of a population of immune lymphocytes [15].

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# EFFECT OF AN ANTIOXIDANT INHIBITOR OF THE 3-HYDROXYPYRIDINE SERIES ON THE CELL-MEDIATE IMMUNE RESPONSE

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In connection with the search for effective immunoregulators the study of antioxidants which affect the immune response is very important [5]. We know that administration of natural (vitamin E) or synthetic (ionol, santoquin) antioxidants is known to stimulate humoral and cellular immunity in experimental animals [6], whereas antioxidants belonging to the β-hydroxy derivatives of heterocyclic compounds containing nitrogen exhibit marked immunodepressive activity [3, 4].

The writers previously discovered the immunodepressive action of an antioxidant inhibitor belonging to the 3-hydroxypyridine class (preparation OP-6) on a model of synthesis of antibodies against sheep's red blood cells, and also during allografting of the skin in mice [1, 3].

The object of the present investigation was to continue the study of the immunodepressive activity of compound OP-6, using methods of simultaneous evaluation of mitostatic and lymphotoxic action [2] and interaction between sensitized lymphocytes and target cells [7].

TABLE 1. Mitostatic and Lymphotoxic Activity of Compound OP-6 on Sublethally Irradiated Mice

| Dose of compound, mg/kg | Mean No. of CFU per spleen after admin. of comp. (M ± m) | Mitostatic effect | Mean No. of CFU per spleen after injection of compound and $2 \cdot 10^6$ lymphocytes (M ± m) | No. of surviving CFU (in %) – lymphotoxic effect |
|---|---|---|---|---|
| – | 12,1±1,3 | — | 4,4±0,9 | 36,7 |
| 50 | 12,5±0,9 | Absent | 9,2±0,8 | 66,6 |
| 100 | 12,2±1,2 | " | 8,1±0,6 | 72,6 |
| 150 | 11,8±1,9 | " | 10,7±0,8 | 88,5 |
| 200 | 12,1±1,2 | " | 11,6±0,9 | 96,1 |

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