PHARMACOLOGY

DISTRIBUTION OF β-PHENYL-γ-AMINOBUTYRIC ACID (PHENYGAM) IN THE ORGANISM AND CERTAIN INDICES OF ITS CENTRAL EFFECTS

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β-Phenyl-γ-aminobutyric acid—the original domestic preparation synthesized at the department of organic chemistry of A. I. Gertsen Pedagogical Institute, under the supervision of Professor V. V. Perekalin—in contrast to γ-aminobutyric acid (GABA), exerts an inhibiting effect upon the central nervous system after the usual administration [2]. The influence of phenygam on animals is expressed in an inhibition of the orientative reaction, an inhibition of the motor activity, a disturbance of the coordination of movements, hypothermia, potentiation of narcosis, etc. In view of the combination of effects that it induces, phenygam may be assigned to the group of tranquilizers.

Since GABA practically does not penetrate at all through the hematoencephalic barrier, it is of interest to determine the degree of permeability of this barrier to phenygam, to study the distribution of the latter in the organs and tissues, and to compare its content in the brain with the changes observed in the function of the central nervous system. In addition, to determine the mechanism of the action of phenygam, it was necessary to investigate its influence on the GABA level in the brain.

EXPERIMENTAL PROCEDURE

The experiments were conducted on rats and rabbits. Phenygam was administered intravenously or intraperitoneally in doses of 50-200 mg/kg.

Since phenygam is close in chemical structure to GABA, we used the principle widely used for determining various amino-acids—electrophoretic or chromatographic separation on paper—for its detection. Just like most amino acids, phenygam gives a color reaction with ninhydrin, which can be used for subsequent quantitative determination by photometric methods. The preparation of tissue extracts for the determination of phenygam in them was conducted according to the method of Roberts, which we modified somewhat [1]. Phenygam was determined in aqueous extracts by paper electrophoresis. Electrophoresis was conducted for 24 h in acid buffer (acidic acid - pyridine - water in an 8:1:44 ratio) with pH 2.5, under the following conditions: voltage 6 V/cm, current strength 20 mA. The electrophoretograms were stained with 0.25% ninhydrin solution in acetone, followed by photometry. Under such conditions, phenygam and GABA can be distinctly separated on one electrophoretogram. The former is characterized by a somewhat lower electrophoretic mobility than GABA, and occupies a different position from the other amino acids present in the tissues. The sensitivity of the method used is insufficient (4 mg %).

In a dose of 50 mg/kg, phenygam reduces the motor activity and the reaction to the effect of external stimuli (light, sound, touch); the animals become listless; the limbs slide apart, and the head hangs down. When the dose is increased, all the enumerated symptoms increase.

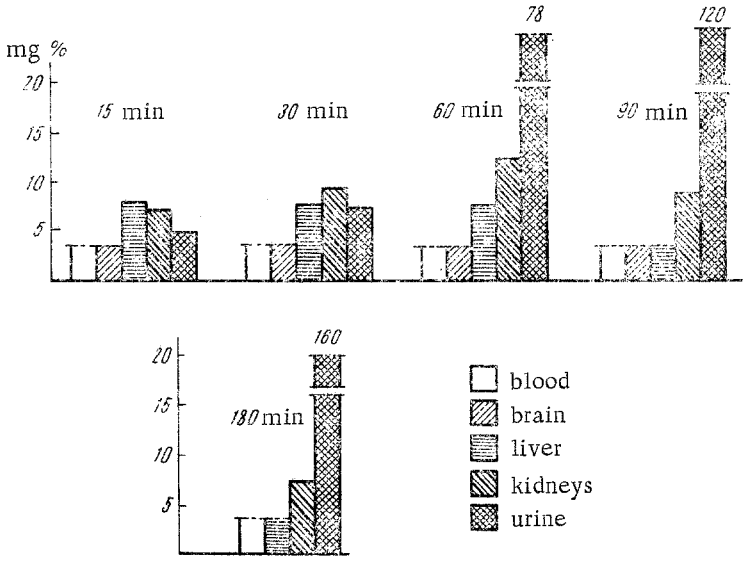

Fig. 1. Distribution of phenygam in the organs of the rabbit after intravenous injection of the preparation in a dose of 100 mg/kg.

Phenygam Content in the Tissues of Various Organs

Tissue	No. of Expt.	Phenygam content	
		in μg	in % of amount of preparation introduced
Blood	5	41.2±1.5	82
Urine	3	48.3	96
Brain	7	42.8±2.9	86
Kidneys	6	42.2±2.7	84
Liver	10	9.3±1.5	19

RESULTS

When phenygam was administered intravenously to rabbits and rats in a dose of 100 mg/kg, after 15 min it was already detected in the liver, kidneys, and urine. Only traces of the preparation were found in the brain and blood. However, considering the low sensitivity of the method, we may speak of real amounts of it found in these tissues. The nature of the distribution of phenygam remains the same 30, 60, 90, and 180 min after administration. In all the periods studied, traces of it were detected in the brain. In the kidneys, the content of this preparation increased with time; large amounts of it were found in the urine. Phenygam rapidly left the blood canal, and only traces of the preparation were detected in the blood after 15-30 min. After 180 min, there was no longer any phenygam in the blood (Fig. 1).

In order to determine to what degree phenygam is bound to the tissues, we conducted a special series of experiments in vitro. To a definite weight sample of brain, liver, kidney tissue, blood, or urine, we added 50 μg of phenygam and then produced extracts as usual, in which we determined the content of the preparation (see table).

As can be seen from the table, there is a negligible bonding of phenygam by the tissue in the blood, brain, and kidneys—the losses comprise an average of 16%; for the liver these losses are very great—81%. Phenygam is practically not bound in the urine. If we consider this circumstance, then the true indices characterizing the distribution of phenygam in the tissues will be different. During the first 15-60 min, the greatest amount of phenygam was detected in the liver; then its content in the liver was sharply reduced and remained substantial only in the kidneys and urine. It is still unclear how the conversion of phenygam in the liver may occur. One thing is undoubted—it is not an enzymatic pathway, since the phenomenon described was also observed in experiments with boiled extracts, in which enzyme action was excluded.

On the basis of the data obtained, we may assume that phenygam, in contrast to GABA, penetrates through the hematoencephalic barrier, and its concentration (less than 4 mg %) in the brain is sufficient for a substantial change in the function of the central nervous system. Let us mention that in spite of a pronounced inhibition of the nervous system, no changes occur in the level of GAMA in the brain, and thus phenygam does not exert its central effect on account of an increase in the GABA content in the brain.

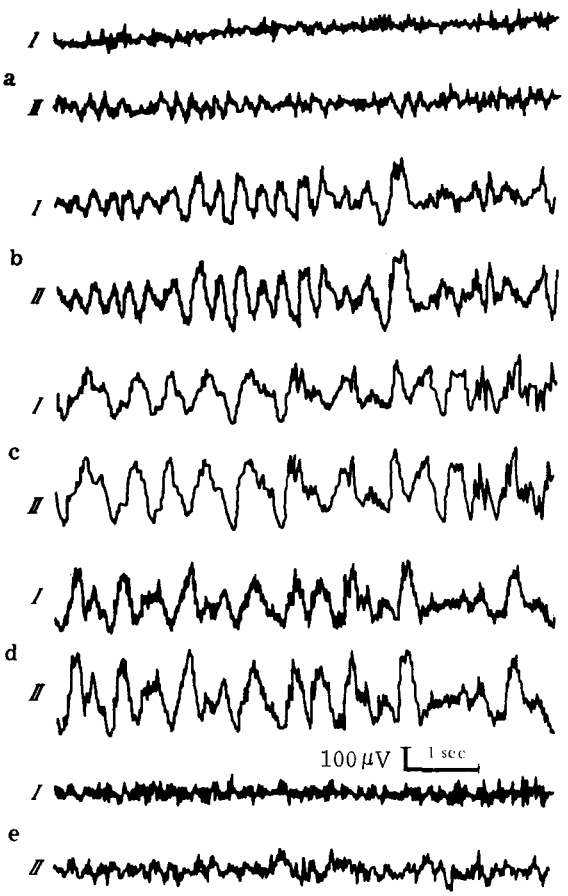

Fig. 2. Effect of phenygam on the rabbit EEG. a) Norm; b, c, d, e) 30, 60, 120 min and 24 h after intravenous injection of 100 mg/kg phenygam; I) takeoff from the frontal region; II) takeoff from the parietal-occipital region.

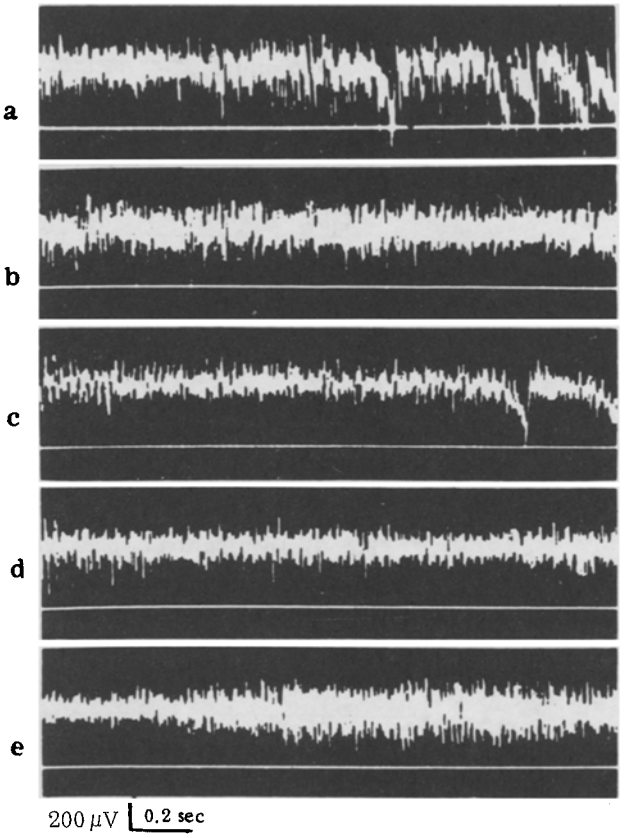

Fig. 3. Effect of phenygam on the EMG in the myotatic reflex of the rabbit. a) Normal state; b, c, d, e) 30, 60, 120 min, and 24 h after intravenous administration of phenygam to rabbit in a dose of 100 mg/kg.

To characterize the central effect of phenygam, we investigated its influence on the bioelectric activity of the brain. The experiments were conducted on rabbits with electrodes implanted in the frontal and parietal-occipital regions. The potential takeoff was unipolar. The EEG was recorded on a two-channel ink-recording encephalograph. A slow high-amplitude activity, which remained during the entire observation period (2 h), was recorded on the EEG 15-30 min after intraperitoneal or intravenous injection of phenygam in a dose of 50-100 mg/kg. On the following day, no changes were detected in the nature of the EEG (Fig. 2).

As has already been mentioned, phenygam sharply reduces the motor activity; hence, it was of interest to study the nature of its influence on the biopotentials of the muscles, in particular, on the myotatic reflex (reaction to stretching of the gastrocnemius muscle).

In the normal state, potentials with a rhythm of 130-150 osc/sec and an amplitude of 300-400 μV, with individual discharges of up to 600 μV, appear on the EMG in a response to stretching of the muscle. After the injection of phenygam, the frequency of the biocurrents did not change significantly, but the amplitude was reduced by an average of 20-25% (Fig. 3).

One of the properties of phenygam is an ability to increase the blood sugar level (by 80-100% at a dose of 100 mg/kg). The hyperglycemic effect is directly proportional to the introduced dose. The greatest increase in the blood sugar is observed 90 min after administration of the preparation. On the following days, the blood sugar level

lies within normal limits. It is interesting to note that the nature of the sugar curves after glucose loading (1 g/kg internally) is unchanged in this case. The hyperglycemia after the injection of phenygam is close in nature to the hyperglycemia induced by aminazine. It may be assumed that the hyperglycemic effect of phenygam, just like that of aminazine, is due to their influence on the centers that regulate carbohydrate metabolism.

Thus, phenygam, penetrating into the brain even in negligible amounts, exerts a strong central action, which is evidenced by changes in the EEG and EMG.

SUMMARY

A study was made on the distribution of β-phenyl-γ-aminobutyric acid (phenygam) in the rabbit organs and tissues.

Phenygam was determined by the method of electrophoretic division (sensitivity of method 4 mg %). A quarter of an hour after intravenous injection in a 100 mg/kg dose, phenygam is found in considerable amounts in the liver, kidneys, and urine, and as traces—in the blood and brain. In the liver, phenygam is subject to conversion rather than enzymatic disintegration, which was proved by experiments in vitro. Phenygam fails to influence the GABA level in the brain. Although phenygam penetrates from the blood into the brain only slightly, the amounts of it which gain access to the central nervous system are still large enough to cause changes in the behavior of animals. In the EEG this is manifested by a marked slow-down in the rhythm and an increase in the range of potentials taken from the frontal and the sincipito-occipital region. The myotatic reflex is little changed under the influence of phenygam. The latter is capable of a distinct hyperglycemic effect which is apparently due to its influence on the carbohydrate metabolism centers.

LITERATURE CITED

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2. R. A. Khaunina, Byull. éksper. biol., 1 (1964) p. 54.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
