NEURO-ENDOCRINE RELATIONSHIPS IN EXPERIMENTAL HYPERTHYROIDISM

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We know that the origin of the principal manifestations of hyperthyroidism is largely connected with increased activity of the sympathetico-adrenal system [6, 7].

In recent years evidence has accumulated of the beneficial effect of phenothiazine derivatives in hyperthyroidism [8, 9, 10]. These drugs possess marked sedative and adrenolytic properties. Their mechanism of action is associated with blocking of adrenergic processes in the substantia reticularis of the brainstem [7, 5] and also with the sympatholytic effect on the peripheral adrenergic structures [4].

The purpose of the present investigation was to study the action of one of the phenothiazine derivatives – aminazine (largactil) – on the state of certain somatovegetative functions in experimental hyperthyroidism.

EXPERIMENTAL METHOD

The investigations were carried out on 4 dogs. The sedative action of aminazine was studied by the changes in the behavior of the animals and the state of their conditioned reflex activity (by the motor defensive method with electrodermal reinforcement).

The adrenolytic effect of the drug was investigated by the changes in the pressor action of adrenalin, which was injected intravenously in a dose of 0.5 ml of a 1:40,000 solution, 20-25 minutes after the intravenous injection of aminazine.

The dose of aminazine used remained constant – 1 mg/ kg. In the conditioned reflex chamber the drug was injected 20 minutes before the experiment.

The action of aminazine on the circulation was studied outside the chamber from the changes in the arterial pressure and the ECG findings. Experimental hyperthyroidism was induced by feeding the dogs on thyroidin, in a dose of 0.5 g per kg body weight daily for 10 days. Experiments to study the sensitivity of the dogs to aminazine during administration of thyroid were carried out after an interval of 3-4 days.

EXPERIMENTAL RESULTS

In control experiments aminazine had an obvious sedative effect – soon after injection of the drug the dogs fell asleep, hung on their straps, and developed an unusual stereotype of movements; all the animals showed a pronounced enophthalmos.

A total or partial loss of positive conditioned reflexes was observed, with a lengthening of the latent periods, and diminution of the value of the motor and respiratory components (Fig. 1, a). In some experiments there was also observed a diminution of the unconditioned reactions appearing in association with electrical stimulation of the skin.

In this particular dose, aminazine produced a more or less hypotensive effect in all the dogs – from 5-10 minutes after injection of the drug the diastolic pressure in the various dogs fell by 10-33% and the systolic by 5-25% (in relation to the initial pressures, taken as 100). A more potent hypotensive effect was observed in the animals with a higher initial level of the arterial pressure.

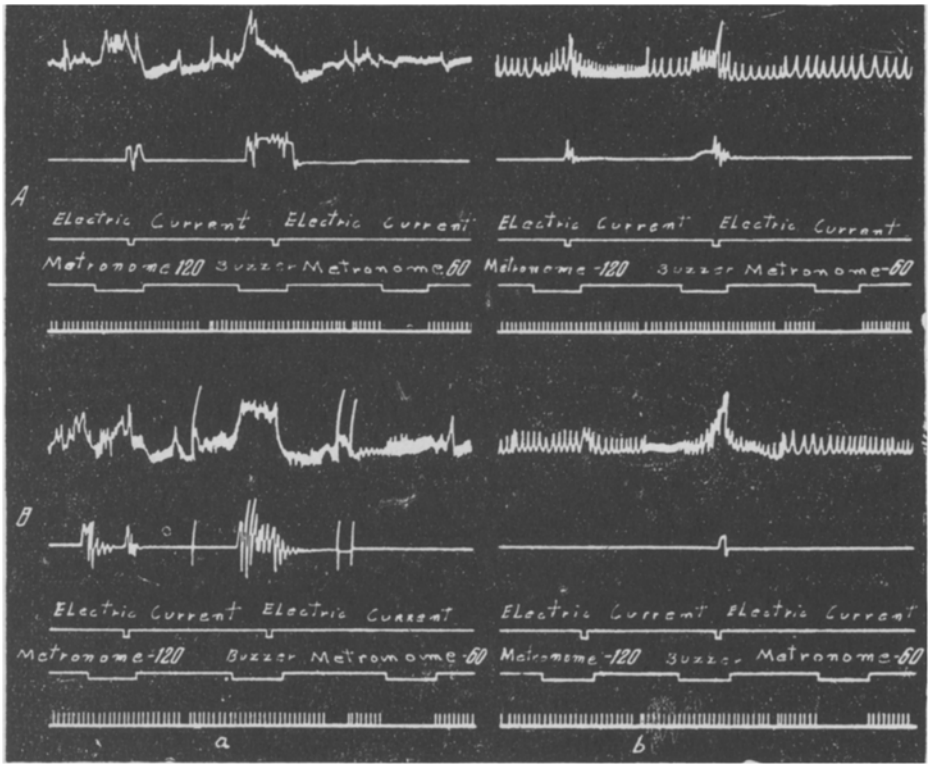

Fig. 1. The action of aminazine on the motor and respiratory components of the defensive conditioned reflexes during hyperthyroidism in the dog Belyi.
A) control experiments before injection of aminazine (a) and 20 minutes after injection of aminazine (b); B) hyperthyroidism: before injection of aminazine (a) (4th day of thyroidin administration), and 20 minutes after injection of aminazine (b) (10th day of feeding with thyroidin). Significance of the curves (from above down): respiration, motor reactions, marker of unconditioned stimulation with the electric current, marker of the conditioned stimuli, time marker (1 second).

In Tarzan, for instance, the arterial pressure fell 15 minutes after injection of aminazine from 170/120 to 130/80 mm of mercury, and in Belyi under the same conditions it fell from 130/80 to 120/70 mm of mercury.

The hypotensive effect of aminazin was accompanied by changes in the ECG findings – the R – R intervals were lengthened (bradycardia), the sinus (respiratory) arrhythmia was enhanced, as shown by the difference between $R-R_{Max}$ and $R-R_{Min}$, and also there was lengthening of the QRST complex (on the average by 0.03-0.05 seconds) and an increase in the positive potential of T_2.

The adrenolytic action of the drug was shown by diminution or distortion of the pressor reaction to adrenalin.

In the dog Ryzhii, for instance, adrenalin, given before the injection of aminazine, increased the arterial pressure from 150/110 to 200/150, 180/140 and 160/120 mm of mercury (at the 1st, 2nd and 3rd minutes respectively); after preliminary injection of aminazine the action of adrenalin in the 1st minute did not alter the arterial pressure, in the 2nd minute it fell (from 140/100 to 130/90 mm of mercury) and in the 3rd minute it regained its initial values (Fig. 2, a).

Experimental hyperthyroidism, caused by feeding the animals on thyroidin, was accompanied by considerable changes in these indices which we were studying.

The conditioned reflex activity of the dogs was altered after only the first dose of thyroidin, and moreover the character and degree of expression of these changes in the various dogs were different. In all 4 dogs, starting from the first days of administration of the hormone, the excitation of the respiratory component of the defensive reflexes was increased (the inspiratory dyspnea was intensified), the motor conditioned components were enhanced, and motor unrest appeared in the intervals between the stimuli.

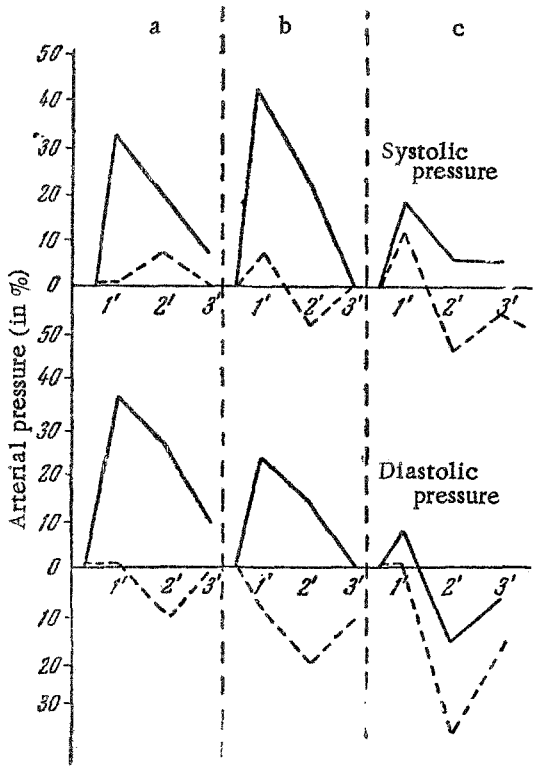

Fig. 2. The adrenolytic action of aminazine in association with hyperthyroidism in the dog Ryshii. Legend: ——— action of adrenalin; – – – – action of adrenalin after preliminary injection of aminazine; a) control; b) on the 3rd day of administration of thyroidin; c) on the 7th day of administration of thyroidin.

In animals showing strong excitation (Buyan and Tarzan) a shortening of the latent periods of the conditioned reflexed and frequent disinhibition of differentiation between motor and respiratory components were observed.

In animals with relatively weak excitation (Belyi and Ryzhii), thyroidin caused shortening of the latent periods in the first days of its administration, and on the following days it caused their lenghtening. Differentiation in these dogs was less often disinhibited, and mainly this affected the respiratory component.

From the 3rd day of administration of thyroidin, the arterial presure in all the dogs began to rise and the amplitude of the pulse increased; as the hyperthyroidism developed these phenomena increased.

In the dog Buyan, for instance, on the 7th day of administration of thyroidin the arterial pressure rose from 150/ 100 to 190/ 130 mm of mercury, and in Tarzan – from 170/ 120 to 200/ 140 mm of mercury. The increase in the arterial pressure and in the amplitude of the pulse were accompanied by marked changes in the ECG findings.

All the dogs showed considerable tachycardia, the pulse rate reaching 200 beats per minute, and under these circumstances the sinus arrhythmia diminished. In addition, in some animals there was shortening of the P – Q interval (by 0.03-0.04 second) and of the QRST complex (by 0.02-0.03 second) and increase in the negative potential of T_2.

Finally, the production of hyperthyroidism altered the sensitivity of the animals to adrenalin: its pressor action in the first days of feeding with thyroidin was enhanced, but later it decreased, and in some experiments adrenalin actually produced a perverted reaction, especially on the diastolic pressure.

In Tarzan, for instance, in control experiments, during the first minute of its action adrenalin increased the arterial pressure from 170/ 120 to 260/ 160 mm of mercury; on the third day of feeding with thyroidin – from 180/ 130 to 220/ 140 mm of mercury, and on the 7th day of administration of thyroidin adrenalin raised the systolic pressure from 200 to 240 mm of mercury and lowered the diastolic from 140 to 130 mm of mercury.

The induction of hyperthyroidism in the dogs thus caused a whole series of disturbances, the origin of which could be accounted for by changes in the excitation of the somatic and vegetative divisions of the central nervous system and by the peripheral action of thyroidin.

The enhanced respiratory components, associated with the action of the conditioned signals, the raised arterial pressure and the increased amplitude of the pulse, the tachycardia and the reduction of the sinus arrhythmia, and also the increased sensitivity of the animals to adrenalin – these all indicated the stimulation of the sympathetico-adrenal function.

In view of the findings of L. A. Orbeli [3], E. A. Asratyan [2] and other workers on the influence of the sympathetic division of the nervous system on the tonus of the cerebral hemispheres, it may be postulated that the change in conditioned reflex activity during hyperthyroidism was connected to a considerable degree with the increased activity of the sympathetico-adrenal system.

Tests of the pharmacodynamic properties of aminazine in dogs with hyperthyroidism have shown that all the effects of this drug observed in control experiments undergo considerable modification under these conditions.

The sedative action of aminazine appeared more intensively and was more prolonged in association with hyperthyroidism. Motor activity was suppressed to a greater degree than in control experiments; the animals remained for a longer time in a state resembling sleep.

Aminazine suppressed the motor and respiratory conditioned reactions more strongly. Under these circumstances there was also observed a weakening, even complete disappearance, of the unconditioned motor reactions connected with the afferent electrodermal stimulation (see Fig. 1, b).

The hypotensive effect of aminazine was more pronounced in association with hyperthyroidism, especially in the first days of thyroidin feeding: the arterial pressure fell after injection of the drug (the diastolic by 15-43%, the systolic by 7-37%).

In Tarzan, for instance, on the 3rd day of administration of thyroidin, aminazine lowered the arterial pressure 15 minutes after its injection from 170/120 to 110/70 mm of mercury, whereas in a control experiment it lowered it from 170/120 to 130/80 mm of mercury.

With the development of increasing hyperthyroidism in all the dogs, with the exception of one (Buyan), the hypotensive action of aminazine (expressed as a percentage) gradually decreased; in absolute figures the hypotensive effect was greater throughout the entire period of hyperthyroidism than in the control experiments.

The action of aminazine on the cardiac rhythm during hyperthyroidism was changed in the following manner.

In 3 dogs, especially in Ryzhii and Buyan, aminazine caused a lesser degree of bradycardia and not such a marked increase in the sinus arrhythmia as in control experiments.

In Ryzhii, for instance, in a control experiment the intervals, $R-R_{Max}$ and $R-R_{Min}$ were increased 15 minutes after injection of aminazine from 0.55-0.45 to 1.25-0.50 second, and on the 7th day of administration of thyroidin – from 0.45-0.40 to only 0.85-0.50 second.

In Belyi, in which initially the pulse was relatively slower and the sinus arrhythmia more marked, aminazine in association with hyperthyroidism caused a more intense bradycardia and sinus arrhythmia. The action of aminazine on the length of systole (QRST) and on the direction of the T_2 wave was fundamentally the same in hyperthyroidism as in the control experiments.

The adrenolytic action of aminazine in association with hyperthyroidism was shown more strongly in all the dogs. Under these conditions aminazine caused a more marked suppression and distortion of the pressor action of adrenalin, especially on the diastolic pressure.

For example, whereas in control experiments adrenalin combined with the administration of aminazine lowered the diastolic pressure of the dog Belyi in control experiments by 20 mm of mercury, on the 7th day of feeding with thyroidin, after the preliminary injection of aminazine, adrenalin lowered the diastolic pressure by 40 mm of mercury. The changes in the adrenolytic properties of aminazine during hyperthyroidism in the dog Ryzhii are shown in Fig. 2.

It can be seen from the results described above that the stimulation of sympathetico-adrenal function observed in association with hyperthyroidism was accompanied by increased sensitivity of the animals to the sedative, hypotensive and adrenolytic actions of aminazine.

On the pharmacological basis of the actions of the phenothiazine derivatives – the blocking effect on the adrenergic mechanisms of the substantia reticularis, and their sympathicolytic properties, it may be postulated that the stimulation of the sympathetico-adrenal function during hyperthyroidism and the origin of its chief manifestations were associated with the increase in the adrenergic activity of the substantia reticularis and with the change in the sensitivity of the peripheral adrenergic structures.

SUMMARY

The author studied the effect of aminazine (1 mg/ kg of body weght) on the somatovegetative functions in dogs with experimental hyperthyroidism induced by feeding them on thyroidin (0.5 gm/ kg). The intensification of the sympathetico-adrenal activity occurring in these conditions is associated with an increased sensitivity of the animals to the sedative, hypotensive and adrenolytic effect of aminazine. Basing upon the mechanism of aminazine action it becomes possible to explain certain manifestations of hyperthyroidism by the rise of the adrenergic activity of reticular formation and that of the sensitivity of peripheral adrenoreactive structures.

LITERATURE CITED

[1] P. K. Anokhin, Fiziol. Zhur. SSSR, 43, 11, 1071-1085 (1957).

[2] É. A. Asratyan, Fiziol. Zhur. 18, 5, 739-760 (1935).

[3] L. A. Orbeli, Lectures on the Physiology of the Nervous System, (Leningrad, 1935). [In Russian].

[4] D. A. Kharkevich, Byull. Éksptl. Biol. i Med., 43, 2, 58-60 (1957).*

[5] D. Bovet and V. B. Longo, XX International Physiological Congress, 306 (Bruxelles, 1956).

[6] E. Gellhorn and J. Feldmann, Endocrinology, 29, 467-474 (1941).

[7] J. W. Hinton, Surgery, 35, 491-492 (1954).

[8] H. Kleinsorger and K. Rösner, Die Phenothiazinderivate in der inneren Medicin, (Jena, 1956).

[9] R. Milin and P. Shtern, Med. Pregled., 8, 280-285 (1955).

[10] E. Straus and J. Hiller, Med. Klin., 49, 1073-1075 (1954).

* Original Russian pagination. See C. B. Translation.