

# THE RELATIONSHIP BETWEEN THE CONCENTRATIONS OF THYROTROPIC HORMONE IN THE HYPOPHYSIS AND THE PERIPHERAL BLOOD

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No final solution has been reached of the problem of whether the anterior lobe of the hypophysis is a storage gland in which the processes of production and secretion of hormones may occur at different times, or whether the hormones produced enter the peripheral blood continuously.

The results of clinical observations and experimental investigations give the impression that the hypophysis is a gland of "continuous action" and that the hormones which it produces enter the blood stream immediately. If this hypothesis is correct, changes in the quantity of the various hormones in the hypophysis must be correspondingly reflected in their content in the blood. Experimental research has in fact shown that in rats after thyroidectomy the content of thyrotropic hormone increases in both the hypophysis and the blood serum [12]. In electrolytic lesions of the anterior hypothalamus, a decrease in the content of thyrotropic hormone in the anterior lobe of the hypophysis was accompanied by a corresponding fall in the level of this hormone in the blood [10].

After the prolonged administration of goitrogenic substances to animals, many authors found an increase in the concentration of thyrotropic hormone in the hypophysis [2,3,7]. Under these circumstances an increase in the concentration of the thyrotropic hormone in the blood is also observed [7-9].

Feeding rats on thiourea or sulfadiazine [12] caused a decrease in the content of thyrotropic hormone in both the hypophysis and the blood serum. The different level of the thyrotropic hormone concentration in the hypophysis of females and males in summer and winter is reflected by corresponding changes in the concentration of this hormone in the blood [13].

In the present investigation our object was to determine whether changes in the content of thyrotropic hormone in the hypophysis are accompanied by parallel changes in its concentration in the blood.

## METHOD

In view of data showing an increase in the content of thyrotropic hormone in the hypophysis 10 days after removal of the superior cervical sympathetic ganglia in rabbits [1,4,6] or after feeding these animals with 6-methylthiouracil [2,3], we first practised removal of the superior cervical sympathetic ganglia, and secondly, administration of 6-methylthiouracil (6MTU).

Our previous investigations on rabbits showed that a decrease in the content of thyrotropic hormone in the hypophysis may be caused by a combination of chronic stimulation of the sciatic nerve with feeding with 6MTU [5], and also by administration of chlorpromazine for 10 days (R. D. Vyazovskaya). We therefore fed the experimental animals with 6 MTU in association with stimulation of the sciatic nerve or administration of chlorpromazine.

Experiments were carried out on 24 male rabbits, weighting 2-2.5 kg. The concentration of thyrotropic hormone in the hypophysis and blood was estimated in guinea pigs. In all 30 guinea pigs were used.

The superior cervical sympathetic ganglia were removed in a one-stage surgical operation, without anesthesia. For 20 days the animals received 6MTU by mouth in a dose of 250 mg/kg body weight daily. Chronic stimulation of the sciatic nerve was applied through a silver wire in the upper third of the thigh, for 30 days. These rabbits received 6 MTU in the above dose for 20 days, starting on the 10th day after operation. Chlorpromazine was given by mouth in a dose of 20 mg/kg body weight for 10 days. At the end of the experimental period the rabbits were sacrificed by air embolism.

In order to determine the concentration of thyrotropic hormone in the hypophysis, guinea pigs of the 3rd and 4th series were grafted subcutaneously on each of 2 successive days with the hypophysis of rabbits which had

Concentration of Thyrotropic Hormone in the Hypophysis and Blood of Rabbits

Treatment given (donors)	Height of cells of thyroid epithelium of recipient guinea pigs in ( $\mu$ ) after receiving: extract of rabbits hypophyses				
	control	experiment	criterion of significance	control	experiment
Removal of the superior cervical sympathetic ganglia		$12.396 \pm 0.089$ $11.676 \pm 0.098$ $M = 12.036 \pm 0.093$	19.0	$8.604 \pm 0.075$ $7.992 \pm 0.077$ $8.671 \pm 0.083$ $8.256 \pm 0.079$ $M = 8.31 \pm 0.076$	$8.202 \pm 0.069$ $9.06 \pm 0.082$ $11.280 \pm 0.098$ $8.07 \pm 0.065$ $M = 9.156 \pm 0.076$
Administration of chlorpromazine	$9.51 \pm 0.096$ $9.58 \pm 0.09$ $M = 9.545 \pm 0.093$	$7.548 \pm 0.079$ $8.97 \pm 0.085$ $M = 8.259 \pm 0.082$	10.3		$7.686 \pm 0.058$ $7.44 \pm 0.084$ $8.976 \pm 0.090$ $6.996 \pm 0.053$ $M = 7.77 \pm 0.071$
Administration of 6MTU		$10.87 \pm 0.10$ $10.65 \pm 0.10$ $M = 10.76 \pm 0.10$	24.7	$7.18 \pm 0.057$ $7.22 \pm 0.048$ $6.88 \pm 0.055$ $8.45 \pm 0.073$ $M = 7.43 \pm 0.058$	$9.20 \pm 0.088$ $8.09 \pm 0.096$ $9.37 \pm 0.099$ $8.24 \pm 0.077$ $M = 8.7 \pm 0.090$
Stimulation of the sciatic nerve + 6MTU	$7.8 \pm 0.065$ $7.83 \pm 0.066$ $M = 7.81 \pm 0.065$	$5.65 \pm 0.065$ $6.21 \pm 0.066$ $M = 5.93 \pm 0.065$	20.6		$5.48 \pm 0.053$ $5.76 \pm 0.055$ $4.70 \pm 0.057$ $5.41 \pm 0.057$ $M = 5.33 \pm 0.055$
					26.2

11.8

26.2

received the same treatment. The recipients were sacrificed 100 hours after the first graft. The 1st and 2nd series of guinea pigs received injections of rabbit hypophysis, preliminarily dried in acetone, in the form of a suspension in physiological saline, for 4 days in a total dose of 2 hypophyses per guinea pig. The animals were sacrificed 72 hours after the first injection. When the latter method was used, a much more intensive reaction was observed in the thyroid gland of the guinea pigs than after grafting of the hypophysis.

Thyrotropic hormone was precipitated from the blood of the rabbit by Fellingner's method [11], and assayed simultaneously in two guinea pigs. The criterion of the content of thyrotropic hormone in the hypophysis or blood was the change in the mean value of the height of the epithelial cells of the thyroid gland of the guinea pig (recipient) receiving the hypophysis or blood extract.

Because of seasonal variations in the concentration of thyrotropic hormone in the hypophysis, in each series we determined the concentration of this hormone in control rabbits concurrently with the determinations in the experimental animals. Series which were done at the same time had a common control.

The mean figures obtained in the experimental groups were compared with the results established for the control rabbits of the particular series. The values obtained were treated by the methods of variational statistics. The difference between the experimental and control values was regarded as significant if the value of the criterion of significance  $r$  was equal to or greater than  $3 (r \geq 3) *$ .

## RESULTS

In the first place we studied the height of the cells of the thyroid epithelium in intact guinea pigs sacrificed at different periods of the year; in the autumn-winter period its value was  $5-5.5\mu$  and in the spring-summer period it was  $4-4.8\mu$ .

The figures in the table show that removal of the superior cervical sympathetic ganglia in rabbits led to an increase in the concentration of thyrotropic hormone in the hypophysis by comparison with the controls. Whereas the mean height of the cells of the epithelium of the thyroid gland of the recipient guinea pigs  $M$  after receiving injections of a suspension of the hypophyses of intact control rabbits was  $9.545\mu$ , after receiving injections of hypophyses of rabbits undergoing ganglionectomy this value was  $12.036\mu$ . This increase was significant, for the criterion of significance  $r = 19$ .

The level of thyrotropic hormone in the blood of the rabbits was correspondingly higher ( $M = 9.156\mu$ ) after removal of the superior cervical sympathetic ganglia than in the control animals, in which  $M = 8.381$  ( $r = 7.7$ ).

Administration of 6MTU led to an increase in the concentration of thyrotropic hormone in the hypophysis of the experimental rabbits by comparison with the controls, for the mean height of the cells of the thyroid epithelium of the recipients  $M$  after grafting of the hypophy-

ses of rabbits receiving 6MTU was  $10.76\mu$ ; the hypophyses of the control (intact) rabbits in this series caused an increase in the height of the cells of the thyroid epithelium of the recipients to an average of  $7.81\mu$ . This difference was statistically significant, for  $r = 24.7$ .

Whereas after the action of 6MTU the concentration of thyrotropic hormone in the hypophysis was raised, the concentration of this hormone in the blood of these donor rabbits was higher ( $M = 8.7\mu$ ) than in the control series tested at the same time, in which the height of the cells of the thyroid epithelium of the recipients was on the average  $7.77\mu$  ( $r = 11.8$ ).

After administration of 6MTU in association with stimulation of the sciatic nerve, the concentration of thyrotropic hormone in the hypophysis of the rabbits was lowered ( $M = 5.93\mu$ ) by comparison with the controls, in which  $M = 7.81\mu$  ( $r = 20.6$ ). Corresponding to the lowered concentration of thyrotropic hormone in the hypophysis, the concentration of this hormone in the blood was also lowered in these animals ( $M = 5.33\mu$ ) by comparison with the level in the control animals ( $M = 7.43\mu$ ). The criterion of significance of the lowering of the concentration of this hormone in the blood  $r = 26.2$ .

Injection of a suspension of hypophyses of rabbits receiving chlorpromazine into recipient guinea pigs caused a much smaller increase in the height of the cells of the thyroid epithelium ( $M = 8.259\mu$ ) than in the case of control animals, in which  $M = 9.545\mu$  ( $r = 32.8$ ). When the blood of rabbits receiving chlorpromazine was tested it was also found that the concentration of thyrotropic hormone in it was lower than that in the blood of the control animals. In the first case the height of the cells of the thyroid epithelium of the recipients  $M = 7.77\mu$ , and in the second case  $M = 8.381\mu$ . The fall was significant, since  $r = 5.2$ .

It follows from analysis of the results obtained that a change in the concentration of thyrotropic hormone in the hypophysis is reflected by a corresponding change in its concentration in the blood. An increase in the concentration of the hormone in the hypophysis after removal of the superior cervical sympathetic ganglia, or administration of 6MTU, for instance, was accompanied by an increase in the concentration of this hormone in the peripheral blood, whereas a lowered concentration of thyrotropic hormone in the hypophysis (resulting from the action of 6MTU in association with stimulation of the sciatic nerve or of the action of chlorpromazine) corresponded to small concentrations of this hormone in the blood also. Hence it follows that the thyrotropic hormone, after its synthesis in the hypophysis, is not retained in the parenchyma of the gland but at once enters the blood stream.

\* The criteria of significance  $r$  were determined from the formula: 
$$r = \frac{M_{\text{expt}} + M_{\text{control}}}{\sqrt{m_{\text{expt}}^2 + m_{\text{control}}^2}}$$

where  $M$  is the mean height of the cells of the thyroid epithelium of the guinea pigs;  $m^2$  is the mean square error.

The anterior lobe of the hypophysis must therefore be regarded as a gland of merocrine type, with continuous secretion.

#### SUMMARY

Simultaneous determinations of the content of thyrotropic hormone demonstrated a clear-cut parallelism between the shifts in the concentration of this hormone appearing in the hypophysis and the peripheral blood of rabbits.

The rise of the thyrotropic hormone content in the hypophysis, observed after removal of the upper cervical sympathetic ganglia or after administration of 6-methylthiouracil, was accompanied by an increase of the level of this hormone in the peripheral blood.

On the other hand reduction in the concentration of the thyrotropic hormone in the hypophysis during the administration of 6-methylthiouracil while, at the same time, stimulating the sciatic nerve, or after administration of chlorpromazine corresponded to a decrease in the level of the hormone in the peripheral blood.

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