# EFFECT OF PHENYGAM (β-PHENYL-γ-AMINOBUTYRIC ACID) ON THE PITUITARY-ADRENAL SYSTEM OF RATS

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Phenygam increases the 11-hydroxycorticosteroid (11-HCS) concentration in the blood plasma and adrenals of rats. Dexamethasone slightly modifies the action of phenygam but hypophysectomy abolishes it completely. Comparison of the effect of Dexamethasone on the action of phenygam and other psychotropic agents that also raise the plasma 11-HCS level shows a difference in the mechanism of the stimulant action of phenygam and certain neuroleptics (chlorpromazine, haloperidol) and tranquilizers (meprobamate, seduxen).
KEY WORDS: phenygam; 11-hydroxycorticosteroids.

Phenygam – β-phenyl-γ-aminobutyric acid – is an original Soviet preparation with a sedative and tranquilizing action [1, 7, 8]. In connection with this spectrum of its pharmacological activity it was decided to study the effect of phenygam on the pituitary-adrenal system, with its role in the formation of reactions of stress, tension, anxiety, etc., i.e., states for which the administration of phenygam is indicated.

## EXPERIMENTAL METHOD

Experiments were carried out on male rats weighting 160-240 g at all seasons of the year. In this way it was hoped to explain the considerable fluctuations in the normal values and the severity of the reactions. To reduce to a minimum changes conncected with a change of environment, the rats were brought into the laboratory 24 h before the experiment. The 11-hydroxycorticosteroids (11-HCS) in the blood plasma and adrenals were determined fluorimetrically by the method of Usvatova and Pankov [4] in the modification of Stabrovskii and Severovostokova [3] on a type BIAN fluorimeter. Hypophysectomy was carried out by the transocular route, using a semistereotaxic apparatus designed by Fedotov and Bagramyan [5, 6]. The rats were used in the experiment on the 3rd or 4th day after the operation. The correct and total removal of the pituitary was verified after decapitation by visual inspection of the region of the sella turcica. The adrenals were homogenized in a mixture consisting of 25% ethanol and 75% physiological saline. ACTH was injected subcutaneously and the other preparations intraperitoneally.

TABLE 1. Effect of Phenygam on 11-HCS Concentration in Rat Blood Plasma

| Preparation | Dose (mg/kg) | 11-HCS concentration (μg %) |
|---|---|---|
| Water | | 9,2±0,3 (57) |
| Phenygam | 25 | 11,7±0,24 (13) |
| " | 50 | 20,3±1,84* (18) |
| " | 75 | 26,8±1,55* (7) |
| " | 100 | 29,4±1,09* (39) |
| " | 200 | 25,4±0,71* (22) |

Notes: 1) Decapitation 60 min after injection of phenygam. Number of rats in parentheses. 2) Results for which $P < 0.001$ marked by an asterisk.

## EXPERIMENTAL RESULTS AND DISCUSSION

Intraperitoneal injection of phenygam led to a definite increase in the 11-HCS concentration in the blood plasma of the rats (Table 1). This rose considerably after a dose of 50 mg/kg, but any further increase in response to a subsequent increase in dose was small. Because of this fact, all subsequent tests were carried out with a dose of 100 mg/kg, giving a stable effect that was always reproducible.

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TABLE 2. Effect of Prolonged Administration of Phenygam on 11-HCS Concentration in Rat Blood Plasma

| Group No. | Preparation: administration for 9 days | Preparation: injection on the 10th day, 1 h before sacrifice | 11-HCS concn. (μg %) | P |
|---|---|---|---|---|
| 1 | Water | Water | 9,6±1,2 | |
| 2 | " | Phenygam | 39,0±2,34 | $P_{1-2}<0,001$ |
| 3 | Phenygam | Water | 7,1±0,5 | $P_{1-3}>0,05$ |
| 4 | " | Phenygam | 26,3±2,76 | $P_{3-4}<0,01$ |

Note: Eight rats in each group. Phenygam injected once a day in a dose of 100 mg/kg.

TABLE 3. Effect of Phenygam on 11-HCS Concentration in Blood Plasma and Adrenals of Rats

| Preparation | 11-HCS concentration: in plasma (in μg %) | 11-HCS concentration: in adrenals (in μg/g) |
|---|---|---|
| Water | 13,6±1,7 | 745,3±163,1 (18,3±1,1) |
| Phenygam | 39,1±3, 6 | 1602,3±159,1 (17,8±0,6) |

Notes. 1) Each group contained 13 rats. Phenygam injected 1 h before decapitation in a dose of 100 mg/kg. 2) Weight of adrenals in mg/100 g body weight in parentheses.

The maximal effect was found after 30 min (it was not tested sooner) and it persisted for more than 3 h. The changes in the 11-HCS concentration in the plasma occurred simultaneously with the pharmacological effects (on motor activity, movement coordination, body temperature) of phenygam, which were clearly visible as early as 30 min after injection of the preparation and continued for 2-4 h, depending on the dose given. The ability of phenygam to increase the plasma 11-HCS concentration was maintained during its prolonged administration (for 10 days), although, like the pharmacological effects, it became a little weaker.

Besides increasing the 11-HCS concentration in the blood plasma, phenygam also increased their concentration in the adrenals, although the weight of the adrenals was unchanged (Table 3).

To study the nature of the increase in 11-HCS induced by phenygam the substance Dexamethasone was used, for in the modern view [2, 11, 13], it inhibits the secretion and liberation of ACTH mainly through inhibiting the liberation of corticotropin-releasing factor from the hypothalamus; its weaker effect on other structures of the mesencephalon and on the pituitary itself is likewise not ruled out. The results given in Table 4 show that dexamethasone modified the action of phenygam negligibly compared with other substances.

TABLE 4. Effect of Dexamethasone on Action of Phenygam and Other Psychotropic Agents and ACTH

| Preparation | Dose (mg/kg) | 11-HCS Concentration (μg %): before injection of Dexamethasone | 11-HCS Concentration (μg %): after injection of Dexamethasone | P |
|---|---|---|---|---|
| Water | | 8,1±0,2 (17) | 2,2±0,3 (10) | 0,001 |
| Phenygam | 100 | 27,6±1,8 (18) | 21,6±1,5 (18) | 0,01 |
| GHBA | 300 | 43,9±3,9 (6) | 42,4±0,8 (5) | Not significantly |
| Chlorpromazine | 5 | 25,1±2,3 (6) | 3,5±0,2 (6) | 0,001 |
| Haloperidol | 2 | 26,7±2,3 (6) | 6,6±1,2 (6) | 0,001 |
| Meprobamate | 100 | 29,4±4,0 (6) | 9,9±1,1 (6) | 0,001 |
| Seduxen | 5 | 26,3±1,0 (10) | 9,7±2,3 (17) | 0,001 |
| ACTH | 15 units | 26,8±0,8 (7) | 26,1±1,6 (7) | Not significantly |

Note. Dexamethasone injected 2 h before the preparations in a dose of 0.6 mg/kg; preparations themselves injected 1 h before decapitation. Number of rats in group shown in parentheses.

TABLE 5. Effect of Hypophysectomy on the Action of Phenygam

| № Group | Group of animals | Preparation | Blood plasma | |
|---|---|---|---|---|
| | | | 11-HCS (μg %) | P |
| 1 | Intact | Water | 12,7±0,9 (37) | |
| 2 | | Phenygam | 25,7±3,6 (5) | $P_{1-2}<0,001$ |
| 3 | Undergoing mock operation | Water | 5,4±1,3 (6) | $P_{1-3}<0,001$ |
| 4 | | Phenygam | 25,1±2,5 (7) | $P_{3-4}<0,001$ |
| 5 | Hypophysectomized | Water | 1,7±0,3 (13) | $P_{1-5}<0,001$ |
| 6 | | Phenygam | 2,0±0,4 (13) | $P_{5-6}$ Not significantly |

| № Group | Group of animals | Preparation | Adrenals | | | |
|---|---|---|---|---|---|---|
| | | | wt. (mg/100 g) | P | 11-HCS (in μg/g) | P |
| 1 | Intact | Water | 14,0±0,3 | | 1036,0±140,3 | |
| 2 | | Phenygam | 14,0±0,5 | $P_{1-2}$ Not significantly | 1854,0±145,6 | $P_{1-2}<0,001$ |
| 3 | Undergoing mock operation | Water | 17,6±1,6 | $P_{1-3}<0,001$ | 450,0±121,2 | $P_{1-3}$ Not significantly |
| 4 | | Phenygam | 14,0±1,1 | $P_{3-4}$ Not signifantly | 977,0±124,5 | $P_{3-4}<0,02$ |
| 5 | Hypophysectomized | Water | 11,3±0,3 | $P_{1-5}<0,001$ | 240,0±45,7 | $P_{1-5}<0,001$ |
| 6 | | Phenygam | 12,3±0,4 | $P_{1-6}$ Not significantly | 100,0±37,7 | $P_{1-6}=0,05$ |

Note. Phenygam injected 1 h before decapitation in a dose of 100 mg/kg. Number of rats in parentheses.

To study the role of the pituitary in the stimulant action of phenygam a series of experiments was carried out on hypophysectomized rats. The results in Table 5 show that phenygam does not raise the 11-HCS level in the plasma and adrenals of hypophysectomized rats. Phenygam thus does not act directly on the adrenal. In hypophysectomized rats, moreover, the sedative action of phenygam was not weakened. It follows from these results that the action of phenygam is indirect, through its effect on the pituitary. However, to answer the question whether phenygam acts directly on the pituitary or on mesencephalic structures connected with the pituitary, and also to establish whether an important role in this action is played by reflex effects from the periphery, further experiments must be carried out, notably experiments in which phenygam is applied directly onto the pituitary in doses without a resorptive action.

It is interesting to compare the results described above on the stimulant effect of phenygam on the pituitary-adrenal system of rats with the observed effects of other psychotropic drugs.

Many psychotropic agents are known to increase the activity of the pituitary-adrenal system and to increase the concentration of corticosteroids in the plasma and adrenals [10]. However, the mechanism of the stimulant action of these drugs evidently differs from that of phenygam. Reserpine and chlorpromazine stimulate the liberation of corticotropin-releasing factor from the hypothalamus [9, 12], as a result of which the corticosteroid level is raised. As the present experiments showed, the effect of chlorpromazine is completely abolished by dexamethasone. Possibly the other psychotropic agents studied (haloperidol, meprobamate, seduxen) act through the hypothalamus, for their effect also was abolished by dexamethasone. So far as phenygam and the compound GHBA (the sodium salt of γ-hydroxybutyric acid) with a closely related structure are concerned, their effect, like that of ACTH, was unchanged by dexamethasone. It must

accordingly be postulated that phenygam acts not through the hypothalamus, but either through certain other mesencephalic structures or through direct stimulation of the pituitary gland.

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