ROUTES OF TRANSMISSION OF CEREBRAL CORTICAL INFLUENCES TO THE THYROID GLAND

M. G. Amiragova

Institute of Normal and Pathologic Physiology (Director – Active Member AMN SSSR V. N. Chernigovsky), AMN SSSR, Moscow

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The regulatory action of the central nervous system on the thyroid gland has now been generally accepted.

However, no final answer to the question of the routes by which this influence is transmitted has yet been found.

Some authors consider that impulses sent by the CNS reach the thyroid only by way of the thyrotropic hormone of the hypophysis [9, 10, 11, 12]. Others hold the view that cortical influences can reach the thyroid by direct neural pathways, without pituitary mediation. In a number of cases this view is based, however, on the assumption that the presence of extensive innervation in the thyroid cannot be without significance in the regulation of its secretory activity [1, 4, 7, 8]. Some authors limited their search for pathways for cortical influences to experiments with extirpation of the pituitary [2].

The present investigation is devoted to a study of routes of transmission of cortical influences to the thyroid, using electrodefensive conditioned reflex activity technique.

EXPERIMENTAL METHODS

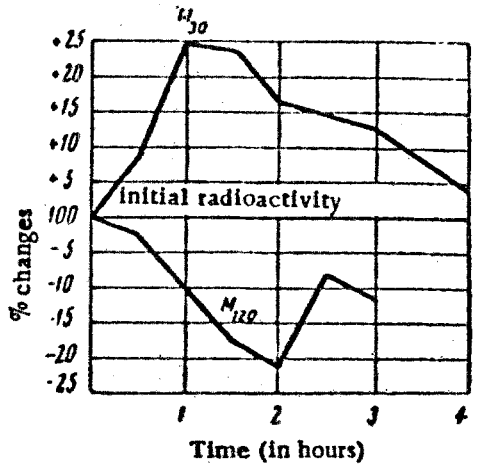
In order to study the influence of the cerebral cortex on thyroid activity conditioned electrocutaneous defensive reflexes to the sound of a metronome – 120 strokes per minute – displaced from the unconditioned stimulus by 20 seconds, were established. Differentiation was developed to 30 strokes of the metronome per minute. Electric current from an induction coil, exceeding the threshold strength by 1-2 cm was used as the unconditioned stimulus.

The functional state of the thyroid gland was determined by estimating its content of radioactive iodine. Radioactivity of the thyroid was measured by a gamma-ray ("AMM-4") counter tube placed in a thin-walled aluminum cover and connected with the apparatus by a flexible screened cable. Such a tube was firmly attached by means of a collar to the neck over the thyroid. Radioactive iodine was introduced as the sodium salt, without carrier, in doses of 2-5 μ cu per dog. Thyroid radioactivity was measured 48 hours after administration of labelled iodine when no more absorption could be detected. Counts were made every hour over a period of 3-4 hours while the animal was in the chamber. Percentage changes were calculated with respect to the initial radioactivity which was taken as 100%.

At the beginning of this work a careful study was made of fluctuations in radioactive iodine levels in the thyroid in response to the dog being placed in the chamber and in the special stand. It was found that the radioactive content of the thyroid remained unchanged under these conditions, the fluctuations in its level being within physiologic limits and not exceeding $\pm$ 10%.

EXPERIMENTAL RESULTS

The use of electric current as unconditioned stimulus enhances secretion of radioactive iodine by the thyroid. As early as one hour following a single stimulation of the paw by electric current there is appreciable decrease in radioactive iodine in the thyroid; maximal drop in radioactivity is observed after 2 hours, the average percentage of change being -20.1 ± 1.3. Only after 3-4 hours a tendency to restoration of radioactive iodine content to the initial value becomes apparent.



Effect of defensive conditioned reflexes on radioactive iodine content of the thyroid gland.

It is known that the electrocutaneous defensive conditioned reflex is usually established very rapidly. Another distinctive feature of this reflex is that if it is reinforced only in those cases when the conditioned reaction is absent the conditioned connection is established extremely quickly and the dog does not go into a state of inhibition [3, 5, 6]. In making use of this feature of the defensive reflex it was possible to stage experiments without reinforcement over prolonged periods of time; this enabled us to observe function of the thyroid subjected to impulses from the cerebral cortex only.

The radioactive iodine content of the thyroid falls under the influence of positive conditioned reflexes. This reaction becomes apparent an hour after placing the animal in the chamber and reaches a maximum at the end of 2 hours. The average percentage of changes equals 21.2 ± 4.6 (see figure). The thyroid reacts in almost the same way to the unconditioned electric stimulus.

Thus both the unconditioned stimulus and the conditioned defensive reflex established on the basis of electric reinforcement are able to stimulate the secretion of products of thyroid activity into the blood to practically the same degree.

The influence of differentiation inhibition on secretion of radioactive iodine by the thyroid was studied in those experiments in which the inhibitory stimulus was used in isolation; this stimulus, similarly to the positive stimulus, was applied up to 10 times in the course of the first hour, with 5-minute intervals. The figure shows that as early as 30 minutes after application of M30 increased radioactive iodine content in the thyroid can be observed; during the subsequent 2 hours the gland's radioactivity remains at a high level and only after 3-4 hours returns to the original level. In those cases in which differentiation was disinhibited thyroid radioactivity fell, i.e., a reaction corresponding to the action of the positive metronome frequency was observed.

These investigations indicate that changes in thyroid activity take place depending on the functional state of the CNS. Excitation of the cerebral cortex is associated with increased secretion of radioactive iodine by the thyroid and, consequently, secretion of products of its activity is increased; when the cortex is in a state of inhibition accumulation of labelled iodine in the thyroid is observed, indicating slowed secretion of products of its activity into the blood.

What are the mechanisms mediating the influence of cerebral cortex on thyroid function?

As already mentioned, a number of authors at present consider that CNS influences on the thyroid are mediated exclusively by the hypophysis. To discover whether the hypophysis was indeed the sole humoral link in the regulation of thyroid secretory activity a series of experiments on hypophysectomized animals was carried out. The results showed that under the influence of defensive conditioned reflexes stimulation of secretion of the products of thyroid activity into the blood occurred in these animals in the same way as prior

to operation; this reaction was, it is true, not as constant as in intact animals since in a number of cases a converse effect was observed, viz. accumulation of radioactive iodine in the thyroid, and in some cases no effect at all was detected. Nonetheless these data demonstrate that changes in the functional state of the cortex can be felt in the activity of the thyroid even in the absence of the hypophysis (Table 1).

TABLE 1

Effect of Electrodefensive Conditioned Reflexes on Radioactive Iodine Content of the Thyroid in Hypophysectomized Animals (Changes are Given in Percentage with Respect to Initial Radioactivity)

Date of experiment	Change in radioactive iodine content of the thyroid time (in minutes)					
	60	90	120	150	180	210
28/V 1956	0	+11	−22	−32	−32	—
29/V	0	+16	+16	—	—	—
30/V	−14	−21	−14	—	—	—
31/V	+9	--	+2	−4	−8	—
4/VI	−12	--	−17	—	−17	—
8/VI	−37	—	−22	—	−15	—
22/XI	+20	+18	+14	+18	+20	—
26/XI	0	—	+9	0	+9	+9
28/XI	+18	+18	+36	+22	—	—
29/XI	−3	--	+2	—	0	+10
3/XII	−20	--	−25	—	−30	—
4/XII	−21	—	−26	—	−16	—
10/XII	+16	—	+8	—	—	—
11/XII	−15	—	−35	—	−15	—
12/XII	+47	--	+24	—	—	—
13/XII	−24	--	−24	—	−24	—

TABLE 2

Effect of Electrodefensive Conditioned Reflexes on Radioactive Iodine Content of the Thyroid After Removal of the Right Adrenal and Transection of the Greater Splanchnic Nerve on the Left (Changes are Given in Percentage with Respect to the Initial Radioactivity)

Date of experiment	Change in radioactive iodine content of the thyroid time (in minutes)						
	60	90	120	150	180	210	240
22/VI 1956	+10	+20	+22	+16	—	—	—
25/VI	—	—	+21	+18	+18	+7	—
26/VI	−22	—	−22	−17	−16	—	—
28/VI	−18	−16	−5	−11	—	—	—
2/VII	+2	+12	+2	+3	−12	0	—
6/VII	−24	−38	−34	—	−28	—	−20
14/VIII	−2	−2	+9	−2	−2	+4	+6
16/VIII	−17	−17	−14	−10	−5	—	—
17/VIII	−17	−14	−12	−11	−9	—	—
29/X	−51	--	−31	—	−5	—	—

For further analysis of the mechanism of transmission of cortical influences to the thyroid an attempt was made to elucidate the role of the adrenals. With this in view, the adrenal gland was removed from one side and the splanchnic nerve was transected on the other. The hypophysis was not removed in these dogs. Experiments were performed 1-3 weeks after operation. Table 2 shows that under the influence of positive conditioned reflexes a decrease of labelled iodine content in the thyroid was observed in most experiments. This indicated that cortical influences on the thyroid were realized under these conditions also.

In the light of our investigations it was imperative to consider the existing concepts of transmission of impulses from the CNS to the thyroid by direct neural pathways. If this were so, then neither removal of the hypophysis nor the subsequent removal of one adrenal and interruption of connection with the CNS of the other adrenal should impair the regulatory influence of the cerebral cortex on the thyroid. However, experiments showed that dogs deprived of the hypophysis and one adrenal and with denervation of the other adrenal showed complete disappearance of transmission of cortical influences to the thyroid. In these animals the thyroid reaction to unconditioned electrocutaneous stimulation also disappeared (Table 3).

TABLE 3

Effect of Electrodefensive Conditioned Reflexes on Radioactive Iodine Content of the Thyroid After Removal of the Hypophysis and the Right Adrenal and Transection of the Greater Splanchnic Nerve on the Left (Changes are Given as Percentage with Respect to the Initial Radioactivity)

Date of experiment	Change in radioactive iodine content of the thyroid, time (in minutes)						
	60	90	120	150	180	210	240
27/VI 1956	+4	+8	+12	—	+12	—	—
3/VII	+5	+5	−0	+5	+5	+10	+10
5/VII	0	—	−6	—	0	—	—
7/VII	+8	—	+8	—	+8	—	+8
9/VII	−4	—	0	0	0	−7	—
10/VII	0	—	+14	—	+7	—	+7
11/VII	+5	—	−5	—	+11	—	+11
13/VII	0	—	+4	—	+4	—	+6
14/VII	+5	—	+5	—	+2	—	0
10/VIII	−3	—	+6	—	−3	—	—
11/VIII	0	—	+9	—	+4	—	—
18/X	0	—	0	—	−3	—	—
20/X	−9	—	−3	—	−3	—	—
22/X	+4	—	+11	—	+11	—	—
After administration of thyrotropic hormone							
10/XII 1956	0	—	0	—	+8	—	—
11/XII	0	—	0	—	0	—	—
12/XII	0	—	0	—	0	—	—
15/XII	0	+11	—	−11	—	0	—
In experiments with electric reinforcement							
30/VI 1956	−11	0	0	0	−17	−11	—
25/X	−4	0	−8	−12	−8	−4	—
2/XI	0	—	+2	—	0	—	—
5/XI	−5	−9	−7	−3	−3	—	—
9/XI	0	11	−4	—	—	—	—
16/XI	+6	—	+6	—	0	—	+4

Note. Quadratic deviation of radioactivity value did not exceed 5%.

In addition, the experiments showed that in these animals there was depression of thyroid activity. It could be supposed that it was this depression which was the cause of the observed phenomena. To check this it was necessary to stimulate thyroid function in the operated animals and retest its reaction to conditioned reflexes against this background. The animals were given 4 ml thyrotropic hormone "Ambinon" (each ml containing 100 I.U.). Secretion of radioactive iodine by the thyroid increased after each administration of the hormone. Twice repeated administration of the hormone increased thyroid function almost threefold. Thus, before administration of the hormone the maximal absorption of radioactive iodine reached only 6% after 24 hours; after administration of the hormone maximal absorption of radioactive iodine was 17%. Experiments performed against the background of hormone-stimulated thyroid activity showed that fluctuations of iodine level in the thyroid under the influence of defensive conditioned reflexes in this case too were within physiologic limits; under these conditions the thyroid did not react to unconditioned electrocutaneous stimuli either (see Table 3).

These experiments give grounds for considering that following simultaneous severance of connection between the CNS and the hypophysis and adrenals cerebral cortical influences on the thyroid become impossible. The presence of either the hypophysis or the adrenals is consequently essential for mediation of cortical influences on the thyroid.

B. V. Aleshin and N. S. Demidenko [2] obtained definite reaction from the thyroid when they placed silver plates on the premotor area of the cerebral cortex in dogs both intact and deprived of the hypophysis. The authors regard changes in the thyroid in experiments with hypophysectomized animals as proof of direct influence on it of the nervous system. It is difficult to agree with these authors' conclusions since they do not take into account transmission of cortical influences by way of the adrenals. There is every reason to believe that transmission of cerebral cortical influences to the thyroid is effected by the adrenals in hypophysectomized animals and not by direct neural pathways as maintained by the authors cited above.

Our experiments thus demonstrate that the activity of the thyroid is dependent on regulatory influences of the cerebral cortex.

Cerebral cortical influences on the thyroid gland are mediated not only by the hypophysis but also by the adrenals.

SUMMARY

The effect of changes of the functional condition of the brain cortex on the changes of radioactive iodine content of the thyroid gland was studied. The functional condition of the cortex was changed by formation of the positive and inhibitory electrodefensive conditioned reflexes.

It was established that the influence of the central nervous system is transmitted to the thyroid gland by way of hypophysis or suprarenal glands. The regulating influence of the cerebral cortex does not reach the thyroid gland after removal of hypophysis and one of the suprarenal glands with complete interruption of connection between the central nervous system and the other suprarenal gland.

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